REVIEW

Consensus statement on the use of rituximab in patients with rheumatoid arthritis

J S Smolen, E C Keystone, P Emery, F C Breedveld, N Betteridge, G R Burmester, M Dougados, G Ferraccioli, U Jaeger, L Klareskog, T K Kvien, E Martin-Mola, K Pavelka, The Working Group on the Rituximab Consensus Statement

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A large number of experts experienced in the treatment of rheumatoid arthritis were involved in formulating a consensus statement on the use of B cell-targeted treatment with rituximab in patients with rheumatoid arthritis. The statement was supported by data from randomised controlled clinical trials and the substantial literature on oncology. The statement underwent three rounds of discussions until its ultimate formulation. It should guide clinicians in the use of this newly approved biological agent in treating patients with rheumatoid arthritis.

Ample evidence is available to suggest that persistent active rheumatoid arthritis leads to major joint destruction and disability.[1] Therefore, to minimise inflammation, it is important to interfere with the disease process using disease-modifying antirheumatic drugs (DMARDs), including biological agents. This is best achieved by early institution of such treatment and adherence to tight control of disease activity using appropriate measures to decide on timely changes in therapeutic strategies.[2] Despite the changes in treatment paradigms, which over the recent years included earlier use and higher doses of methotrexate (MTX), combination DMARDs and the use of biological agents,[3] there remains a large proportion of patients who either do not respond sufficiently to these new therapeutic strategies, experience toxicity or have contraindications, resulting in a large unmet need currently being challenged by the development of new treatment methods.

See end of article for authors' affiliations

Correspondence to: Professor J S Smolen, Department of Rheumatology, Third Department of Internal Medicine, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria; josef.smolen@wienkav.at

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SCOPE AND PURPOSE

A group of rheumatology experts (the main authors) from several regions in Europe and Canada, experienced in clinical research, the use of biological agents and the development of consensus statements,[4–6] gathered in Vienna to formulate a consensus statement and guidance document on the use of rituximab in arthritis clinics for routine care of patients with rheumatoid arthritis. They were supported by a patient representative and a haematologist who was experienced in the use of rituximab in benign and malignant haematological diseases. Subsequently, the draft of the resulting consensus statement was presented in another meeting for further discussion, amendment and finalisation to 30 experts including the patient representative (the Working Group).

Given that current treatments fail to achieve low disease activity or remission, as defined by composite disease activity indices,[2] in many patients, additional treatments are needed, particularly those with novel modes of action and different potential toxicities. One such therapy, recently licensed in the US and in Europe, is rituximab, a chimeric monoclonal anti-CD20 antibody that selectively depletes CD20-expressing B cells.

We have had the opportunity of discussing the accrued knowledge in the use of rituximab and of formulating our jointly shared views on the following:

- Indications, considerations and screening for initiating rituximab
- Treatment dose and comedication
- Evaluation of response and considerations for repeat treatment
- Contraindications and adverse events
- Research agenda

To this end, we reviewed the published literature on the efficacy of rituximab in treating patients with rheumatoid arthrits using both full publications and abstracts; abstracts were included given the paucity of fully published information.

Although extensive literature is available on the toxicity of rituximab in patients with non-Hodgkin's lymphoma,[7–9] which can also be obtained from the package insert or summary of product characteristics, relatively limited information is available with respect to safety issues in patients with rheumatoid arthritis. Extrapolating side effects observed in patients with non-Hodgkin's lymphoma to those with rheumatoid arthritis may not be appropriate, as both comedications and comorbidites usually differ between these diseases. The statement presented below has been developed in line with recent literature on the generation of such recommendations.[10] Categories of evidence will be indicated next to each reference

Abbreviations: ACR, American College of Rheumatology; SCDAI, Simplified composite Disease Activity Index; DAS28, 28-joint Disease Activity Score; DMARD, disease-modifying antirheumatic drug; HACA, human antichimeric antibody; MTX, methotrexate; SDAI, simplified Disease Activity Index; TNF, tumour necrosis factor

Table 1 Evidence hierarchy (modified from Shekelle *et al*[11])

Category of evidence	Type of study
Ia	Meta-analysis of RCTs or >1 RCT with similar results
Ib	RCT
Iia	Controlled study without randomisation
IIb	Quasi experimental study
III	Non-experimental descriptive studies such as comparative, correlation and case–control studies
IV	Expert committee reports or opinion or clinical experience of respective authorities, or both

RCT, randomised controlled trial.

in line with published guidelines[11]; however, it was agreed to modify this guidance document by assigning category Ia to the availability of ⩾2 randomised controlled trials with similar results (table 1).

BACKGROUND

Rituximab is licensed for non-Hodgkin's lymphoma and has been given to >700 000 patients.[12] Rituximab has been recently approved by the Food and Drug Administration in the US and by the Committee for Medicinal Products for Human Use of the European Agency for the Evaluation of Medicinal Products in Europe for the treatment of patients with rheumatoid arthritis who have had an inadequate response to tumour necrosis factor (TNF) blockers. In these patients, rituximab is given intravenously as two 1-g infusions (with intravenous glucocorticoid premedication; table 2), separated by 2 weeks.[12 13]

In early studies, rituximab has shown efficacy when used alone (category Ib) and in combination with other agents, including MTX[14] (category Ia). The efficacy and durability of monotherapy seems to be less than that of combination treatment with MTX (category Ib). Subsequent studies on rituximab in combination with MTX have proved to be successful in markedly reducing inflammatory activity and increasing functional ability and the quality of life[12] (category Ia). In responding patients, the duration of the response to a single course of rituximab usually lasts >6 months[15] (category III). The data on radiographic progression at 1 year in patients with previous inadequate response to anti-TNF drugs showed considerable retardation of joint destruction[16] (category Ib).

RECOMMENDATIONS

Indication

At present, in line with the current licensed indications, rituximab may be used in patients with rheumatoid arthritis who qualify for treatment with biological agents and have had an inadequate response or intolerance to ⩾1 TNF-blocking agents [17]; patients with a contraindication to TNF inhibitors have not yet been adequately studied. Before concluding that a patient has not responded to a TNF blocker, attempts should be made to improve the current regimen by optimising the DMARD or anti-TNF treatment[18] considering national guidelines.

Current evidence on the efficacy of rituximab relates to rheumatoid factor-positive patients[13 14] (category Ia). In the phase III study on TNF non-responders, a marked response was seen in rheumatoid factor-negative patients,[12] whereas in another study on rheumatoid factor-negative patients who were not part of the primary end point analysis, the response was not different from placebo-treated patients, although the response to placebo was unusually high[13] (table 3). As both studies comprised small numbers of rheumatoid factor-negative patients, the role of rheumatoid factor and other potential predictors of treatment outcome on rituximab will be clarified by ongoing studies.

Considerations for initiating treatment

Before treatment, an individual therapeutic goal should be established with each patient by the treating physician. The doctor should be experienced in the diagnosis and treatment of rheumatoid arthritis, including the use of biological agents. The primary objective for the patient should be relief from symptoms, especially pain, stiffness and fatigue; prevention of disability; improved mobility; and better quality of life. This will be best realised by achieving a low disease activity state or even remission by composite disease activity indices.[2 19–25]

So far, there has been no evidence of a markedly increased risk of infections or other serious adverse events in patients who initiated rituximab after TNF blockers compared with patients who initiated rituximab after conventional treatment with DMARDs; however, in the phase II and phase III studies, patients had discontinued etanercept for 4 weeks or infliximab and adalimumab for 8 weeks before treatment with rituximab. Exclusion criteria comprised evidence of major systemic involvement due to rheumatoid arthritis, other major illnesses or laboratory abnormalities, and a history of recurrent relevant infections.[12 13]

Most of the patients studied in the phase II or phase III clinical trials on rituximab had high disease activity. Thus, patients considered for treatment generally should have active disease defined as at least moderate disease activity by composite scores, such as by the 28-joint Disease Activity Score, DAS28 (⩾3.2), the simplified Disease Activity Index, SDAI (>11) or similar indices.[2]

Screening before initiating rituximab

Initiation of rituximab should be preceded by recording a detailed history (regarding chronic or recent comorbidity, such as cardiovascular and pulmonary diseases, recurrent infections and allergies) and a complete physical examination to consider

Table 2 Doses of rituximab and glucocortiocids in three randomised controlled clinical trials

Study	Rituximab dose	Intravenous glucocorticoids	Oral Glucocorticoids
Edwards *et al*[14]	2×1000 mg	2×100 mg MP on days 1 and 15	60 mg P, days 2, 4–7+30 mg P, days 8–14
Emery *et al*[13]	2×1000 mg or 2×500 mg	(1) 0 (2) 2×100 mg MP* (3) 2×100 mg MP*	(1) 0 (2) 0 (3) 60 mg P on days 2–7+30 mg P on days 8–14
	No marked difference in efficacy between the two rituximab doses	Premedication markedly reduced infusion-related adverse events after the first infusion; no appreciable difference in efficacy	Oral P did not influence infusion reactions to the second infusion
Cohen *et al*[12]	2×1000 mg	2×100 mg MP*	60 mg P on days 2–7+30 mg P on days 8–14

DMARD, disease-modifying antirheumatic drug; MP, methylprednisolone; P, prednisone.
*Edwards *et al*'s[14] study comprised a population of patients with active disease despite traditional treatment with DMARDs. In Emery *et al*'s[13] study, two thirds of the patients had active disease despite traditional treatment with DMARDs, whereas one third had active disease despite treatment with TNF inhibitors. In Cohen *et al*'s[12] study, all patients had active disease despite treatment with TNF inhibitors.

Table 3 Results in rheumatoid factor-negative and rheumatoid factor-positive patients

Patients	Rituximab/placebo (n)	ACR20 on rituximab (%)	ACR20 on placebo (%)	p Value	Reference
Total studied	308/209*				
RF pos (%)	79/79*	54	19	<0.001	Cohen *et al*[12]
RF neg (%)	21/21*	41	12	<0.001	
RF pos	128†/128	54	28	<0.03	Emery *et al*[13]
RF neg	63†/21	48	52	NR	

ACR, American College of Rheumatology; neg, negative; NR, not reported; pos, positive; RF, rheumatoid factor.
*Numbers reported for the safety population; it is not clear whether identical patients were assessed for efficacy (ie, the ACR responses indicated), but the numbers or proportions should be similar and the %ACR responses are as reported.
†Patients on 2×1000 mg rituximab only.

possible contraindications. Chest radiography was carried out in the clinical trials, but may not be mandatory.

In the clinical trials on rituximab, patients were pre-screened for hepatitis B and C. The oncology literature has reports of patients with hepatitis B and C undergoing rituximab treatment: patients with hepatitis C were successfully treated without further prophylaxis[26] (category IV); those with hepatitis B were also successfully treated with rituximab, usually with antiviral (lamivudine) prophylaxis[27] (category IV).[28] However, cases of reactivated, fulminant hepatitis B have been reported with rituximab[29] (category IV). Currently, there is no experience on patients with rheumatoid arthritis positive for hepatitis B or C. Rituximab does not seem to increase the risk of infections in patients with HIV with lymphoma[8 30] (category IIb). In the oncology literature, rituximab does not markedly add to the risk of infections induced by chemotherapy; this includes opportunist infections[8] and also herpes zoster infections, although there was one case of disseminated and fatal herpes zoster infection.[8 31] As always, the individual benefit–risk ratio should be considered and discussed with the patient. Although routine testing for hepatitis C is discretionary, expert advice is that hepatitis B status should be obtained, as practised in haemato-oncology,[27] in view of the reported risk of reactivation of hepatitis B (see also adverse events section), although more data will also be needed regarding hepatitis C.

Some data from the oncology literature indicate that in patients receiving rituximab, response to vaccination may be ineffective[8] and, therefore, vaccinations with inactivated vaccines, such as hepatitis B, pneumococcal and influenza vaccines, should be considered before treatment with rituximab (category IV). More data are needed on the potential risk of vaccination with live vaccines, which, therefore, are not recommended for rituximab-treated patients.

In general, patients who did not respond to TNF-blocking treatment will also have been pre-screened for the presence of active or latent tuberculosis. In the rheumatoid arthritis clinical trials on rituximab before TNF inhibitors, patients with active tuberculosis were excluded, but patients were not screened for latent tuberculosis by PPD testing. In this context, it should be remembered that rituximab is used in rheumatoid arthritis in combination with two pulses of glucocorticoid and continuous treatment with MTX, which by itself may reactivate tuberculosis. However, there is no evidence of an increased frequency of tuberculosis in patients with lymphoma treated with rituximab[8] and, therefore, at this time there is no evidence indicating the necessity to systematically screen patients for tuberculosis before using rituximab in those with rheumatoid arthritis.

Apart from routine laboratory tests usually performed in patients with rheumatoid arthritis before initiating new treatments, it may be useful to determine baseline immunoglobulin levels, as decreased levels of immunoglobulin (Ig)M have been observed with rituximab over time[32] (category III). In clinical trials, B cell levels have been measured, but the utility of these measurements in routine practice is not proved. On the other hand, no data are available regarding the safety of rituximab in patients with hypogammaglobulinaemia and, therefore, rituximab should not be used for treating rheumatoid arthritis in such rare instances.

Treatment dose and comedication

In patients who have received prior TNF blocker treatment, rituximab has been used and licensed at a dose of 1000 mg per infusion on days 1 and 15.[12] However, a lower dose of 500 mg per infusion has also been studied in a population consisting predominantly of patients with prior inadequate response to traditional DMARDs, with notable efficacy compared with that to placebo[13] (category Ib); the American College of Rheumatology (ACR)20, 50 and 70 response rates in patients treated with 2×500 mg rituximab were 55%, 33% and 13% compared with 54%, 34% and 20%, respectively, in patients receiving 2×1000 mg rituximab.

In the phase II trial, the ACR responses of patients treated with rituximab in combination with MTX (ACR20, ACR50 and ACR70: 73%, 43% and 23%, respectively) were numerically superior to those receiving rituximab monotherapy (65%, 33% and 15%, respectively). As the difference between responses to rituximab monotherapy and the placebo control arm (ACR20, ACR50 and ACR70: 38%, 13% and 5%, respectively) did not reach statistical significance for ACR50 and ACR70 responses[14] (category Ib), rituximab is licensed only in combination with MTX (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm, http://www.emea.eu.int/humandocs/Humans/EPAR/mabthera/mabthera.htm). In clinical practice this will usually be a dose of 10–25 mg MTX per week, unless adverse events preclude such doses. Nevertheless, rituximab monotherapy was also shown to be more effective (ACR20 response) than placebo[14] (category Ib). Data are available from the phase II trials on cyclophosphamide as comedication, but this expert group thought that cyclophosphamide is usually not an appropriate comedication, taking into account the potential serious side effects with this drug.[10] No data are currently available on the concomitant use of other DMARDs, including TNF inhibitors.

To reduce the frequency and severity of infusion reactions, patients should receive 100 mg methylprednisolone intravenously before rituximab infusions, and antihistamine (category Ib); this is particularly indicated before the first infusion and should also be given before the second infusion of each cycle, although the indication may not be as strong in the second infusion.[13 33] Paracetamol and antihistamines may be required, but there is no evidence from the trials on patients with rheumatoid arthritis that antihistamines should be used systematically, although they have been used for premedication in all clinical trials on rheumatoid arthritis.

Evaluation of response

Routine rheumatological assessments should be performed at baseline and periodically according to the national standards of care for therapies with biological agents and MTX. Response to rituximab should be assessed by validated response criteria, including numerical evaluation of the number of tender and swollen joints (eg, using the DAS28, SDAI or CDAI) and an acute-phase response (eg, erythrocyte sedimentation rate or C reactive protein level, or both). Other appropriate measurements include, for example, patient's or physician's global assessments (visual analogue scale or five-point scale), pain assessment (100 mm visual analogue scale) and functional assessment (Health Assessment Questionnaire). As a guideline to treatment, we suggest a response in the DAS28 score of $\geqslant$1.2 or equivalent measure should be regarded as a minimum improvement. A low disease activity range (DAS28 $\leqslant$3.2, SDAI $<$11 or Clinical Disease Activity Index (CDAI) $<$10) and a maximisation of functional ability and quality of life should be the target for the rheumatologist to aim for with regard to a desirable disease state[2] (category C). In most patients, a response is usually seen by 16 weeks after the first infusion[12–14] (category Ia). It should be noted, however, that the intravenous glucocorticoid premedication will produce an early, albeit usually a transient, response before 8 weeks. It is important that this is communicated to the patients.

Rituximab usually leads to rapid B cell depletion (category Ia); however, presently, the value of routine monitoring of B cell counts, or immunoglobulin levels, is not proved.

Considerations for repeated treatment

At present, the only evidence of efficacy of repeated treatment comes from studies on patients who had a prior response to rituximab with subsequent loss of effect. A patient should be regarded as a responder if the response criteria are met after an observation period of at least 16 weeks from the initiation of treatment according to the recommended dosing schedule. There is an association between loss of response and return of B cells, although B cell levels usually remain below levels at baseline at the time of loss of response[12] (category III).[13]

Repeated treatment should be considered, after at least 24 weeks (category IV), in responders who have considerable residual disease activity or who deteriorate clinically after having initially responded. Moderate disease activity (DAS28 $>$3.2, CDAI $>$10 or SDAI $>$11)[2] is considered by the authors to be significant residual disease activity. Clinical deterioration has not been formally defined. However, a deterioration in the clinical status, such as an increase in DAS28 of $\geqslant$0.6 or an equivalent change in disease activity, is considered as a clinically relevant deterioration. In patients who had experienced a loss of their response, repeated treatment was given with an interval of $\geqslant$24 weeks from the initial course of rituximab[15 34] (category III). The optimal repeated treatment schedule is being investigated. In the repeated treatment studies, responding patients, especially those who reach low disease activity, were not treated again until clinical deterioration, which is usually experienced at 6–12 months after the initial infusion[15] (category III). Although data have limitations, repeated treatment has usually resulted in responses similar to that of initial treatment. No data are currently available on repeated treatment in patients who failed to respond to the initial course.

Treatment with TNF blockers in rituximab non-responders

TNF blockers have been used in a limited number of patients who did not respond to rituximab and who continued to have B cell counts below normal[35] (category IV). A numerical increase in serious infections was observed. In this study, TNF blockers were initiated usually at least 4 months after rituximab (when insufficient treatment response would be judged). Therefore, careful consideration of the individual risk–benefit ratio is mandatory in the context of a potential carry-over effect of the previous rituximab treatment. Further data are needed. Likewise, the safety of using abatacept or anakinra before or after rituximab needs to be established.

CONTRAINDICATIONS AND ADVERSE EVENTS

Contraindications

Contraindications to rituximab include hypersensitivity to rituximab or other murine proteins, active severe infections and severe heart failure (New York Heart Association class IV; http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm, http://www.emea.eu.int/humandocs/Humans/EPAR/mabthera/mabthera.htm).[17] In non-Hodgkin's lymphoma, contraindications have been restricted to hypersensitivity to components of this product or murine proteins. Patients with active infections (acute or chronic) should not be treated with rituximab. Safety in children has not been established.

Adverse events

The tolerability and safety of rituximab has been well described in the clinical trials on patients with rheumatoid arthritis and review articles on non-Hodgkin's lymphoma[12] (category III).[8 13 14] The most frequent adverse events are infusion reactions (30–35% with the first infusion with concomitant glucocorticoids). Fewer reactions are observed with the second infusion[12] (category Ib).[13 14] They are usually mild to moderate, but may require therapeutic intervention (additional paracetamol, antihistamines, bronchodilators, eventually glucocorticoids). Severe infusion reactions are uncommon. Their frequency is reduced by the use of concomitant intravenous steroids as recommended for rheumatoid arthritis, and only rarely lead to withdrawal from treatment (category III; http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm, http://www.emea.eu.int/humandocs/Humans/EPAR/mabthera/mabthera.htm).[12–14 17]

In the clinical trials carried out on patients with rheumatoid arthritis to date, a small increase was seen in serious infections (but not opportunist infections, including tuberculosis) in patients receiving rituximab at 2$\times$1000 mg compared with those receiving placebo: 4.7/100 *v* 3.2 patient-years in the DANCER study and 5.2/100 *v* 3.7 patient-years in the REFLEX study[12 13] (category III). Currently, no available data suggest an increased risk of opportunist infections (including tuberculosis) in either populations, with rheumatoid arthritis or lymphoma[7] (category III),[8] with the exception of individuals with T cell deficiency in HIV infection[36] (category III). Table 4 lists the more frequent ($\geqslant$1%) adverse events.

In the oncology literature, late-onset neutrocytopenia has been reported in 8% of patients treated with rituximab monotherapy and combination treatment and may occur up to 1 year after treatment[37] (category III); this required treatment with granulocyte colony-stimulating factor in some patients.

To date, there have been no safety signals regarding malignancies; however, with respect to rheumatoid arthritis, larger databases on safety data are required before any firm conclusions can be drawn.

As rituximab is a chimeric antibody, human antichimeric antibodies (HACAs) may occur and have been reported in as many as 9.2% of patients with rheumatoid arthritis (see http://www.emea.eu.int/humandocs/Humans/EPAR/mabthera/mabthera.htm).[14 17] However, although adverse events related to HACA are rare, a case of a severe allergic reaction was reported in which HACAs apparently prevented B cell depletion[17] (category IV).

Table 4 Adverse events observed in ⩾1% of patients with rheumatoid arthritis

	Pooled phase II study population		Phase III study population	
	MTX+placebo n = 189	Rituximab+MTX n = 232	MTX+placebo n = 209	Rituximab+MTX n = 308
Acute infusion reactions*				
Hypertension	10 (5)	22 (9)	11 (5)	21 (7)
Nausea	14 (7)	19 (8)	5 (2)	22 (7)
Rash	6 (3)	18 (8)	9 (4)	17 (6)
Fever	1 (<1)	12 (5)	7 (3)	15 (5)
Pruritus	1 (<1)	14 (6)	4 (2)	12 (4)
Urticaria	0	2 (<1)	3 (1)	10 (3)
Rhinitis	2 (1)	6 (3)	4 (2)	8 (3)
Throat irritation	0	5 (2)	0	6 (2)
Hot flush	4 (2)	2 (<1)	0	6 (2)
Hypotension	11 (6)	10 (4)	1 (<1)	5 (2)
Chills	3 (2)	13 (6)	6 (3)	3 (<1)
Infections and infestations				
Any infection	56 (30)	85 (37)	78 (37)	127 (41)
Urinary tract infections	8 (4)	14 (6)	17 (8)	15 (5)
Upper respiratory tract	28 (15)	31 (13)	26 (12)	48 (16)
Lower respiratory tract	10 (5)	9 (4)	5 (2)	8 (3)
General disorders				
Asthenia	0	3 (1)	1 (<1)	6 (2)
Gastrointestinal disorders				
Dyspepsia	3 (2)	9 (4)	0	7 (2)
Abdominal pain upper	3 (2)	7 (3)	1 (<1)	4 (1)
Metabolism and nutritional disorders				
Hypercholesterolaemia	1 (<1)	3 (1)	0	6 (2)
Musculoskeletal disorders				
Arthralgia or musculoskeletal pain	8 (4)	18 (7)	6 (3)	17 (7)
Muscle spasms	0	1 (<1)	2 (1)	7 (2)
Osteoarthritis	1 (<1)	4 (2)	0	6 (2)
Nervous system				
Paraesthesia	2 (1)	4 (2)	1 (<1)	8 (3)
Migraine	0	4 (2)	2 (1)	5 (2)

Values are n (%).
Data from http://www.emea.eu.int/humandocs/Humans/EPAR/mabthera/mabthera.htm.
*In addition to the events tabulated above, medically relevant events reported uncommonly in the rituximab-treated population and considered potential to treatment include the following. General disorders: generalised oedema; respiratory disorders: bronchospasm, wheezing, laryngeal oedema; skin and subcutaneous disorders: angioneurotic oedema, generalised pruritus; immune system disorders: anaphylaxis, anaphylactoid reaction.

The currently available data are derived from short-term studies and, therefore, long-term safety of repeated courses of rituximab needs to be established.

ADDITIONAL ASPECTS TO BE CONSIDERED AND RESEARCH AGENDA

Rituximab might be considered before TNF blockers when there are contraindications to TNF-blocking treatments[5] (category IV), especially a history of B cell lymphoma where rituximab, on the basis of its prior licensed indication, could be viewed a treatment of choice. Although more data are needed on the safety of rituximab in patients with milder forms of congestive heart failure (New York Heart Association classes I–III), demyelinating disorders or opportunist infections, the efficacy of rituximab in individual patients with multiple sclerosis suggests a potential for its applicability under such conditions[8 38] (category IV).

In addition to rheumatoid arthritis, rituximab might have a therapeutic role in patients with vasculitis, connective tissue diseases and other autoimmune conditions[39 40] (category IV). Similar considerations apply to patients with rheumatoid arthritis with concomitant vasculitis and overlap syndrome.

No available data suggest that intercurrent events, such as new-onset malignancies, infections or surgery should be handled differently than under other circumstances of immunosuppression. Also, no data are available suggesting that previous malignancies are reactivated, have a poorer prognosis or are induced by rituximab. Further studies are required for the same.

Although a few patients have become pregnant in the context of rituximab therapy, and have had apparently normal pregnancies[41] (category IV), much more data are required before safety recommendations for pregnancy can be produced, and until that time contraception is recommended. Rituximab should also be avoided in lactating women until safety data are available (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm, http://www.emea.eu.int/humandocs/Humans/EPAR/mabthera/mabthera.htm).[17]

In the context of glucocorticoid use with rituximab, adverse events due to glucocorticoids need to be considered.

Further data are warranted on the optimal dose, the interval between treatment courses and safety issues associated with multiple repeat treatments. Studies to answer the question of the relative merits of rituximab over another TNF inhibitor or an alternative biological agent in patients who have not responded to one TNF blocker are justified. More data on the combinations of rituximab with DMARDs other than MTX are needed, as many patients do not tolerate MTX.

No data are available on treatment with rituximab in early rheumatoid arthritis; this is currently being studied. In

Points to consider for treatment with rituximab

Indication
- Rheumatoid arthritis (RA) with inadequate response to (or intolerance of) tumour necrosis factor (TNF) inhibitors
  - Active RA (at least moderate disease activity)
- Possibly: RA with contraindication to TNF inhibitors (especially lymphoma) and inadequate response to disease-modifying antirheumatic drugs such as methotrexate (MTX)

Pretreatment screening
- History and physical examination
  - Consider possible contraindications
  - Consider radiograph of the chest
- Routine laboratory testing
- Immunoglobulin levels
- Testing for hepatitis B

Treatment dose and comedication
- Two 1000 mg intravenous infusions separated by 2 weeks
  - 100 mg intravenous methylprednisolone or equivalent before infusions
- Weekly MTX to increase efficacy

Evaluation and definition of response
- Validated composite indices to assess response
- Minimum improvement of 28-joint Disease Activity Score (DAS28) of $\geqslant 1.2$ or equivalent measure
  - Aim for low disease activity state (DAS28 <3.2, simplified disease activity index (SDAI) $\leqslant 11$, Clinical disease activity index (CDAI) $\leqslant 10$) or remission (DAS28 $\leqslant 2.6$, SDAI $\leqslant 3.3$ or CDAI $\leqslant 2.8$)
  - Aim for improvement in function and quality of life; minimum response is usually achieved in 16 weeks

Repeated treatment
- Should be considered in responders after week 24
  - Residual active disease (at least moderate disease activity, ie, DAS28 $\geqslant 3.2$, SDAI >11, CDAI >10)
  - Reactivation of disease from low disease activity (increase in DAS28 of $\geqslant 0.6$ or equivalent)

Adverse events in RA
- Infusion reactions (30–35% after the first infusion; less with the second infusion)
  - Severe infusion reactions may occur but are rare
- Slight increase in infections
  - Opportunist infections (including tuberculosis) not reported to date in RA
- Additional adverse events have been reported in the oncology literature but not in RA to date

Contraindications
- Allergy to rituximab
- Clinically relevant comorbidities, including active infections and severe heart failure (New York Heart Association class IV)
- Pregnancy

addition, exploration of rituximab as an induction regimen and as a drug before the use of TNF inhibitors should be undertaken.

Treatment with rituximab should be included in long-term registries of biological agents. In addition to other benefits, such registries generate information on the long-term effectiveness of single courses (durability of response), and the safety and effectiveness of multiple courses of rituximab. Identification of predictors of response to treatment should be investigated. Pharmacoeconomic analyses are warranted.

Further analyses are needed to identify biomarkers of response, and indicators for re-treatment, such as B cells or B

cell subsets (in peripheral blood or tissues), and levels of C reactive protein, B cell-activating factor and rheumatoid factor.

In the context of this research agenda and when information on rituximab in the treatment of patients with rheumatoid arthritis has accrued, an update of this consensus statement will be considered.

CONCLUSIONS

Rituximab, currently in combination with MTX, is a new therapeutic option for treatment of patients with rheumatoid arthritis, particularly patients who have previously not responded to TNF blockers. It constitutes a major advance in the therapeutic armamentarium for patients with rheumatoid arthritis. Like other biological agents, rituximab does not cure the rheumatoid arthritis and the disease relapses after varying periods of time after response to treatment, requiring re-treatment. How the dose and dosing interval may be adapted during long-term treatment with rituximab has not yet been established. This and other questions clearly have to be included in a future research agenda. Box 1 provides a brief summary (points to consider) of this consensus statement. The group was aware that healthcare systems differ widely between countries. This consensus and opinion of experts should therefore be regarded only as a general framework for the initiation and continuation of rituximab for patients with rheumatoid arthritis, from which specific conclusions that fit the situations in individual countries better can be derived for the benefit of the patients.

Authors' affiliations

J S Smolen, Division of Rheumatology, Department of Internal Medicine III, Medical University of Vienna; Second Department of Medicine, Hietzing Hospital Vienna, Vienna, Austria
E C Keystone, Rebecca MacDonald Centre for Arthritis and Autoimmunity, Mount Sinai Hospital, University of Toronto, Toronto, Canada
P Emery, Leeds Teaching Hospitals Trust, Chapel Allerton Hospital, Leeds, UK
F C Breedveld, Arthritis Care, London, UK
N Betteridge, Leiden University Medical School, Leiden, The Netherlands
G R Burmester, Department of Rheumatology, Charité Hospital, Humboldt University, Berlin, Germany
M Dougados, Department of Rheumatology, Hopital Cochin, René Descartes University, Paris, France
G Ferraccioli, Division of Rheumatology, Institute of Internal Medicine and Geriatrics, Catholic University of the Sacred Heart, Rome, Italy
U Jaeger, Division of Haematology, First Department of Internal Medicine, Medical University of Vienna, Vienna, Austria
L Klareskog, Department of Rheumatology, Karolinska Hospital, Stockholm, Sweden
T K Kvien, Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway
E Martin-Mola, Rheumatology Department, Hospital Universitario La Paz, Universidad Autonoma de Madrid, Madrid, Spain
K Pavelka, Institute and Clinic of Rheumatology, Charles University Prague, Prague, Czech Republic

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Members of the Working Group on the Rituximab Consensus Statement: Jordi Carbonell, Bernard Combe, Maurizio Cutolo, Thomas Dörner, Angela Gause, Juan Gomez-Reino, Carlos Gonzales Fernandes, John D Isaacs, José Luis Marenco, Xavier Mariette, Marco Matucci-Cerinic, Carlo-Maurizio Montecucco, Hubert Nüßlein, Mikkel Østergaard, Eliseo Pascual, Piet van Riel, Andrea Rubbert, Raimon Sanmarti, Zoltan Sekanecz, Paul-Peter Tak, Hans-Peter Tony, Gabriele Valentini, Guido Valesini.

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