Update on Rituximab: An Established Treatment for All Immune-Mediated Kidney Diseases?

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Key Words

Rituximab · Immune-mediated kidney disease · Systemic lupus erythematosus · Lupus nephritis · Antineutrophil cytoplasm antibody · Idiopathic membranous nephropathy

Abstract

Rituximab, a monoclonal antibody directed against the CD20 antigen, found on certain B-cell subsets, results in significant B-cell depletion and has been increasingly used in immune-mediated renal disease and transplantation. Although originally applied to what were considered antibody-mediated diseases, it has become clear that auto- and alloreactive B cells contribute in many ways to immune dysfunction, and the benefit of B-cell depletion extends beyond reduction in auto- or alloantibody levels. Most positive data regarding the benefit of rituximab in immune-mediated kidney disease have come from uncontrolled cohort studies, with the only positive controlled clinical trials demonstrating efficacy for the treatment of systemic vasculitis. While negative trials may have potentially missed clinical effects due to trial design, there may be significant differences in responses in different diseases or lack of efficacy due to therapeutic overlap when used with certain drug combinations. Rituximab is a novel treatment that provides a clear alternative for patients in different clinical situations, and allows for

customization of therapy. However, much remains to be understood as to how best to use it in a cost-effective manner, when not to use it, and what the long-term impact of therapy may be.

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Introduction

Rituximab has now become established as an important component of many protocols for the treatment of immune-mediated kidney diseases and antibody-mediated transplant disorders. In this review article we focus on the recent evidence for its benefit, and adverse effects, concentrating on its use in immune-mediated glomerular disease.

Rituximab is a genetically engineered chimeric monoclonal antibody, directed against the CD20 antigen, and contains murine heavy and light chain variable regions with a human IgG1 constant region [1]. CD20 is expressed on the surface of immature and mature B cells, but not on plasma cells, and mediates cellular proliferation and differentiation (fig. 1). Rituximab binds CD20 on the B-cell surface and induces apoptosis or cell lysis through complement-dependent and -independent mechanisms. Thus, administration of rituximab results

Fig. 1. B-cell development. CD20 is expressed on the surface of immature and mature B cells, and mediates their proliferation and differentiation [adapted from 2].

in rapid depletion of circulating and tissue CD20-expressing B cells which persists for 6–9 months in the majority of patients, although this can be highly variable [2].

Rituximab was first approved in 1997 to treat non-Hodgkin's B-cell lymphoma. Since then it has been licensed for use in chronic lymphocytic leukaemia, rheu-

matoid arthritis and, more recently, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). In addition, it has increasingly been used off-label to treat a variety of systemic immune-mediated diseases, as well as being an integral part of antibody-mediated transplant rejection and desensitization protocols. In a form of reverse translation, the success following the clinical use of rituximab has highlighted the critical role of B cells in the pathogenesis of various immune-mediated disorders, which had not previously been fully appreciated.

B cells contribute to the (auto)immune response through (i) the processing and presentation of (auto)antigen to T cells, (ii) the production of cytokines (e.g. TNF- α , IL-4 and IL-10), and (iii) their maturation into plasma cells with the production of (auto)antibodies. Rituximab induced depletion of B cells, which correlates with both rituximab levels and the Fc γ IIIa genotype on immune effector cells, interferes with all of these mechanisms [3]. Clinical benefit of rituximab therapy is usually associated with the extent and duration of B-cell depletion; however, depletion of B cells in peripheral blood does not always correlate with tissue depletion, sometimes muddying the relationship between measured B-cell number and clinical effect. Additionally, through alteration in proportions of B-cell subsets, rituximab may augment regulatory T-cell function, reduce NK cell activity, inhibit macrophage activation and following B-cell repopulation promote the return of immunomodulatory transitional B cells.

The optimum dosing regimen for rituximab is unknown. There are two widely used schedules. The first developed for use in lymphoma consists of four weekly intravenous doses of 375 mg/m², while in treating autoimmune disease, two 1 g intravenous doses given 2 weeks apart are used. However, neither is used exclusively (the 2 $\times$ 1 g regimen was used in the main systemic lupus erythematosus (SLE) trials while the 375 mg/m² regimen was used in AAV trials) and variations of these regimens, including those based on the degree of B-cell depletion, are used in some cohort studies, as outlined below. Further work is really needed to establish what the most cost-efficient and efficacious method of drug delivery is.

Safety and Tolerability

Over half a million people worldwide have received rituximab therapy during the last 15 years. In the majority of these patients, it appears to be safe and well tolerated [4]. However, common adverse effects include infu-

sion reactions manifested by fever, chills, headache, nausea, bronchospasm, hypotension and angioedema [5]. The majority of these reactions are mild, occur during the first infusion, and are less frequent with subsequent infusions. Severe mucocutaneous reactions and fatal infusion reactions (including adult respiratory distress syndrome, myocardial ischaemia and arrhythmias) have very rarely been reported.

Antibodies directed against the murine component of rituximab, termed human anti-chimeric antibodies, may develop, but their exact incidence and clinical significance are uncertain. Albert et al. [6] found anti-chimeric antibodies in approximately a third of SLE patients treated with rituximab and while their development may be associated with poor B-cell depletion, interestingly it does not appear to alter the clinical response [7]. The incidence in many other diseases has not been thoroughly or systematically assessed. A small proportion of patients with antibodies develop serum sickness, characterized by rash, fever and arthralgia, 1–2 weeks after administration of the drug, which may influence subsequent drug use.

Infectious complications are more common, occurring in up to 50% of patients in the early post-treatment period, but are usually mild. They often comprise of upper respiratory tract infections, and viral infections with herpes zoster and influenza. More serious infections are rare, but reactivation of mycobacterial infections, hepatitis B, CMV and JC polyomavirus can occur following rituximab treatment, with some practitioners adding in viral and bacterial prophylaxis for the duration of B-cell depletion. Progressive multifocal leukoencephalopathy (PML) is perhaps the most significant complication resulting from infection or reactivation of JC virus, and leads to an often-fatal demyelinating disease of the CNS. Carson et al. [8], however, identified only 57 cases of PML amongst patients treated with rituximab from its license in 1997 up until 2008 and many of those patients had underlying conditions which themselves were risk factors for PML development (such as lymphoproliferative diseases) and had also been treated with other immunosuppressive therapies.

Longer-term data on the safety of rituximab is beginning to emerge, including in the setting of treatment for systemic vasculitis. Smith et al. [9] described safe repeat treatment with rituximab over a 2-year period in the setting of maintenance therapy for AAV (total dose 6 g), findings corroborated by both Rhee et al. [10], and long-term follow-up in the rituximab in ANCA vasculitis (RAVE) trial [11]. However, low immunoglobulin levels and an increased risk of infections may complicate lon-

ger-term rituximab use. Besada et al. [12] reviewed the outcome of 35 patients treated with rituximab induction and then maintenance over a period of up to 7 years (median total rituximab dose of 8 g). All the patients had a clinical response, but 37% had to discontinue rituximab treatment over this time frame, mainly due to hypogammaglobulinaemia. Moreover, 26% of patients had severe infections and the risk factors identified were the cumulative dose of previous cyclophosphamide (CYP), a low CD4 count, and a significant drop in total immunoglobulins after the first rituximab infusion. In addition, 29% developed chronic infections and the risk factors for this were low IgG levels and the cumulative rituximab dose. It is therefore important to monitor immunoglobulin levels following long-term or repeated rituximab therapy and remain vigilant for early signs of infection.

Clinical Use of Rituximab

Significant recent trials and major cohort studies of rituximab use in glomerular disease are summarized in table 1. For some conditions only smaller cohorts or case studies are available and it should be remembered that they are subject to significant reporting bias, with fewer published studies reporting a lack of benefit.

Systemic Lupus Erythematosus and Lupus Nephritis

SLE is the prototypic immune complex disease involving the production of a wide range of autoantibodies with deposition of immune complexes in various organs. It is therefore not surprising that rituximab has been used in this setting. Renal involvement is common in SLE (up to 75% of patients have some abnormality during the course of disease) and it remains the strongest predictor of overall morbidity and mortality. Whilst 5-year survival among patients with class IV nephritis has improved over the last 50 years (from 17% to over 80%), there remains a significant mortality, and there has been less improvement in the rates of end-stage kidney disease (with 10–20% of patients with lupus nephritis (LN) needing renal replacement therapy) despite recent advances in management [13].

The primary aim in the management of LN is the induction of remission; this greatly improves both patient and renal survival (with 95% of patients and 94% renal survival at 10 years if remission is achieved rather than 60% of patients and 31% renal survival at 10 years if remission is not achieved) [14]. Trials have established the role of low-dose CYP (Euro-Lupus) and mycophenolate

Table 1. Recent trials and cohort studies of rituximab treatment in various glomerular diseases

Reference	Trial type	n	Dose rituximab	Indication rituximab	Other IS	Definition response/endpoints	Outcome
<i>SLE</i>							
UK-BIOGEAS [20]	Pooled analysis	164	56% 2 × 1 g 44% 375 mg/m ²	10% first line 44% relapse 46% refractory	99% steroid 76% other IS (MMF or CYP)	CR: Normal serum creatinine, inactive urinary sediment and 24-hour urinary albumin >0.5 g PR: >50% improvement in all renal parameters that were abnormal at baseline, with no deterioration in any parameter 6 and 12 months	CR: 27% (6/12), 30% (12/12) PR: 40% (6/12), 37% (12/12) NR: 33%
EXPLORER [23]	RCT	257	2 × 1 g (1 and 6 months)	Refractory disease (extrarenal)	Steroid and other IS (MMF, AZA or MTX)	CR: BILAG C scores or better in all organs at week 24 without experiencing a severe flare (1 new domain with a BILAG A score or 2 new domains with a BILAG B score) from day 1 to week 24, and maintaining this response without a moderate or severe flare (at least 1 new domain with a BILAG A or B score) to week 52 PR: (1) achieving BILAG C scores or better at week 24 and maintaining this response without a new BILAG A or B score for 16 consecutive weeks, (2) achieving no more than 1 organ with a BILAG B score at week 24 without achieving at least 1 new BILAG A or B score to week 52, or (3) achieving a maximum of 2 BILAG B scores at week 24 without developing BILAG A or B scores in new domains until week 52 if the baseline BILAG score for the patient was 1 A score plus at least 2 B scores, at least 2 A scores, or at least 4 B scores	Any response at 52 weeks: 28% placebo, 29% rituximab (placebo vs. rituximab) No significant difference
LUNAR [24]	RCT	144	2 × 1 g (1 and 6 months)	Class II or IV lupus nephritis	Steroids and MMF	CR: Normal serum creatinine level if abnormal at baseline or a serum creatinine rise <15% if normal at baseline, inactive urinary sediment (<5 RBCs/hpf and absence of RBC casts), and uPCR <50 PR: Serum creatinine rise <15% of baseline, urinary sediment not significantly worse (RBCs/hpf <50% above baseline and no RBC casts), and at least a 50% decrease in proteinuria (uPCR <100 if baseline <300 or uPCR <300 if baseline >300) NR: Not meeting criteria CR or PR, early termination, missing data or initiation new IS prior to week 52 At 1 year	CR: 26.4 vs. 30.6% PR: 30.6 vs. 15.3% (rituximab vs. placebo) No significant difference
RITUXILUP [25]	Observational	50	2 × 1 g (days 1 and 15)	Class III, IV or V lupus nephritis	Pulsed steroid only and MMF	Renal remission = serum creatinine no greater than 15% above baseline CR: uPCR <50 mg/mmol PR: uPCR >50 mg/mmol but non-nephrotic and >50% reduction	CR: 72% (median time 36 weeks) PR: 18% (median time 32 weeks)

Table 1 (continued)

Reference	Trial type	n	Dose rituximab	Indication rituximab	Other IS	Definition response/endpoints	Outcome
<i>ANCA-associated vasculitis</i>							
RITUXVAS [29]	Randomized, open-label	44	375 mg/m ² for 4 consecutive weeks	New diagnosis ANCA vasculitis with renal involvement	RTX group: Steroid, i.v. CYP 15 mg/kg twice, no AZA CYP (control) group: Steroid, i.v. CYP 15 mg/kg 2–3 weekly for 3–6 months, AZA maintenance	Sustained renal remission (SRR): BVAS 0 for a least 6 months Serious adverse events (SAEs) Follow-up for 1 year	SRR: 76% RTX vs. 82% CYP SAEs: 42% RTX vs. 36% control No significant differences between regimens
RAVE [30]	Randomized, double-blind, double-dummy	197	375 mg/m ² for 4 consecutive weeks	Relapsed or new diagnosis of severe MPO- or PR3-ANCA-associated vasculitis	RTX group: steroids CYP (control) group: steroids, oral CYP 2 mg/kg and switch to AZA if remission at 3–6 months	BVAS 0 and successful completion of prednisolone taper at 6 months	64% RTX vs. 53% CYP at 6 months (non-inferior) (48 vs. 39% 12 months; 39 and 33% at 18 months) RTX superior in relapsing disease at 6 (67 vs. 42%) and 12 months (49 vs. 42%)
Smith et al. [9]	retrospective	73		Relapsed or refractory ANCA-associated vasculitis	Group A: RTX 375 mg/m ² for 4 consecutive weeks or 2 × 1 g Group B: RTX 2 × 1 g followed by 1 g every 6 months for 2 years	Relapse rate at 2 years	73% relapse group A vs. 12% relapse group B
MAINRITSAN [31]	RCT	117	5 doses of 500 mg over 18 months	ANCA vasculitis: remission achieved	RTX vs. AZA (2 mg/kg/day)	Major relapse rate (EULAR/ACR criteria) at 28 months	10.7% (RTX) vs. 45.3% (AZA)
<i>Cryoglobulinaemia</i>							
Saadoun et al. [37]	Prospective cohort	93	375 mg/m ² for 4 consecutive weeks or 1 g × 2	HCV-CV	IFN/RBV + RTX vs. IFN/RBV alone	1. Time to clinical remission 2. Renal response rate 3. Cryoglobulin clearance 4. VH1-69+ clonal B cells	1. 5.4 vs. 8.4 months 2. 80 vs. 40% 3. 68 vs. 43% 4. 10 vs. 19%
Dammacco et al. [38]	Prospective randomized	37	375 mg/m ² for 4 consecutive weeks, then at 6 and 11 months	HCV-MC	IFN/RBV + RTX vs. IFN/RBV alone	Complete response rate	54 vs. 33%
De Vita et al. [39]	RCT	59	1 g × 2	CV	RTX (+steroids) vs. conventional (steroids alone, AZA/ CYP or PP	Treatment survival at 12 months	63 vs. 4%

Table 1 (continued)

Reference	Trial type	n	Dose rituximab	Indication rituximab	Other IS	Definition response/endpoints	Outcome
Sneller et al. [40]	RCT	24	375 mg/m ² for 4 consecutive weeks	HCV-CV	RTX vs. best available therapy	Remission at 6 months (BVAS 0)	83 vs. 8%
<i>Idiopathic membranous nephropathy</i>							
Ruggenenti et al. [45]	Observational	100	375 mg/m ² for 4 consecutive weeks or single dose 375 mg/m ² (second infusion only if the circulating B cells >5 cells/mm ³ the morning after the completion of the first RTX infusion)	IMN Proteinuria >3.5 g/24 h and creatinine clearance >20 ml/min/1.73 m ² despite 6 months conservative Rx		CR or PR: <0.3 and <3 g/24 h proteinuria and >50% reduction vs. baseline	65% response (27 CR and 38 PR)
Fervenza et al. [46]	Observational	18	375 mg/m ² for 4 consecutive weeks repeated at 6 months regardless of response	IMN proteinuria >5 g/24 h and creatinine clearance >30 ml/min/1.73 m ² despite 4 months conservative Rx		CR: Proteinuria <0.3 g/24 h PR: proteinuria <3.5 g/24 h; >50% reduction in peak proteinuria along with serum albumin >3 g/dl for both	CR: 4/18 PR: 12/18
<i>MCD/FSGS</i>							
Munyentwali et al. [53]	Observational	17	375 mg/m ² for 2–4 with retreatment in some if relapse or B-cell repopulation	SDNS or SRNS (15/17 biopsy-proven MCD)		Relapse during follow-up (median 26 months)	No relapse: 11 (65%) One relapse: 4 multiple relapses: 2
Bruchfeld et al. [54]	Case series	16	Variety of different dosing regimens (total dose 1–2.8 g)	Steroid-resistant or -dependent MCD (adults)			CR: 13 (81%) PR: 2 7 relapses (median follow-up 44 months)
Takei et al. [55]	Prospective	25	375 mg/m ² at 0 and 6 months	Steroid-dependent MCD (adults)			CR: 25 (100%) 4 relapses (12 months' follow-up)

AZA = Azathioprine; CR = complete remission; CYP = cyclophosphamide; FSGS = focal and segmental glomerulosclerosis; IMN = idiopathic membranous nephropathy; IS = immunosuppressive agents; MCD = minimal change disease; MMF = mycophenolate mofetil; MTX = methotrexate; NR = no response; PP = plasmapheresis; PR = partial remission; RCT = randomized controlled trial; RTX = rituximab; SDNS = steroid-dependent nephrotic syndrome; SRNS = steroid-resistant nephrotic syndrome.

mofetil (MMF) (ALMS – induction/phase 1) as induction agents in LN [15, 16], with most patients maintained on MMF or azathioprine (AZA) (found to be equivalent in the Euro-Lupus Maintain study, but with MMF superior-

ity in the ALMS maintenance study) [17, 18]. However, significant numbers of patients demonstrate inadequate or slow responses to these agents with, for example, just over a 50% response rate at 24 weeks using either CYP or

MMF in the ALMS study, and 16% treatment failure in the low-dose CYP arm of Euro-Lupus. In addition, these agents have significant side effects and some tolerability issues, particularly relevant in a disease that affects predominantly young women. Moreover, all these regimens are based on significant steroid usage, which is poorly tolerated by many patients, is associated with particular adverse events, and may be a significant contributor to the increased risk of premature cardiovascular disease and death in this patient population [19]. It is in this setting that rituximab has been tested.

Initial data on the use of rituximab induction in LN comes from the UK-BIOGEAS registry, which pooled data from 164 patients with biopsy-proven LN who were treated with rituximab across a number of European centres [20]. Rituximab was used as first-line therapy in 10%, for disease relapse in 44% and for refractory disease in 46% (with the majority having been previously treated with CYP, AZA or MMF). Both the 1 g $\times$ 2 and 375 mg/m² $\times$ 4 dosing regimens were used. The majority of patients were also treated with steroids and 76% were treated with another immunosuppressive (CYP or MMF). Complete response (CR) was defined as a normal serum creatinine with inactive urinary sediment and 24-hour urinary albumin <0.5 g, while a partial response (PR) was a >50% improvement in all renal parameters that were abnormal at baseline, with no deterioration in any parameter. A CR or PR was seen in 67% of patients at 6 and 12 months.

Whilst this and other retrospective studies [21, 22] have suggested a role for rituximab in SLE, evidence for benefit in randomized control trials is lacking. Two randomized controlled trials (RCTs) have evaluated the role of rituximab in extrarenal (EXPLORER) and renal (LUNAR) lupus, but both failed to reach their primary endpoint [23, 24].

EXPLORER studied 257 patients with moderate-severely active extrarenal lupus (as defined by a BILAG A score in at least one organ system or a BILAG B score in at least two organ systems) despite background immunosuppressive therapy using MMF, AZA, or methotrexate. All patients continued their background immunosuppression in addition to starting a course of higher-dose steroids (commencing at 0.5–1 mg/kg prednisolone and weaning over 52 weeks). They were randomized in a 2:1 ratio to 1 g rituximab or placebo given on days 1, 15, 168, and 182. No difference was found between the two groups in terms of response to treatment, determined by changes in BILAG scores, at 52 weeks. In this trial the predominant disease activity at entry was related to mucocutane-

ous or musculoskeletal systems. These features are readily responsive to steroids and may therefore not have allowed a further clinical benefit to be seen following rituximab use.

By contrast, LUNAR studied 144 patients with biopsy-proven class III or IV LN. This was an add-on study in which all patients were treated with steroids using pulsed intravenous methylprednisolone followed by daily oral prednisolone starting at 0.75 mg/kg/day and weaned to <10 mg/day by week 16, as well as MMF (target dose 3 g/day). Patients were randomized in a 1:1 ratio to 1 g rituximab or placebo on days 1, 15, 168, and 182. The primary endpoint was overall (CR and PR) renal response at 52 weeks. CR was defined in this trial as a normal serum creatinine level if abnormal at baseline or a serum creatinine rise <15% if normal at baseline, inactive urinary sediment (<5 RBCs/hpf and absence of RBC casts), and urinary protein creatinine ratio (uPCR) <50 mg/mmol; PR was defined as a serum creatinine rise <15% of baseline, urinary sediment not significantly worse (RBCs/hpf <50% above baseline and no RBC casts), and at least a 50% decrease in proteinuria (uPCR <100 if baseline <300 or uPCR <300 if baseline >300); whilst patients were classified as having no response (NR) if they did not meet the criteria for CR or PR, terminated treatment early, if there was missing data or if new immunosuppression was initiated prior to week 52. There was no significant difference between the renal response rates at week 52 in the rituximab or placebo arms. Overall response rates were 56.9% with rituximab and 45.8% for placebo: CR 26.4 vs. 30.6% and PR 30.6 vs. 15.3% (rituximab vs. placebo). There was, however, a significantly greater improvement in serological markers (anti-dsDNA and complement levels) in the rituximab-treated group and subgroup analysis suggested a potential benefit with regard to PR rates.

The two RCTs appeared to be at odds with the previous uncontrolled experience and there has been much debate about whether the trials were inadequately designed or powered to tease out an additional benefit of rituximab over conventional therapy. The LUNAR study set a fairly stringent composite endpoint and was powered to detect a 20% increase in CR and a 5% increase in PR. There was no difference in CR but a 15% increase in PR in the rituximab group. The trial, however, was underpowered for this to reach significance. In addition to the size of the study, duration of follow-up may also have been an issue. Given the response in serological markers with rituximab during the trial period, there may have been a lag with the clinical response and a potentially greater number of complete responders over a longer follow-up period.

There remain many advocates for the use of rituximab in LN and its real benefit may be in developing steroid minimization or avoidance regimens. Data reporting a steroid-sparing maintenance regimen in active LN (RITUXILUP), using pulsed intravenous methylprednisolone, rituximab 1 g at days 1 and 15, and maintenance MMF has recently been published with encouraging results [25]. In 50 patients who were treated with this regimen, 72% achieved a CR (serum creatinine no greater than 15% above baseline and uPCR <50 mg/mmol) and 18% achieved a PR (serum creatinine no greater than 15% above baseline and uPCR >50 mg/mmol but non-nephrotic and >50% reduction). This protocol is now being tested against a conventional steroid and MMF regimen in an ongoing RCT.

Antineutrophil Cytoplasm Antibody AAV

Renal involvement in AAV usually manifests as a pauci-immune focal necrotizing crescentic glomerulonephritis (GN), often with rapidly progressive kidney injury. This may be part of a systemic vasculitis such as granulomatosis with polyangiitis or microscopic polyangiitis or may be limited to the kidney (renal-limited vasculitis). As with SLE, treatment consists of induction and maintenance phases but unlike SLE there is robust evidence for the use of rituximab in both the induction and maintenance phases of the disease.

Numerous studies including key EUVAS trials established a role for steroids and CYP as induction therapy in AAV. The CYCLOPS study demonstrated that in conjunction with steroids, pulsed intravenous CYP was as effective as daily oral CYP in inducing remission and resulted in a reduced cumulative CYP dose with less leukopenia [26]. However, more recent long-term follow-up from this study demonstrated that the pulsed regimen was associated with a higher risk of relapse (21 vs. 40% (daily oral vs. pulsed) relapse at a median follow-up of 4.3 years) [27].

However, such early CYP protocols carried significant toxicity, and much of the early mortality in AAV was thought to be due its use alongside steroids [28]. It was as a result of this toxicity that alternative agents were eagerly sought and the reason for the adoption of rituximab in early cohort studies. Since then the anecdotal reports were translated into randomized trials and a balanced view of the role of rituximab has emerged. Two randomized trials, rituximab versus CYP in AAV (RITUXVAS) and rituximab in AAV (RAVE), have demonstrated the efficacy of rituximab as an induction agent in AAV and it was on the basis of these that the Food and Drug Admin-

istration and the European Medicines Agency recently granted licenses for its use [29, 30].

In RITUXVAS, 44 patients with newly diagnosed AAV and advanced renal involvement received a standard glucocorticoid regimen and were randomized in a 3:1 ratio to either rituximab (375 mg/m² for 4 consecutive weeks) with two doses of intravenous CYP (with the first and third rituximab infusions) and no AZA maintenance, or intravenous CYP (every 2–3 weeks for 3–6 months) followed by AZA maintenance. The primary endpoints were sustained remission rates (BVAS of 0 for at least 2 months) at 12 months and severe adverse events. No difference was found between the groups with regard to either endpoint, with sustained remission achieved in 76% of the rituximab group and 82% of the control group. Interestingly, there was also no difference in serious adverse events (42% rituximab vs. 36% control), and there was a high mortality rate of 18% at 1 year in both groups, reflecting the enrolled population of elderly AAV patients with advanced renal disease.

RAVE was a double-blind, placebo-controlled, non-inferiority trial that included both newly diagnosed and relapsing patients with MPO- and PR3-AAV. A total of 197 patients with severe disease (BVAS >2) were randomized to a rituximab-based regimen (rituximab 375 mg/m² for 4 consecutive weeks) or a CYP-based regimen (using oral CYP). If patients achieved remission between 3 and 6 months they were switched to AZA in the CYP group and to placebo in the rituximab group. Both groups received high-dose glucocorticoids, which were tapered over 5 months in the absence of disease flare. The primary endpoint was a BVAS of 0 and successful completion of the prednisolone taper at 6 months. This was achieved in 64% of patients in the rituximab group compared with 53% in the CYP group, reaching significance for non-inferiority. Notably, in the subgroup analysis, rituximab was significantly more efficacious than CYP in achieving the primary endpoint in the setting of relapsing disease (67 vs. 42%, rituximab vs. CYP, respectively). No difference was found between the treatment groups when comparing outcome according to ANCA type, renal function, severity of disease (including alveolar haemorrhage), or age of the patients. Again, serious adverse events were equally common in both treatment groups.

These two studies confirmed that rituximab-based regimens are as effective as CYP in achieving remission in AAV, in patients presenting with advanced renal disease (including dialysis dependency) and alveolar haemorrhage, while it appeared superior in those with relapsing disease. However, neither study demonstrated a bet-

ter adverse effect profile despite avoidance of CYP and this may suggest that much of the morbidity and mortality previously ascribed to CYP may be due to high-dose steroids used in both trials. Longer-term follow-up from the RAVE trial has recently been published [11]. The groups were followed to 18 months. As stated, the rituximab group had received no maintenance therapy after 6 months whereas the CYP group had received AZA. CR rates in the rituximab group were 64, 47 and 39% at 6, 12 and 18 months, respectively, compared with 53, 39 and 33% with CYP-AZA. In those with relapsing disease, the superior effect of rituximab was maintained at 12 months but not at 18 months at which time the majority of patients in the rituximab group had repopulated their B cells, suggesting that in those with relapsing disease, further doses of rituximab may be warranted.

At what stage rituximab should be re-administered has been debated. Preemptive re-treatment with rituximab every 6 months has been shown to be of benefit with regard to relapse rates when compared with a watchful policy of re-treating at signs of clinical relapse. Smith et al. [9] demonstrated that retreatment with 1 g rituximab every 6 months for 2 years reduced the rate of relapse from 73 to 12% compared with those given no further rituximab treatment post-induction.

Several ongoing randomized trials investigating the use of rituximab as maintenance therapy are addressing the issue of efficacy using different dosing regimens compared with standard therapies. An open-label study in France (MAINRITSAN) compared AZA (2 mg/kg/day) to rituximab (5 doses of 500 mg over 18 months) in 117 patients with AAV in whom remission had been achieved [31]. A reduced relapse rate (45.3 vs. 10.7%, respectively) was demonstrated at 28 months in the rituximab arm. This has led to a second trial (MAINRITSAN 2), which is comparing two differing treatment strategies, the first replicates the previous dosing in MAINRITSAN and the second stipulates a first dose of rituximab which is only repeated 6 months later if the B-cell count is $>0/\text{mm}^3$ or the ANCA titre is rising [32]. The RITAZAREM study is currently recruiting patients and comparing rituximab maintenance (1 g every 4 months) with AZA at standard doses [33]. Our own recent retrospective data [61] have demonstrated that in AAV (but not SLE) treatment with a single dose of rituximab which is repeated only if the CD19 count is not depleted (to $0.005 \text{ cell}/\text{mm}^3$ or less) provides equivalent remission induction as a standard two 1 g doses or the weekly $375 \text{ mg}/\text{m}^2$ regimen, suggesting that further refinements of the treatment regimens may be pos-

sible, altering the significant economic burden of using monoclonal antibody therapy.

Cryoglobulinaemic Vasculitis and Glomerulonephritis

Most cases of cryoglobulinaemic vasculitis (CV) and GN are secondary to viral (usually hepatitis C)-driven clonal B-cell expansion. However, geographical differences occur, and while hepatitis C-associated mixed cryoglobulinaemia is common in Southern Europe, cases of idiopathic mixed essential cryoglobulinaemia unrelated to viral infection may still be found in Northern Europe [34, 35]. B-cell expansion, by whatever means, results in the synthesis of high levels of IgM with rheumatoid factor activity, and these antibodies, in turn, bind viral particles and polyclonal IgG forming mixed cryoglobulins. The immune complexes bind endothelial cells and promote local complement activation and recruitment of inflammatory cells, which mediate a leukocytoclastic small vessel vasculitis often involving the skin, nervous system and the kidney (frequently resulting in a membranoproliferative GN).

Cryoglobulins are commonly found in chronic hepatitis C infection but may be clinically silent, or produce only mild disease (affecting only the skin). Rarely, they may be associated with severe organ damage and their management is complicated by the risk of traditional immunosuppression in patients with active viraemia. A recent review summarizes an approach to the management of hepatitis C-related CV (HCV-CV) [36]. Therapy is targeted at the underlying infection (using antivirals alone) in mild disease, while immunosuppression targeting the B-cell clones is reserved for more severe disease and this is the setting for rituximab use.

Rituximab in combination with antivirals is more effective than antivirals alone. Saadoun et al. [37] compared the use of pegylated-interferon- α /ribavirin (Peg-IFN- α /Rbv) alone with Peg-IFN- α /Rbv in conjunction with rituximab ($375 \text{ mg}/\text{m}^2 \times 4$ or $1 \text{ g} \times 2$) in 93 patients with HCV-CV, the majority of whom had histological confirmation of disease. There was a shorter time to clinical remission (5.4 vs. 8.4 months), better renal response rates (80 vs. 40%) defined as normalization of creatinine and disappearance of haemoproteinuria, and higher rates of cryoglobulin clearance (68 vs. 43%) in the rituximab group. Treatment was tolerated well without worsening of HCV viraemia in the rituximab arm.

Dammacco et al. [38] found a similar benefit of adding rituximab to antiviral therapy and reported CR rates (disappearance or improvement in clinical features, disappearance of cryoglobulins, undetectable HCV RNA and

disappearance of B-cell clonality from blood) in 54% in the combined rituximab/antiviral-treated cohort compared with 33% in the antiviral-alone treatment group. Patients were followed up for 3 years after the completion of treatment. Of those that responded, 83% in the combined rituximab/antiviral group maintained CR to 3 years as opposed to only 40% in the antiviral group.

As regards comparison of rituximab to other immunosuppressives, outcomes favour rituximab in two recent RCTs [39, 40]. De Vita et al. [39] randomized 59 patients with CV to treatment with rituximab (1 g $\times$ 2, with steroids) or to conventional treatment [one of: steroids alone (59%), AZA (10%), CYP (14%), or plasmapheresis (17%)]. In those with hepatitis C, antiviral therapy had previously failed, been poorly tolerated or was considered to be contraindicated. The primary endpoint was the proportion of patients continuing to take their treatment (i.e. survival of treatment) at 12 months. This was achieved in 63% of the rituximab group compared with 4% in the non-rituximab group. The main reason for treatment failure in the non-rituximab arm was lack of response or worsening target organ manifestations. There were 7 patients with GN in the rituximab arm, 57% of whom responded to treatment.

Sneller et al. [40] randomized 24 patients with HCV-CV who had failed to respond to antiviral therapy to treatment with rituximab (375 mg/m² weekly for 1 month) or standard treatment with augmented immunosuppression or introduction of alternative immunosuppression. The primary endpoint of remission at 6 months was achieved in 83% of patients in the rituximab arm compared with 8% of controls. The majority of patients in the rituximab arm who were on steroids at entry had been weaned off these by 6 months and there was no worsening of HCV infection in the rituximab group. Four patients in each arm had glomerular involvement at entry – all of those in the control group experienced a decline in eGFR over 6 months whereas all of those in the rituximab group either maintained stable renal function or had improvement in eGFR.

Hence, rituximab has a defined role in management of HCV-CV. It is important to note, however, that unlike HCV, rituximab is currently contraindicated in hepatitis B or HIV infection with detectable viral load.

Rituximab also appears to be of benefit in the management of cases of mixed essential (non-infectious) CV. In the CryoVas survey of non-infectious CV, rituximab with corticosteroids showed greater therapeutic efficacy compared with corticosteroids alone or with alkylating agents in achieving complete clinical, renal, and immunologic

response [41]. Infection rates were high, however, with 29% of patients experiencing severe infections with this regimen.

Primary Glomerular Diseases

Idiopathic Membranous Nephropathy

There is considerable ongoing debate about the use of immunosuppression in idiopathic membranous nephropathy (IMN). Recent KDIGO guidelines suggest that in those that are treated with immunosuppression, the use of 6 months of alternating monthly cycles of steroids and an alkylating agent (CYP or chlorambucil) (Ponticelli regimen) be used as first line [42]. This regimen, however, may be contraindicated for many (due to the high steroid dosages) or poorly tolerated [43]. Calcineurin inhibitors may be used as second-line agents but are associated with significant relapse rates upon cessation and long-term concerns regarding nephrotoxicity. In addition, the recent membranous study comparing these regimens head to head clearly demonstrated that in patients with declining renal function, calcineurin-based regimens are associated with poorer long-term renal outcome than steroid/alkylating agent-based regimens [44]. These data, in addition to the recent advances in our understanding of the pathogenesis of IMN as an autoantibody-mediated disease, makes B-cell depletion an attractive and rational therapeutic strategy.

There are promising observational data on the use of rituximab but data from randomized trials is still lacking. Remuzzi and colleagues [45] first described rituximab use in IMN in the early 2000s and since then this group has treated all patients with biopsy-proven IMN (creatinine clearance >20 ml/min/1.73 m² and proteinuria >3.5 g/24 h despite 6 months of full-dose ACEi and optimization of conservative therapy) with rituximab as first-line treatment (using 375 mg/m² weekly for 4 weeks up until 2005; after this, a single dose of 375 mg/m² was given, with a second infusion of the same dose only if the level of circulating B cells the morning after completion of the first rituximab infusion was >5 cells/mm³). The outcomes of 100 consecutive patients treated in this way have recently been published [45]. The median follow-up was 29 months during which 65 patients achieved a CR (<0.3 g/24 h proteinuria and >50% reduction vs. baseline) or PR (<3 g/24 h proteinuria and >50% reduction vs. baseline). 18 of these patients relapsed, 11 of whom responded to a further course of rituximab.

Fervenza et al. [46] also published encouraging results from a small cohort of patients with IMN followed up for 2 years. Patients were entered if they had biopsy-proven

IMN and persistent proteinuria >5 g/24 h (creatinine clearance >30 ml/min/1.73 m²) despite 4 months of maximum conservative treatment. Patients were treated with 375 mg/m² rituximab weekly for 4 weeks repeated at 6 months regardless of clinical response. Eighteen patients (out of 20) completed 24 months of follow-up at which point 4 were in CR and 12 in PR (CR defined as proteinuria <0.3 g/24 h, PR as proteinuria <3.5 g/24 h; $>50\%$ reduction in peak proteinuria along with serum albumin >3 g/dl for both).

Hence, early reports are promising but randomized data directly comparing rituximab to other immunosuppressive regimens and information on the optimal dose and duration of treatment is currently lacking. Several randomized trials are currently recruiting to compare rituximab against conservative management alone (GEM-RITUX) or cyclosporine (MENTOR), and a trial is planned to compare rituximab in conjunction with tacrolimus with a Ponticelli-like regimen (STARMEN) [47–49].

Minimal Change Disease and Focal Segmental Glomerulosclerosis

A good response to steroids is seen in the majority of patients with minimal change disease (MCD). However, steroid dependency will develop in up to 40%. In these, alkylating agents, calcineurin inhibitors, antiproliferative and immunomodulatory agents have been used as steroid-sparing agents, with a mixed response reported. There are increasing data from observational studies on the use of rituximab in steroid-resistant (SRNS) and steroid-dependent (SDNS) nephrotic syndrome in children [usually secondary to MCD or focal segmental glomerulosclerosis (FSGS)] [50, 51]. Less has been published with regard to adults, and randomized trials are lacking in both populations.

Ronco and colleagues [52] described a case of adult multirelapsing MCD treated successfully with rituximab in 2007 and recently reported a case series of 17 adults with SDNS or frequently-relapsing nephrotic syndrome (FRNS) treated with B-cell depletion [53]. All had been previously treated with prolonged steroid courses and the majority had received another immunosuppressant drug. 10 of the patients were treated after steroid-induced remission (uPCR <100 mg/mmol), the others were treated with higher levels of proteinuria. Eleven patients had no relapse at a median follow-up of 26.7 months and this was associated with a significant reduction in steroids and other immunosuppressive treatment. Rituximab was given at a dose of 375 mg/m² weekly for 2–4 weeks with retreatment in 4 patients due to repopulation of B cells. Six

patients relapsed during follow-up, usually in the setting of B-cell recovery. Four of these responded to a further course of steroids and rituximab while 2 patients suffered multiple relapses, and were unresponsive to treatment.

Bruchfeld et al. [54] report a Swedish cohort of 16 adult patients with steroid-dependent or -resistant MCD who were treated with rituximab (a variety of doses with total exposure ranging from 1 to 2.8 g). Thirteen patients achieved CR (normalization of albumin and resolution of proteinuria), whilst 2 achieved a PR ($>50\%$ reduction in proteinuria). Rituximab use enabled discontinuation or tapering of steroid use to below levels where relapses had occurred in the past. Seven patients relapsed over a median follow-up of 44 months.

Takei et al. [55] undertook a prospective trial of rituximab use (375 mg/m² at 0 and 6 months) in 25 adults with steroid-dependent MCD. All patients achieved a CR and rituximab use allowed a significant reduction in the dose of steroid used. There were 4 relapses over the course of 12 months' follow-up, all of which were associated with B-cell repopulation, suggesting a higher or repeated dose of rituximab may have been needed.

Data on rituximab specifically in primary FSGS is sparse and limited to case reports and very small case series. Randomized studies are needed to further evaluate the role of rituximab in both MCD and primary FSGS. NEPHRUTIX has completed recruitment to evaluate the role of rituximab in severe cyclosporine-dependent nephrotic syndrome in children but there are no active trials at present in adults [56].

Other Glomerular Diseases

Treatment of membranoproliferative GN in the setting of hepatitis C or cryoglobulinaemia is outlined above. There are few data on the use of rituximab in MPGN outside this setting or for the use of rituximab in IgA nephropathy. Sugiura et al. [57] prospectively assessed the role of a single dose of rituximab in 24 patients with a variety of glomerular diseases including 5 with IgA nephropathy and reported no benefit in those with IgA disease. There is, however, a trial currently recruiting comparing rituximab with conservative management in IgA nephropathy.

Similarly, data on the use of rituximab in fibrillary GN is limited. A recent series on the long-term renal outcome of fibrillary GN patients included 7 patients treated with rituximab [58]. Of these patients, 5 (71%) achieved a renal response as compared to only 16 and 14% in those treated with other immunosuppression and without immunosuppression, respectively. Larger collaborative studies are

needed to establish the role of immunosuppression in the management of fibrillary GN, in particular with regard to B-cell depletion.

Finally, reports have recently been published on the use of rituximab in anti-GBM disease [59]. Being an antibody-mediated disease, rituximab seems a rational choice of treatment. The authors identified 5 cases of anti-GBM disease treated with rituximab, 4 of whom recovered renal function and remained dialysis-independent. However, given the rarity of anti-GBM disease and the paucity of clinical trial data on this condition, it seems unlikely that a trial comparing rituximab with standard CYP-based treatment will ever be carried out. It therefore remains an option for those patients in whom CYP may be contraindicated or in whom it may want to be avoided.

Conclusions

Rituximab has an increasing role in a variety of different immune-mediated glomerular diseases. Evidence is robust in only a few, most notably ANCA-associated disease, and multiple trials are ongoing examining its role in others. It is generally a safe and well-tolerated drug, espe-

cially in the short term. More data is required with regard to long-term use and optimal dosing regimens. Treatment targeted to B-cell response seems a rational approach, which has been reported in small cohorts and is now being tested in randomized trials. Lastly, there are significant cost implications with the use of rituximab as induction and/or maintenance therapy, but with the expiration of patent and the development of many bio-similars, as well as the possible use of lower doses adjusted to B-cell levels, the cost will be driven down [60].

Key Points

- Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen on the surface of immature and mature B cells.
- It is licensed for use in AAV.
- It is used off-license to treat a variety of immune-mediated kidney diseases (e.g. LN, CV and IMN).
- It is safe and well tolerated in most.
- Long-term use may be complicated by hypogammaglobulinaemia and increased infectious complications.
- Optimal dosing is unclear.
- The development of bio-similars and dosing targeted to B-cell response may reduce cost.

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