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

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INTRODUCTION AND AIMS: Immunoglobulin A vasculitis (IgAV), formerly Henoch-Schönlein purpura, is a systemic vasculitis characterized by purpura, arthritis, gastrointestinal symptoms and glomerulonephritis. In children the disease course is usually benign. In adults IgAV is rarer but more severe with renal failure in approximately 30% of patients and frequent evolution to end-stage renal disease. Standard therapy includes corticosteroids and/or immunosuppressive drugs but its efficacy is controversial. Only few case reports describe rituximab (RTX) in IgAV treatment. In this case series we report a multicentre experience on RTX use in adult-onset IgAV with severe organ involvement, either as add-on therapy or as monotherapy.

METHODS: We included all patients with adult-onset IgAV treated with RTX in eight Nephrology or Rheumatology Centres. Disease activity was assessed using BVAS at diagnosis, at RTX initiation and at months 1, 6 and 12. Remission was defined by BVAS=0 or BVAS≤5 if all scores were due to persistent haematuria or proteinuria with stable or improving renal function.

RESULTS: Twenty-two patients were included in the study. Clinical and laboratory data at diagnosis are described in *table 1*. Sixteen patients received RTX as add-on therapy and six as monotherapy. The median disease duration at the start of RTX was 13.5 months (IQR 0.75-25.75). Sixteen patients (73%) had received other immunosuppressive treatments before RTX. For these patients, the indication to RTX was refractory disease (eight patients) or a relapsing disease (eight patients). The patients who received RTX as first-line therapy had contraindications to standard therapy (six patients). At RTX initiation, 18 patients presented with skin manifestations, 15 patients had gastrointestinal involvement, 18 had kidney involvement and 16 arthritis/arthralgia. The median BVAS, eGFR and 24h-proteinuria were respectively 15 (IQR 9.5-19.8), 82 ml/min/mq (IQR 65-101) and 1700 mg (IQR 750-2375) (*table 2*). Fifteen (68%) patients had undergone kidney biopsy at diagnosis. An extracapillary proliferative glomerulonephritis was observed in 60% of the biopsies (*table 1*). One month after RTX, 10 patients (45.5%) achieved clinical remission. At month six, 16 patients (72.7%) had achieved remission and six (17.3%) had active disease (three because of persisting disease and three because of relapse after remission). 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) (*table 2*). 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). 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.

RTX was well tolerated, only 1 patient developed a serious adverse event (bullous skin reaction) and had to stop RTX.

	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/1.73m²*	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/m²/week x4	15 (68.2)
1 g x2 (two weeks apart)	7 (31.8)

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

	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/1.73m²*	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)

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

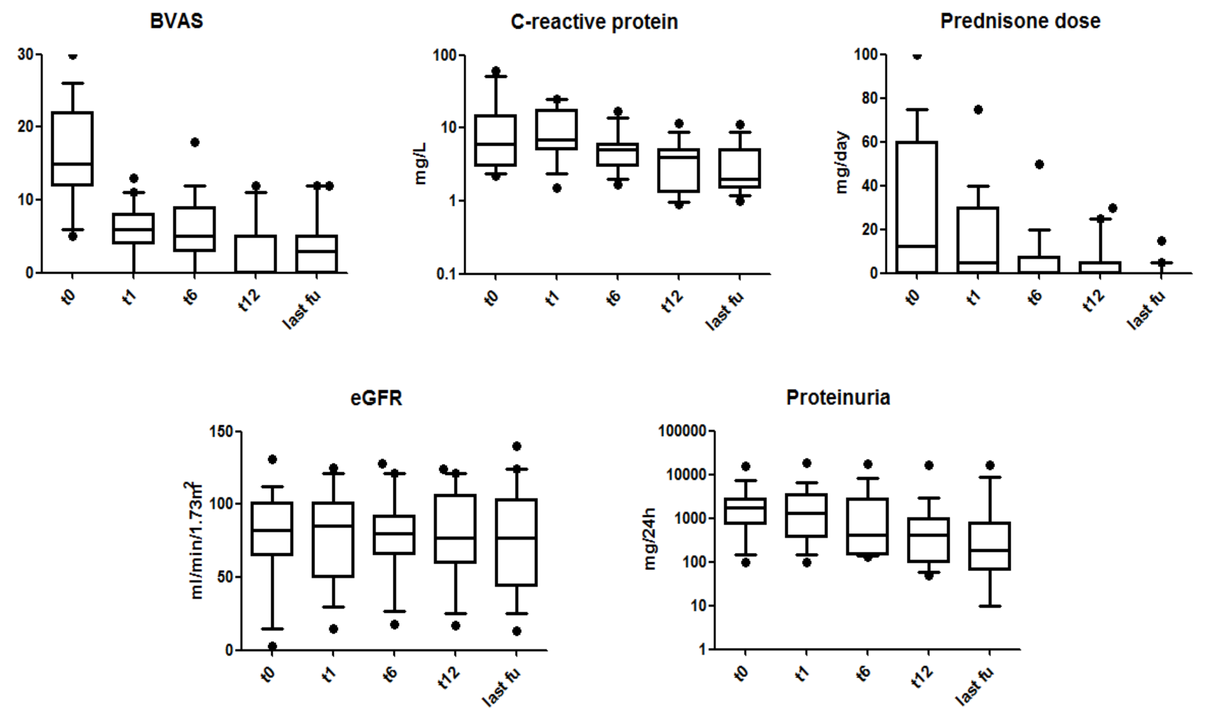

Figure 1. Variations in Birmingham Vasculitis Activity Score (BVAS), C-reactive protein (CRP) levels, prednisone dose, estimated glomerular filtration rate (eGFR) and 24h-proteinuria throughout the study period. Significant reductions in BVAS ($p<0.0001$), CRP ($p=0.0005$), prednisone dose ($p<0.0001$) and 24h-proteinuria ($p<0.0001$) were observed after RTX therapy. No significant change of eGFR was found ($p=0.59$).

CONCLUSIONS: This is, to our knowledge, the largest case series on RTX for adult-onset IgAV. Our results suggest that RTX might be a good and safe option for the treatment of this disease. Larger studies are needed to confirm our findings.

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