Brief Report: Rituximab for the treatment of adult-onset IgA vasculitis (Henoch-Schönlein purpura)

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ABSTRACT

Immunoglobulin A (IgA) vasculitis (IgAV), formerly Henoch-Schönlein purpura, is a systemic small-vessel vasculitis characterised by IgA1-dominant immune deposits. Its clinical manifestations include purpura, gastrointestinal involvement, arthralgias/arthritis, and glomerulonephritis.[1] IgAV is the most common vasculitis in children, whereas it is rare in adults. Childhood-onset IgAV usually has a benign course only requiring supportive care. In adults, its prognosis is worse, particularly because of the high frequency and severity of renal involvement; indeed, adult-onset IgAV leads to advanced chronic kidney disease (CKD) or end-stage renal disease (ESRD) in 10-30% of the cases.[2]

The treatment of adult-onset IgAV is still a matter of debate. Glucocorticoids and immunosuppressive drugs are routinely used especially in patients with organ- or life-threatening manifestations.[3] However, the efficacy of these treatments is controversial. In the only randomised trial performed in adult-onset IgAV, the addition of cyclophosphamide to glucocorticoids failed to provide any clear benefit.[4] Other immunosuppressive agents such as azathioprine, mycophenolate mofetil or cyclosporine have only been reported in anecdotal cases.[3,5] Therefore, there is an unmet need for effective therapies in adult-onset IgAV.

The anti-CD20 monoclonal antibody rituximab (RTX) has become a standard treatment for remission-induction and remission-maintenance in patients with small-vessel vasculitides such as anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis.[6,7] RTX induces B-cell depletion and thus dampens the expansion of plasma cells that produce pathogenic autoantibodies. RTX can also impair antigen-presentation by B-cells or reduce B cell-mediated stimulation of T-cells and other inflammatory cell types.[6] Recently, a few reports have shown that RTX may be effective for adult-onset IgAV, but they were based on single cases or small case series including up to five patients.[8-10] In this multicentre, observational study, we analyse the effectiveness and safety of RTX in adult-onset IgAV patients who were either relapsing/refractory or had contraindications to conventional glucocorticoid/immunosuppressive therapy.

Twenty-two patients were included in this study. Six cases were described in previous papers;[8,10] the data presented here regarding these six patients are based on a longer follow-up than that originally reported. Of the 22 patients, 12 were men; their median age at

diagnosis was 37.5 years (interquartile range, IQR, 22.8–49.8). At diagnosis, the most frequent clinical manifestation was purpura (21 patients, 95.5%); it predominantly affected the lower limbs and was necrotic or bullous in six cases (27.3%). Gastrointestinal involvement was found in 18 patients (81.8%); all of them experienced abdominal pain and seven (39%) gastrointestinal haemorrhage. Twenty patients (90.9%) had kidney involvement. The median estimated glomerular filtration rate (eGFR) was 76 ml/min/1.73m^2 (IQR 65–104), and the median 24h-proteinuria 1900 mg (IQR 580–3275) *(table 1)*. One patient was dialysis-dependent at diagnosis but became dialysis-free after initial therapy (before RTX). Fifteen patients (68.2%) underwent kidney biopsy, which confirmed IgAV in all cases. A diffuse endo- and/or extra-capillary IgAV-glomerulonephritis (classes 3-4) was observed in nine cases (60%). At diagnosis, disease activity assessment showed a median Birmingham Vasculitis Activity Score (BVAS) of 16.5 (IQR 13.0–23.8) (*table 1*).

Sixteen patients (73%) had received other treatments prior to RTX: all of them had received glucocorticoids, alone or combined with cyclophosphamide, azathioprine, mycophenolate mofetil or other drugs (*table 1*). These 16 patients received RTX (only one as monotherapy) for refractory or relapsing disease. The remaining six patients received RTX as first-line therapy (five as monotherapy and one together with low-dose glucocorticoids) because they had contraindications to standard-dose glucocorticoids or other immunosuppressive agents. Overall, 16 patients received RTX as add-on therapy while six as monotherapy.

At RTX initiation, 18 patients (81.8%) had skin manifestations, 15 (68.2%) gastrointestinal involvement, 18 (81.8%) kidney involvement, and 16 (72.7%) arthritis and/or arthralgia. The median BVAS was 15.0 (IQR 9.5–19.8); the median eGFR was 82 ml/min/1.73m^2 (IQR 65-101) and the median 24h-proteinuria 1700 mg (IQR 750-2375) (*table 2*).

One month after RTX, 10 patients (45.5%) had achieved remission; BVAS significantly decreased (p=0.0005) (*figure 1*). At month 6, 16 patients (72.7%) were in remission and six (17.3%) had active disease (three because of persisting disease and three because of relapse after remission) (*table 2*); as compared with baseline, BVAS and prednisone dose significantly decreased (p=0.0008 and p=0.03, respectively). At month 12, 16 patients (72.7%) were in remission and six (17.3%) had active disease (persistent disease in five and

relapse in one); significant reductions vs. baseline were observed for BVAS (p=0.0005), proteinuria (p=0.001), CRP (p=0.0007), and prednisone dose (p=0.01) (*figure 1*). Thus, during the first 12 months after RTX, remission was achieved by 20 patients (cumulative incidence of remission 90.9%), four of whom relapsed.

The median follow-up from the start of RTX was 24 months (IQR 18-48). At last follow-up, 18 patients were in remission, three had active disease, and one was deceased (month 60). Of the patients in remission, five were taking low-dose glucocorticoids (2.5-5 mg/day of prednisone). Significant reductions from RTX initiation through last follow-up were observed for BVAS (p<0.0001), 24h-proteinuria (p<0.0001), CRP (p=0.0005), and prednisone dose (p<0.0001) (*figure 1*). eGFR did not change significantly. At last follow-up, one patient had reached ESRD requiring hemodialysis (month 13 after RTX), one had stage 4 CKD, four had 24h-proteinuria>1g; eight patients were taking ACE-inhibitors or angiotensin-receptor blockers. Microhematuria persisted in eight patients.

When considering the entire follow-up, we recorded relapses in seven of the 20 patients (35%) who had achieved remission. Relapses occurred within a median of 12 months (IQR 6.5-15) after RTX; they involved the kidney in four cases, the gastrointestinal tract in one and the skin in two. Of the four patients with kidney relapses, three were successfully re-treated with RTX, while one received ACE-inhibitors and then progressed to ESRD. The two patients with skin relapses were successfully treated with either sulfasalazine (one case) or low-dose glucocorticoids (one case); the patient with gastrointestinal relapse also responded to resumption of low-dose glucocorticoids.

Circulating $CD19^+$ B-cell levels were not systematically tested and were only available for 11 patients, all of whom achieved B-cell depletion ($<0.01 \times 10^9$ cells/L) after RTX; given the paucity of data, we could not establish any association between B-cell return and relapse.

RTX therapy was generally well tolerated. Two patients experienced infusion reactions: one developed urticaria (grade 3) which responded to oral steroids, while the other developed mild and self-limited dyspnoea (grade 2). These reactions did not preclude subsequent drug infusions. One patient died because of advanced liver cirrhosis (of undetermined aetiology) and pneumonia (month 60 after RTX), but this fatal event was probably unrelated to RTX, given the long period of time elapsed since RTX administration.

Adult-onset IgAV is a rare, often severe, small-vessel vasculitis; if left untreated, it usually has an adverse prognosis.[2] Current treatments, including high-dose glucocorticoids and cyclophosphamide, are only partially effective and their toxicity may be high.[3,4] Our results identify RTX as an effective therapeutic option. In our study, RTX was given for refractory/relapsing disease or as first-line therapy when conventional immunosuppressive agents were contraindicated. The remission rate after RTX was 91%, with most patients achieving remission within six months of RTX therapy. Remission was defined on the basis of the BVAS, a widely used score for disease activity assessment in systemic vasculitides. However, other parameters such as CRP levels and prednisone dose also significantly declined after RTX. Renal outcomes were good: although eGFR remained stable, the reduction in proteinuria was highly significant (approximately 5-fold at end of follow-up vs. baseline). Only one patient reached ESRD and one developed stage 4 CKD.

Relapses were common (relapse rate 35%) after RTX-induced remission; their clinical presentation was variable, and in severe cases re-treatment with RTX proved effective. Overall, RTX was well tolerated; no major treatment-related adverse events were recorded.

The potential mechanisms of action of RTX in IgAV are only speculative. As in IgA nephropathy,[11] also in IgAV immune-complexes containing galactose-deficient IgA1 (Gd-IgA1) are thought to accumulate in target organs and initiate tissue damage. We could neither measure serum Gd-IgA1 nor Gd-IgA1-containing immune-complexes; total serum IgA levels, available in 17/22 patients, showed a slight, progressive reduction after RTX (p=0.03) (*supplementary figure 1*). However, the slow kinetics and the little extent of IgA reduction did not seem to mirror the clinical activity of RTX. We also performed immunohistochemistry on renal and skin biopsies of IgAV patients (*supplementary figure 2*) to investigate which cell types infiltrate target tissues: $CD20^+$ B-cells were either absent or scarce, whereas most infiltrating cells were $CD3^+$ T-cells or $CD163^+$ macrophages. Thus, although it cannot be excluded that RTX in IgAV reduces the expansion of IgA-producing plasma cells or hits tissue-infiltrating B-cells, its therapeutic efficacy most likely results from the impairment of other B-cell functions such as antigen-presentation and T-cell co-stimulation, as already postulated in ANCA-associated vasculitis and other autoimmune conditions.[12-13]

Our study has limitations, mainly related to its retrospective nature and the relatively small sample size. However, it still represents the largest reported experience on the use of RTX in adult-onset IgAV. In conclusion, in our cohort of adult-onset IgAV patients, RTX effectively induced disease remission, allowed glucocorticoid tapering and was well tolerated. Larger, controlled studies are warranted to clarify its role in the management of this rare condition.

CONCISE METHODS

Patients and treatment

We reviewed the clinical records of all patients with adult-onset IgAV treated with RTX at nine different Vasculitis Centres in Europe. The diagnosis of IgAV was based on the 1990 American College of Rheumatology criteria[14] and the 2012 revised Chapel Hill Consensus Conference nomenclature.[1] All patients had to have a biopsy-proven diagnosis of IgAV. The patients were included if: i) their age at IgAV diagnosis was >18 years; ii) they had severe involvement of at least one organ (including biopsy-proven IgAV-related nephritis class III-IV;[2] gastrointestinal involvement with haemorrhage, ischemia, perforation and/or abdominal pain unresponsive to common analgesics and lasting for >24h; pulmonary haemorrhage, episcleritis, cardiac and central nervous system involvement); iii) other systemic autoimmune or neoplastic diseases were excluded; iv) RTX was given for the treatment of relapsing or refractory disease or because there were contraindications to the use of standard-dose glucocorticoids and/or conventional immunosuppressants. Allowed RTX schedules included 375 mg/m^2/week for four consecutive weeks or 1000 mgx2 given two weeks apart; RTX could be given alone or on top of other immunosuppressive therapies. Glucocorticoids and other immunosuppressants were tapered or withdrawn according to local practice. RTX was obtained by local hospital pharmacies for off-label use; all patients signed an informed consent. The study was performed in accordance with the declaration of Helsinki.

Data collection and disease activity assessment

We retrieved data regarding patient demographics, clinical manifestations, disease duration and treatments prior to RTX therapy and during the post-RTX follow-up, and reviewed all the pathology reports of diagnostic biopsies. With regards to the post-treatment follow-up, we collected clinical and serological data at specific time-points (months 1, 6, 12, and last follow-

up). eGFR was calculated using the CKD-EPI formula. Information regarding any type of adverse events was also collected; adverse events were graded using the Common Terminology Criteria for Adverse Events version 4.0.[15] Disease activity was evaluated using the Birmingham Vasculitis Activity Score (BVAS), version 3.[16] This score refers to new or worsening symptoms due to vasculitis activity, with higher scores indicating a more active disease. Remission was defined by BVAS=0, or BVAS≤5 if all scores were due to persistent haematuria or proteinuria in the presence of stable or improving renal function. Relapses were defined as an increase in disease activity requiring the reinstitution of glucocorticoids/other immunosuppressants or a significant increase in glucocorticoid dose (>50% for prednisone doses ≥15 mg/day or >100% for doses ≤12.5 mg/day).

Renal biopsy

Renal biopsy findings compatible with a diagnosis of IgAV-nephritis were classified as follows according to Pillebout *et al.*[2] class 1, mesangiopathic glomerulonephritis; class 2, focal and segmental glomerulonephritis (segmental endo- and/or extra-capillary proliferation involving less than 50% of the glomeruli); class 3, diffuse and severe endocapillary proliferative glomerulonephritis; class 4, endo- and extra-capillary glomerulonephritis; class 5, global glomerular sclerosis involving >90% of the glomeruli.

Statistical analysis

Continuous variables were expressed as median and IQR, while categorical variables as n(%). Variations of continuous variables between two time-points were assessed using the Wilcoxon's test. Variations in continuous variables across different time-points (baseline, month 1, month 6, month 12, last follow-up) were assessed using Friedman's test. p values were corrected using Dunn's test for multiple comparisons. Corrected p values <0.05 were considered statistically significant. Statistical analysis was performed using GraphPad Prism 5.

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Table 1. Main characteristics of the 22 patients with IgA vasculitis enrolled in the study

	n=22
Male gender, n (%)	12 (54.5)
Age at diagnosis, median (IQR)- *years*	37.5 (22.8-49.8)
Organ involvement at diagnosis, n (%)	
Skin	21 (95.5)
Gastro-intestinal	18 (81.8)
Kidney	20 (90.9)
Joint	17 (77.3)
Other sites*	1 (4.5)
BVAS, median (IQR)	16.5 (13.0-23.8)
eGFR (CKD-EPI), median (IQR)- *ml/min/1.73m^2*	76.0 (65.0-104.0)
Proteinuria, median (IQR)- *mg/24h*	1900 (580-3275)
Kidney biopsy¶, n (%)	15 (68.2)
Class I	4/15 (26.7)
Class II	2/15 (13.3)
Class III	6/15 (40.0)
Class IV	3/15 (20.0)
Treatments before RTX, n (%)	
Glucocorticoids	16 (72.7)
Cyclophosphamide	7 (31.8)
Azathioprine	7 (31.8)
Mycophenolate mofetil	9 (40.9)
Other	7 (31.8)
Disease duration at the time of RTX therapy, median (IQR)- *months*	13.5 (0.8-25.8)
Indication for RTX therapy, n (%)	
Refractory disease	8 (36.4)
Relapsing disease	8 (36.4)
Contraindications to conventional steroid/IS therapy	6 (27.3)
RTX schedule, n (%)	
375 mg/m^2/week x4	15 (68.2)
1 g x2 (two weeks apart)	7 (31.8)

Data are presented as n(%) or median (interquartile range, IQR)
¶Kidney biopsy findings are classified according to Pillebout *et al.* (ref #2)
* one patient had pancreatic involvement

Abbreviations used in the table. IQR: interquartile range; BVAS: Birmingham Vasculitis Activity Score; eGFR: estimated glomerular filtration rate; CKD-EPI: chronic kidney disease epidemiology collaboration; RTX: Rituximab; IS: immunosuppressive

Table 2. Frequencies of organ involvement and main disease parameters at different time-points

	Time after RTX treatment			
	Baseline n=22	**Month 1 n=22**	**Month 6 n=22**	**Month 12 n=22**
Active organ involvement, n (%)				
Skin	18 (81.8)	5 (22.7)	1 (4.5)	3 (13.6)
Gastro-intestinal	15 (68.2)	0	2 (9.1)	1 (4.5)
Kidney	18 (81.8)	13 (59.1)	3 (13.6)	3 (13.6)
Joint (arthritis/arthralgia)	16 (72.7)	4 (18.2)	2 (9.1)	1 (4.5)
BVAS, median (IQR)	15.0 (9.5–19.8)	6.0 (4.5-8.5)	5.0 (4.5-10.5)	5.0 (1.5-8.0)
eGFR (CKD-EPI), median (IQR)- *ml/min/1.73m^2*	82.0 (65.0–101.0)	92.0 (54.0-98.5)	78.0 (66.2-90.7)	77.0 (60.0-106.0)
Proteinuria, median (IQR)- *mg/24h*	1700 (750 – 2375)	1730 (618-3708)	479 (150-3000)	493 (100-1000)
Concomitant treatments, n (%)				
Glucocorticoids and/or immunosuppressants	16 (72.7)	11 (50.0)	6 (27.3)	4 (18.2)
Glucocorticoids	15 (68.2)	11 (50.0)	6 (27.3)	4 (18.2)
Immunosuppressants	7 (31.8)	5 (22.7)	4 (18.2)	4 (18.2)
Patients in remission, n (%)	-	10 (45.5)	16 (72.7)	16 (72.7)

Abbreviations used in the table. RTX: Rituximab; BVAS: Birmingham Vasculitis Activity Score; IQR: interquartile range; eGFR: estimated glomerular filtration rate; CKD-EPI: chronic kidney disease epidemiology collaboration

FIGURE LEGENDS

Figure 1. *Variations in Birmingham Vasculitis Activity Score (BVAS), C-reactive protein (CRP) levels, prednisone dose, estimated glomerular filtration rate (eGFR) and 24h-proteinuria throughout the study period*. Significant reductions in BVAS ($p<0.0001$), CRP ($p=0.0005$), prednisone dose ($p<0.0001$) and 24h-proteinuria ($p<0.0001$) were observed after RTX therapy. No significant change of eGFR was found ($p=0.59$). These variations were calculated using Friedman's test and corrected using Dunn's test for multiple comparisons.

In the plots, the boxes indicate the 25^{th}-75^{th} percentile, the bar inside the boxes indicates the median, the whiskers indicate the 10^{th}-90^{th} percentile, and the dots the outliers.

Abbreviations: BVAS: Birmingham Vasculitis Activity Score; eGFR: estimated glomerular filtration rate. t0, t1, t6, t12, last-fu denote respectively the time of Rituximab therapy, month 1, month 6, month 12 and last follow-up.

Supplementary figure 1. *Variations in total IgA serum levels throughout the study period*. Serum IgA levels slightly but significantly declined over time ($p=0.03$ using Friedman's test)

Supplementary figure 2. *Immunohistochemical characterisation of the main inflammatory cell types in renal and skin lesions from patients with IgA vasculitis*. The images show representative findings obtained from 3 renal biopsies and 3 skin biopsies of patients with adult-onset IgA vasculitis. Renal biopsy findings are shown in figures A, C, E, G and I, and skin biopsy findings in figures B, D, F, H and J. A and C show endo- and extra-capillary glomerulonephritis with dominant IgA deposits at immunofluorescence. At immunohistochemical analysis, the main infiltrating cells are $CD163^+$ macrophages (E), and $CD3^+$ T-cells (G), whereas $CD20^+$ B-cells are scarce (I). B and D show leukocytoclastic vasculitis of the skin with dominant IgA deposits at immunofluorescence. At immunohistochemical analysis, the main infiltrating cells are $CD163^+$ macrophages (F), and $CD3^+$ T-cells (H), whereas $CD20^+$ B-cells are absent (J).

A, B: haematoxylin and eosin, original magnification x20, bar 200 um. C, D: immunofluorescence staining using anti-IgA antibodies; original magnifications x40 (C), x20 (D), bar 200 um (C), 150 um (D). E, F: immunohistochemical staining using anti-CD163 antibody, original magnification x20. G, H: immunohistochemical staining using anti-CD3 antibody, original magnification x20. I, J: immunohistochemical staining using anti-CD20 antibody, original magnification x20