Various therapies have been used for the management of rheumatoid arthritis (RA) over the last several decades. Gold salts, available since the 1920s, were used for their disease-modifying activity in rheumatoid arthritis (RA) treatment for many years, until the development of newer disease-modifying antirheumatic drugs (DMARDs) including methotrexate (MTX) and also sulfasalazine (sulphapyridine bound with aspirin). The first reported use of MTX in RA was in 1951 (see Fig. 1). By the late 1980s, MTX was commonly used in the management of RA. Since that time, there have been major developments in the treatment of RA, with not only more rational use of MTX (with an increase in prescribed weekly dosage from 5–7.5 mg to 20–25 mg) but also the introduction of biologic DMARDs, the first of which to enter the Australian market was etanercept, followed by adalimumab, anakinra, rituximab, abatacept, tocilizumab, golimumab and certolizumab (the dates to market in Figure 1 denote EU approval for use in RA). New classes of immunomodulatory drugs expected to become available soon include agents that inhibit SYK (spleen tyrosine kinase), Janus kinases (JAK) and interleukin-17 (IL-17). Prof. Jones believes that these new agents will very likely bring changes to the market.

Future prospects include agents that inhibit the formation of the IL-6/IL-6R complex, and also biosimilars or follow-on biologics.

**Figure 1. RA treatment milestones.**

Prof. Jones considers the 2010 American College of Rheumatology/European League Against Rheumatism (ACR-EULAR) classification criteria for RA to be a marked improvement upon the 1987 ACR criteria. Unfortunately, such criteria cannot be drawn up for some of the other autoimmune diseases such as lupus, where the cause of the disorder remains unknown and it is not clear as to which treatments are effective.

**Effect of treatment on radiographic progression**

In 2003, a systematic review by Prof. Jones and colleagues that assessed and ranked the efficacy of pharmacological interventions on radiological progression in RA used evidence from 25 placebo-controlled trials to demonstrate that infliximab, cyclosporin, sulfasalazine, leflunomide, MTX, parenteral gold, corticosteroids, auranofin and the interleukin-1 receptor antagonist (IL-1RA) were all statistically better than placebo in terms of change in erosion scores. All agents were equivalent statistically, except for infliximab (which was superior to the last 5 agents). Findings were similar for the odds of progression, with...
Further support for this view comes from the TEMPO (MTX-naïve) trial, in which combination treatment with etanercept and MTX in active RA was significantly better in retarding radiographic progression compared with MTX or etanercept alone (mean total Sharp scores at 52 weeks of −0.54, 2.80 and 0.52, respectively; all p<0.001). An analysis of data dating to June 2009 from 10,396 patients with RA registered with the British Society for Rheumatology Biologics Register (BSRBR) evaluated the effect of different concomitant bDMARDs (no bDMARD; MTX; leflunomide; sulfasalazine; MTX+sulfasalazine; MTX+HCQ; or MTX+sulfasalazine+HCQ) on the persistence with anti-TNF therapies in patients with RA. Discontinuations due to adverse events (AEs) and discontinuations due to lack of efficacy were examined in both the cohort treated with anti-TNF plus MTX (n=4,418) and those on anti-TNF therapy alone (n=3,339). Interestingly, more discontinuations occurred due to toxicity with monotherapy compared to the combination (24.9% vs 20.3% of patients; adjusted HR 1.47 [95% CI 1.30 to 1.65]). Usually, two drugs are associated with worse toxicity than is one single agent in the treatment of RA. Not surprisingly, more discontinuations occurred due to lack of efficacy in the anti-TNF monotherapy arm compared to the combination arm (22.9% vs 21.7%; adjusted HR 1.34 [95% CI 1.20 to 1.51]). Thus, patients receiving monotherapy were more likely to discontinue their first anti-TNF therapy compared to those receiving anti-TNF plus MTX combination therapy.

A recently updated meta-analysis by Prof. Jones and colleagues summarises the evidence for bDMARDs and radiographic damage when used either alone or in combination with MTX (see Fig. 2). For a bDMARD in combination with MTX alone, most therapies studied (etanercept, adalimumab, infliximab, certolizumab, tocilizumab and rituximab) were statistically similar to each other in regard to efficacy at slowing X-ray progression using either of two outcomes (standardised mean difference [SMD] and odds of progression), with infliximab ranking first in both outcomes. Importantly, this effect was additional to MTX; thus, the overall benefit is moderate to large in magnitude. The exceptions to this benefit were abatacept (no effect on odds of progression) and golimumab (no effect on standardised mean difference), despite golimumab being a fully humanised version of infliximab. Prof. Jones thinks that this is probably due to the timing of the trials; gross progression occurred and therefore a large effect is discernible in the early infliximab trial, whereas there was only minimal progression (and therefore not much of a difference) in the placebo plus MTX arm in the golimumab trial published in 2011.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Reference</th>
<th>Follow-up period</th>
<th>Number</th>
<th>SMD (95% CI)</th>
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<tr>
<td>Infliximab</td>
<td>Lipsky et al</td>
<td>54 weeks</td>
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<td>Adalimumab</td>
<td>Keystone et al</td>
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<td></td>
<td>Breedveil et al</td>
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<td></td>
<td>Pooled</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rituximab</td>
<td>Tak et al</td>
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<td>443</td>
<td>−0.46 (−0.65 to −0.28)</td>
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<td></td>
<td>Cohen et al</td>
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<td></td>
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<td>−0.44 (−0.58 to −0.30)</td>
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<td>Etanercept</td>
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<td></td>
<td>Klareskog et al</td>
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<td>430</td>
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<td></td>
<td>Pooled</td>
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<td>−0.37 (−0.50 to −0.23)</td>
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<tr>
<td>Certolizumab pegol</td>
<td>Smolen et al</td>
<td>24 weeks</td>
<td>373</td>
<td>−0.29 (−0.51 to −0.08)</td>
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<td>Abatacept</td>
<td>Kremer et al</td>
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<td>586</td>
<td>−0.21 (−0.39 to −0.04)</td>
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<td></td>
<td>Westhovens et al</td>
<td>12 months</td>
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<td>−0.33 (−0.51 to −0.14)</td>
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<tr>
<td></td>
<td>Pooled</td>
<td></td>
<td></td>
<td>−0.26 (−0.39 to −0.14)</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Emery et al</td>
<td>12 months</td>
<td>541</td>
<td>−0.09 (−0.26 to +0.08)</td>
</tr>
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</table>

Figure 2. bDMARD plus MTX vs MTX alone for total X-ray score. Increasingly lower percentages of patients are progressing in terms of radiographic damage, arguably because RA treatments have improved over time. In their analysis of the odds of progression of radiographic damage ranked by effect size, Prof. Jones and colleagues found that 83% of the placebo plus MTX arm in the infliximab trial progressed, whereas in the more recent tocilizumab LITHE trial, just 33% of the placebo arm did so (see Fig. 3 on p. 3). The only odds ratio failing to show significance is that for abatacept (although it is trending in the right direction), while golimumab is significant. The results are driven by the few outliers (as most patients are not experiencing change in X-ray scores over time).
Abatacept  
Golimumab  
Rituximab  
Adalimumab  

Week 24 in patients with active, longstanding RA who had an inadequate response to anti-TNF therapy. Four biologic combination trials all TNF failure trials: they can be categorised as TNF failure, TNF discontinued due to side effects, and inability to afford anti-TNF therapy. Four biologic combination trials all TNF failure trials: they can be categorised as TNF failure, TNF discontinued due to side effects, and inability to afford anti-TNF therapy. All other reasons cited for transferring probably lack justification.

Confronted with secondary failure in a patient who has responded well to a first TNF inhibitor monotherapy for out to 5 years and illustrate three key points:

1. Remission with tocilizumab does not peak early. Remission rates appear to peak at around 1 to 2 years and all of the long-term data support this phenomenon.
2. In both AMBITION45 and SATORI, tocilizumab was significantly superior to MTX and particularly so in SATORI, which Prof. Jones explained is due to the low maximum dose of MTX in Japan (8 mg/week) based on the registration trials.
3. In Australia, etanercept, adalimumab and tocilizumab have been approved as monotherapy, whereas abatacept and rituximab have to be given with MTX.

In their examination of the effect of bDMARD monotherapy on X-ray progression, Prof. Jones and colleagues report an SMD value of –0.43 for tocilizumab monotherapy, which is superior to the SMD for adalimumab in combination with MTX (–0.44) in PREMIER, while SMD values for etanercept and adalimumab monotherapies were about half that for tocilizumab (–0.26 and –0.23, respectively) and golimumab monotherapy was ineffective with an SMD of only –0.03.17 Thus, monotherapy with tocilizumab appears to be effective for disease control and slowing disease progression.

Several tocilizumab monotherapy studies have shown clinical and radiographic benefit: CHARISMA,14 SATORI,15,16 SAMURAI18 and STREAM19 (LTE study). The results from STREAM cover tocilizumab monotherapy for out to 5 years and illustrate three key points:

1. Firstly, remission with tocilizumab does not peak early. Remission rates appear to peak at around 1 to 2 years and all of the long-term data support this phenomenon.
2. Secondly, the response is durable over time and the data are not biased by dropouts due to lack of efficacy. Only 1 of 143 patients withdrew as a result of an unsatisfactory response.
3. Finally, 87% of patients reduced and 31% stopped prednisolone.
The aim of the multicentre phase III AMBITION study was to evaluate the efficacy and safety of tocilizumab monotherapy versus MTX monotherapy in patients with active RA who had not previously failed MTX/biologics treatment. At Week 24, DAS28 remission was achieved by 12% of MTX recipients and by 34% of the tocilizumab group (OR 5.8; 95% CI 3.3 to 10.4). Furthermore, remission rates increased over time with tocilizumab; among 234 tocilizumab monotherapy recipients who entered a long-term extension study, 50% achieved remission at 60 weeks.

Therapeutic responses with tocilizumab were faster than with those with MTX, with a significantly higher mean number of swollen joints, a higher mean Health Assessment Questionnaire-Disability Index (HAQ-DI) score, higher mean haemoglobin level and higher mean FACIT-Fatigue score at 2 weeks. A total of 3986 patients were classified as either inadequate responders to DMARD-IR patients, inadequate responders to anti-TNF (TNF-IR) patients, or as monotherapy patients who had not failed MTX. Data were collected for up to 180 weeks. Clinically significant improvements in ACR50 values were achieved with tocilizumab treatment in all groups at week 96. Notably, the monotherapy group appeared to do better than either of the other two groups, but Prof. Jones pointed out that one reason for the better outcomes might be because disease duration was shorter in the AMBITION study than in the other studies. Importantly, the pooled data analysis also showed that at Week 96 in the AMBITION study, 40.4% of patients had no swollen joint counts and 55% had ≤1.

Pooled data from several randomised, controlled studies of tocilizumab, as well as long-term, open-label extension studies in the treatment of RA reveal that ACR50 response rates, with or without concomitant DMARDs, were maintained or continued to improve with increasing duration of treatment, as shown in Figure 4. A total of 3986 patients were classified as either inadequate responders to DMARD-IR patients, inadequate responders to anti-TNF (TNF-IR) patients, or as monotherapy patients who had not failed MTX. Data were collected for up to 180 weeks. Clinically significant improvements in ACR50 values were achieved with tocilizumab treatment in all groups at week 96. Notably, the monotherapy group appeared to do better than either of the other two groups, but Prof. Jones pointed out that one reason for the better outcomes might be because disease duration was shorter in the AMBITION study than in the other studies. Importantly, the pooled data analysis also showed that at Week 96 in the AMBITION study, 40.4% of patients had no swollen joint counts and 55% had ≤1.

Some evidence indicates that it is possible to predict clinical response to tocilizumab. In an analysis of DAS28 remission rates in AMBITION at Week 24 by previous exposure to MTX or DMARDs, prior exposure was found to have no effect, whereas duration of disease did make a difference: in patients with disease duration <2 years, the frequency of DAS28 remission was higher compared to patients with disease duration ≥2 years (42% vs 28%; corresponding values for MTX groups were 18% and 7%, respectively). Clearly, tocilizumab has greater effect in early disease. Autoantibody status did not greatly affect response in AMBITION, with 73% of patients in the RF-positive tocilizumab group and 64% of the RF-negative group achieving ACR20 status (corresponding values for RF-positive and RF-negative MTX groups were 57% and 37%, respectively). The magnitude of benefit appeared greater in the seronegative arm, primarily due to MTX being much less effective. In a pooled analysis of data from all five phase III tocilizumab trials, the higher the CRP values at baseline, the greater the likelihood of response. Approximately 30% of patients in the lowest CRP quartile (<0.68 mg/dL) and approximately 45% of patients in the highest CRP quartile (≥3.21 mg/dL) achieved ACR50. This finding reflects the clinical experience of Prof. Jones, whereby of all 50 patients he has treated with tocilizumab, the only treatment failure has been a patient with CRP <10. ACT-RAY recruited patients with inadequate response to MTX and randomised them to receive add-on tocilizumab or switch to tocilizumab monotherapy. It should be noted that after Week 24, open-label DMARD (excluding MTX) use was permitted in patients with moderate-to-high disease activity in both arms; approximately a third of patients in both the monotherapy and combination arms took this option. Several between-group comparisons failed to show clinically relevant superiority of the combination strategy over the switch to tocilizumab monotherapy strategy and the switch group did not do as well as the combination arm, although the between-group differences only differed numerically, not statistically. While both treatment strategies showed a highly clinical treatment effect in DAS28-ESR remission rates at Week 24, the superiority of the add-on arm could not be demonstrated: DAS28 <2.6 was achieved by 40.4% of patients in the add-on arm vs 34.8% of the monotherapy arm (p=0.09). The only statistically significant difference between arms was seen for LDA (low disease activity state; DAS28 <≤3.2) in favour of add-on (61.7% vs 51.4%; p=0.029; Δ 10.3%). This cessation of MTX had no effect upon radiographic progression in ACT-RAY, which was characterised by low rates in both groups that did not differ significantly as assessed by Genant-Sharp score progression up to 1 year. Reassuringly, a pooled analysis of several thousand patients from OPTION, TOWARD, RADIATE and AMBITION who were treated with tocilizumab for up to 1.5 years found no reports of clinical liver dysfunction and an incidence rate of serious infections including tuberculosis (TB) of just 3.9 per 100 patient-years associated with tocilizumab 8 mg/kg. In addition, neutrophil count <1x10^9/L during treatment occurred in only 3.7% of all patients (OR 0.7; 95% CI 0.2 to 2.3; p=NS). Thus, patients were less likely to acquire infections when they dropped in neutrophil count. Prof. Jones believes this phenomenon illustrates a process of margination, whereby during tocilizumab treatment, neutrophils marginate and adhere to the blood vessel wall, so are not detected in circulating blood. The analysis revealed key predictors of risk factors for infection during tocilizumab therapy:

- age bracket; age ≥65 years has double the risk of infection during tocilizumab therapy (OR 5.3; 95% CI 1.9 to 13.5).
- diabetes (OR 2.0; 95% CI 1.2 to 3.3)
- history of infection (OR 2.2; 95% CI 1.5 to 3.1)
- and baseline corticosteroid use (OR 1.8; 95% CI 1.2 to 2.6).

Consequently, Prof. Jones would be reluctant to prescribe tocilizumab to older, frailter patients on corticosteroids and those with background diabetes. In such cases, he would not regard tocilizumab as the treatment of choice.
After commencing tocilizumab, disease markers have at least one serious adverse event. Between the treatment groups, with 3% in each group reported (p=0.0389); the likelihood of CDAI remission was twice as high in tocilizumab treatment compared to adalimumab (51.5% at 24 weeks compared with adalimumab (10.5%). Tocilizumab was also associated with significantly better rates of DAS28 remission (39.9%) and low disease activity (p<0.0001). Tocilizumab was also associated with a lower rate of serious infections than all of the other biologics (overall p-value = 0.027), although Prof. Jones points out that this result is debatable: much of the trial evidence comes from Eastern Europe, which is associated with high rates of TB (the placebo group had higher rates of TB than in any of the other trials). He suggests that tocilizumab is probably the agent of choice in patients with high infection rates or with current infections.

Response to tocilizumab can be predicted by biomarker. A recent investigation of abatacept in 32 patients with RA showed that patients who had low baseline numbers of CD8+CD28– T cells were over 4 times more likely to achieve remission within 6 months than patients with higher CD8+CD28– T cell levels. The ADACTA trial tested superiority in patients with RA of ≥6 months’ duration who were MTX-intolerant or for whom continued treatment with MTX was inappropriate. Patients were randomised to receive tocilizumab 8 mg/kg IV every 4 weeks or adalimumab 40 mg subcutaneously (SQ) every 2 weeks for 24 weeks. At 24 weeks, the primary endpoint (mean change from baseline in DAS28) was reduced by a significantly greater amount with tocilizumab than with adalimumab (~3.3 vs -1.8; p<0.0001). Tocilizumab was also associated with significantly better rates of DAS28 remission (39.9%) and low disease activity (51.5%) at 24 weeks compared with adalimumab (10.5% and 19.8%, respectively; p<0.0001 for both comparisons). A post-hoc analysis of clinical disease activity index (CDAI) scores at Week 24 revealed remission rates (unadjusted, no control for multiple testing) of 17.2% for tocilizumab and 9.3% for adalimumab (p=0.0389); the likelihood of CDAI remission was twice as high with tocilizumab. Adverse events in ADACTA were very similar between the treatment groups, with 3% in each group reported to have at least one serious adverse event.

Conclusions

Most bDMARDs have equivalent efficacy.

- Anti-TNFs work best when combined with MTX, even though three are approved as monotherapy.
- Tocilizumab is the best option as monotherapy (e.g. when MTX intolerance is present) and works best when the CRP is raised.
- MabThera works best when seropositive disease is present.
- Abatacept (or MabThera) seems the best option in cases at high risk of infection.
- The drug of choice in those with a cancer history is uncertain, but best data probably favour MabThera.
- The biomarker data have been disappointing, but T cell subsets may predict response to abatacept.

Case 1:
- 41-year-old male
- Married, keen squash player in excellent health
- Six-month history severe RA involving hands, feet, knees and elbows
- Swollen joint count (SJC) 48
- RF 560, CCP 230, ESR 125, CRP 131
- Intolerant and only partially responsive to steroid injections, MTX and leflunomide. At 6 months’ follow-up, SJC was 60 and CRP >100.

**Treatment of choice: tocilizumab 8 mg/kg.** After commencing tocilizumab, disease markers showed improvement and by 9 months, SJC = 0. He remains on tocilizumab at 2 years.

Case 2:
- 79-year-old retired clerical worker
- PMH ex-smoker, IHD, Sjögren’s syndrome, abdominal aortic aneurysm
- Seropositive RA since his early sixties
- On prednisone and MTX since diagnosis
- No response to plaquenil and SASP
- Commenced leflunomide in 2001
- Adalimumab added in 2004 with good effect but ceased after life-threatening sepsis
- Recurrent episodes of sepsis also led to cessation of leflunomide and MTX, resulting in marked worsening of joints
- MTX recommenced at 5 mg per week in late 2006

**Treatment of choice: abatacept IV or SC plus MTX or MabThera plus MTX, with third choice being gold injections.**

Case 3:
- 25-year-old female with seropositive RA since age 16
- Partial response to etanercept after failing MTX 25 mg/week SC and plaquenil (SJC reduces from 35 to 15)
- Swapped to adalimumab with similar partial response (SJC 10, CRP 42)

**Treatment of choice: tocilizumab.**

Case 4:
- 59-year-old female with seropositive RA since age 38 referred to you for the first time
- Has only ever been treated with natural therapy and prednisolone in doses from 5 mg increasing to 15 mg during frequent flares as GP says nothing else works or is too toxic to use
- Widespread deformity typical of longstanding RA. Severe secondary OA of R knee, both hips and flexion deformities of elbows with evidence of extensor tendon rupture at the wrist
- Mild synovitis
- ESR 56, CRP 1

**Treatment of choice: etanercept monotherapy.**
References


