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THERAPEUTIC ASPECTS IN AUTOIMMUNITY

Rituximab therapy for IgA-vasculitis with nephritis: a case series and review of the literature

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Abstract Henoch–Schonlein purpura, also called IgA-vasculitis, is a systemic small vessels vasculitis with immunoglobulin A1-dominant immune deposits. The optimal treatment remains controversial. Because IgA-vasculitis is characterized by leukocyte infiltration of the blood vessel walls along with immunoglobulin A deposition, and because glucocorticosteroids inhibit inflammatory processes, early administration of glucocorticosteroids has been postulated to be effective, but this indication remains controversial. Immunosuppressive agents (azathioprine, cyclophosphamide, cyclosporine, mycophenolate) have been used in combination with glucocorticosteroids without definitive evidence of effectiveness. The efficacy of rituximab in adult IgA-vasculitis has been reported in few cases. We described a monocentric experience on the use of rituximab in adult IgA-vasculitis with biopsy-proven nephritis. The patients achieved a complete remission of nephritis and syndromic manifestations, and no patients experienced adverse reactions. These data have been compared with the limited literature nowadays available.

Keywords IgA-vasculitis · Henoch–Schonlein purpura nephritis · Henoch–Schonlein treatment · Rituximab · B cell depletion therapy · ANCA-associated vasculitis

Introduction

Henoch–Schonlein purpura (HSP), also called IgA-vasculitis (IgAV) [1, 2], is a systemic small vessels vasculitis with immunoglobulin A1-dominant immune deposits [3]. The disease is characterized by a tetrad of clinical manifestations: palpable purpuric rash, arthralgia/arthritis, gastrointestinal symptoms (i.e., abdominal pain, gastrointestinal bleeding) and renal disease (so-called Henoch–Schonlein purpura nephritis, HSPN) [4–6]. However every organ can be involved as a result of a systemic leukocytoclastic vasculitis [7, 8]. Some patients may be managed with supportive therapy only. Because IgAV is characterized by leukocyte infiltration of the blood vessel walls along with immunoglobulin A deposition, and because glucocorticosteroids (GC) inhibit inflammatory processes, early treatment with corticosteroids has been postulated to be effective [9, 10]. There is some evidence that glucocorticoids reduce the severity and enhance the rate of resolution of extrarenal symptoms, especially arthritis, abdominal pain and swelling [11]. Treatment provides symptomatic relief, but there are no relevant long-term benefits in using GC in terms of shortening the length of the illness or reducing recurrences or progression of nephritis [12–14]. Immunosuppressive agents (azathioprine, cyclophosphamide, cyclosporine, mycophenolate) have been used in combination with corticosteroids [10, 15–18]. One randomized open-label trial of cyclophosphamide in HSPN concluded that the addition of cyclophosphamide to corticosteroids provided no benefit in adults [18]. No other randomized study has been undertaken to evaluate the efficacy of any treatment modality

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[19]. Rituximab is a monoclonal antibody to the CD20 antigen on B cells that was initially designed and approved for the treatment of non-Hodgkin's B cell lymphoma in 1997. In the last 15 years, it has been used in many immune-mediated diseases, beginning with rheumatoid arthritis [20], and now extending into several other fields [21].

Rituximab (RTX) has been successfully used in SLE [22–24] and vasculitis with pathogenic antibodies or immune complexes deposition, such as cryoglobulinemia [25, 26] or ANCA-associated vasculitis [27–31]. The impact of B lymphocytes on disease activity and its specific role in the pathogenesis of IgAV remains to be explained definitively, at least in part as the consequence of the limited number of studies investigating B cell subsets. Because of the putative role of B cells in the pathogenesis of IgAV [32], RTX appears a potential therapeutic tool. RTX acts via antibody-dependent, cell-mediated cytotoxicity, complement-dependent cytotoxicity and apoptosis and effectively depletes B cells for 6–9 months in more than 80 % of pts [33, 34]. Only a few adult HSP patients treated with RTX have been reported in literature up to now.

We described our experience on RTX use in a small series of adult IgA-vasculitis with biopsy-proven aggressive glomerulonephritis.

Methods

This series comprises five adults (three males and two females) affected by HSPN. Baseline date are shown in Table 1. Diagnosis was based on a combination of clinical assessment, serological tests and histological analysis according to EULAR criteria [35].

Patient 1

In July 2007, a 70-year-old Caucasian female was admitted to our hospital to investigate leg purpura, microhematuria and proteinuria (2 g/die). She had a history of hypertension, type 2 diabetes (on diet therapy only) and chronic gastritis. In 2001 and 2007, she had two episodes of leg purpura associated with arthritis. Two previous skin biopsies showed a leukocytoclastic vasculitis (IF not performed). Renal biopsy showed 16 glomeruli (four sclerotic). Light microscopy revealed extensive mesangial hypercellularity with expanded matrix and three glomeruli with epithelial crescents and fibrinoid necrosis. A moderate extent of interstitial fibrosis was also present. Immunofluorescence (IF) study was positive for IgA with mesangial pattern with extension to glomerular membranes. IgG, C3 and fibrinogen were weakly positive with a similar mesangial pattern. The patient was given a pulse steroid therapy (methylprednisolone 1 g/day for 3 days) with subsequent oral prednisone (progressively tapered) associated with mycophenolate mofetil (2 g 7 day) without relief of cutaneous vasculitis. Five doses of intravenous immunoglobulins (400 mg/kg/die) were administrated without effects. After 2 months, RTX therapy was started (375 mg/m^2 once weekly for 4 weeks). In the following 8 years, he had had only one transient cutaneous relapse, while the urinary protein excretion remained undetectable. No relevant adverse effects have been observed.

Patient 2

In March 2013, a 21-year-old Caucasian male was admitted to our hospital with a previous diagnosis of IgA-vasculitis. He had 3-year history of leg purpura (a skin biopsy revealed a small-vessel leukocytoclastic vasculitis) with necrotic ulcers, urinary abnormalities (microhematuria and proteinuria) and abdominal pain treated initially with prednisone and then with many immunosuppressive agents (azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, intravenous immunoglobulins) because of incomplete response and repeated relapses. Despite a maintenance treatment with full doses of prednisone and mycophenolate mofetil, the patient developed urinary abnormalities (microhematuria with subnephrotic proteinuria). A renal biopsy was performed, and 42 glomeruli had been examined. Light microscopy revealed mesangial hypercellularity with

Table 1 Patient data

Patients (*n*°)	Gender	Age at diagnosis	Therapy before RTX	Organ involvement	Follow-up
1	F	70	CS, MMF, IGIV	S, K, J°	8 years
2	M	21	CS, Cyp, CyA, AZA, IGIV, MMF	A, K, S*	33 months
3	M	43	–	A, K, S, J°	18 months
4	F	26	C	K, S*, J	7 months
5	M	55	–	K, A, J, S	3 months

CS corticosteroids, *MMF* mycophenolate mofetil, *IGIV* intravenous immunoglobulins, *Cyp* cyclophosphamide, *CyA* cyclosporine, *AZA* azathioprine, *S* skin with (*) necrotic ulcers, *A* abdomen, *K* kidney, *J* joint involvement with (°) frank arthritis

expanded matrix. There was limited interstitial fibrosis. Blood vessels were normal. Immunofluorescence was positive for IgA (predominant), IgM, C3 and fibrinogen in mesangial lesions. The patient received two doses of 1000 mg RTX 2 weeks apart. MMF and prednisone were tapered and discontinued 4 months later. In July 2014, the patient had a severe cutaneous relapse with necrotizing ulcers and a reappearance of urinary abnormalities and was given two more RTX infusions (1000 mg 2 weeks apart) with a maintenance therapy of 500 mg of RTX every 4 months. Presently, microhematuria and proteinuria are undetectable, and no cutaneous relapse has been occurred. No adverse effect has been detected.

Patient 3

In May 2014, a 43-year-old Chinese male was admitted to our hospital to investigate a macroscopic hematuria. The hematuria was preceded by upper respiratory tract infection. He had a history of liver diseases (alcoholic and HCV-related) and two episodes of leg purpura (with reported spontaneous resolution). A previous skin biopsy showed a leukocytoclastic vasculitis (IF not performed). Arthritis, purpura and abdominal pain were absent at the admission. Blood pressure was normal. Laboratory tests revealed a nephritic syndrome with a rapidly progressive renal failure (Crs 5.6 mg/dl). Renal biopsy achieved 35 glomeruli. Light microscopy revealed a mesangial hypercellularity with expanded matrix, tubular erythrocyte casts with necrotic epithelial cells. There was no interstitial fibrosis. Blood vessels were normal. Immunofluorescence study was positive for IgA in mesangial lesions with segmental extension into basal membranes. IgG, IgM, C3, C4, C1 were weakly positive in the same pattern. During hospitalization, the patient developed palpable purple, arthralgias and rectal bleeding. Corticosteroid treatment was started using methylprednisolone pulses, but after the second dose the patient developed a steroid-related psychosis. The drug was quickly stopped, and a single dose of 1000 mg of RTX was administered. There were no adverse events. After 18 month-follow-up, the patient did not show any recurrence of skin rush or rectal bleeding, the Crs was 1.1 mg/dl and urinary protein excretion is undetectable.

Patient 4

In March 2015, a 26-year-old Caucasian female was firstly investigated for leg purpura, microhematuria, proteinuria and arthralgias. She had a previous diagnosis of Rokitansky's syndrome and a 2-year history of purpura with necrotic ulcers, and arthralgia treated with low dose of oral prednisone. In April 2014, she was admitted to another hospital for worsening symptoms. Urinary tests showed microhematuria. A skin biopsy revealed a small-vessel neutrophilic vasculitis. A diagnosis of IgA-vasculitis was performed, and the patient was treated with oral prednisone. One year later, the patient was admitted in our hospital for recurrent flares (purpura and arthralgias) despite steroid therapy. The laboratory tests confirmed microhematuria and revealed proteinuria (1 g/die) with normal renal function. Renal biopsy achieved 40 glomeruli (4 sclerotic). Light microscopy revealed mesangial hypercellularity with expanded matrix, two glomeruli presented with epithelial crescent, two had segmental areas of fibrinoid necrosis. There was no interstitial fibrosis. Blood vessels were normal. Immunofluorescence study was positive for IgA (predominant), IgM, C3 and fibrinogen in a mesangial pattern. The patient received 1 g/die for 3 days of methylprednisolone and progressively tapering oral prednisone. Because of the persistent symptoms and the appearance of renal involvement despite steroid therapy, the patient was also given four doses of RTX (375 mg/m^2 once weekly for 4 weeks). There was no relevant adverse event. Seven months after therapy with rituximab proteinuria is undetectable.

Patient 5

In October 2015, a 55-year-old Caucasian male was admitted to our hospital to investigate leg purpura, microhematuria and proteinuria (1.5 g/die). The symptoms were preceded by upper respiratory tract infection. He had a history of hyperglycemia (treated with metformin). Arthralgia and abdominal pain were present at the admission. Blood pressure was normal. Laboratory tests confirmed a nephritic syndrome. The biopsy skin showed a leukocytoclastic vasculitis. Renal biopsy achieved 31 glomeruli (two sclerotic). Light microscopy revealed a mesangial hypercellularity with expanded matrix, three glomeruli had segmental areas of fibrinoid necrosis. There was no interstitial fibrosis. Immunofluorescence study was positive for IgA and C3 in mesangial lesions with segmental extension into basal membranes. Corticosteroid treatment was started, but after few days the patient developed hyperglycemia and irritability. The drug was stopped, and four doses of RTX (375 mg/m^2 once weekly for 4 weeks) were administrated. There were no adverse events. After 3 month-follow-up, the patient did not show any recurrence of skin rush, arthralgia or abdominal pain, the Crs is 1.0 mg/dl and urinary protein excretion is 0.5 g/day.

Results

We presented five cases of adult-HSPN successfully treated with RTX, mainly as a rescue therapy. Three patients were previously given a conventional immunosuppressive

therapy without benefit. GC therapy was quickly discontinued in the other two patients for severe adverse effects, including a newly-onset psychosis.

The patients achieved a complete renal remission. One patient needed a maintenance RTX therapy due to relapses of cutaneous vasculitis. In all remission persisted for the entire follow-up. No severe adverse events related to the RTX were observed.

Discussion

The optimal therapeutic strategy for IgAV in adults remains controversial. The goals of the treatment are amelioration of acute symptoms, mitigation of short-term morbidity and prevention of chronic renal failure. However, several patients receive only supportive therapy. Since IgAV is characterized by leukocyte infiltration of the blood vessel walls along with immunoglobulin A deposition resulting in vascular injury and necrosis, and GCs inhibit these inflammatory processes, early treatment with GCs has been proposed as an effective strategy for all three therapeutic goals [9, 36, 37]. 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 [38, 39]. Although nephritis is the most serious long-term complication of IgAV, few data are available to determine the best treatment [40]. There is some evidence that glucocorticoids reduce the severity and enhance the rate of resolution of extra-renal symptoms, especially arthritis, abdominal pain and swelling [41]. Though this therapy provides symptomatic relief, evidence of long-term benefit in terms of shortening the overall length of the illness, or reducing recurrences and progression of nephritis or preventing renal involvement is lacking [11–14].

In a randomized, double-blind, placebo-controlled trial, administration of prednisone 1 mg/kg/day for 2 weeks, tapered over 2 more weeks, resulted in resolution of renal involvement and reduced severity and duration of abdominal and joint pain. This scheme was no effective in purpura [13]. Immunosuppressive agents (including azathioprine [39], cyclophosphamide, cyclosporine [16, 42], mycophenolate [15]) have been used in combination with corticosteroids with different results [9, 37, 38]. Halling et al. [19] reported a retrospective study which failed to demonstrate a superiority of the combination of corticosteroids plus cyclophosphamide compared to corticosteroids alone. A randomized controlled trial in 24 patients [42] suggested that cyclosporine may be more beneficial than corticosteroids alone in pts with nephrotic range proteinuria [12]. Plasmapheresis, alone or in conjunction with immunosuppressive agents, has also been used in patients with severe, usually crescentic, renal involvement. This treatment has claimed to obtain good short- and medium-term outcome [43–45]. The data on the beneficial effects of mycophenolate mofetil are limited. Han et al. [46] compared a combination of mycophenolate mofetil with low-dose prednisone versus a full-dose prednisone alone as induction therapy for IgA nephritis with heavy proteinuria (>2.0 g/24 h). After a median follow-up of 28 months in both groups, the overall remission rate was 80.8 % in the full-dose prednisone group and 77.8 % in the mycophenolate mofetil group, suggesting the two regimens to be comparative effective.

Rituximab, a chimeric anti-CD20 monoclonal antibody, was successfully used in vasculitis associated with pathogenic antibodies or immune complex deposition cryoglobulinemia, such as ANCA-associated [26] or cryoglobulinemic vasculitis [10, 31, 47, 48]. The role of ANCA in HSP is controversial. Whereas some studies have found IgA class of ANCA in variable percentages of patients with HSP, others have not been able to detect such antibodies. Other autoantibodies including IgA rheumatoid factor and IgA anticardiolipin antibodies (aCL) have been also found in some patients with acute HSP [49]. RTX, by depleting B cells, might reduce the formation of IgA containing immuno complexes and limited IgAV disease activity. Moreover, previous studies showed a possible role of B cells in the pathogenesis of IgAV. Wierciński et al. assessed the main lymphocytes subpopulations of peripheral blood in 21 children with IgA nephropathy or Schonlein–Henoch purpura. The results showed an increased percentage of B lymphocytes (CD19) in children with IgAV and increased IgA in serum [50]. These findings were confirmed by another paper that indicated an increased B-lymphocyte percentage and function, high immunoglobulins, normal or elevated complement in children with HSP [51]. Despite this possible involvement of B cells in the pathogenesis of IgAV, to our knowledge, cases of HSPN patients treated with rituximab reported in the literature are very few and poorly documented with regard to renal involvement (Table 2). Bellan et al. [52] described the case of a female patient who achieved long-term remission of HSP with rituximab after multiple relapses occurred along a course lasting more than 20 years. Ishiguro et al. reported the case of a 68-year-old woman with purpura nephritis associated with nephrotic syndrome. Following treatment with corticosteroids and cyclophosphamide, proteinuria mildly decreased, while additional rituximab therapy achieved a complete remission [53]. Pindi Sala et al. [54] reported the case of a 49-year-old woman who, 8 years after a kidney transplantation, developed a HSP taking combined immunosuppressive therapy (tacrolimus and azathioprine). She

Table 2 Summary of the studies reporting the use of RTX in HSP

Author (Refs.)	Study design	Numbers of patients treated with RTX	Year of publication	Dosage of RTX	Reason for administering RTX
Bellan et al. [40]	Case report	1	2015	4 weekly RTX (375 mg/m^2)	Disease relapse
Ishiguro et al. [41]	Case report	1	2013	4 weekly RTX (375 mg/m^2)	Persistent proteinuria
PindiSala et al. [42]	Case report	1	2014	Two iv infusions of 1000 mg given 2 weeks apart	Disease relapses and corticosteroid dependence
Pillebout et al. [19]	Case report	1	2011	Two iv infusions of 1000 mg given 2 weeks apart	Fist-line therapy
Donnithorne et al [43]	Case series (pediatric)	3	2009	Two iv infusions of 1000 mg given 2 weeks apart	No response to previous treatment
Fenoglio et al. (present study)	Case series	5	2016	AR or Lymphoma protocols	No response or intolerance to previous treatment/first-line therapy

received systemic corticosteroid treatment, and subsequently, because of relapses and corticosteroid dependence, the patient was treated with rituximab. Successful outcome was observed along 2 years of follow-up. Pillebout et al. [55] reported the case of a 49-year-old patient with moderate nephritis and severe skin HSP who has been treated with rituximab because of relapsing and corticosteroid-dependent disease. The treatment obtained a complete and sustained skin and renal remission. Only a single pediatric case series (3 pts) is present in literature. Donnithorne et al. [56] reported the efficacy of RTX therapy in standard treatment-refractory, chronic HSP. All three patients responded to one or two courses of RTX without serious adverse events.

In conclusion, to our knowledge, this is the first case series report describing successful treatment of adult HSP with the B cell-depleting antibody RTX. This is consistent with the previous reported benefits of RTX in other forms of vasculitis [26, 57, 58] and underlies the role of B lymphocytes in the pathogenesis of IgAV. B cells are important players of the immune response.

While evidence supported by RCTs is lacking, the existing reports suggest RTX to be not only an effective treatment in severe and refractory HSPN but also a first-line therapy, and with high chance of long-lasting remission. Randomized prospective trials comparing conventional agents (i.e., steroids and standard immunosuppressive agents) and RTX are obviously needed in order to prove safety profile, a steroid-sparing opportunity, and the superiority of RTX over supportive or standard treatment. However, IgA-vasculitis is a rare condition with an estimated incidence of 1 case/100,000 Caucasians/year [32]. It is unlikely that the results of a well-designed randomized controlled study can be achieved in a short time. Meanwhile, a trial with RTX in patients with severe IgA-vasculitis either refractory or intolerant to conventional immunosuppressive agents should be considered.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest, nor any financial interest with regard to the present paper.

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