Evidence for the Use of Intravenous Immunoglobulins—A Review of the Literature

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Published online: 10 July 2009
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Abstract Intravenous immunoglobulins (IVIg) were first introduced in the middle of the twentieth century for the treatment of primary immunodeficiencies. In 1981, Paul Imbach noticed an improvement of immune-mediated thrombocytopenia, in patients receiving IVIg for immunodeficiencies. This opened a new era for the treatment of autoimmune conditions with IVIg. Since then, IVIg has become an important treatment option in a wide spectrum of diseases, including autoimmune and acute inflammatory conditions, most of them off-label (not included in the US Food and Drug Administration recommendation). A panel of immunologists and internists with experience in IVIg therapy reviewed the medical literature for published data concerning treatment with IVIg. The quality of evidence was assessed, and a summary of the available relevant literature in each disease was given. To our knowledge, this is the first all-inclusive comprehensive review, developed to assist the clinician when considering the use of IVIg in autoimmune diseases, immune deficiencies, and other conditions.

Keywords Intravenous immunoglobulins · Intravenous gamma globulins · Autoimmunity · Evidence · IVIg · IgIV

Abbreviations
y/o year old
IVIg intravenous immunoglobulins
RCT randomized controlled trial
IFN interferon
CS corticosteroids
BMT bone marrow transplantation
HCV hepatitis C virus
PD prednisone
CP cyclophosphamide
CNS central nervous system
MPGN membranous-proliferative glomerulonephritis
MP methylprednisolone
PP plasmapheresis
LMWH low-molecular-weight heparin
LDA low-dose aspirin
NYHA New York Heart Association
EF ejection fraction
CHF congestive heart failure
DCM dilated cardiomyopathy
PPCM | peripartum cardiomyopathy  
CIP | chronic idiopathic pericarditis  
NLE | neonatal lupus erythematosus  
MMP | mucous membrane pemphigoid  
EDSS | expanded disability status scale  
VLCFA | very-long-chain fatty acids  
GTOE | glycerol trioleate/erucic supplementation  
INCAT | inflammatory neuropathy cause and treatment disability score  
MCV | motor conduction velocities  
CMAP | compound muscle action potential  
MRC | medical research council  
scale  
RRMS | relapsing–remitting multiple sclerosis  
Ref | reference  
MTX | methotrexate  
MMF | mycophenolate mofetil  
CAA | coronary artery aneurysm  
CRP | C-reactive protein  

**Introduction**

Intravenous immunoglobulins (IVIg) are gamma globulins purified from the pooled plasma of thousands of donors, typically containing more than 95% of unmodified immunoglobulin G (IgG) and only trace amounts of IgA or IgM. Immune globulin products from human plasma were first used in 1952 to treat immune deficiencies. About 30 years later, Paul Imbach observed that patients with immune thrombocytopenia and agammaglobulinemia receiving immunoglobulins as immune replacement therapy recovered from their thrombocytopenia [1]. This was the first observation to suggest treatment of autoimmune diseases with IVIg. Later on, the ability to administer large quantities of immunoglobulin intravenously was gained owing to technological advances, among them the improvement in plasma fractionation. As a result, IVIg slowly became an important treatment option in a number of diseases beyond primary immune deficiencies, including autoimmune and acute inflammatory conditions, most of them off-label indications. These indications have crossed over into almost every medical specialty. The US Food and Drug Administration (FDA) has approved the use of IVIg for the following six conditions: primary immunodeficiencies, immune thrombocytopenic purpura (ITP), Kawasaki disease, hematopoietic stem cell transplantation, chronic B cell lymphocytic leukemia, and pediatric HIV. Many off-label indications have emerged; some of these new indications for IVIg are based on solid clinical evidence; others are based on relatively few data or anecdotal reports (case series, case reports). This lack of firm evidence is due to the difficulty in performing appropriate clinical trials in diseases with low prevalence. There is a need for an evidence-based guidance for the use of IVIg to help improve patient care consistency.

Another issue is the efficacy of different preparations of IVIg. The FDA has recommended the use of particular preparations of IVIg for each labeled indication in accordance to the specific preparation used to demonstrate a beneficial effect. Of course, there is selection bias since generally only a few preparations have been tested for a given disease. This is in recognition of the difficulty to reproduce the properties of an IVIg preparation, which may vary from one manufacturer to the other due to differences in the donor population, number of donors, period of donation, production methods, virus/bacteria inactivation methods, etc. IVIg properties may also vary from batch to batch made by the same manufacturer, complicating homogeneity even more.

Possible mechanisms of action of IVIg in autoimmune and inflammatory diseases are: intact Fc-dependent blockage of IgG (as in ITP), inhibition of membrane attack complexes (C5b-C9) and activated components C3b and C4b (as in Kawasaki’s disease), and anti-idiotypes against autoantibodies (as in acquired hemophilia due to autoantibodies against factor VIII). IVIg also contains various cytokines and natural antibodies that may act against pathogens, altered molecules, cells, autoreactive B cell clones, and tumors.

**Methods**

A panel of immunologists and internists with experience in IVIg therapy reviewed the medical literature indexed in PubMed using specific terms for each specific disease/condition AND (“IVIg” OR “IgIV” OR “Intravenous Immunoglobulin*” OR “gamma globulin*”). There was no limitation on language, year of publication, or publication status. We used all clinical data ranging from multicentered randomized controlled trials (RCT) and meta-analysis to case reports. From each article, we extracted details of the study design, number of patients, type of intervention including the dose and IVIg preparation used (if mentioned), and response to treatment. The relevant data were summarized in a hierarchical manner according to the study design and number of participants. When evidence was based on higher level of evidence studies, such as RCTs, lower levels of evidence studies (such as case control studies) were disregarded. Specific diseases were classified in tables according to the specialty they belong to and are followed by a short summary of recommendations, including the level of evidence and the strength of recommendation, as assessed by known guidelines (Table 1) [2]. To our knowledge, this is the first comprehensive review which summarizes all up-to-date published data regarding the
usage of IVIg in autoimmune diseases, immune deficiencies, and other indications.

Results

The tables below summarize the clinical data gathered from studies dealing with IVIg treatment for different conditions. Each table is followed by our evidence-based recommendations for the usage of IVIg.

The following conditions refer to (Table 2).

SLE—systemic flare-up

Level of evidence B Systemic lupus erythematosus (SLE) is a multisystemic disease with various manifestations. There is some evidence that IVIg, given in patients without an increased risk for thromboembolic events or renal failure, is a safe and beneficial adjunct therapy for SLE patients with systemic flare-ups who are resistant to or refuse conventional treatment (strength of recommendation IIa).

Lupus myocarditis

Level of evidence C Lupus myocarditis is an uncommon but severe complication of SLE. There is no consensus on the specific treatment of SLE myocarditis. Most reports describe treatment with high-dose corticosteroids (CS), followed by either cyclophosphamide or azathioprine, in addition to conventional treatment for heart failure. There is little evidence that IVIg is effective when immunosuppressive therapy fails (strength of recommendation IIa).

SLE and thrombocytopenia

Level of evidence B As with the treatment of ITP, IVIg seems to be useful in managing the bleeding complications of patients with lupus-associated thrombocytopenia (strength of recommendation I).

Subacute cutaneous lupus erythematosus

Level of evidence C Standard therapy for subacute cutaneous lupus erythematosus (SCLE) includes CS (topical, intralesional, systemic), antimalarials, and other immunosuppressive agents. IVIg may be considered in refractory cases, but more study should be done (strength of recommendation IIa).

Level of evidence C Kikuchi, also called histiocytic necrotizing lymphadenitis, is a rare benign disease. There is little evidence that treatment with IVIg is superior to other antiinflammatory treatments (strength of recommendation IIa).

Adult Still disease

Level of recommendation C Giving the fact that adult Still disease responds to CS and biological and anti-tumor necrosis factor (TNF) treatment, there is low-level evidence that IVIg has an additional benefit for treatment of this disease (strength of recommendation IIa).

Systemic vasculitis (including GA and MPA)

Level of recommendation B Immunosuppression with CSs and cytotoxic agents should be used in systemic vasculitis before considering IVIg. There is however some evidence that IVIg might be useful and therefore in refractory cases it may be worth to try (strength of recommendation IIa).

Churg–Strauss syndrome

Level of evidence B CSS is a rare disease. The initial management of CSS consists of high doses of CS. For patients with severe disease or those who are unresponsive to CS, treatment with IVIg was warranted (strength of recommendation IIa).

Hepatitis C virus with autoimmune features

Level of evidence B Infection with hepatitis C virus (HCV) may be associated with a variety of autoimmune phenomena causing a therapeutic dilemma for treatment with interferon alpha (IFN alpha), which stimulates autoimmune symptoms, or with CS, which may lead to an increase of viral load. Treatment with IVIg may act synergistically with
| Disease                                      | Ref. | Study design | Intervention including dose and IVIg preparation used | Number of patients | Results/response                                                                 |
|---------------------------------------------|------|--------------|--------------------------------------------------------|--------------------|----------------------------------------------------------------------------------|
| Systemic lupus erythematosus (SLE) systemic flare-up | [37] | Controlled trial | IVIg 0.4 g/kg for 5 days, between 1 and 8 monthly courses (mean 5; ISIIVEN-Instituto Sierovaccinogeno, Italiano ISI SpA.) | 20 patients with active SLE | Beneficial clinical response in 17 out of 20 pts ($p<0.0001$); especially in arthritis, fever, thrombocytopenia, and CNS lupus |
|                                             | [38] | Uncontrolled multicenter trial | IVIg 0.4 g/kg for 5 days | 13 females with acute exacerbation of SLE | After IVIg treatment, the modified European Consensus Lupus Activity Measurement (mECLAM) declined in 12 out of 13 pts by $\geq 3$ points ($p=0.0002$) |
|                                             | [39] | Uncontrolled trial | 30 g of sulfonated IVIg preparation on days 1–4 and 21–24 | 12 patients with mild-to-moderate active SLE | Within 6 weeks, the mean Systemic Lupus Activity Measure (SLAM) score declined from 7.3 to 5.25 ($p<0.01$); in a minority, this effect lasted 5–12 months |
| Lupus myocarditis                           | [40] | Case series | IVIg 0.4 g/kg per day for 5 days, in addition to CP or MMF (given to 2 patients) | 3 patients with lupus myocarditis and severe deterioration in contractile functions; high-dose CS had little effect | Marked clinical improvement; decreased need for CS |
|                                             | [41] | Case report | IVIg 0.4 g/kg per day for 5 days | 1 patient with lupus myocarditis refractory to CS | Marked improvement of severe cardiac dysfunction after one course of IVIg |
| SLE and thrombocytopenia                    | [42] | Retrospective trial | IVIg 2 g/kg for 2 to 5 days | 31 patients with severe thrombocytopenia associated with SLE refractory to PD treatment | A transient response was observed in 20 patients (65%); no sustained response was observed |
| Subacute cutaneous lupus erythematosus (SCLE) | [43] | Case series | IVIg with starting doses of 1 g/kg for 2 days, followed by 0.4 g/kg monthly, until disease resolution or for 6 months | 12 patients with resistant SCLE | 5 patients had complete or near-complete clearing of their skin disease; two had partial improvement and 3 had limited responses |
|                                             | [44] | Case series | IVIg 0.3 g/kg per day for 5 days each month for 12 months | 7 patients with skin disease (5 had systemic LE; two had SCLE) | IVIg was unable to control cutaneous disease efficiently |
|                                             | [45] | Case series | IVIg | 3 patients with SCLE resistant to topical and systemic therapy | Good response |
|                                             | [46] | Case report | IVIg 2 g/kg monthly | 30-year-old woman with SCLE | Good response |
| Various manifestations of SLE               | [47] | Various case reports | Different IVIg preparations and doses | 26 patients with specific lupus manifestations refractory to standard Tx.: autoimmune hemolytic anemia (2), acquired factor VIII inhibitors (2), acquired von Willebrand disease (2), pure red cell aplasia (3), pancytopenia (1), myelofibrosis (1), pneumonitis (2), pleural effusion (1), pericarditis (2), myocarditis (2), CNS | Improvement of SLE-related condition |
| Disease                                                                 | Ref.       | Study design | Intervention including dose and IVIg preparation used | Number of patients | Results/response |
|------------------------------------------------------------------------|------------|--------------|--------------------------------------------------------|--------------------|-----------------|
| For lupus nephritis, see kidney section                                |            |              |                                                        |                    |                 |
| For Kawasaki disease, see cardiology section                          |            |              |                                                        |                    |                 |
| Kikuchi Disease                                                        | [48]       | Case report  | IVIg 0.4 g/kg per day for 3 days                       | A 35-year-old patient with Kikuchi, refractory to steroids and thalidomide | Adefinite improvement in her facial swelling occurred within 4 days, followed by gradual but complete resolution of lymphadenopathy over the subsequent 8 weeks, despite stopping steroid medication |
|                                                                        | [49]       | Case report  | IVIg 1 g/kg per day for 2 days, plus PD (2 mg/kg per day) | 2 children who had Kikuchi complicated with hemophagocytic syndrome | One responded dramatically; second case responded partially to IVIg and fully after PD was added |
| Still’s disease                                                        | [50]       | Uncontrolled trial | Patients received monthly IVIg | 7 patients unresponsive or poorly responsive to nonsteroidal anti-inflammatory drugs | 5 patients responded after 4–6 treatments; 2 failed to respond |
|                                                                        | [51]       | Uncontrolled trial | Between 1 and 8 IVIg monthly infusions with a dose of 1 g/kg per day for 2 days | 7 patients suffering from adult Still's disease | All patients improved but relapsed after 3–24 months |
|                                                                        | [52]       | Case report  | 2 courses of IVIg 1 g/kg for 2 days | 23-year-old patient with flare-up of disease while taking salicylates at gestational week 22 | Significant clinical and laboratory improvement |
| Granulomatous arteritis (GA, Wegener's granulomatosis)                 | [53]       | Multicentered RCT | 14 patients received IVIg 2 g/kg in 5 days (sandoglobulin Novartis) vs. 14 placebo | 34 patients with ANCA-associated vasculitis (GA or MPA), refractory to CS or CP | Reduction in Birmingham Vasculitis Activity Score of 50% in 14/17 and 6/17 of the IVIg and placebo groups, respectively |
|                                                                        | [54]       | Uncontrolled trial | Patients received IVIg (Sandoglobulin) | 14 patients with GA who responded poorly to standard therapy | All patients were in full and partial remission after 8 weeks; clinical benefit was maintained a year later |
|                                                                        | [55]       | Uncontrolled trial | Single or multiple courses of IVIg, 30 g/day, over 5 days | 15 patients with GA who responded poorly to standard therapy | 40% of patients benefited from IVIg treatment but without complete remission |
|                                                                        | [56]       | Uncontrolled trial | Monthly IVIg, 0.4 g/kg for 5 days, 1–6 cycles (Isiven Instituto Sierovaccinogeno, Italiano ISI Sp.A.) | 10 patients with GA, CSS, or undifferentiated vasculitis which were refractory to standard treatment | IVIg treatment was found beneficial in 6 out of the 10 patients |
|                                                                        | [57]       | Uncontrolled trial | IVIg 0.5 g/kg per day for 4 days; Sandoglobulin (Sandoz, Basel, Switzerland) | 3 patients with GA not treated with immunosuppressants before | One patient had full remission; one had transitional response; one had no response |
| Microscopic polyangiitis (MPA)                                         | [58]       | Uncontrolled trial | IVIg 0.4 g/kg per day for 5 days, before or along with CS or CP (kenketsu velilon-I, Teijin Co., Ltd., Tokyo or kenketsu Glovenon-I, Nihon pharmaceutical Co., Ltd., Tokyo, Japan) | 30 patients with MPA plus rapidly progressive glomerulonephritis | At 6 months, renal and general survival were 92% and 93%, respectively, compared to 70% and 74% with conventional therapy in other studies |
|                                                                        | [57]       | Uncontrolled trial | IVIg 0.5 g/kg per day for 4 days (Sandoglobulin, Sandoz, Basel, Switzerland) | 3 patients with MPA not treated with immunosuppressants before | One patient had full remission; one had transitional response; one had no response |
| Disease                                      | Ref. | Study design | Intervention including dose and IVIg preparation used                                                                 | Number of patients | Results/response                                                                                                                                 |
|----------------------------------------------|------|--------------|------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| Churg–Strauss syndrome (CSS)                 | [59] | Controlled trial | All patients received PS and CP in severe cases; 9 received monthly PP, followed by IVIg 1 g/kg for 2 days (Ig vena N IVH; Sclavo, Siena, Italy) | 18 patients with CSS | After 12 months, all patients in the IVIg group and 4 (44%) in the control group were in remission; a significant favorable outcome was kept after 3 years ($p<0.01$) |
| Autoimmune hepatitis (AIH)                  | [61] | Case report  | IVIg was initiated because of adverse affects of long-term steroid therapy IVIg 0.4 g/kg for 5 days, and then IFN alpha 3 times a week, compared to treatment with IFN alpha alone | A patient with chronic AIH | Immediate clinical, serological, and histological improvement                                                                                     |
| Autoimmune features in hepatitis C virus (HCV) infection | [62] | RCT          | IVIg 0.4 g/kg for 5 days, compared to treatment with IFN alpha alone                                                    | 42 patients with HCV and autoimmune phenomena | A higher percentage of patients who received IFN alpha plus IVIg showed complete virological and histological responses                          |
| Henoch–Schönlein purpura (HSP)              | [63] | Cohort study | IVIg 1 g/kg for 2 days, every month for 3 months (Biotransfusion, Roissy, France)                                       | 11 adult patients with severe IgA nephropathy (9 idiopathic, 2 with HSP) | Substantial improvement in glomerular filtration rate and kidney functions; 2 patients with HSP had resolution of other systemic symptoms          |
| Mixed connective tissue disease (MCTD)       | [64] | Case report  | IVIg (Tegelines) 1 g/kg per day for 2 days                                                                          | A 10-year-old boy with HSP and severe abdominal manifestations refractory to treatment with CS | Digestive symptoms disappeared within 3 days                                                                                                    |
| Systemic sclerosis (SSc)                    | [65] | Case report  | Patient was treated with IVIg                                                                                         | A 26-year-old woman with HSP with nephrotic syndrome refractory to CS 46-year-old man with HSP and MPGN | Dramatic resolution                                                                                                                                |
|                                              | [66] | Case report  | IVIg (polyglobulin N containing maltose) 0.4 g/kg, for 2 days                                                          | 56-year-old man with HSP and severe digestive manifestations | Developed hemolysis and rapid deterioration renal function                                                                                      |
|                                              | [67] | Case report  | IVIg 1 g/kg for 2 days                                                                                               | The patient’s purpura and abdominal syndrome improved dramatically |                                                                                                                                              |
| Systemic sclerosis (SSc)                    | [68] | Case report  | IVIg 0.4 g/kg for 5 days                                                                                            | A woman with MCTD and fasciitis | Quick improvement of her symptoms and decreased CRP                                                                                              |
|                                              | [69] | Case report  | Patient was treated with IVIg                                                                                         | A 69-year-old man with MCTD and nonresponsive skin eruptions | Successful control of disease                                                                                                                   |
| Systemic sclerosis (SSc)                    | [70] | Controlled trial | IVIg 0.4 g/kg daily for 5 days, monthly for 3–6 cycles                                                               | 15 patients with SSc | Treatment resulted in significant improvement in quality of life ($p<0.03$) and a decrease in Rodnan skin score ($p<0.001$)                        |
|                                              | [71] | Case series  | IVIg 0.4 g/kg daily for 5 days                                                                                        | 5 patients with diffuse SSc | Marked long-term improvement in skin thickness from 2 weeks of treatment ($p<0.01$)                                                             |
|                                              | [72] | Controlled trial | Monthly IVIg 0.4 g/kg for 4 days, for 6 months                                                                       | 7 female patients with SSc (5 limited, 2 diffuse), with | Significant improvement in joint swelling and pain ($p<0.03$), as                                                                                  |
| Disease | Ref. | Study design | Intervention including dose and IVIg preparation used | Number of patients | Results/response |
|---------|------|--------------|------------------------------------------------------|--------------------|------------------|
| Severe refractory joint involvement | [73] | Case report | 3–6 cycles of IVIg 0.4 g/kg for 5 days; ISIVEN (Instituto Sierovaccinogeno, Italiano ISI SpA, Italy) | 3 patients with rapid deteriorating SSc refractory to treatment | well as skin score ($p<0.003$), after 6 months of therapy |
| Juvenile rheumatoid arthritis (JRA) | [74] | Multicentered RCT | Bimonthly IVIg 1.5–2.0 g/kg for the first 2 months, then monthly for up to 6 months (Ivegami, Immuno AG, Vienna) after 3 and a half months was switched to placebo | 25 patients with resistant JRA | 19 (76%) had moderate to large improvement; the group which switched to placebo showed rapid loss of this effect |
| Rheumatoid arthritis (RA) | [75] | RCT | Patients were additionally treated with high-dose IVIg or MP | 20 patients with JRA treated with MTX and CS | Clinical effects were rapid in both groups |
| | [76] | Retrospective cohort | IVIg monthly for 3–54 months | 27 patients with systemic JRA | 20 patients responded after 6 months, especially systemic features and CS dependence |
| | [77] | Controlled trial | High-dose IVIg | 16 children with severe juvenile chronic arthritis | Mild–moderate systemic, articular and laboratory improvement in most patients |
| Polymyositis (PM) and dermatomyositis (DM) | [85] | RCT | Received PD 25 mg plus IVIg 2 g/kg or placebo every month for 3 months | 15 patients with treatment-resistant DM | Significant improvement of muscle strength ($p<0.018$) and neuromuscular symptoms ($p<0.035$), with IVIg treatment compared to placebo |
| | [86] | Controlled trial | IVIg or standard therapy | 16 patients with PM or DM | Clinical and functional remission in a higher percentage (81%) that |
IFN alpha, achieving a better response to IFN treatment in patients with chronic HCV associated with autoimmunity (strength of recommendation IIa).

Henoch–Schönlein purpura/IgA nephropathy

Level of evidence B There is some evidence that IVIg treatment may be effective for systemic and kidney disease, rather than sucrose/mannose in the preparation (strength of recommendation IIa).

Mixed connective tissue disease

Level of evidence C Mixed connective tissue disease (MCTD) is an autoimmune condition which combines features of polymyositis, systemic lupus erythematosus, scleroderma, and dermatomyositis and is thus considered an overlap syndrome. There is scarce evidence that treatment with IVIg helps to improve skin manifestations in MCTD (strength of recommendation IIa).

Systemic sclerosis

Level of evidence B Systemic sclerosis is characterized by hardening and scarring of the skin and inner organs. There is some evidence that treatment with IVIg helps to improve skin and systemic symptoms (strength of recommendation I).

Juvenile rheumatoid arthritis

Level of evidence A There is evidence that IVIg is useful for the treatment of patients with severe chronic JRA;
its treatment may help also reduce the need for CS and other immunosuppressive therapy (strength of recommendation I).

Rheumatoid arthritis

Level of evidence B There is hardly any convincing evidence that IVIg benefits patients with RA (strength of recommendation IIb).

Sjögren’s disease

Level of evidence C There is some evidence that patients with ataxic sensory neuropathy refractory to immunosuppressive therapy will benefit from IVIg (strength of recommendation IIa).

Myopathies (PM, DM, and IBM)

Level of evidence B In patients with DM and PM that are resistant or partially responsive to conventional therapies, IVIg was effective (strength of recommendation I).

Level of evidence A In IBM, IVIg showed marginal improvements in muscle strength which were nonsignificant and thus were not recommended (strength of recommendation III).

Behcet’s disease

Level of evidence C Behcet’s disease is a multisystemic disorder presenting with recurrent oral and genital ulcers as well as ocular and central nervous system involvement. The severe cases may respond to systemic CSs, interferon, or anti-TNF therapy. There is some evidence to support IVIg treatment for refractory eye and skin involvement (strength of recommendation I).

The following conditions refer to (Table 3).

Acquired hemophilia

Level of evidence B There is weak evidence that IVIg is useful in the treatment of acquired hemophilia. IVIg may be tried in the case in which CS and cytotoxic agents fail or when facing an emergency situation as an additional therapy IVIg (strength of recommendation IIa).

Acquired hypogammaglobulinemia

Level of evidence A There is strong evidence that IVIg is of benefit in reducing the number and severity of infections in patients with acquired hypogammaglobulinemia in the context of hematological malignancy (strength of recommendation I). While this is true, both cost and the potential of adverse effects, most prominently acute renal failure and thromboembolic phenomena [3–5], prevent a clear-cut recommendation for the use of IVIg in acquired hypogammaglobulinemia. With this in mind, IVIg may be recommended at the replacement dose of 400 mg/kg each 3 to 4 weeks in cases in which severe or recurrent infections have occurred.

Pure red cell aplasia

Level of evidence C Pure red cell aplasia may be immune-mediated due to a background neoplasia, most frequently hematologic, or due to an immune disease or an immune response triggered by drugs. It may also occur secondary to parvovirus B19 infection which may also lead to aplastic anemia. Treatment of the causative disease is the most important issue. Weak evidence supports the use of IVIg in pure red cell aplasia. IVIg may however be used in the case in which first-line therapy (i.e., CS and immunosuppressive drugs) fails to achieve a remission (strength of recommendation I). IVIg is first-line therapy in immunosuppressed hosts in which infection with parvovirus B19 results in pure red cell aplasia.

Acquired von Willebrand syndrome

Level of evidence B and C According to Federici and colleagues [6], 48% of the cases of acquired von Willebrand syndrome are associated with lymphoproliferative diseases, 15% with myeloproliferative disorders, and 21% with cardiovascular diseases. In another paper, Federici and colleagues [7] claim that 33% of the reported cases are associated with a monoclonal gammopathy of uncertain significance. Then, the detection and specific treatment of the underlying disease is as important as the immediate therapy of the coagulation disorder. In accordance to the scant existing evidence of IVIg therapy in this disorder, IVIg should be used in cases of standard therapy (desmopressin and factor VIII/von Willebrand factor concentrate) failure and in urgent situations as an addition to such therapy (strength of recommendation IIb). IVIg may also be used in the preparation for surgery.

Aplastic anemia

Level of evidence C While idiopathic aplastic anemia can be transient as in the case of parvovirus-B19-induced bone marrow depression, idiopathic aplastic anemia should first be treated with immunosuppressive drugs like CS or cyclosporine or with antithymocyte or antilymphocyte immunoglobulins as well as supportive blood components transfusions. Stem cell
| Disease                                | Ref. | Study design               | Intervention including dose and IVIg preparation used                                                                 | Number of patients | Results/response                                                                 |
|----------------------------------------|------|---------------------------|------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------------------------------------------------------------------|
| Acquired hemophilia                    | [93] | Prospective multicenter study | Induction with IVIg (5% Gamimune-N, Miles Inc, Berkeley, CA, USA) 2 g/kg over 2 or 5 days, maintenance with 0.4 g/kg by clinician decision | 19 patients        | 8 of 16 assessable patients (50%) had inhibitors reduced in more than 25%; in one third of these responses, concomitant CS treatment may have influenced results |
|                                        | [94] | Review of published case reports | Different IVIg preparations, dose ranging from 1.6 to 2.8 g/kg over 2–7 days                                           | 26 patients        | 16 of 26 patients (62%) had inhibitors reduced in more than 25%; 7 of 26 patients (27%) had clinical benefit |
|                                        | [94] | Case series               | IVIg (Sandoglobulin) 2 g/kg over 5 days                                                                            | 4 patients         | 2 of 4 patients (50%) had inhibitors reduced in more than 25%, but with no clinical benefit in 2 of 4 patients, the inhibitor reductions were no assessable due to concomitant CS or CP treatment, with clinical benefit in doubt |
| Acquired hypogammaglobulinemia         | [95] | Review of published case reports | Different IVIg preparations and doses; IVIg therapy alone                                                           | 35 patients        | 30% had inhibitors reduced in more than 25% and clinical benefit |
|                                        | [96] | Case series               | Prednisolone 1 mg/kg per day with IVIg 2 g/kg over 2–5 days                                                        | 7 patients         | 5 of 7 patients (71%) had inhibitors reduced in more than 25% |
|                                        | [97] | RCT crossover study       | 6 months IVIg (0.3 g/kg per month, Ig-Vena N, Siena, Siena, Italy) or placebo, then switch for 12 months and switch again for 6 months | 42 CLL patients    | IVIg treatment yielded more infection free patients at 6 months than placebo (20 vs. 9, p<0.01) as well as at 12 months (13 vs. 6, p=0.02) |
|                                        | [98] | RCT crossover study       | 12 months IVIg 0.4 g/kg (Gammagard, Hyland Therapeutic Division, Baxter Healthcare, Glenoak, CA, USA) every 3 weeks or placebo, then switch for 12 months | 12 B cell CLL or NHL patients with hypogammaglobulinemia | During IVIg treatment, there were more infection-free patients than during placebo administration (6 vs. 1, p=0.001); in addition, 10 of 12 had lower rates of severe bacterial infection while on IVIg (p=0.001) |
|                                        | [99] | RCT                        | 18 g IVIg or albumin each 3 weeks for 12 months                                                                   | 42 CLL patients    | Fewer infections in IVIg-treated (29% vs. 61%, p=0.04) |
|                                        | [100]| RCT                       | IVIg 0.4 g/kg (Gammagard, Baxter Healthcare) or albumin every month for 12 months                                | 82 patients        | Fewer severe infections in IVIg-treated (21% vs. 56%, p=0.02) |
|                                        | [101]| RCT                       | IVIg (Endobulin, Immuno) 0.4 g/kg or no treatment each month, for 6 months                                        | 60 children        | 19 serious infection in IVIg-treated compared with 38 in placebo-treated patients (p=0.019) |
|                                        | [102]| RCT                       | Cefatexitom and amikacin with or without IVIg                                                                       | 33 children        | No septicemia/pneumonia on IVIg treatment compared with 10 cases in placebo-treated (p=0.002) |
|                                        |      |                           |                                                                      |                    | Less infections in IVIg-treated patients                                      |
|                                        |      |                           |                                                                      |                    | Shorter fever duration in IVIg group (5.2 vs. 7.9 days, p<0.05) |
|                                        |      |                           |                                                                      |                    | Similar neutropenia and hospitalization duration |
| Study Design | Intervention and Dose | Number of Patients | Results/Response |
|-------------|----------------------|--------------------|------------------|
| **Clinical Trials** |
| [103] RCT | IVIg (Gammagard Baxter Healthcare Corporation Hyland Division) 0.4 g/kg or placebo every 3 weeks for 12 months | 84 CLL patients with hypogammaglobulinemia or a history of infection | Overall fewer bacterial infections in the IVIg group (23 vs 42, p=0.01) |
| [104] RCT crossover study | 6 months IVIg 0.3 g/kg per month (Ig-Vena N, Scavo, Siena, Italy) or no therapy, then switch for 12 months and switch again for 6 months | 25 multiple myeloma patients with hypogammaglobulinemia | Even more marked difference in those who completed 1 year (14 vs 36, p=0.001) |
| [105] Two trials: RCT and RCT crossover study | 12 months IVIg 0.4 g/kg every 3 weeks (Gammagard Baxter Healthcare Corporation Hyland Division) or placebo, then switch for 12 months (only in the case of the RCT crossover trial) | RCT trial: 81 patients with B cell CLL or low-grade NHL patients with hypogammaglobulinemia | RCT trial: less bacterial infections in the IVIg group (23 vs 42, p=0.01) |
| | | RCT crossover study: 12 patients with B cell CLL or low-grade NHL patients with hypogammaglobulinemia | RCT crossover trial: larger number of patients free of severe infections in the IVIg group (6 vs 1, p=0.001) |
| **Case Reports** |
| [106] Case series | IVIg 2 g/kg over 5 days | 3 pure red cell aplasia patients | Good response in all patients |
| [107] Case series | IVIg 2 g/kg (2 patients received Sandoglobulin, Sandoz, Switzerland, 2 patients received Veinoglobulin, Institut Merieux, France) over 5 days | 4 patients with red cell aplasia, one idiopathic, another with well-differentiated lymphoma and 2 with B cell CLL | Good response in all patients |
| [108] Case report | IVIg | 42-year-old male with parvovirus-B19-induced red cell aplasia after stem cell transplantation | Good response |
| [109] Case report | IVIg 2 g/kg over 5 days | 36-year-old male with parvovirus-B19-induced red cell aplasia after liver transplantation | Good response |
| [110] Case report | IVIg (Panglobulin, ZLB Bioplasma, AG, Bern, Switzerland) 2 g/kg over 2 days | 14-year-old male with parvovirus-B19-induced red cell aplasia after renal transplantation | Good response but development of osmotic sucrose-related renal failure |
| [111] Case report | IVIg 1 g/kg single dose | 26-year-old female with parvovirus-B19-induced red cell aplasia after CHOP chemotherapy, rituximab, and radiotherapy | Good response |
| [112] Case report | IVIg | Relapsing pure red cell aplasia in a patient with B-cell chronic lymphocytic leukemia, refractory to PD and CP | Good response |
| [113] Case report | IVIg 4 g/kg over 10 days | Patient with parvovirus-B19-induced red cell aplasia after renal transplantation | Good response |
| [114] Case report | IVIg | 41-year-old male patient with acquired immunodeficiency syndrome and parvovirus-B19-induced red cell aplasia | Good response |
| Disease | Ref. | Study design | Intervention including dose and IVIg preparation used | Number of patients | Results/response |
|---------|------|-------------|------------------------------------------------------|-------------------|----------------|
|         | [115]| Case series | IVIg 1 to 2 g/kg over 1 to 2 days + maintenance dose 0.4 g/kg each month | 8 patients with acquired immunodeficiency syndrome and parvovirus-B19-induced red cell aplasia | Good response in 8 of 8 patients, 6 of 8 needed also maintenance IVIg |
|         | [116]| Case report | 0.3 g/kg IVIg (Venilon, Teijin, Osaka) over 6 days | 28-year-old female patient with common variable immunodeficiency and parvovirus-B19-induced red cell aplasia | Good response |
|         | [117]| Case report | 1 g/kg IVIg | 34-year-old male with acquired immunodeficiency syndrome and parvovirus-B19-induced red cell aplasia | Good response |
|         | [118]| Case report | 2 g/kg IVIg (Intragam, CSL) over 5 days | Male patient with acquired immunodeficiency syndrome and parvovirus-B19-induced red cell aplasia | Good response |
|         | [119]| Case report | 2 g/kg IVIg then variable maintenance doses | 26-year-old male patient with acquired immunodeficiency syndrome and parvovirus-B19-induced red cell aplasia | Good response |
|         | [120]| Case report | IVIg | Female patient with chronic idiopathic pure red cell aplasia | Good response including 2 uneventful pregnancies during treatment |
|         | [121]| Case report | 2 g/kg IVIg over 5 days | 22-year-old female patient with systemic erythematosus lupus and pure red cell aplasia, after failure of CS therapy | Good and immediate response |
|         | [122]| Case report | 4 g/kg IVIg (Sandoglobulin) over 10 days, subsequent additional shorter courses and plasmapheresis due to immune-complex disease | 24-year-old female patient with parvovirus-B19-induced red cell aplasia after liver transplantation | Late response; it is questionable that the late response is due to IVIg due to the late timing |
|         | [123]| Case report | 2 g/kg IVIg (Sandoglobulin, Sandoz, East Hanover, NJ, USA) over 5 days, subsequent maintenance courses | 4-year-old patient pure red cell aplasia | Good and long-term response, weaned of blood transfusions |
|         | [124]| Case report | 2 g/kg IVIg over 5 days, subsequent maintenance courses | 65-year-old Waldenström's macroglobulinemia patient with parvovirus-B19-induced pure red cell aplasia | Good and long-term response, weaned of blood transfusions |
| Acquired von Willebrand syndrome | [7] | Prospective noncontrolled study with sequential treatments | Desmopressin and factor VIII/von Willebrand factor concentrate where compared to IVIg 2 g/kg over 2 days (Sandoglobulin, Novartis or Ig-Vena Sclavo) | 10 MGUS patients with acquired von Willebrand syndrome: 8 had IgG-kappa or lambda, 2 had IgM-kappa | Transient increase in plasma von Willebrand factor with desmopressin and factor VIII/von Willebrand factor concentrate; IVIg infusion in IgG-MGUS resulted in a more sustained increase starting on day 4 and returning to preinfusion levels on day 21 |
| Ref. | Study design | Intervention including dose and IVIg preparation used | Number of patients | Results/response |
|------|-------------|------------------------------------------------------|--------------------|------------------|
| [95] | Case series | IVIg                                                  | 9 acquired von Willebrand syndrome patients | Good response in 30% |
| [125] | Case report | IVIg 0.9 g/kg over 3 days                             | 43-year-old patient with multiple myeloma and gastrointestinal bleeding due to acquired von Willebrand syndrome not responsive to vasopressin | Rapid hematological correction after 4 days, bleeding control |
| [126] | Case report | IVIg                                                  | 2 SLE patients with von Willebrand syndrome | Good response in one of the 2 patients |
| [1] | Case report | IVIg                                                  | 2 patients with idiopathic aplastic anemia | No response |
| [127] | Case report | IVIg                                                  | Aplastic anemia patient unresponsive to antithymocyte globulin and CS | Good response |
| [128] | Case report | IVIg                                                  | Aplastic anemia due to parvovirus B19 infection in a heart transplant recipient | Good response |
| [129] | Case report | IVIg (ISIVEN, Instituto Sierovaccinogeno, Italiano ISI SpA) 2 g/kg over 5 days | 66-year-old woman with idiopathic aplastic anemia, unresponsive to CS | Good response |
| [130] | Multicenter noncontrolled study + review of published cases | IVIg (generally Sandoglobulin, Basel, Switzerland, but also Gamimmune N, Cutter Biological, Emeryville, CA, USA; Venilon, Teijin Institute, Tokyo; Sanglopor, Sankyo Institute, Tokyo) 2.5–7 g/kg over 5–7 days | 73 patients with autoimmune hemolytic anemia: 36 from multicenter study, 37 from review of published cases | 29 patients (39.7%) responded to IVIg: hepatomegaly and low pretreatment hemoglobin were correlated with good response |
| [131] | Case series | IVIg 0.4–1 g/kg for 5–3 days                          | 20 infants with neutropenia | 50% responded after IVIg as compared to 100% with G-CSF and 57% with CS |
| [132] | Case series | IVIg 3 g/kg over 3 days                               | 6 infants with neutropenia | Fast but transient rise in neutrophils in all |
| [133] | Case series | IVIg single or multiple courses + CS                  | 40 patients (children and young adults) | Remission in 9/40, transient response in 26/40 (overall improvement in 87%) |
| [134] | Case series | IVIg plus CS for either acute hemolysis or thrombocytopenia | 5 pediatric patients | Transient effect that needed immunosuppressant therapy for maintenance |
| [135] | Case report | IVIg 0.4 g/kg for 5 days                              | 3 patients with ES refractory to conventional therapy, including CS and splenectomy in all of the patients, vincristine in 2, and CP in one | 2 patients failed to respond, but the third had a clinical remission after IVIg therapy |
| [136] | Case report | IVIg 0.4 g/kg for 5 days                              | A patient with steroid resistant ES associated with dermatomyositis | IVIg was transiently effective, but a sustain remission was achieved with CP |
| [137] | Nonrandomized study | IVIg, 1 g/kg weekly, or CS given to pregnant women | 37 pregnant women with previous pregnancy with alloimmune thrombocytopenia: 27 received IVIg, 10 received CS | There was an increase in platelets and no intracranial bleeding in 26% of patients/fetus treated with IVIg as compared with 10% of those treated with CS; in addition, there was no increase in platelets and no intracranial bleeding in 41% of patients/fetus treated with IVIg as compared with 20% of those treated with CS |
| Disease                                      | Ref. | Study design                  | Intervention including dose and IVIg preparation used                                                                 | Number of patients | Results/response                                                                                     |
|---------------------------------------------|------|-------------------------------|----------------------------------------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------------------------------------------------------|
| Stem cell/bone marrow transplantation: infections and graft-versus-host disease | [138] | RCT                           | 16 weekly doses since 1 week before transplantation of either IVIg (Sandoglobulin, Novartis Pharma, Rueil-Malmaison) 0.05, 0.25, and 0.5 g/kg or placebo | 200 patients with allogeneic stem cell transplantation | No protection against infections; GVHD and mortality were similar                                    |
|                                             | [139] | Randomized trial             | 64 patients received 0.4 g/kg per week of IVIg (Sandoglobulin, Sandoz, Switzerland); 64 patients received 0.1 g/kg per week of CMV-IgG | 128 patients with allogeneic bone marrow transplantation | No significant difference in the occurrence or severity of acute or chronic GVHD, infections, or survival |
|                                             | [140] | RCT                           | 123 patients received 0.5 g/kg per month of IVIg; 127 patients did not receive IVIg, from the fourth to the 12th month after transplantation | 250 patients with allogeneic bone marrow transplantation | No significant difference in the occurrence of chronic GVHD, infections, or survival               |
|                                             | [141] | Randomized trial             | All received CMV-negative blood products, 25 received IVIg (1 g/kg per week) starting before pretransplant conditioning and then for 17 additional weeks | 48 patients after allogeneic BMT, CMV seronegative, which received CMV seropositive or seronegative BMT | No difference in the number of bacterial/fungal infections, fewer non-CMV viral infections in the IVIg group (9 vs 15, \( p = 0.03 \)), less grade \( \geq II \) of GVHD in the IVIg group, \( p = 0.04 \) |
|                                             | [142] | Multicenter RCT              | IVIg (Venoglobulin S 5%, Alpha Therapeutic Corporation, L.A., CA, USA), 0.1, 0.25, or 0.5 g/kg, started 2 days before transplant, continued weekly for 90 days and then monthly until 1 year after transplant | 618 allogeneic bone marrow transplant recipients | Acute GVHD occurred in 39% (80/206) in the 0.1-g/kg group, 42% (88/208) in the 0.25-g/kg group, 35% (72/204) in the 0.5 g/kg group |
|                                             | [143] | Randomized trial             | IVIg (Sandoglobulin, Sandoz Pharmaceuticals, East Hanover, NJ, USA) 0.5 g/kg per week administered since the beginning of the cytotoxic therapy or nothing | 170 autologous bone marrow transplant patients | IVIg did not reduce infection of infection-related death                                               |
|                                             | [144] | RCT                           | IVIg (Gamimune N, Cutter Biological, Berkeley, CA, USA) 0.5 g/kg per week to day 90, then 0.5 g/kg per month to day 360 after transplantation or nothing | 382 patients after bone marrow transplantation | Lower risk of gram-negative septicemia \( (p=0.0039) \) in IVIg and of local infection \( (p=0.029) \) |
| Hemolytic disease of the newborn            | [145] | Meta-analysis of 3 not-blinded RCT | IVIg and phototherapy or phototherapy alone | 189 patients | Less use of exchange transfusion in the IVIg group; when given for prophylaxis RR=0.21 \( (p<0.001) \), when given as treatment RR=0.36 \( (p<0.006) \) |
| Study | Design | Intervention and Dose | Number of Patients | Results/Response |
|-------|--------|-----------------------|--------------------|------------------|
| [146] | Meta-analysis of 3 RCTs | IVIg and phototherapy or phototherapy alone | 189 patients | Overall less use of exchange transfusion in the IVIg group: RR = 0.28 (p < 0.00001) |
| [147] | Case series | IVIg (Endobulin HT, Immuno AG, Vienna, Austria) 0.4 g/kg (single infusion) was administered within 24 h of transfusion | 5 patients are known to develop non-ABO post-transfusional hemolytic reactions | No transfusion reaction and sustained increase in hematocrit |
| [148] | Case report | IVIg (Sandoglobulin) 75 gr. over 3 days + CS | Rh-negative patient with anti-Jk, anti-K, and anti-Kp | Increase in hemoglobin, no evidence for hemolysis |
| [149] | Case reports | IVIg 2 g/kg over 5 days + high-dose MP | 2 patients with sickle cell disease who developed a hemolytic reaction after compatible blood transfusion | Increase in hemoglobin and reticulocytes |
| [150] | Case reports | IVIg 2 g/kg over 5 days + high-dose MP | 2 patients with sickle cell disease who developed a hemolytic reaction after compatible blood transfusion | Increase in hemoglobin and reticulocytes |
| [151] | Case report | IVIg (Sandoglobulin, 1 g/kg per day for 1 to 2 days) + CS | Patient with sickle cell disease who developed a hemolytic reaction after compatible blood transfusion | Increase in hemoglobin and reticulocytes |
| [152] | Case control study | IVIg 0.4-2.4 g/kg (Gamimmune N, Cutter Etobicoke, Ontario, Canada) over 1–6 days (0.4 g/kg per day) | 18 children with postdiarheal hemolytic uremic syndrome, 9 received IVIg | No benefit of IVIg treatment |
| [153] | Case control study | IVIg 2 g/kg (Sandoglobulin) over 5 days in 8 patients, FFP in 12 patients, no treatment in 23 patients | 43 children with hemolytic uremic syndrome; 8 received IVIg | Improvement in platelet count against FFP (p < 0.05) and against no treatment (p < 0.01) |
| [154] | Case series | IVIg 0.4 g/kg per day, from 1 to 20 infusions; these patients were also treated with CS, also PP in 15 patients | 17 patients with thrombotic thrombocytopenic purpura | 10/17 (58.8%) patients had remission, 8/17 (47%) complete remission |
| [155] | Case control study | IVIg 2 g/kg over 5 days in 29 patients only; all the patients received PP and CS | 44 patients with thrombotic thrombocytopenic purpura | No benefit of IVIg treatment |
| [156] | Case series | IVIg (Sandoglobulin in 2 cases, Octagam in one case) 2 g/kg over 2 days | 3 patients with heparin-induced thrombocytopenia | Increase in platelet count |
| [157] | Case report | IVIg | 51-year-old woman with heparin-induced thrombocytopenia and pulmonary embolism | Increase in platelet count starting 20 h after first IVIg infusion |
| [158] | RCT crossover study | Weekly IVIg (Polygam) courses of 2 g/kg over 2 days or normal saline, for 4 weeks, then crossover | 12 HIV patients with HIV-related thrombocytopenia | IVIg consistently and reproducibly raised platelet count after infusion; no patient with placebo did so (p < 0.00003) |
| [159] | RCT not blinded | IVIg 2.1 g/kg over 3 days (Gammagard SD, Baxter Bioscience, Glendale, CA) or high-dose MP 15 mg/kg per day for 3 days | Acute immune thrombocytopenic purpura adult patients, 56 randomized to IVIg, 60 to MP | Faster response and higher platelet counts in the IVIg group (p = 0.006) |
| [160] | RCT nonblinded | IVIg 2 g/kg over 5 days (7 patients), PD 1 mg/kg per day (13 patients) or both IVIg and PD (12 patients) | 32 acute immune thrombocytopenic purpura adult patients | No difference in response rates or in requirements for splenectomy or in bleeding |
| Disease | Ref. | Study design | Intervention including dose and IVIg preparation used | Number of patients | Results/response |
|---------|------|--------------|-------------------------------------------------------|--------------------|-----------------|
| Acute immune thrombocytopenic purpura | [161] | RCT nonblinded | IVIg 2 g/kg over 2 days (19 patients) or PD with starting dose of 4 mg/kg per day and then tapering until discontinuation by day 21 (18 patients) or no therapy (16 patients) | 53 children with acute immune thrombocytopenic purpura and less than 20,000 platelets per microliter | Both IVIg- and PD-treated children reached platelet counts over 50,000 per microliter faster than children not treated (p<0.001) Median time to reach more than 50,000 platelets per microliter was lower in IVIg group (2 days) than in PD group (4 days), p<0.001 |
| | | | | | |
| | [162] | Partially randomized trial; patient's family chose no treatment or treatment (IVIg or CS upon randomization) | IVIg 1.6 g/kg over 2 days (12 patients) or MP with starting dose of 30 mg/kg per day for 3 days and then 20 mg/kg per day for 4 days (12 patients) or no therapy (26 patients) | 50 children with acute immune thrombocytopenic purpura and less than 20,000 platelets per microliter | Both IVIg- and MP-treated children reached platelet counts over 20,000 per microliter and 50,000 per microliter faster than children not treated, p<0.01 |
| Immune thrombocytopenic purpura in HIV | [163] | Controlled clinical trial | IVIg 2 g/kg of IVIg over 2 days, followed by IVIg 1 g/kg on day 15 | 14 patients with HIV-related thrombocytopenia (median platelet count 17,000/mm$^3$) | All achieved resolution of their bleeding by day 8, but this was temporary |
| Chronic immune thrombocytopenic purpura | [164] | Controlled clinical trial | IVIg 0.04 g/kg per week during 5 weeks | 13 thrombocytopenic AIDS patients | All patients responded in the first week but only 4 were responders after 3 months |
| | [165] | Prospective noncontrolled trial | IVIg 2 g/kg over 2 or 5 days (BT681m, Biotest Pharma GmbH, Dreieich, Germany) in accordance to randomization, followed for 28 days | 24 chronic immune thrombocytopenic purpura adult patients | 91.7% of patients underwent a fast raise (in 2–5 days) of platelet count over 50,000 per microliter; at the end of the 28 days of follow-up, half of the patients had still platelet count over 50,000 per microliter |
| | [166] | Prospective noncontrolled trial | Induction with IVIg 1 or 2 g/kg (Biotransfusion, Roissy, France) over 2 days and 6 more maintenance infusions of IVIg 1 g/kg starting when platelets fell below 50,000 per microliter and then every 2 to 3 weeks unless platelets are over 150,000 per microliter or response is exhausted | 20 chronic immune thrombocytopenic purpura adult patients | Initial response in all 18 evaluable subjects, 13 complete (>150,000 per microliter), 5 partial (>50,000 per microliter); no difference between both induction doses; maintenance: at 90-day failure in 61% (11 of 18), partial response (>50,000 per microliter in 2 of 18, 11%) and complete response (>150,000 per microliter in 5 of 18, 28%) |
| Posttransfusional purpura | [167] | Case series | IVIg | 17 patients with severe thrombocytopenia after blood transfusion | In 16 patients, normal platelet counts were reached within days; 5 patients relapsed and again had a good response to new IVIg administration |
| | [168] | Case series | IVIg 0.4 g/kg per day, for 2–10 days | 5 patients with severe thrombocytopenia after blood transfusion | Immediate raise in platelet count and cessation of bleeding in 4 of 5 patients (80%) |
| | [169] | Case series | IVIg, variable doses ranging from 1 to 2 g/kg per day | 3 patients with thrombocytopenia after blood transfusion | Good response in 2 of 3 patients |
| Disease Ref. Study design | Intervention including dose and IVIg preparation used | Number of patients | Results/response |
|--------------------------|-----------------------------------------------------|--------------------|------------------|
| [170] Case series        | IVlg                                                | 6 renal transplant patients with hemophagocytic syndrome | Good response in all the cases |
| [171] Case series        | IVlg                                                | 7 children with hemophagocytic syndrome treated with IVIg only | 3 of 7 (43%) survived |
| [172] Case series        | IVlg 2 g/kg over 2 days in one case, over 5 days in the other | 2 cases of EBV-associated hemophagocytic syndrome treated with IVIg only | 2 of 2 (100%) survived |
| [173] Case series        | IVlg                                                | 8 children with infection-associated hemophagocytic syndrome treated with IVIg | 0 of 8 (0%) survived |
| [174] Case series        | IVlg 1 g/kg per day for 1 or 2 days                 | 3 children with infection-associated hemophagocytic syndrome treated with IVIg | 3 of 3 (100%) survived |
| [175] Case report        | IVlg                                                | A healthy patient with CMV-related hemophagocytosis | Symptoms and laboratory abnormalities improved dramatically after the onset of the treatment |
| [176] Case report        | 2 courses of IVlg 0.4 g/kg per day for 5 days, separated by 3 weeks, adjunctive to radiotherapy | 49-year-old patient with rapidly progressive polyneuropathy associated with osteosclerotic myeloma | After 2 courses of IVlg improvement of respiratory and sexual function and gate, disappearance of numbness; doing well after 1 year |
| [177] Case report        | IVlg 0.4 g/kg per day for 4 (case 1) or 5 days (case 2) adjunctive to prednisolone 30–50 mg/day | A 55-year-old man (case 1) and a 43-year-old woman (case 2) with late-stage POEMS syndrome | No change in motor and sensory impairment; case 1 continued to deteriorate and died after 6 months due to sepsis and DIC |
| [178] Case report        | IVlg (one course)                                   | A patient with POEM and Castleman's disease | No effect |
| [179] Case report        | IVlg 0.5 g/kg every 15 days for 4 months (case 1) and for 12 and 7 months, respectively (case 2) adjunctive with IFN alpha (2×10^6 IU SC 3 times a week) | 2 patients with diffuse B cell posttransplant lymphoproliferative disorder | Complete disappearance of all lesions after 3 months of the therapy in case 1 and after 7 months in case 2, remission for 47 months and 33 months, respectively |

*POEMS syndrome* polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.
transplantation is always the alternative in the case of failure of the aforementioned treatments. Due to the low level of evidence of IVIg for the treatment of idiopathic aplastic anemia, we cannot recommend its liberal use but it may be tried in the case of treatment failure, before stem cell transplantation is performed (strength of recommendation IIb).

Autoimmune hemolytic anemia

*Level of evidence B* Immunosuppression with CS and then cytotoxic agents should be used in autoimmune hemolytic anemia before considering IVIg. There is however some evidence that IVIg might be useful and therefore in refractory cases before considering splenectomy it may be worth a try (strength of recommendation IIb).

Autoimmune neutropenia

*Level of evidence C* Although immune neutropenia may also be an adverse effect resulting from IVIg treatment as have been published elsewhere [8], IVIg has been used to treat immune neutropenia. The evidence is weak and responses are not as good as those with CS and granulocyte colony-stimulating factor (strength of recommendation IIb).

Evans’ syndrome

*Level of evidence C* Evans’ syndrome is usually a therapy-resistant condition that has been treated combining CS, IVIg, and immunosuppressive therapy. Although convincing evidence is lacking for the use of IVIg in view of the severity and the refractory nature of several cases of Evans’ syndrome, IVIg may be considered among the treatment options generally together with CS with or without immunosuppressive therapy (strength of recommendation IIb).

Fetal/neonatal alloimmune thrombocytopenia

*Level of evidence B* The only study comparing IVIg against other treatment (CS), although nonrandomized, suggests that IVIg raises the platelet number and prevents intracranial bleeding in a significant percentage of treated patients. The level of evidence is low, but the alternatives for prenatal treatment of fetuses at risk are not better and the risks involved are huge (strength of recommendation IIb).

Stem cell/bone marrow transplantation

*Level of evidence A* Strong evidence denies any benefit from the use of IVIg around stem cell/bone marrow transplantation, both from the infectious or from the graft-versus-host disease point of views (strength of recommendation III).

Hemolytic disease of the newborn

*Level of evidence A* There is clear evidence for the use of IVIg when facing newborn hemolysis as it reduces the need of plasmapheresis (PP) therapy (strength of recommendation I).

Hemolytic transfusion reaction

*Level of evidence C* There is no reliable evidence to recommend the use of IVIg to prevent or to treat hemolytic transfusion reactions (strength of evidence IIb).

Hemolytic transfusion reaction in sickle cell disease

*Level of evidence C* Apart from two papers reporting two cases and another case, there is no evidence to recommend the use of IVIg either to prevent or to treat hemolytic transfusion reactions in sickle cell patients, specially taking into consideration the additional risk of thrombosis due to a change in the rheologic properties of the blood after IVIg infusion (strength of recommendation IIb).

Hemolytic uremic syndrome

*Level of evidence B* There is conflicting evidence that IVIg benefits patients with hemolytic uremic syndrome (strength of recommendation IIb).

Thrombotic thrombocytopenic purpura

*Level of evidence B* There is no evidence that IVIg benefits patients with thrombotic thrombocytopenic purpura (strength of recommendation III).

Heparin-induced thrombocytopenia

*Level of evidence C* There is low-level evidence that IVIg is useful for this disease. On the other hand, thromboembolic phenomena, which are part of the heparin-induced thrombocytopenia clinical picture, might be enhanced by the rheologic blood changes after IVIg infusion. Therefore, IVIg should not be generally recommended for this disease (strength of recommendation IIb).

HIV-associated thrombocytopenia

*Level of evidence B* Evidence comes only from one crossover randomized placebo-controlled trial which supports the use of IVIg in HIV-associated thrombocytopenia, especially when platelet count is very low or the risk of bleeding is high (strength of recommendation IIa).
Acute immune thrombocytopenic purpura

*Level of evidence A* Since Imbach’s observation [1], acute ITP has been the prototype of IVIg-responsive immune disease. There is consistent evidence that IVIg is beneficial in children with ITP (*strength of recommendation I*). Notwithstanding this, CS therapy is still the first-line treatment for ITP, and single-dose anti-D immunoglobulin [9, 10] is a good alternative for Rh-positive patients. IVIg should be considered when there is bleeding or when the bleeding risk is high or upon failure of other treatments. In adult acute ITP patients, there is no placebo-controlled RCT, but when compared with CS IVIg induces a faster response. Again, CS is the first-line treatment for adults but IVIg may be given in severe or refractory cases. There is weak evidence that IVIg can improve mother and fetal prognosis in pregnancy. IVIg may be used when a fast correction in platelet number is needed.

Immune thrombocytopenic purpura in HIV

*Level of evidence B* By the merits of its own research, IVIg may be considered to treat ITP in the context of HIV. Although no hard evidence exists due to the fact that this particular group of patients has not been investigated as well as has non-HIV-related ITP, it will be hard to argue that the recommendation of the latter may not be extended to HIV-related ITP (*strength of recommendation I*).

Chronic immune thrombocytopenic purpura

In chronic ITP, IVIg has so far not demonstrated a plausible benefit. Only prospective noncontrolled trials are available and we found only one evaluating maintenance IVIg for chronic ITP, in which the overwhelming majority of patients had a recrudescence of thrombocytopenia in spite of a good initial response to IVIg (level of evidence and strength of recommendation B-IIb). A small number of patients benefited and therefore IVIg might be tried in drug refractory cases of chronic ITP in which there is a contraindication for splenectomy.

Posttransfusional purpura

*Level of evidence C* Series of patients treated with fast response to IVIg suggest a benefit of IVIg treatment in posttransfusional purpura, although with low-level of evidence. In the context of a patient with severe risk to bleeding or actual bleeding, IVIg can be used if the diagnosis of posttransfusional purpura is made (*strength of recommendation IIb*).

Hemophagocytic syndrome

*Level of evidence C* Hemophagocytic syndrome is a severe reaction leading to high mortality. Inconsistent and low-level evidence do not warrant a clear-cut recommendation of IVIg for this syndrome. However, due to the lack of effective and standardized treatment in an otherwise highly lethal disease, IVIg may be used along with other therapies like monoclonal antibodies, CS, cytotoxic drugs, and support measures (*strength of recommendation IIb*).

POEMS

*Level of evidence C* There are only anecdotal reports, both showing benefit and lack of benefit. There is no evidence that IVIg has a beneficial effect on polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (*strength of recommendation IIb*).

Diffuse B cell posttransplant lymphoproliferative disorder

*Level of evidence C* There is no convincing evidence that IVIg has any beneficial effect in this disease (*strength of recommendation IIb*).

The following conditions refer to (Table 4).

Cytomegalovirus

*Level of evidence B* IVIg is not used for the treatment of CMV infection but may be helpful in treatment of hemophagocytic syndrome related to CMV and other viruses (see hematology section); there is some evidence for its effectiveness in preventing seroconversion in transplant patients who are immunosuppressed (*strength of recommendation IIa*).

Human immunodeficiency virus

*Level of evidence B* IVIg can reduce infections in children with perinatal HIV but has not been proven to reduce mortality (*strength of recommendation IIa*).

Malaria

*Level of evidence B* No evidence for the effectiveness of IVIg in the treatment in malaria exists (*strength recommendation III*).

Postpolio syndrome

*Level of evidence A* Postpolio syndrome (PPS) typically affects survivors of poliovirus infection, 15–20 years after the original infection, with fatigue, muscular weakness, and pain. There are two RCTs demonstrating some inconsistent evidence for the effectiveness of IVIg treatment on quality of life, pain, and muscle strength in patients with PPS (*strength of recommendation IIa*).
| Disease | Ref. | Study design | Intervention including dose and IVIg preparation used | Number of patients | Results/response |
|---------|------|--------------|--------------------------------------------------------|--------------------|-----------------|
| Cytomegalovirus (CMV) | [180] | Controlled trial | IVIg 0.25 g/kg weekly for 8 weeks, starting on the operative day | 40 renal transplanted patients with negative serology for CMV | Effective prophylaxis, associated with excellent 1-year allograft survival |
| Human immunodeficiency virus (HIV) child infection | [181] | RCT | IVIg 0.4 g/kg or placebo (0.1% albumin) every 28 days | 372 symptomatic children infected with HIV | Significant reduction in serious infections \( p=0.01 \) and hospitalizations \( p=0.03 \), in the IVIg group only for those entering treatment with CD4+ lymphocyte ≥200; no effect on mortality |
| HIV-associated thrombocytopenia—see hematology section | | Controlled trial | IVIg (Gamimune-N, Miles Pharmaceutical Co.), 0.2 g/kg monthly for 1 year | 135 symptomatic and asymptomatic children with perinatal HIV | Significant reduction in the frequency of bacterial infections in the symptomatic group |
| Malaria | [183] | RCT | All were treated with IV quinine dihydrochloride; in addition, patients were randomized to receive either IVIg, 0.4 g/kg over 3 h, or placebo | 31 children with *Plasmodium falciparum* parasitemia and coma | Of 16 patients receiving immunoglobulin, 5 (31%) died, and 5 survivors had neurological sequelae; of 15 patients receiving placebo, one (7%) died and 2 had sequelae (trial was stopped) |
| Postpolio syndrome (PPS) | [184] | Controlled trial | IVIg was prepared from 180 donors after infection screening; 6 patients were treated with a 0.1 g/kg dose given over 3 days, one with a single 0.02 g/kg dose, and one with a single 0.02 g/kg dose | 8 Thai patients with *P. falciparum* parasitemia | Clearance of parasites and symptoms was as fast as or faster than with drugs |
| | [185] | Multicentered RCT | 90 g of IVIg during 3 days, repeated after 3 months | 142 patients: 73 with IVIg and 69 placebos | Mild improvement in median muscle strength \( p=0.03 \), vitality \( p=0.04 \), no change and quality of life \( p=0.3 \) |
| | [186] | RCT | Patients were randomized to IVIg, 2 g/kg, or placebo | 20 patients with PPS | No effect was seen with IVIg treatment on muscle strength and fatigue; however, IVIg patients reported significantly less pain 3 months after treatment |
| | [187] | Open clinical trial | 90 g of IVIg (30 g daily for 3 days) | 14 patients with PPS | Significant improvement in the quality of life, no change in muscle strength and physical performance |
| Sepsis | [188] | Meta analysis of RCTs from PubMed | Different preparations of relatively low doses of IVIg for severe sepsis, mostly surgical patients with gram-negative infections | 14 RCTs published between 1988 and 2006 were included | Significant but heterogenic reduction in mortality associated with use of IVIg \( p<0.0005 \); this result was not confirmed when only high-quality studies were analyzed |
| West Nile Virus (WNV) | [189] | Case report | 0.4 g/kg IVIg preparation from donors that contained a high titer of anti-WNV antibodies (1:1,600) | 42-year-old male lung transplant recipient with severe WNV encephalitis | Complete disappearance of signs and symptoms within 48 h |
| | [190] | Case report | IVIg 0.4 g/kg for 5 days (Omr-IgG-am, Omrix Biopharmaceutical Ltd., Tel Hashomer, Israel) | 70-year-old with chronic lymphatic leukemia and coma due to WNV | Level of consciousness returned to normal over 5 days |
| Prophylaxis for infections (in intensive care units (ICU)) | [191] | RCT | Patients received standard IVIg, 0.4 g/kg, hyperimmune globulin (HG), 0.4 g/kg, or placebo, weekly, for a maximum of 4 doses | 329 posturgical patients admitted to the surgical ICU | Significantly lower infections and hospital days in the IVIg group vs. placebo or HG \( p=0.003 \); no lesser mortality/shock |
| Disease                                                                 | Ref. | Study design | Intervention including dose and IVIg preparation used                                                                 | Number of patients | Results/response                                                                 |
|------------------------------------------------------------------------|------|--------------|------------------------------------------------------------------------------------------------------------------------|--------------------|----------------------------------------------------------------------------------|
| Prophylaxis for infections (in immune-compromised patients)             | [192] | RCT          | Patients received IVIg (36 g) versus 0.03% albumin                                                                      | 150 trauma patients in ICU ventilated for >24 h | Decreased overall incidence of infection ($p=0.02$) and antibiotic need in IVIg group |
|                                                                        | [193] | RCT          | Ten patients received IVIg and ten albumin                                                                             | 20 patients with extensive thermal injury         | No statistically significant difference was found between mortality rates of the groups |
|                                                                        | [194] | RCT          | 18 received IVIg, 0.4 g/kg, and 14 placebo within 48 h of admission                                                    | 33 children (mean age, 6.67 years) with severe head injuries | No effect on the incidence of secondary infections                              |
|                                                                        | [195] | RCT          | Within 12 h of ICU admission, 1 g/kg of IVIg or human albumin divided over 4 days                                       | 39 trauma patients in an ICU                     | No difference in overall infection rates, but fewer pneumonias ($p=0.003$) and non-catheter-related infections ($p=0.04$); no difference in ICU length of stay or antibiotic use |
|                                                                        | [196] | RCT          | Patients were randomly assigned to either 20 g IVIg or saline                                                          | 40 postoperative open-heart surgery patients with cutaneous anergy preoperatively              | Infection incidence 5% in IVIg versus 43% placebo ($p=0.007$)                   |
|                                                                        | [143] | RCT          | 82 received IVIg weekly, 0.5 g/kg, from the initiation of cytotoxic therapy to the resolution of neutropenia and 88 were untreated controls | 170 neutropenic patients undergoing BMT or severe myelosuppressive therapy | The use of IVIg did not prevent infection; fewer deaths occurred among controls due to a higher incidence of fatal hepatic veno-occlusive disease in patients receiving IVIg |
| Necrotizing fasciitis (NF)                                              | [197] | RCT          | Monthly IVIg 0.4 g/kg or placebo for 1 year                                                                           | 82 patients with stable multiple myeloma         | Less infection sepsis in the IVIg group ($p=0.002$)                             |
|                                                                        | [198] | Controlled trial | 16 were treated with ≥1 mg/kg of IVIg; all were treated with antibiotics and debridement                             | 20 patients with NF                              | No difference in case fatality                                                  |
|                                                                        | [199] | Controlled trial | Patients were treated with effective antimicrobials, high-dose IVIg; surgery was either not performed or only limited exploration was carried out | 7 patients with severe NF                        | All patients survived                                                          |
|                                                                        | [200] | Controlled trial | Patients that had hypotension and multiorgan failure were treated with a single dose of IVIg 50 g in addition to antibiotics | 11 patients with toxic shock syndrome with or without NF | Ten patients were fully recovered                                               |
|                                                                        | [201] | Case report   | Patient declined on antibiotic therapy and was treated with IVlg, 0.4 g/kg (Omr-IgG-am 5% IV, Omrix, Israel)               | A renal transplant lupus patient with NF         | A marked improvement in patient’s condition on the next day                     |
| Recurrent otitis media (OM)                                             | [202] | RCT          | IVIg or placebo                                                                                                       | 22 otitis-prone children, 1–4 years old          | No significant difference in the frequency of OM attacks or other respiratory tract IVIg group |
|                                                                        | [203] | Controlled trial | IVIg                                                                                                                  | 9 children with recurrent sinopulmonary infections which failed to improve after antibiotic Tx | Significant decrease in the episodes of sinusitis and OM                        |
| Varicella (transmission prevention)                                     | [204] | Controlled trial | IVIg prophylaxis (single-dose 0.5 g/kg) administered soon after birth or postnatal contact, either alone or with IV acyclovir | 24 newborns whose mother had a varicella rash within 14 days before and after delivery | Treatment with IVIg + acyclovir effectively prevented perinatal varicella       |
|                                                                        | [205] | Controlled trial | IVIg 0.04 to 0.045 g/kg per day for 5 to 9 days was given soon after birth, along with acyclovir                      | 5 infants whose mothers had varicella            | Some had a mild–moderate transient rash but none had constitutional symptoms    |
Sepsis

Level of evidence A Sepsis is a life-threatening condition, resulting mainly from the patient's immune response to a severe infection. Significant but heterogenic reduction in mortality with IVIg treatment in septic patients was demonstrated in a meta-analysis of 14 RCTs. These results were not confirmed when only high-quality studies were analyzed (strength of recommendation IIa).

West Nile

Level of evidence C Infection with West Nile virus can cause fatal encephalitis in immunosuppressed and elderly patients, in which case effective treatment is lacking. The effectiveness of IVIg in these situations is supported by a few case reports and may be considered (strength of recommendation IIa).

Infection prophylaxis—in immune-compromised patients

Level of evidence A There is conflicting evidence regarding the usefulness of IVIg treatment for these patients. It should be taken into consideration that patients treated with IVIg after bone marrow transplantation (BMT) may have a higher incidence of fatal hepatic veno-occlusive disease (strength of recommendation IIa).

Infection prophylaxis—in intensive care units

Level of evidence A Treatment with IVIg has not proven to reduce infectious-related mortality in postsurgical patients, but there is inconsistent evidence that IVIg reduces ICU-related infections and hospital stay in these patients (strength of recommendation IIa).

Necrotizing fasciitis

Level of evidence B Necrotizing fasciitis is caused by deep-skin infection with bacteria, mainly group A streptococcus. The mainstay of nuclear factor treatment is prompt surgical exploration and antibiotic therapy. IVIg might have additional benefit to antibiotic therapy for treatment of patients who refuse surgery or are not surgical candidates. (strength of recommendation IIa).

Recurrent otitis media

Level of evidence B There is weak evidence that IVIg is useful in the treatment of recurrent otitis media (strength of recommendation IIb).

Table 4 (continued)

| Disease | Ref. | Study design | Intervention including dose and IVIg preparation used | Number of patients | Results/response |
|---------|------|--------------|-------------------------------------------------------|-------------------|-----------------|
| Varicella (pulmonary disease) | [206] | Case report | IVIg and IV acyclovir | 2 cases of varicella infection complicated by severe pulmonary involvement previously healthy adults | Gradual clinical improvement after administration |
| | [207] | Case report | IVIg, 2.5 g every 12 h, with IV acyclovir and ABx | A healthy adult with severe respiratory failure due to varicella pneumonia | Gradual clinical improvement after administration |
| | [208] | Case report | IVIg and IV acyclovir | 32-year-old patient with varicella and ARDS | Quick improvement |
| | [209] | Case report | Patient was mechanically ventilated and treated with IVIg and acyclovir | 26-year-old with ARDS secondary to varicella pneumonia | Quick improvement |
| Varicella (complicated with ITP) | [210] | Case report | IVIg | ITP in a 3-year-old girl with an active varicella infection | Drastically improved bleeding and active varicella infection |
| | [211] | Case report | IVIg, 0.4 g/kg per day for 3 days, and acyclovir | 40-year-old with bleeding due to varicella-related ITP | The platelet counts increased to 254,000 per microliter over the next 5 days, and the skin rashes associated with varicella subsided within a week |
Varicella

Level of evidence B Some evidence that IVIg is effective in preventing perinatal transmission of varicella. IVIg may also be used for treatment adults with severe respiratory failure due to varicella pneumonia (level of recommendation IIa).

The following conditions refer to (Table 5).

Perinatal hemochromatosis

Level of evidence B Although the best level of evidence is not strong, the improvement shown for treated pregnancies is beyond the natural possibility of a subsequent spared pregnancy which has been estimated to be approximately 40% ([11] #110). In view of this data and the difficulty for large RCTs, IVIg may be considered to prevent recurrent perinatal hemochromatosis (strength of recommendation IIa).

Recurrent pregnancy loss excluding antiphospholipid syndrome

Level of evidence A There is evidence that IVIg improves the outcome of pregnancy in secondary recurrent miscarriage (in women that had a previous pregnancy that reached at least the second trimester (strength of recommendation IIb)). This has so far not been shown for primary recurrent miscarriage (strength of recommendation III).

Recurrent pregnancy loss due to antiphospholipid syndrome

Level of evidence A The evidence is against the use of IVIg in pregnancy of women affected by antiphospholipid syndrome (strength of recommendation III).

Prevention of infection after premature rupture of membranes

Level of evidence B Evidence from a small RCT indicates that IVIg may reduce the rate of fetal infection after premature rupture of membranes (strength of recommendation IIa).

Failure of in vitro fertilization

Level of evidence A The evidence is scarce but the only meta-analysis based on data from three RCTs found a benefit in the number of live births in women treated with IVIg. After in vitro fertilization (IVF) failure, IVIg along with IVF techniques may be weighted (strength of recommendation IIb).

The following conditions refer to (Table 6).

Congestive heart failure

Level of evidence B A randomized double-blind study has demonstrated significant increase of ejection fraction (EF) and improved quality of life following IVIg administration, regardless of the congestive heart failure (CHF) cause. CHF is a proinflammatory state due to an increase of cytokines such as TNF-α and interleukin (IL)-1. Some of the cytokines have been shown to induce myocardial dysfunction due to negative inotropic effect [12]. Another possible mechanism in CHF pathogenesis is mediated by anti-β1 adrenergic receptor (strength of recommendation IIa).

Dilated cardiomyopathy

Level of evidence B Dilated cardiomyopathy (DCM) is caused by various triggers or may be idiopathic. Immune abnormalities and autoantibodies may play a role in the pathogenesis. Nevertheless, no significant effect was noted following IVIg administration in recent-onset DCM compared to placebo [13]. A trial on 17 patients with idiopathic DCM showed significant improvement of EF and quality of life compared with placebo [14]. Therefore, IVIg treatment in DCM remains controversial, and it is possible that IVIg treatment is beneficial in specific subpopulation and when treatment is initiated at a certain time window (strength of recommendation IIb).

Peripartum cardiomyopathy

Level of evidence C Peripartum cardiomyopathy (PPCM) is a rare disorder. It is believed that autoimmune mechanisms play a role in the pathogenesis. In a small nonrandomized retrospective trial, there was a significant improvement of EF following IVIg administration compared with conventional treatment. Although there is partial evidence of IVIg effectiveness in PPCM, its use should be considered due to the generally poor prognosis of PPCM patients who show no clinical improvement (strength of recommendation IIa).

Myocarditis

Level of evidence B Treatment with CS or cytotoxic agents was found ineffective [15, 16]. In an RCT trial of 62 patients with new-onset DCM of which some had myocarditis [13], there was no significant difference in EF improvement between IVIg and placebo group. Nevertheless, in a prospective nonrandomized trial, there was a significant improvement of fractional shortening compared to control. We conclude that further research is warranted regarding IVIg use in myocarditis due to inconclusive results (strength of recommendation IIb).
| Disease                                      | Ref. | Study design                                                                 | Intervention including dose and IVIg preparation used | Number of patients | Results/response                                                                 |
|---------------------------------------------|------|-------------------------------------------------------------------------------|-------------------------------------------------------|--------------------|----------------------------------------------------------------------------------|
| **Perinatal hemochromatosis**               | [212] | Case–control study; previous patients’ pregnancies used as their own controls | IVIg 1 g/kg weekly since week 18                       | 15 patients (16 pregnancies) with previous pregnancies resulting in perinatal hemochromatosis | Good outcome (survived with or without medical therapy) in 15 gestations treated with IVIg; in historical controls of the same mothers, 2 pregnancies had good outcome and 13 had poor outcome (fetal or neonatal death, or liver failure necessitating liver transplantation), \( p = 0.0009 \) |
| **Recurrent pregnancy loss excluding antiphospholipid syndrome** | [213] | Meta-analysis                                                                 | IVIg                                                  | 442 women with recurrent spontaneous miscarriages (at least 3) from eight RCTs; secondary recurrent miscarriages are defined as those in women that had at least a previous successful birth | No significant difference \( (p = 0.21) \) between women with primary recurrent miscarriages treated with IVIg or without; however, there was a significant improvement of live births when IVIg was given to women with secondary recurrent miscarriages \( (p = 0.03) \) |
|                                             | [214] | Meta-analysis IVIg versus placebo or no treatment                             | IVIg                                                  | 303 women with idiopathic recurrent abortions from 8 RCTs | No benefit of IVIg on recurrent pregnancy loss |
|                                             | [215] | Meta-analysis                                                                 | IVIg                                                  | 246 women with recurrent spontaneous miscarriages (at least 2) from 5 RCTs; secondary recurrent miscarriages are defined as those in women that had at least a previous successful birth | No significant difference between women with primary recurrent miscarriages treated with IVIg or without; not enough patients to conclude something about women with secondary recurrent miscarriages but there was a trend towards improvement |
|                                             | [216] | RCT                                                                          | 29 women received IVIg, 29 placebos; IVIg was administered from weeks 5–10 weekly at 0.8 g/kg every week, from weeks 10–20 at 0.8 g/kg every 2 weeks and from weeks 20–26 at 1 g/kg every 2 weeks; no IVIg as given after week 26 | 58 women with recurrent spontaneous miscarriages (at least 4); secondary recurrent miscarriages are defined as those in women who had at least a previous pregnancy that progressed to week 26 or more | No benefit in primary recurrent miscarriages but a trend towards improvement among women with secondary recurrent miscarriages |
|                                             | [217] | Meta-analysis IVIg in 125 patients, 115 received placebo                      | IVIg                                                  | 240 women with recurrent spontaneous miscarriages | No benefit of IVIg |
|                                             | [217] | RCT                                                                          | IVIg (Gammonativ) 20 g every 3 weeks, 5 courses after confirmation of pregnancy | 41 women with recurrent spontaneous miscarriages | No benefit of IVIg neither for women with primary or secondary recurrent miscarriage |
|                                             | [218] | RCT                                                                          | 22 patients received IVIg (Sclavo) 50 g over 2 days upon confirmation of pregnancy (weeks 5–7) and again 25 g 3 weeks later | 46 women with recurrent spontaneous miscarriages | No benefit of IVIg |
|                                             | [219] | RCT                                                                          | 47 patients received IVIg 0.5 g/kg every month starting up to 4 months before pregnancy and until weeks 28–32 of pregnancy; 48 patients received placebo | 95 women with recurrent spontaneous miscarriages (2 or more) | More live births in women receiving placebo \( (p = 0.04) \) |
| Disease | Ref. | Study design | Intervention including dose and IVIg preparation used | Number of patients | Results/response |
|---------|------|--------------|------------------------------------------------------|-------------------|-----------------|
| [220]   | RCT  | IVIg (Nordimmun, Novo-Nordisk, Gentofte, Denmark) 25–40 g per dose according to patient weight every 2 weeks until week 34 of pregnancy or placebo | 34 women with secondary recurrent spontaneous abortion (subsequent to a birth or including at least one second trimester miscarriage) | No benefit of IVIg |
| [221]   | RCT  | IVIg initial dose 30 g, then 20 g every 3 weeks until week 25 (Verum, Immuno GmbH, Heidelberg, Germany) or placebo | 64 women with primary recurrent spontaneous abortion | No benefit of IVIg |
| [222]   | Meta-analysis | IVIg given in addition to heparin and aspirin | 58 women with recurrent miscarriages due to antiphospholipid syndrome in 2 RCTs | Increased risk of pregnancy loss or premature birth in the group receiving IVIg |
| [223]   | Randomized trial | 21 women received IVIg (IgVENA N; Sclavo, Siena, Italy) at the dose of 0.8 g/kg over 2 consecutive days as initial dose followed by 0.4 g/kg each month up to week 31; 19 women received aspirin 75 mg/day up to week 34 + heparin 5,700 IU/day up to week 37 | 40 women with at least 3 abortions due to antiphospholipid syndrome were treated since conception with IVIg or heparin + aspirin | More live births (84% against 57%, not significant difference) in the aspirin + heparin group ($p=0.06$) |
| [224]   | RCT  | IVIg 2 g/kg (Gamimune-N, Bayer Corporation, West Haven, CT, USA) over 2 days every 4 weeks through 36 weeks’ gestation | 16 pregnant women (no more than 12 weeks’ gestation) with recurrent miscarriages due to antiphospholipid syndrome received low-dose aspirin and heparin and received random IVIg or placebo | No benefit of IVIg |
| [225]   | Prospective two-center trial study | 29 were treated with PD and LDA; 53 received IVIg 0.5 g/kg (Alphaglobin, Grifols International, Pisa, Italy) for 2 consecutive days, once a month from the 5th to the 32nd week of pregnancy | 82 pregnant women with a history of recurrent fetal loss and APS | Live-birth rates were equivalent between groups (78% vs 76%), mean birth weight was higher in the IVIg group gestational hypertension and diabetes were found significantly more often in the PD group (14% vs 5%), respectively ($p<0.05$) |
| [226]   | Case series | Patients were treated with heparin (15), LDA (18), and CS (6); additionally, they received IVIg 0.4 g/kg for 5 days monthly from the first or early second trimester | 19 pregnancies of 15 women with APS and recurrent fetal loss | The live-birth rate was 84%; compared to approximately 70% described in literature without IVIg |
| [227]   | Controlled trial | In phase III, they received heparin + LDA with or without IVIg | 121 women with APS, who failed to achieve live births after 2 IVF attempts with heparin + LDA | The birth rate was 41% when IVIg was added and anti-PS or anti-PE involving IgG or IgM isotypes were present, as compared with 17% when H + A alone was administered; the IVF outcome did not improve when IVIg was administered in association with any other single APS antibodies |
Pericardial diseases

Level of evidence C Pericardial involvement in Kawasaki disease may be seen in 6.3% to 24.5% of patients and may be complicated by cardiac tamponade despite IVIg therapy [17, 18], occasionally due to rupture of coronary aneurysms. There is a consensus that IVIg significantly decreases coronary aneurysms, but little is known regarding direct effect on the pericardium in the setting of mucocutaneous lymph node disease. It seems that septated pericarditis in Kawasaki disease response dramatically to IVIg but further research is warranted [19] (strength of recommendation IIb).

Low-dose IVIg therapy was found to be beneficial in 60% of lupus patients with pericarditis in a case series [20] (strength of recommendation IIa).

Chronic idiopathic pericarditis (CIP) appears in up to 25% of acute pericarditis cases. It may be associated with viral infections and autoantibodies [21]. There is limited evidence on the role of IVIg as an alternative therapy for prolonged steroid or colchicine treatment in CIP (strength of recommendation IIa).

Atherosclerosis

Atherosclerosis is believed to be mediated also by humeral and cellular immune mechanisms. There are accumulating data that support a role of IVIg in prevention of atherosclerosis. Possible mechanisms include decrease of matrix metalloproteinase 9 secretion from mononuclear cells [22], increase of IL-10 [12], and decrease of oxidized low-density lipoprotein uptake by macrophages [23]. Nevertheless, clinical trials are required in order to establish the relationship between IVIg use and atherosclerosis therapy.

Kawasaki disease

Level of evidence A It is the leading cause of acquired heart disease in the USA. Kawasaki disease is an FDA-approved absolute indication for IVIg therapy. The frequency of CA aneurysm development and associated morbidity and mortality have been dramatically decreased as a result of IVIg therapy when given within 10 days following the onset of fever. A single dose of 2 g/kg of IVIg over 10 H is usually

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**Table 5** (continued)

| Disease | Ref. | Study design | Intervention including dose and IVIg preparation used | Number of patients | Results/response |
|---------|------|--------------|------------------------------------------------------|--------------------|-----------------|
| Pericardial diseases | [228] | Controlled trial | IVIg 0.3 g/kg every 3 weeks until the 16th to 17th week of pregnancy | 38 women after 3 or more consecutive first trimester spontaneous abortions and APS | Pregnancy proceeded beyond the first trimester in 34 of the patients (89.4%), and 31 patients (81.4%) gave birth to healthy infants at 37 to 42 weeks’ gestation |
| | [229] | Case control | IVIg 0.5 g/kg for 2 days from the fifth week of pregnancy and repeated every 4 weeks until the 33rd week of gestation | 14 women with a history of recurrent spontaneous abortion and APLA | No significant biometrical differences between the groups were seen; no fetal or neonatal growth retardation was seen |
| Premature rupture of membranes | [230] | RCT | IVIg (Pentaglobin, Biotest, Frankfurt/Main, Germany) 20 g, 24–48 h after premature rupture of membranes; thereafter, 10 g was administered in weekly intervals | 18 women with premature rupture of membranes | Infants in treated group showed less laboratory and clinical signs compatible with perinatally acquired infection ($p<0.002$); less chorioamnionitis in treatment group ($p<0.036$) |
| Failure of in vitro fertilization | [231] | Meta-analysis | IVF along with or without IVIg | Women with IVF failure | Improvement in live-birth rate ($p=0.012$) |
| | [232] | RCT | IVIg (Gamimune 5%, Bayer Canada Inc., Etobicoke, Canada) 0.5 g/kg or placebo (saline), first infusion on the day of embryo transfer or during preceding 72 h, second infusion 4 weeks later upon evidence of embryonic heart activity | 51 women after IVF failure | No significant improvement in implantation, pregnancy, or live birth rate |
### Table 6 The use of intravenous immunoglobulins in cardiac disease

| Disease                        | Ref.   | Study design     | Intervention including dose and IVIg preparation used                                                                 | Number of patients                                                                 | Results/response                                                                 |
|-------------------------------|--------|------------------|------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Congestive heart failure (CHF)| [14]   | RCT              | Octagam (Octapharma) 0.4 g/kg per day for 5 days followed by monthly dose of 0.4 mg/kg for 5 months, compared with placebo | 40 patients with symptomatic CHF (NYHA II/III) and ejection fraction (EF) <40% due to idiopathic dilated cardiomyopathy (42.5%) or secondary to ischemic heart disease; 20 patients (9 idiopathic DCM, 11 coronary artery disease) received IVIg; 20 patients received placebo | IVIg induced significant increase of EF by means of 5 EF units, regardless of the cause of CHF, compared to no significant change of EF in the placebo group; improved quality of life in 73% compared to 40% in placebo group; \( p \) value < 0.05 |
| Dilated cardiomyopathy (DCM)  | [13]   | RCT              | Gamimmune N, 10% (Bayer Corporation), 1 g/kg IV each day on 2 consecutive days, compared to placebo                     | 62 patients with new-onset DCM and EF \( \leq 40\% \) (with symptoms for less than 6 months); both idiopathic DCM and myocarditis patients were included; 33 patients received IVIg, and 29 patients were treated with placebo | Mean EF improved from 0.25±0.08 to 0.41±0.17 following 6 months for all patients; there was no significant difference in EF improvement between IVIg and placebo group |
| Peripartum cardiomyopathy (PPCM)| [233]  | Retrospective study, case series | 2 g/kg of IVIg given as 1 g/kg q.d. on 2 consecutive days along with conventional therapy, compared to conventional therapy alone | 17 patients with PPCM; 6 received IVIg; all with NYHA class II–IV and EF<40%, within 6 months from delivery | In the control group, 1 patient died (9.09%), and others had a mean improvement of EF by 13±13 EF units, compared to 26±8 EF units in the IVIg group; \( p \) value 0.042 |
| Myocarditis                   | [234]  | Case series      | Total dose of 1 to 2 g/kg IVIg over 48 h (Venilon, Venoglobulin-II, and Polyglobin-N preparations were used); all patients received conventional therapy | 9 patients: 6 patients with acute myocarditis, 3 patients with acute dilated cardiomyopathy; NYHA III and IV | Mean EF improved significantly, from 19.0±7.5% to 35.4±9.1% following IVIg treatment; \( P \) value<0.01 |
| [235]                        |        | Prospective nonrandomized trial | IVIg (Immuno AG, Vienna), total dose of 2 g/kg over a maximum of 24 h; some of the IVIg groups were treated with an additional dose of 1 g/kg a week later, compared with conventional therapy | 46 patients with acute onset disease and severely depressed EF; 21 patients received IVIg; a control group of 25 patients was collected from retrospective files | There was no significant change of survival in the IVIg group compared to control; IVIg group had a higher fractional shortening than control during 3- to 6-month follow-up period; the control group failed to normalize EF; \( p \) value 0.033 |
| Chronic idiopathic pericarditis (CIP) | [21] | Case series | Five monthly cycles of 0.4 g/kg per day for 5 consecutive days, followed by administration every 2 months | 4 patients with CIP | Remarkable response in 3 patients, and a long-standing remission with no need for further steroid treatment; 1 patient with partial response |
| Pericardial diseases          | [19]   | Case report      | Total dose of 2 g/kg of IVIg, and 100 mg/kg per day of acetylsalicylic acid for 14 days                                 | 1 patient with Kawasaki disease, left anterior descending artery aneurysm and septated pericardial effusion | 2 weeks following treatment initiation, there was disappearance of the pericardial effusion and no change of the coronary aneurysm |
| [17]                        |        | Case report      | IVIg treatment starting at the 16th day following initial presentation, total of 2 g/kg, and 30 mg/kg per day of MP for 5 days | 1 patient with Kawasaki disease, complicated by cardiac tamponade | Failure of treatment and need for salvage pericardiocentesis |
| [20]                        |        | Case series      | Low-dose IVIg therapy—approximately 0.5 g/kg every 5±2 weeks for 6±6 courses                                         | 62 lupus patients, of which several developed pericardial disease | 60% of affected patients had resolution of pericardial involvement |
| Disease                             | Ref.  | Study design          | Intervention including dose and IVlg preparation used                                                                 | Number of patients | Results/response                                                                                                                                 |
|------------------------------------|-------|-----------------------|------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| Kawasaki disease (KD)              | [236] | Meta-analysis         | Low (≤80 mg/kg) and high doses (>80 mg/kg) of aspirin and low (≤1 g/kg) to high doses (>1 g/kg) of IVlg over 3–5 days     | Review of all published papers from 1967 to 1993; 30–60 days of follow-up | The rates of coronary aneurysms were significantly reduced due to IVlg therapy compared to aspirin alone; high-dose IVlg had lower aneurysm rates compared with low-dose therapy; higher aspirin dose did not alter outcome; p value<0.0001 |
|                                   | [237] | Meta-analysis of RCT  | Patients received: (1) various doses of IVlg, plus aspirin, versus placebo; (2) different doses of IVlg (0.1, 0.2, 0.4 g/kg for 5 days); (3) IVlg 0.4 g/kg for 5 days Vs 2 g/kg once; (4) comparison between 4 types of preparations | 16 RCTs of patients with KD | (1) Significant decrease in new CAAs, fever, and hospitalization at 30 days with IVlg RR (95% CI)=0.74 (0.61 to 0.90) but only trend at 60 days (p=0.06); (2) dose comparisons showed a decrease in the number of new CAAs with increased dose; (3) less CAA for 2 g/kg once RR (95%)=4.47 (1.55 to 12.86); (4) no difference |
|                                   | [238] | Multicenter RCT       | IVlg 0.4 g/kg for 4 days, with or without aspirin                                                                       | 153 patients (78 with KD, 75 controls) | Reduction of echocardiogram-proven CAA from 23% to 8% at 2 weeks (p=0.01) and from 18% to 4% at 7 weeks (p=0.005) |
|                                   | [239] | Case control study    | IVlg 2 g/kg per day at 1–5 or 5+ days from fever onset                                                                    | 178 patients with KD (89 in each group) | Patients treated within 5 days had shorter fever duration (p<0.001) and less CAA at 1 year (p=0.02) |
|                                   | [240] | RCT                   | IVlg 2 g/kg per dose and aspirin; four different brands were used in four groups: Venoglobulin-S (brand A; Alpha Therapeutics, Los Angeles, CA, USA), Gamimune_N (brand B; Bayer Therapeutics, Elkhart, IN, USA), Intraglobin F (brand C; Biotest Pharma, Dreieich, Germany), “CBSF” human immunoglobulin (brand D; Scottish National Blood Transfusion Service Protein Fractionation Center, Edinburgh, Scotland, UK) | 435 patients with KD | Patients receiving brand C had higher rates of CAAs (p=0.01), nonresponsiveness (p=0.001) and giant aneurysm (p=0.008) |
|                                   | [241] | RCT                   | Patients were divided to 2 groups receiving IVlg 1 or 2 g/kg, plus aspirin                                               | 242 children with KD | There was no significant difference in the incidence of CAL (p>0.05) |
|                                   | [242] | Multicenter prospective RCT | Group A: Tx with IVlg 2 g/kg and additional 2 g/kg for nonresponders; group B: IVlg 1 g/kg, and additional dose first 1 g/kg then 2 g/kg for nonresponders; IVlg used: Venilon (Teijin Pharma, Japan), Venoglobulin-IH (Venesis, Japan) or Polyglobin-N (Bayer Yakuhin, Japan) | 109 patients with KD divided to 2 groups | No significant difference in CAA between the patients; discriminate analysis suggested that 52.4% of the patients in group A could be treated with 1 g/kg IVlg only |
recommended along with a high dosage of aspirin [24]. Failure of IVIg treatment in Kawasaki disease and the need for several consecutive IVIg doses is usually caused by delayed initiation of treatment [17]. Detailed treatment algorithms may be found elsewhere [25] (strength of recommendation I).

Rheumatic fever

Level of evidence B Because there is no efficient treatment for established rheumatic carditis, several agents have been proposed in an attempt to change the natural history. IVIg has failed to change clinical outcome and disease progression and therefore is not recommended for treatment of acute rheumatic fever (strength of recommendation III).

Congenital heart block in neonatal lupus erythematosus

Level of evidence C Neonatal lupus erythematosus is a rare disease that is associated with anti-Ro and anti-La autoantibodies [26]. A single case series of eight subjects had

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Table 6 (continued)

| Disease                  | Ref. | Study design    | Intervention including dose and IVIg preparation used                                                                 | Number of patients | Results/response                                                                 |
|--------------------------|------|-----------------|--------------------------------------------------------------------------------------------------------------------------|--------------------|---------------------------------------------------------------------------------|
| Rheumatic fever (RF)     | [244] | RCT             | IVIg (Intragam, from Commonwealth Serum Laboratories) 1 g/kg on days 1 and 2 and 0.4 g/kg on days 14 and 28               | 59 patients with RF, diagnosed according to Jones criteria; 27 patients received IVIg and 32 patients received placebo | IVIg did not affect the natural history of RF during 52 weeks of follow-up       |
| Congenital heart block   | [27]  | Case series     | 1 gm/kg IVIg (Sandoglobulin; Novartis, Bern, Switzerland), at 14th and 18th weeks of gestation; PD (40 mg/day) from the 14th week, which was tapered down to 10 mg/day | 8 pregnant women with past history of an affected child with neonatal lupus | 1 child was born with erythematous skin rash, and 1 child had congenital heart block—interestingly, his mother was the only patient that refused PD intake |
| Awaiting for cardiac transplantation | [245] | Controlled trial | 1 to 3 monthly courses of IVIg 2 g/kg administered in 4 divided daily doses or high-dose IVIg therapy (3 g/kg) in poorly responsive patients; all patients received monthly 0.5–1.0 g/m² cyclosporine | 16 sensitized patients with left ventricular assist device (LVAD) awaiting cardiac transplantation; results were compared to plasmapheresis (n=4) and to cyclosporine alone (n=28) | Within 1 week of infusion of IVIg, the reactivity of IgG antibodies for allogeneic HLA class I molecules was reduced by a mean of 33%; high-dose IVIg for unresponsive patients resulted in a mean reduction of 20%; IVIg has earlier onset of action and greater efficacy than plasmapheresis; waiting time for donation was significantly reduced from 7.1 to 3.3 months; p value<0.05 |
|                           | [246] | Retrospective, nonrandomized, controlled trial | IVIg, 10 g daily for 3 days or conventional therapy following LVAD transplantation | 51 nonsensitized patients with CHF, who received left ventricular assist device (LVAD) awaiting cardiac transplantation received either IVIg (n=26) or conventional therapy (n=25) | Low-dose IVIg therapy failed to reduce sensitization rate in nonsensitized LVAD patients who received blood transfusion during bridge time to cardiac transplantation |
|                           | [247] | Case series     | IVIg 2 g/kg given 1 day before the Norwood procedure, repeated 3 weeks and 4 months later                                     | 7 infants with hypoplastic left heart syndrome who underwent Norwood procedure with cryopreserved allograft pulmonary artery patch | IVIg did not prevent sensitization of the previously unsensitized patients |
nonconclusive results regarding the effect of IVIg and PD in prevention of congenital heart block [27] (strength of recommendation IIb).

Cardiac transplantation

*Level of evidence C* IVIg has anti-idiotypic properties, as well as human leukocyte antigen molecules that may neutralize high panel reactive antibodies in sensitized patients awaiting cardiac transplantation. There is some evidence for IVIg benefit in patients with left ventricular assist device who are awaiting cardiac transplantation (strength of recommendation IIa). Nevertheless, IVIg did not reduce sensitization in previously unsensitized patients who underwent Norwood procedure (strength of recommendation III).

The following conditions refer to (Table 7).

Ophthalmic IgA bullous disease

*Level of evidence C* Linear IgA bullous disease may affect the eye (in 67% of patients) and may present as chronic cicatrizing conjunctivitis. Systemic disease may be treated with systemic CS and dapsone. In poorly responsive patients, IVIg treatment may be used, although its use should be further investigated (strength of recommendation IIa).

Mucous membrane pemphigoid

*Level of evidence C* Mucous membrane pemphigoid (MMP) may involve the eye. There is some evidence for the beneficial effect of IVIg in MMP that involves the eye. IVIg may provide more rapid control of symptoms and prevents remissions during long-term follow-up [28, 29]. This notion should be supported by larger randomized trials (strength of recommendation IIa).

Ocular Behcet’s disease

*Level of evidence C* There are some but limited data regarding the potential benefit of IVIg use in Behcet's disease. Further study is required. Nevertheless, IVIg should be carefully considered in patients resistant to conventional immunosuppressive therapy (strength of recommendation IIa).

Optic neuritis

*Level of evidence A* The natural history of optic neuritis in multiple sclerosis patients is not altered by IVIg transfusion, neither clinically nor radiologically. Therefore, IVIg is not recommended in that setting (strength of recommendation III).

Inflammatory pseudotumor of orbit

*Level of evidence C* There is anecdotal evidence for the possible beneficial role of IVIg in the treatment of inflammatory pseudotumor of orbit (strength of recommendation IIb).

Birdshot retinochoroiditis

*Level of evidence C* Birdshot retinochoroiditis is a rare inflammatory disease (bilateral autoimmune posterior uveitis of idiopathic origin). Without immunosuppressive treatment, a progressive visual deterioration will occur in 80% of patients [30]. There is supporting evidence for the use of IVIg, especially in patients unresponsive to other therapies (strength of recommendation IIa).

Orbital myositis

*Level of evidence C* It is caused by inflammatory process of unknown etiology, which is confined to the orbit. There are very limited data on the effect of IVIg in patients with orbital myositis. Such treatment might be considered in symptomatic patients resistant to other therapies (strength of recommendation IIa).

Refractory uveitis

*Level of evidence C* Most cases of refractory uveitis (RU) are associated with autoimmune mechanisms. There are some data supporting the use of IVIg in resistant RU, although more research is required in order to establish clinical guidelines (strength of recommendation IIa).

Graves’ ophthalmopathy

*Level of evidence B* It seems that IVIg is as efficient as CS in the treatment of Graves’ ophthalmopathy. Nevertheless, despite similar clinical response to treatment, IVIg was associated with fewer side effects and the study group showed more tolerance towards it. Therefore, we conclude that IVIg should be considered in CS intolerance (strength of recommendation I).

Paraneoplastic visual loss

*Level of evidence C* There is limited evidence for the benefit of IVIg in cancer-associated retinopathy. Nevertheless, since spontaneous recovery usually does not occur, IVIg may be used in progressive visual compromise in addition to CS or plasmapheresis (strength of recommendation IIb).

The following conditions refer to (Table 8).
| Disease                                    | Ref. | Study design               | Intervention including dose and IVIg preparation used                                                                 | Number of patients | Results/response                                                                 |
|-------------------------------------------|------|---------------------------|------------------------------------------------------------------------------------------------------------------------|-------------------|----------------------------------------------------------------------------------|
| Ophthalmic IgA bullous disease            | [248] | Case report               | Monthly IVIg treatment, 4 g/kg per month, with graduate discontinuation following clinical improvement                  | 1 patient         | Improvement of clinical symptoms with maximal effect 10–12 days following infusion; decrease of circulating IgA anti-97-kDa epidermal protein |
| Mucous membrane pemphigoid (MMP)          | [28]  | Nonrandomized controlled trial | IVIg, 2 g/kg per cycle, cycles were repeated every 2–4 weeks, compared to conventional immunosuppressive therapy         | 16 patients       | Remission was achieved after 4 months in IVIg group vs 8.5 months in control group; IVIg had less recurrence and decreased progression; \( p \) value<0.05 |
| Ocular Behcet’s disease                   | [91]  | Case series               | IVIg 0.4 g/kg per day: 5 times in first week, 3 more in the next months and once every 20 days for total of 3 months    | 4 patients        | Control of acute inflammation and preservation of remission for 1 year; marked improvement of visual acuity |
| Optic neuritis                            | [249] | RCT                       | 27 patients were treated with IVIg (Gamimmune N; Bayer Pharmaceutical Division, West Haven, CT, USA) 0.4 g/kg per day for 5 days followed by 3 monthly single cycles vs placebo (\( n=28 \)) | 55 patients       | No difference between treatment groups was observed; there was no absolute reversal of persistent visual loss; the trial was terminated by the National Eye Institute |
| Inflammatory pseudotumor of orbit         | [250] | RCT                       | IVIg 0.4 g/kg per day (Immunoglobulin SSI liquid; Statens Serum Institute, Copenhagen, Denmark), infused on days 0–2, and 1 to 2 months later (\( n=34 \)) vs placebo (\( n=34 \)) | 68 patients       | No immediate or delayed effects were observed; there was no change in visual acuity, MRI findings and visual evoked potential results |
| Birdshot retinochoroiditis                | [252] | Case series               | IVIg 0.4 g/kg per day for 4 days; then 0.6 g/kg per day for 2 days, every 4 weeks                                        | 37, of which 18 were followed up | Visual acuity of 53% of patients’ eyes has increased by 2.6±1.5; in 29% of patients, visual acuity remained stable, and in 18% of eyes VA have decrease |
| Inflammatory pseudotumor of orbit         | [30]  | Case series               | IVIg 1.6 g/kg every month for 6 months, followed by 1.2–1.6 g/kg every 6–8 weeks                                         | 18 patients       | In patients with visual acuity of 20/30, there was increase in visual acuity in 53.8% of eyes and decrease of acuity in 7.7% while there was no change in the remaining eyes |
| Orbital myositis                          | [253] | Case report               | IVIg (Venimmun) 0.3 g/kg per day for 3 days                                                                           | 1 patient         | Both clinical and tomographic resolution within 2 weeks                           |
| Refractory uveitis                        | [254] | Case series               | IVIg (Baxter Healthcare, Glendale, CA, USA), 0.5 g/kg per day for 3 days each month; median of 7.5 cycles              | 10 patients       | Both clinical and tomographic resolution within 2 weeks                           |
|                                          |      |                           |                                                                                                                        |                   | 50% sustained improvement of visual acuity, 20% have required a reduced doses of immunosuppressive therapy without disease progression; the patient with sarcoidosis had improved vision and reduced need for immunosuppression, although that effect was not sustained 4.5 months following |
Lupus nephritis

*Level of evidence B* A few case reports and a single RCT clearly indicate the efficacy of IVIg in the treatment of lupus nephritis. In all cases, patients had a beneficial response to IVIg and a significant improvement of renal function was noted. Therefore, IVIg is recommended as an alternative treatment in lupus nephritis or in cases that conventional immunosuppressive treatment fails (*strength of recommendation I*).

Renal transplant rejection

*Level of evidence C* Although evidence for the use of IVIg in renal transplant rejection is limited to case reports and case series results showed that IVIg may be effective for treating acute or chronic renal transplant rejection. IVIg may improve renal function and reverse Ab-mediated rejection. IVIg may be considered among the treatment options generally together with immunosuppressive therapy (*strength of recommendation I*).

ANCA-associated rapidly progressive glomerulonephritis (RPGN)

*Level of evidence C* There is weak evidence indicating significant benefit from the use of IVIg in antineutrophil cytoplasmic antibody (ANCA)-associated RPGN. Several case series and case reports showed that IVIg may improve renal function and therefore is recommended as a potential therapy for ANCA-associated RPGN (*strength of recommendation I*).
| Disease                                      | Ref.  | Study design           | Intervention including dose and IVIg preparation used | Number of patients | Results/response                                                                 |
|----------------------------------------------|-------|------------------------|--------------------------------------------------------|-------------------|----------------------------------------------------------------------------------|
| Membranous nephropathy                       | [260] | Retrospective uncontrolled trial | IVIg 0.4 g/kg every 21 days (mean duration of treatment was 15 months equal to 21 cycles) | 13 adult patients (8 males, 5 females) with primary membranous glomerulonephritis | 5 patients had complete remission  
                                                                              5 patients had partial remission  
                                                                              3 patients no clinical remission but presented marked reduction in proteinuria |
|                                              | [261] | Case series            | IVIg 0.4 g/kg per day for 3 days every 21 days (3 courses), then once every 3 weeks for 10 months | 9 patients with biopsy-confirmed idiopathic membranous nephropathy | 5 patients with normal renal function: 4 had complete remission, 1 had partial remission  
                                                                              4 patients with moderate renal insufficiency; 1 had complete remission, 2 had partial remission, 1 had no response |
|                                              | [262] | Retrospective analysis | IVIg 0.1–0.15 g/kg per day for 6 days, 1–3 courses | 86 with primary membranous glomerulonephritis | 30 patients were treated with IVIg: 13 patients had complete remission; 11 patients had partial remission; 3 patients had continued nephrotoxic state with renal dysfunction; 3 patients reached end-stage renal disease |
| IgA nephropathy                              | [263] | Single-arm, nonrandomized study | IVIg 2 g/kg monthly for 6 months | 14 patients with progressive IgA nephropathy | 6 patients received IVIg; the mean loss of renal function and proteinuria were significantly reduced in the IVIg group (p=0.024, p=0.015, respectively) |
|                                              | [63]  | Open prospective cohort study | IVIg 2 g/kg per month for 3 months followed by IMIg for another 6 months | 11 patients with moderate IgA nephropathy | Proteinuria, glomerular filtration rate, and histologic index of activity were significantly decreased |
| BK-virus-associated nephropathy in renal allograft recipients | [264] | Case series | IVIg 2 g/kg over 2–5 days + immunosuppression | 8 renal allograft recipients with BK-virus-associated nephropathy | 88% of the patients were dialysis free and had stable renal function after follow-up of 15 months |
|                                              | [265] | Case report            | IVIg 0.6 g/kg, 5 doses repeated every 4–6 weeks | A pediatric renal transplant patient recipients with BK-virus-associated nephropathy | Stabilized renal function, reduced viral load, and resolved histological findings were noted after IVIg treatment |
| ANCA-associated rapidly progressive glomerulonephritis (RPGN) | [266] | Case series | IVIg 0.4 g/kg per day for 5 days + CS ± CP after IVIg | Twelve patients with MPO-ANCA-associated RPGN (7 men, 5 women) | After IVIg treatment, a significant reduction was noted in white blood cell count (p<0.05), in C-reactive protein values (p<0.001), in Birmingham vasculitis; Activity Score (p<0.001) and in the rate of change in 1/Cr (p<0.05) |
|                                              | [58]  | Case series            | IVIg 0.4 g/kg per day for 5 days + immunosuppressive therapy | 30 patients with MPO-ANCA-associated RPGN (male 17, female 13) | After IVIg, significant reduction in CRP (p<0.001), improvement in serum creatinine in 63% of patients; at 3 months, disease activity was completely reduced; at 6 months, renal survival rate was 92% and life survival was 93% |
|                                              | [267] | Case report            | IVIg (Omr-IgG-am5%IV) 0.5 g/kg per day for 4 days after immunosuppressive therapy | A 68 year-old woman with RPGN | Significant improvement in renal function after IVIg treatment |
BK-virus-associated nephropathy in renal allograft recipients

**Level of evidence C** The use of IVIg in BK-virus-associated nephropathy in renal allograft recipient is limited only in a few case reports. Nevertheless, in these cases, IVIg showed significant efficacy and with concomitant reduction of immunosuppression it may be considered as one of the treatment options in this disease (*strength of recommendation I*).

IgA nephropathy

**Level of evidence B** Results coming from a single-arm nonrandomized study and a prospective cohort study showed that IVIg may be effective in treating severe IgA nephropathy and therefore it may be considered as a possible treatment option. However, RCTs are needed to confirm this efficacy (*strength of recommendation I*).

Membranous nephropathy

The efficacy of IVIg in membranous nephropathy was studied in few retrospective trials and a case series. Results from these studies indicate that IVIg may be effective in induction of remission. Although there is no strong evidence, IVIg may be considered as an additional option in treatment of membranous nephropathy (*strength of level of evidence C; recommendation I*).

The following conditions refer to (Table 9).

### Table 8 (continued)

| Disease | Ref. | Study design | Intervention including dose and IVIg preparation used | Number of patients | Results/response |
|---------|------|--------------|-------------------------------------------------------|--------------------|-----------------|
| Renal transplant rejection | [268] | Case reports | IVIg | A 66-year-old male and a 14-year-old boy with MPO-ANCA-associated RPGN | Significant improvement in both patients including renal function after IVIg treatment |
| | [269] | Prospective pilot trial | IVIg 1 g/kg per dose every week for 4 weeks + rituximab 1 week after last IVIg infusion | 6 pediatric renal transplant recipients with chronic antibody-mediated rejection | 4/6 responded to IVIg with significant improvement in glomerular filtration rate \( p<0.05 \); 2/6 no response |
| | [270] | Case report | IVIg 0.5 g/kg every other day for 4 cycles + rituximab + plasmapheresis | A 46-year-old female renal transplant recipient with antibody-mediated rejection | Improvement in renal function |
| | [271] | Case report | IVIg 0.15 g/kg within 72 h of transplantation, and 0.1 g/kg every 2 weeks for 4 doses, followed by monthly infusions for 2 doses + plasmapheresis + monoclonal anti-T lymphocyte antibody therapy | A 14-year-old renal transplant recipient with antibody-mediated rejection | Improvement in renal function and reverse of Ab-mediated rejection |
| | [272] | Case series | IVIg 2 g/kg | 7 renal transplant recipient with antibody-mediated rejection | IVIg-induced reversion of acute rejection in all patients and reduced donor-specific anti-HLA alloantibody levels |
| Lupus nephritis | [273] | RCT | During 18 months, 5 received IVIg 0.4 g/kg once a month, 9 continued CP | 14 patients with proliferative lupus nephritis | Treatment with IVIg as maintenance therapy was safe and effective as CP |
| | [274] | Case series | IVIg, 0.4 g/kg for 5 days, of ISIVEN (Istituto Sierovaccinogeno Italiano I.S.I.S.A, Italy) | 7 lupus nephritis patients who failed to respond to at least PD and CP | All patients had a beneficial response to IVIg; all had significant decrease in proteinuria |
| | [275] | Case report | IVIg 2.8 g/kg, one dose | A 39-year-old female SLE patient with lupus serositis and nephritis | Clinical improvement and significant decrease in proteinuria. |
| | [276] | Case report | IVIg 12.5 g/day for 5 successive days after CS and plasmapheresis treatment | A 34-year-old Japanese female patient with rapidly progressive lupus nephritis associated with anti-MPO antibodies | Significant improvement of renal function after IVIg treatment |
Autoimmune blistering diseases

Pemphigus vulgaris

*Level of evidence B* There is some evidence that IVIg have steroid-sparing effect and may be effective as monotherapy and/or adjunctive therapy in patients with previously severe unresponsive pemphigus vulgaris (*strength of recommendation IIa*).

Pemphigus foliaceus

*Level of evidence C* Adjunctive to standard immunotherapy treatment with IVIg may cause improvement in clinical course and may have steroid-sparing effect in previously steroid-dependent patients with refractory pemphigus foliaceus (*strength of recommendation IIa*).

Bullous pemphigoid

*Level of evidence C* In some severe cases of bullous pemphigoid, IVIg was found to be effective as monotherapy and adjunctive therapy as well; it had steroid-sparing effect and led to improvement of quality of life (*strength of recommendation IIa*).

Mucous membrane pemphigoid

*Level of evidence C* There is some evidence that IVIg monotherapy may be at least as effective as standard immunosuppressive treatment and lead to quick therapy response and better quality of life (*strength of recommendation IIa*).

Epidermolysis bullosa acquisita, linear IgA disease, pemphigoid gestationis

*Level of evidence C* The sparse data of positive effect of IVIg on severe cases of epidermolysis bullosa acquisita, linear IgA disease, and pemphigoid gestationis were published (*strength of recommendation IIa*).

Summary

In autoimmune blistering diseases, the treatment with IVIg may be effective and has to be implicated in cases with severe disease, resistant to conventional therapy or those who experienced severe complications of such therapy.

Other immune-mediated dermatoses

Stevens–Johnson syndrome and toxic epidermal necrolysis

*Level of evidence C* The randomized studies have not been performed and the current knowledge about effectiveness of IVIg in SJS and TEN is based on results of multiple prospective noncontrolled studies, retrospective case series, and case reports. The data are limited and inconclusive (*strength of recommendation IIb*).

Atopic dermatitis

*Level of evidence B* The current data based on single, randomized, controlled, and evaluator-blinded trial and number of prospective noncontrolled studies suggest that IVIg may be effective as monotherapy in pediatric patients and as adjunctive therapy in adults. However, in view of the low-cost effectiveness of IVIg, this treatment should be used in cases of severe disabling atopic dermatitis (*strength of recommendation IIa*).

Urticaria

*Level of evidence C* A number of case reports and case series describe the beneficial effect of IVIg in chronic idiopathic and autoimmune urticaria, but randomized controlled studies are still lacking. The use of IVIg has to be limited to severe unresponsive cases of chronic urticaria or in case of severe complications of conventional treatment (*strength of recommendation IIa*).

Psoriasis

*Level of evidence C* Only three cases of severe resistant psoriasis with psoriatic arthritis responsive to treatment with high-dose immunoglobulin were reported. We conclude that there is now evidence of effectiveness of IVIg in psoriasis (*strength of recommendation IIb*).

Pyoderma gangrenosum

*Level of evidence C* IVIg was successfully used in few cases of previously unresponsive pyoderma gangrenosum, but its systematic use cannot be recommended (*strength of recommendation IIa*).

Miscellaneous dermatoses

*Level of evidence C* Several case reports and case series showed IVIg to be effective for nephrogenic fibrosing dermopathy, pretibial myxedema, and Arndt–Gottron scleromyxedema, but still well-controlled studies are lacking. We suppose that IVIg can be used in severe cases of these rare conditions, unresponsive to conventional treatment (*strength of recommendation IIa*).

The following conditions refer to (Table 10).
Table 9  The use of intravenous immunoglobulins in dermatologic diseases

| Results/response                                                                 | Number of patients                                                                                                                                                                                                 | Intervention including dose and IVIg preparation used                                                                                                                                                                                                 | Study design       | Ref.   | Disease               |
|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|--------|-----------------------|
| 21/21 reached sustained remission; mean time to clinical response 4.5 months; maintenance therapy for a mean 22.7 months; compared to pretreatment period the study subjects received a lower dosage of CS and immune-suppressive therapy, had fewer side effects, recurrences, and relapses, needed fewer hospital admissions and days of hospital stay ($p<0.001$), and reported better quality of life ($p<0.0001$) | 21 patients with severe pemphigus vulgaris unresponsive to corticosteroid and immune-suppressive agents                                                                                                                                  | Monotherapy 2 g/kg given in 3 days in 4-week interval until complete healing, afterwards after 6, 8, 10, 12, 14, and 16 weeks if patient is disease free; end point—disease free with a 16-week interval between the 2 infusion cycles; adjunctive to other systemic therapy, not effective in the beginning of trial | Uncontrolled trial | [277]  | Pemphigus vulgaris   |
| 10/12 (83%) responded, 6/12 (50%) had complete remission and 4/12 (33%) partial response; 72% decline of pemphigus antibody levels and steroid-sparing effect | 12 patients with severe unresponsive pemphigus vulgaris                                                                                                                                                                                                                       | IVIg for 6 months as adjuvant to immune-modulating therapy                                                                                                                                                                                                  | Uncontrolled trial | [278]  |                       |
| No new lesions and 72% decline of pemphigus antibodies levels after 1 week, 80% reduction of extent of existing lesions in 5/6 patients after 2 weeks, 41% reduction of steroid doses after 3 weeks | 6 patients with active pemphigus vulgaris, unresponsive to at least 2 months of CS therapy                                                                                                                                                                                      | IVIg 2 g/kg in 5-day cycles (as 5% solution, Venoglobulin S; Alpha Therapeutics Co, LA, CA, USA) concurrent with CS and cyclophosphamide 100–150 mg/day                                                                                                                                 | Uncontrolled trial | [279]  |                       |
| Significant reduction of total PD dose ($p=0.004$), duration of PD therapy ($p=0.003$), and number of relapses ($p<0.001$); CS was discontinued over a mean period of 4.3 months | 15 patients with steroid-dependent pemphigus vulgaris, mean follow-up of 6.2 years                                                                                                                                            | IVIg 1 to 2 g/kg given in 3 doses on 3 consecutive days as a 4- to 5-h infusion at a frequency of every 3 to 4 weeks adjunctive to CS (no other immunosuppressive therapy was allowed); intervals were increased to 6, 8, 10, 12, 14, and 16 weeks, if clinical response was achieved                                                                 | Retrospective analysis | [280] |                       |
| 38/39 on adjunctive therapy improved; in monotherapy group, no change in 2 patients, worth in 1 | 42 patients with pemphigus vulgaris                                                                                                                                                                                                                                          | IVIg 2 g/kg per month in 37 patients; 0.3 g/kg per day in 4 patients, 0.25 g/kg per day in 1 patient; Sandoglobulin® in 10, Puimmun® in 1, NA in 31 adjunctive in 39, monotherapy in 3                                                                                                                                 | Review of published case reports | [239]  |                       |
| 6/7 did not respond; 1/7 had partial response with >50% improvement (but died 1 month after IVIg cycle of pneumonitis) | 7 patients with pemphigus vulgaris | As adjunctive therapy in the dose of 2 g/kg per cycle, 4/7 patients received Venoglobulin®; other 3 patients received Gammagard/Gamma P.I.V/Gamimmune, mean duration of treatment was 7 months                                                                                                                                 | Case series         | [281]  |                       |
| 11/11 had effective clinical response in mean of 5.3 months, clinical remission for a mean period of 18.6 months after discontinuation of IVIg; After IVIg, the study subjects received a lower dosage of CS ($p=0.001$), had fewer side effects ($p=0.002$), recurrences, and relapses ($p=0.001$), had fewer hospital admissions and days of hospital stay ($p<0.01$), and had better quality of life ($p=0.001$) compared to pretreatment period | 11 patients with refractory pemphigus foliaceus                                                                                                                                         | IVIg 2 g/kg given over 3 days in 4-week interval until complete healing, afterwards after 6, 8, 10, 12, 14, and 16 weeks if patient is disease free; end point—disease free with a 16-week interval between the 2 infusion cycles; adjunctive to other systemic therapy, previously not effective | Uncontrolled trial | [282]  | Pemphigus foliaceus  |
| Results/response | Number of patients | Intervention including dose and IVIg preparation used | Study design | Ref. | Disease |
|------------------|--------------------|-------------------------------------------------------|--------------|------|---------|
| 8/8 significant reduction of antidesmoglein antibodies after 4 months of treatment (p NA), nondetectable titers after 13 months, serological remission after additional observation period of 5 months | 8 patients with severe pemphigus foliaceus | IVIg | Uncontrolled trial | [283] | |
| CS gradually discontinued over a mean period of 2.8 mo, with resulting reduction of PD total dose (p=0.005), total duration of PD treatment (p=0.02) and number of relapses (p=0.002) according to pre-IVIg therapy. All improved | 7 steroid dependent pemphigus foliaceus patients. | In the beginning of the trial adjunctive to CS and as monotherapy afterwards. | Uncontrolled trial | [284] | |
| 15/15 clinical response within mean of 2.9 months; all patients demonstrated fewer hospital admissions, fewer relapses and recurrences, significant steroid-sparing effect (were tapered over a mean period of 3.3 months), and quality of life improvement compared to pre-IVIg therapy (p<0.0001) | 28 patients with pemphigus foliaceus | Adjunctive IVIg 1 to 2 g/kg per month, 0.27 g/kg per month in 1, continued for several weeks to more than 5 months | Review of published case reports | [239] | |
| 12/17 (70%) improved; 5/17 (30%) had no change; in some patients, high-dose IVIg had systemic steroid-sparing effect; the lack of response was observed in low-dose or single-effusion cases; early treatment, multiple treatment cycles, and concomitant immunosuppressive treatment led to longer and more sustained remissions | 17 patients with severe bullous pemphigoid | IVIg 2 g/kg over 3 days by 4–5-h infusion adjunctive to oral PD, given every 4 weeks, until clinical stabilization; intervals were gradually increased to 6, 8, 10, 12, 14, and 16 weeks (mean number of cycles 14.7) | Review of published case reports | [285] | Bullous pemphigoid |
| 1/3 complete response after 4 cycles, maintained with 5 additional cycles; 2 patients had no response | 3 patients with bullous pemphigoid | Adjunctive therapy with 2 g/kg per month of Venoglobulin® in 2 and Carimune® in 1 of 3 patients for mean 7 months | Case report | [281] | |
| 19/22 improved on adjunctive therapy, 8/12 improved on monotherapy within 2 weeks–4 months | 34 patients with bullous pemphigoid | Adjunctive 22, monotherapy in 12 2 g/kg per month in 32 patients, 0.1 g/kg per day for 5 days and 0.3 g/kg per day for 5 days (low dose), 10 patients as monotherapy and 8 adjunctive to immunosuppressive therapy | Review of published case reports | [239] | |
| Clinical response in 7/7 patients, treated with IVIg, after a mean period of 4.5 months, sustained remission after a mean treatment period of 26.9 months, improvement of quality of life after IVIg therapy (p<0.001); reduction of antibody titers in both groups (p=0.015), but faster in IVIg group (p=0.03) | 7 patients (mean age of onset 55.5) on IVIg monotherapy vs. 7 random patients (mean age of onset 55) with severe (+3) oral pemphigoid; treatment period 12 months | Monotherapy with 1 to 2 g/kg per month IVIg vs. conventional immunosuppressive treatment (PD and dapsone or AZA or MTX or tacrolimus or CP); adjunctive local treatment with sublesional injections of triamcinolone acetonide (proven not to be systemically absorbed by serum cortisol levels) was given to patients in both groups | Controlled trial | [287] | Mucous membrane pemphigoid |
| Significant improvement, reduction of relapses, duration and total dosage of corticosteroid therapy and quality of life after IVIg (p NA) | 15 patients with severe mucous membrane pemphigoid | IVIg 1 to 2 g/kg per month | Uncontrolled trial | [284] | |
| Results/response | Number of patients | Intervention including dose and IVIg preparation used | Study design | Ref. | Disease |
|------------------|--------------------|------------------------------------------------------|--------------|------|---------|
| All patients improved within 2–6 months on combination therapy and within 4–6 months on monotherapy, steroid-sparing effect in adjunctive therapy group | 43 patients with mucous membrane pemphigoid | IVIg 1–3 g/kg over 3–5 days for 2–4 weeks; adjunctive/monotherapy 28/15 | Review of published case reports | [239] |         |
| Improved 3/3 on adjunctive and 2/3 monotherapy, 1/1 UV protection | 7 patients with epidermolysis bullosa acquisita 16–59 years old, all males | IVIg 0.4 g/kg per day for 5 days, 2–6 weeks (4), 2 g/kg per day 2 weeks (1), 0.04 g/kg per day for 5 days 3–4 weeks (1), 1.2 g/kg per month (1) Polyglobulin® in 1, Sandoglobulin® in 3, NA 3; adjunctive therapy 3, monotherapy 3, 1 UV protection for 1–4 months | Review of published case reports | [239] | Epidermolysis bullosa acquisita |
| All improved | 3 patients 45–67 years old with linear IgA disease | Sandoglobulin® 0.4 g/kg per day over 5 days in 1 patient; 2 patients received 4 g/kg per month regimen (preparation NA); 2 patients received CS as additional treatment | Review of published case reports | [239] | Linear IgA disease |
| Complete response after 5 cycles of IVIg (3.5 months), IVIg continued for additional 10.5 months | 1-week-old newborn with linear IgA disease | Adjunctive therapy with Venoglobulin® 1 g/kg every 2–4 weeks for 14 months | Case report | [281] |         |
| Steroid-sparing effect, maintained with cyclosporine and low-dose prednisolone; cyclosporine was stopped 16 months after delivery | 17-year-old female with pemphigoid gestationis, developed at 20 weeks gestation in her 1st pregnancy | 2 g/kg per month for 2 months adjunctive to CS | Case report | [288] | Pemphigoid gestationsis |
| Objective response in all patients within a mean of 2 days, skin healing within 8.3 days, slow healing in patients with underlying diseases, an overall survival rate of 100% | 12 patients with SJS (mean age 44) | Commercially available IVIg at a mean dose of 0.6 g/kg per day for an average of 4 days as monotherapy | Retrospective multicenter study | [289] | Stevens-Johnson syndrome |
| The average duration of fever was 8 days in IVIg-treated vs. 14 in non-IVIg-treated group (p=0.06); the mean stay in hospital was 12 days in IVIg-treated vs. 15 days in non-IVIg-treated group (p=0.5) | Total of 12 patients (mean age 6 years), 7 IVIg-treated and 5 non-IVIg-treated | IVIg as single infusion at 1.5–2.0 g/kg given on an average of 3 hospital days | Retrospective series report | [290] |         |
| No mortality, arrest of disease progression in 1–5 days (mean 2.83), re-epithelialization in a mean of 7.33 days (range 5–13); the average duration of hospital stay was 12.5 days | 12 patients (average age 27.2 years, 4 children 7–12 years old); the average affected body area was 57.5% | IVIg 0.5–1.0 g/kg per day for 4–5 days adjunctive to standard care protocol, infusion started on average 1.58 days | Uncontrolled trial | [291] | Toxic epidermal necrolysis |
| 90% of patients survived; one patient with previous history of severe heart disease died as a result of cardiac arrest during the first day of treatment | 10 patients with TEN with predicted mortality rate 35% according to SCORTEN | IVIg 0.4 g/kg per day for 5 days started within 3 days from the onset of TEN | Prospective single center uncontrolled trial | [292] |         |
| Progression of epidermal detachment in 22/34, more deaths than predicted by prognostic SCORTEN score (11 (32%) instead of 8.2 (24%)), most deaths in elderly with renal impairment | 34 patients with a mean of 4.3 days after onset of SJS (n=9), SJS/TEN (n=5), TEN (n=20) | IVIg 2 g/kg within 2–5 days (30 patients treated with Tegeline (Laboratoire français du Fractionnement et des Biotechnologies, France), 2 with Sandoglobulin® (Novartis, France), 2 with Gammagard® (Baxter, France), only Gammagard did not include sucrose) | Uncontrolled trial | [293] |         |
| Study design       | Ref. | Disease  | Intervention including dose and IVIg preparation used | Results/response |
|-------------------|------|----------|------------------------------------------------------|------------------|
| Retrospective     | [294]| TEN      | IVIg 0.75–1 g/kg per day for 3 days adjunctive to intravenous prednisolone 0.25–0.5 g/day for 1–3 days | Mortality rate was 20% in IVIg-treated patients vs. 50% in non-IVIg group (overall mortality of 33%) |
| Case series       | [295]| TEN      | IVIg 0.5 g/kg per day for 4 days (2 patients), 1 patient was switched after 24 h to 0.6 g/kg per day for 2 days due to further deterioration | 9 patients with TEN—all treated with Cs; 5/9 received IVIg as adjunctive therapy |
| Case series       | [296]| TEN      | Commercially available IVIg at mean dose of 0.7 g/kg per day for a mean of 4 days given as monotherapy | 7/7 survived, a cessation of blistering in 7/7 patients within an average of 2 days; in published cases, time to objective response could be ascertained in 20 patients: cessation of blistering after an average of 2.5 days; patients with concomitant Cs treatment were noted to have a longer time to objective response |
| Retrospective     | [297]| TEN      | IVIg 0.5–0.75 g/kg per day for 4 consecutive days, started with average delay of 3.2 days after blisters onset | Time to objective response was 2.3±1.2 days; duration of IVIg treatment was 4±0.9 days; objective response rate was 90%; survival rate was 88%; time to complete healing was 15±9.5 days; the odds of survival decreased per year of life (p=0.02) and increasing epidermal detachment (p=0.03); more underlying disease in the group of nonsurvivors (p=0.05) |
| Retrospective     | [298]| SJS/TEN  | IVIg 1 g/kg per day (Sandoglobulin®, Sandoz, France) immediate or delayed by 1 month (meanwhile intensive therapy with emollients and topical Cs (limited to class II 60 g/month)), for 2 days in 8-h infusion, as monotherapy | 83% reduction of mortality (1 patient died instead of 5.8 expected based on SCORTEN) |
| Case series       | [299]| TEN      | Flebogamma® 5% 2 g/kg per month given in 2–5 days for 6 months as adjunctive treatment, followed for 3 months | The average time to arrest of progression was 2.1 days; complete re-epithelialization was 8.1 days and length of hospitalization 13.6 days; no mortality |
| Case series       | [300]| TEN      | Alphaglobin® (Grifols, UK) or Sandoglobulin® (Novartis, UK) 2 g/kg per month in 3–5 days adjunctive to Cs | No difference in length of stay, mechanical ventilation, severity of inflammatory response or incidence of sepsis, wound progression, time to healing, and mortality |
| Case report       | [301]| TEN      | No difference of SCORAD index and in global evaluation of disease severity by patients at day 30 | Improvement in skin score (mEASI) was apparent in responders (4/6 patients) from 2 to 3 months and continued to improve over a 6-month period; after 7 months, there was a significant reduction of the overall mEASI; CD69-expressing T cells decreased to 60% from baseline; no change of TNF-a and IFN-g |
| Case report       | [302]| TEN      | Alphaglobin® (Grifols, UK) or Sandoglobulin® (Novartis, UK) 2 g/kg per month in 3–5 days adjunctive to Cs | No difference in length of stay, mechanical ventilation, severity of inflammatory response or incidence of sepsis, wound progression, time to healing, and mortality |
| Case report       | [303]| TEN      | Alpha***globin® (Grifols, UK) or Sandoglobulin® (Novartis, UK) 2 g/kg per month in 3–5 days adjunctive to Cs | 3/3 patients improved skin scores, allowing reduction of steroid dose |
Table 9 (continued)

| Results/response | Number of patients | Intervention including dose and IVIg preparation used | Study design | Ref. | Disease |
|------------------|--------------------|--------------------------------------------------------|--------------|------|---------|
| 9/10 were available for analysis; 6/9 showed slight improvement of skin lesions; 2/9 were unchanged and 1/9 worsened; there were no steroid-sparing effect, change in mean IgE, lymphocyte response to PHA, Candida, tetanus, and anti-CD3 antibody, and change in RAST positivity to negativity | 10 patients (7–64 years old): 1 patient with hyper-IgE syndrome and 9 patients with atopic dermatitis | Aza, Hxc Adjunctive to CS in 6/10 Venoglobulin® I (10%) 2 g/kg per month for 7 months | Open, single center | [304, 305] | Atopic dermatitis |
| 9/10 patients less than 6 years old improved on monotherapy; 1 patient with WAS failed to improve after 1 treatment cycle; 17/22 adults received adjunctive therapy; 10/17 (59%) improved; the longest time to response was 3–4 months | 32 patients (8 months to 64 years old) with atopic dermatitis | 2 g/kg per month for 1 to 11 cycles, 1 patient with WAS 1 g/kg per month for 1 month; 14/32 patients received IVIg as monotherapy, 5 patients Bayer Biological Co., 6 patients Plebogamma®, 10 patients Venoglobulin I®, 3 patients Sandoglobulin®, Alphaglobulin®, 8 patients preparation NA | Review of published case reports | [305] | Atopic dermatitis |
| 9 of 10 patients responded: 3 patients with complete remission sustained 3 years later; 2 patients with temporary complete remission; 4 patients improved subsequent to treatment; total urticaria activity score assessed by physician and by patient with the use of visual analog score at 2 and 6 weeks improved significantly (p<0.01) without significant change of the positivity of autologous serum injection test | 10 patients with severe chronic autoimmune urticaria | 0.4 g/kg per day for 5 days as 3% solution in normal saline on the first day, followed by a 6% solution on the succeeding 4 days (Sandoglobulin®, Novartis, UK); symptomatic treatment with cetirizine 20 mg/day was taken by all patients | Case series | [306] | Chronic urticaria |
| After the 1st application of IVIg, urticaria score was reduced to 1, maintained with repeated administrations of IVIg in intervals of 4 weeks 95% resolution over 3.5 months without concomitant therapy | A 63-year-old woman with a 2-year history of chronic urticaria with urticaria score of 4/8 despite H1-and H2-blockers | Low-dose IVIg 0.2 g/kg every 4 weeks adjunctive to standard antihistamine therapy | Case report | [307] | Solar urticaria |
| 5 of 8 responded: 3 remission (2 after one and 1 after 3 cycles); 2 patients improved; responders improved with 3 or fewer infusions; 3 patients failed to improve after 2–6 cycles of IVIg; ASST was not a predictor of response to IVIg | A 28-year-old female with 41-month history of severe chronic urticaria | 1 cycle of Venoglobulin® 2 g/kg in 5 days as monotherapy | Case report | [281] | Delayed pressure urticaria |
| After 3 cycles tolerated visible light and 15 min of intense solar exposure, SU has disappeared after 1 year | 8 adult patients with steroid-dependent refractory delayed pressure urticaria (concomitant with chronic urticaria 8/8, angioedema 4/8, cholinergic urticaria 1, and dermographism 1) | 2 g/kg per month (Scottish National Blood Transfusion Service) over 2 to 3 days, followed by antihistamines and CS | Uncontrolled trial | [308] | Delayed pressure urticaria |
| Taper off of CS and prolonged remission; recurrence and remission of symptoms were associated with changes of IVIg lot and source | 55-year-old woman suffered from resistant solar urticaria for 3 years | IVIg | Case report | [309] | Solar urticaria |
| 2 patients experienced dramatic improvement in both their joints and skin and a fall in inflammatory markers; 1 patient had improvement in arthritis but little change in skin involvement | A female patient with resistant solar urticaria | IVIg 2.5 g/kg over 3 days | Case report | [310] | Solar urticaria |
| 3 patients with treatment-resistant psoriasis and psoriatic arthritis | A 54-year-old man | IVIg 0.4 g/kg every 3 weeks (Panglobulin® or Gamimune N® according to availability) adjunctive to CS | Case report | [311] | Angioedema with hypereosinophilia syndrome |
| | | IVIg (Octagam®, Octapharma, Coventry, UK) 2 g/kg over 3 to 4 days adjunctive to conventional treatment; in 2 cases, improvement was sustained with additional cycles of IVIg; in 1 case, information is not | Case series | [312] | Psoriasis |
| Study design | Ref. | Disease | Intervention including dose and IVIg preparation used | Results/response |
|--------------|------|---------|------------------------------------------------------|-----------------|
| 7 of 10 patients demonstrated clearance of lesions; in 6/7 of cases, the efficacy maintained with repeat IVIg infusions | | | | Available IVIg 2 g/kg per month in 3 days, 9/10 in conjunction with CS and MMF and/or cyclosporin; IVIg was stopped after 2 to 3 cycles in case of ineffectiveness |
| Stabilization of pyodermagangrenosum and steroid-sparing effect in both patients | | | | IVIg 2 g/kg per month for 6 months adjunctive to CS |
| Improvement of range of joints motion and laxity of skin after 1 month but no further improvement after the 2nd and the 3rd cycles of IVIg | | | | IVIg 2 g/kg in 5 days for 3 months |
| Clinical improvement in all patients after 2–9 months with reduction of skin thickness by US evaluation (4/7), reduction of mucopolysaccharide skin content (3/7), disappearance of lymphocytic skin infiltration and IgG deposition (2/7) | | | | Stabilization of pyodermagangrenosum and steroid-sparing effect in both patients |
| 8 patients had complete (2) or partial (6) response, but in all the effect was transient, requiring reinfusion and maintenance therapy | | | | IVIg in dose 0.4–1.0 g/kg per day for 2–5 days for a total 2 g/kg every month for 6 months as monotherapy after failure of other treatment modalities |
| All patients had cutaneous improvement as well as improvement in ureteral stricture, vocal strength, and dysphagia | | | | IVIg 0.4 g/kg per day for 5 days every 5 weeks (Gammagard; Baxter Healthcare Corp, Hyland Immuno, Glendale, CA, USA) |
| First patient had significant reduction in skin scores (36/60 to 11/60) for 1 year only; second had a dramatic sustained response with continued Tx (interval subsequently increased to 10 weeks) | | | | Improvement after the first treatment, continuous skin softening and reduction of induration, sustained response to treatment after 20 courses |
| Improvement after the first treatment, continuous skin softening and reduction of induration, sustained response to treatment after 20 courses | | | | Progressive clinical improvement over several months allowing discontinuation of PD but rapid deterioration afterwards with lethal CVA despite reinstating PD and CP |
| A positive response after 2 cycles | | | | Marked clinical improvement, maintained with repeated IVIg infusions |
| Marked clinical improvement, maintained with repeated IVIg infusions | | | | Complete clearance of skin lesions, sustained effect after 1 year without treatment |
Kaposi’s sarcoma

Level of evidence C A patient with polymyositis and Kaposi sarcoma had remission of both conditions on IVIg therapy (strength of recommendation IIb).

Metastatic melanoma

Level of evidence C Stabilization of metastatic melanoma was shown in the small group of patients after addition of IVIg to standard therapy (strength of recommendation IIb).

Chemotherapy-induced oral mucositis

Level of evidence C IVIg was shown to be effective in preventing severe recurrent chemotherapy-induced oral mucositis in two patients treated with methotrexate (strength of recommendation IIa).

Thymus carcinoma

Level of evidence C Anecdotal case report describes complete remission of metastatic malignant thymoma after four cycles of IVIg given to myasthenic patient (strength of recommendation IIb).

Thymoma and immunodeficiency (Good syndrome)

Level of evidence C After thymectomy, two patients with Good syndrome were maintained with IVIg for developed immunodeficiency; one of them developed Kaposi sarcoma after 3 years (strength of recommendation IIb).

The following conditions refer to (Table 11).

Summary

There are still no randomized controlled trials evaluating efficacy of IVIg and it cannot be recommended for treatment of epithelial or other solid malignancies.

Diabetes mellitus

Level of evidence C There is some evidence that IVIg therapy can improve the Neuropathy Impairment Score in patients with diabetic demyelinating polyneuropathy (strength of recommendation IIa). A few case reports describe regression of symptoms of proximal diabetic neuropathy, diabetic amyotrophy, and cranial nerve neuropathy in different diabetic patients treated with IVIg (strength of recommendation IIa). We conclude that evidence for the use of IVIg in diabetic neuropathies is poor and its systematic use cannot be recommended.
| Results/response                                                                 | Number of patients                                                                 | Intervention including dose and IVIg preparation used                                                                 | Study design | Ref. | Disease                                   |
|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|--------------|------|-------------------------------------------|
| Considerable improvement of KS skin lesions after 2 weeks, disappearance of 6 of 8 skin lesions after 1 month; after 3 cycles, only 1 remnant skin lesion; after 2 years of monthly treatment, no relapse of KS or progression of polymyositis | 45-year-old patient with polymyositis, who developed KS when given immunosuppressive therapy for polymyositis | IVIg 0.4 g/kg per day for 5 days (Sandoglobulin®, Sandoz, Switzerland) adjunctive to low-dose PD | Case report   | [327] | Kaposi’s sarcoma (KS)                     |
|                                                                                 | 2 of 9 (22%) patients had stabilization of disease (one for 8 months)            | IVIg 1 g/kg (VIGAM® LIQUID, BPL, UK, contains 0.5 g sucrose per gram of immunoglobulin) given over a 1- to 3-day period at a maximum dose of 25 g/day for up to 8 h, every 3 weeks (during 3 or 6 months in case of nonprogression according to CT/ MRI) adjunctive to standard therapy | Uncontrolled trial | [328] | Metastatic melanoma                       |
| No mucositis after MTX treatment followed by IVIg in both cases                  | 15-year-old male and a 5-year-old girl, who developed grade 3 mucositis after every course of MTX | 0.2 g IVIg/kg applied 27 h after the 24-h MTX infusion                                                              | Case report   | [329] | Chemotherapy-induced oral mucositis       |
| Complete remission of thymoma after 4 cycles of IVIg confirmed by FDG-PET       | A patient with metastatic malignant thymoma and myasthenic crisis                | IVIg                                                                                                                   | Case report   | [330] | Thymus carcinoma                          |
| Case 1 developed immunodeficiency 2 years after the resection of thymoma, maintained with IVIg and low-dose CS; case 2 was maintained with IVIg and was stable but developed Kaposi sarcoma 3 years afterwards | Case 1—a 51-year-old woman Case 2—an 89-year-old man | Monthly IVIg 0.4 g/kg                                                                                                  | Case report   | [331] | Thymoma and immunodeficiency (Good syndrome) |
Hashimoto’s encephalopathy

*Level of evidence C* A rare case of autoimmune encephalopathy during thyrotoxic phase of Hashimoto’s disease only partially responded to immunosuppressive therapy with adjuvant intravenous immunoglobulin (*strength of recommendation IIb*).

X-linked adrenoleukodystrophy

*Level of evidence B* Therapeutic efforts including dietary therapy and immunomodulation with IVIg fail to improve prognosis in patients with X-linked adrenoleukodystrophy and BMT remains the only treatment that can reverse early neurological manifestations and adrenal impairment of ALD (*strength of recommendation III*).

Waterhouse–Friderichsen syndrome

*Level of evidence C* No evidence supports the use of IVIg in Waterhouse–Friderichsen syndrome due to meningococcal sepsis (*strength of recommendation III*).

Autoimmune polyendocrine syndrome

*Level of evidence C* No evidence supports the use of IVIg in autoimmune polyendocrine syndrome type 2 (*strength of recommendation IIb*).

The following conditions refer to (Table 12).

Acute disseminated encephalomyelitis

*Level of evidence C* There is weak evidence coming out from several case reports that IVIg may be a useful treatment option either as a combination therapy with CS or in cases that steroid treatment fails (*strength of recommendation I*)

Adrenoleukodystrophy

*Level of evidence B* Taking into consideration the limited evidence (one RCT) and the unfavorable effect of IVIg treatment, at this point, IVIg should not be used as treatment of adrenoleukodystrophy (*strength of recommendation III*).

Amyotrophic lateral sclerosis

*Level of evidence C* No benefit was observed from the use of IVIg in two case series. Considering the weak evidence and the negative outcome, IVIg is not recommended for the treatment of amyotrophic lateral sclerosis (*strength of recommendation III*).

Autism

*Level of evidence C* The use of IVIg in autism is only limited to case series and the effect is questionable. IVIg is not recommended at the moment for the treatment of autism (*strength of recommendation III*).

Chronic inflammatory demyelinating polyneuropathy

*Level of evidence A* Several RCTs evaluated the effectiveness of IVIg. The results of these studies are strongly pointing to the useful effect of IVIg in patients with chronic inflammatory demyelinating polyneuropathy. IVIg should be considered as an additional option in combination with other immunosuppressive agents (*strength of recommendation I*).

Opsoclonus myoclonus

*Level of evidence C* In this rare syndrome, IVIg was reported in several case reports and a retrospective study proved that it induced significant response. Although there is no strong evidence, IVIg may be considered as an additional option in treatment of opsoclonus myoclonus (*strength of recommendation I*).

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections PANDAS

*Level of evidence B* Results coming from one small RCT testing the effect of IVIg showed significant improvement in symptoms; therefore, IVIg is recommended as an additional option for treatment of PANDAS (*strength of recommendation I*).

Multiple sclerosis

*Level of evidence A* Data from several RCTs and a meta-analysis showed significant differences between IVIg and placebo favoring the use of IVIg in relapsing–remitting multiple sclerosis (MS). On the other hand, a recent RCT including 127 patients with relapsing–remitting MS treated with IVIg or placebo showed no significant difference in the proportion of relapse-free patients among treated groups. Another recent RCT including 231 patients showed that IVIg can delay progression of disease in primary chronic progressive MS but no significant difference in progression was noted for secondary chronic progressive MS. To conclude, IVIg may be used as an alternative therapy in relapsing–remitting MS and in primary chronic progressive MS when standard immunosuppression therapy fails (*strength of recommendation IIb*).
Table 11 The use of intravenous immunoglobulins in endocrine disorders

| Results/response                                                                 | Number of patients                          | Intervention including dose and IVIg preparation used | Study design          | Ref     | Disease                                      |
|---------------------------------------------------------------------------------|---------------------------------------------|------------------------------------------------------|-----------------------|---------|---------------------------------------------|
| 21 of 26 patients showed improvement of the mean Neuropathy Impairment Score (NIS) from 61.5±26.0 to 33±29.6 (p<0.001); improvement of NIS was more frequent in patients with a conduction block (100%) vs. in those who did not (66.7%; p=0.03); relapses occurred less in the responders who had a conduction block (9.1%) vs. in those who did not (50%; p=0.04) Reached 80% reduction of pains and significant recovery of muscle strength | 26 patients with DDP evaluated at baseline, at the end of 4 weeks of IVIg therapy, afterwards every few months, mean follow-up period of 25 months. | IVIg 0.4 g/kg for 5 days | Prospective open label | [332] Diabetic demyelinating polyneuropathy |
| All defective cranial nerve findings disappeared during the 1st month and did not recur during 8 months of follow-up | A 57-year-old man with type 2 diabetes and painful proximal diabetic neuropathy with muscle weakness and atrophy | IVIg 0.4 g/kg for 5 days | Case report [333] | Proximal diabetic neuropathy |
| 5 days after IVIg easy fatigability of thigh disappeared and of the strength of shoulder girdle muscle improved; 1 year after IVIg treatment, there was normal muscle strength and significant improvement of atrophy | A 55-year-old woman, with 12-year history of DM, developed simultaneous right VII and left III, IV, and VI cranial nerve pulses | IVIg 0.4 g/kg for 5 days | Case report [334] | Cranial nerve neuropathy in diabetes mellitus |
| Rapid improvement of fasting serum glucose levels, stabilization of renal function, and decrease in the donor-specific class II antibodies | A 45-year-old man with IDDM and diabetic amyotrophy | IVIg 0.4 g/kg per day for 5 days | Case report [335] | Diabetic amyotrophy |
| Partial response to IVIg and complete resolution of weakness after CP, asymptomatic after 1 year without treatment | A 44-year-old man with long-standing poorly controlled IDDM | 3 doses of 0.5 g/kg per day of IVIg, started on day 14 posttransplant and given every other day adjunctive to standard posttransplant therapy, plasmapheresis, and rituximab | Case report [336] | Pancreas allograft rejection |
| Within 10 weeks after IVIg, muscle weakness and sensory disturbances disappeared, but tendon reflexes stayed slightly depressed; the patient was treated with IVIg every 3 months due to IVIg-dependent course | A 17-year-old man with known IDDM and a subclinical Hashimoto’s thyroiditis and a new onset of asymmetric weakness and atrophy in arms | Monthly infusions of IVIg 0.4 g/kg per day for 5 consecutive days followed by 6 cycles of CP 1 g/m² | Case report [337] | Multifocal motor neuropathy, type 1 diabetes, and Hashimoto’s thyroiditis |
| Partial response to CS and IVIg and antiepileptic medication (probably due to lowering of seizure threshold by antithyroid drugs and beta-blockers); continued with immunosuppressive therapy (high-dose CS and AZA) but relapsed after 2 months, recovered after thyroidectomy | A 64-year-old man with clinical and laboratory findings supportive for MMN, high titers of anti-GM1-Abs and subclinical Hashimoto’s thyroiditis | IVIg 0.4 g/kg per day for 5 days, repeated every 3 months due to IVIg-dependent course of the disease | Case report [338] | Multifocal motor neuropathy and Hashimoto’s thyroiditis |
| Partial response to CS and IVIg and antiepileptic medication | A 34-year-old woman with encephalopathy and thyrotoxic Hashimoto’s thyroiditis | IVIg 2 g/kg in 3 days adjunctive to high-dose CS and plasmapheresis | Case report [339] | Thyrotoxic autoimmune encephalopathy |
| See ophthalmology section | | | | | Grave’s ophthalmopathy |
Guillain–Barré

*Level of evidence A* There is strong evidence, several randomized controlled trials, and a meta-analysis that prove that IVIg is of benefit in improving the disability grade in patients with Guillain–Barré syndrome. No significant difference between IVIg and PP was found. IVIg should be considered as a treatment option in Guillain–Barré syndrome (*strength of recommendation I*).

Paraproteinemic neuropathy (IgM)

*Level of evidence A* There is no reliable evidence to recommend the use of IVIg in paraproteinemic neuropathy. A restricted number of RCT’s and a systematic review showed only modest benefit with IVIg in the short term (*strength of recommendation IIb*).

Lambert–Eaton myasthenic syndrome

*Level of evidence B* A single small RCT showed significant improvement in patients suffering from Lambert–Eaton myasthenic syndrome with the use of IVIg compared to placebo. Therefore, it is acceptable to consider the use of IVIg in this rare and severe neurological syndrome (*strength of recommendation I*).

Stiff-person syndrome

*Level of evidence B* Data from a small randomize control trial and several case reports showed that the use of IVIg led to significant improvement in patients with stiff-person syndrome and was superior to placebo. IVIg should be considered as a treatment option in this syndrome especially if the first-line treatment fails (*strength of recommendation I*).

Intractable childhood epilepsy

*Level of evidence A* Two RCTs investigated the efficacy of IVIg in patients with intractable childhood epilepsy compared with placebo. Results from these studies do not support benefit from the use of IVIg. Therefore, IVIg is not recommended for the treatment of intractable childhood epilepsy (*strength of recommendation III*).

Critical illness polyneuropathy

*Level of evidence C* There is no reliable evidence (level of evidence C-III) to recommend the use of IVIg in the treatment of critical illness polyneuropathy (*strength of recommendation III*).
Table 12  The use of intravenous immunoglobulins in neurological diseases

| Disease                  | Ref.     | Study design | Intervention including dose and IVIg preparation used | Number of patients | Results/response                                                                 |
|-------------------------|----------|--------------|--------------------------------------------------------|--------------------|----------------------------------------------------------------------------------|
| Opsoclonus myoclonus    | [344]    | Case reports | IVIg 3 doses of 0.3 g/kg over 4 months + rituximab     | 2 patients        | Significant clinical improvement without relapses                                |
|                         | [345]    | Case report  | IVIg 0.4 g/kg per day for 5 days + prednisolone +     | A 41-year-old woman | Complete recovery                                                                 |
|                         |          |              | clonazepam                                            | with idiopathic    |                                                                                  |
|                         | [346]    | Case report  | IVIg 30 g/day for 5 days with 5 repeated doses after  | A 36-year-old man  | Accelerated recovery                                                              |
|                         |          |              | 2 months + CS                                         | with parainfectious|                                                                                  |
|                         | [347]    | Case report  | IVIg + ACTH + CS                                      | A patient with     | Partial recovery                                                                  |
|                         |          |              |                                                       | childhood-onset    |                                                                                  |
|                         | [348]    | Case report  | IVIg initially 5.5 g and 6 additional courses at a     | A 22-month-old girl| Partial recovery                                                                  |
|                         |          |              | dosage of 2.5 g and 7 courses at a dosage of 5 g      | with neuroblastoma-|                                                                                  |
|                         |          |              | every 2 to 3 weeks + ACTH                             | associated         |                                                                                  |
|                         | [349]    | Case report  | IVIg + ACTH                                           | A 27-year-old woman| Complete recovery                                                                  |
|                         |          |              |                                                       | with severe        |                                                                                  |
|                         | [350]    | Case report  | IVIg 1 g/kg for 2 days with 12 additional doses given  | An 18-month-old    | Complete recovery                                                                 |
|                         |          |              | every 4–6 weeks                                       | black girl         |                                                                                  |
|                         |          |              |                                                       | with neuroblastoma-|                                                                                  |
|                         | [351]    | Case report  | High-dose IVIg                                        | A 14-month-old     | Complete recovery                                                                  |
|                         |          |              |                                                       | male with infantile|                                                                                  |
|                         | [352]    | Retrospective| IVIg + CS                                             | 9 patients with     | Idiopathic opsoclonus myoclonus: 2/9 complete recovery, 1/9 partial recovery, 2/9 |                                                                                  |
|                         |          | study       |                                                       | idiopathic and     | remission                                                                         |
|                         |          |              |                                                       | paraneoplastic      |                                                                                  |
|                         |          |              |                                                       | opsoclonus myoclonus|                                                                                  |
| PANDAS                  | [353]    | RCT          | IVIg 1 g/kg per day for 2 days vs PP vs placebo       | 29 children        | At 1 month, significant improvement in global impairment (p=0.0009), obsessive-  |
|                         |          |              |                                                       | with severe         | compulsive symptoms (p=0.006), anxiety (p=0.001), depression (0.002); at       |                                                                                  |
|                         |          |              |                                                       | infection-triggered| 1 year, more than 80% of patients receiving IVIg or PP remained improved         |                                                                                  |
|                         |          |              |                                                       | exacerbations of    |                                                                                  |
|                         |          |              |                                                       | obsessive-compulsive|                                                                                  |
|                         |          |              |                                                       | disorder (OCD) or   |                                                                                  |
|                         |          |              |                                                       | tic disorders,     |                                                                                  |
| Multiple sclerosis (MS) | [354]    | RCT          | IVIg 0.2 g/kg–0.4 g/kg every 4 weeks for 48 weeks     | 127 patients       | At 1 year, there was no significant difference in the proportion of relapse-    |
|                         |          |              |                                                       | vs placebo          | free patients among treated groups                                               |                                                                                  |
|                         | [355]    | RCT (primary | IVIg 0.4 g/kg per month for 24 months vs placebo      | 231 patients       | IVIg can delay progression of disease in primary chronic progressive MS; no     |
|                         |          | and secondary|                                                       | with primary       | significant difference in progression was noted for secondary chronic          |
|                         |          | chronic      |                                                       | (PPMS) and secondary|(SPMS) chronic progressive MS; no improvement in neurological functions with    |
|                         |          | progressive  |                                                       | (SPMS) chronic      | IVIg                                                                           |
|                         |          | MS)          |                                                       | progressive MS      |                                                                                  |
Table 12 (continued)

| Disease                      | Ref.     | Study design                  | Intervention including dose and IVlg preparation used | Number of patients | Results/response                                                                                                                                 |
|------------------------------|----------|-------------------------------|------------------------------------------------------|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| [356] RCT (secondary progressive MS) | Monthly IVlg 1 g/kg for 27 months vs placebo | 34 patients with secondary progressive (SP) MS | No reduction in the relapse rate or the progression of disability |
| [357] Retrospective study (relapsing–remitting MS) | IVlg treatment at a mean time of 3.4±1.8 years at a mean dose of 15.5±8.3 g/month | 308 patients with RRMS | 69% reduction of mean annual relapse rate was observed after IVlg treatment initiation |
| [358] RCT (secondary progressive MS) | IVlg 1 g/kg per month for 27 months vs placebo | 318 patients with secondary progressive multiple sclerosis | No effect on the time to confirmed progression on the EDSS, annual relapse rate, and the change in T2 lesion load on MRI |
| [359] Meta-analysis | IVlg 0.15–2 g/kg for 12–24 months vs placebo | 4 RCT (265 patients with RRMS) | Significant beneficial effect: on the annual relapse rate (p=0.00003), on the proportion of relapse-free patients (p=2.1×10⁻⁸) |
| [360] RCT | IVlg 0.15–0.2 g/kg per month for 2 years vs placebo | 148 patients with RRMS | Progression of disability was reduced in 24% of the patients with therapeutic efficacy to be noted in the first 6 months of the treatment |
| [361] RCT (relapsing remitting MS) | IVlg 0.4 g/kg for 5 days followed by once every 2 months for 2 years vs placebo | 40 patients with RRMS | Reduction in yearly exacerbation rate (p=0.0006 (overall)) |
| [362] RCT (relapsing remitting MS) | IVlg 1 g/kg for 2 days every 4 weeks for 24 weeks vs placebo | 17 patients with relapsing–remitting or relapsing progressive multiple sclerosis | 11 had no exacerbations during IVlg treatment compared with only 6 on placebo (p=0.05) |
| Guillian–Barré syndrome (GBS) | Systematic review meta-analysis | IVlg 0.2–1 g/kg per day for 2–6 days vs PP vs immunoabsorption vs supportive care | 11 RCT (913 patients) | Improvement on the disability grade scale with intravenous immunoglobulin (IVlg), weighted mean difference WMD of 0.02 (95% confidence interval (CI) 0.25 to 0.2); no significant difference between IVlg and plasma exchange |
| [364] Open-labeled study | IVlg 0.4 g/kg per day for 5 days | 11 patients younger than 15 years old, diagnosed with moderate or severe GBS | After 2 weeks, 72.7% of patients improved by one or more grades and 36.4% improved by 2 or more grades, measured on the Hughes’ functional grade FG scale |
| [365] RCT | IVlg 0.4 g/kg per day for 3 or 6 days | 39 patients with Guillian–Barré syndrome | No significant difference in time to assisted walking in the 2 groups (p=0.08); significantly shorter time |
Table 12  (continued)

| Disease                          | Ref.     | Study design            | Intervention including dose and IVIg preparation used | Number of patients | Results/response                                                                 |
|---------------------------------|----------|-------------------------|-------------------------------------------------------|--------------------|---------------------------------------------------------------------------------|
| [366] RCT (IgG anti-GM1-positive subgroup) | IVIg vs plasmapheresis | 24 patients with Guillain–Barré syndrome | IVIg-treated patients had: significantly lower Hughes grade scores 1, 3, and 6 months after onset ($p=0.03$); higher probability to regain independent locomotion at 6 months ($p=0.044$); more frequent rapid recovery within 4 weeks ($p=0.03$) |
| [367] RCT                        | IVIg 0.4 g/kg per day for 5 days vs plasma exchange | 379 adult patients with Guillain–Barré syndrome | IVIg is equivalent to plasmapheresis in reducing the amount of disability at 4 weeks after treatment |
| [368] RCT                        | IVIg 0.4 g/kg per day for 5 days vs plasma exchange | 150 patients with Guillain–Barré syndrome | 53% of patients treated with IVIg improved compared to 34% in the PP group ($p=0.024$) |
| Paraproteinemic neuropathy (IgM) | Systematic review | 5 trials (97 patients with IgM antmyelin-associated glycoprotein paraproteinemic neuropathy) | 2 trials with 33 patients suggest that IVIg may sometimes produce short-term benefit (in terms of improvement in Modified Rankin Scale at 2 weeks and 10-m walk time at 4 weeks) and is relatively safe |
| [370] Crossover RCT               | IVIg 2 g/kg over 1 to 2 days vs placebo | 22 patients with paraproteinemic demyelinating neuropathy | After 4 weeks, the overall disability significantly decreased during the IVIg period ($p=0.001$) compared to the placebo period where it was unchanged; the mean difference between the treatment effects was significant ($p = 0.05$) |
| [371] Crossover RCT               | IVIg vs placebo given monthly for 3 months | 11 patients with demyelinating polyneuropathy associated with monoclonal IgM antibodies | Modest benefit with IVIg |
| Amyotrophic lateral sclerosis    | Case series | IVIg 0.4 g/kg per day for 5 days followed by monthly 2-day infusions + CP | 7 patients with amyotrophic lateral sclerosis | All patients worsened according to MRC and/or bulbar and/or Rankin scores |
| [373] Case series                | IVIg monthly for 3 months | 9 patients with rapidly progressive amyotrophic lateral sclerosis | All patients worsened after 3 months with decrease in mean total muscle scores (megascores) |
| Lambert–Eaton myasthenic syndrome | Crossover RCT | IVIg 1 g/kg per day for 2 days vs placebo | 9 with Lambert–Eaton myasthenic syndrome | IVIg showed significant improvements in limb, respiratory, and bulbar muscle strength measures ($p=0.017$ to 0.038) and a significant decline in serum calcium channel antibody titers ($p=0.028$) |
| Disease                      | Ref.    | Study design | Intervention including dose and IVIg preparation used                                                                 | Number of patients | Results/response                                                                                                                                 |
|------------------------------|---------|--------------|-----------------------------------------------------------------------------------------------------------------------|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Stiff person syndrome        | [375]   | Case series  | IVIg                                                                                                                   | 3 patients        | Improvement after treatment                                                                                                                   |
|                              | [376]   | Uncontrolled | IVIg                                                                                                                   | 3 patients        | Improvement after treatment                                                                                                                   |
|                              | [377]   | Case report  | IVIg                                                                                                                   | 1 patient         | Long-term remission after treatment                                                                                                           |
|                              | [378]   | Crossover    | IVIg 2 g/kg once a month for 3 months vs placebo                                                                     | 14 patients        | Improvement after treatment                                                                                                                   |
| Adrenoleukodystrophy         | [379]   | RCT          | IVIg 1 g/kg per day every 15 days for 3 months and every month for 1 year + VLCFA-restricted diet + GTOE vs VLCFA-restricted diet + GTOE | 12                 | No significant differences in deterioration of neurological symptoms in the 2 groups according to EDSS score                                    |
| Intractable childhood epilepsy| [380]   | RCT          | IVIg 0.1–0.4 g/kg (7 infusions in 6 weeks total time) vs placebo                                                      | 61 patients        | No significant difference between the groups studied; no relationship between IVIg dose and efficacy                                      |
|                              | [381]   | Crossover    | IVIg 0.4 g/kg (Sandoglobulin) 2 infusions each with an interval of 2 weeks vs placebo                                 | 10 patients        | 2/10: immediate reduction in their high-frequency and invariable seizure activity from 42% to 100% and a less abnormal EEG |
|                              |         | RCT          |                                                                                                                       |                   | 8/10: unchanged general condition, no EEG changes                                                                                              |
| Critical illness polyneuropathy | [382]  | Retrospective | IVIg 0.3 g/kg per day for 3 days                                                                                     | 16 patients        | 8/16 patients of multi-organ failure with sepsis without the development of critical illness polyneuropathy had been treated with IVIg immediately after the diagnosis of sepsis |
|                              |         | chart analysis |                                                                                                                       |                   | 7/16 who eventually developed critical illness polyneuropathy were not treated with IVIg                                                      |
|                              | [383]   | Case series  | IVIg                                                                                                                   | 3 patients        | No improvement after treatment                                                                                                                 |
| Rasmussen’s encephalitis     | [384]   | Case series  | IVIg, CS, CP, therapeutic PP (TPE), protein A, immunoglobulin G (IgG), immunoadsorption (PAI)                          | 15 patients        | In 11 patients treated with IVIg, 1 had reduction of seizure frequency by >50% and improvement of neurologic condition or resolution of status epilepticus and 2 had reduction of seizure frequency by up to 50%; in the rest, 5 had no effect and in the 3 effect was not assessable |
|                              | [385]   | Case report  | IVIg 0.4 g/kg per day for 5 days once a month                                                                       | 1 patient         | Improvement after IVIg therapy with a >75% reduction in seizures and                                                                         |
| Disease                                      | Ref. | Study design | Intervention including dose and IVIg preparation used | Number of patients | Results/response                                                                 |
|---------------------------------------------|------|--------------|-------------------------------------------------------|--------------------|----------------------------------------------------------------------------------|
| [386] Case reports                          |      | IVIg 0.4 g/kg per day for 5 days once a month       | 2 patients with advanced adult-onset Rasmussen's encephalitis |                    | mild improvement in neurologic performances                                      |
| [387] Case series                           |      | IVIg ± high-dose CS                                 | 19 patients with Rasmussen’s encephalitis                |                    | Significant improvement in seizure control, hemiparesis, and cognition           |
| Chronic inflammatory demyelinating polyradiculoneuropathy | [388] Crossover RCT                                                                                     | IVIg 1 to 2 g/kg over 1 to 2 days every 3 weeks for 24 weeks vs placebo | 117 patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) | 54% of patients treated with IVIg and 21% treated with placebo improved according to INCAT disability score ($p=0.0002$); IVIg patients had a longer relapse time compared with placebo ($p=0.011$) in the extension phase |
| [389] Crossover RCT                          |      | IVIg 2 g/kg over 1 to 2 days vs oral prednisolone for 6 weeks | 24 patients with CIDP                                    |                    | Both treatments showed marked improvement in INCAT disability scores after 2 weeks; no significant difference between the 2 treatments |
| [390] RCT                                   |      | IVIg 1 g/kg per day for 2 days vs placebo           | 53 patients with untreated CIDP                          |                    | Average muscle score (AMS) was significantly improved in the IVIg group ($p=0.0006$) at day 42; IVIg significantly improved nerve conduction; according to Hughes’ functional disability scale IVIg group showed better improvement than placebo ($p=0.019$) |
| [391] Crossover RCT                          |      | IVIg 0.4 g/kg per day for 5 days vs placebo         | 30 patients with definite or probable CIDP of chronic progressive (16 patients) or relapsing (14 patients) course |                    | At 4 weeks, significant improvement with IVIg in neurological disability score (NDS; $P<0.0001$) in clinical grade (CG; $P<0.002$) and in grip strength (GS; $P<0.001$); significant improvement in summed MCV ($P<0.0001$) and in summed (CMAP) amplitudes ($P<0.03$) |
| Myasthenia gravis                            | [392] Systematic review                      | IVIg vs no treatment or placebo or plasma exchange     | 6 RCT ($n=371$)                                          |                    | There is insufficient evidence to determine the efficacy of IVIg in myasthenia gravis |
| [393] RCT                                   |      | IVIg 2 g/kg over 2 days vs placebo                  | 51 patients with worsening weakness due to myasthenia gravis |                    | According to quantitative myasthenia gravis (QMG) score at day 14, there was a significant improvement in the IVIg group ($p=0.047$) which continued at day 28 |
| [394] RCT                                   |      | IVIg 2 g/kg vs placebo                               | 15 patients with myasthenia gravis                      |                    | No significant differences between the 2 groups were cleared |
### Table 12 (continued)

| Disease                                    | Ref. | Study design | Intervention including dose and IVIg preparation used | Number of patients | Results/response |
|--------------------------------------------|------|--------------|--------------------------------------------------------|--------------------|------------------|
| Acute disseminated encephalomyelitis       | [397] Case report | IVIg 2 g/kg once and repeat bolus of 150 g on week 3 and 4; previous treated with CS with no response | A 20-year-old male with postvaccination acute disseminated encephalomyelitis | 1 patient treated with IVIg and 10 patients treated with CS alone had complete response; from 5 patients treated with combined therapy, 2 had complete response and 3 partial or no response | Rapid response with partial recovery over 1 year |
| Acute disseminated encephalomyelitis       | [398] Case series | IVIg 2 g/kg over 2 days or MP or IVIg 2 g/kg over 2 days + MP | 6 children with severe acute disseminated encephalomyelitis | 1 patient treated with IVIg and 10 patients treated with CS alone had complete response; from 5 patients treated with combined therapy, 2 had complete response and 3 partial or no response | |
| Acute disseminated encephalomyelitis       | [399] Case series | IVIg 0.4 g/kg per day for 5 days | 5 adult patients, 3 of them affected by classic disseminated encephalomyelitis and 2 by a postinfectious myelitis | Marked functional improvement in all patients starting from day 5 with maximum effect at 3 weeks | |
| Acute disseminated encephalomyelitis       | [400] Case report | IVIg + CS for 3 days | A child with atypical acute disseminated encephalomyelitis | Complete response | |
| Acute disseminated encephalomyelitis       | [401] Case report | IVIg + CS | A 3-year-old boy with severe acute disseminated encephalomyelitis | Complete response | |
| Acute disseminated encephalomyelitis       | [402] Case reports | IVIg 30 g/day for 5 days and 3 additional monthly courses of 30 g + CS IVIg 50 g/d for 2 days + CS. | 2 adult women with acute disseminated encephalomyelitis | Complete response in both patients | |
| Autism                                     | [403] Case series | IVIg 0.04 g/kg monthly for 6 months | 7 patients with childhood autism | No statistically significant changes on behavioral measures after 6 months | |

PANDAS pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections

### Rasmussen’s encephalitis

**Level of evidence C** There is weak evidence indicating significant benefit of IVIg in Rasmussen’s encephalitis either used as monotherapy or combined with other therapies. It should be considered as one of the treatment options in this disease *(strength of recommendation I)*.

### Myasthenia gravis

**Level of evidence A** Several RCTs and a meta-analysis examined the efficacy of IVIg in patient with myasthenia gravis. Results are conflicting. A recent meta-analysis concluded that there is insufficient evidence to determine the efficacy of IVIg in myasthenia gravis. IVIg may be used as treatment for myasthenia gravis.
### Table 13: The use of intravenous immunoglobulins in immunodeficiencies

| Disease                                | Ref.   | Study design | Intervention including dose and IVIg preparation used                                                                 | Number of patients | Results/response                                                                                                                                                                                                                                                                                                                                 |
|----------------------------------------|--------|--------------|------------------------------------------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| X-linked agammaglobulinemia (XLA)      | [404]  | Retrospective trial | IVIg was given at doses of >0.25 g/kg every 3 weeks (mean individual residual IgG levels of 700 mg/dl); 24 patients received IVIg from the “Establissements de Transfusion Francais,” others Sandoglobulin (Novartis Institute, Basel) and Endoglobulin (Immuno France, Marseilles) for 3,690 cumulated months | 31 patients with XLA at mean age of 24 months followed for a median time of 123 months | The incidence of bacterial infections requiring hospitalization fell from 0.4 to 0.06 per patient year \( (p<0.001) \); the incidence of bacterial infections requiring hospitalization was lower for the periods when patients had residual level of IgG>800 mg/dl than for the period of levels <800 mg/dl \( (p<0.001) \); however, viral or unidentified infections still developed (enteroviral meningitis 3, exudative enteropathy 3, aseptic arthritis 1); at last follow-up, 30 patients were alive at median age of 144 months (range, 58 to 253) |
|                                        | [405]  | Retrospective trial | Patients were treated with different regiments of IVIg between 1965 and 1990; 20 patients were treated before any IVIg was available; 14 patients received IMIg in dose of <0.1 g/kg every 3 weeks; 9 patients were treated at dosages up to 0.2 g/kg every 3 weeks; 15 patients received IVIg at dosages between 0.35 and 0.6 g/kg every 3 weeks (patients receiving different replacement regiments were assigned to more than one group if they received respective regimen for a minimum of 1 year) | 29 patients with XLA | A significant increase in trough serum IgG \( (p=0.0001) \) and a significant decrease in the incidence of pneumonias \( (p=0.038) \) and number of days spent in the hospital in high-dose IVIg group compared with other groups \( (p=0.005) \); improvement in therapeutic outcome was particularly evident when high-dose IVIg was started before the age of 5; bacterial meningitis, chronic pulmonary disease, and bronchiectasis occurred in IMIg but not in any of IVIg groups |
|                                        | [406]  | Retrospective trial | IVIg 0.3–0.4 g/kg every 3 to 4 weeks                                                                                                                                              | 23 patients with XLA treated with IVIg for a mean period of 6.8±4.1 years | Significant decrease of the incidence of pneumonia requiring treatment or hospitalization \( (p=0.006) \) and hospitalizations due to pneumonia \( (p=0.08) \) |
|                                        | [407]  | RCT           | GamaSTAN 20 ml in 2 IM injections every 4 weeks vs. 0.15 g/kg IVIg every 4 weeks (Cutter Laboratories, Inc., Berkeley, CA, USA) during 242 months of treatment                                                                 | 22 patients with antibody deficiency (9 with XLA); 14 (5 with XLA) received IVIg, 13 (7 with XLA) received ISg; 7 patients (3 with XLA) received both ISg and IVIg in separate courses | Less acute infections per month of treatment in IVIg group \( (p<0.01) \); in XLA subgroup, mean 0.8 vs. 2.7); in patients who received separate courses of both IVIg and ISg, infection rate was lower on IVIg \( (p<0.05) \); in XLA subgroup, mean 0.3 vs. 4.7 |
|                                        | [408]  | RDB crossover | Standard-dose IVIg (adults 300 mg/kg and children 0.4 g/kg every 4 weeks) for 9 months, followed by 3-month washout period and                                                            | 41 patients with primary hypogammaglobulinemia (19 patients with XLA) | High-dose therapy significantly reduced the number (mean, 3.5 vs. 2.5 per patient \( p=0.004) \) and 4.3 vs. 3.4 in XLA |
| Disease                              | Ref.         | Study design     | Intervention including dose and IVlg preparation used                                                                 | Number of patients | Results/response                                                                                                                                 |
|-------------------------------------|--------------|------------------|--------------------------------------------------------------------------------------------------------------------------|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Wiscott–Aldrich syndrome (WAS)      | [409]        | Retrospective    | 21 patients with WAS                                                                                                    | 21 patients with WAS | Only 4 episodes of severe acute bacterial infection in 451 patient months after splenectomy                                                        |
| Hyper-IgE syndrome (Job syndrome)   | [410]        | Case series      | IVIg 0.18–0.58 g/kg every 2–4 weeks and antibiotic prophylaxis with acyclovir and/or fluconazole in some cases          | 3 adult patients with hyper-IgE syndrome                          | Marked improvement in tendency to infections                                                                                                  |
|                                     | [411]        | Case report      | Monthly IVIg and interferon gamma, three times a week since age 3; he received also prophylaxis with antibiotic and fluconazole | 15-year-old boy with hyper-IgE syndrome                          | Good control of disease                                                                                                                       |
|                                     | [412]        | Case report      | IVIg 2 g/kg (Venoglobulin I-Alpha Therapeutic Corporation, Los Angeles, CA, USA) monthly for 7 courses                  | Patient with hyper-IgE syndrome                                   | No improvement                                                                                                                                   |
| IgG subclass deficiencies           | [413]        | Case series      | IVIg                                                                                                                     | 8 children with recurrent infections, failure to thrive, hypergamma globulinemia and IgG2 subclass deficiency | Clinical resolution                                                                                                                            |
|                                     | [414]        | Case series      | IVIg (Sandoglobulin) 6–12 g monthly                                                                                  | 3 members of a family (2 children, 1 adult) with recurrent severe respiratory infections and IgG2 subclass deficiency | Clinical resolution                                                                                                                            |
| Specific antibody deficiency        | [415]        | Case report      | IVIg monthly 7 courses                                                                                                   | A-6-year old child with chronic rhinosinusitis, nasal polyps and IgG3 deficiency            | Clinical improvement                                                                                                                          |
|                                     | [416]        | Case report      | IVIg monthly                                                                                                            | A 2-year-old child with recurrent sinopulmonary infections and IgG2 deficiency                  | Clinical improvement                                                                                                                          |
|                                     | [417]        | Cases report     | IVIg 10–15 g every 3 weeks for 6 months                                                                              | 2 patients with treatment-resistant osteomyelitis of the jaw, one with IgG2 deficiency, and the other with IgG3 deficiency | Clinical improvement in both patients                                                                                                           |
|                                     | [418]        | Retrospective    | Part of this patients received IVIg                                                                                   | 75 patients with recurrent infections and low response to pneumococcal polyvalent vaccine     | Reduction in number of infections                                                                                                               |
|                                     | [203]        | Series report    | IVIg                                                                                                                     | 9 children with recurrent sinopulmonary infections and poor response to *Haemophilus influenza* type b capsular polysaccharide | Reduction of infections upon start of IVIg treatment and recurrence after discontinuation                                                      |
|                                     | [419]        | Case report      | IVIg                                                                                                                     | Patient with Smith–Lemli–Opitz syndrome, frequent infections and absent response to Pneumovax | Same frequency of infections, less severity                                                                                                    |
| Disease                        | Ref.  | Study design | Intervention including dose and IVIg preparation used | Number of patients | Results/response                                                                                                                                 |
|-------------------------------|-------|--------------|--------------------------------------------------------|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| Hyper-IgM syndrome (HIGM)     | [420] | Case control study | IVIg was administered every 4 weeks and serum IgG levels were consistently maintained above 4 or 5 g/l in most patients | 29 patients with HIGM due to activation-induced cytidine deaminase deficiency, suffering from recurrent infections | After IVIg therapy was initiated, frequency of infections markedly decreased                                                                 |
|                               | [421] | Case control  | IVIg                                                   | 9 patients with HIGM and recurrent infections | Regression in the manifestations of infection                                                                                                             |
|                               | [422] | Case control  | IVIg, 0.25–0.3 g/kg every 4 weeks for 1 year          | 6 patients with HIGM and recurrent infections | Severity and frequency of infections decreased significantly                                                                                             |
|                               | [423] | Case report   | IVIg with antibiotics, chloroquine, and PD            | A 6-year-old with HIGM and severe recurrent respiratory infections | Mild improvement with a decrease in the inflammatory infiltrate in thoracoscopic biopsy                                                                 |
|                               | [424] | Case report   | IVIg and prophylactic antibiotic therapy              | A 6 years old with CD40 ligand deficiency, chronic neutropenia, and HIGM | Management of neutropenia, better quality of life with decreasing occurrence of infection                                                               |
| Transient hypogamma of infancy (THI) | [425] | Case report   | IVIg                                                   | A 5-month-old boy with HIGM and severe pneumonia refractory to antibiotics | His pneumonia improved; after that, he had no recurrent infections                                                                                       |
|                               | [426] | Case report   | IVIg every 4 weeks                                    | 1-year-old girl with THI and *Staphylococcus aureus* sepsis refractory to antibiotics | Gradual improvement                                                                                                                                 |
| Severe combined immunodeficiency (SCID) | [427] | Case report   | Treated with antibiotics and IVIg                     | 1-year-old boy with THI and recurrent sepsis | Fewer infections                                                                                                                                 |
| Common Variable Immune Deficiency (CVID) | [428] | Case control  | Monthly IVIg                                           | 45 children surviving BMT for SCID | Effective as adjuvant for BMT                                                                                                                     |
|                               | [429] | Case series   | The number of pneumonia episodes was compared prior to and after initiation of IVIg maintenance therapy for 6.6±5.2 years (0.3–0.4 g/kg every 3 to 4 weeks) | 50 patients with confirmed CVID | Prior to IVIg therapy, 84% of patients had an episode of pneumonia, and 22% had recurrent pneumonias; following IVIg administration, 22% of the patients have acquired pneumonia; this change was found to be statistically significant (p<0.001) |
|                               | [33]  | Case series   | Data were collected retrospectively; all the patients were treated by 3 modalities: no IVIg, low-dose IVIg (0.2 g/kg every 3 weeks), and standard-dose IVIg (0.4 g/kg every 3 weeks) | 7 patients diagnosed with CVID | Number of infections per patient-year was 5 in the no-IVIg period, 2.79 in the low-dose period (p=0.002), and 1.53 in the standard-dose period (p=0.02); lower respiratory tract infections were markedly decreased due to IVIg therapy |
|                               | [32]  | Case series   | IVIg (Sandoglobulin and/or Nordimmune), 0.4 g/kg every 3 to 4 weeks; the follow-up period was 41.5±35.4 months | 26 patients diagnosed with CVID | IVIg therapy was associated with significant decrease of annual hospitalization due to pneumonia: from 88.5% to 46% (p=0.0025); a significant decrease of total hospital admissions was also observed (from 3.4 to 0.7 per year, p<0.0005) |
severe acute exacerbations (strength of recommendation IIa).

The following conditions refer to (Table 13).

X-linked agammaglobulinemia

Level of evidence B Retrospective analyses revealed that IVIg is beneficial in terms of reduction of acute and chronic infections and days of stay in the hospital. Intravenous route is preferred over intramuscular administration of immunoglobulin and the number and severity of complications are inversely correlated with the dose of IVIg (strength of recommendation I).

Wiscott–Aldrich syndrome

Level of evidence C Despite relatively low evidence of effectiveness of IVIg, the majority of WAS patients are treated with IVIg, which appears to be effective in reduction of acute and chronic infections in these immunodeficient patients (strength of recommendation IIa).

Hyper-IgE syndrome (job syndrome)

Level of evidence C There is weak evidence that IVIg is useful in the treatment of hyper-IgE syndrome. IVIg may be tried in cases in which recurrent life-threatening diseases cannot be controlled by antibiotic prophylaxis (strength of recommendation IIb).

IgG subclass deficiencies

Level of evidence C There is scarce evidence that IVIg is useful in the treatment of IgG subclass deficiencies. Most of the experience reported is patients with IgG2 deficiency. In our opinion, when antibiotic treatment is not effective, IVIg would be a reasonable alternative (strength of recommendation IIb).

Specific antibody deficiency

Level of evidence B This is a heterogeneous group. Specific deficiency of antibodies after vaccination has been found to correlate with infection susceptibility. Most of the published experience regarding IVIg is in patients with deficiency of antibodies to capsular polysaccharide. IVIg has been reported to be beneficial in some cases. This is not surprising as antibodies to bacterial capsular polysaccharide are contained in IVIg [31]. The evidence for the use of IVIg in specific antibody deficiency is not strong but might be warranted when recurrent infection is present and it is possible to demonstrate low antibody responses to a relevant vaccine (strength of recommendation IIa).

Hyper-immunoglobulin-G syndrome

Level of evidence B The hyper-IgM syndrome (HIGM) is a rare hereditary immune deficiency, characterized by a low or nil level of IgG and IgA and a normal or increased level of IgM, predominately affecting boys. Its clinical manifestations are dominated by recurrent infection, notably of the digestive tube, the ears, nose, and throat and the lungs. IVIg may be considered to treat patients with HIGM and recurrent infections (strength of recommendation I).

Transient hypogammaglobulinemia of infancy

Level of evidence C Transient hypogammaglobulinemia of infancy is characterized by a prolongation and accentuation of the physiologic hypogammaglobulinemia normally occurring during the first 3 to 6 months of life and recovers spontaneously between 18 and 36 months of age. Infants with transient hypogammaglobulinemia of infancy (THI) may remain asymptomatic or develop recurrent sinopulmonary infections, but severe or life-threatening infections are rare. In general, supportive and antimicrobial therapies are sufficient management for the treatment of specific infections in patients with THI. In cases in which infections are severe or refractory to conventional therapy, IVIg is sometimes considered although literature reports are lacking (strength of recommendation I).

Severe combined immunodeficiency

Level of evidence B SCID is a severe form of heritable immunodeficiency in which both “arms” of the adaptive immune system are defected. These babies, if untreated, usually die within 1 year due to severe recurrent infections. Treatment with BMT is successful, and IVIg is used as an adjuvant for this therapy (strength of recommendation I).

Common variable immune deficiency

Level of evidence C Common variable immune deficiency (CVID) is an idiopathic hypogammaglobulinemia. World Health Organization diagnostic criteria are well established [32]. Both B and T cells dysfunction have been observed [33]. There are both theoretical logic and experimental evidences that support IVIg administration in CVID (strength of recommendation IIb).

Primary phagocytic defect

Many different genetic diseases will ultimately result in primary phagocytic defect: cyclic neutropenia, severe congenital neutropenia, Shwachman–Diamond syndrome, leu-
kocyte adhesion deficiency, Rac2 deficiency, interferon-γ and IL-12 defects, chronic granulomatous disease, myeloperoxidase deficiency, Chediak–Higashi syndrome, and neutrophil-specific granule deficiency [34]. An extensive PubMed-based search revealed little if any information regarding the efficacy of IVIg in the above entities.

IgA deficiency

IgA deficiency may be associated with preventable anaphylaxis or anaphylactoid reaction following IVlg transfusion [35]. This adverse reaction is encountered in patients with selective IgA deficiency and high titer of anti-IgA antibodies. In those patients, anaphylaxis can be avoided by the use of IgA-depleted IVlg preparation [36].

Discussion

This article summarizes most of the studies dealing with IVlg administration that were publicized until recently. We have included an array of clinical conditions, some in which the use of IVlg is expected according to their pathogenesis, such as primary immunodeficiencies and rheumatic diseases, and others somewhat less obvious indications including cardiac and oncologic diseases. In some diseases, the usage of IVlg was found to be highly recommended (with a level of evidence A and strength of recommendation I): Kawasaki disease, acquired hypogammaglobulinemia, juvenile rheumatoid arthritis, hemolytic disease of the newborn, acute immune thrombocytopenic purpura, chronic inflammatory demyelinating polyneuropathy, and Guillain–Barré syndrome. For many other diseases, treatment with IVlg was found effective as well, but this was less well established, either due to a lack of well-designed studies or due to conflicting evidence among them. In some diseases, there is a strong recommendation against using IVlg (with a level of evidence A and strength of recommendation III): stem cell/bone marrow transplantation, inclusion body myositis, recurrent pregnancy loss due to antiphospholipid syndrome, optic neuritis, and intractable childhood epilepsy. Nevertheless, the effectiveness of IVlg in such a large span of diseases fortifies the accumulating evidence that many pathological conditions are autoimmune mediated.

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