B cell-depleting therapy with rituximab or ofatumumab in immunoglobulin A nephropathy or vasculitis with nephritis

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Abstract

Background: Approximately 30% of adult patients with immunoglobulin A (IgA) nephropathy (IgAN) or IgA vasculitis with nephritis (IgAVN) develop end-stage renal disease during long-term follow-up. In particular, patients with nephritic–nephrotic syndrome have an increased risk of rapid progression. Conventional immunosuppressive therapy with corticosteroids (CSs) may be insufficient for disease control and is associated with a number of side effects. Rituximab (RTX) has been shown to be well tolerated and effective in a range of glomerular diseases, but there is little information on its therapeutic potential in IgAN. The humanized anti-CD20 monoclonal antibody ofatumumab (OFAB) may be an alternative drug for patients intolerant or unresponsive to RTX, but so far there is no report on its use in IgAVN or IgAN.

Methods: We describe clinical outcomes after 17–22 months in four adult patients with biopsy-confirmed IgAVN or IgAN treated with RTX or OFAB as well as CS soon after diagnosis. All presented with nephritic–nephrotic syndrome and one had crescentic IgAN. Rebiopsy was performed in two cases.

Results: RTX and OFAB were well tolerated. Albuminuria was <250 mg/day in three patients at last evaluation and two regained normal renal function. In all cases, renal function improved after therapy. In one patient with severe IgA vasculitis, rebiopsy showed disappearance of subendothelial but not mesangial immune complexes. In the case with crescentic IgAN, rebiopsy after 9 months showed no active necrotic lesions.

Conclusions: B cell–depleting therapy may be an alternative treatment for patients with IgAN or IgAVN and nephritic–nephrotic syndrome. A possible CS-sparing effect should be further evaluated in randomized controlled clinical trials.

Key words: Henoch–Schönlein purpura with nephritis, IgA nephropathy, IgA vasculitis, ofatumumab, rituximab
Introduction

Immunoglobulin A vasculitis with nephritis (IgAVN), previously known as Henoch–Schönlein purpura, is a systemic disease characterized by the manifestation of leukocytoclastic vasculitis in the skin and IgA-containing immune complexes in the glomerular mesangium, proliferation of mesangial cells, infiltration of inflammatory cells and progressive glomerular injury in the same pattern as in IgA nephropathy (IgAN). Enteritis and arthritis may also occur [1]. The wide range of clinical manifestations in IgAVN and IgAN contribute to the lack of evidence-based optimal therapy recommendations, especially in cases of nephritic-nephrotic syndrome at risk of progression to end-stage renal disease (ESRD) [2–5]. Rituximab (RTX) is a murine/human chimeric monoclonal antibody directed against and depleting CD20 B cells, increasingly used in immune-mediated renal disease such as anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AVV), lupus nephritis, membranous nephropathy or relapsing minimal change disease [6,7]. Ofatumumab (OFAB) is a novel fully human antibody that binds to a different epitope on CD20 than RTX and was, like RTX, originally licensed for the treatment of B cell malignancies [8]. There is limited experience so far with its therapeutic potential in inflammatory renal disease but it has been suggested that it can be useful in patients who are hypersensitive or unresponsive to RTX. Recently the efficacy of OFAB was demonstrated in five children with nephrotic syndrome resistant to conventional therapy and RTX [9]. A few case reports have been published on the positive therapy effects of RTX in IgAVN but there is no information on the use of OFAB in this disease [10–12]. An earlier prospective study of single-dose RTX treatment on top of corticosteroids (CSs) in five patients with non-nephrotic IgAN showed no reduction of proteinuria after 6 months. However, repeated doses of RTX were effective and well-tolerated in a few cases of recurrent IgAN after renal transplantation [13, 14]. Here we report on four adult patients with IgAVN or primary IgAN, all recently biopsied, who presented with nephritic-nephrotic syndrome and were treated at our department with either RTX or OFAB. All patients have been followed for at least 17 months and in two cases re-biopsy was performed.

Materials and methods

Clinical and laboratory data were obtained by chart review. Renal function was estimated by using creatinine levels and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula developed by Levey et al. [15]. Renal biopsies were evaluated by the local pathologist. All patients have given their informed consent to this publication.

Results

Case 1

A 19-year-old obese woman with a history of purpura in childhood sought medical attention in June 2014 due to purpura, abdominal pain and arthralgia. When first seen by a rheumatologist, blood pressure (BP) was 135/85 mmHg, C-reactive protein (CRP) 28 mg/L (normal <3 mg/L), creatinine 61 μmol/L (normal for women <90 μmol/L) and urinary dipstick (U-dipstick) positive for hematuria and proteinuria. A skin biopsy showed necrotizing leukocytoclastic vasculitis. Immunofluorescence (IF) staining was not performed. Complete laboratory evaluation 2 days later revealed an increase of creatinine to 99 μmol/L, plasma albumin (p-alb) 34 g/L (normal 36–48 g/L), urine sediment (U-sediment) with 4–10 erythrocytes (Erys), 2–5 granular casts/high power field (hpf) and urine albumin:creatinine ratio (ACR) 538 mg/mmol (normal <3 mg/mmol). At admission to the nephrology department after another 3 days, p-alb had decreased to 28 g/L and massive edema developed. Intravenous methylprednisolone (MPE) pulses were started immediately, followed by oral prednisolone (PSL). Renal biopsy on day 7 from admission confirmed a diagnosis of IgAVN showing nine glomeruli with moderate mesangial proliferation, infiltration of granulocytes, but no crescents/necrosis [the MEST score, describing the degree of mesangial hypercellularity (M), segmental glomerulosclerosis (S), endocapillary hypercellularity (E) and tubular atrophy/interstitial fibrosis (F), was M1S0E1T0, according to the Oxford classification of IgAN] [16]. IF staining was positive in the mesangium for IgA and C3 and some IgG. Aggravated nephrosis with a urine ACR of 1633 mg/mmol and a hesitancy to continue high-dose steroids because of severe obesity led to the decision to add RTX on day 9. Due to recurrent bronchospasm early during the infusion, RTX was discontinued. Instead, the patient was given OFAB, which was well tolerated. (For a detailed description of therapy, including doses and correlation to the clinical course, see Table 1 and Figure 1.) Albuminuria has been below <200 mg/day and creatinine has been normal since January 2015 and remained so at the latest follow-up in May 2016 (Table 1).

Case 2

In June 2014, a 49-year-old female smoker with a history of asthma and severe eczema presented with abdominal pain, hematochezia, purpura, mild eosinophilia, edema and a BP of 120/70 mmHg. Owing to a skin infection, she had recently been treated with antibiotics, betamethasone (BMS) and methotrexate, being intolerant to PSL. A skin biopsy showed leukocytoclastic vasculitis with negative IF. At admission to the nephrology ward, creatinine was 102 μmol/L, p-alb 23 g/L and CRP 50 mg/L. U-sediment showed 11 Erys/hpf and urine albumin:creatinine ratio (ACR) 538 mg/mmol (normal <3 mg/mmol). At admission to the nephrology ward, creatinine was 102 μmol/L, p-alb 23 g/L and CRP 50 mg/L. U-sediment showed 11–20 Erys/hpf and no granular casts and the urine ACR was in the nephrotic range (414 mg/mmol). Abdominal computed tomography (CT) revealed enteritis in the terminal ileum. Fecal calprotectin (F-calprotectin), a marker of intestinal inflammation, was as high as 1572 mg/kg (normal <50 mg/kg). Renal biopsy at day 4 showed no crescents or necrotic lesions. There was extensive endocapillary but no mesangial proliferation and no tubulointerstitial changes (Oxford classification M0E1S0T0). IF was strongly positive for IgA and weakly positive for IgG, IgM and C1q. Electron microscopy revealed immune complex (IC) deposition both in the mesangium and the subendothelium of capillary walls (Figure 2A). There were no clinical or serologic signs of lupus erythematosus and the final diagnosis was IgAVN. During therapy with MPE pulses and intravenous BMS (specified in Figure 1 and Table 1), the nephritic–nephrotic syndrome worsened. RTX was therefore given the day after renal biopsy, followed by mycophenolate mofetil (MMF). Creatinine continued to increase to 622 μmol/L and the patient’s bloody diarrhea persisted. MMF was stopped and 2 more doses of RTX were given 1 month later. Thereafter, the clinical condition slowly improved.

In April 2015, the urine ACR was 19 mg/mmol and creatinine 140 μmol/L. Shortly after cessation of BMS in August 2015, the patient again started to suffer from frequent diarrhea and arthralgia, her urine ACR increased to 149 mg/mmol and creatinine was stable at 95 μmol/L. Low-dose BMS was restarted and azathioprine (AZA) was added. Examination of the terminal ileum by magnetic resonance imaging showed minimal...
inflammation compared with the earlier extensive CT findings and F-calprotectin had normalized. A gastroenterologist was consulted but did not find any evidence for a concomitant diagnosis of inflammatory bowel disease or coeliac disease. Biopsy of the kidney in October 2015 showed that 5 of 16 glomeruli were totally sclerosed and segmental sclerosis was present in 3–4 glomeruli. There were no crescents or necrosis, only mild mesangial proliferation and mild interstitial fibrosis, classified as M0E0S1T1. Treatment was started as a possible kidney stone passage. At that time, creatinine was 228 µmol/L (normal for men <100 µmol/L). Two years earlier he had abdominal pain and macrohematuria that had been interpreted as a possible kidney stone passage. At that time, creatinine was 88 µmol/L and U-dipstick showed 3+ hemoglobin and 2+ albumin, but this did not result in any follow-up. Clinical examination at the current admission revealed a BP of 120/70 mmHg and no edema or purpura. CRP was 98 mg/L, p-alb was 28 g/L and U-sediment again contained 21+ albumin, but this did not result in any follow-up. Clinical examination at the current admission revealed a BP of 120/70 mmHg and no edema or purpura. CRP was 98 mg/L, p-alb was 28 g/L and U-sediment showed 21+ albumin, but this did not result in any follow-up. Clinical examination at the current admission revealed a BP of 120/70 mmHg and no edema or purpura.

Case 3

A 28-year-old woman with a family history of IgAN presented in January 2014 at the emergency care unit with macrohematuria, fever and an unspecific skin rash on her buttocks in conjunction with a viral upper respiratory tract infection. BP was 139/74 mmHg. She had previously experienced macrohematuria without rash during viral infections. At this first visit, her creatinine was 217 µmol/L, CRP 36 mg/L, p-alb 29 g/L and U-dipstick 3+ for hematuria and proteinuria. U-sediment contained 4–10 Erys and 2–5 granular casts/hpf. Two weeks later, BP was 107/62 mmHg, creatinine had spontaneously decreased to 109 µmol/L, but the urine ACR was 160 mg/mmol. At the time of renal biopsy, 1 month after the first visit, creatinine had again increased to 233 µmol/L, p-alb was 26 g/L and U-sediment again contained granular casts. Histopathologic examination revealed a diagnosis of IgAN with cellular crescents in 5 of 17 glomeruli (31%) with an Oxford classification of M1E0S1T1. Treatment was started with MEF pulses, followed by PSL. RTX was given on days 10 and 24 after diagnosis. (For doses, see Table 1 and Figure 1.) A month later, the creatinine level was 78 µmol/L and albuminuria was 1.9 g/day. PSL was tapered over 12 months, prolonged due to persistent proteinuria (urine ACR 77–102 mg/mmol). After 13 months the patient became pregnant and angiotensin-converting enzyme inhibitor (ACEI) had to be stopped, but proteinuria continued to decrease and the urine ACR was 8.8 mg/mmol in October 2015 when she was 30 weeks into her pregnancy. The patient was lost to follow-up due to her move to another town.

Case 4

A 19-year-old man was admitted to hospital in December 2014 due to fever, a sore throat, macrohematuria and a creatinine of 228 µmol/L (normal for men <100 µmol/L). Two years earlier he had abdominal pain and macrohematuria that had been interpreted as a possible kidney stone passage. At that time, creatinine was 88 µmol/L and U-dipstick showed 3+ hemoglobin and 2+ albumin, but this did not result in any follow-up. Clinical examination at the current admission revealed a BP of 120/70 mmHg and no edema or purpura. CRP was 98 mg/L, p-alb 28 g/L and urine ACR 437 mg/mmol. U-sediment showed 21–50 Erys and 0–1 granular casts/hpf. PSL 60 mg/day was started 6 days before renal biopsy. Histologic examination showed crescents or necrosis in 25 of 35 glomeruli (80%), with 3 glomeruli being totally

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**Table 1. Clinical presentation and immunosuppressive therapy in four patients with IgAN or IgAVN and nephritic–nephrotic syndrome treated with either RTX or OFAB on top of CS**

| Case number, age, sex, diagnosis (renal biopsy) | Systemic CS treatment | B cell-depleting therapy and other ISls | Change in laboratory values pre and post-RTX/OFAB |
|-----------------------------------------------|------------------------|----------------------------------------|-------------------------------------------------|
| 1 19, female, IgAVN (no crescents)           | MEP 500 mg iv daily × 3 | RTX 280 mg × 1 OFAB 300 mg (125 mg/m² BSA) first dose, then 500 mg weekly × 3 | Cr (µmol/L) Day of first RTX 96 65 58 22 |
|                                              | PSL 60 mg/day in 2 weeks over 8 months |                                       | UAC (mg/mmol) 1589 11 9 |
|                                              | BSM oral 1.5 mg/day at admission |                                       | p-alb (g/L) 17 39 38 |
| 2 49, female, IgAVN (no crescents)          | MEB 500 mg iv daily × 2 | RTX 600 mg × 4 during 2 months (326 mg/m²) | Cr (µmol/L) 101 142 87 22 |
|                                              | BMS max 8 mg/day iv or oral (0.1 mg/kg/day) in 2 weeks, tapered over 19 months |                                       | UAC (mg/mmol) 56 37 67 |
|                                              | AZA 50 mg × 2/day for 4 weeks |                                       | p-alb (g/L) 16 28 30 |
|                                               | MMF 1 g/day for 2 weeks |                                       | U-Hb (dipstick) 3+ 3+ 1+ |
| 3 27, female, IgAN (31% crescents)          | MEP 500 mg iv daily × 3 | RTX 1 g (633 mg/m²) × 2 every other week | Cr (µmol/L) 110 71 60 20 |
|                                              | PSL 50 mg/day (0.94 mg/kg/day) tapered over 12 months |                                       | UAC (mg/mmol) 59 101 119 |
|                                              | MEP 500 mg iv daily × 3 | RTX 1 g (635 mg/m²) × 2 every other week | p-alb (g/L) 30 29 – |
|                                              | PSL 60 mg/day (0.6 mg/kg/day) for 1 month, tapered over 7 months |                                       | U-Hb (dipstick) 3+ 0 0 |
|                                              | MMF 1 g/day started 4 months after last RTX dose, ongoing |                                       | Cr (µmol/L) 208 170 196 17 |
|                                               | UAC (mg/mmol) 39 49 41 |
| 4 19, male, crescentic IgAN (80% crescents)  | MEP 500 mg iv daily × 3 | RTX 1 g (635 mg/m²) × 2 every other week | UAC (mg/mmol) 317 100 83 |
|                                              | PSL 60 mg/day (0.6 mg/kg/day) tapered over 8 months |                                       | p-alb (g/L) 24 38 34 |
|                                              | MMF 1 g/day started 4 months after last RTX dose, ongoing |                                       | U-Hb (dipstick) 3+ 0 2+ |

**Change in laboratory values pre and post-RTX/OFAB**

- **Cr** (µmol/L), **UAC** (mg/mmol), **p-alb** (g/L), **U-Hb** (dipstick)

- **Estimated glomerular filtration rate (eGFR)** according to the CKD-EPI equation by Levey et al. [15]. **ISls**, immunosuppressives; **eBDS**, enteral budesonide; **iv**, intravenous; **Cr**, creatinine; **U-Hb**, urine hemoglobin, **FU**, follow-up.

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sclerosed. There were no signs of vasculitis in larger vessels. Positive mesangial IF staining for IgA and C3 confirmed a diagnosis of IgAN. The Oxford classification was M1E1S1T0. Treatment was intensified with MEP pulses and RTX (for doses and timing, see Table 1 and Figure 1). One month after diagnosis, creatinine had decreased from a maximum of 358 µmol/L to 215 µmol/L and the urine ACR was 146 mg/mmol. After 4 months, MMF was added. A rebiopsy was performed in September 2014 when creatinine had stabilized at ∼186 µmol/L and the urine ACR was 25 mg/mmol. The histologic material contained 25 glomeruli without any active necrotic lesions, total sclerosis was detected in 10 of 25 glomeruli and there was moderate tubulointerstitial fibrosis. IF was moderately positive for IgA and C3 in the mesangium (Oxford classification M1E1S1T1) One year after diagnosis there was no microhematuria found by dipstick or U-sediment. However, since then proteinuria, microhematuria and creatinine have started to slowly increase again (Table 1, Figure 1). We are planning re-treatment with RTX (without CS) and cessation of MMF.

Additional treatment
According to our routine protocol for RTX treatment, pretreatment with 100 mg intravenous hydrocortisone, 0.5–1 g paracetamol and anti-histamine was given to all patients before the administration of RTX or OFAB to prevent allergic reactions. All patients were treated with renin–angiotensin system (RAS) blockade at maximum tolerated doses and mean BP during follow-up was 120/71 mmHg (case 1), 124/73 mmHg (case 2), 107/64 mmHg (case 3) and 126/79 mmHg (case 4), respectively. In patient 3, RAS blockade was stopped during pregnancy and in patient 1 it was stopped after 18 months due to low blood pressure after a 25-kg weight reduction by diet and gastric bypass surgery. Patients 2 and 4 were also treated with statins and all patients had a dietary consultation and lifestyle recommendations. Trimetoprim-sulfamethoxazol prophylaxis against Pneumocystis carinii infection was given for 6 months in cases 1, 2 and 4 following guidelines for RTX treatment in AAV.

Further laboratory results
In all patients presented here, CD19 B cells were normal before and undetectable 2 weeks after the first course of at least 500 mg RTX or 300 mg OFAB. At the time of relapse in cases 2 and 4, CD19 cells again were detectable in peripheral blood. Serologic tests for ANCA or ANA antibodies and hepatitis B serology were negative. Routine complement analyses (C3, C4, C1q and C3d) were normal in all cases.

Adverse events
Patient 1 had a moderate allergic reaction to RTX and treatment was therefore changed to OFAB, which was well tolerated. Patient 2 had influenza A virus infection 7 months after the start of immunosuppression therapy was considered unrelated to therapy. At that time she was also treated for clinically suspected herpes simplex infection. CS therapy resulted in significant weight gain, development of persistent striae and mood disorders in three of four patients.
Discussion

There is an unmet need for alternative and more effective therapies in patients with IgAVN and IgAN at risk of renal progression [17]. The four patients described had a clinical picture of acute nephritic–nephrotic syndrome with or without extrarenal disease manifestations. The addition of RTX or OFAB at varying dosages seemed to enable lower CS doses than recommended in nephrotic IgAN [2]. All patients also received optimal supportive therapy as suggested by Floege et al. [5]. Improvement of renal function was seen in all patients in conjunction with follow-up at 17–22 months. Cases 1–3 had low-grade albuminuria (<250 mg/day), in one of these even decreasing during pregnancy when ACEi had to be stopped. Our positive results are in line with earlier reports on RTX therapy in IgAV and in recurrent IgAN/IgAVN [10–12, 14, 18, 19]. However, Sugura et al. [13] did not find any proteinuria reduction 6 months after single-dose RTX in 5 non-nephrotic IgAN patients. The positive effect in IgAVN and IgAN observed in our cases may be explained by the fact that all the patients were in a highly active inflammatory state, defined by the presence of endocapillary proliferation and/or crescent formation in renal biopsy, similar to the cases with recurrent IgAN described by Chancharoenthana et al. [14]. The mechanisms of RTX therapy in IgAN/IgAVN are unknown, but besides a possible immunological effect on B cells, there may also be a direct effect on podocytes by stabilization of the cytoskeleton as described by Fornoni et al. [20]. This could in part explain its beneficial effect in other nephrotic disorders with or without the presence of autoantibodies. In accordance with our routines when treating other forms of glomerulonephritis, we gave four courses of RTX in the heavily nephrotic patients and only two repeated courses in those with proteinuria <3.5 g/day, based on the results of pharmacokinetic studies performed in membranous nephropathy indicating that proteinuria may have an impact on the half-life of RTX [21].

Treatment with OFAB has not been reported in IgAN/IgAVN but has been used in some pediatric cases with RTX-resistant nephrotic syndrome [9]. Regarding the doses of OFAB, we chose a cautious approach. A dose of 700 mg per administration has been recommended for maximum effect and safety in patients with rheumatoid arthritis [22–24]. Preliminary positive results of an enteric-release formulation of budesonide in IgAN [25], currently under evaluation after a phase 2b clinical trial, made us try enteral budesonide treatment in case 2 as remission-maintaining therapy instead of systemic steroids.

Repeated renal biopsy of native kidneys after RTX therapy, as performed in two of the cases, has not been described earlier in IgAN or IgAVN. Interestingly, electron microscopic examination of the rebiopsy in case 2 fifteen months after the start of therapy revealed the disappearance of subendothelial but not mesangial ICs. Rebiopsy in case 4 after 9 months showed the disappearance of crescents. Reduced IF staining for IgA after RTX therapy was established by Chancharoenthana et al. [14]. Crescentic lesions had disappeared in some but not all of the IgAN patients in a recently published study by Shen et al. [26] where rebiopsy had been performed after a mean of 10 months following CS and cyclophosphamide (CYC) therapy. Electron microscopic findings on
IC distribution were not described in their study. The varying clinical outcome in crescentic IgAN has been reported by Lv et al. [27]. The diagnostic delay in our patient who had unrecognized symptoms of glomerulonephritis for 2 years may have had an impact on the outcome. In crescentic IgAN, current guidelines suggest the use of steroids and CYC analogous to the treatment of AAV. We considered CYC treatment in case 4 but hesitated due to the conflicting results in recently performed retrospective and randomized controlled studies on IgAN and IgAV [28–30]. The young age of the patients was a consideration in avoiding cytotoxic treatment.

It may be that initial plasma exchange could have further improved renal function in cases 2 and 4. The rationale behind such an approach, which has had favorable results in some earlier reports on severe IgAN or IgAVN, is to rapidly remove circulating IgA-containing immune complexes [31–33]. Most of those previous studies have been performed in children, who may have a better prognosis [34]. Reporting bias may have an impact on our knowledge about effects of unconventional treatment methods and clearly the number of patients was rather limited to draw any robust conclusions [35].

We cannot exclude that CS alone, maybe in higher doses, would have given similar clinical results. However, a recently performed randomized clinical trial on the use of CS and CYC in patients with IgAN at risk of renal progression (STOP-IgAN) underlines the lack of proven efficacy and the substantial risk of side effects with all kinds of immunosuppressive treatment, including B cell–depleting therapy. In concordance with the findings in the STOP-IgAN trial, we observed a reduction of hematuria after immunosuppressive therapy in three of four patients. As discussed by Davin and Coppo, early effective treatment is important for the outcome [3, 36]. New treatment approaches are currently under investigation and may give us the opportunity to intervene in the pathogenesis of IgAN/IgAVN at an earlier stage of the disease and with possibly fewer side effects than conventional treatment [37].

In conclusion, this case series demonstrates that B cell–depleting therapy with RTX or OFAB may be an effective treatment option in patients with IgAN or IgAVN and clinical as well as histological signs of highly active inflammation. Repeated treatment may be necessary and further follow-up is required to evaluate the long-term clinical outcome and safety of this treatment approach. The rarity of rapid progressive glomerulonephritis in IgAN and IgAVN needs to be addressed in multicenter clinical trials and B cell–depleting therapy without any CS should be further evaluated. Results are awaited from an open-label randomized trial on RTX versus supportive care in IgAN that has recently been completed (ClinicalTrials.gov:NCT00498368).

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Conflict of interest statement

None declared.

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