Rituximab in severe immunoglobulin-A vasculitis (Henoch-Schönlein) with aggressive nephritis

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Received on March 8, 2020; accepted in revised form on April 16, 2020.

Clin Exp Rheumatol 2020; 38 (Suppl. 124): S195-S200.

Keywords: IgA vasculitis, rituximab, glucocorticosteroid, immunosuppressants.

Competing interests: none declared.

ABSTRACT

Objective. *Immunoglobulin-A vasculitis (IgAV) is a systemic small-vessel vasculitis in which renal involvement indicates severity of illness, and chronic kidney disease represents the most serious long-term complication. No treatment at present is specifically recommended for IgAV. Recently, rituximab (RTX) has been shown to be effective in case series of adults with IgAV. However, long term results are lacking. Aim of the study is to evaluate the effectiveness of RTX as induction therapy and maintenance of remission in adults with severe IgAV and aggressive glomerulonephritis.*

Methods. *This study included 12 adult-onset patients, 8 males and 4 females, mean age 45.1 years (range 19-75) with a mean follow-up duration of 33.7 months (range 6-144). All patients had a severe IgAV with biopsy proven crescentic nephritis. RTX was given for the treatment of a refractory disease or because of definite contraindications to standard therapies.*

Results. *Eleven patients (91.7%) achieved a clinical response at 6 months. Ten patients had a complete response (CR) while one had a partial response and was given an additional dose of RTX after 12 months for persistent proteinuria (1gr/24 hrs) despite systemic remission. He achieved a CR 6 months later. One patient was considered unresponsive to RTX and was switched to MMF. Among the 10 patients with CR, 1 needed maintenance doses of RTX every 6 months for iterative relapsing of severe purpura, 1 relapsed after 15 months and received a new induction course showing a CR again. A significant decrease in BVAS (p=0.031) and 24-hour-proteinuria (p=0.043) from RTX initiation through the last follow-up has been detected. One patient, who had a CR with RTX alone died after 6 months for therapy-unrelated cardiovascular cause.*

Conclusion. *RTX proved to be effective and safe for induction and maintenance of long-lasting remission in severe IgAV with aggresive renal involvement. Data also suggest that RTX can be indicated not only for refractory cases, but can be also proposed as a first line therapy.*

Introduction

Henoch-Schönlein purpura (HSP), also called immunoglobulin-A vasculitis (IgAV), is a systemic small-vessel vasculitis with IgA1-dominant immune deposits (1, 2).

The whole spectrum of disease is characterised by a tetrad of clinical manifestations, including palpable purpuric rash, arthralgia/arthritis, gastrointestinal symptoms (*i.e.* abdominal pain, gastrointestinal bleeding) and renal disease (3, 4). However, several organs can be involved as a result of a systemic leukocytoclastic vasculitis (5).

IgAV is the most common type of vasculitis in childhood, but is much less frequent in adults, who more often show a worse outcome (4). This is mainly related to the presence of renal involvement. Indeed, while approximately 1% of all IgAV patients develop chronic kidney disease (6), this figure gets up to 11% in adults (7). This is why there is a need to define the optimal treatment of IgAV, especially in adults.

The current clinical practice guidelines suggest that patients with urine protein-to-creatinine ratio of >1 face a moderate-to-high risk of progressive kidney function loss (8). Pillebout *et al.* (9) pointed out advanced age (>50 years) at onset to be a powerful predictor of severe renal failure. Other authors (10, 11) emphasised that lower serum albumin predicted IgAV progression in patients with initially normal renal function.

In patients with IgAV, vascular inflammation is characterised by IgA1 and

complement factors deposition and large neutrophil infiltrates. Using a double staining with an anti-IgA polyclonal antibody and a monoclonal antibody directed to galactose-deficient IgA1, namely KM55, on biopsy specimens from IgAV patients, Suzuki *et al*. (12) demonstrated a definite impairment of IgA1 glycosilation with exposition of subjacent residues which might function as new neoepitopes and foster the appearance of IgG anti-undergalactosilated IgA.

On the other hand, Hu *et al*. (13) identified alterations of subsets of B cells that may contribute to the IgAV development, including an increased expression of CD86, a protein expressed on antigen-presenting cells and activated B cells that provides costimulatory signals necessary for $CD4^+$ T cells, while B reg were found to be significantly lower in IgAV pts and serum IgA concentration was positively related with the number of $CD38^+CD19^+$B cells. Recently, the role of T cells and their interactions with B cells in the pathogenesis of IgAV has also become a focus of research as well (14).

Despite an increased knowledge on pathogenesis, management of IgAV continues to be a challenge, especially in adults who are at higher risk of renal involvement.

Based on some data showing a decreased severity and enhanced rate of resolution of extra-renal symptoms, especially arthritis, abdominal pain and swelling (8), glucocorticoids (GC) used to be thought as a reasonable first line therapy in adults. Actually, apart from symptomatic relief, no relevant long-term benefits in terms of shortening the length of the illness or reducing recurrences or progression of nephritis could be achieved (15, 16).

Immunosuppressive agents (azathioprine [AZA], cyclophosphamide [CYC], cyclosporine [CYC], mycophenolate mofetil [MMF]) have been used in combination with GC (17, 18). A randomised open-label trial failed to demonstrate any benefit of combining CYC to GC in adults. In a recent paper Gazel *et al*. aimed to investigate the disease cours, relapse rate and prognostic factor in a retrospective cohort of adult IgA vasculitis. Patients were treated with gliocorticosteroids alone or in association with traditional immunosuppressant (AZA or CYC). The authors concluded that more effective treatment options are needed in a subgroup of patients with IgAV to prevent the damage related with the vasculitis, especially with more severe disease (19). No randomised study has been undertaken to evaluate the efficacy of other immunosuppressants. Finally, there are limited case reports describing some benefits by bortezomib (20). Recently RTX has been suggested as an effective option for adult onset IgAV (21). We previously reported a pilot experience on 5 adults, including 3 cases who were refractory to conventional therapies, and 2 who were treated in front line regimen. All of them achieved complete renal remission, one patient required maintenance RTX therapy due to cutaneous relapses (22). Subsequently our cases were integrated into a multicentre observational study in which data for 22 adult patients were collected (23). Significant reduction in BVAS, C-reactive protein levels, prednisone dose, and proteinuria throughout the study period was observed. No change in the estimated GFR was found. In summary, 91% of the patients achieved remission following RTX therapy. In most cases, remission was obtained within 6 months from starting RTX therapy. A putative limitation of that study relied just on its multicentre character. Indeed, 22 clinically heterogeneous pts had been collected from 9 centres (meanly 2.4 pts/centre) with different RTX schemes and management attitudes.

Here we describe our extended experience on RTX use in a more homogeneous series of IgAV adults with aggressive glomerulonephritis.

Table I. Patient characteristics at the onset and previous treatments.

	Sex	Age at diagnosis	Organ involvement	Duration of follow-up (months)	Maintenance therapy	BVAS at onset
Pt 1	F	70	S,K,J°	144	No	13
Pt 2	M	21	A,S,K	61	RTX 2 yrs	15
Pt 3	M	43	A,S,K,J°	34	No	30
Pt 4	F	26	S,K,J	20	No	15
Pt 5	M	55	A,S,K,J	15	No	25
Pt 6	M	57	K,S	20	No	13
Pt 7	M	49	A,S*,K,J	28	RTX (reinduction after 18 months)	24
Pt 8	F	19	A,S,K,J°	29	RTX/MMF	17
Pt 9	M	42	A,S,K,J	27	RTX (single dose after 10 months)	25
Pt 10	M	59	A,S,K	6	No	13
Pt 11	M	75	S,K	12	No	18
Pt 12	F	25	A,K,J	9	No	18

S: skin with (*) necrotic ulcers; A: abdomen; K: kidney; J: joint involvement with (°) frank arthritis; RTX: rituximab; MMF: mycophenolate mofetil.

Patients and methods

Diagnosis was based on a combination of clinical assessment, serological tests and histological analysis according to EULAR criteria (24). All patients received 4 weekly doses of RTX (375 mg/m2/week) given alone or together with low dose GC (5 patients). Seven patients (58.3%) receive RTX as a first-line therapy (3 as monotherapy and 4 with low-dose GC) because of contraindications to standard dose GC or immunosuppressive agents. Five patients (41.7%) had been previously administered other treatments (3 CS alone, and the other 2 GC combined with immunosuppressants) (Table I). All patients who had been previously given other treatments, received RTX alone.

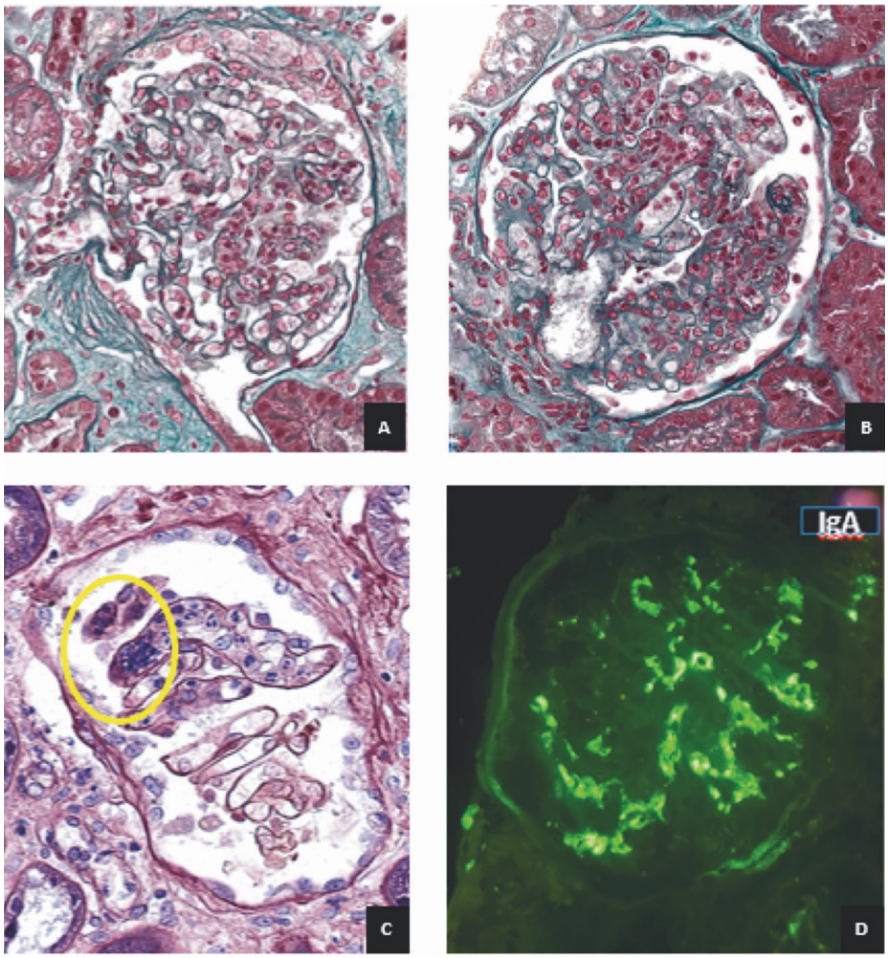

Fig. 1. Kidney involvement during IgA vasculitis relapse.
A: Extracapillary proliferation. **B**: Endocapillary proliferation. **C**: Fibrinoid necrosis. **D**. Immunoglobulin A deposit on immunofluorescence microscopy.

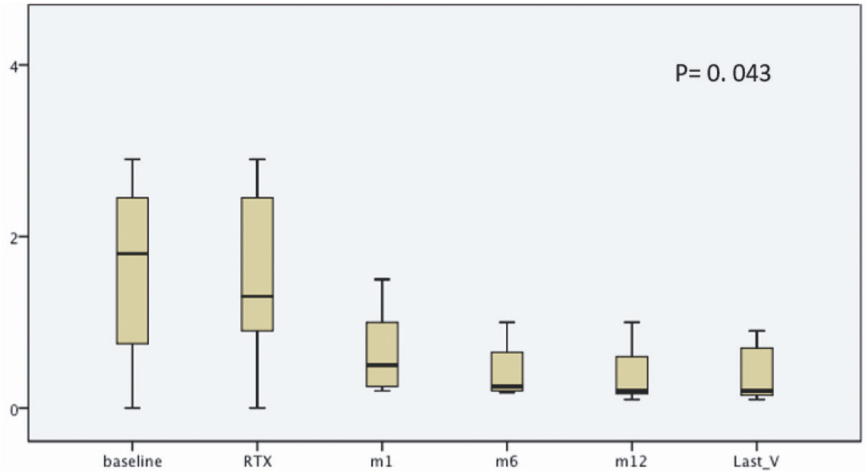

Fig. 2. Variations in Birmingham Vasculitis Activity Score (BVAS) during follow-up obtained by Dunnet test.

At the time of RTX initiation, all patients had a severe biopsy-proven renal involvement with extracapillary proliferation (7 to 43% of glomeruli). The mean Crs value was 2.06 mg/dl (range 0.8-5.1 mg/dl), mean estimated GFR was 63.4 ml/minute/1.73 m^2 (range 11-111 ml/minute/1.73 m^2) and the mean proteinuria was 2.26 g/24 hours (range 0.3-2.9 g/24 hours). Eleven out of 12 patients (91.7%) had a cutaneous manifestation with necrotic lesions in 6 cases. Joint involvement was observed in 10 out of 12 patients (83.3%): arthralgia in 7 and ultrasonography-proven arthritis in 3. A gastrointestinal involvement was present in 6 patients.

RTX was obtained by local hospital pharmacies for off-label use, according to the rules for the management of Rare Diseases of Piedmont (North-West Italy). All patients gave their informed consent.

Clinical and serologic data at months 1, 3, 6, 12, and at the last follow-up visit were carefully collected together with information regarding any types of adverse events (AEs). Disease activity was evaluated using BVAS version 3 (12). This score refers to new or worsening symptoms due to active vasculitis, with higher scores indicating more active disease. Complete remission was defined as a BVAS of 0, or as a BVAS of ≤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, as defined by BVAS, requiring either the reinstitution of GC or immunosuppressants, or an increase in GC dose (>50% for prednisone doses ≥15 mg/day or >100% for doses ≤12.5 mg/day).

Results

Patients included 8 males and 4 females, mean age at diagnosis 45.1 years (range 19–75 years). Five out of 12 patients were described in a previous report (22). Their data in the present cohort refer to a longer follow-up period than that originally reported. The median duration of the follow-up was 33.7 months (range 6–144 months).

Eleven patients (91.7%) achieved a clinical response at 6 months. Ten patients had a CR, while 1 had a partial response and was given an additional dose of RTX after 12 months, due to persistent proteinuria (1gr/24 hrs) despite systemic remission. He achieved a CR 6 months later. One patient did not respond to RTX and was switched to MMF. Among the 10 patients with CR, 1 needed maintenance doses of RTX (500 mg every 6 months) due to relaps-

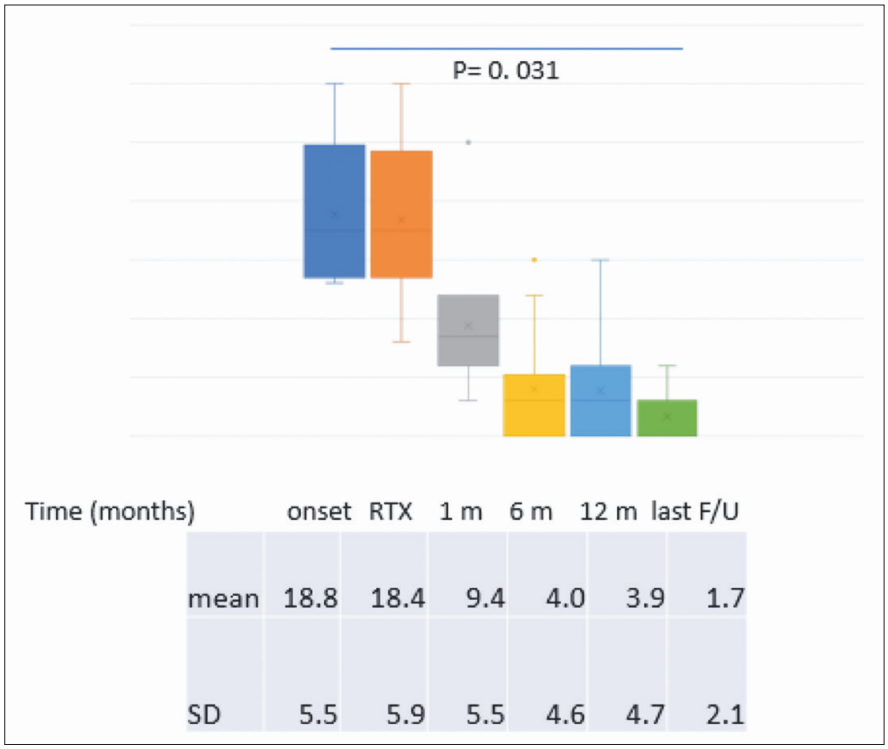

Fig. 3. Variations in proteinuria during follow-up obtained by Dunnet test.

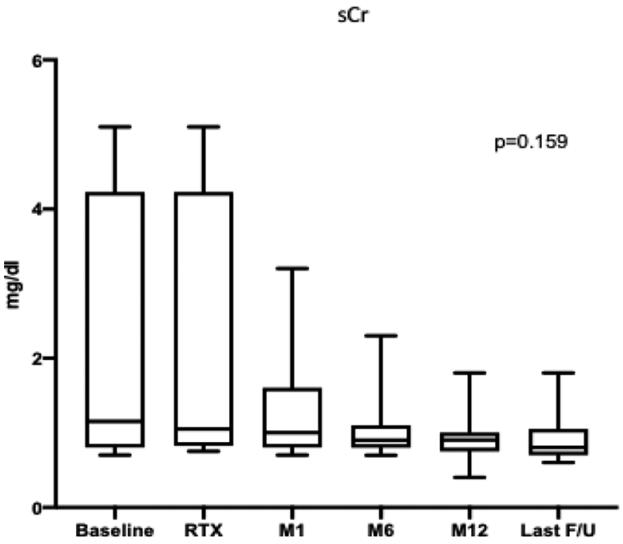

Fig. 4. Variations in renal function sCr during follow-up obtained by Dunnet test.

ing of severe purpura; 1 relapsed after 15 months and, after a second renal biopsy (Fig.1), received a new induction course, showing again CR.

A significant BVAS decrease was detected from 18.8 to 1.7, p=0.031 and in 24-hour proteinuria from 2.26 g/24 hours (range 2.9–0.3) to 0.48 (range 0.1–1), p=0.043 from RTX initiation through the last follow-up visit (Fig. 2 and 3). With regards to the renal function, a downward trend in creatinine values from 2.2 mg/dl (range 0.7–5) to 0.93 (range 0.6–1.8) was observed, but without statistically significant differences (Fig. 4).

All patients had a persistent response at the end of follow-up.

Circulating $CD19^+$ B cell levels were tested in 11 patients, all of whom achieved B cell depletion (<0.01 x 10^9 cells/liter) within 3 months of therapy. In the patient who experienced a relapse after the 15th months, the B cell return was detected between the 9th and 12th month after RTX administration.

RTX was generally well tolerated; no patients experienced major adverse events. One patient had a urinary tract infection resolved after target antibiotic therapy. One patient, who had a CR with RTX alone, died after 6 months of follow-up for treatment-unrelated cardiovascular cause.

Discussion

The definitive therapeutic strategy for IgAV in adults remains to be defined. The goals of the treatment are improvement of acute symptoms, mitigation of short-term morbidity and prevention of chronic renal failure. Since IgAV is characterised by leukocyte infiltration of the blood vessel walls, along with immunoglobulin A deposition resulting in vascular injury and necrosis, early treatment with GC has been proposed for all three therapeutic goals, as it inhibits these inflammatory processes (25, 26). However, GC indication and efficacy remain controversial. Specific treatment of nephritis should be considered in patients with heavy proteinuria and/or impaired renal function at the onset (27). Although nephritis is the most serious long-term complication of IgAV, few data are available to determine the best treatment . There is some evidence that GC reduce the severity and enhance the rate of resolution of extra-renal symptoms, especially arthritis, abdominal pain and swelling (28). Though this therapy provides symptomatic relief, evidence of long term benefit either in terms of shortening the overall length of the illness, or reducing recurrences and progression of nephritis or preventing renal involvement is lacking (8).

RTX was successfully used in vasculitis associated with pathogenic antibodies or immune complex deposition, such as ANCA-associated (29) or cryoglobulinaemic vasculitis (30).

Recently, some case reports and case series reported encouraging results of treatment of IgAV with anti-CD20 antibody (33-37). The effect of RTX is likely mediated by specific drug-related effects on abnormal B cell clones. By depleting B cells, RTX might reduce the formation of IgA containing immune reactants and limited IgAV dis-

ease activity. Wiercinski *et al*. assessed the main lymphocytes subpopulations of peripheral blood in children with IgAV (31). They showed an increased percentage of B lymphocytes (CD19). These findings were confirmed by another study that showed an increased B-lymphocyte percentage and function (32). Moreover, it has been suggested that the therapeutic efficacy of RTX may also result from the interference on other B cell functions, including antigen presentation and T cell co-stimulation (29).

Despite a strong rationale for treating IgAV with RTX, cases reported in literature remain limited and poorly documented, especially with regard to renal involvement (33-37).

In the present study, RTX was given for refractory/relapsing disease or as first-line therapy when conventional treatment was contraindicated. The remission rate after RTX treatment was high (91.7%), with most patients achieving remission within 6 months. Renal outcomes were good with stable sCr and estimated-GFR and significant reduction in proteinuria. At the end of the follow up, only 1 patient had a renal function impairment. Notably, all patients refractory to other treatments achieved a CR with RTX monotherapy. Only one patient needed a reinduction (which was again successful) for relapse.

Our study has limitations related to its retrospective nature and sample size which, however, reflects the rarity of IgAV with crescentic glomerulonephritis. This extended experience confirms the initial results and supports the use of RTX in the treatment of severe IgAV with aggressive renal involvement. In this high risk patients, RTX proved to be effective and safe for induction and maintenance of long-lasting remission. Moreover, present data suggest that RTX is not only effective for refractory IgAV, but can be definitely proposed as a first-line therapy.

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