EULAR guidelines on ANCA-associated vasculitis in the real life

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Abstract

Anti-neutrophil cytoplasmic antibodies-associated vasculitides (AAVs) are a heterogenous group of inflammatory diseases which primarily involve small vessels and include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). They present heterogeneous clinical manifestations, while their diagnosis and management still remain a challenge for clinicians.

Nowadays, the treatment is based on two different regimens: the remission-induction treatment and the remission-maintenance treatment.

The therapeutic armamentarium has grown over the years, with the aim to lessen adverse effects, improve quality of life of patients and maintain the disease under control. Biological treatments are the future: they act on different pathogenic pathways and may offer possibilities in the future a personalized management approach tailored to actual clinical manifestations.

The latest guidelines were published in 2015 by the European League Against Rheumatism (EULAR) and still represent the vade mecum for the management of AAVs.

In this review, we will focus on the principal strategies to treat AAVs. We discuss the remission-induction therapy and the remission-maintenance therapy; we have also distinguished the management of GPA and MPA from that of EGPA, because of their different clinical pictures.

Introduction

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAVs) are a group of rare diseases which primarily affect the small vessels. The term encompasses three different syndromes, namely granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). Although, they share some common clinical features and a common response to treatment, it is important to outline that EGPA is phenotypically different from MPA and GPA. Indeed, in EGPA, ANCA are positive in 30-40% of cases, whereas in GPA/MPA they are present in 70-90% of cases. Moreover, not all EGPA patients present with a pathologic evidence of vasculitis. For this reason, EGPA has also been classified among the hypereosinophilic syndromes.

Glucocorticoids (GCs) have been the mainstay of treatment for years, as for other vasculitides. Nevertheless, in the last decades the therapeutic regimen has been revolutionized by the addition of disease modifying anti-rheumatic drugs (DMARDs), such as cyclophosphamide (CYC), mycophenolate mofetil (MMF) or azathioprine (AZA) and more recently biologics, like rituximab (RTX).

The advances in treatment have led to an increased rate of long-term relapse-free remission and have reduced the toxicity associated to the therapy.

The last European League against Rheumatism/European Renal Association-European Dialysis and Trasplant Association (EULAR/ERA-EDTA) recommendations for the management of vasculitis were published in 2015.

This paper included 15 statements divided into induction of remission and maintenance of remission strategies. Strategies vary based on the clinical findings and on the presence of organ- or life-threatening manifestations (e.g. rapidly progressive renal failure or pulmonary hemorrhage).

In this review, we will discuss the available treatments for AAVs.

Discussion

Remission-induction therapy in granulomatosis with polyangiitis and microscopic polyangiitis

Current recommendations suggest different therapeutic strategies based on the clinical findings and the severity of the clinical picture.

For remission-induction of new onset of organ- or life-threat-
ening disease, it is recommended to start with a combination of GCs and either CYC or RTX.8

For a few decades, CYC has been known to be effective in the induction of remission in AAVs.9 At the beginning, not only was it considered able to induce remission, but it was also used to maintain remission and spare GCs with the aim to decrease the toxicity related to GC treatment, however long-term oral administration of CYC was associated with important adverse events. In particular, in elderly patients, there is a considerable risk of severe infections and malignancy (especially urological and lymphoma), whereas in the younger patients it can cause infertility.

A few years later, pulsed intravenous regimens were approved. CYCLOPS is the largest trial which compared oral administration versus pulsed intravenous regimens (2 mg/kg a day vs 15 mg/kg two-three weeks apart, respectively).10 The overall results showed that pulsed CYC regimen induced remission of ANCA-associated vasculitis in the same proportion of patients as the oral regimen and with a reduced cumulative cyclophosphamide dose, thus causing fewer cases of leukopenia.11 The long-term follow-up of CYCLOPS trial revealed a higher rate of at least one major relapse among patients treated with intravenous pulsed regimens, but the overall survival remained similar. Moreover, the risk of complications (especially, bladder-related) was lower in patients treated with pulsed CYC.12

RTX has been inherited from the oncology and its dose regimens have been derived from hematologic and rheumatoid arthritis protocols (375 mg/m² × 4 weekly and 1 g × 2 biweekly, respectively).13 Two randomized controlled trials (RCTs), RAVE and RITUXVAS, investigated the efficacy of RTX versus a standard therapy with CYC in AAVs.14,15 Both studies have used the hematologic protocol (375 mg/m² × 4, weekly), but in RITUXVAS two pulses of CYC were added to RTX. Both studies showed the non-inferiority of RTX compared to CYC. Moreover, in the RAVE trial, RTX was more effective in relapsing forms. Lately, also low-dose regimens of RTX (375 mg/m² × 2 weekly) were investigated in a monocentric retrospective study and reported no differences compared to higher dose regimens in terms of complete response and relapse rate.16 Notably, trimethoprim/sulfamethoxazole (800 mg/160 mg every other day or 400/80 mg daily) is recommended for the prophylaxis of Pneumocistis jirovecii’s pneumonia, when not contraindicated.17,19

Methotrexate (MTX) and MMF are approved for the treatment of milder clinical pictures.8 Recently, MMF was compared to CYC in a RCT involving 132 patients affected by GPA or MPA without any life-threatening condition (MYC CYC trial).20 MMF (2 g a day) was non-inferior to pulsed CYC (regimen derived from the CYCLOPS trial) in the remission-induction. However, relapses occurred earlier and more frequently in the MMF group. This risk may be acceptable in order to avoid potential CYC side effects.20

Regarding MTX, RCTs showed non-inferiority of oral administration (20-25/week) when compared to CYC to induce remission in patients newly diagnosed with early ANCA-associated vasculitis, but the long-term follow-up revealed less effective disease control, therefore it is contraindicated in more serious clinical conditions. Moreover, patients with renal involvement were excluded from the trial.21

Life-threatening conditions, such as rapidly progressive renal impairment (defined by serum creatinine >500 µmol/L or >5.8 mg/dL) or pulmonary hemorrhages may require plasma-exchange (PEX). Its role has been discussed widely in the literature, but it remains unclear whether the add-on of PEX to a standard remission-induction regimen can actually achieve better outcomes.22 Walsh et al. conducted a RCT to investigate the efficacy of PEX (seven plasma exchanges within 14 days after randomization) versus GCs alone in patients affected by AAVs complicated by life-threatening conditions. They also compared two different dosage regimens of GCs (a standard-dose and a lower one).23 No differences were identified in the rates of end-stage kidney disease or death between the two arms, moreover there were no differences in terms of outcomes between standard-dose and low-dose of GCs, but the group exposed to lower GC doses developed fewer side effects.23

In summary, the correct management of AAVs should be tailored on the basis of the patient clinical picture. The presence of end-stage organ damages or life-threatening conditions requires the prompt initiation of CYC or RTX together with GCs, whereas the role of PEX is still debated, even if the results of a large trial did not show that the addition of PEX to standard therapy offered any benefits in patients with severe ANCA-associated vasculitis. For less serious conditions, MTX or MMF may have a role.

**Remission-maintenance therapy in granulomatosis with polyangiitis and microscopic polyangiitis**

CYC and high doses of GCs cannot be maintained for long periods, due to their important toxicity.7 Recommendations suggest that AZA, RTX, MTX and MMF are less toxic compared to CYC in order to maintain remission.

The CYCAZAREM trial demonstrated the non-inferiority of AZA (2 mg/kg/day) compared to CYC in preventing relapses. Since then, AZA is used as a first-line therapy in maintaining remission after inducing remission with CYC or RTX.24

With regard to RTX, two main RCTs (MAINRITSAN and MAINRITSAN 2) explored its role in maintaining remission. MAINRITSAN compared low-dose RTX (at a fixed dose of 500 mg on days 0 and 14 and at months 6, 12, and 18 after study entry) to daily AZA until month 22 and showed that RTX was more effective than AZA in reducing major relapses.25 MAINRITSAN2 evaluated two different regimens with RTX. In particular, the authors compared the regimen used in MAINRITSAN versus individually-tailored RTX infusions (based on B-cell repopulation and ANCA positivity) and found no differences in their effectiveness. Individually tailored-arm patients received fewer rituximab infusions, however no differences in side effects were observed between the two arms.26

MMF was compared to AZA in the IMPROVE trial: both drugs were reduced after 12 and 18 months and then withdrawn after 42 months. MMF was less effective than AZA in maintaining disease remission, in particular relapses were more common in the MMF group compared with the AZA group.27 Both treatments had similar adverse event rates.

Data about the ideal duration of the maintenance treatment are lacking. However, a prolonged remission maintenance therapy with azathioprine/prednisolone for longer than 24 months after diagnosis reduced the relapse risk down to 48 months and improved renal survival in AAVs.28 In particular, the tapering of GCs is still debated, and whether it is better to withdraw steroids or to maintain a low dose is not clear. Shorter courses of GCs proved to be associated to a greater risk of relapse (e.g. the REMAIN trial).28 Recently, avacopan, a C5a receptor inhibitor, was studied as a substitute for high doses of GCs or as an add-on to low-doses of GCs in the induction of remission in AAVs. C5a receptor inhibition with avacopan was effective in replacing high-dose GCs and, as expected, results showed a lower incidence of the typical adverse event.
events associated with a long-term use of high doses of GCs (e.g., hypertension, diabetes, psychiatric syndromes).29

**Treatment strategies in eosinophilic granulomatosis with polyangiitis**

It is now clear that EGPA is phenotypically different from other AAVs, indeed it represents a clinical entity between vasculitis and hypereosinophilic syndromes.30,31 The vasculitic features (e.g., purpura, glomerulonephritis, neuropathy) are typical of ANCA positive patients, whereas eosinophilic symptoms are more frequent among ANCA negative patients.3

For the vasculitic manifestations, we refer to the available treatments for the other AAVs,4 even if the majority of trials did not include EGPA patients.

With regard to RTX, only retrospective studies demonstrated its efficacy both in induction/remission and in remission-maintenance.32,33 Ongoing RCTs aim to validate its role in EGPA, as in the other AAVs.

In particular, the REOVAS trial (ClinicalTrials.gov NCT02807103) is comparing RTX and conventional treatments in the induction of remission both in newly-diagnosed and relapsing EGPA, whereas MAINRITSREG (ClinicalTrials.gov NCT03164473) is evaluating the maintenance of remission and the steroid-sparing effect of RTX versus AZA.

Eosinophil-driven symptoms, mainly asthma and ear-nose-throat (ENT) manifestations, often require long courses of GCs with a high rate of side effects. Moreover, flares of asthma and ENT manifestations do not imply a flare of vasculitis. Therefore, experts agree that it is more appropriate to treat separately systemic and respiratory symptoms of EGPA.30

Lately, also biologic treatments taken from the therapeutic armamentarium for chronic asthma were studied.34 Omalizumab is a humanized anti-IgE monoclonal antibody which prevents the IgE-mediated degranulation of eosinophils.35 Two small series of EGPA patients demonstrated that omalizumab was able to reduce GCs doses, but a complete response evaluated with pulmonary function tests and symptoms was achieved only in 35-55%.36,37

Mepolizumab (MEPO) is a monoclonal antibody, which blocks the binding of interleukin (IL)-5 to its receptor. Its role in EGPA was investigated in a large double-blind RCT.38 The two arms included patients with relapsing/refractory EGPA: in the MEPO arm they were treated with MEPO 300 mg administered subcutaneously every 4 weeks. Mepolizumab resulted in significantly more weeks in remission and a higher proportion of participants in remission than the placebo did, thus justifying a reduced use of GCs. However, only approximately half of the participants treated with MEPO had a protocol-defined remission. Most patients included in this trial presented a glucocorticoid-dependent asthma without symptoms of active vasculitis. Therefore, it is not clear whether MEPO is effective in the treatment of the vasculitic manifestation of the disease. Furthermore, longer follow-ups are needed to detect the relapse rate and evaluate its role in clinical practice at lower doses and other trials to define the efficacy of MEPO on the vasculitic manifestations of EGPA. Other monoclonal antibodies anti IL-5 include benralizumab and reslizumab. Moreover, agents against IL-4 and IL-13 proved effective in chronic asthma and may play a role in EGPA, too.39-41

**Real-life management**

As is well known, RCTs are pivotal in the development of therapeutic guidelines, but the need to minimize the biases require strict inclusion criteria and short follow-ups. Often, they do not permit the generalization of results and are unable to detect possible delayed adverse events. It is important to complement them with observation studies, which re-create clinical scenarios that are more similar to real-life settings.32

In AAVs, observational data are scarce and a lot of questions still remained open. In particular, more studies are needed to define the duration of the maintenance therapy and the correct doses of the drugs.

In most cases, AAVs respond well to the induction treatment, but in 70% of cases relapses occur during the follow-up and 20% develop a refractory disease.43

RTX has become the standard therapy in real-life management both in the induction and remission management. Indeed, it is better tolerated than CYC, does not cause infertility in young patients and seems to be more effective than CYC in patients with PR3-ANCA associated vasculitis and in those with a relapsing disease. We know that re-treatment is required in order to avoid relapses, and long-term RTX treatment can cause/worsen hypogammaglobulinemia. Circulating ANCs against proteinase-3 (PR-3), GPA phenotype and previous relapses were described as risk factors for a relapsing disease.44 Unfortunately, data about a possible withdrawal of maintenance treatment with RTX in the long-term follow-up are still missing.

Puéchal et al. evaluated a large cohort of 114 GPA treated with RTX both for the induction of remission and its maintenance during two years.45 Relapse free survival was 85% and the RTX retention rate was 78%. All patients received 1 g two weeks apart or 375 mg/m² every week for a month during the induction treatment and then 500 mg every six months for the maintenance. Interestingly, authors differentiated vasculitic manifestations (e.g. diffuse alveolar hemorrhage, glomerulonephritis and peripheral nervous system involvement) from granulomatous manifestations (such as orbital granuloma, pachymeningitis or granulomatous ENT involvement) and found that the latter were associated with a greater probability of remission failure. Indeed, it was reported that the granulomatous microenvironment could prevent B cell depletion by increasing the levels of B cell activating factor (BAFF) and the adhesion molecules.46

In most trials, patients affected by EGPA are excluded. The Five Factor Score (FFS) is a useful prognostic value used in clinical practice: the five items (serum creatinine >150 µmol/L, myocardial involvement, severe gastrointestinal involvement, age >65 years and the absence of ENT manifestations) correlate with increased mortality and each item scores 1 point.47 Therefore, following the EGPA task force, the add-on of a cytotoxic drug (i.e. CYC) is recommended for FFS >1.48 In the clinical practice, the treatment is tailored to patients’ clinical manifestations and comorbidities; and a careful evaluation of the risk over benefit ratio is required.

With regard to biologic treatments, RTX plays a role in inducing and maintaining remission both in ANCA positive and negative EGPA patients.48 A scheduled course of RTX showed to be superior in reducing the relapse-rate, when compared to RTX given on-demand at the time of a relapse.49 On the contrary, it is not yet clear, if MEPO could play a role in the treatment of vasculitic manifestations. However, it is safe and efficacious in controlling GC-dependent asthma and real-life data demonstrated its superiority over omalizumab.49

It is still unclear whether asthmatic and/or ENT exacerbations
are true relapses or signs of chronic sequelae of EGPA. Indeed, in these patients the poor control of respiratory symptoms often require long-term use of GCs with subsequent adverse events. The clinical practice teaches us that EGPA is a multi-faceted disease and the damage is caused both by vasculitic- and eosinophil-driven inflammation. Moreover, symptoms tend to vary at the different stages of the natural clinical history. In EGPA a multi-staging approach to control both vasculitis and eosinophilic symptoms may be an appropriate option.

Conclusions

AAVs are a group of diverse diseases which share some common clinical features and typically affect small vessels. The inflammatory response causes a necrotizing damage which may lead to end-organ dysfunction and in more serious cases may be life-threatening. Immunosuppressants are the cornerstone of the therapeutic armamentarium. For decades, high doses GCs and CYC represented the only weapon against AAVs, with a high rate of side effects. Later, many other drugs were approved for the treatment of AAVs.

EULAR/ERA-EDTA recommendations for managing AAVs date back 2015 and include 15 statements approved by an expert panel with clinical expertise in the field of vasculitis. Nowadays, management includes both DMARDs and biologic therapies. Targeted therapies against a particular pathogenic pathway and tailored to the patients’ clinical symptoms will represent the future, but the road is still long.

References

1. Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised international chapel hill consensus conference nomenclature of vasculitides. Arthritis Rheum 2013;65:1-11.
2. Comarmond C, Pagnoux C, Khellaf M, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. Arthritis Rheum 2013;65:270-81.
3. Sinico RA, Di Toma L, Maggiore U, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. Arthritis Rheum 2005;52:2926-35.
4. Holle JU, Wieczorek S, Gross WL. The future of ANCA-associated vasculitis. Rheum Dis Clin North Am 2010;36:609-21.
5. Villiger PM, Guillemin L. Microscopic polyangiitis: clinical presentation. Autoimmun Rev 2010;9:812-9.
6. Valent P, Klion AD, Horny HP, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. J Allergy Clin Immunol 2012;130:3.
7. Rossi GM, Peyronel F, Fenaroli P, et al. New therapeutics for ANCA-associated vasculitides: 10 years devoted to lessen toxicity. Clin Exp Rheumatol 2020;38:18-22.
8. Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitides. Ann Rheum Dis 2016;75:1583-94.
9. Fauci AS, Katz P, Haynes BF, Wolff SM. Cyclophosphamide therapy of severe systemic necrotizing vasculitis. N Engl J Med 1979;301:235-8.
10. De Groot K, Harper L, Jayne DRW, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med 2009;150:10.
11. De Groot K, Adu D, Savage COS. The value of pulse cyclophosphamide in ANCA-associated vasculitis: Meta-analysis and critical review. Nephrol Dial Transplant 2001;16:2018-27.
12. Harper L, Morgan MD, Walsh M, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: Long-term follow-up. Ann Rheum Dis 2012;71:955-60.
13. Felicetti M, Treppo E, Posarelli C, et al. One year in review 2020: vasculitis. Clin Exp Rheumatol 2020;38:3-14.
14. Jones RB, Tervaert JWC, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010;363:211-20.
15. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221-32.
16. Takakuwa Y, Hanaoka K, Kiyokawa T, et al. Low-dose rituximab as induction therapy for ANCA-associated vasculitis. Clin Rheumatol 2019;38:1217-23.
17. Chung JB, Armstrong K, Schwartz JS, Albert D. Cost-effectiveness of prophylaxis against Pneumocystis carinii pneumonia in patients with Wegener’s granulomatosis undergoing immunosuppressive therapy. Arthritis Rheum 2000;43:1841-8.
18. Vincent F, Bensoussan TA. Pneumocystis carinii pneumonia: a major complication of immunosuppressive therapy in patients with Wegener’s granulomatosis. Am J Respir Crit Care Med 1995;152:1424.
19. Jarrousse B, Guillemin L, Bindi P, et al. Increased risk of Pneumocystis carinii pneumonia in patients with Wegener’s granulomatosis. Clin Exp Rheumatol 1993;11:615-21.
20. Jones RB, Hiemstra TF, Ballarin J, et al. Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: A randomised, non-inferiority trial. Ann Rheum Dis 2018;78:3.
21. Faurcheau M, Westman K, Rasmussen N, et al. Long-term outcome of a randomized clinical trial comparing methotrexate to cyclophosphamide for remission induction in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2012;64:3472-7.
22. Jayne DRW, Gaskin G, Rasmussen N, et al. Randomized trial of plasma exchange or high-dose methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol 2007;18:2180-8.
23. Walsh M, Merkel PA, Peh CA, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. N Engl J Med 2020;382:622-31.
24. Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003;349:36-44.
25. Guillemin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med 2014;371:1771-80.
26. Charles P, Terrier B, Ferrodeau É, et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: Results of a multicentre, randomised controlled, phase III trial (MAINRIT-SAN2). Ann Rheum Dis 2018;77:1144-50.
27. Hiemstra TF, Walsh M, Mahr A, et al. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: A randomized controlled trial. JAMA J Am Med Assoc 2010;304:2381-8.

28. Karras A, Pagnoux C, Haubitz M, et al. Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis. Ann Rheum Dis 2017;76:1662-8.

29. Jayne DRW, Bruchfeld AN, Harper L, et al. Randomized trial of C5a receptor inhibitor avacopan in ANCA-associated vasculitis. J Am Soc Nephrol 2017;28:2756-67.

30. Groh M, Pagnoux C, Baldini C, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. Eur J Intern Med 2015;26:545-53.

31. Mahr A, Moosig F, Neumann T, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): Evolutions in classification, etiopathogenesis, assessment and management. Curr Opin Rheumatol 2014;26:16-23.

32. Mohammad AJ, Hot A, Arndt F, et al. Rituximab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Ann Rheum Dis 2016;75:396-401.

33. Emmi G, Rossi GM, Urban ML, et al. Scheduled rituximab maintenance reduces relapse rate in eosinophilic granulomatosis with polyangiitis. Ann Rheum Dis 2018;77:952-4.

34. Trivioli G, Terrier B, Vaglio A. Eosinophilic granulomatosis with polyangiitis: Understanding the disease and its management. Allergy Eur J Allergy Clin Immunol 2005;60:302-8.

35. Bousquet J, Cabrera P, Berkman N, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. Allergy Eur J Allergy Clin Immunol 2005;60:302-8.

36. Celebi Sozener Z, Gorgulu B, Mungan D, et al. Omalizumab in the treatment of eosinophilic granulomatosis with polyangiitis (EGPA): Single-center experience in 18 cases. World Allergy Organ J 2018;11:1.

37. Haldar P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med 2009;360:973-84.

38. Wechsler ME, Akuthota P, Jayne D, et al. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. N Engl J Med 2017;376:1921-32.

39. Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med 2018;378:2475-85.

40. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med 2018;378:2486-96.

41. Corren J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. N Engl J Med 2017;377:936-46.

42. Monti S, Grosso V, Todoerti M, Caporali R. Randomized controlled trials and real-world data: differences and similarities to untangle literature data. Rheumatology (Oxford) 2018;57:vi54-8.

43. De Groot K, Rasmussen N, Bacon PA, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52:2461-9.

44. Walsh M, Flossmann O, Berden A, et al. Risk factors for relapse of antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2012;64:542-8.

45. Puéchal X, Iudici M, Calich AL, et al. Rituximab for induction and maintenance therapy of granulomatosis with polyangiitis: A single-centre cohort study on 114 patients. Rheumatol (United Kingdom) 2019;58:401-9.

46. Ferraro AJ, Smith SW, Neil D, Savage COS. Relapsed Wegener’s granulomatosis after rituximab therapy - B cells are present in new pathological lesions despite persistent “depletion” of peripheral blood. Nephrol Dial Transplant 2008;23:3030-2.

47. Guillevin L, Lhote F, Gayraud M, et al. Prognostic factors in polyarteritis Nodosa and Churg-Strauss syndrome: A prospective study in 342 patients. Medicine (Baltimore) 1996;75:17-28.