CLINICAL INVESTIGATION

Biologic monotherapy for the treatment of rheumatoid arthritis

Clin. Invest. (2011) 1(9), 1291–1300

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Methotrexate monotherapy for rheumatoid arthritis is considered efficacious and safe, but an inadequate treatment response and intolerance are common. Patients unresponsive to methotrexate or other disease-modifying antirheumatic drugs may receive biologic disease-modifying antirheumatic drugs (bDMARDs) as monotherapy, or in combination with methotrexate. Of the 17 bDMARD monotherapy clinical trials reviewed here, studies with tocilizumab consistently demonstrated superiority over methotrexate for clinical signs, symptoms and radiographic progression. Evidence for clinical outcomes with anti-TNF agents is less consistent, although adalimumab and etanercept slow radiographic progression. Evidence for other bDMARDs is limited, but rituximab and abatacept may have clinical efficacy. In conclusion, available data suggest tocilizumab is the treatment of choice where methotrexate is considered unsuitable as a co-therapy.

Keywords: abatacept • adalimumab • biologic • etanercept • golimumab • methotrexate • monotherapy • rheumatoid arthritis • rituximab • tocilizumab

Rheumatoid arthritis (RA) is a chronic systemic inflammatory condition characterized by joint pain, stiffness and swelling due to synovial inflammation and effusion, and can lead to destruction of joints resulting in disability. The American College of Rheumatology (ACR) and The European League Against Rheumatism guidelines for the treatment of RA recommend methotrexate (MTX) as first-line monotherapy, or in combination with other disease-modifying antirheumatic drugs (DMARDs) [1,2]. For those patients who do not respond to MTX or other DMARDs (sequentially or in combination), adding a biologic DMARD (bDMARD) to the treatment regimen is typically considered as the next step.

Methotrexate is considered the anchor drug in RA, both on the basis of its efficacy and safety as monotherapy, as well as its ability to increase the efficacy of bDMARDs when used in combination [3]. It is also often used in combination with other nonbiologic DMARDs. MTX may also provide survival benefit by reducing cardiovascular mortality [4]. However, approximately 10–30% of RA patients are MTX-intolerant and discontinuation is common in clinical practice [4]. The most common adverse effects of MTX are ulcerative stomatitis, leukopenia, nausea and abdominal distress [5]. For those patients who require treatment with a bDMARD and cannot tolerate MTX, combination therapy with other DMARDs or biological monotherapy is necessary. Moreover, in a growing culture of polypharmacy, the need for biologic monotherapy options may be important for RA patients who are also receiving treatment for other conditions such as osteoporosis or cardiovascular disease.

The aim of this paper is to review the evidence for efficacy of bDMARD monotherapy in RA. A literature search for clinical trial data on biologic monotherapy in RA published between 1990 and April 2011 was conducted using PubMed.

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The following search terms were used: rheumatoid arthritis, biologic, monotherapy, disease-modifying antirheumatic drugs, DMARDs, anti-TNF inhibitor, interleukin inhibitor, T-cell inhibitor, B-cell inhibitor, etanercept, adalimumab, certolizumab pegol, golimumab, anakinra, abatacept, tocilizumab and rituximab. Included studies were limited to clinical trials only, and no head-to-head studies between bDMARD monotherapy were identified. Titles and abstracts of all identified references were screened. Articles that clearly did not address the search terms were excluded and selected articles were reviewed in full. Where possible, data for approved doses of the particular product under review were included. The outcomes reported were ACR20, ACR50, ACR70 and 28-joint count Disease Activity Score (DAS28) remission (DAS28 <2.6) rates and change in Sharp scores at either 6 or 12 months (where available). A total of 17 biologic monotherapy clinical

Table 1. Baseline characteristics in trials evaluating monotherapy.

Trial	Biologic	Active comparator	N	Disease duration[†]	DAS	Patient population	Radiographic assessment	Ref.
Moreland *et al.* (1999)	Etanercept	No	234	11–13	N/R	DMARD-IR	No	[8]
ERA	Etanercept	MTX	632	11–12 months	N/R	MTX-naive	Yes	[6,9]
TEMPO	Etanercept	MTX	686	6.3–6.8	5.5–5.7[‡]	DMARD-IR	Yes	[10,11]
COMET	Etanercept	MTX	398	8.8–9.3 months	5.0–6.5[§]	MTX-naive + TNFi-naive	Yes	[13]
The Etanercept Study 309 Investigators	Etanercept	SSZ	260	5.6–7.1	5.0–5.2[§]	SSZ-IR + TNFi-naive	No	[7]
van de Putte *et al.* (2004)	Adalimumab	No	544	9.3–11.9	7.02–7.09[§]	DMARD-IR	No	[17]
PREMIER	Adalimumab	MTX	799	0.7–0.8	6.3–6.4[§]	MTX-naive	Yes	[18]
FAST4WARD	Certolizumab pegol	No	220	8.7–10.4	6.3[¶]	DMARD-IR	No	[19]
GO-BEFORE	Golimumab	MTX	637	2.9–4.1	6.2–6.3[§]	MTX-naive	Yes	[21,41]
GO-FORWARD	Golimumab	MTX	444	4.5–6.7	5.9–6.1[§]	MTX-IR	Yes	[22,41]
AMBITION	Tocilizumab	MTX	673	6.2–6.4	6.8[¶]	MTX-naive/free + TNFi-naive/free	No	[28]
SAMURAI	Tocilizumab	DMARDs	302	2.2–2.4	6.5[§]	DMARD-IR	Yes	[29]
SATORI	Tocilizumab	MTX	125	8.5–8.7	6.1–6.2[§]	MTX-IR	No	[30,31]
Bresnihan *et al.* (1998)	Anakinra	No	472	3.7–4.3	N/R	DMARD-IR	Yes	[33]
Moreland *et al.* (2002)	Abatacept	No	214	10.6–13.0	N/R	DMARD-IR	No	[36]
ARRIVE	Abatacept	No	1046[#]	11.6	6.2[††]	TNF-IR	No	[37]
Edwards *et al.* (2004)	Rituximab	MTX	161	9–12	6.8–6.9[‡‡]	MTX-IR	No	[39]

[†]Values are years except where indicated.
[‡]DAS.
[§]DAS in 28 Joints (DAS 28).
[¶]DAS28 assessed using erythrocyte sedimentation rate.
[#]n = 43 in open-label monotherapy substudy.
[††]DAS28 assessed using C-reactive protein.
[‡‡]DAS28 and patient self-assessment of disease activity substudy.
DAS: Disease activity score; DMARD: Disease-modifying antirheumatic drug; IR: Inadequate response; MTX: Methotrexate; SSZ: Sulfasalazine; TNFi: Anti-TNF agent.

trials in RA were identified; a summary of the study drugs, patient characteristics and end points assessed is provided in **Table 1**. The patient populations varied widely with respect to disease duration and outcomes measured, but all studies included subjects with active disease.

Antitumour necrosis factor agents

■ Etanercept

Etanercept is approved for use as monotherapy in patients with active RA [6]. Compared with placebo and sulfasalazine monotherapy in different trials, etanercept was superior in all clinical outcomes reported, including ACR scores and the DAS28 [7,8]. However, etanercept (25 mg twice weekly) appeared to show similar clinical outcomes to MTX monotherapy (17–19 mg/week) at 6 months with respect to clinical outcomes in both the ERA and TEMPO studies [9,10], although it was superior to MTX at earlier timepoints in the ERA study **(Figures 1–3)** [6,9].

In the ERA study, the primary efficacy end point was numeric ACR area under the curve (ACR-N AUC) at 6 months, which represents the cumulative response over time. At 3, 6, 9 and 12 months, patients in the etanercept group had significantly greater AUCs for ACR-N than patients in the MTX (group $p < 0.05$ at all time points) [9]. However, this was due to an earlier response in the etanercept group. By 6 months, separation between etanercept and MTX was apparent only for ACR70 ($p < 0.05$) but not ACR20 or ACR50. Thereafter, responses were similar between the two groups and differences were not significant at 12 months [9].

In the TEMPO study, there was no statistically significant difference in ACR20, ACR50 or ACR70 responses at week 24 between the etanercept monotherapy and MTX monotherapy **(Figures 1–3)** groups [6,10]. Similarly, no differences in DAS28 remission (DAS28 < 2.6) between monotherapy groups were observed at week 24 **(Figure 4)** [11].

The COMET study compared etanercept in combination with MTX versus MTX monotherapy during the first year, and then etanercept monotherapy was investigated in the second year [12,13]. Removing MTX resulted in a decrease in clinical and radiographic responses at week 104 compared with etanercept plus MTX. Clinical remission (DAS28 <2.6) at week 104 was achieved by 57 and 50% in the combination and step-down regimens, respectively. Similar results were reported in a 24-week Japanese study that compared the addition of etanercept to MTX with the substitution of etanercept for MTX in patients with active RA and an inadequate response to MTX where the ACR20 response rate was significantly greater in the combination group [14]. In the ADORE study, which compared etanercept monotherapy or

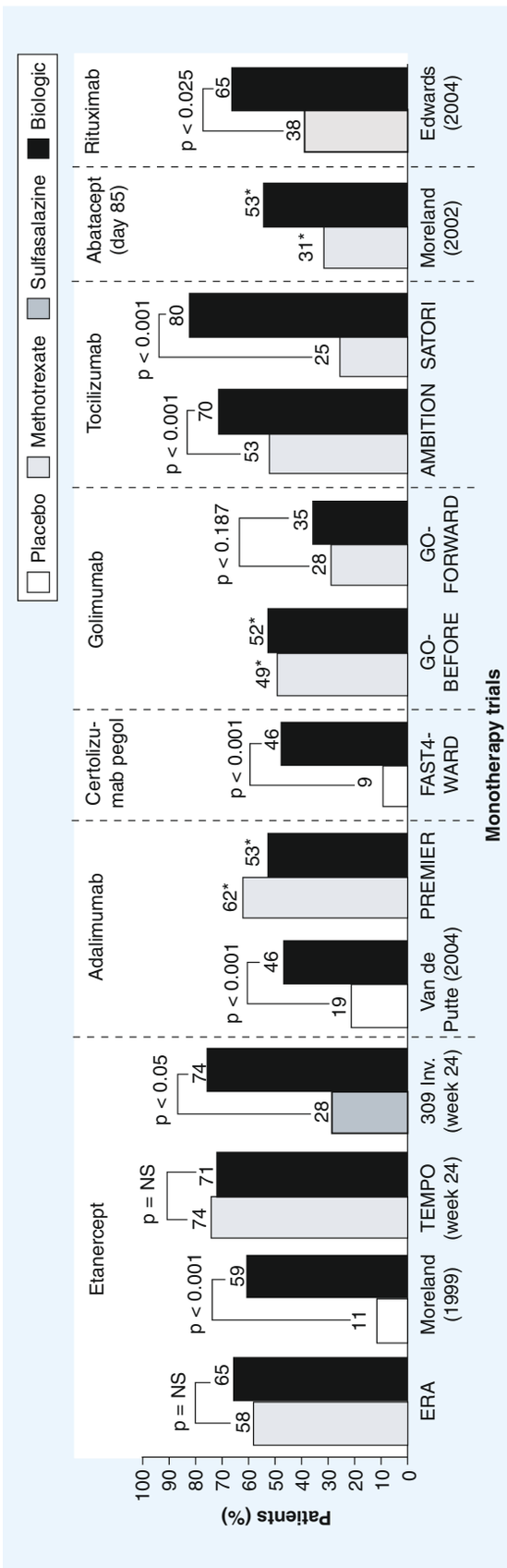

Figure 1. American College of Rheumatology 20% improvement criteria (ACR20) responses at 6 months in monotherapy trials. Results shown are for approved doses with the exception of golimumab (dose shown = 100 mg; approved dose = 50 mg). Abatacept results are at day 85.
*p-value not reported.
Data taken from [7–10,17–19,22,23,28,30,31,36,39].

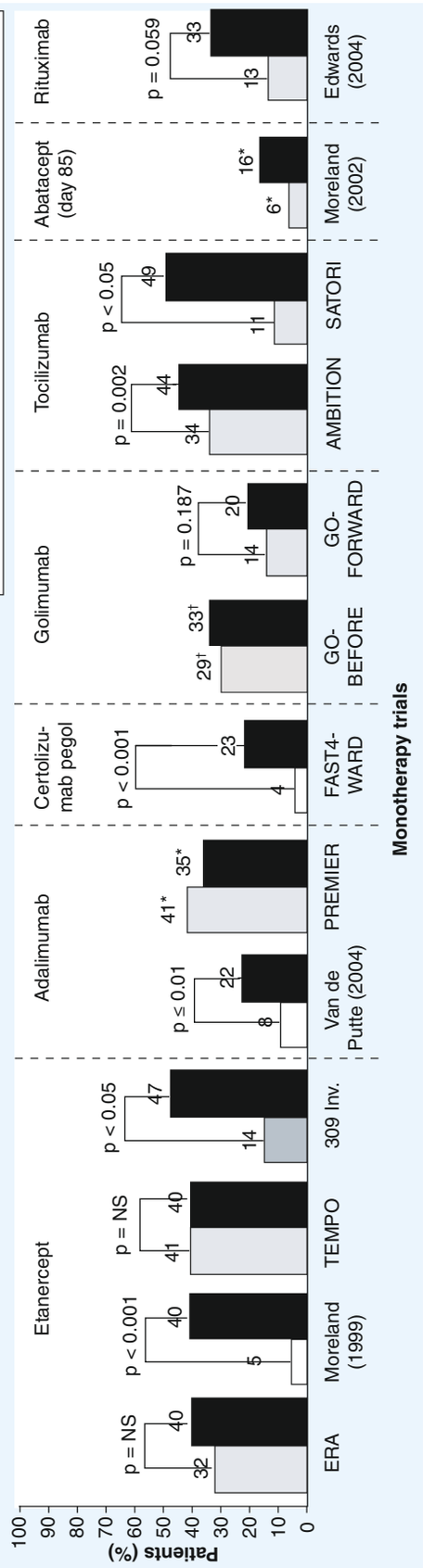

Figure 2. American College of Rheumatology 50% improvement criteria (ACR50) responses at 6 months in monotherapy trials. Results shown are for approved doses with the exception of golimumab (dose shown = 100 mg; approved dose = 50 mg). Abatacept results are at day 85.
*p-value not reported.
†Non-inferiority criterion was met suggesting that response was similar.
Data taken from [7–10,17–19,22,23,28,30,31,36,39].

etanercept plus MTX, ACR20, ACR50 and ACR70 response rates were similar between the two treatment groups at week 16 [15].

■ Adalimumab

Adalimumab is also approved for use as monotherapy for RA [16]. In a placebo-controlled trial, patients receiving adalimumab 40 mg fortnightly demonstrated significantly higher response rates in terms of ACR20 ($p \leq 0.001$), ACR50 and ACR70 (both $p \leq 0.01$) at week 26 [17].

In the PREMIER study, there were three treatment arms: adalimumab as monotherapy, MTX monotherapy, and adalimumab in combination with MTX in patients with active RA for up to 3 years disease duration and with no previous exposure to MTX [18].

MTX monotherapy produced numerically, but not statistically higher, ACR20, ACR50 and ACR70 responses than adalimumab monotherapy at weeks 26 (Figures 1–3), 52, 76 and 104 [16,18]. Clinical remission (DAS28 < 2.6) at week 52 was achieved by 23% of patients in the adalimumab monotherapy group and 21% of patients in the MTX monotherapy group (Figure 4) [18].

■ Certolizumab pegol

Certolizumab pegol is approved as monotherapy and is superior to placebo in terms of ACR responses, but there are no comparative data with MTX (Figures 1–3) [19,20].

■ Golimumab

In both the GO-BEFORE and GO-FORWARD studies [21,22], golimumab monotherapy at a dose of 100 mg (note that the licensed dose is 50 mg once a month in combination with MTX [23]) administered subcutaneously once a month was not superior to MTX monotherapy at any time point (Figures 1–3) [21,22]. However, there was a trend toward a superior DAS28 (assessed using erythrocyte sedimentation rate [ESR]) remission rate at 6 months with golimumab ($p = 0.087$) (Figure 4) [22]. Golimumab is not currently approved for use as a monotherapy in RA, only in combination with MTX [23].

■ Infliximab

Infliximab is only approved in combination with MTX [24,25]. To the best of our knowledge there are no randomized controlled trials comparing infliximab monotherapy with MTX monotherapy.

IL-6 inhibitors

■ Tocilizumab

Tocilizumab is approved for use as monotherapy, at 8 mg/kg given once every 4 weeks, as an intravenous infusion (although the recommended starting dose in

the USA is 4 mg/kg, followed by an increase to 8 mg/kg based on clinical response) [26,27]. There have been three Phase III monotherapy trials to date [28–31]. In all three studies, DAS28 remission with tocilizumab was superior to MTX at 6 and 12 months **(Figure 4)**. The lower remission rates in the MTX arms in the Japanese studies (i.e., SAMURAI and SATORI) compared with AMBITION most likely reflect the lower approved doses of MTX in Japan. ACR20, ACR50 and ACR70 response rates were also superior with tocilizumab in the two studies where they are reported (i.e., SATORI and AMBITION) **(Figures 1–3)**. An increased frequency of abnormal hepatic enzymes has been shown with the combination of MTX and tocilizumab, but liver enzyme elevations are less common with tocilizumab monotherapy than MTX monotherapy [26].

Other bDMARDS

■ Anakinra

Anakinra is currently approved as a monotherapy or in combination with DMARDs at a dose of 100 mg/day administered subcutaneously [30]. Anakinra monotherapy has demonstrated modest clinical efficacy, but not superiority compared with placebo, although the approved dose was not evaluated [32,33].

■ Abatacept

The approved dose of abatacept is 10 mg/kg, administered intravenously at weeks zero, two and four, and every 4 weeks thereafter [34]. The drug is approved for use as monotherapy in the USA, but not in other countries [34,35].

In a Phase II study, the efficacy of different doses of abatacept monotherapy were investigated in DMARD-inadequate response (IR) patients **(Table 1)** [36]. At day 5, ACR20, ACR50 and ACR70 responses were numerically greater with abatacept 10 mg/kg versus placebo, but statistical significance was not reported **(Figures 1–3)** [36].

Although not randomized, ARRIVE was an open-label study of abatacept in patients with an inadequate response to anti-TNF therapy **(Table 1)** [37]. The majority of patients received abatacept in combination with DMARDs. However, a small proportion (n = 43) of the US patients in the trial received abatacept monotherapy. Of the monotherapy patients, 48.8% achieved a clinically meaningful improvement in DAS28 assessed using C-reactive protein (a decrease from baseline of ≥1.2 units), compared with 56.1% of patients receiving abatacept plus background DMARD [37].

■ Rituximab

The recommended dose for rituximab is 1000 mg by intravenous infusion followed by a second 1000 mg intravenous infusion 2 weeks later. The drug is not approved

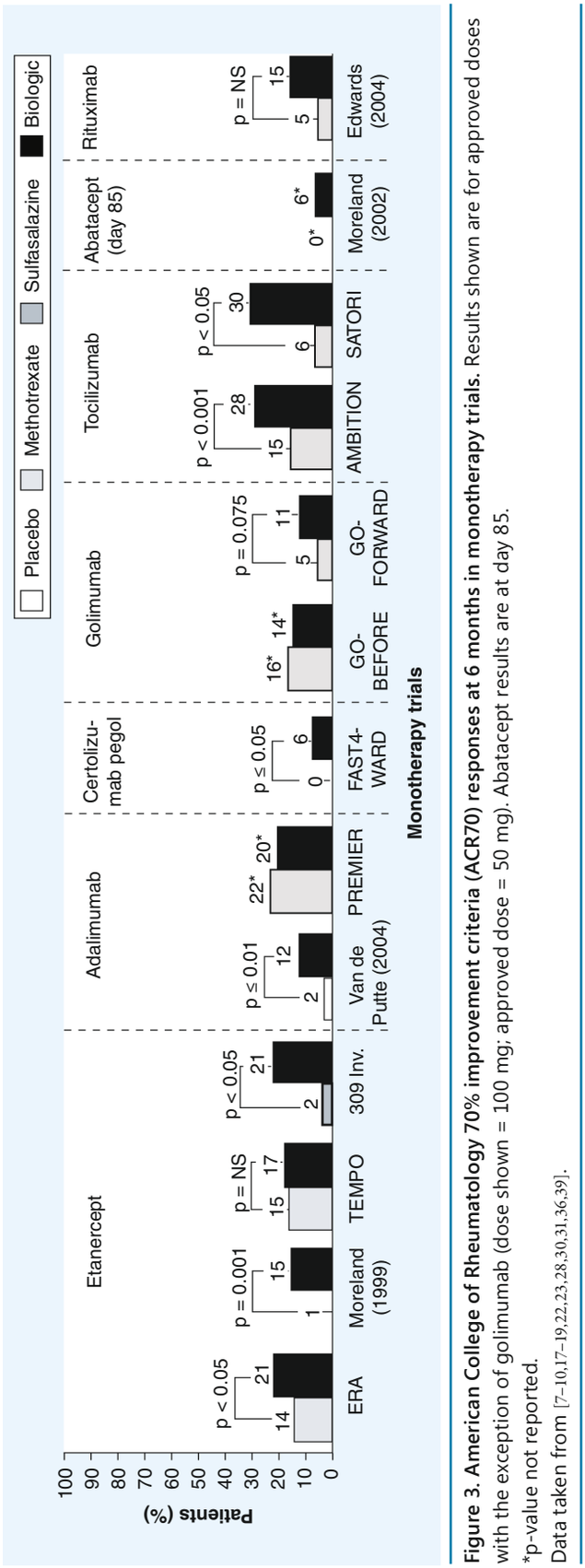

Figure 3. American College of Rheumatology 70% improvement criteria (ACR70) responses at 6 months in monotherapy trials. Results shown are for approved doses with the exception of golimumab (dose shown = 100 mg; approved dose = 50 mg). Abatacept results are at day 85.
*p-value not reported.
Data taken from [7–10,17–19,22,23,28,30,31,36,39].

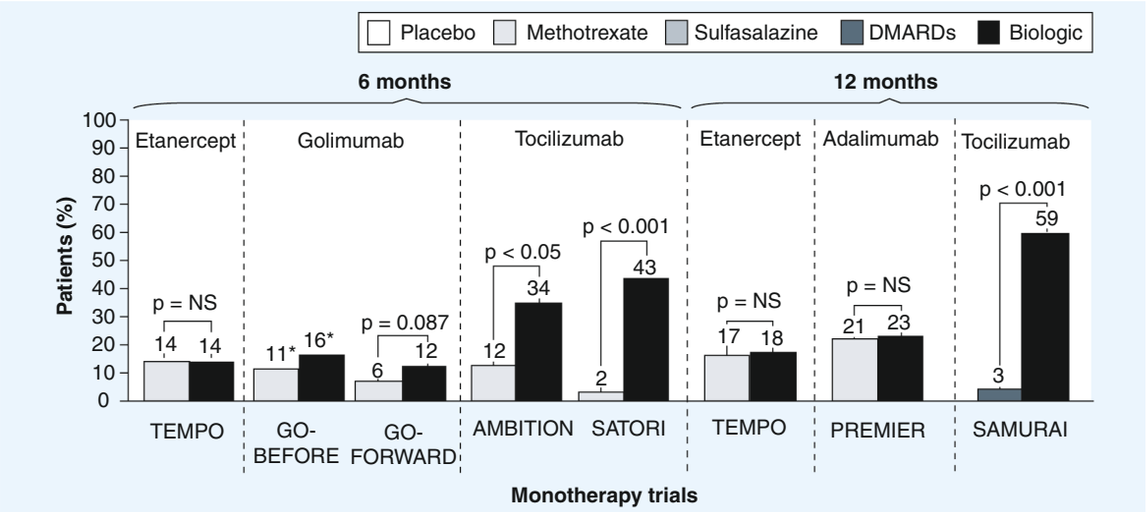

Figure 4. Disease activity score remission at 6 and 12 months in monotherapy trials. Results shown are for approved doses with the exception of golimumab (dose shown = 100 mg; approved dose = 50 mg).
*p-value not reported.
DMARD: Disease-modifying antirheumatic drug.
Data taken from [11,18,21,22,28–31].

for use as monotherapy in RA [38]. In a Phase II trial, rituximab monotherapy demonstrated superior clinical efficacy versus MTX in terms of ACR20 response in MTX-IR patients, with a consistent trend toward superiority of ACR50 and ACR70 responses [39]. Similar results were seen in a small 16-week study of rituximab monotherapy versus the combination of rituximab plus MTX [40].

Radiographic outcomes

Radiographic disease progression, assessed using total Sharp score has been shown to be slower with etanercept monotherapy than with MTX over 6 months, but not at 12 months in the ERA study [9]. When looking at Sharp erosion score, there was a significant improvement at both 6 months (0.30 vs 0.68; p = 0.001), and 12 months (0.47 vs 1.03; p = 0.002) with etanercept versus MTX [9]. In the TEMPO study, the mean change from baseline in modified TSS (mTSS) at week 52 was 2.80 units in the MTX monotherapy group, and 0.52 units in the etanercept monotherapy group (p = 0.0469 vs MTX); a statistically significant improvement in erosion score was also seen with etanercept monotherapy (p = 0.002) (Table 2) [10].

In COMET, radiographic nonprogression (mean change in modified total Sharp/van de Heijde score [mTSS] ≤ 0.5) at week 104 was achieved by 90 and 75% of patients, respectively (p = 0.008) [13]. Adalimumab monotherapy was more effective than MTX at inhibiting radiographic progression, reflected by a significantly lower mean increase in mTSS in the adalimumab group than the MTX group at week 52 (3.0 vs 5.7 units) and week 104 (5.5 vs 10.4 units; both p < 0.001) [18]. The mean change in erosion score at week 52 was significantly lower with adalimumab than MTX (p < 0.001) [18].

In both the GO-BEFORE and GO-FORWARD studies, golimumab monotherapy, was no different to MTX monotherapy although rates of change were low in both groups [21,22,41]. For tocilizumab monotherapy, there was significantly less radiographic change in mTSS at week 52 compared with patients receiving conventional systemic DMARDs, primarily MTX (p < 0.01) [29]. Similarly, the change in erosion score was significantly lower with tocilizumab monotherapy (p < 0.001) [29]. There were no monotherapy studies with radiographic end points for other bDMARDs reviewed here.

Conclusion

There are relatively few published studies for bDMARD monotherapy. Of these, monotherapy with tocilizumab has consistently shown superiority over MTX for signs, symptoms and radiographic progression. For anti-TNF agents, there is much less consistency in the published data. Etanercept has a faster onset of action than MTX at a mean dose of 19 mg/week, but from 6 months there is no difference between groups [9]. For other anti-TNF agents there is no evidence suggesting that they are superior for signs and symptoms.

However, in terms of radiographic outcomes, convincing evidence is available for adalimumab in early disease [18], and there is suggestive evidence supporting etanercept in both the ERA and TEMPO studies (although only the latter was significant) [9,10]. There is currently no evidence to suggest that golimumab affects radiographic progression, although the rate of change in the MTX arm was small, which may be a result of including patients with less severe disease [21,22,41]. This disconnect between signs and symptoms and radiographic progression for anti-TNF agents is somewhat hard to explain, but this observation has also been shown for denosumab, which slows radiographic disease progression but has no effect on clinical signs and symptoms [42]. In this context, it is noteworthy that both anti-TNF agents and tocilizumab rapidly decrease bone turnover markers, which may reflect both direct and indirect effects on bone [43–45] suggesting this disconnect may be due to an additional direct effect on bone. For clinical outcomes only, there is suggestive, but not totally consistent, evidence for the other bDMARDs rituximab and abatacept [37,39].

These studies suggest that tocilizumab may be the treatment of choice where MTX is not considered suitable for use as a co-therapy. Consistent with this, preliminary week 24 results from the ACT-RAY study also demonstrate that tocilizumab plus MTX does not have superior clinical efficacy to tocilizumab alone in patients with inadequate response to MTX [46]. This appears more applicable in light of the liver data, which suggest that combination therapy is more likely to cause liver function abnormalities. However, there are limited data comparing MTX plus tocilizumab versus tocilizumab alone [47], and radiographic data are also limited; thus, further studies are needed to make this conclusion more robust.

Anti-TNF agents appear to function well with MTX without any appreciable increase in toxicity, which may support their optimum use in combination with MTX even when some are approved as monotherapy. Although a number of anti-TNF agents are superior to placebo or sulfasalazine, the magnitude of benefit is quite small, as shown in this review. In most countries, abatacept and rituximab are not approved as monotherapy, but Phase II data reviewed here suggest that they could be considered as such. There are few data available for bDMARDs in combination with other traditional DMARDs, with the exception of leflunomide and anti-TNF agents, which may offer a more tolerable alternative to MTX [48].

While the scope of our review has been limited to the results of clinical trials with biologic monotherapy in RA, it is important to acknowledge the findings of 'real-life' health outcomes data from RA registries that complement clinical trial evidence. For example, data from the

Table 2. Radiographic outcomes reported in key clinical trials for biologic monotherapy at baseline and at 52 weeks.

Trial	Baseline mTSS		Mean change in mTSS		p-value	Baseline sharp erosion score		Mean change in sharp erosion score		p-value	Ref.
	Comparator	Biologic	Comparator	Biologic		Comparator	Biologic	Comparator	Biologic		
ERA	12.9	12.4	1.59	1.00	0.11	7.5	6.4	1.03	0.47	0.002	[6,9]
TEMPO	26.8	21.8	2.8	0.52	0.0469	11.5	8.0	1.68	0.21	0.0077	[10,11]
PREMIER	21.9	18.8	5.7	3.0	<0.001	13.6	11.3	3.7	1.7	<0.001	[18]
GO-BEFORE	19.7	20.4	1.37	1.25	0.266	11.3	11.7	0.74	0.76	NS	[41]
GO-FORWARD	36.7	37.4	1.10	0.89	0.967	18.7	19.1	0.17	0.23	NS	[41]
SAMURAI	30.6	28.3	6.1	2.3	<0.01	13.9	13.8	3.2	0.9	<0.001	[29]

mTSS: Modified total Sharp score.

Consortium of Rheumatology Researchers of North America (CORRONA) registry confirm the increasing use of TNF inhibitors as monotherapy in the treatment of both early and established RA in clinical practice [49]. In this large cohort of RA patients, 30% of those treated with TNF inhibitors received them as monotherapy [49]. We have outlined in this paper the efficacy of biologic agents as a monotherapy and have reviewed evidence that monotherapy with the IL-6 inhibitor tocilizumab produced superior treatment outcomes compared with MTX. These developments may impact on the current treatment paradigm for biologics in RA.

Finally, the clinical use of biologic monotherapy raises the possibility that the function of single cytokines in RA can be analyzed *in vivo* to further elucidate the pathogenic mechanisms of disease and appropriate therapeutic targets. However, the pathophysiology of RA is complex and may involve many molecules and multiple proinflammatory cytokines, including IL-6 and TNF. Therefore, the value in taking an *in vivo* approach to determine therapeutic targets may be limited.

Future perspective

The use of anti-TNF agents in RA is widespread and there is considerable experience of these drugs as a first-line treatment, particularly for patients with severe RA. In patients who are intolerant to MTX and those who are refractory to anti-TNF regimens, tocilizumab is likely to become the monotherapy of choice once more clinical experience is gained. The publication of long-term safety data will further support its use, in addition to the consistent evidence of its efficacy emerging from clinical trials. Despite this, there is a paucity of head-to-head studies comparing bDMARDs as monotherapy for RA and, in an increasingly crowded market, there is a need for robust comparative data to support evidence-based treatment strategies for individual patients. With this in mind, there is also a clear need to define appropriate predictors of response to different bDMARDs that will help inform rational treatment decisions in RA over the next 5–10 years.

Financial & competing interest disclosure

Both G Jones and A Taylor have received speakers fees, travel grants and research grants as well as served on advisory boards for Merck Sharp and Dohme, Abbott, Roche, Bristol-Myers Squibb and Union Chimique Belge all of whom make biological disease modifying anti-rheumatic drugs. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Andrew Franklin (Health Interactions Pte Ltd., Sydney, Australia) supported by Roche Products Pty Ltd., and David Poppelwell (Roche Products Pty Ltd.) provided some editorial assistance.

Executive summary

- Methotrexate (MTX) is the anchor drug in rheumatoid arthritis (RA) on the basis of its efficacy and safety as monotherapy, and its ability to increase the efficacy of biologic disease-modifying antirheumatic drugs (bDMARDs) when used in combination.
- 10–30% of RA patients are MTX-intolerant and discontinuation is common. Combination therapy with other DMARDs or biological monotherapy may be necessary.
- Of the bDMARD monotherapy data available, anti-TNF agents have shown inconsistent superiority to MTX in clinical outcomes (American College of Rheumatology and Disease Activity Score in 28 joints responses).
- Monotherapy with etanercept or adalimumab (but not other anti-TNFs) is more effective than MTX monotherapy in reducing radiographic progression as assessed by modified total Sharp scores and erosion scores.
- Tocilizumab monotherapy has consistently demonstrated superiority to MTX in reducing clinical signs, symptoms and radiographic progression.
- Other bDMARDs such as rituximab and abatacept may also be superior to MTX for signs and symptoms.
- Available data suggest that tocilizumab should be the treatment of choice where MTX is not considered suitable for use as a co-therapy.

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- ▪▪ of considerable interest

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