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REVIEW

Effect of biologic therapy on radiological progression in rheumatoid arthritis: what does it add to methotrexate?

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Abstract: There have been substantial advances in the treatment of rheumatoid arthritis in recent years. Traditional disease-modifying antirheumatic drugs (DMARDs) have been shown to have small effects on the progression of radiographic damage. This quantitative overview summarizes the evidence for biologic DMARDs and radiographic damage either alone or in combination with methotrexate. Two outcomes were used (standardized mean difference and odds of progression). A total of 21 trials were identified of which 18 had useable data. For biologic monotherapy, tocilizumab, adalimumab, and etanercept were significantly better than methotrexate, with tocilizumab ranking first in both outcomes while golimumab was ineffective in both outcomes. For a biologic in combination with methotrexate compared with methotrexate alone, most therapies studied (etanercept, adalimumab, infliximab, certolizumab, tocilizumab, and rituximab) were effective at slowing X-ray progression using either outcome, with infliximab ranking first in both outcomes. The exceptions to this were golimumab (no effect on standardized mean difference) and abatacept (no effect on odds of progression). This effect was additional to methotrexate; thus, the overall benefit is moderate to large in magnitude, which is clearly of major clinical significance for sufferers of rheumatoid arthritis and supports the use of biologic DMARDs in those with a poor disease prognosis.

Keywords: rheumatoid, trials, meta-analysis, radiographs, biologic, disease-modifying antirheumatic drugs, DMARDs

Introduction

Rheumatoid arthritis is the most common inflammatory arthritis, with a prevalence of 0.5%–1.0% in Western countries.[1] Although systemic, the disease occurs primarily in the joints, resulting in erosion of cartilage and bone, and subsequent destruction and deformity. Serious long-term functional disability commonly occurs within 10–20 years, thus early and aggressive therapy to slow radiographic progression is ideal.

A number of nonbiologic treatments slow radiographic progression,[1] but generally the effect of these agents is small and often limited by toxicity. Methotrexate is generally prescribed for first-line therapy in those with active rheumatoid arthritis; however, inadequate response and patient intolerance are common reasons for discontinuation. A systematic review[1] of randomized, placebo-controlled studies found evidence to support the efficacy of traditional disease-modifying antirheumatic drugs (DMARDs), ie, cyclosporine, sulfasalazine, leflunomide, methotrexate, parenteral gold, corticosteroids, and auranofin. These seven agents did not differ statistically in their efficacy and all appear effective in decreasing radiological progression in rheumatoid arthritis. Anakinra also had a small effect in this review. The magnitude of effect for

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methotrexate was a standardized mean difference of 0.36, which is considered small.[2] Surprisingly, antimalarials were ineffective at preventing radiographic progression.

Newer treatments include biologic DMARDs. Most of the current evidence stems from studies of combination therapy with standard DMARDs, but there are some studies of biologic DMARD monotherapy. While generally clinically effective, these trials have varying results, the magnitude of benefit is hard to compare between trials, and there are no head-to-head trials. Therefore, the aim of this paper was to review the evidence for efficacy of biologic combination therapy in rheumatoid arthritis by calculating standardized outcomes, so that different treatments could be ranked and compared according to their effect on reducing radiographic change.

Materials and methods

Search strategy

Relevant trials were identified utilizing the advanced search functions of the Cochrane controlled trials register, Medline, and Embase up to December 2011. The keywords used were "rheumatoid arthritis", "X-ray", "treatment", and "biologics", as well as the names of specific biologics. Search filters were applied to identify the most relevant results. This was supplemented by manually searching the bibliographies of relevant published reviews and papers and advice from experts in the field.

Inclusion criteria

To satisfy the inclusion criteria for this meta-analysis, studies were required to be randomized, double-blind trials that examined the effectiveness of pharmacological interventions for reducing radiographic progression in rheumatoid arthritis. Specifically, we were interested in studies which compared methotrexate monotherapy with biologics, both as monotherapy and in combination with methotrexate. Studies were included if a placebo (or equivalent) control group was present, if the reported outcomes included radiographic scoring of X-ray damage, and if there was a minimum period of 24 weeks of observation. Furthermore, concomitant use of intramuscular or intravenous corticosteroids, nonsteroidal anti-inflammatory drugs, and other DMARDs were permitted as long as the dosage remained constant throughout the duration of the first 24 weeks of the trial. Only articles published in English were included, to allow full-text evaluation. Participants in the studies needed to have adult rheumatoid arthritis, as defined by the 1987 American College of Rheumatology Criteria.[3] Trials were excluded when clear inclusion criteria were not listed, if participants had forms of arthritis other than rheumatoid arthritis, or if the published information was inadequate for data extraction.

Data extraction

In order to minimize errors in data extraction, efficacy data was extracted from the relevant reports by two authors (ED, MK) working independently. Afterwards, the results of data extraction were compared, and any disagreements were resolved by discussion or involvement of a third investigator (GJ). Where possible, radiographic scores obtained at 12 months were preferred to minimize heterogeneity associated with different trial durations.

Outcome measures and statistics

The principal outcome measure examined by this review was combined radiographic scoring of bone erosion and joint space narrowing in joints and using any validated scoring method, including Larson, Sharp, and modified Sharp scoring systems. In order to compare different studies directly, two dimensionless outcome measures were calculated, ie, the standardized mean difference and the odds of worsening X-ray scores.

Standardized mean difference

Treatment and comparison groups are compared in terms of a standardized score, where the difference is converted to standard deviation units for that particular measure. This was calculated by utilizing the standardized mean difference function within Revman, which required the number analyzed in the treatment and placebo groups, the mean change in total radiographic scores, and the standard deviation of this mean change. The trials included (see below) several treatment groups that were administered different dosages; the radiographic scores selected were those from the intervention group receiving closest to the approved drug doses. By convention,[2] the standardized mean difference values of 0.2, 0.5, and 0.8 are considered small, medium, and large.

Odds of radiographic progression

The odds of radiographic progression was defined as the number of patients in each treatment group who had worsening X-ray scores divided by the number of patients remaining in that group at follow-up. The definition of worsening X-ray scores varied slightly amongst different studies, but

was generally defined as either a change in total Sharp score of more than 0 or more than 0.5. An odds ratio was then calculated by comparing the odds of radiographic progression in the intervention group compared with the placebo group.

Where the standard deviation (SD) for the mean change in radiographic scores was not reported, we calculated the SD where possible. If the confidence interval was provided for the mean change, we calculated the SD using the formula $\sigma\Delta\bar{x} = \bar{x} - upper\ or\ lower\ limit / \pm 1.96 \times \sqrt{n}$. If the confidence interval was not present but the standard deviation of the baseline radiographic scores was present, it was possible to impute the value by using the formula $\sigma_{Change} = \sqrt{\sigma_{Baseline}{}^2 + \sigma_{Final}{}^2 - (2 \times 0.5 \times \sigma_{Baseline} \times \sigma_{Final})}$ However, for the latter method, an initial estimate of the correlation coefficient between baseline and final scores was obtained, separately for both the treatment and placebo groups, using the following formula $Correlation\ coefficient = \sigma_{Baseline}{}^2 + \sigma_{Final}{}^2 - \sigma_{Change}{}^2 / 2 \times \sigma_{Baseline} \times \sigma_{Final}$. This was calculated by back-calculations and subsequent averaging of the computed values from four of the studies used in the meta-analysis (specifically those with the largest sample size) to yield a final correlation coefficient value.

It is important to note that, for agents where there were multiple trials, standardized mean difference and odds ratio values were pooled using the random effect pooling option in Revman.[4] Heterogeneity was also assessed using the tau statistic in Revman.

Results

Description of trials

A total of 16 combination treatment trials and six monotherapy trials (18 in total) were included in this study, with a total of 4620 and 2191 patients, respectively. There were three trials examining etanercept[5–7] and certolizumab pegol,[8–10] two for adalimumab,[11,12] infliximab,[13,14] golimumab (two trials in one paper),[15] rituximab,[16,17] tocilizumab,[18,19] and abatacept.[20,21] Most trials were in methotrexate inadequate responders, but some were in early disease. One trial of etanercept[22] and two trials of denosumab[23,24] were excluded due to lack of extractable data. Some trials had incomplete data so were only included in analyses where extractable data were available. Unpublished data were provided by Abbott for data missing from the PREMIER trial. The original data are listed in Table 1. All trials were positive apart from ERA (etanercept) and GO-FORWARD (golimumab).

Biologic plus methotrexate versus methotrexate

The standardized mean difference results for a biologic plus methotrexate are given in Table 2. Despite variations in disease duration, amount of X-ray damage, and previous medications, there was no statistical heterogeneity for any outcome. With the exception of golimumab, all agents added significantly to methotrexate. The magnitude of additional benefit was small to moderate and of similar magnitude for the remaining agents but somewhat larger for infliximab.

The odds of progression are given in Table 3. All agents except abatacept demonstrated a significant reduction in the odds ratio for progression. However, there was variation in the magnitude of benefit, with odds ratios ranging from 0.19 to 0.71, and infliximab again having the largest effect.

Biologic monotherapy versus methotrexate

The standardized mean difference results for biologic monotherapy versus methotrexate are given in Table 4 and odds of progression in Table 5. Broadly similar results are obtained. Tocilizumab, adalimumab, and etanercept were significantly better than methotrexate, with tocilizumab ranking first in both outcomes while golimumab was ineffective in both outcomes.

Discussion

This quantitative overview provides convincing evidence that, when combined with methotrexate, most biologics are effective at slowing X-ray progression assessed by mean change or odds of progression. The exceptions to this are golimumab (mean change) and abatacept (odds of progression). The magnitude of benefit from methotrexate was a standardized mean difference of 0.36.[1] The estimates from this study are additional to the effect of methotrexate. Therefore, the total effect from the combination of biologics and methotrexate will be greater. For example, for infliximab plus methotrexate, the effect is estimated as a standardized mean difference of 1.04 (0.36 + 0.68), which is a large effect. For most agents, the total benefit is high-moderate to large in magnitude, which is clearly of major clinical significance for sufferers of rheumatoid arthritis. It is worthwhile pointing out that the scores did not decrease, with only two exceptions (one trial of infliximab and one of etanercept), suggesting that these agents slow progression rather than stop it. The results were not statistically different between agents, although infliximab was superior to the bottom four agents in each table. This should be interpreted with caution

Table 1 Radiographic outcomes reported in clinical trials for biologic combination therapy with methotrexate or as monotherapy at baseline and at 52 weeks

	Baseline X-ray score		Mean change in X-ray score		*P* value
	MTX	**Biologic + MTX**	**MTX**	**Biologic + MTX**	
Agent + methotrexate					
Infliximab[13]	82	75	4.0	0.25	<0.001
Infliximab[14]	–	–	25.0	−1.57	<0.001
Adalimumab[11]	66.4	72.1	2.7	0.1	<0.001
Etanercept[6]	26.8	21.8	2.8	−0.54	<0.0001
Adalimumab[12]	21.9	18.1	5.7	1.3	<0.001
Abatacept[20]	44.9	44.5	2.3	1.2	0.012
Certolizumab[10]	46.5	39.6	1.2	0.2	<0.01
Abatacept[21]	6.7	7.5	0.63	1.06	0.04
Rituximab[16]	32.5	30.6	2.81	1.14	<0.0001
Golimumab[15,*]	19.7	18.7	1.37	0.74	0.015
Golimumab[15,*]	36.7	29.7	1.1	0.93	0.855
Tocilizumab[19]	28.5	28.8	1.13	0.29	<0.0001
Rituximab[17]	7.4	7.7	0.74	0.23	<0.001
	MTX	**Biologic**	**MTX**	**Biologic**	
Monotherapy					
Etanercept[5]	12.9	2.4	1.59	1.00	0.11
Etanercept[22]	26.8	21.8	2.8	0.52	0.0469
Adalimumab[12]	21.9	18.8	5.7	3.0	<0.001
Tocilizumab[18]	30.6	28.3	6.1	2.3	<0.01
Golimumab[15,*]	19.7	20.4	1.37	1.25	0.266
Golimumab[15,*]	36.7	37.4	1.10	0.89	0.967

Notes: *First line of data is from GO-BEFORE and the second is from GO-FORWARD. Not all trials reported data in this format.
Abbreviation: MTX, methotrexate.

for two reasons. Firstly, the trials were not head-to-head so this is an indirect comparison. Secondly, the characteristics of patients with rheumatoid arthritis in the trials have changed over time. The patients in the infliximab trials had a very high rate of progression compared with the other trials, creating more potential for a greater benefit. It is also possible that the weight-based dosing of infliximab compared with the other anti-tumor necrosis factor agents may confer an additional benefit. In contrast, the golimumab trials may have been negative due to less strict inclusion criteria and a resultant low rate of progression (noted in Tables 1 and 2), making it difficult to show a positive result. Indeed, a further study using magnetic

Table 2 Biologic plus methotrexate versus methotrexate for total X-ray score in rank order

Medication	Reference	Follow-up period	Number	SMD (95% CI)
Infliximab	Lipsky et al[13]	54 weeks	173	**−0.63 (−0.87 to −0.38)**
Adalimumab	Keystone et al[11]	12 months	299	−0.45 (−0.68 to −0.22)
	Breedveld et al[14]	12 months	372	−0.45 (−0.65 to −0.24)
	Pooled			**−0.45 (−0.60 to −0.29)**
Rituximab	Tak et al[17]	12 months	443	−0.46 (−0.65 to −0.28)
	Cohen et al[16]	24 months	468	−0.41 (−0.59 to −0.22)
	Pooled			**−0.44 (−0.58 to −0.30)**
Etanercept	Emery et al[7]	12 months	476	−0.37 (−0.55 to −0.19)
	Klareskog et al[6]	12 months	430	−0.36 (−0.55 to −0.17)
	Pooled			**−0.37 (−0.50 to −0.23)**
Certolizumab pegol	Smolen et al[10]	24 weeks	373	**−0.29 (−0.51 to −0.08)**
Abatacept	Kremer et al[20]	12 months	586	−0.21 (−0.39 to −0.04)
	Westhovens et al[21]	12 months	459	−0.33 (−0.51 to −0.14)
	Pooled			**−0.26 (−0.39 to −0.14)**
Golimumab	Emery et al[15]	12 months	541	**−0.09 (−0.26 to +0.08)**

Note: Bold text indicates pooled results for each agent.
Abbreviations: CI, confidence interval; SMD, standardized mean difference.

Table 3 Odds of progression of radiographic damage ranked by effect size: therapy plus methotrexate versus methotrexate

Agent	Trial	Treatment*	Placebo*	OR (95% CI)
Infliximab	Breedveld et al[14]	24%	83%	0.07 (0.02, 0.29)
	Lipsky et al[13]	11%	31%	0.26 (0.14, 0.50)
	Pooled			**0.19 (0.09, 0.41)**
Etanercept	Klareskog et al[6]	20%	43%	0.34 (0.21, 0.54)
	Emery et al[7]	20%	41%	0.36 (0.23, 0.56)
	Pooled			**0.35 (0.26, 0.47)**
Tocilizumab	Kremer et al[19]	16%	33%	**0.39 (0.25, 0.62)**
Adalimumab	Breedveld et al[12]	36%	63%	0.33 (0.22, 0.51)
	Keystone et al[11]	38%	54%	0.52 (0.33, 0.83)
	Pooled			**0.41 (0.27, 0.64)**
Certolizumab pegol	Keystone et al[8]	31%	48%	0.48 (0.34, 0.69)
	Keystone et al[9]	26%	41%	0.51 (0.35, 0.75)
	Pooled			**0.50 (0.38, 0.64)**
Rituximab	Cohen et al[16]	43%	61%	0.48 (0.33, 0.71)
	Tak et al[17]	36%	47%	0.64(0.44, 0.93)
	Pooled			**0.57 (0.43, 0.76)**
Golimumab	Emery et al[15]	31%	40%	**0.64 (0.44, 0.94)**
Abatacept	Westhovens et al[21]	39%	47%	**0.71 0.49, 1.03)**

Note: *Treatment refers to biologic DMARD plus methotrexate while placebo refers to the methotrexate plus placebo group. Bold text indicates pooled results for each agent.
Abbreviations: CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug; OR, odds ratio.

resonance imaging assessment of joint damage did show a beneficial effect of golimumab.[25] Golimumab and infliximab are very similar chemically, with the former being fully humanized, so this seems the most likely explanation for the variation in efficacy. With most patients not changing X-ray scores in trials, it may be that the odds of progression may be a more sensitive outcome measures than the mean change, as is seen for golimumab. However, most agents were significant in both outcome measures with the other exception being abatacept, which was not significant for the odds of progression. In total, these results suggest that all currently available biologic DMARDs work well for decreasing disease progression when combined with methotrexate.

There is less evidence for monotherapy when the biologic is used without methotrexate. Only three agents were effective. Tocilizumab seems to have similar or slightly less efficacy than when combined with methotrexate, which would be consistent with the recent ACT RAY study.[26] Conversely, adalimumab and etanercept were better than methotrexate but the magnitude of benefit was smaller than when these were used in combination with methotrexate. When combined with the clinical data suggesting they are of similar efficacy to methotrexate as monotherapy,[27] this suggests these latter two agents are best given with methotrexate. Golimumab monotherapy was ineffective for both outcomes.

There are some potential limitations. Missing data are present in some categories, but most trials had data included in at least one of the outcome measures, suggesting that this did not have a major effect. The excluded etanercept trial appeared to have broadly similar results to the included trials.[22] The two denosumab trials both suggested that denosumab prevented erosions without affecting disease

Table 4 Biologic monotherapy versus methotrexate: standardized mean difference for total X-ray score

Medication	Reference	Follow-up period	Number analyzed	SMD (95% CI)
Tocilizumab	Nishimoto et al[18]	12 months	300	**–0.43 (–0.65, –0.20)**
Etanercept	Bathon et al[5]	12 months	395	–0.28 (–0.48, –0.08)
	Klareskog et al[6]	12 months	424	–0.24 (–0.43, –0.05)
	Pooled			**–0.26 (–0.40, –0.12)**
Adalimumab	Breedveld et al[14]	12 months	531	**–0.23 (–0.40, –0.05)**
Golimumab	Emery et al[15] GO-BEFORE[15]	12 months	319	–0.02 (–0.24, +0.20)
	Emery et al[15] GO-FORWARD[15]	12 months	222	–0.04 (–0.30, +0.23)
	Pooled			**–0.03 (–0.20, +0.14)**

Note: Bold text indicates pooled results for each agent.
Abbreviations: CI, confidence interval; SMD, standardized mean difference.

Table 5 Odds of progression of radiographic damage ranked by effect size: monotherapy versus methotrexate

Medication	Reference	Patients progressing		OR (95% CI)
		Treatment	Placebo	
Tocilizumab	Nishimoto et al[18]	44%	61%	**0.50 (0.31, 0.82)**
Adalimumab	Breedveld et al[14]	49%	63%	**0.57 (0.37, 0.89)**
Etanercept	Klareskog et al[6]	32%	43%	0.63 (0.42, 0.93)
	Bathon et al[5]	28%	40%	0.58 (0.38, 0.88)
	Pooled			**0.61 (0.45, 0.81)**
Golimumab	Emery et al[15] GO-BEFORE[15]	39%	46%	0.76 (0.98, 1.23)
	Emery et al[15] GO-FORWARD[15]	34%	31%	0.89 (0.49, 1.61)
	Pooled			**0.81 (0.56, 1.17)**

Note: Bold text indicates pooled results for each agent.
Abbreviations: CI, confidence interval; OR, odds ratio.

activity, but the clinical significance of this is uncertain.[23,24] In some included trials, there is also a disconnect between radiographic results and disease activity. This is most notable for etanercept and adalimumab monotherapy where the radiographic data are more convincing than the clinical data. Publication bias would seem unlikely because there are few trials overall, and even negative trials are published. Secondly, heterogeneity between trials in terms of variation in disease duration and severity may cause problems with pooling of studies, but this was not present for any of the pooled 52-week results, suggesting broadly similar results over this time frame, even given the differing rates of progression and varying disease duration. This observation is consistent with the previous results in our earlier meta-analysis.[1] Lastly, there are limited trials comparing combination therapy with methotrexate or biologic therapy. Cyclosporin also seemed to add to methotrexate for radiographic outcomes in two trials, and the magnitude of benefit appears similar to that of biologic DMARDs.[1,28] Triple therapy is better than monotherapy for long-term radiographic outcomes in early rheumatoid arthritis,[29] and a recent trial suggested that etanercept plus methotrexate was superior to triple therapy for radiographic but not clinical outcomes.[30] This suggests there is insufficient information on which to base decision-making at this point in time.

Implications for practice

In a patient who can take methotrexate, all biologic DMARDs (with the possible exception of infliximab and golimumab) have similar efficacy, thus can be selected without reference to their effect on radiographic progression. In the not uncommon patient who cannot take methotrexate, the data favor tocilizumab as the treatment of choice at this time. Given the lower severity of disease in more recent trials, more sensitive methods for assessing disease progression are needed for future clinical trials in rheumatoid arthritis.

Disclosure

GJ has received speaker's 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 which make biological DMARDs. The other authors have no conflicts of interest in this work.

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