Research Review
PRODUCT REVIEW

Rituximab (MabThera®)

About the Reviewer

Dr Peter Chapman
BSc, MBChB, MD(Otago) FRACP, PGDipMSM(Otago)

Dr Peter Chapman is the Clinical Director of Rheumatology, Immunology & Allergy at the Canterbury District Health Board. His interests include autoimmune inflammatory arthritis, gout and connective tissue diseases.

About Research Review

Research Review is an independent medical publishing organisation producing electronic publications in a wide variety of specialist areas.

Product Reviews feature independent short summaries of major research affecting an individual medicine or technique. They include a background to the particular condition, a summary of the medicine and selected studies by a key New Zealand specialist with a comment on the relevance to New Zealand practice.

Research Review publications are intended for New Zealand medical professionals.

This review discusses the evidence in support of the use of rituximab (MabThera®), a chimeric human monoclonal antibody against the CD20 protein that is expressed on naive, mature and memory B cells, which has proven to be highly effective in the treatment of patients with moderate-to-severe rheumatoid arthritis (RA).

Good clinical evidence (which is discussed in this review) demonstrates the safety and efficacy of rituximab for methotrexate and/or tumour necrosis factor (TNF)-α refractory patients with RA. In the key clinical studies, rituximab significantly increased the proportions of patients achieving at least a 20% improvement in American College of Rheumatology (ACR) score compared with methotrexate monotherapy; a benefit that was independent of age, gender, body surface area, race, number of prior treatments or disease status. Rituximab was consistently highly effective compared to methotrexate alone in patients seropositive for rheumatoid factor and/or anti-cyclic citrullinated peptide (CCP) antibodies. Rituximab also showed clinically and significantly meaningful improvement on ACR-core set measures and clinical disease activity indices.

In New Zealand, rituximab is indicated for use in combination with methotrexate for the treatment of patients with severe active RA who have had an inadequate response or intolerance to other disease-modifying agents.

RA is a chronic inflammatory disease of unknown aetiology. It is the most common autoimmune disease affecting the joints.[1] RA affects approximately 1% of the population[1] and is a significant cause of disability.[2] Usually diagnosed between the 3rd and 5th decade of life, it has a 2–3 times higher prevalence in women[2] and in persons of European and Asian ancestry.[1] RA prevalence increases with age, affecting approximately 6% of the Caucasian population older than 65 years of age, and there is evidence that in recent years, prevalence may be increasing in women.[3]

Clinical presentation of RA usually involves symmetric polyarthritis with joint swelling, particularly in the hands and feet, and patients experience morning stiffness lasting one hour or longer. The synovium lining joint capsules is the first structure to be affected; inflammatory processes lead to cartilage and bone destruction.[4] Extra-articular manifestations include subcutaneous nodules, vasculitis, interstitial lung disease and inflammatory eye disease.

The quality of life for patients with RA is significantly impacted by pain, loss of physical function and fatigue, and disease progression is associated with severe financial burden;[5] more than one-third of patients experience work disability, which occurs fairly early after disease onset;[6] by 5 years after diagnosis, only 68% of patients are still working.[7] In patients with extra-articular disease and those with treatment-related adverse effects including gastrointestinal toxicity, tumours and infections, life expectancy is shortened by 3–5 years.[8] Additionally, RA increases the risk of cardiovascular disease and heart failure by 50% and over 200%, respectively.[9,10]

Over the last 30 years, significant improvement in patient outcomes was achieved with the introduction of the folic acid metabolism inhibitor methotrexate, particularly with earlier, more intensive treatment. The development of TNF-targeting agents and interleukin-1 (IL-1) resulted in greater improvements in slowing disease progression and reduction in disability.

The American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) 2010 classification criteria greatly improved the diagnostic approach to RA (see Table 1).[11] Whereas the older diagnostic criteria did not differentiate between patients with a limited course of arthritis and those in which RA would eventually develop, the new criteria enable early intervention, which improves outcomes, limits functional disability and prevents joint damage.

Table 1. ACR/EULAR 2010 classification criteria[11]

Variable		Score
A)	Joint involvement	
	1 large joint	0
	2–10 large joints	1
	1–3 small joints (with or without large joint involvement)	2
	4–10 small joints (with or without large joint involvement)	3
	10 joints (including at least 1 small joint)	5
B)	Serological findings	
	Negative RF and negative ACPA	0
	Low positive RF or low positive ACPA	2
	High positive RF or high positive ACPA	3
C)	Acute phase reactants	
	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
D)	Duration of symptoms	
	<6 weeks	0
	≥6 weeks	1

RF = rheumatoid factor; ACPA = anti-citrullinated protein antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

A score of ≥6/10 is necessary for definite classification. Although a lower score is not classifiable as RA, the patient's status can be reassessed and the criteria might be fulfilled cumulatively over time.

Synovitis might not be clinically evident in some patients with early RA, particularly those who are seronegative for ACPA and RF. Magnetic resonance imaging and high resolution ultrasonography may identify bone oedema, bone erosions and synovitis that is not apparent during clinical examination.[12]

Pathophysiology

It is hypothesised that an autoimmune process is activated by an external trigger such as infection, cigarette smoke or trauma.[13] This reaction leads to chronic joint inflammation, synovial hypertrophy and possible extra-articular manifestations.[13]

Early in the disease, interaction between genetic susceptibility and environmental factors alters post-transcriptional regulation and self-protein citrullination.[4] Under normal circumstances, citrullination is a normal physiological process in dying cells, which do not come into contact with the immune system. When clearance is inadequate, citrullinated proteins and peptidylarginine deiminase enzymes do contact the immune system, creating citrullinated antigens. The effects of this are the development of immune complexes and loss of tolerance to "self".[4] The relationship between synovial involvement and loss of tolerance to self has yet to be elucidated, but synovitis occurs when leucocytes infiltrate the synovium.[4] Pathophysiology is purported to involve specific T and B lymphocytes, monocytes, macrophages, endothelial cells and fibroblasts.[14,15] TNF-alpha and interleukin 6 (IL-6) are thought to play the most central role in the pathogenesis of RA.[4] B cells have been demonstrated by recent research to act at multiple stages of the inflammatory response by disrupting T cell antigen presentation and by upregulating expression of proinflammatory cytokines and autoantibodies that together contribute to the inflammatory destruction seen in RA.[14,16,17]

Treatment of rheumatoid arthritis

The management of RA involves pharmacological treatment, including disease-modifying antirheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, as well as non-pharmacological approaches including psychological, physical and occupational therapy.[18] While the foundation of RA treatment is DMARDs, treatment with these agents has undergone significant change over the last 10 years, and the introduction of new and highly effective DMARDs, particularly biological agents that target tumour necrosis factor, IL-1 and IL-6 receptors, B cells and T-cell co-stimulation, has left rheumatologists overwhelmed by the evidence presented in clinical studies. Such a plethora of information complicates decision making as to which is the most effective treatment pathway. A recent survey at the annual European Congress of Rheumatology found inconsistencies in therapeutic targets and strategies.[19] These inconsistencies may be based in part on patient preferences, reimbursement and funding policies, and doctors' attitudes and settings. Accordingly, the EULAR stated that by 2012, they would provide standards of care, and promote access to optimal care of people with musculoskeletal conditions in Europe. It was the EULAR taskforce's objective to find consensus on recommendations for the management of RA with synthetic and biological DMARDs.[18] The recommendations are based on evidence from 5 systematic literature reviews that were discussed and summarised, as below:

The EULAR recommendations are based on three "overarching" principles:

1) That rheumatologists are the specialists who should primarily care for patients with RA
2) Treatment should be based on a shared decision between patient and rheumatologist and be aimed at the "best care"
3) Both treatment and productivity costs must be considered by the treating rheumatologist

The 15 final recommendations were:

1) Treatment with synthetic DMARDs is commenced at RA diagnosis
2) In every patient, treatment is aimed at remission or low disease activity as soon as possible. If treatment targets are not met, treatment should be adjusted every 1-3 months with strict monitoring
3) Methotrexate should be included as a first-line strategy
4) Where methotrexate is contraindicated, leflunomide, sulphasalazine or injectable gold should be part of the first-line treatment
5) In DMARD-naive patients (irrespective of corticosteroid therapy), DMARD monotherapy may be used
6) The addition of corticosteroids to DMARD monotherapy or combination therapy provide benefit as initial short-term treatment, but must be tapered as rapidly as clinically possible
7) When treatment with an initial DMARD fails to reach the treatment target, switching to another synthetic DMARD should be considered, or where poor prognostic factors are present, switching to a biological DMARD
8) In patients not responding to methotrexate or other synthetic DMARDs (with or without corticosteroids), biological DMARDs should be commenced such as a TNF inhibitor
9) Patients for whom a TNF inhibitor has failed should receive another TNF inhibitor, rituximab, abatacept or tocilizumab
10) In cases of severe refractory RA, or where the previously mentioned DMARDs or biological agents are contraindicated, azathioprine, cyclosporine A or cyclophosphamide can be considered
11) Intensive medication should be considered in all cases, although patients with poor prognostic factors have the most to gain
12) If the patient is in remission (with corticosteroids tapered), tapering of biological DMARDs can be considered, especially if combined with a synthetic DMARD
13) In long-term sustained remission, careful titration of synthetic DMARD can be considered as a shared decision between doctor and patient
14) DMARD-naive patients with poor prognostic factors should be considered for combination therapy with methotrexate and a biological agent
15) Factors outside of disease activity such as structural damage progression, safety concerns and comorbidities should be considered when adjusting treatment

Biological DMARDs

In clinical trials, 25-40% of participants failed to achieve a response (ACR 20% improvement criteria) to anti-TNF therapies.[20-22] Until recently, non-responders or those not able to tolerate one TNF inhibitor were switched to another, despite all TNF inhibitors having a similar mechanism of action. It was thought that the different characteristics of the anti-TNF agents (varying pharmacokinetic and chemical structures and production of drug-neutralising antibodies) would produce a more effective response.[23]

IL-1 and IL-6 inhibitors, B-cell depleting antibodies and T-cell co-stimulation inhibitors are biological agents with differing mechanisms of action that have more recently become available. These agents overcome class-associated primary failure and/or adverse effects that occur with TNF inhibitors, and the efficacy of these agents has been confirmed in large, placebo-controlled randomised clinical trials (RCTs).[24-27]

Rituximab pharmacology

Rituximab is a chimeric human monoclonal antibody against the CD20 protein that is expressed on naive, mature and memory B cells. Its mechanism of action includes direct apoptosis, complement-dependant cytotoxicity and antibody-dependant cellular cytotoxicity which leads to significant depletion of the B cell population.[28-31] It also increases expression of interferon-I response genes.[32]

Data are lacking as to the safety and effectiveness of rituximab in paediatric populations.[33] Dose adjustments are not required in elderly patients (aged >65 years).[33]

Rixtuximab is contraindicated in patients with known hypersensitivity to this treatment, to any component of the product or to murine proteins.[33]

Dosage and administration

Rituximab dosing instructions stipulate that patients should always be premedicated with an analgesic/anti-pyretic and an antihistamine agent prior to each infusion of rituximab.[33]

Premedication with glucocorticoids, administered as IV methylprednisolone 100 mg or its equivalent, should be completed 30 minutes before rituximab infusion to reduce the incidence and severity of infusion-related reactions.[33]

The recommended dosage of rituximab for RA is two 1000 mg IV infusions, separated by two weeks.[33] This may be repeated every 16 to 24 weeks, as necessary.[33] Long-term clinical trial data have demonstrated that efficacy improves over time and number of doses.[34]

Funding

PHARMAC's decision in October 2012 to list rituximab (inj 100 mg per 10 mL and inj 500 mg per 50 mL) in the national Hospital Medicines List in Section H of the Pharmaceutical Schedule from the date of its implementation (1 July 2013) means that rituximab is now funded in all District Health Board hospitals for patients with RA.[35] Rituximab will not be funded in the community for RA at this stage.[35]

CLINICAL EFFICACY: KEY TRIALS

Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE))[36]

Summary: The results of this phase III trial suggest that a lower dosage of rituximab (2×500 mg) might be similar in efficacy to the approved dose of rituximab (2×1000 mg) in patients with active RA who are biological-naïve with an inadequate response to methotrexate. No significant differences between the rituximab doses were apparent in either clinical or safety outcomes.

Methods: SERENE involved 511 patients aged 18–80 years with RA that was uncontrolled despite ≥12 weeks' treatment with methotrexate 10–25 mg/week. Patients underwent a minimum 2-week washout period for all DMARDs but continued on methotrexate (10–25 mg/week) plus folic acid ≥5mg (or equivalent).

Patients were randomised to one of 3 regimens: rituximab 2×500 mg, rituximab 2×1000 mg, or placebo administered by intravenous infusion on days 1 and 15. Between weeks 16 and 23, non-responders (<20% improvement in swollen joint count or tender joint count) were permitted additional treatment with one non-biological DMARD, which continued until the end of the study. From week 24, eligible patients (not in remission) or placebo recipients continued in an open-label phase and received rituximab 2×500 mg.

Assessment tools included ACR core set (swollen joint count, tender joint count, patient assessment of global status, an acute phase reactant [erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)], health professional assessment of global status, physical function, and pain), the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and the Medical Outcomes Study 36-item Short Form Health Survey (SF-36).

Results:

Results at 24 weeks

Both rituximab-treated groups experienced significantly greater mean decreases in all components of the ACR core set ($p \leq 0.0007$) and mean changes in DAS28-ESR (Disease Activity Score 28 points-erythrocyte sedimentation rate) compared with placebo recipients (see Table 2). Significantly higher numbers of rituximab-treated patients achieved EULAR responses, low disease activity and remission than placebo recipients ($p<0.05$). Rituximab recipients also had statistically significant improvements in patient-reported outcomes measured by SF36, Health Assessment Questionnaire Disability Index (HAQ DI) and FACIT-F scores.

Declines in mean IgA, IgG and IgM levels were greater in rituximab-treated patients than in the placebo group. In the rituximab 2×500 mg, rituximab 2×1000 mg and placebo groups, the proportion of patients achieving IgA levels below the laboratory lower limit of normal (LLN) were 1.9%, 2.6% and 1.4%, respectively. Corresponding values for IgG were 1.9%, 1.3% and 0%, respectively, and for IgM, 6.4%, 6.6% and 0%, respectively.

Results at 48 weeks

Mean DAS28-ESR scores demonstrated either maintenance or improvement in levels of disease activity in rituximab-treated patients, and ACR responses were maintained compared with week 24, with most endpoints showing improvement (see Table 2). EULAR responses were also maintained. There were no statistically significant differences in clinical endpoints between rituximab doses.

Table 2. SERENE trial: ACR responses[36]

Percentage of patients achieving ACR response (ITT analysis)	Placebo + MTX (n=172)	Rituximab 2×500 mg + MTX (n=167)	Rituximab 2×1000 mg + MTX (n=170)
24 weeks			
ACR20	23.3%	54.5%*	50.6%*
ACR50	9.3%	26.3%*	25.9%*
ACR70			
48 weeks (% patients)			
ACR20		55.7%	57.6%
ACR50		32.9%	34.1%
ACR70		12.6%	13.5%

ITT = intent-to-treat; MTX = methotrexate.
* $p \leq 0.0001$.

Tolerability

During the 24-week, placebo-controlled period, the incidence of all adverse events (AEs) was similar across all groups. Infusion-related reactions (IRRs) occurred more frequently with the first infusion across all treatment groups than with the second infusion. IRRs were highest in patients receiving the first rituximab infusion 1000mg than with 500mg or placebo at 25%, 19% and 14% respectively. Infections were lower in the rituximab groups than in placebo recipients. Serious infection rates for rituximab 2×500 mg, rituximab 2×1000 mg and placebo recipients were 1.26, 2.46 and 8.83 events per 100 patient-years, respectively.

During the 48-week period, the overall safety profile was similar for both rituximab groups.

Expert Commentary:
This is an interesting study comparing lower dose (2 x 500mg rituximab) with standard (and Medsafe-approved dose) 2×1000 mg rituximab, which demonstrates similar efficacy and tolerability at 24 weeks. However, these patients were methotrexate-inadequate responders and my impression is that anti-TNF inadequate responders may be a more refractory group. I would consider using the 500 mg rituximab dose as a follow-up dose in those RA patients who achieve an excellent response to the initial standard 2×1000 mg dose.

EVIDENCE ON TNF INHIBITOR CYCLING:

B cell depletion may be more effective than switching to an alternative anti-tumor necrosis factor agent in rheumatoid arthritis patients with inadequate response to anti-tumor necrosis factor agents[37]

Summary: The outcomes from this study suggest that treatment with rituximab may be more effective than switching to an alternative TNF inhibitor in patients with RA with persistent active disease despite anti-TNF therapy.

Methods: This study was nested within the Swiss Clinical Quality Management RA (SCQM-RA) cohort and included 116 patients with RA who had had an inadequate response to at least 1 anti-TNF agent and subsequently received either 1 cycle of rituximab (2×1000 mg + concomitant corticosteroids; n=50) or a second or third alternative TNF inhibitor (n=66). In the alternative TNF inhibitor-treated group, 49% received fortnightly adalimumab 40mg subcutaneously (SC). Twenty-seven percent received 50mg weekly etanercept SC and 24% received infliximab intravenously (starting dose 3 mg/kg). Patients were followed-up for a median of 9 months.

Results: The mean decrease in DAS28 at 6 months in patients receiving rituximab or alternate TNF inhibitor was –1.61 and 0.98, respectively. Rituximab recipients also had more favourable responses in other secondary DAS variables; the reductions in tender joints and in ESR were significantly greater in the rituximab recipients than those receiving alternate TNF inhibitors (both $p<0.01$). There were no significant differences in tolerability between groups. TNF inhibitor-treated patients experienced more dermatological reactions than rituximab (9 vs 1 events, respectively; $p<0.03$) but fewer infusion reactions (3 vs 0 events, respectively; $p=0.04$).

Which subgroup of patients with rheumatoid arthritis benefits from switching to rituximab versus alternative anti-tumour necrosis factor (TNF) agents after previous failure of an anti-TNF agent?[38]

Summary: The results of this study suggest that in patients with RA who have discontinued previous anti-TNF treatment because of ineffectiveness, switching to rituximab is more effective than switching to an alternative TNF inhibitor.

Methods: A later prospective SCQM-RA cohort study by the same research group also compared the efficacy and tolerability of switching from one TNF inhibitor to another, to treatment with rituximab in patients who had an inadequate response to one or more TNF inhibitors. The study also aimed to determine which subgroup of patients derived the most benefit from switching to rituximab. A total of 155 patients received rituximab and 163 received a second or third TNF inhibitor. They were followed-up for a median 11 months. The rituximab-treated patients had a higher prevalence of rheumatoid factor (RF) ($p=0.02$), higher disease activity ($p<0.001$) and higher functional disability scores.

Results: The improvement in DAS28 during the first year was more favourable in the rituximab group than in the alternate TNF inhibitor-treated patients ($p=0.016$), but when the reason for switching was ineffectiveness of a previous TNF inhibitor, the improvement in DAS28 was significantly greater for rituximab recipients than the alternate TNF inhibitor-treated group ($p=0.03$). Sixty-one percent of rituximab recipients compared with 37% of TNF inhibitor recipients had a DAS28 improvement of >1.2 units ($p=0.001$). The researchers found no effect modification according to the number of previous TNF inhibitor failures, or by concomitant DMARD use. Doctors reported an AE in 8% of patients, with no differences between groups.

Expert Commentary:
These two studies from a carefully monitored RA cohort group (one retrospective, one prospective) compare rituximab with an alternative TNF inhibitor in patients failing their initial anti-TNF agent. This scenario is very pertinent to the New Zealand setting. Both studies show a more favourable response switching to rituximab, but importantly in the prospective study, the response was greater in 'refractory' anti-TNF patients compared to anti-TNF 'intolerant' patients.

Relative effectiveness of rituximab versus an alternative TNF inhibitor in patients with RA and an inadequate response to a single previous TNF inhibitor: results from SWITCH-RA, a global, comparative effectiveness, observational study[39]

Summary: Following discontinuation of a first TNF inhibitor, starting treatment with rituximab was associated with significantly better efficacy at 6 months as measured by DAS28-ESR compared with switching to an alternative TNF inhibitor.

Methods: Outcomes are reported for 602 patients who switched to rituximab and 505 who commenced an alternative TNF inhibitor, following the first TNF inhibitor failure. The rituximab cohort (vs patients on alternative TNF inhibitors) had a mean RA disease duration of 8.9 years (vs 7.6; p=0.056) and a mean initial TNF inhibitor duration of 25.4 months (vs 25.2; p=0.227). At the time of switching, rituximab patients had greater mean baseline DAS28-3-ESR for the study overall (5.5 vs 5.0; p<0.001), for the 824 patients who discontinued initial TNF inhibitor therapy due to inefficacy (5.3 vs 4.7; p<0.001) and for the 264 patients who discontinued due to intolerance (5.0 vs 4.5; p=0.019).

Results: The primary endpoint was the change from baseline over 6 months in the DAS28, based on DAS28-3-ESR, which excludes the patient's global health component. At 6 months, greater decreases in DAS28-3-ESR were recorded in the rituximab cohort than in the alternative TNF inhibitor cohort overall (–1.5 vs –1.1; p=0.008) and the "inefficacy" sub-cohort (–1.5 vs –1.0; p=0.007), but not the "intolerance" sub-cohort (–1.0 vs –0.9; p=0.877). Rituximab was also associated with a greater decrease in ESR compared with values in the alternative TNF inhibitor group, both overall (–15.2 vs –9.2; p=0.009) and in the "inefficacy" sub-cohort (–12.8 vs –6.8; p=0.035). Rates of AEs and serious AEs were similar between the treatment cohorts.

Seropositive rheumatoid arthritis patients with an inadequate response to TNF inhibitors achieve improved clinical effectiveness after switching to rituximab versus switching to an alternative TNF inhibitor[40]

Summary: SWITCH-RA data were also used in this comparison of the relative effectiveness of rituximab versus an alternative TNF inhibitor according to serological status. Among seropositive patients, those who switched to rituximab achieved significantly greater improvements at 6 months compared with those who switched to an alternative TNF inhibitor. No between-group differences in efficacy were seen at 6 months in the seronegative cohort.

Methods: The analysis included 728 patients who completed 6 months of therapy with a second biological (rituximab = 405; TNF inhibitor = 323). A higher proportion of patients in the rituximab group were seropositive compared with the alternative TNF inhibitor group (RF = 82.7% vs 67.0%; anti-CCP = 66.3% vs 62.0%). Baseline DAS28-3-ESR scores in seropositive and seronegative patients at the time of switching were significantly higher in the rituximab group than in the alternative TNF inhibitor group.

Results: In the seropositive cohort, rituximab significantly reduced the DAS28-3-ESR score at 6 months compared with the alternative TNF inhibitor treatment. No significant improvements in DAS28-3-ESR were observed at 6 months in the seronegative cohort.

Decreases in ESR at 6 months were greater in the seropositive patients who were receiving rituximab than in those receiving an alternative TNF inhibitor (–14.4 vs –7.3; p=0.006). Corresponding values for the seronegative cohort were not statistically significant (–13.4 vs –10.4; p=0.582).

The benefit of rituximab treatment varied in patients who were seropositive according to the reason for interrupting the previous TNF inhibitor treatment. Patients who were seropositive who discontinued a first TNF inhibitor due to inefficacy achieved significantly better responses with rituximab compared with those receiving an alternative TNF inhibitor. Responses in seropositive patients who discontinued a first TNF inhibitor due to intolerance did not significantly differ between the two treatment groups.

Expert Commentary:
These two abstracts presented at EULAR 2012 and ACR 2012 from a large observational study confirm better efficacy switching to rituximab in anti-TNF inadequate responders overall, however, there are two important messages:

(1) A greater benefit was only seen in those patients who were anti-TNF 'refractory'. In those patients who were anti-TNF 'intolerant' equivalent efficacy was found in changing to a different anti-TNF agent.

(2) Furthermore, the superior response to rituximab was only seen in seropositive RA patients who were anti-TNF 'refractory'.

Therefore, in RA patients who are seronegative and/or anti-TNF 'intolerant', changing to an alternative anti-TNF inhibitor would be a reasonable option.

Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks[26]

Summary: At 24 weeks, a single course of rituximab with concomitant methotrexate provided significant and clinically meaningful improvements in disease activity in active, longstanding RA refractory to TNF inhibitor therapy.

Methods: The Randomized Evaluation of Long-Term Efficacy of Rituximab (REFLEX) in RA was a 2-year phase III RCT of rituximab therapy in patients with moderately-to-severely active RA. IV rituximab (2×1000 mg) and methotrexate was compared with placebo and methotrexate in patients who had had an inadequate response to infliximab, adalimumab, or etanercept.

Results: A total of 54% of placebo recipients and 82% of rituximab-treated patients completed the 24 weeks. At every time point between 8 and 24 weeks, DAS28 scores were statistically significant between treatment groups (p<0.0001) (see Table 3). There were statistically significant reductions in all individual improvement ACR criteria in the rituximab-treated group compared with placebo, and also clinically meaningful improvements in fatigue, disability and health-related quality of life (HAQ DI, FACIT-F and SF-36) with a trend towards reduced disease progression in radiographic endpoints. Changes from baseline in joint-narrowing scores were significantly reduced (p=0.016) compared with the placebo group. More RF-positive patients than RF-negative patients had a ACR20 response at 24 weeks (54% vs 41%). Mean immunoglobulin levels remained within normal limits for all patients, despite B cell depletion. Fourteen percent of rituximab patients had positive human antichimeric antibody titres.

Table 3. REFLEX trial: ACR/EULAR response rates[26]

Endpoint (ITT analysis)	Placebo + MTX (n=201)	Rituximab 2×1000 mg + MTX (n=298)
ACR response		
ACR20	18%	51%*
ACR50	5%	27%*
ACR70	1%	12%*
EULAR response		
Moderate response	20%	50%
Good response	2%	15%
Low disease	2%	15%
Remission	0%	9%

ITT = intent-to-treat; MTX = methotrexate; EULAR response: moderate = DAS28 <5.1 and improvement between 0.6 and 1.2; good = DAS28 <3.2 and improvement of >1.2; low disease = DAS28 <3.2; remission = DAS28 <2.6.

* p<0.0001.

A total of 88% of placebo recipients and 85% of rituximab recipients reported any AE during the study period. A greater number of placebo recipients experienced severe AEs than rituximab recipients (23% vs 18%). The frequency of AEs occurring at ≥5% were similar between groups except for RA exacerbation, which occurred in 42% of placebo recipients compared with 21% of rituximab-treated patients. Infusion-associated AEs were higher in the rituximab group than in the placebo group (29% vs 23%).

Sustained inhibition of structural damage in patients with rheumatoid arthritis and an inadequate response to tumor necrosis factor inhibitors prior to rituximab treatment: 5-year data from the REFLEX study[34]

Summary: The impact of rituximab treatment over 5 years on progressive joint damage has been reported for patients who participated in the REFLEX open-label extension study. Patients originally randomised to rituximab treatment had enhanced inhibition of progressive joint damage at 5 years compared with patients originally randomised to placebo and later rescued with rituximab. Both groups showed continued improvement in progressive joint damage inhibition over time, with the placebo cohort progressing more rapidly than the rituximab cohort.

Methods: A post-hoc analysis was conducted on ITT patients with an X-ray at baseline and at the 5-year timepoint, comprising 79 patients who were randomised at baseline to placebo who subsequently received rituximab as rescue therapy and 105 patients originally randomised to rituximab. X-rays of the hands and feet were read at baseline and years (Y) 1, 4, and 5.

Results: In the placebo-rituximab group, 71 patients were rescued with rituximab during Y1 and a further 6 patients after Y1. Patients in both groups received up to 12 rituximab courses (mean of 5 courses over the 5 years). In both groups, the mean change in modified Total Sharp Score (mTSS) continued to decrease to Y5: change from baseline at Y5 was 5.51 for placebo-rituximab patients and 3.21 for rituximab patients. Similar effects were observed for erosion scores and joint space narrowing. The annualised progression rate decreased from 2.08 (baseline to Y1) to 0.89 (Y1 to Y4) and 0.25 (Y4 to Y5) in placebo-rituximab patients, and from 0.91 to 0.56 and 0.33 for the same periods in rituximab patients. Between Y4 and Y5, placebo-rituximab treatment was associated with similar rates of progressive joint damage to those with rituximab-only.

Expert Commentary:
The REFLEX study, published in 2006, was one of the earlier RA studies demonstrating the efficacy of rituximab in anti-TNF inadequate responders with 6-month response rates clearly superior to placebo (ACR20 51% vs 18%, ACR50 27% vs 5%, ACR70 12% vs 1%). As borne out in later studies, there was a modest difference (54% vs 41%) in ACR20 rates between RF-positive and RF-negative patients.

Five-year X-ray data from the REFLEX open-label extension study (ACR abstract 2011) demonstrates enhanced inhibition of progressive joint damage in the rituximab group compared to the placebo group given 'rescue-rituximab' (the majority within the first year of the study). As expected, the greatest differences were seen between years 1 and 4, with no difference seen between years 4 and 5 (at which point both groups had been on rituximab for > 2–3 years). This is consistent with most studies indicating prevention of structural joint damage with effective disease control, in this case rituximab, in a RA cohort resistant to anti-TNF therapy.

Sustained inhibition of progressive joint damage with rituximab plus methotrexate in early active rheumatoid arthritis: 2-year results from the randomised controlled trial IMAGE[41]

Summary: Rituximab 2×1000 mg plus methotrexate produced sustained improvements in radiographic, clinical and functional outcomes over 2 years.

Methods: A total of 755 methotrexate-naïve patients with early, active RA were randomised to receive rituximab 2×500 mg plus methotrexate, rituximab 2×1000 mg plus methotrexate, or placebo plus methotrexate. All patients received IV methylprednisolone 100mg before all infusions.

Results: Most of the progressive joint damage occurred during the first 6 months of the study in the rituximab-treated patients, with progression almost halted over the next 18 months, but the reasons for this are not known. Significantly greater improvements in modified Total Sharp Score, total erosion score and joint space narrowing scores were seen at 2 years in both rituximab groups compared with the placebo group (see Table 4). Rituximab treatment also resulted in higher numbers of patients achieving ACR20/50/70/90 scores and major clinical response compared with patients in the placebo group over the 2-year period. Improvements in physical function were sustained throughout the second year of treatment in the rituximab group, resulting in significantly greater mean decreases in HAQ DI score compared to those attained by the placebo group. The safety profile was similar across all three groups.

Table 4: Inhibition of progressive joint damage at 2 years in the IMAGE study[41]

Endpoints (Modified ITT analysis)	Rituximab 2×500 mg + MTX (n=233)	Rituximab 2×1000 mg + MTX (n=239)	Placebo + MTX (n=244)
mTSS	0.76[a]	0.41[b]	1.95
Erosion score	0.50[c]	0.23[b]	1.32
Joint space narrowing	0.26	0.18[d]	0.63

ITT = intent-to-treat; MTX = methotrexate; mTSS = modified Total Sharp Score.

[a] p=0.0041; [b] p<0.0001; [c] p=0.0019; [d] p=0.0183.

Expert Commentary:
This study demonstrates superior efficacy for the rituximab/methotrexate combination compared to methotrexate monotherapy in early active RA in both the low dose (2×500 mg) and standard dose (2×1000 mg) rituximab regimens. Although rituximab is not funded in early RA in New Zealand, there may be cases where anti-TNF is contraindicated (e.g. recent malignancy, bronchiectasis, recurrent infection) and where rituximab may be preferred on an individual patient basis.

In this early RA cohort, clinical response to rituximab 2×500 mg and 2×1000 mg regimens were similar; however, the 1000mg dose appeared to be more effective in inhibition of progressive joint damage. The importance of this difference to individual patients is yet to be determined.

As outlined earlier, my individual preference would be to use the 1000mg dose x 2 initially and then consider the lower dose in those with an excellent response.

LONG-TERM SAFETY DATA:

Long-term safety of rituximab: 10-year follow-up in the RA global clinical trial program[42]

Summary: This long-term follow-up of rituximab data demonstrates a consistent safety profile, with good tolerability over time and multiple treatment courses.

Methods: As of September 2011, 3595 patients with moderate-to-severe active RA (All-Exposure population; all patients exposed to at least one or part of one rituximab infusion, regardless of dose, within the RA global clinical trial programme) had received up to 19 courses of rituximab over the 10-year observation period (14,008 patient-years). Of these patients, 1145 had follow-up >5 years (7716 patient-years) (>5-year population). The placebo population comprised 818 patients (1107 patient-years) with a mean duration of follow-up of 1–1.5 years.

Results: In the All-Exposure cohort, IRR was the most frequent AE; most were grade 1 or 2 in intensity, were rarely serious and generally occurred following the first infusion of the first course (789 patients; 22%). Rates of AEs, serious AEs and infections were comparable across analysis populations and generally remained stable over time and multiple courses. Overall serious infection rates in the rituximab All-Exposure and >5-year sub-population were 3.80 events/100 patient-years and 2.76 events/100 patient-years, respectively, comparable to the rates in the placebo population (3.79 events/100 patient-years). Pneumonia was the most frequently reported serious infection (2% of rituximab patients). Serious opportunistic infections were rare (0.05/100 patient-years in the rituximab cohort vs 0.09/100 patient-years in the placebo cohort). No increased risk of malignancy over time or course was evident, and myocardial infarction rates (0.40 events/100 patient-years) were consistent with rates in the general RA population (0.48–0.59 events/100 patient-years).

Analysis of infection risk in patients with limited return of peripheral B cells after a period of two years or more following any rituximab treatment course in RA clinical trials[43]

Summary: The same RA global clinical trial data were examined for the risk of infection and the long-term safety of prolonged peripheral B cell depletion following rituximab treatment. No clear association was found between any rituximab treatment course and an increased risk of infections, including serious infections.

Methods: The study population consisted of 345 patients with limited return of peripheral B cells after ≥2 years from the rituximab All-Exposure population (comprising 3194 patients as at September 2010; 11,962 patient-years, with up to 9.5 years of follow-up, and up to 17 courses of rituximab treatment). Limited return of peripheral B cells was defined as a CD19 count below the lower limit of normal (80 cells/μL) after a period of ≥2 years (104 consecutive weeks) following any course of rituximab.

Results: Limited return of peripheral B cells over ≥2 years was not associated with an increased risk of infections in terms of rates, clinical pattern, or severity. Infection rates per 100 patient-years were lower in patients with low CD19 for ≥2 years versus the All-Exposure cohort and patients with an inadequate response to a TNF inhibitor. Serious infection rates in patients were similar to those in other populations (overlapping 95% confidence intervals) and were most comparable to the rates seen in patients classified as TNF inhibitor inadequate responders (rituximab-indicated population). In the subgroups of patients with limited return of peripheral B cells, there were no apparent differences in types or outcomes of serious infections.

Expert Commentary:

The two previous papers report long-term (up to 10 years) safety data on RA patients treated with rituximab, with some patients receiving up to 19 courses. The 10-year observation period (14,008 patient-years) on the whole is reassuring with no increase in serious infection, malignancy and myocardial infarction compared to rates in the 'placebo' RA population. Overall serious infection rates in the all-exposure group, >5-year sub-population and placebo population were 3.8 events/100 patient-years, 2.76 and 3.79, respectively. Pneumonia was the most frequently reported serious infection (2% of rituximab patients). I strongly advise all my rituximab patients to receive the annual 'flu vaccine and 'Pneumovax' vaccine, and ideally, prior to initial rituximab treatment.

The same RA global clinical data examined infection risk in those patients with prolonged lymphopenia (specifically CD19B cells < lower limit of normal, 80 cells/uL) at 2 years. 345 patients were identified and there was no difference in serious infection rates in these patients compared to other similar RA populations.

Conclusion – Expert Reviewer:

Rituximab is a welcome addition for the New Zealand rheumatologist treating anti-TNF inadequate responder RA patients. It was formally PHARMAC-funded from July 2013 as part of the national Hospital Medicines List (HML) for District Health Boards. At this stage, it is not funded in the private practice setting, although negotiations are ongoing.

Rituximab would appear to be the treatment of choice in seropositive RA patients who prove refractory to an anti-TNF agent. In patients who are seronegative and/or are intolerant to their initial anti-TNF agent, the available literature suggests equivalent efficacy of an alternative anti-TNF agent compared to rituximab.

Preliminary studies involving genotyping (eg. *FCGR3A*)[44] and synovial gene expression profiles[45] suggest that in the future we may be able to better identify those RA patients who will have a sustained response to rituximab. Currently, however, such 'personalised' healthcare remains an aspirational goal.

There is no firm data to guide us as to whether one should treat all patients at 6-monthly intervals or 'at flare'. There is emerging evidence that regular 6-monthly treatment compared to 'at flare' may enhance inhibition of radiographic progression. Regular treatment with the lower 500mg paired infusions appears to provide similar clinical efficacy to the standard 1000mg dose, but perhaps at the cost of increased joint damage. Such treatment decisions will need to be made on an individual patient basis. Most authorities recommend that (if tolerated) patients should be prescribed methotrexate in combination with rituximab. The case for leflunomide and other DMARDs in methotrexate-intolerant patients is less clear.

Ideally, all patients should have the annual 'flu vaccine and 'Pneumovax' vaccine prior to commencing treatment. A case may be made for selected patients (e.g. recent malignancy, certain infection risks such as bronchiectasis) to proceed directly to rituximab rather than an anti-TNF agent.

The long-term data to date are reassuring, but these patients need to be followed vigilantly. Patient and General Practitioner education and clear communication is important, as with all of our immunosuppressed patients.

References

1. Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheum. 2008;58(1):15-25.
2. Corbett M, et al. Factors predicting death, survival and functional outcome in a prospective study of early rheumatoid disease over fifteen years. Br J Rheumatol. 1993;32(8):717-23.
3. Crowson CS, et al. The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. Arthritis Rheum. 2011;63(3):633-9.
4. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;365(23):2205-19.
5. Bansback N, et al. The economics of treatment in early rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2009;23(1):83-92.
6. Allaire S, et al. Contemporary prevalence and incidence of work disability associated with rheumatoid arthritis in the US. Arthritis Rheum. 2008;59(4):474-80.
7. Sokka T, et al. Work disability remains a major problem in rheumatoid arthritis in the 2000s: data from 32 countries in the QUEST-RA study. Arthritis Res Ther. 2010;12(2):R42.
8. Turesson C, et al. Occurrence of extraarticular disease manifestations is associated with excess mortality in a community based cohort of patients with rheumatoid arthritis. J Rheumatol. 2002;29(1):62-7.
9. Maradit-Kremers H, et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum. 2005;52(2):402-11.
10. Nicola PJ, et al. Contribution of congestive heart failure and ischemic heart disease to excess mortality in rheumatoid arthritis. Arthritis Rheum. 2006;54(1):60-7.
11. Aletaha D, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-81.
12. Szkudlarek M, et al. Ultrasonography of the metacarpophalangeal and proximal interphalangeal joints in rheumatoid arthritis: a comparison with magnetic resonance imaging, conventional radiography and clinical examination. Arthritis Res Ther. 2006;8(2):R52.
13. Firestein GS. Kelley's textbook of rheumatology. 2012, Saunders: Philadelphia, Pa.; London. p. 1 online resource.
14. Dorner T, Burmester GR. The role of B cells in rheumatoid arthritis: mechanisms and therapeutic targets. Curr Opin Rheumatol. 2003;15(3):246-52.
15. Smith JB, Haynes MK. Rheumatoid arthritis – a molecular understanding. Ann Intern Med. 2002;136(12):908-22.
16. Edwards JC, et al. Do self-perpetuating B lymphocytes drive human autoimmune disease? Immunology. 1999;97(2):188-96.
17. Takemura S, et al. T cell activation in rheumatoid synovium is B cell dependent. J Immunol. 2001;167(8):4710-8.
18. Smolen JS, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis. 2010;69(6):964-75.
19. Schoels M, et al. Follow-up standards and treatment targets in rheumatoid arthritis: results of a questionnaire at the EULAR 2008. Ann Rheum Dis. 2010;69(3):575-8.
20. Keystone EC, et al. Once-weekly administration of 50 mg etanercept in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2004;50(2):353-63.
21. Lipsky PE, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med. 2000;343(22):1594-602.
22. Weinblatt ME, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. 2003;48(1):35-45.
23. Haraoui B. Is there a rationale for switching from one anti-tumor necrosis factor agent to another? J Rheumatol. 2004;31(6):1021-2.
24. Emery P, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008;67(11):1516-23.
25. Genovese MC, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med. 2005;353(11):1114-23.
26. Cohen SB, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006;54(9):2793-806.
27. Buch MH, et al. Lack of response to anakinra in rheumatoid arthritis following failure of tumor necrosis factor alpha blockade. Arthritis Rheum. 2004;50(3):725-8.
28. Silverman GJ, Weisman S. Rituximab therapy and autoimmune disorders: prospects for anti-B cell therapy. Arthritis Rheum. 2003;48(6):1484-92.
29. Shan D, et al. Apoptosis of malignant human B cells by ligation of CD20 with monoclonal antibodies. Blood. 1998;91(5):1644-52.
30. Reff ME, et al. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood. 1994;83(2):435-45.
31. Golay J, et al. Biologic response of B lymphoma cells to anti-CD20 monoclonal antibody rituximab in vitro: CD55 and CD59 regulate complement-mediated cell lysis. Blood. 2000;95(12):3900-8.
32. Verweij CL, Vosslamber S. New insight in the mechanism of action of rituximab: the interferon signature towards personalized medicine. Discov Med. 2011;12(64):229-36.
33. Medsafe New Zealand Medicines and Medical Devices Safety Authority. Mabthera® Data Sheet. 17 January 2013. http://medsafe.govt.nz/profs/Datasheet/m/Mabtherainf.pdf
34. Keystone E et al. Sustained inhibition of structural damage in patients with rheumatoid arthritis and an inadequate response to tumor necrosis factor inhibitors prior to rituximab treatment: 5-year data from the REFLEX study. Arthritis Rheum. 2011;63 Suppl 10:2208.
35. PHARMAC. Pharmaceutical Management Agency. Decision on proposal for various Roche products: rituximab, bevacizumab, valganciclovir and midazolam. 11 October 2012.
36. Emery P, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). Ann Rheum Dis. 2010;69(9):1629-35.
37. Finckh A, et al. B cell depletion may be more effective than switching to an alternative anti-tumor necrosis factor agent in rheumatoid arthritis patients with inadequate response to anti-tumor necrosis factor agents. Arthritis Rheum. 2007;56(5):1417-23.
38. Finckh A, et al. Which subgroup of patients with rheumatoid arthritis benefits from switching to rituximab versus alternative anti-tumour necrosis factor (TNF) agents after previous failure of an anti-TNF agent? Ann Rheum Dis. 2010;69(2):387-93.
39. Emery P, et al. Relative effectiveness of rituximab versus an alternative TNF inhibitor in patients with RA and an inadequate response to a single previous TNF inhibitor: results from SWITCH-RA, a global, comparative effectiveness, observational study. EULAR 2012. Abstract: FRI0200.
40. Rubbert-Roth A, et al. Seropositive rheumatoid arthritis patients with an inadequate response to TNF inhibitors achieve improved clinical effectiveness after switching to rituximab versus switching to an alternative TNF inhibitor. ACR Annual Meeting Abstracts. 2012;64:467.
41. Tak PP, et al. Sustained inhibition of progressive joint damage with rituximab plus methotrexate in early active rheumatoid arthritis: 2-year results from the randomised controlled trial IMAGE. Ann Rheum Dis. 2012;71(3):351-7.
42. van Vollenhoven RF, et al. Long-term safety of rituximab: 10-year follow-up in the RA global clinical trial program. Ann Rheum Dis. 2012;71 Suppl 3:195.
43. Mease P, et al. Analysis of infection risk in patients with limited return of peripheral B cells after a period of two years or more following any rituximab treatment course in RA clinical trials. EULAR 2012. Abstract: FRI0201.
44. Ruyssen-Witrand A, et al. Fcγ receptor type IIIA polymorphism influences treatment outcomes in patients with rheumatoid arthritis treated with rituximab. Ann Rheum Dis. 2012;71(6):875-7.
45. Hogan VE, et al. Pretreatment synovial transcriptional profile is associated with early and late clinical response in rheumatoid arthritis patients treated with rituximab. Ann Rheum Dis. 2012;71(11):1888-94.