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The rational use of biologics in rheumatoid arthritis

Making Education Easy

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Dr Jones attended Sydney University, graduating with first-class honours in Medicine in 1985. He then did training in Internal Medicine and Rheumatology in Sydney and Newcastle. He became a fellow of the Royal Australasian College of Physicians in 1991. While at Newcastle he also did a Masters degree in Clinical Epidemiology. He then moved to the Garvan Institute in Sydney, where he completed a doctorate in Osteoporosis Epidemiology in 1994. He is also a fellow of the Australian faculty of Public Health Medicine. Since 1995 he has been in Hobart, Tasmania, where he combines clinical practice and research. He is currently Professor of Rheumatology and Epidemiology and Head of the Musculoskeletal Unit at the Menzies Research Institute as well as Head of the Department of Rheumatology at Royal Hobart Hospital. An NHMRC Practitioner Fellowship funds his position. He is also the current Medical Director of the Arthritis Foundation of Australia. He has received grants from competitive and non-competitive sources totalling over $12 million dollars and has published >240 articles, primarily on the epidemiology of osteoporosis and osteoarthritis.

In more recent years he has concentrated on both industry-sponsored and investigator-initiated clinical trials. He has received awards and given numerous oral presentations at the annual scientific meetings of the American Society for Bone and Mineral Research, the American College of Rheumatology, OARSI and EULAR. His current research interests are the development of peak bone mass and fracture aetiology in children, genetic and environmental risk factors for osteoarthritis, health promotion, the role of environmental factors such as diet and physical activity in osteoporosis and fractures in the elderly, clinical trials and meta-analysis.

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This publication is a summary of a recent presentation by Graeme Jones, Professor of Rheumatology and Epidemiology and Head of the Musculoskeletal Unit at the Menzies Research Institute, and Head of the Department of Rheumatology at Royal Hobart Hospital, Australia. He addressed rheumatologists, rheumatology nurse specialists and other health professionals in Wellington, Dunedin and Auckland, from 16–18 October 2012 on the uptake of biologics in the treatment of rheumatoid arthritis.

Treatment milestones in rheumatoid arthritis

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).[1] By the late 1980s, MTX was commonly used in the management of RA.[2] 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.

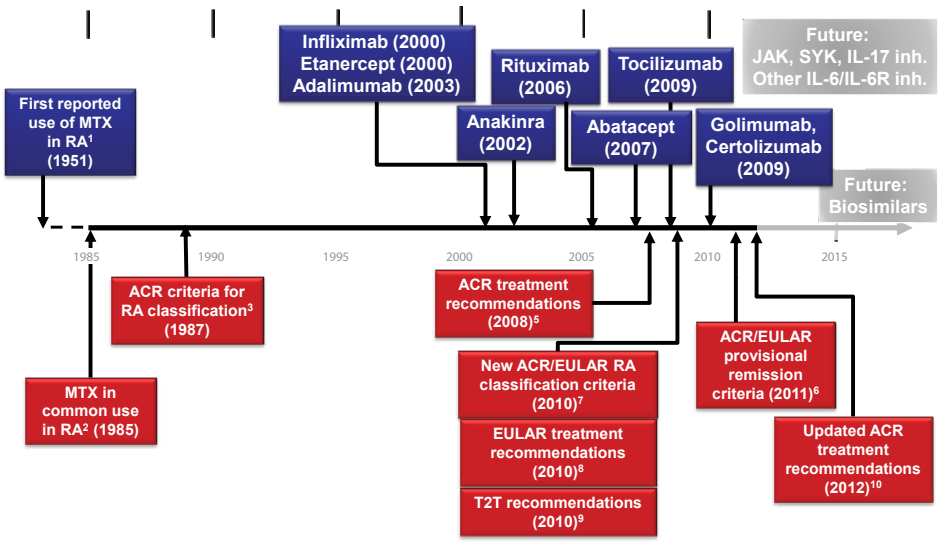


Figure 1. RA treatment milestones.[1-10]

Prof. Jones considers the 2010 American College of Rheumatology/European League Against Rheumatism (ACR-EULAR)[7] classification criteria for RA to be a marked improvement upon the 1987 ACR criteria.[3] 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.[11] 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

the exception of auranofin (p=0.06) and the infliximab-MTX comparison (p=0.07). Notably, IL-1RA was almost as effective as auranofin in terms of disease modification, but IL-1RA is no longer available in the Australian market. Other agents, including pamidronate, chloroquine, hydroxychloroquine (HCQ), minocycline and cyclophosphamide did not reach statistical significance in either outcome measure.

MTX remains part of the first treatment strategy in patients with moderate-to-severe RA.[8] In the belief that starting MTX at 10 mg per week is too conservative, Prof. Jones initiates patients on subcutaneous (SC) MTX 25 mg weekly for the first 8 weeks.

Australian regulations mandate a 6-month delay from the time of patient consultation to initial treatment with a bDMARD. Patients must first undergo intensive therapy with ≥2 DMARDs (preferably MTX) selected from an approved list: MTX, HCQ, leflunomide, sulfasalazine, azathioprine, cyclosporin, myocrisin and auranofin. Prof. Jones describes this list as interesting, considering that HCQ is included in the first 4 agents despite proof of its lack of efficacy in RA; azathioprine is also listed, despite no evidence at all for it being effective as a disease-modifier.

The 6-month rule in Australia has recently been validated by clinical trial evidence.[12] MTX plus etanercept and oral triple therapy (MTX plus sulfasalazine plus HCQ) were both superior to MTX monotherapy at 24 weeks. However, patients with moderate disease activity (as determined by a Disease Activity Score in 28 joints using the erythrocyte sedimentation rate [DAS28-ESR] of ≥3.2 at week 24) were stepped up from MTX monotherapy to etanercept after 24 weeks. By 12 months, there were no differences between any of the groups in either disease activity or X-ray progression. Prof. Jones admits that this does not apply to all patients; MTX alone is not greatly effective at preventing damage in patients with a rheumatoid factor (RF) >200, C-reactive protein (CRP) >30 and a swollen joint count >17.

Combination therapy vs MTX alone

Evidence from the DE011 (DMARD-IR)[13] and PREMIER (MTX-naïve)[14] trials demonstrates that adalimumab (ADA) plus MTX combination therapy results in better outcomes compared to ADA alone. In DE011, American College of Rheumatology (ACR) 20 Responder index (ACR20) responses at Week 26 (primary endpoint) were not remarkably better with ADA 40 mg every 2 weeks than with placebo (46% vs 19%; p≤0.001). In PREMIER, ADA was administered at the approved dosage of 40 mg SC every 2 weeks. In that trial, ACR50 responses at Week 52 (co-primary endpoint) were achieved by fewer of the ADA monotherapy group than by those on MTX alone (41% vs 46%); combination therapy with ADA plus MTX was the only group to resemble the 60:40:20 treatment rule for RA, with 62% of those on combination treatment achieving ACR20 by Week 52 (p<0.001 vs ADA alone).

Tumour necrosis factor (TNF) inhibitors may have a greater effect on bone change than they do upon disease activity. In the PREMIER trial, radiographic outcomes were significantly improved by combination ADA plus MTX compared with either ADA or MTX alone: the mean change from baseline in total Sharp score was significantly smaller in the combination treatment arm at both year 1 and year 2 (1.3 and 1.9 Sharp units, respectively; p≤0.002) than in patients in the MTX arm (5.7 and 10.4 Sharp units) or the ADA arm (3.0 and 5.5 Sharp units). Prof. Jones concludes that this evidence demonstrates that patients need to take both a TNF inhibitor plus MTX in order to gain the most benefit.

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).[15]

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 DMARDs (no DMARD; MTX; leflunomide; sulfasalazine; MTX+sulfasalazine; MTX+HCQ; or MTX+sulfasalazine+HCQ) on the persistence with anti-TNF therapies in patients with RA.[16] 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).[17] For a bDMARD in combination with MTX compared 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,[14] 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.[18]

Medication	Reference	Follow-up period	Number	SMD (95% CI)
Infliximab	Lipsky et al	54 weeks	173	**–0.63 (–0.87 to –0.38)**
Adalimumab	Keystone et al	12 months	299	–0.45 (–0.68 to –0.22)
	Breedveld et al	12 months	372	–0.45 (–0.65 to –0.24)
	Pooled			**–0.45 (–0.60 to –0.29)**
Rituximab	Tak et	12 months	443	–0.46 (–0.65 to –0.28)
	Cohen et al	24 months	468	–0.41 (–0.59 to –0.22)
	Pooled			**–0.44 (–0.58 to –0.30)**
Etanercept	Emery et al	12 months	476	–0.37 (–0.55 to –0.19)
	Klareskog et al	12 months	430	–0.36 (–0.55 to –0.17)
	Pooled			**–0.37 (–0.50 to –0.23)**
Certolizumab pegol	Smolen et al	24 weeks	373	**–0.29 (–0.51 to –0.08)**
Abatacept	Kremer et al	12 months	586	–0.21 (–0.39 to –0.04)
	Westhovens et al	12 months	459	–0.33 (–0.51 to –0.14)
	Pooled			**–0.26 (–0.39 to –0.14)**
Golimumab	Emery et al	12 months	541	**–0.09 (–0.26 to +0.08)**

Figure 2. bDMARD plus MTX vs MTX alone for total X-ray score.[17]

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,[19] just 33% of the placebo arm did so (see Fig. 3 on p. 3).[17] 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).

Agent	Trial	Treatment*	Placebo*	OR (95% CI)
Infliximab	Breedveld et al	24%	83%	0.07 (0.02 to 0.29)
	Lipsky et al	11%	31%	0.26 (0.14 to 0.50)
	Pooled			**0.19 (0.09 to 0.41)**
Etanercept	Klareskog et al	20%	41%	0.34 (0.21 to 0.54)
	Emery et al	20%	41%	0.36 (0.13 to 0.56)
	Pooled			**0.35 (0.26 to 0.47)**
Tocilizumab	Kremer et al	16%	33%	0.39 (0.25 to 0.62)
Adalimumab	Breedveld et al	36%	63%	0.33 (0.22 to 0.51)
	Keystone et al	38%	54%	0.52 (0.33 to 0.83)
	Pooled			**0.41 (0.27 to 0.64)**
Certolizumab pegol	Keystone et al	31%	48%	0.48 (0.34 to 0.69)
	Keystone et al	26%	41%	0.51 (0.35 to 0.75)
	Pooled			**0.50 (0.38 to 0.64)**
Rituximab	Cohen et al	43%	61%	0.48 (0.33 to 0.71)
	Tak et al	36%	47%	0.64 (0.44 to 0.93)
	Pooled			**0.57 (0.43 to 0.76)**
Golimumab	Emery et al	31%	40%	0.64 (0.44 to 0.94)
Abatacept	Westhovens et al	39%	47%	0.71 (0.49 to 1.03)

Note: *Treatment refers to bDMARD plus MTX while placebo refers to the MTX plus placebo group.

Figure 3. Odds of progression of radiographic damage ranked by effect size: therapy plus MTX vs MTX alone.[17]

Limited DMARD data are available apart from combined with MTX. A post-hoc analysis of the phase IIIb REALISTIC trial, involving the TNF inhibitor certolizumab pegol with MTX, reveals similar and significant ACR20 responses at Week 12 with all certolizumab pegol subgroups regardless of concomitant DMARD use at baseline.[20] In this trial, patients with active RA that had failed to respond to ≥1 DMARD were randomised to certolizumab pegol (400 mg at Weeks 0, 2 and 4, followed by 200 mg every 2 weeks) or placebo (every 2 weeks) plus current therapy stratified by previous TNF inhibitor use, concomitant MTX use and disease duration (<2 vs ≥2 years). Addition of certolizumab pegol to current therapy (MTX, sulfasalazine, or leflunomide) was associated with a significantly more rapid clinical response that was consistent in all strata, and resulted in improved function and reduced disease activity, compared with control groups. Interestingly, this published post-hoc analysis omits a fourth comparison from the trial showing that the addition of certolizumab pegol to HCQ is of no value.

bDMARD cycling

No good trial data exist as to cycling between adalimumab and etanercept; only registry data are available. In practice, Prof. Jones will only cycle from either agent to the other when confronted with secondary failure in a patient who has responded well to a first TNF inhibitor and has lost clinical response at a later time. Such cases make sense to transfer to another anti-TNF. All other reasons cited for transferring probably lack justification.

ACR50 response at Week 24 in biologic combination trials

A number of trials have evaluated post-TNF failure, but strictly speaking these are not 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 have reported significant and clinically meaningful improvements in ACR50 response at Week 24 in patients with active, longstanding RA who had an inadequate response to ≥1 anti-TNF therapies:

- Golimumab + MTX vs placebo + MTX[21]
- Abatacept 10 mg/kg + MTX vs placebo + MTX (phase III ATTAIN trial)[22]
- Rituximab 1g + MTX vs placebo + MTX (phase III REFLEX trial)[23]
- Tocilizumab 8 mg/kg + MTX vs placebo + MTX (phase III RADIATE study)[24]

Among all four trials, the highest ACR50 response was seen with tocilizumab and the lowest response with the placebo arm in that same study, although tocilizumab was not significantly better than the other biologics.

The REALISTIC trial investigators assessed DAS28 (CRP) change at Week 12 by prior TNF use.[20] The analyses found that certolizumab pegol ± DMARD(s) was superior to placebo ± DMARD(s) irrespective of prior anti-TNF use.

Results from the RADIATE trial are notable for their constancy of remission rate, in that patients responded regardless of the number of failed TNF antagonists.[24,25] DAS28 remission (DAS28 <2.6) rates at week 24 were 30.9%, 31.4% and 25.0% in tocilizumab 8 mg/kg recipients refractory to one anti-TNF, two anti-TNFs and three anti-TNFs, respectively. In particular, of the patients who had failed three prior anti-TNFs, DAS28 remission rates were 0.0% in both the tocilizumab 4 mg/kg and placebo groups. In Prof. Jones' opinion, these outcomes endorse tocilizumab as the primary drug of choice in primary TNF failures.

How to choose which treatment to use?

The REFLEX study has provided evidence of ACR responses at 24 weeks in anti-TNF inadequate responders: rituximab was effective in both rheumatoid factor (RF)-positive and RF-negative patients, but was clearly better in the RF-positive cohort.[26] No CCP data are available.

How best to treat those patients who are unable to use MTX? When surveyed by Prof. Jones, rheumatologists worldwide claim that only 10% of their patients are on monotherapy with anti-TNFs. However, registry data have shown that around one-third of biologic-treated RA patients are receiving the biologic as monotherapy in Europe, the USA and Australia.[16,27-34] Prof. Jones noted that these figures assume patients fill their MTX scripts. Some study data indicate that a number of patients never fill their MTX scripts and Prof. Jones also suspects that many patients are not taking their MTX if there is no increase in mean corpuscular volume.

A comparison of 17 bDMARD monotherapy clinical trials investigated ACR20 responses in four groups of patients: placebo-, MTX-, sulfasalazine- and biologic-treated patients:[35-43]

- Etanercept was not significantly superior to MTX in ERA[36] or TEMPO,[15] but was significantly better than sulfasalazine (Etanercept Study 309 Investigators)[37] and placebo (Moreland, 1999)[38]
- Adalimumab was superior to placebo (DE011)[13] but not to MTX in PREMIER[14]
- Certolizumab pegol has proven superior to placebo[39] (no MTX comparisons exist)
- Golimumab was not significantly different to MTX in GO-BEFORE[18] or GO-FORWARD[18]
- In both AMBITION[40] and SATORI,[41] 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.
- 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.

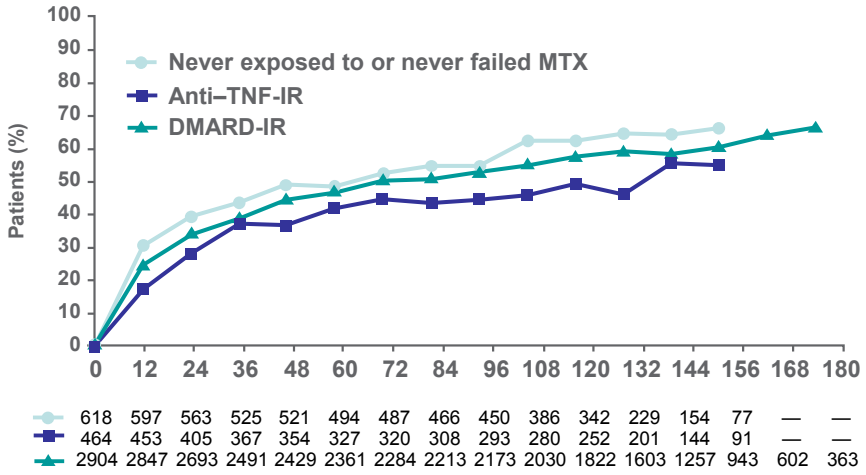
Several tocilizumab monotherapy studies have shown clinical and radiographic benefit: CHARISMA,[44] SATORI,[41,45] SAMURAI[46] and STREAM[47] (LTE study). The results from STREAM cover tocilizumab monotherapy for out to 5 years and illustrate three key points:

- 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.
- 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.
- 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.[40] At Week 24, DAS28 remission was achieved by 12% of MTX recipients and by 34% of the tocilizumab group (OR 5.8; 95% 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.[48]

Therapeutic responses with tocilizumab were faster than 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.[40,48-50]

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.[51] 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.



For TJC and SJC, LOCF was used for individual assessment; the total joint count used data available (not LOCF). No imputation was made for missing HAQ-DI score, CRP, ESR, or VAS assessment. Patients without the required data at a specific time were excluded from the summary statistics at that time.

Figure 4. ACR50 response over time.[51]

Is it possible to predict tocilizumab response?

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,[52] 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).[53,54] 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).[55] 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.[56] Approximately 30% of patients in the lowest CRP quartile (<0.68 mg/dL) and approximately 45% of patients in the highest pre-treatment CRP category (>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.[57] 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 LDAS (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.[58] 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 developing a serious infection (OR 1.9; 95% CI 1.3 to 2.9)
- 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, frailer patients on corticosteroids and those with background diabetes. In such cases, he would not regard tocilizumab as the treatment of choice.

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Head-to-head comparative data

Encouragingly, head-to-head clinical trial evidence exists, allowing for direct comparisons. The phase III AMPLE study data are interesting, revealing that abatacept is comparable to anti-TNF therapy (adalimumab in AMPLE) in efficacy (by non-inferiority analysis) with similar kinetics of response and inhibition of radiographic progression at one year.[59] Notably, over the first month, abatacept was a little faster than adalimumab in ACR20, 50 and 70 responses, and very similar thereafter at all timepoints. Serious infection rates were 2.2% with abatacept and 2.7% with adalimumab at one year. Importantly, a Cochrane network meta-analysis demonstrates that abatacept is 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).[60] He suggests that abatacept is probably the agent of choice in patients with high infection rates or with current infections.

Response to abatacept 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.[61]

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.[62] Patients were randomised to receive tocilizumab 8 mg/kg IV every 4 weeks or adalimumab 40 mg subcutaneously (SC) 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.

RA vignettes

Case 1:

- 41-year-old male
- Married farmer, 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

2007 – 2008:

- Joints reasonable on prednisolone, MTX and etanercept but ESR and CRP remained high, requiring steroid bursts to meet continuing PBS criteria for anti-TNF therapy
- Repeated febrile episodes, including lobar pneumonia with three hospital admissions
- ANA and DNA negative
- MTX stopped but prednisolone and etanercept continued
- Joints clinically worse but patient 'felt better'

May 2009:

- Polyarticular flare on etanercept and prednisolone 10 mg daily
- SJC 30
- ESR 85, CRP 62

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 (SCJ 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.

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