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Original article

Recommendations for the use of rituximab in anti-neutrophil cytoplasm antibody-associated vasculitis

Mary-Jane C. J. Guerry[1,2], Paul Brogan[3], Ian N. Bruce[4,5], David P. D'Cruz[6], Lorraine Harper[7], Raashid Luqmani[8], Charles D. Pusey[9], Alan D. Salama[10], David G. I. Scott[11], Caroline O. S. Savage[12], Richard A. Watts[13,14] and David R. W. Jayne[1]

Abstract

Objectives. To perform a literature review and develop recommendations for the use of rituximab in ANCA-associated vasculitis.

Methods. A committee of experts (five rheumatologists, five nephrologists and one paediatrician) conducted a modified Delphi exercise to identify five topics for a systematic literature search. The evidence was then reviewed, categorized according to international criteria and assimilated to form five recommendations statements and a research agenda.

Results. Forty-three studies met the review criteria. These included two randomized controlled trials and a predominance of small, uncontrolled series. In refractory ANCA-associated vasculitis, remission rates of >80% are obtained with rituximab. In newly diagnosed disease, rituximab is at least as effective as conventional therapy. Fifteen recommendations were made. Their strength was restricted by the low quality of the evidence. Six areas for future research were identified.

Conclusion. On the basis of the available evidence and expert consensus, recommendations have been made for the use of rituximab as a treatment of ANCA-associated vasculitis. Further questions, in particular regarding long-term outcomes, remain to be explored.

Key words: recommendations, rituximab, vasculitis, antibodies, anti-neutrophil cytoplasmic, Wegener's granulomatosis, microscopic polyangiitis, Churg–Strauss syndrome.

CLINICAL SCIENCE

[1]Vasculitis and Lupus Unit, Department of Medicine, Addenbrooke's Hospital, Cambridge, UK, [2]Intensive Care Unit, Salengro University Hospital, Lille, France, [3]Rheumatology Department, Great Ormond Street Hospital for Children, London, [4]Arthritis Research UK Epidemiology Unit, School of Translational Medicine, Manchester Academic Health Sciences Centre, Manchester Royal Infirmary [5]The Kellgren Centre for Rheumatology, Manchester NIHR Biomedical Research Centre, Central Manchester University Hospitals Foundation Trust, Manchester, [6]The Lupus Research Unit, The Rayne Institute, St Thomas' Hospital, London, [7]Department of Nephrology, School of Immunity and Infection, University of Birmingham, Birmingham, [8]NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, [9]Department of Medicine, Renal Section, Imperial College London, [10]UCL Centre for Nephrology, Royal Free Hospital, London, [11]Rheumatology Department, Norfolk and Norwich University Hospital Trust, Norwich, [12]Department of Nephrology, College of Medical and Dental Sciences, University of Birmingham, Birmingham, [13]Ipswich Hospital NHS Trust, Ipswich and [14]Department of Rheumatology, Norwich Medical School, University of East Anglia, Norwich, UK.

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Correspondence to: David Jayne, Vasculitis and Lupus Unit, Box 57, Department of Medicine, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, UK. E-mail: dj106@cam.ac.uk.

Introduction

The ANCA-associated vasculitides comprise WG, microscopic polyangiitis, Churg–Strauss syndrome and renal-limited vasculitis. Treatment recommendations have been formalized with induction therapy of higher dose glucocorticoids and CYC (achieving initial remission rates of 70–90%), followed by lower dose glucocorticoids with AZA or MTX for remission maintenance [1]. Limitations of these approaches include refractory and relapsing disease and drug toxicity, which contributes to morbidity and mortality. Newer agents have included MMF, LEF, IVIGs, anti-TNF-α and rituximab.

Rituximab is a chimeric, monoclonal anti-CD20 antibody that selectively depletes B lymphocytes, but not plasma cells. Initially used for the treatment of B-cell lymphomas, it was licensed for RA in 2006. A rationale

Table 1 Levels of evidence

Category	Evidence
1a	From meta-analysis of randomized controlled trials
1b	From at least one randomized controlled trial
2a	From at least one controlled study without randomization
2b	From at least one type of quasi-experimental study
3	From descriptive studies, such as comparative studies, correlation studies or case–control studies
4	From expert committee reports or opinions and/or clinical experience of respected authorities

for rituximab in ANCA-associated vasculitis was based on its potential to deplete $CD20^+$ precursors of ANCA-secreting plasma cells and impede B-cell cytokine-supported plasma cell survival in inflammatory niches. Activated B cells correlate with disease activity, and auto-antigen-specific B cells are present at sites of inflammation. Finally, the regulation of T lymphocytes, known to be important in these diseases, is interdependent on B-cell function. We aimed to develop a recommendations statement (based on a literature review) by a multidisciplinary panel of physicians experienced in the field of ANCA-associated vasculitis.

Methods

This guidance is termed recommendations as opposed to guidelines or points to consider, as it can provide guidance but needs to be tailored to meet individual requirements. It is intended for use by health-care professionals, medical students and specialist trainees, pharmaceutical industries and drug regulatory organizations.

The committee consisted of five rheumatologists (I.N.B., D.P.D., R.L., D.G.I.S. and R.A.W.), five nephrologists (D.R.W.J., L.H., C.D.P., A.D.S. and C.O.S.S.), one paediatrician (P.B.) and a clinical fellow (M.-J.C.J.G.) who coordinated the study and performed the literature search. This project received an unrestricted grant from Roche (UK) who played no role in its design, conduct or conclusions.

A modified Delphi exercise was carried out to identify the scope of the recommendations. This identified five points for the literature search. A search string was then agreed to identify publications in PubMed; for example, Wegener Granulomatosis [MeSh] AND rituximab [Substance Name]. This was repeated for the other conditions: Churg–Strauss syndrome [MeSh] AND rituximab [Substance Name]. Microscopic polyangiitis is not a MeSH in PubMed and was inserted as free text in all fields. To identify papers that may have been indexed as ANCA-associated vasculitis, an additional search using the terms Antibodies, Antineutrophil Cytoplasmic [MeSh] AND Vasculitis [MeSh] was performed. The search was not limited to a time frame or by language. A manual search of abstracts presented at the annual meetings of the European League against Rheumatism, ACR, American Society of Nephrology, European Renal Association, International Society of Nephrology from 2002 to 2009, and the 2009 International Vasculitis and ANCA workshop was performed.

Each paper was reviewed and included if one or more of the topics identified in the modified Delphi exercise were studied. Review articles, case reports featuring fewer than three patients (except for those describing children or cases of Churg–Strauss syndrome), and publications with insufficient outcome data were discarded. Identified papers were categorized and the evidence graded according to international criteria (Table 1) [2]. The evidence was then reviewed by the committee and assimilated to form five statements and a research agenda.

Results

Modified Delphi exercise and literature review

Agreed items from the modified Delphi exercise are listed in Table 2. The literature search revealed a predominance of information from uncontrolled studies and case reports. Thirty-two papers were identified, including two randomized controlled trials. The manual search of the abstracts of meetings added 11 studies. Two unpublished studies were included.

Recommendations

Recommendation 1. What are the indications for rituximab as a treatment of ANCA-associated vasculitis?

1.1 In newly diagnosed ANCA-associated vasculitis

Rituximab is as effective as CYC for remission induction of previously untreated patients. Rituximab may be preferred, especially when CYC avoidance is desirable. (Level of evidence 1b.)

Two recent randomized controlled trials reported that initial induction therapy with rituximab achieved similar remission rates to CYC (Table 3) [3, 4]. In the rituximab in vasculitis (RITUXVAS) study ($n = 44$), complete remission was achieved in 82% of patients who received rituximab, and 91% who received CYC (non-significant). In the rituximab for ANCA-associated vasculitis (RAVE) study ($n = 197$), 64% of those who received rituximab were in remission and steroid free at 6 months, *vs* 54% of those who received CYC (non-significant). The duration of follow-up was 12 and 6 months, respectively, and the effect of rituximab induction on longer term outcomes

TABLE 2 Questions resulting from the modified Delphi exercise

No	Question
1.	What are the indications for rituximab as a treatment of ANCA-associated vasculitis?
1.1	In newly diagnosed ANCA-associated vasculitis
1.2	In refractory and/or relapsing disease
1.3	According to patient subgroups
1.3.1	WG with head and neck manifestations
1.3.2	Paediatric ANCA-associated vasculitis
1.3.3	Churg–Strauss syndrome
2.	What is the optimal induction dosage regimen?
3.	What are the longer term outcomes of treatment with rituximab?
3.1	Relapse rate
3.2	Potential predictors of relapse
3.3	Re-treatment with rituximab
4.	How should other immunosuppressive therapies be prescribed in patients treated with rituximab?
4.1	Should CYC be administered concomitantly with rituximab?
4.2	Should other immunosuppressives be continued following rituximab?
4.3	What glucocorticoid regimen should be adopted in patients treated with rituximab and can glucocorticoids be stopped?
5.	How safe is rituximab in ANCA-associated vasculitis?
5.1	Infective risk
5.2	Other risks
6.	Research agenda
6.1	Rituximab cost-effectiveness for induction
6.2	Role of rituximab in maintenance of remission
6.3	Steroid avoidance
6.4	Long-term safety of rituximab
6.5	Definition and characterization of rituximab-refractory disease
6.6	Indication of rituximab in other vasculitides

is not known. No cost-effectiveness comparison between CYC and rituximab has been performed and no clear safety benefit, apart from CYC sparing was demonstrated. Further data are required before rituximab can be recommended in preference to CYC in the setting of ongoing infection. CYC avoidance is desirable in the presence of ongoing chronic infection, known CYC intolerance or hypersensitivity, or when there is a high risk of infertility or malignancy. Consequently, where CYC avoidance is desirable, rituximab is an effective alternative.

1.2 In refractory and/or relapsing disease

Rituximab is an effective treatment of refractory and/or relapsing forms of ANCA-associated vasculitis and can be recommended when conventional therapy has failed. (Level of evidence 1b.)

Validated outcome measures are used to formally define refractory disease (drug intolerance, frequent relapses, persistent or true refractory disease) [5], which affects 20–30% of patients. In a planned subgroup analysis of relapsing patients in the RAVE trial, an increased rate of response occurred with rituximab, as compared with CYC [4]. Other evidence regarding the use of rituximab as rescue therapy in these patients relies on small, uncontrolled series. Twenty-four such reports (featuring three or more cases) have been published, involving over 230 patients (Table 3). These studies reflect a decade's experience and show rituximab to be efficacious in intractable ANCA-associated vasculitis, with >80% of patients achieving partial or complete remission. The presence or absence of ANCA and ANCA subtype did not appear to influence rituximab response rates.

1.3 According to patient subgroups

1.3.1 WG with head and neck manifestations

Rituximab is an effective treatment of refractory head and neck manifestations of WG and can be recommended when conventional therapy has failed. (Level of evidence 2b/4.)

Published reports include a high proportion (>50%) of patients with refractory head and neck manifestations of WG, with remission rates after rituximab of >80%. In the largest cohort study to date, partial or complete remission was achieved in 88% of cases at 6 months, and all four non-responding patients went into remission after a second course of rituximab [23]. Controversy surrounding the efficacy of rituximab in retro-orbital granulomata has derived from one study [6], in which poor response may have been attributable to a lower rituximab dosing regimen (four doses of 375 mg/m^2 administered monthly rather than weekly). Remission rates have been >80% in subsequent reports (Table 4). Some authors suggest that because these refractory head and neck lesions

Table 3 Rituximab treatment for ANCA-associated vasculitis: short- and long-term outcomes

Study	Study design	Level of evidence	Number of patients; age;[a] RTX indication	Outcome	Relapse (months after RTX); follow-up, months[a]
[6]	PCS	2b/4	8; 38; R	CR 2/8; PR 1/8	NR; 18
[7]	RCS	4	8; 44; R	CR 5/8; PR 1/8	1/8 (12); (6–48)
[8]	RCS	4	11; NR; R	CR or PR 10/11	NR; NR
[9]	RCT	2b	8; NR; R	CR 2/8; PR 3/8	1/8 (28); 30
[10]	RCS	4	6; 14; R	CR or PR 6/6	2/6 (15, 24); 16
[11]	PCS	2b/4	9; 56; R	CR 8/9; PR 1/9	2/9 (12, 13); 19
[12]	PCS	4	4; 44; R	CR 1/4	NR; 12
[13]	RCS	4	6; 35; R	CR or PR 6/6	4/6 (14); 23
[14, 15]	RCS	4	6; 52; R	CR 5/6; PR 1/6	3/6 (18–24); 41
[16]	RCS	4	11; (16–70); R	CR 10/11	0; 20
[17][b]	RCS	4	65; 47; R&M	CR 49/65; PR 15/65	28/49 (11.5); 20
[3]	RCT	1b	33 RTX *vs* 11 CYC; 68; I	CR 27/33[c]	2/27 (5,6);[c]12
[18]	PCS	4	11; 31; R	CR 10/11; PR 1/11	2/11 (7, 12); 14
[19]	PPT	2b/4	10; 57; R	CR 10/10	1/10 (9); 18
[20]	RCS	4	15; 45; R	CR 6/15; PR 8/15	3/14 (7–14); 15
[21]	PCS	2b/4	21; 61; I	CR 20/21; PR 1/21	2/21 (9, 30); 22
[22]	PCS	2b/4	7; 69; I	CR or PR 7/7	0; 13
[23][b]	RCS	4	34; 47; R	CR 25/34; PR 9/34	2/34 (NR); 25
[24]	RCS	4	4; 36; R	PR 4/4	4/4 (2); NR
[25]	RCS	4	3; 32; R	PR 3/3	NR; 24
[26]	RCS	4	7; 61; R	CR or PR; 7/7	NR; >12
[27]	RCS	4	4; 41; R	CR 4/4	0; 20
[28][d]	PCS	4	8; 39; R	CR or PR 8/8	5/8 (16); (5–42)
[29][b]	PPT	2b/4	11; 52; R	CR 9/11; PR 1/11	6/10 (16.5); 23
[30]	PCS	4	10; 53; R	CR 9/10; PR 1/10	3/10 (12–24); 33
[4]	RCT	1b	99 RTX *vs* 98 CYC; 53; R&I[e]	CR 70/99[c]	NR;[c] 6
[31]	RCS	4	10; 58; R	CR 4/10; PR 6/10	0; 12
[32]	RCS	4	13; 58; R	CR or PR 13/13	2/13 (30, 41); 19
[33]	RCS	4	9; 42; R	CR 9/9	6/9 (11.5); NR
Summary					
Diagnosis, %		WG 77; MPA 19			
ANCA positivity, %		96			
Renal involvement, %		50			
Rate of complete remission, median (range) %		89 (25–100)			
Overall rate of remission (CR and PR), median (range) %		100 (25–100)			

[a]Median or (range). [b]The study by Martinez Del Pero *et al*. includes patients reported in the survey by Jones *et al*. Both publications include all cases reported by Smith *et al*. [c]No difference between CYC and rituximab treatment groups. [d]We have included these data although there are inconsistencies in the reports, and some of the patients may have been included in either of the papers by Keogh *et al*. [e]Forty-nine per cent of patients were treated for newly diagnosed ANCA-associated vasculitis, 51% for relapsing and/or refractory disease. RTX: rituximab; PCS: prospective case series; RCS: retrospective case series; RCT: randomized controlled trial; PPT: prospective open-label pilot trial; NR: not reported; R: relapsing/refractory disease; M: maintenance treatment; I: initial treatment in newly diagnosed ANCA-associated vasculitis; CR: complete remission; PR: partial remission; MPA: microscopic polyangiitis.

seem slower to respond, resistance to rituximab should probably not be declared until the patient has received at least two courses and been followed for at least 6 months [7, 23].

1.3.2 Paediatric ANCA-associated vasculitis

Rituximab should be considered for the treatment of children with ANCA-associated vasculitis that fails to respond to conventional induction therapy with glucocorticoids and CYC; or for patients with relapsing disease where there is particular concern regarding cumulative glucocorticoid and/or CYC toxicity. (Level of evidence 4.)

Steroid and cytotoxic-sparing regimens are of particular advantage to young patients, decreasing glucocorticoid-induced complications and the risk of future infertility or malignancy. The use of rituximab has been reported

in 13 children [10, 34–38]. The most commonly used dosage was 750 mg/m^2 (maximum dose 1 g) administered on two occasions separated by a 2-week interval, typically accompanied by i.v. CYC. All patients in one study achieved partial remission, allowing glucocorticoids to be significantly reduced without major adverse events [10]. Two subsequent major relapses (15 and 24 months after rituximab) responded to repeat treatment (P.B., 2010, data not published).

1.3.3 Churg–Strauss syndrome

Response rates in refractory and/or relapsing Churg–Strauss syndrome appear similar to other vasculitides and rituximab may be considered when conventional therapy has failed. (Level of evidence 4.)

Outcomes of rituximab as treatment of refractory Churg–Strauss syndrome appear as successful as in other forms of ANCA-associated vasculitis (Table 5). However, only 20 cases have been reported in 12 studies. Two reports of severe bronchospasm during rituximab infusion (covered with anti-histamines but not with steroids) have raised concern over possible hypersensitivity reactions triggered by rituximab in Churg–Strauss syndrome [38]. The risk of such reactions may be reduced by an increase in the dose of prophylactic steroids (level of evidence 4).

Recommendation 2. What is the optimal induction dosage regimen?

Both commonly used rituximab protocols (375 mg/m^2/week for 4 weeks; 1000 mg repeated after 2 weeks) appear equally effective for induction of remission, but have not been formally compared; therefore, both can be recommended. (Level of evidence 4.)

In most studies, including both randomized controlled trials [4, 5], rituximab dosing has copied that used in lymphoma: 375 mg/m^2/week for 4 weeks. Others have adopted the protocol used in RA: two infusions of 1000 mg each, given 2 weeks apart. The four-dose regimen results in a higher total dose (2.5–3 g) and greater drug wastage than the two-dose course. No dose-ranging studies have been performed in vasculitis to ascertain the optimal protocol, and small, single-centre studies have been unable to compare different dosing regimens. However, responses do not seem to differ and one retrospective series of 65 patients found that both regimens induced similar rates of remission (81 and 75%,

Table 4 Rituximab therapy for retro-orbital granulomata

Study	Number of patients with ROG/total	Outcome
[6]	5/8	PR 1/5
[7]	2/8	CR or PR 0/2
[13]	1/6	PR 1/1
[16]	2/11	CR 2/2
[23]	5/34	CR 4/5 PR 1/5
[25]	1/3	PR 1/1
[28]	3/8	CR 2/3 PR 1/3
[31]	7/10	CR 7/7

ROG: retro-orbital granulomata; PR: partial remission; CR: complete remission.

Table 5 Rituximab in Churg–Strauss syndrome

Study	Study design	Number of CSS patients/total	Outcome in CSS patients
[38]	Case report	2/2	Full course not received (bronchospasm)
[39]	Case report	2/2	CR 1/2 PR 1/2
M.-J.C.J.G., 2010, data not published[a]	RCS	9/9	CR 8/9 PR 1/9
[40]	Case report	1/1	CR
[41]	Case report	2/2	CR 2/2
[20]	RCS	1/15	CR
[26]	PCS	1/7	CR
[42]	Case report	2/2	CR 1/2 PR 1/2
[17]	RCS	5/65	CR 4/5 PR 1/5
[43][b]	Case report	1/1	PR 1/1
[29]	PPT	1/11	CR
[32]	RCS	1/13	CR or PR

[a]Five patients have been reported by Jones *et al.* (including one patient previously reported by Pepper *et al*. and two by Koukoulaki *et al.*—one of whom was also reported by Smith *et al.*). [b]CSS with CNS involvement; duration of follow-up only 16 weeks. CSS: Churg–Strauss syndrome; RCS: retrospective case series; PCS: prospective case series; PPT: prospective open-label pilot trial; CR: complete remission; PR: partial remission.

respectively) [17]. Lower dosages have been tested, appearing less efficacious [6].

Recommendation 3. What are the longer term outcomes of treatment with rituximab?

3.1 Relapse rate

The overall response to rituximab in refractory disease may be superior to that seen with alternative therapies in similar cohorts of patients. There is insufficient evidence on long-term outcomes with rituximab when compared with conventional therapy in newly diagnosed patients.

Relapse after rituximab is common and patients should be monitored accordingly. (Level of evidence 4.)

Varying relapse rates have been reported, but it is difficult to draw conclusions because follow-up lengths were usually short (Table 3). In the largest survey of long-term outcomes, relapse occurred in 28 of the 49 patients who experienced complete remission initially (57%). The median time to relapse was 1 year. Quality and duration of response following rituximab treatment appeared to be superior to those following alternative therapies [17]. In previously untreated patients, only 12-month data are available from one randomized controlled trial: 4 (15%) patients randomly assigned to rituximab have relapsed [*vs* 1 (10%) of those who received CYC] [3].

3.2 Potential predictors of relapse

No biomarker reliably predicts relapse. (Level of evidence 3.)

Relapse has been preceded by an elevation in ANCA-binding levels [18, 30]. However, most relapses have occurred without major change in ANCA levels [17]. Furthermore, in one survey no difference in initial ANCA subtype or status (MPO-ANCA *vs* PR3-ANCA, or positive *vs* negative) was found between relapsing and non-relapsing patients [17].

Peripheral B-cell depletion after rituximab was achieved in almost all published cases, and is often used as an indicator of efficacy. The same survey of 65 patients found B cells unreliable for guiding re-treatment, with 48% of flares (13 out of 27) occurring before B-cell restoration, and 32% (8 out of 25) of patients in whom B cells returned not experiencing a relapse [17]. Similar findings were recorded in smaller cohorts [24, 30]. Other studies found that peripheral B-cell reconstitution is evident in all patients who suffer a relapse [33], and patients with prolonged B-cell depletion have lower relapse rates [29]. No differences in disease subtype or organ system involvement was noted between relapsing and non-relapsing patients [17].

3.3 Re-treatment with rituximab

Repeat rituximab is recommended for a relapse following rituximab-induced remission. (Level of evidence 4.)

Pre-emptive re-treatment may be considered in order to reduce relapse rates. (Level of evidence 4.)

Published data on re-treatment with rituximab have shown it to be effective at relapse. No randomized trial of re-treatment protocols has been carried out. Some patients have been treated only on relapse, some when ANCA levels were rising or on peripheral B-cell reconstitution. Neither of these biomarkers is a dependable predictor of relapse (see Question 3.2). In 2006, one centre started routine pre-emptive re-treatment, regardless of B-cell or ANCA status. This appears to be safe and effective for the prevention of relapse: flares occurred in only 10% of the patients who received 6 monthly, 1 g doses of rituximab, *vs* 73% in those who were not routinely re-treated. Optimal timing and dosing of subsequent rituximab courses remain to be determined [23, 29, 38, 44, 45]. A randomized controlled trial of rituximab *vs* AZA as maintenance therapy is currently ongoing [maintenance using rituximab in remission after vasculitis (MAINRITSAN)].

Recommendation 4. How should other immunosuppressive therapies be prescribed in patients treated with rituximab?

4.1 Should CYC be administered concomitantly with rituximab?

We do not recommend the routine use of CYC with rituximab.

CYC may be considered in severe, life or organ-threatening presentations such as rapidly progressive GN in order to achieve rapid disease control. (Level of evidence 4.)

CYC administration with rituximab was based on the rationale that it contributed to B-cell depletion, disease control and prevented the formation of human anti-chimeric antibodies. Its use has not been supported by evidence from RA [46], and it is not clear whether there was any benefit in the minority of reports in ANCA-associated vasculitis that used concomitant CYC. The time to remission after rituximab has been on average 2 months and additional CYC has been used in rapidly progressive presentations. A randomized controlled trial in severe renal ANCA-associated vasculitis (RITUXVAS) employed two doses of CYC (15 mg/kg) with the first course of rituximab [3]. The RAVE trial did not include CYC in the rituximab group, yet achieved at least comparable rates of remission [4].

4.2 Should other immunosuppressants be continued following rituximab?

No conclusion can be drawn from current data regarding the prescription of other immunosuppressing drugs with rituximab.

Maintenance immunosuppression with MMF, MTX or AZA was continued in most published series. However, in a subset of 40 patients included in the largest retrospective cohort survey, concomitant therapies were systematically

withdrawn once sustained remission had been achieved. The authors found that the rate of relapse was not increased in these patients, as long as pre-emptive rituximab re-treatment was considered as a long-term strategy. Continuous rituximab allowed appreciable weaning of prednisone and other immunosuppressive therapies in one study of 26 immunosuppression-dependent patients, with 71% of patients off all cytotoxic agents at 12 months [45]. Information from both randomized controlled trials is currently insufficient due to short follow-up, but neither used maintenance immunosuppression [3, 4].

4.3 What glucocorticoid regimen should be adopted in patients treated with rituximab and can glucocorticoids be stopped?

High-dose intravenous or oral glucocorticoids may be administered with the initial rituximab course in order to obtain rapid control of disease. (Level of evidence 4.)

There is no clear evidence to guide steroid tapering.

Most patients receive i.v. or high-dose oral glucocorticoids with the first course of rituximab. Both recent randomized trials included high-dose glucocorticoids in the initial induction of remission phase to help obtain early disease control. Plasma cells, which are not depleted by rituximab, are sensitive to high-dose methylprednisolone.

As in the standard protocols, all CS regimens are based on gradual tapering. In the earliest publications, most patients remained on long-term low doses. In spite of this, relapses often occurred, and many clinicians now attempt to withdraw glucocorticoids altogether. Of 99 patients treated with rituximab in the RAVE trial, it was possible to obtain glucocorticoid-free remission in 64% [4].

Recommendation 5. How safe is rituximab in ANCA-associated vasculitis?

There is no convincing evidence that rituximab increases the frequency of severe infections when used in the treatment of vasculitis. Other drug-related adverse events occur with similar frequency to that seen in other indications. (Level of evidence 4.)

We recommend that patients receive vaccinations at least 1 month before their first dose of rituximab. (Level of evidence 3.)

5.1 Infective risk

The safety profile of rituximab in lymphoma is well established [47]. In autoimmunity, safety data are principally available from the licensed use of rituximab (in combination with MTX) for patients with RA. The two randomized controlled trials of rituximab in ANCA-associated vasculitis found no significant difference in severe adverse event rates between groups treated with rituximab and those treated with CYC [3, 4]. In the RITUXVAS trial, overall incidence of infections was comparable in both treatment groups (66 per 100 patient-years with rituximab, 60 per 100 patient-years with CYC), but follow-up is as yet only 12 months.

In retrospective cohorts of patients, concomitant or previous immunosuppression is a confounding factor in attempting to attribute infective adverse events to rituximab. In ANCA-associated vasculitis severe infections affect 20–30% of patients. Incidence was 0.19 per patient-year in one study and was increased in the first year of rituximab treatment [48]. This is higher than in RA, but lower than in vasculitis trials with deoxyspergualin or alemtuzumab [49, 50]. Severe hypogammaglobulinaemia induced by rituximab is rare (affecting $<5\%$ of patients). The number of rituximab courses does not appear to affect changes in immunoglobulin (Ig) levels. Patients with infection have been shown to have significantly lower immunoglobulin G (IgG) and IgM levels than those without infection [48].

Rituximab-induced neutropenia is another risk factor for infective complications. Catapano *et al*. [48] found neutrophil levels $<1.10^9$/l in 6 out of 105 patients, but only one of them experienced a severe infection, which resolved with i.v. antibiotics.

Most cases of progressive multifocal leucoencephalopathy (due to JC virus) in association with rituximab have been in oncological or transplantation patients in whom it is difficult to ascertain imputability to rituximab, concomitant immunosuppression or to their disease. Although there have been two cases in patients receiving rituximab for SLE (US Food and Drug Administration. FDA Alert: rituximab, http://www.fda.gov/cder/drug/Infopage/rituximab/default.htm; December 2006) and one in RA (http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm187791.htm, October 2009), to our knowledge none has been reported in ANCA-associated vasculitis. Patients treated with rituximab demonstrate diminished or abolished primary response to most vaccines. Pre-existing antibody levels appear to be unaffected.

5.2 Other risks

The most frequent adverse events are infusion-related reactions including flu-like symptoms and dyspnoea (occurring in 41% of vasculitis patients) [48]. Smith *et al*. [29] reported human anti-chimeric antibody positivity in two out of eight patients. Both relapsed and were re-treated; one then failed to achieve complete B-cell depletion and had only a short-lived clinical response [29]. In RA, no clear evidence has been found that human anti-chimeric antibodies interfere with the safety or efficacy of subsequent courses. There remains a possibility of rare severe events that will only become apparent when large numbers of patients have been treated.

Recommendation 6. Research agenda

The cost/benefit ratio of rituximab needs to be compared with conventional protocols for induction and maintenance of remission. Future studies should also focus on earlier and more rapid weaning of steroids. Continued follow-up of RAVE and RITUXVAS patients will yield

answers to questions on long-term outcomes (e.g. relapse rates and adverse effects). Issues that need to be more specifically addressed in future studies include long-term toxicity, reliable biomarkers to predict relapse and treatment options in rituximab-refractory disease (Table 2).

Discussion

These recommendations for the use of rituximab in ANCA-associated vasculitis have arisen from results of a Delphi exercise and a systematic literature review. Despite the relatively low levels of evidence and recent nature of the studies, for this uncommon disorder the existing data were felt sufficiently strong to recommend rituximab for refractory ANCA vasculitis and as an alternative to CYC for previously untreated patients. The introduction of CYC in the treatment of vasculitis 40 years ago was a major advance and its combination with glucocorticoids was the first reliable therapy that could achieve full disease control. Much of the clinical research in this area since has considered the toxicity of CYC and how this can best be managed by reducing exposure. To have an effective, safe alternative to CYC is, therefore, a major advance. The two randomized trials did not show a safety benefit of rituximab; therefore, it is reasonable to continue the routine use of CYC for remission induction, and the cost-effectiveness of rituximab when compared with CYC has not been assessed. Furthermore, the relapse risk after rituximab induction when compared with CYC is not known and until more details become available such patients merit close monitoring.

We recognize the potential for bias especially at earlier stages in clinical development of a new therapeutic agent. There is potential for positive reporting bias in uncontrolled trials, but results from these studies have been consistent and reproduced in the randomized trials. There is also the potential for bias from the commercial support for these recommendations. However, no commercial interest played a role in this report, which represents the opinions of a panel experienced in the treatment of vasculitis.

Although the current data are felt strong enough to support our recommendations, it is not known whether rituximab may actually be superior to CYC or what the optimal remission maintenance strategies are after rituximab. The relatively short follow-up, especially of the randomized controlled trials, emphasizes the lack of knowledge on the impact of rituximab on long-term outcomes. No major safety problems with rituximab were identified in the larger studies, but some concerns over the infective and allergic risk of rituximab remain that need to be addressed in the future.

The effectiveness of B-cell depletion points to the potential of other B-cell modulating therapies. Other agents currently under evaluation for the treatment of the ANCA-associated vasculitides include deoxyspergualin, alemtuzumab and anti-TNF-α agents [49, 50], but evidence to recommend their use is far weaker than that for rituximab. Rituximab is an advance in the treatment of ANCA-associated vasculitis and has a place in the therapeutic armament as an alternative to CYC or for refractory disease. Further questions remain, which will be explored over the coming decade.

Rheumatology key messages

- Rituximab is an effective therapy in refractory ANCA-associated vasculitis.
- In newly diagnosed disease, outcomes appear as good with rituximab as with CYC.
- Long-term efficacy and safety of rituximab in newly diagnosed ANCA-associated vasculitis remain to be determined.

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References

1 Mukhtyar C, Guillevin L, Cid MC *et al*. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis 2009;68:310–7.

2 Dougados M, Betteridge N, Burmester GR *et al*. EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees. Ann Rheum Dis 2004;63:1172–6.

3 Jones RB, Cohen Tevaert JW, Hauser T *et al*. Randomised trial of rituximab versus cyclophosphamide in ANCA

associated renal vasculitis 'RITUXVAS'. N Engl J Med 2010;363:211–20.

4 Stone JH, Merkel PA, Seo P *et al*. Rituximab versus cyclophosphamide for induction of remission in ANCA-associated vasculitis: a randomized controlled trial (RAVE). N Engl J Med 2010;363:221–32.

5 Hellmich B, Flossmann O, Gross WL *et al*. EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis 2007;66:605–17.

6 Aries PM, Hellmich B, Voswinkel J *et al*. Lack of efficacy of rituximab in Wegener's granulomatosis with refractory granulomatous manifestations. Ann Rheum Dis 2006;65: 853–8.

7 Brihaye B, Aouba A, Pagnoux C, Cohen P, Lacassin F, Guillevin L. Adjunction of rituximab to steroids and immunosuppressants for refractory/relapsing Wegener's granulomatosis: a study on 8 patients. Clin Exp Rheumatol 2007;25(1 Suppl. 44):S23–7.

8 Callejas Rubio JL, Camps MT, Garcia-Hernandez F. Treatment with rituximab of autoimmune disease: results from AADEA's registry. Med Clin 2008;130:79.

9 De Menthon M, Cohen P, Pagnoux C *et al*. Infliximab (IFX) vs rituximab (RTX) for refractory Wegener's granulomatosis (WG): a prospective, randomized, multicenter study on 21 patients. APMIS 2009;117(Suppl. 127):72.

10 Eleftheriou D, Melo M, Marks SD *et al*. Biologic therapy in primary systemic vasculitis of the young. Rheumatology 2009;48:978–86.

11 Eriksson P. Nine patients with anti-neutrophil cytoplasmic antibody-positive vasculitis successfully treated with rituximab. J Intern Med 2005;257:540–8.

12 Garcia Hernandez FJ, Ocana Medina C, Gonzalez Leon R *et al*. Rituximab for treatment of patients with systemic autoimmune diseases. Med Clin 2007;128:458–62.

13 Henderson SR, Copley SJ, Ind PW, Salama AD. Effective treatment of granulomatous lesions in Wegener's granulomatosis with rituximab. APMIS 2009; 117(Suppl. 127):70.

14 Henes J, Kanz L, Koetter I. Rituximab and leflunomide for Wegener's granulomatosis: a long-term follow-up. Rheumatol Int. Advance Access published March 27, 2010, doi: 10.1007/s00296-010-1462-x.

15 Henes JC, Fritz J, Koch S *et al*. Rituximab for treatment-resistant extensive Wegener's granulomatosis-additive effects of a maintenance treatment with leflunomide. Clin Rheumatol 2007;26: 1711–5.

16 Jeannin G, Gregorini G, Toninelli C *et al*. Rituximab added to 'maintenance therapy' in granulomatous relapses of Wegener granulomatosis. APMIS 2009;117(Suppl. 127):79.

17 Jones RB, Ferraro AJ, Chaudhry AN *et al*. A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2009;60:2156–68.

18 Keogh KA, Wylam ME, Stone JH, Specks U. Induction of remission by B lymphocyte depletion in eleven patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52:262–8.

19 Keogh KA, Ytterberg SR, Fervenza FC, Carlson KA, Schroeder DR, Specks U. Rituximab for refractory Wegener's granulomatosis: report of a prospective, open-label pilot trial. Am J Respir Crit Care Med 2006;173: 180–7.

20 Lovric S, Erdbruegger U, Kumpers P *et al*. Rituximab as rescue therapy in anti-neutrophil cytoplasmic antibody-associated vasculitis: a single-centre experience with 15 patients. Nephrol Dial Transplant 2009;24:179–85.

21 Mansfield N, Hamour S, Habib AM *et al*. CycLowVas: a rituximab(RTX)-based cyclophosphamide (CYP)-sparing regime. APMIS 2009;117(Suppl. 127):69.

22 Marinaki S, Skalioti C, Darema M, Papadaki P, Iniotaki A, Boletis I. pANCA vasculitis in older patients: safe and effective treatment with low immunosuppression in combination with the mAb rituximab. APMIS 2009; 117(Suppl. 127):74.

23 Martinez Del Pero M, Chaudhry A, Jones RB, Sivasothy P, Jani P, Jayne D. B-cell depletion with rituximab for refractory head and neck Wegener's granulomatosis: a cohort study. Clin Otolaryngol 2009;34:328–35.

24 Molloy E, Koening C, Hernandez-Rodriguez J, Clark T, Langford C, Hoffman G. Relapses in rituximab (RIT)-treated Wegener's granulomatosis (WG) patients despite peripheral B-cell depletion. APMIS 2009;117(Suppl. 127): 78.

25 Omdal R, Wildhagen K, Hansen T, Gunnarsson R, Kristoffersen G. Anti-CD20 therapy of treatment-resistant Wegener's granulomatosis: favourable but temporary response. Scand J Rheumatol 2005;34:229–32.

26 Roccatello D, Baldovino S, Alpa M *et al*. Effects of anti-CD20 monoclonal antibody as a rescue treatment for ANCA-associated idiopathic systemic vasculitis with or without overt renal involvement. Clin Exp Rheumatol 2008; 26(3 Suppl. 49):S67–71.

27 Sanchez-Cano D, Callejas-Rubio JL, Ortego-Centeno N. Effect of rituximab on refractory Wegener granulomatosis with predominant granulomatous disease. J Clin Rheumatol 2008;14:92–3.

28 Seo P, Specks U, Keogh KA. Efficacy of rituximab in limited Wegener's granulomatosis with refractory granulomatous manifestations. J Rheumatol 2008;35: 2017–23.

29 Smith KG, Jones RB, Burns SM, Jayne DR. Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis: remission, relapse, and re-treatment. Arthritis Rheum 2006;54:2970–82.

30 Stasi R, Stipa E, Del Poeta G, Amadori S, Newland AC, Provan D. Long-term observation of patients with anti-neutrophil cytoplasmic antibody-associated vasculitis treated with rituximab. Rheumatology 2006;45:1432–6.

31 Taylor SR, Salama AD, Joshi L, Pusey CD, Lightman SL. Rituximab is effective in the treatment of refractory ophthalmic Wegener's granulomatosis. Arthritis Rheum 2009;60:1540–7.

32 Wendt M, Gunnarsson I, Bratt J, Bruchfeld A. Rituximab in ANCA-associated vasculitis (AAV), a case series. APMIS 2009;117(Suppl. 127):80.

33 Yazdani R, Sama A, Jones N, Gaywood I, Lanyon P. Long-term outcomes of B-cell depletion in refractory vasculitis and timing of re-treatment. APMIS 2009; 117(Suppl. 127):72.

34 Tamura N, Matsudaira R, Hirashima M *et al*. Two cases of refractory Wegener's granulomatosis successfully treated with rituximab. Intern Med 2007;46:409–14.

35 Patel AM, Lehman TJ. Rituximab for severe refractory pediatric Wegener granulomatosis. J Clin Rheumatol 2008;14:278–80.

36 Brunner J, Freund M, Prelog M *et al*. Successful treatment of severe juvenile microscopic polyangiitis with rituximab. Clin Rheumatol 2009;28:997–9.

37 Hugle B, Solomon M, Harvey E *et al*. Pneumocystis jirovecii pneumonia following rituximab in Wegener's granulomatosis. Arthritis Care Res. Advance Accessed published June 25, 2010, doi: 10.1002/acr.20279.

38 Bouldouyre MA, Cohen P, Guillevin L. Severe bronchospasm associated with rituximab for refractory Churg-Strauss syndrome. Ann Rheum Dis 2009;68:606.

39 Donvik KK, Omdal R. Churg-Strauss syndrome successfully treated with rituximab. Rheumatol Int 2009; 31:89–91.

40 Kaushik VV, Reddy HV, Bucknall RC. Successful use of rituximab in a patient with recalcitrant Churg-Strauss syndrome. Ann Rheum Dis 2006;65:1116–7.

41 Koukoulaki M, Smith KG, Jayne DR. Rituximab in Churg-Strauss syndrome. Ann Rheum Dis 2006;65:557–9.

42 Pepper RJ, Fabre MA, Pavesio C *et al*. Rituximab is effective in the treatment of refractory Churg-Strauss syndrome and is associated with diminished T-cell interleukin-5 production. Rheumatology 2008;47:1104–5.

43 Saech J, Owczarczyk K, Roesgen S, Petereit H, Hallek M, Rubbert A. Successful use of rituximab in a patient with Churg-Strauss syndrome and refractory CNS involvement. Ann Rheum Dis 2009;69:1254–5.

44 Jones RB, Laurino S, Chaudhry A, Catapano F, Smith KG, Jayne DRW. Protocolized vs non-protocolized rituximab treatment for refractory ANCA-associated systemic vasculitis. APMIS 2009;117(Suppl. 127):76.

45 Rhee EP, Laliberte KA, Niles JL. Continuous anti-B-cell therapy: successful adjunct to treatment for ANCA-associated vasculitis. APMIS 2009;117(Suppl. 127):69.

46 Edwards JC, Szczepanski L, Szechinski J *et al*. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med 2004;350:2572–81.

47 Plosker GL, Figgitt DP. Rituximab: a review of its use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. Drugs 2003;63:803–43.

48 Catapano F, Jones RB, Walsh M, Chaudhry A, Jayne DRW. Safety and tolerability of rituximab in vasculitis and systemic lupus erythematosus [abstract]. APMIS 2009;117(Suppl. 127):68–81.

49 Flossmann O, Baslund B, Bruchfeld A *et al*. Deoxyspergualin in relapsing and refractory Wegener's granulomatosis. Ann Rheum Dis 2009;68:1125–30.

50 Walsh M, Chaudhry A, Jayne D. Long-term follow-up of relapsing/refractory anti-neutrophil cytoplasm antibody associated vasculitis treated with the lymphocyte depleting antibody alemtuzumab (CAMPATH-1H). Ann Rheum Dis 2008;67:1322–7.