



North East Treatment
Advisory Group

Rituximab (MabThera®) in rheumatoid arthritis: non-NICE approved indications

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Summary

- NICE guidance is extensive with respect to the treatment of rheumatoid arthritis. However there may still be some small patient groups which are not catered for and there is a desire to use rituximab in these patients: Rituximab monotherapy or in combination non-methotrexate DMARDs in patients who are intolerant or contraindicated to methotrexate (essentially off-license use); rituximab with methotrexate in aTNF-naïve patients (non-NICE).
- The evidence for off-license use of rituximab either as monotherapy or in combination with a non-methotrexate DMARD is limited and characterised by a few small studies of low methodological quality and short follow-up. The evidence demonstrates that rituximab monotherapy is comparable in terms of safety and efficacy to rituximab plus methotrexate. Evidence for non-methotrexate DMARDs is almost entirely limited to the combination with leflunomide. This evidence also demonstrates equivalent efficacy with rituximab plus methotrexate although potentially with a less favourable safety profile.
- Evidence for use of rituximab in aTNF-naïve patients is more extensive but limited to the combination of rituximab plus methotrexate. Nonetheless, the evidence demonstrates similar efficacy and safety profiles to established rituximab treatment populations (i.e. post-aTNF patients) and to methotrexate monotherapy. However, few if any patients were specifically contra-indicated to aTNF and many of the contra-indications to aTNF may also lead to contra-indication of methotrexate.
- Overall, the evidence base for non-NICE use of rituximab in RA is equivocal and would benefit greatly from better focused prospective studies with longer follow-up. However, for the expected small numbers of patients with severe RA there may be few other effective or safe treatment options. Of concern is the poor reporting of safety outcomes, especially for off-license use of rituximab.
- Rituximab is a costly therapy and must be administered within a specialist (secondary care) facility. Compared with oral DMARDs it is substantially more costly, although it is one of the least costly biological therapies which are recommended by NICE in RA. The rituximab treatment regimen permits flexibility of repeat course intervals and where these can be extended beyond the minimum interval mean patient costs will be correspondingly reduced.

Introduction and background

Rheumatoid arthritis (RA) is a chronic, progressive and potentially debilitating auto-immune disease characterised by inflammation of joint tissue. Uncontrolled RA results in significant pain and disability leading to increased morbidity and mortality. It is estimated that 1% of the population in England and Wales has rheumatoid arthritis and of these approximately 15% have severe disease.^{1,2 3}

The exact aetiology of RA is unknown and there is currently no cure however advances in the understanding of the disease process have led to the development of numerous treatments to reduce pain, improve physical function, and reduce disease progression. The goal of early treatment is to achieve clinical and radiological remission, reduce functional limitations, and minimise or prevent joint damage. Treatments include combinations of pharmacological and non-pharmacological interventions.^{1,3,4}

The severity and extent of RA in response to treatment can be measured clinically using a number of assessment scores. One of the most widely used is from the American College of Rheumatology known as ACR scores (ACR20, ACR50, ACR70). The score requires a specified improvement in the proportion of swollen and tender joints (20%, 50% or 70% respectively), overall health assessment, pain, disability and circulating inflammatory markers. The disease activity score (DAS) is a clinical index of RA disease activity calculated using a formula that includes counts for 44 tender and swollen joints, a measure of circulating inflammatory markers and an evaluation of general health by the patient. DAS28 is similar to the original DAS but counts only 28 joints for assessment. The range of the DAS28 is 0 to 9.4 with any score > 5.1 indicating severe disease. The European League Against Rheumatism (EULAR) response criteria use the individual change in DAS and the level of DAS reached to classify trial participants as good, moderate or non-responders to treatment.^{1,3,5}

NICE guidance for RA recommends use of a combination of conventional disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate and at least one other conventional DMARD, plus short-term oral steroids, as first-line treatment, ideally within three months of the onset of persistent symptoms. If combination therapy is not appropriate, for example in people with methotrexate intolerance, NICE recommends monotherapy with other DMARDs.⁶

NICE also recommends the biological tumour necrosis factor inhibitor (anti-TNF or aTNF) drugs adalimumab, etanercept, infliximab, certolizumab or golimumab in combination with methotrexate in adult patients with severe active RA who have failed to respond to at least two DMARDs including methotrexate. In patients unable to tolerate methotrexate or if treatment with methotrexate is considered to be inappropriate, NICE recommends adalimumab, etanercept and certolizumab as monotherapy. An alternative aTNF may be considered when treatment with a first aTNF is ceased due to an adverse event.^{7,8,9}

Rituximab (MabThera®, Roche) is a monoclonal antibody that binds to a specific surface antigen found on some types of white blood cell. It will ultimately induce cell elimination in cells to which it is bound. It is licensed for the treatment of RA in combination with methotrexate in adult patients with severe active disease and an inadequate response or intolerance to other DMARDs including aTNF. A course of rituximab in RA consists of 2 x 1 g intravenous infusions given two weeks apart. The minimum recommended interval between courses is 24 weeks.^{2,10} NICE has recommended rituximab in-line with its licensed indication.¹

Repeat courses of rituximab and methotrexate should only be given following an adequate response to the previous course, defined as improvement in DAS28 of ≥ 1.2 points. If rituximab therapy cannot be given because methotrexate is contraindicated or withdrawn because of an adverse event, NICE recommends adalimumab or etanercept monotherapy as treatment options.¹

NICE has also recommended tocilizumab in combination with methotrexate for treatment of moderate to severe active RA in disease which has responded inadequately to aTNF and rituximab or in whom rituximab is contraindicated or withdrawn because of an adverse effect.¹¹

Although the licensed indication and NICE guidelines specify the use of rituximab with methotrexate following treatment with at least one aTNF, some RA patients may be unsuitable for aTNF due to intolerance or a specific contraindication (see appendix 1). In addition, some RA patients are unable to tolerate methotrexate. NICE has not issued guidance regarding the use of rituximab without methotrexate in RA (i.e. rituximab monotherapy) or in combination with other DMARDs or in patients who cannot use aTNF. The purpose of this appraisal is to assess the evidence regarding the use of rituximab in RA for the following patient groups:

- Combination with non-methotrexate DMARDs (off-license and non-NICE)
- Monotherapy; e.g. where methotrexate is contra-indicated (off-license and non-NICE)
- When aTNF is contra-indicated (not considered by NICE) and rituximab is used as the first-line biological therapy

Clinical evidence

The Yorkshire and the Humber Specialised Commissioning Group commissioned a report from the School of Health and Related Research (ScHARR) at Sheffield University regarding use of rituximab in RA as monotherapy or in combination with non-methotrexate DMARDs in patients intolerant to methotrexate. The report was completed in September 2009 and is summarised in the following pages:¹²

Summary of the ScHARR report¹²

The report was conducted as a systematic literature review of the relevant topic. The methodology appears to be robust and includes data up to and including July 2009.

Of 54 potentially relevant articles identified, one randomised controlled trial and six other studies were included. In addition, ten relevant conference abstracts from EULAR and ACR meetings were also included. None of the evidence was derived from patient populations specifically intolerant to methotrexate.

The main source of evidence in the report was an RCT in patients with lack of efficacy with methotrexate monotherapy.¹³ The original publication is supplemented with a report of longer follow-up.¹⁴ It was a double-blind study in patients with active RA despite methotrexate (n = 161). The trial had four arms; oral methotrexate plus placebo (n = 40), rituximab monotherapy (n = 40), rituximab plus cyclophosphamide (n = 41) and rituximab plus methotrexate (n = 41). Response to treatment was assessed using ACR response criteria. The study found that patients treated with rituximab in combination with either methotrexate or cyclophosphamide showed statistically significant improvements in ACR20 and ACR50 compared with methotrexate plus placebo at 24 and 48 weeks post-baseline. Rituximab monotherapy only showed statistically significant improvement in ACR20 at 24 weeks compared with methotrexate plus placebo. Changes in disease response at 104 weeks after baseline were not statistically significant for any of the treatment arms compared with methotrexate plus placebo. Mean changes from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) score were statistically significant in all treatment groups, and were generally higher in rituximab treatment groups compared with methotrexate plus placebo. Improvements were maximal at 24 weeks and sustained thereafter in the rituximab plus methotrexate group. Mean change from baseline to week 72 was -0.6 with rituximab plus methotrexate (P < 0.0001), -0.6 with rituximab monotherapy (P = 0.01), -0.3 (P ≤ 0.05) with methotrexate plus placebo, and -0.1 (P = 0.05) with rituximab plus cyclophosphamide.

The results of an observational cohort study (n = 116) suggest that treatment with rituximab monotherapy may be more effective than switching to an alternative aTNF in patients with RA and persistent active disease despite aTNF.¹⁵

In a small case series (n = 21) rituximab monotherapy (2 x 1 g two weeks apart) led to a significant reduction in DAS28 score at three months in long-standing multi-DMARD and multi-aTNF resistant RA patients.¹⁶

In a larger case series (n = 39) rituximab monotherapy (2 x 500 mg or 2 x 1 g two weeks apart) significantly improved DAS28 scores in patients with RA where aTNF was either not available or relatively contraindicated. Patients who were on the higher dose regimen appeared to respond slightly better compared with the lower dose regimen.¹⁷

The majority of conference abstracts did not provide sufficiently robust additional evidence due to inappropriate study designs and lack of available data. A report of one study provides some limited evidence to support use of rituximab in combination with leflunomide in patients unable to tolerate methotrexate or in whom methotrexate was contraindicated.¹⁸

Additional evidence

The SchARR report focused on evidence for the use of rituximab in patients with lack of efficacy despite methotrexate. A literature search was conducted to identify evidence regarding the use of rituximab in patients intolerant to aTNF and to identify newer evidence for rituximab in methotrexate-intolerant patients, either as monotherapy or in combination with non-methotrexate DMARDs. Additional information was derived from internet searches and cross-referencing of retrieved articles. Consequently seven additional studies were identified.

aTNF-naïve patients

DANCER¹⁹

The DANCER study compared different rituximab doses plus methotrexate, with or without oral steroids, in patients with established RA who had been treated unsuccessfully with methotrexate or at least one aTNF. 465 patients were randomised to two different rituximab doses (2 x 1 g or 2 x 500 mg) in combination with methotrexate and two alternative steroid regimens. Overall, 71% of patients were aTNF-naïve with no significant differences between randomised groups. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24. Secondary endpoints included ACR 50 and 70, DAS28 and EULAR responses. At week 24, a significantly greater proportion of patients receiving either dose of rituximab achieved an ACR20, 50 and 70 response compared with those receiving placebo plus methotrexate (see table 1). Patients who were naïve to treatment with a biological therapy had numerically higher ACR20 responses than those who had previously received aTNF therapy. There was no statistical comparison between rituximab regimens.

SERENE²⁰

The SERENE study compared two doses of rituximab plus methotrexate in patients with active RA who had an inadequate response to methotrexate alone and in whom no prior biological treatment for RA had been administered (n = 511). Patients with active disease on stable methotrexate were randomly assigned to one of three regimens; rituximab 2 x 500 mg, rituximab 2 x 1 g or placebo. Patients had mean disease duration of seven years, with generally high disease activity. From week 24, patients not in remission (DAS28 \geq 2.6) received a second course of rituximab, and patients initially assigned to placebo switched to rituximab 2 x 500 mg. All patients were followed until week 48. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24. Secondary endpoints included ACR 50 and 70, DAS28 and EULAR responses. At week 24, a significantly greater proportion of patients receiving either dose of rituximab achieved an ACR20 and ACR50 response compared with placebo plus methotrexate (table 1). ACR70 responses were achieved by a greater proportion of patients receiving either dose of rituximab but the difference did not achieve statistical significance. After week 24, 460 patients (90%) received a second course of treatment and 451 completed 48 weeks. ACR responses were maintained in both rituximab groups from weeks 24 to 48. Comparisons between rituximab doses at week 48 did not identify significant differences with any clinical endpoint.

MIRROR²¹

The MIRROR study evaluated rituximab in combination with methotrexate in patients (n = 375) with active RA and an inadequate response to methotrexate, either without aTNF therapy or with no more than one aTNF. Patients with active disease despite stable methotrexate were randomly assigned to one of three regimens comprising two courses of rituximab given 24 weeks apart: low-dose rituximab 2 x (2 x 500 mg); rituximab dose escalation 2 x 500 and 2 x 1 g; and high-dose rituximab 2 x (2 x 1 g). Overall, 74% of patients were naïve to aTNF with no significant differences between groups. The primary endpoint was the proportion of patients achieving ACR20 at week 48. Secondary endpoints included ACR 50 and 70, DAS28 and EULAR responses. At week 48, ACR20 responses did not differ significantly between regimens (table 1). There was a trend towards greater efficacy with the high-dose regimen compared with the low-dose regimen and this was statistically significant for EULAR responses. Other endpoints, although numerically different at 48 weeks, did not reach statistical significance between regimens. ACR20 responses were similar in patients who had received an earlier biological treatment (almost exclusively aTNF) compared with patients who were biological treatment-naïve (65% vs. 67%, respectively). Similarly, ACR 50, 70 and EULAR responses were comparable regardless of prior biological therapy. Within the prior biological subgroup, response rates for the high-dose group were consistently higher than the low-dose group.

Assous²²

A retrospective observational study conducted in three French specialist rheumatology units assessed the efficacy of rituximab (2 x 1 g) plus methotrexate in 50 patients with highly active RA and an inadequate response, or a contraindication to, aTNF.²² Thirty patients had an inadequate response to aTNF therapy, of whom ten had been treated with three aTNF drugs and 14 with two drugs. Twenty patients (40%) were considered to have contraindications to aTNF such as a history of recurrent infections or tuberculosis (n = 11), personal or family history of multiple sclerosis (n = 3), previous lymphoma (n = 3), heart failure (n = 2), or vasculitis during etanercept treatment (n = 1). All had previously received methotrexate. There were no differences in baseline characteristics between subgroups contraindicated to vs. low response to aTNF. The primary endpoint was EULAR response at 24 weeks. Secondary endpoints included change in DAS28 scores. At week 24, a EULAR (moderate + good) response was observed in 90% of patients refractory to aTNF and 70% with a contraindication to aTNF. There was a statistically significant decrease in DAS28 scores compared to baseline for both groups at week 24. There was no significant difference for either outcome measure between the group of patients refractory to aTNF vs. contraindication to aTNF. The study was not powered to establish a definite comparison between RA patients with or without previous use of aTNF drugs.

Renato²³

This small study (n = 20) assessed the efficacy of rituximab (2 x 1 g) as first-line biological in severe RA refractory to a combination of DMARDs, NSAIDs and steroids. All patients continued their background regimen of multiple DMARDs, NSAIDs and steroids. Response to treatment was determined by change in DAS28. All patients were evaluated at 24 weeks for ACR response. At week 24, the ACR 20, 50 and 70 responses were 62%, 42% and 21%, respectively. DAS28 < 2.4 was observed at week 24 in 80% of patients. No patient experienced clinical remission defined by DAS28 score.

Rituximab in combination with non-methotrexate DMARDs.**CERRERA**²⁴

A large population study published in abstract only combined data from ten European registries with 2,265 patients. The effectiveness and safety of rituximab monotherapy (n = 505) or in combination with either methotrexate (n = 1195) or leflunomide (n = 177) was compared. Significantly more patients achieved a EULAR 'good response' at six months when treated with rituximab plus leflunomide (29.1%) compared with rituximab plus methotrexate (20.7%) and rituximab monotherapy (19.5%, p = 0.04 for each vs. rituximab alone). At 12 months a greater proportion of 'good' responders was observed in the rituximab plus leflunomide group (31.4%), while the proportion remained stable in the rituximab plus methotrexate and rituximab monotherapy groups (p = 0.005 and p = 0.01 respectively). Fewer patients on rituximab plus leflunomide (19.2%) required re-treatment during the first 12 months compared with rituximab plus methotrexate (27.9%) or rituximab monotherapy (21.8%). Rituximab plus methotrexate patients received a lower mean methotrexate dose and patients in the rituximab monotherapy group were significantly older and had more severe disease.

Henes²⁵

A small retrospective observational study assessed the efficacy of rituximab plus leflunomide in patients with active RA (n = 10). All were intolerant to methotrexate and all except one received rituximab (2 x 1 g) plus oral leflunomide. Primary outcome measures were change in DAS28 score and EULAR response at six months. The median baseline DAS28 was 5.7 and reduced to 3.5 at six months. EULAR criteria demonstrated that 50% of patients achieved a 'good' response and 20% a 'moderate' response but only one patient achieved remission.

Narvaez²⁶

A larger retrospective study published in abstract only compared the efficacy of rituximab with either methotrexate or leflunomide in patients with active RA and an inadequate response to aTNF and other DMARDs (n = 77). Patients were treated with at least one cycle of rituximab (2 x 1 g) plus either methotrexate (n = 45) or leflunomide (n = 32). The primary endpoint was DAS28 response at six months. Secondary endpoints included the proportion of patients in remission defined by DAS28 and ACR50 and 70 responses. At baseline there were no significant differences between groups in terms of prior DMARDs and aTNF. At six months there was no significant difference in changes in DAS28, remission rates, and EULAR response rates between those who received leflunomide plus rituximab and those on methotrexate plus rituximab. ACR 50 and 70 responses, although numerically different at six months, did not reach statistical significance between groups (22% vs. 13%, and 6% vs. 2%, respectively).

Summary of the clinical evidence

Evidence for rituximab without methotrexate (e.g. off-license) either as monotherapy or in combination with other DMARDs is still developing. Only one small randomised study reports use of rituximab in patients tolerant to methotrexate with little difference observed between methotrexate plus rituximab and those treated with cyclophosphamide plus rituximab. In this study rituximab was also used as a monotherapy with good efficacy, although not significantly different compared with methotrexate plus placebo.

There is limited data available regarding the combination of rituximab with other DMARDs other than rituximab in combination with leflunomide. A number of small observational studies have described the use of rituximab with DMARDs other than methotrexate which have consistently demonstrated the efficacy of rituximab with leflunomide. Indeed, there is some evidence to suggest superiority of leflunomide plus rituximab compared with methotrexate plus rituximab, but this has not been confirmed in randomised studies.

In predominantly aTNF-naïve populations two randomised studies showed that rituximab, when used as the first biological therapy in combination with methotrexate, improves the signs and symptoms of RA compared with methotrexate monotherapy. In a further study involving biological-naïve RA, rituximab plus methotrexate significantly improved clinical outcomes up to 48 weeks.

Guidance (other than NICE)

The British Society for Rheumatology and British Health Professionals in Rheumatology have published joint guidelines regarding off-license use of rituximab and rituximab in aTNF-naïve patients (i.e. non-NICE indications).²⁷ These guidelines update evidence from NICE and EULAR. An important difference is that they do support using rituximab before aTNF therapy in patients with an absolute or relative contraindication to aTNF, based largely on evidence from the DANCER study.¹⁹ The observational study by McGonagle¹⁷ is cited in support of rituximab after conventional DMARD failure and before aTNF therapy.¹⁷ The guidelines also recommend rituximab as monotherapy or in combination with leflunomide if methotrexate is contraindicated, based largely on the Edwards study.¹³ A recommendation for rituximab in combination with leflunomide in patients intolerant to methotrexate is based on the study by Vital¹⁸ and the CERRERA study.²⁴

Safety

Reporting of safety data in the SchARR report is not extensive.¹² Additional literature searches were carried out to fully ascertain the safety of rituximab monotherapy and in combination with DMARDs other than methotrexate, and in patients who cannot tolerate aTNF.

Overview of adverse events as reported in the SchARR report¹²

The safety and tolerability of rituximab in RA has been well described. The safety profile of rituximab is generally consistent across doses and regimens as well as the different patient populations and subgroups. Table 2 presents a pooled summary of the most frequent adverse events observed in two large placebo controlled trials of rituximab in combination with methotrexate in aTNF-naïve patients.^{19,20} This is similar to the safety profile of rituximab in the treatment of RA in general. The most frequent adverse events with rituximab are infusion-related reactions consisting predominantly of; fever, chills, rigors, itching, urticaria/rash, swelling, sneezing, throat irritation, cough, and tightening of the airways, sometimes with blood pressure changes. Infusion related reactions were experienced by a significantly higher proportion of patients treated with rituximab than those who received placebo infusions in clinical trials. Generally, the proportion of patients experiencing an infusion related reaction was higher following the first infusion than following the second infusion of a treatment course. The incidence of infusion reactions decreased with subsequent courses. The majority of infusion reactions were of mild to moderate severity and could be managed through adjustment of the infusion rate. Occasionally therapeutic interventions such as paracetamol, antihistamine and bronchodilators drugs may be required. Premedication with intravenous steroids can significantly reduce the incidence and severity of infusion reactions. Serious infusion reactions are rare but will require drug discontinuation. Other than the higher incidence of acute infusion reactions with rituximab therapy, the overall incidence of adverse events was comparable across treatment groups. The most commonly occurring serious events were infections and gastrointestinal disorders.

Infection risk is of particular concern because of the mode of action of rituximab in affecting white blood cells. Overall, the rate of serious infections for patients receiving rituximab was comparable to those receiving placebo infusions. The most common serious infections involved the respiratory tract; other serious infections included cellulitis, urinary tract infections and gastroenteritis. Rare but serious infections, such as reactivation of hepatitis B, herpes and progressive multifocal leukoencephalopathy, have also been reported with rituximab treatment. No cases of opportunistic infections or tuberculosis were reported.

aTNF-naïve patients

In the two placebo-controlled trials of rituximab plus methotrexate in aTNF-naïve patients the overall incidence of adverse events was similar across all treatment groups (table 2, pooled data), with the most common being infusion reactions.^{19,20} The incidence of infusion reactions was highest with the first infusion of the first course in all treatment groups compared with the second infusion of the same course. In the MIRROR²¹ study of three rituximab regimens, comprising two courses 24 weeks apart, the overall the profile of adverse events was comparable between groups and broadly consistent with those observed during the initial 24 weeks of the DANCER¹⁹ and SERENE²⁰ studies.

Rituximab monotherapy

In the pivotal study by Edwards,¹³ which included patients receiving rituximab monotherapy, the overall incidence of adverse events was similar between treatment groups and placebo with 73% to 85% of patients reporting at least one adverse event; 30% to 45% of patients in each group, including placebo infusions, experienced infusion reactions associated with the first infusion. During the initial 24 weeks sixteen serious adverse events were reported with the highest incidence among patients receiving rituximab plus cyclophosphamide. Serious infections occurred in one patient in the placebo group and four patients across rituximab groups. During extended observation to week 48 the adverse event profile remained consistent with those observed during the initial 24 weeks. There were six additional serious adverse events including two serious infections; one with the rituximab plus methotrexate and one with rituximab monotherapy.¹³

Table 1. Summary results from RCTs evaluating rituximab plus methotrexate in methotrexate-naïve or aTNF-naïve patients.

Study	Intervention	Patients	ACR20	ACR50	ACR70	EULAR (moderate + good)	DAS28 (remission)
DANCER ¹⁹ aTNF-naïve population (71%) At week 24	methotrexate + placebo	149	28	13	5	37	–
	rituximab (2 x 500 mg) + methotrexate	124	55 (p<0.001)	33 (p<0.001)	13 (p<0.003)	73 (p<0.0001)	–
	rituximab (2 x 1 g) + methotrexate	192	54 (p<0.001)	34 (p<0.001)	20 (p<0.001)	67	–
SERENE ²⁰ aTNF-naïve population (100%) At week 24	methotrexate + placebo	172	23	9	5	34	4
	rituximab (2 x 500 mg) + methotrexate	168	54 (p<0.001)	26 (p<0.001)	9	66 (p<0.0001)	16 (<0.01)
	rituximab (2 x 1 g) + methotrexate	172	51 (p<0.001)	26 (p<0.001)	10	63 (p<0.0001)	16 (<0.01)
MIRROR ²¹ aTNF-naïve population (74%) At week 48	rituximab (2 x 500 mg and 2 x 500 mg) + methotrexate	134	64	39	20	73	9
	rituximab (2 x 500 mg and 2 x 1 g) + methotrexate	119	64	39	19	72	13
	rituximab (2 x 1 g and 2 x 1 g) + methotrexate	93	72	48	23	89 (p<0.05)	19

Table 2. Summary of adverse events in the DANCER and SERENE studies^{19,20}

	Methotrexate + placebo	Rituximab (2 x 500 mg) + methotrexate	Rituximab (2 x 1 g) + methotrexate
n	321	291	362
All events	233 (73%)	228 (78%)	294 (81%)
Serious events	19 (6%)	15 (5%)	28 (8%)
Withdrawal due to an adverse event	2 (<1%)	5 (2%)	9 (2%)
Exacerbation of RA	77 (24%)	38 (13%)	42 (12%)
Headache	25 (8%)	17 (6%)	28 (8%)
Upper respiratory tract infection	22 (7%)	25 (9%)	23 (6%)
Nasopharyngitis	25 (8%)	16 (5%)	27 (7%)
Nausea	17 (5%)	15 (5%)	26 (7%)
Diarrhoea	15 (5%)	16 (5%)	13 (4%)
Arthralgia	9 (3%)	10 (3%)	18 (5%)
Hypertension	7 (2%)	10 (3%)	17 (5%)
Dizziness	10 (3%)	8 (3%)	13 (4%)
Fatigue	10 (3%)	8 (3%)	12 (3%)
Rigors	3 (1%)	7 (2%)	13 (4%)
Serious infection	6 (2%)	1 (<1%)	6 (2%)

Rituximab in combination with other DMARDs

There is little safety data available regarding the combination of rituximab with other DMARDs; most relates to rituximab in combination with leflunomide.

In data from ten European registries, published in abstract only, the overall incidence of adverse events was similar between groups; rituximab plus leflunomide (14%), rituximab plus methotrexate (16%), and rituximab monotherapy (16%).²⁴ The incidence of adverse events was also comparable across groups in an observational study, also published only in abstract, of rituximab in combination with either methotrexate or leflunomide.²⁶ In a report of ten patients treated with rituximab in combination with leflunomide the leflunomide dose was reduced in two patients due to newly diagnosed arterial hypertension and raised liver enzymes. Therapy had to be discontinued in two patients because of raised liver enzymes; one with gastrointestinal intolerance and one with oral ulcers.²⁵

Contraindications to rituximab therapy¹⁰

- Hypersensitivity to rituximab or other murine (mouse-derived) proteins
- Active severe infection or severely immunocompromised
- Severe heart failure or severe uncontrolled cardiac disease
- Pregnancy

Warnings and precautions for rituximab¹⁰

Rituximab must be administered in an environment where resuscitation facilities are available.

There are no data on the safety of rituximab in patients with moderate heart failure or severe, uncontrolled cardiovascular disease. The occurrence of pre-existing ischemic cardiac conditions becoming symptomatic has been observed in patients receiving rituximab. Therefore, in patients with a known cardiac history, the risk of cardiovascular complications resulting from IRRs should be considered before treatment with rituximab and patients closely monitored during administration. Since hypotension may occur during rituximab infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the rituximab infusion.

Caution is advised when using rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection. It is recommended that immunoglobulin levels are determined prior to initiating treatment with rituximab. Rarely, a severe viral central nervous system infection known as progressive multifocal leukoencephalopathy has been associated with rituximab therapy and patients must be closely monitored for the signs and symptoms of this infection.

Vaccination status should be reviewed prior to rituximab therapy. Vaccinations should be completed at least four weeks prior to first administration of rituximab.

The safety of immunisation with live viral vaccines following rituximab therapy has not been studied. Therefore vaccination with live virus vaccines is not recommended whilst on rituximab or whilst peripherally B cell depleted. Patients treated with rituximab may receive non-live vaccinations. However, response rates to non-live vaccines may be reduced.

Immunomodulatory drugs may increase the risk of malignancy. Although current data do not suggest any increased risk of malignancy, the possible risk for the development of solid tumours cannot be excluded at this time.

Cost analysis

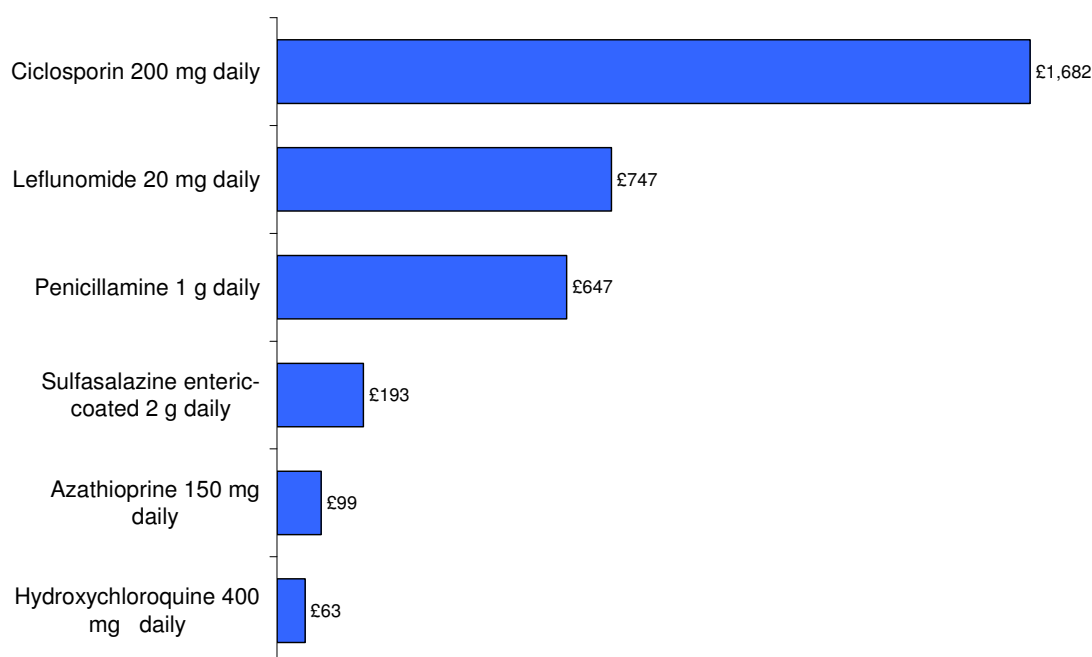
Costs include VAT at 20% unless otherwise indicated

Rituximab is available in 500 mg vials containing concentrate for infusion. Once prepared the infusion volume will be between 250 ml and 1 litre and will need to be given over a minimum of 2.5 hours.¹⁰ The cost of two 500 mg vials (i.e. sufficient for one 1 g infusion) is £2,096.³³ As two 1 g infusions are required per course, the cost of rituximab is £4,191 per course. It is assumed that rituximab is administered in a day case setting similar to that in which cancer treatments are provided. However the cost of these admissions is outside of the Department of Health payment by results tariff. Therefore the cost is assumed to be double the cost of a standard rheumatology follow-up outpatient appointment at £214 (payment by results tariff code WF01A or WF02A). This compares with an initial rheumatology outpatient appointment at £260.³⁴ This estimate has been, in part, arbitrarily derived and the actual cost will be subject to variation depending on contractual arrangements with each providing trust. However, it is likely that admission and administration costs will be small relative to the cost of drug treatment. Other costs associated with administration of rituximab such as infusion equipment and adjuvant drugs are assumed to be included within the admission cost. Using the estimated admission cost, the total cost of a single course of rituximab is £4,619. The annual cost per patient is based on an assumption of two rituximab infusions per annum, itself based on a recommended treatment interval of 24 weeks per course. The annual cost per patient is therefore assumed to be £9,238. Evidence from clinical studies indicates that the actual dose interval is longer at about 46 weeks in aTNF-naïve patients and 33 weeks in patients with prior aTNF exposure.³⁵ If such intervals are realised in practice then this would have a large impact on reducing mean cost per patient.

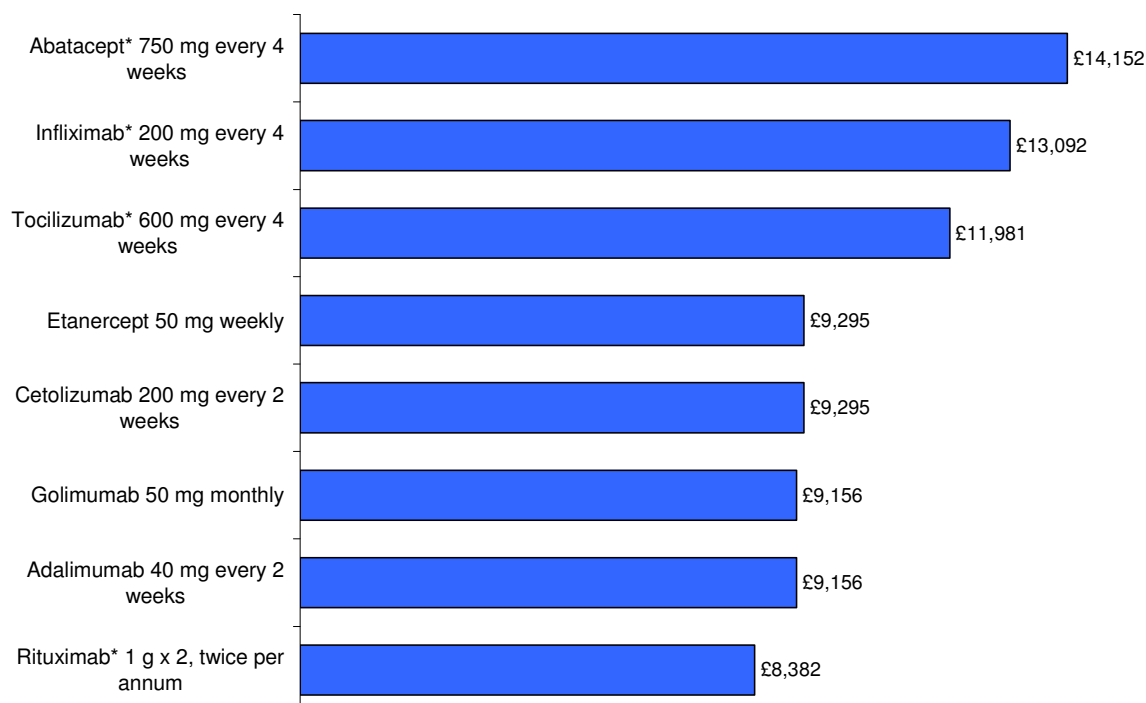
For comparison, patients who cannot tolerate methotrexate or who cannot use aTNF, might reasonably be expected to be treated with a non-methotrexate DMARD. Figure 1 demonstrates the annual cost of some commonly used DMARDs at typical treatment doses. For additional comparison with other biological therapies used in RA, figure 2 demonstrates the annual cost of several aTNF therapies which have been recommended for RA by NICE.

It has not been possible to reliably estimate the volume of patients which might be considered for treatment with rituximab outside of NICE guidance or off-license. However the expectation is that only a small proportion of patients will require treatment for RA which is outside of NICE guidance. There is an estimated 4,000 patients with severe RA within NHS North East therefore even a small proportion of this population could represent a significant volume of patients.^{1,35}

It can be seen from figures 1 and 2 that rituximab is a costly therapy compared with DMARDs but is the least costly biological therapy used in RA.

Figure 1. Annual cost of therapy with DMARDs

Doses are not intended to imply therapeutic equivalence. Prices do not include VAT.

Figure 2. Annual cost of aTNF therapies used in RA

*: These drugs will require secondary care administration therefore costs include VAT at 20% but do not include cost of admission and administration. Other drugs can be self-administered and therefore costs do not include VAT. Doses are not intended to imply therapeutic equivalence. The minimum treatment interval with rituximab has been assumed (six months) whereas in practice longer intervals may be observed which would effectively reduce the mean cost per patient per annum.

Points to consider

NICE guidance provides for multiple RA treatments in many pathways however there are still some gaps; these have been identified locally as patients intolerant or contraindicated to methotrexate or aTNF. In patients who cannot use methotrexate there is a desire to use rituximab as monotherapy or combined with an alternative DMARD. In patients who cannot use aTNF there is a desire to use rituximab within its licensed indication combined with methotrexate.

With respect to evidence for the use of rituximab as monotherapy in RA, the evidence is limited by few and low quality studies, low patient numbers and short follow-up. The available evidence indicates that efficacy is generally similar to that seen with rituximab in combination with a DMARD (including methotrexate) or compared with an aTNF.

With respect to evidence for the use of rituximab in combination with a non-methotrexate DMARD, again the evidence is limited by few and low quality studies. There is little evidence for any DMARD other than leflunomide, for which the evidence indicates generally similar efficacy with other standard treatment options. Adverse effects may be enhanced with leflunomide in-line with the drug's profile

With respect to evidence for the use of rituximab in patients who cannot tolerate aTNF, the evidence base is limited with most evaluations in aTNF-naïve patients as opposed to aTNF-intolerant patients. In addition the majority of the evidence is for use of rituximab in combination with methotrexate, which may also be a problem in patients who cannot tolerate aTNF. Nonetheless, rituximab demonstrates similar efficacy to that seen in other RA populations and appears to be superior to methotrexate alone.

Rituximab is a costly treatment which must be administered within a secondary care setting, thus incurring VAT on drug costs and cost for admission. Rituximab is several times the cost of commonly used DMARD drugs but may cost up to the same amount as self-administered aTNF at about £9,500 per patient per annum. Extended treatment intervals beyond the minimum recommended of six months will effectively reduce the mean cost per patient.

Alternative treatments for severe RA may be DMARD therapy alone, which is less costly than rituximab, and other biological therapies but which might also deliver sub-optimal efficacy. However, most DMARDs are oral treatments which can be prescribed and monitored within primary care. Rituximab will impose lifestyle constraints due to day case admission estimated at up to four admissions per annum.

The safety profile of rituximab monotherapy, in combination with non-methotrexate DMARDs, or in aTNF-naïve patients is poorly reported but appears predictable and similar to the profile of rituximab in combination methotrexate. Leflunomide may impose a higher burden of adverse effects, possibly due specifically to leflunomide. Rituximab monotherapy may present an unfavourable risk:benefit profile with respect to progressive multifocal leukoencephalopathy.

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Author declarations: The lead author has no relevant interests to declare. The report editor has participated in an advisory board regarding a biological product licensed for RA and produced by a competitor pharmaceutical company.

Appendix 1. Contraindications to the use of aTNF therapy.²⁸⁻³²***Absolute***

- Active infections (including tuberculosis, infected prosthesis and sepsis, or risk of sepsis)
- History of recurrent or chronic infections (e.g. bronchiectasis)
- After previous, untreated tuberculosis
- Moderate-to-severe congestive heart failure (NYHA class III/IV)
- Multiple sclerosis or optic neuritis
- Combination treatment with anakinra (IL-1 receptor antagonist)
- Reactive or recent history (past 10 years) of malignancies except for skin cancer
- Concurrent administration of live vaccines

Relative

- Pregnancy
- Lactation
- HIV, hepatitis B and C infection
- Concurrent administration of sulfasalazine
- Use with caution in patients who are at an increased risk of chronic obstructive pulmonary disease, and those who are considered to be at high risk of malignancy due to heavy smoking