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Efficacy of Biologicals in the Treatment of Rheumatoid Arthritis

A Meta-Analysis

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Key Words
Rheumatoid arthritis · Therapies, new · Biologicals · Anti-tumour necrosis factor-α · Anakinra · Abatacept

Abstract
Rheumatoid arthritis (RA) is a chronic multisystem disease. A characteristic feature of RA is persistent inflammatory synovitis, usually involving the peripheral joints in a symmetric distribution. The prevalence of RA is approximately 0.8% of the population (range: 0.3–2.1%); women are affected approximately 3 times more often than men. The current therapeutic approach is to start a disease-modifying agent early in the illness to prevent eventual joint damage. Older disease-modifying anti-rheumatic drugs include methotrexate, sulphasalazine and hydroxychloroquine. Newer ones such as leflunomide and cyclosporin are also used. A recent advance in the management of rheumatoid arthritis is the use of biological agents, which block certain key molecules involved in the pathogenesis of the illness. They include tumour-necrosis-factor-α-blocking agents such as infliximab, etanercept and adalimumab, the anti-CD-20 agent, rituximab, and CTLA-4 Ig abatacept. The present study was planned with the aim of evaluating the efficacy of such newer biological therapies in refractory RA at various time points. Databases including Medline, Embase and the Cochrane Library were searched for all relevant studies up to January 2007. A total of 26 studies were included in present meta-analysis. The method of DerSimonian and Laird [Control Clin Trials 1986;7:177–188] was used to calculated a pooled odds ratio (OR) for the American College of Rheumatology (ACR) criteria 20, 50 and 70, at 24, 54 and 96 weeks. The overall pooled OR were found to be significantly more than the placebo at all 3 time points for all 3 criteria (ACR 20, 50 70). In conclusion, biologicals as a group are highly effective in the treatment of RA. Biologicals were efficacious both in treatment naïve and methotrexate-refractory patients.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease, characterized by symmetrical synovitis, inflammatory exudates in joint cavities and erosion of articular cartilage and marginal bone [1]. Standard therapy for RA aims to suppress inflammation, a consequence of autoimmune activation, for which we use disease-modifying anti-rheumatic drugs (DMARD), corticosteroids and non-steroidal anti-inflammatory drugs [2]. However, a large number of patients treated with traditional DMARD showed an inadequate response [3]. This led to the development of new a class of drugs named biologicals [4].

Biologicals have highly specific action, targeting specific inflammatory proteins in the pathophysiology of RA. The most important of these are strategies targeting tumour necrosis factor-α (TNF-α); these are: TNF-α

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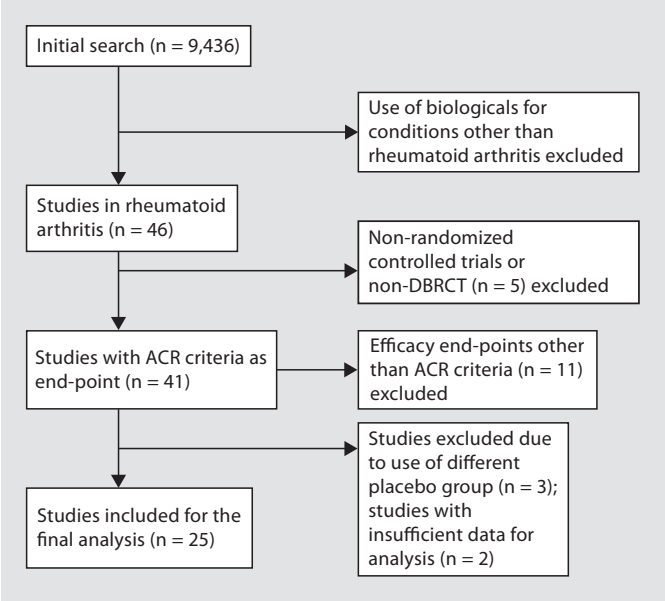

Fig. 1. Flow chart for studies evaluated for inclusion in the meta-analysis.

type II receptor/IgG1 fusion protein (etanercept), chimeric (human and mouse) monoclonal antibody against TNF-α (infliximab) and a humanized monoclonal antibody against TNF-α (adalimumab) [5, 6]. Anakinra, a fusion protein that blocks actions of IL-1, has also been shown to be effective in clinical trials for RA [7]. Abatacept, a selective modulator of CD80 or CD86-CD28 costimulatory signals required for full T cell activation, is another agent recently shown to be effective. All these agents have been shown to be highly effective [8, 9]. A number of other biologicals are being tested for efficacy in clinical trials for RA.

A large number of clinical trials have been conducted comparing biologicals with traditional DMARD [10]. The biologicals have shown superior efficacy, especially during the initial 6 months of treatment, but with progressive therapy this efficacy seems to decline, indicating disease progression. The results also vary with the type of biological used, in addition to a host of other patient characteristics [11]. Consequently, not all the trials have shown consistent improvement over the traditional DMARD at time intervals beyond 6 months. Lastly, as these newer therapies are expensive, the question of their continued use over a prolonged duration needs to be addressed.

The present meta-analysis was planned with the aim of comparing different biologicals to each other, traditional DMARD and placebos, in terms of the American College of Rheumatology (ACR) criteria at different time points (24, 54 and 96 weeks).

Materials and Methods

Two investigators independently searched databases, including Medline, Embase and the Cochrane Library, for all the relevant studies up to January 2007. The following terms were used: 'rheumatoid arthritis AND biologicals', 'anti-TNF-α AND rheumatoid arthritis', 'infliximab AND clinical trials', 'etanercept AND clinical trials', 'adalimumab AND clinical trials', and 'therapeutic uses AND biologicals'. Apart from the electronic search, Index Medicus and cross references of the articles obtained were also checked for any other useful data.

Studies included in the meta-analysis were randomized double-blind trials of infliximab, etanercept, adalimumab and abatacept, in which patients were randomized either to the biological or placebo group. Clinical trials meeting those criteria were collected. Studies were selected in which the patients had active RA (as defined by ACR criteria), despite treatment with traditional DMARD, and the treatment duration with biologicals was at least 12 weeks. For inclusion, the trials had to have a fixed dosage throughout the study period, without any dose titration of the biological. Studies were excluded if interventional studies were not randomized or double-blind. We compared all biological therapies (infliximab, etanercept, adalimumab, anakinra and abatacept) versus placebo alone, or all biological plus methotrexate (or DMARD) versus placebo plus methotrexate (or DMARD).

Data Extraction

Data regarding improvements in ACR 20, ACR 50 and ACR 70 criteria were extracted. Where an improvement in ACR criteria was represented as percentage of patients, it was converted into the number of patients. These improvements in ACR criteria were analyzed at time points of 24, 54 and 96 weeks after the start of treatment. The 24-week group included data from weeks 22 to 30, the 54-week group from weeks 46 to 54 and the 96-week group from weeks 96 to 104.

Analysis

For each trial, the odds ratio (OR) of the effects of biologicals versus placebo with 95% confidence intervals (CI) were calculated for ACR 20, 50 and 70 criteria. The random effects method of DerSimonian and Laird [12] was used to pool the data. The OR at different time points for ACR 20, 50 and 70 was plotted using forest plots. The OR was represented as a box with the 95% CI as whiskers on both sides of the box. The size of each box in a forest plot was adjusted depending upon the weight of the study.

Results

In the initial search, 9,436 studies were identified (fig. 1), which included 246 meta-analyses and 654 reviews. A large number of clinical trials of biologicals in

Table 1. Characteristics of studies included in the meta-analysis

No.	Authors	Subjects randomized, n	Disease characteristics	Active treatment	Placebo	Duration weeks
1	Moreland et al. [28]	158	active RA	etanercept 25 mg (78)	placebo (80)	24
2	Weinblatt et al. [29]	89	active RA	etanercept 25 mg + methotrexate (59)	placebo + methotrexate (30)	24
3	Klareskog et al. [30]	161	active RA	etanercept 25 mg + methotrexate (85)	placebo + methotrexate (76)	52
4	Genovese et al. [42]	424	active RA	etanercept 25 mg + methotrexate (207)	placebo + methotrexate (217)	96
5	Van der Heijde et al. [31]	146	active RA	etanercept 25 mg + methotrexate (71)	placebo + methotrexate (75)	96
6	Maini et al. [17]	428	active RA	infliximab 3 mg every 4 weeks (86) infliximab 3 mg every 8 weeks (86) infliximab 10 mg every 4 weeks (81) infliximab 10 mg every 8 weeks (87)	placebo (88)	30
7	Lipsky et al. [5]	428	active RA	infliximab 3 mg every 4 weeks + methotrexate (88) infliximab 3 mg every 8 weeks + methotrexate (86) infliximab 10 mg every 4 weeks + methotrexate (87) infliximab 10 mg every 8 weeks + methotrexate (81)	placebo + methotrexate (86)	54
8	Maini et al. [18]	428	active RA	infliximab 3 mg every 4 weeks (86) infliximab 3 mg every 8 weeks (86) infliximab 10 mg every 4 weeks (81) infliximab 10 mg every 8 weeks (87)	placebo (88)	102
9	St Clair et al. [19]	1,049	active RA	infliximab 3 mg every 8 weeks + methotrexate (372) infliximab 6 mg every 8 weeks + methotrexate (377)	placebo + methotrexate (291)	54
10	Quinn et al. [20]	20	active RA	infliximab 3 mg (10)	placebo (10)	46
11	Smolen et al. [21]	428	active RA	infliximab 3 mg every 4 weeks + methotrexate (86) infliximab 3 mg every 8 weeks + methotrexate (86) infliximab 10 mg every 4 weeks + methotrexate (81) infliximab 10 mg every 8 weeks + methotrexate (87)	placebo + methotrexate (88)	54
12	Westhovens et al. [22]	1,082	active RA	infliximab 3 mg at weeks 0, 2, 6, 14 + methotrexate (360) infliximab 10 mg at weeks 0, 2, 6, 14 + methotrexate (361)	placebo + methotrexate (361)	22
13	Rau [23]	271	active RA	adalimumab 20 mg every 2 weeks + methotrexate (70) adalimumab 40 mg every 2 weeks + methotrexate (70) adalimumab 80 mg every 2 weeks + methotrexate (70)	placebo + methotrexate (70)	24
14	Furst et al. [24]	636	active RA	adalimumab 40 mg every 2 weeks + DMARD (312)	placebo + DMARD (318)	24
15	Weinblatt et al. [6]	271	active RA	adalimumab 20 mg every 2 weeks + methotrexate (69) adalimumab 40 mg every 2 weeks + methotrexate (67) adalimumab 80 mg every 2 weeks + methotrexate (73)	placebo + methotrexate (62)	24
16	Keystone et al. [25]	618	active RA	adalimumab 20 mg/week + methotrexate (212) adalimumab 40 mg/week + methotrexate (207)	placebo + methotrexate (200)	52
17	Van de Putte et al. [26]	544	active RA	adalimumab 20 mg/week (112) adalimumab 20 mg every 2 weeks (106) adalimumab 40 mg/week (103) adalimumab 40 mg every 2 weeks (113)	placebo (110)	26

Table 1 (continued)

No.	Authors	Subjects randomized, n	Disease characteristics	Active treatment	Placebo	Duration weeks
18	Breedveld et al. [27]	525	active RA	adalimumab 40 mg every 2 weeks + methotrexate (268)	placebo + methotrexate (257)	104
19	Kremer et al. [3]	339	active RA	CTLA-4 Ig 2 mg/kg + DMARD (105) CTLA-4 Ig 10 mg/kg + DMARD (115)	placebo + DMARD (119)	26
20	Genovese et al. [32]	391	active RA	abatacept 10 mg/kg + DMARD (258)	placebo + DMARD (133)	26
21	Kremer et al. [34]	339	active RA	CTLA-4 Ig 2 mg/kg + DMARD (105) CTLA-4 Ig 10 mg/kg + DMARD (115)	placebo + DMARD (119)	48
22	Kremer et al. [33]	652	active RA	abatacept 10 mg/kg + DMARD (433)	placebo + DMARD (219)	48
23	Bresnihan et al. [35]	349	active RA	anakinra 75 mg (115) anakinra 150 mg (115)	placebo (119)	24
24	Cohen et al. [36]	153	active RA	anakinra 1 mg/kg + methotrexate (59) anakinra 2 mg/kg + methotrexate (46)	placebo + methotrexate (48)	24
25	Cohen et al. [37]	501	active RA	anakinra 100 mg + methotrexate (250)	placebo + methotrexate (251)	24

Figures in parentheses represent the number of participants.

conditions other than RA, herbal therapies for RA and observational studies were also included in the initial search. Forty-one potentially relevant studies were obtained. Of these, 11 were excluded on the basis of study end-points other than ACR criteria. Three studies were excluded due to the use of an active comparator other than methotrexate [13–15], and 2 were excluded as only 12 weeks of data were presented [16, 41].

Finally, studies evaluating 11,252 patients were included in the meta-analysis. Seven trials were of infliximab [5, 17–22], 6 evaluated adalimumab [6, 23–27], 5 studied etanercept [28–31, 42], 4 investigated abatacept [3, 32–34], and 3 used anakinra [35–37] (tables 1, 2).

In 3 studies, infliximab infusions were compared with the placebo and all patients had active disease, having received oral or parenteral methotrexate for at least 3 months and a stable dose of at least 12.5 mg/week for at least 4 weeks [18, 19, 21]. In the other 4 studies, all the included patients received methotrexate in a stable dose around 20 mg/week [5, 16, 17, 20]. In 1 study, the methotrexate dose was 12.5 mg/kg [5].

One study compared etanercept directly with a placebo [29]. However, the other 4 studies used methotrexate in both the groups [28, 30–32]. In study by Weinblatt et al. [29], the methotrexate dose was titrated to the desired clinical benefit before starting the etanercept infusions. However, in other studies, methotrexate was used orally in doses up to 20 mg/week [28, 29, 31, 32].

One study, evaluating adalimumab, compared it directly with the placebo [27]. However, all other studies used methotrexate in both the groups after titrating to the fixed entry dose that was previously taken by the patients [6, 22–26].

Abatacept-treated patients, in the trail of Genovese et al. [32], were treatment resistant to TNF antagonists. In the trial, abatacept was compared to a placebo, but all the patients received at least 1 DMARD. In a study by Kremer et al. [33], patients received methotrexate (15 mg/week), although methotrexate at 10 mg/week was acceptable if the patient had a history of toxicity. The duration of this study was 1 year; during the initial 6 months no dose adjustments were made for methotrexate, but after 6 months dose adjustments were allowed. In another study by Kremer et al. [34], 2 doses of abatacept were compared with a placebo in patients on methotrexate. In this study, methotrexate was used in doses ranging from 10 to 30 mg/week. All 3 studies evaluating anakinra used methotrexate up to 20 mg/week in both the groups.

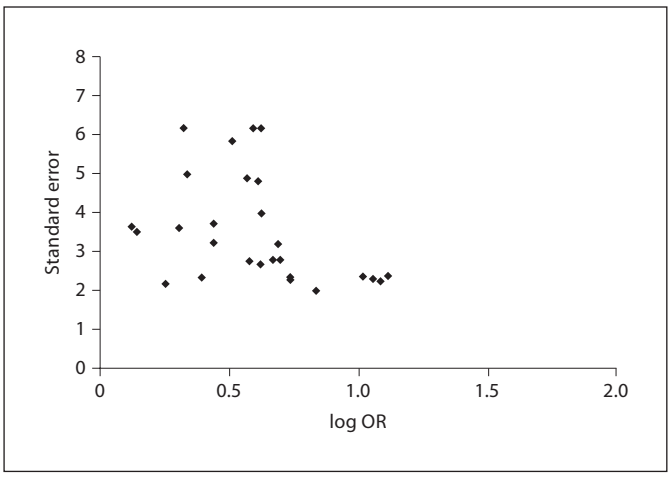

Fig. 2. Funnel plot of studies comparing biologicals with placebo.

Heterogeneity Test

From the shape of the funnel plot, publication bias cannot be ruled out (fig. 2).

ACR 20 Improvement

For the efficacy of biologicals at 24 weeks, 26 studies were analyzed. Biologicals showed better efficacy than the placebo, with OR = 3.69 (95% CI: 3.48–3.87; fig. 3a). Similarly, improvements in ACR 20 criteria at weeks 54 (16 studies) and 96 (8 studies) were significantly larger in the biological groups compared to the placebo group, with OR = 3.31 (95% CI: 2.98–3.64) and OR = 3.0 (95% CI: 2.64–3.35), respectively (fig. 3a).

ACR 50 Improvement

As with ACR 20, the improvements in ACR 50 were better in biological groups compared to the placebo at all time points. The numbers of studies included in analysis were 24 (24-week group), 10 (54-week group) and 8 (96-week group). The pooled OR were 4.26 (95% CI: 4.06–4.45) , 3.60 (95% CI: 2.93–4.26) and 3.20 (95% CI: 2.65–3.76) at 24, 54 and 96 weeks, respectively (fig. 3b).

ACR 70 Improvement

The results of ACR 70 showed that biologicals were better than methotrexate at 2 time points: at week 24 (22 studies) the pooled OR = 4.21 (95% CI: 3.92–4.50; fig. 3c), and at week 54 (4 studies) OR = 4.06 (95% CI: 2.45–5.67; fig. 3c). However, at week 96 (2 studies) the biologicals were not shown to be statistically better than placebo with OR = 1.34 (95% CI: 0.01–2.69; fig. 3c).

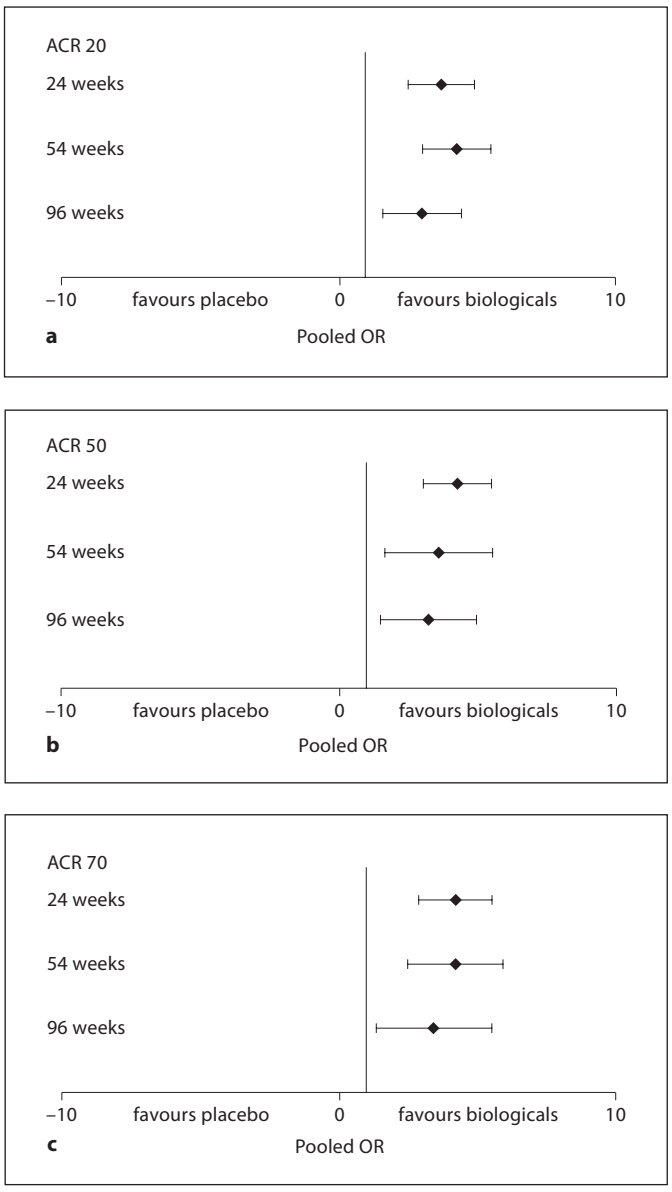

Fig. 3. Pooled OR for ACR 20 (**a**), 50 (**b**) and 70 (**c**) at 24, 54 and 96 weeks.

Discussion

Biologicals are currently indicated for the treatment of patients with active RA after an adequate trial of DMARD, most commonly methotrexate [34]. The results of the present meta-analysis suggest that in patients with an inadequate response to methotrexate, the addition of biologicals is beneficial, as defined by the ACR criteria. These findings further substantiate the available evidence in favour of biologicals.

Table 2. Quality assessment of included studies

Checklist items	Truly random	Randomization		Baseline comparatibility				Blinding				Withdrawal		
		allocation concealment	No. stated	presented	achieved	eligibility criteria specified	co-interventions identified	assessors	administration	participants	procedures assessed	>80% in final analysis	reasons stated	intention to treat analysis
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Moreland et al. [28]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
Weinblatt et al. [29]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
Klareskog et al. [30]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
Genovese et al. [42]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
Van der Heijde et al. [31]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
Maini et al. [17]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
Lipsky et al. [5]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
Maini et al. [18]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
St Clair et al. [19]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
Quinn et al. [20]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
Smolen et al. [21]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
Westhovens et al. [22]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
Rau [23]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
Furst et al. [24]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
Weinblatt et al. [6]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
Keystone et al. [25]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
Van de Putte et al. [26]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
Breedveld et al. [27]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
Kremer et al. [3]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
Genovese et al. [32]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
Kremer et al. [34]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
Kremer et al. [33]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
Bresnihan et al. [35]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
Cohen et al. [36]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√
Cohen et al. [37]	√	n.m	√	√	√	√	√	√	√	√	n.m	x	√	√

n.m = Not mentioned.

Although overall biologicals were better than methotrexate in improving symptoms, individually some of the agents were not significantly better than methotrexate.

Week 24. The overall pooled OR favoured biologicals over methotrexate for ACR 20, 50 and 70. However, individually some studies were not significant. Anakinra, at all of the 5 doses analyzed, did not significantly improve ACR 20 when compared to methotrexate. A higher dose of abatacept (i.e. 10 mg/kg) was more efficacious than a lower dose (i.e. 2 mg/kg), and could achieve statistical significance. In the case of adalimumab, a weekly regimen was found to be better than a bi-weekly regimen, as statistically significant results were obtained with the weekly regimen. In the case of ACR 50, a study evaluating anakinra at doses of 1 mg/kg was the only study that attained significance; all the other doses did not attain statistical significance. Similarly to ACR 20, the lower dose of abatacept was not found to be significantly better than methotrexate. A lower dose of adalimumab (i.e. 20 mg/kg every week or every other week) did not significantly improve the ACR 50 response. Etanercept and anakinra did not significantly improve ACR 70. In the case of adalimumab, the study by Rau [23] did not show any significant improvement.

Week 54. Similar to results of week 24, at week 54 biologicals were better than methotrexate, in terms of overall pooled OR. Individually, the study that did not significantly favour biologicals for ACR 20 was study by Quinn et al. [20] using infliximab (3 mg/kg). The reason for the non-significant results obtained could the small sample size of the study, which was not sufficient to produce significant results. The other 2 studies that did not significantly improve ACR 20 were of adalimumab (bi-weekly regimen) and etanercept. ACR 50 studies using a lower dose of infliximab (i.e. 3 mg) were not significant, whereas higher doses (i.e. 10 mg) produced significant

results. Individual OR for ACR 70 were not significant in cases where lower doses of infliximab and infliximab were given every 8 weeks. Adalimumab in a bi-weekly regimen did not significantly improve either ACR 50 or ACR 70 responses.

Week 96. At 96 weeks, Quinn et al [20] (infliximab) could not attain statistical significance in improving ACR 20, 50 or 70. Also, etanercept did not significantly improve any of the ACR criteria. Adalimumab in a bi-weekly regimen was also not significantly better than methotrexate at 96 weeks.

Efficacy of Biologicals versus Duration of Treatment

One of the most important issues regarding the use of biologicals for prolonged periods, taking into consideration the cost of the therapy, is maintained efficacy of treatment. Plotting OR for ACR 20, 50 and 70 versus time shows that biologicals are efficacious in terms of ACR criteria, but a uniform decline with time is observed (fig. 4).

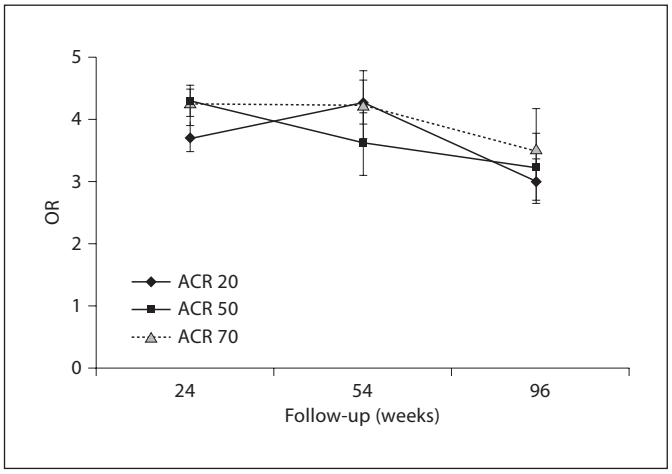

Fig. 4. Changes in ACR response rates for biologicals, measured as OR over time.

Methotrexate Dose

Biologicals, when compared to placebo or methotrexate, have been shown to have better efficacy, but some of the trials have used low to moderate doses of methotrexate. The dose of methotrexate used in most of the studies was between 12 and 20 mg/week. The starting dose being 12.5 mg/week, and then titrated to around 20 mg/week. These doses of methotrexate are considered to be low to moderate doses of methotrexate [39]. Doses between 15 and 25 mg/week are considered to be appropriate. Additionally, in some of the trials, methotrexate was used in its oral form rather than though parenteral administration. This type of study design does not take into consideration the interindividual variations in the bioavailability of methotrexate. Usually, the bioavailability ranges between 25 and 100% [39]. Thus, oral methotrexate at 12–20 mg/week does not make a good comparator drug. Hence, based on results of prospective observational studies and known pharmacological properties of methotrexate, it has been suggested that any new drug should be compared with methotrexate given parenterally and in maximum weekly doses (i.e. up to 25 mg) [40].

Dose of Biologicals Used

In the trials included in the study, the dose of etanercept was 25 mg, given subcutaneously twice weekly, which is the standard FDA-approved dose, and most trials have evaluated this dose. Infliximab, however, has been used in doses ranging from 3 to 10 mg/kg given either every 4 weeks or every 8 weeks. Individual studies show a favourable response with higher doses of infliximab. In studies by Maini et al. [17, 18] and Lipsky et al. [5], higher or more frequent infliximab administration has shown better response rates. The higher dose needs to be titrated based on individual patient tolerability. Adalimumab is given either at 20, 40 or 80 mg every week/every other week. Again higher doses have shown better responses. As in case of infliximab, adalimumab administered every week was more efficacious than a bi-weekly regimen. Even in trials of anakinra, 5 different doses have been used, with higher response rates having higher doses. Abatacept, when used in a higher dose (i.e. 10 mg/kg), was found to be better than a 2 mg/kg dose.

Conclusion

Biologicals as a group are highly effective in the treatment of RA. Biologicals were efficacious both in treatment naïve and methotrexate refractory patients. Individually, these agents have shown a trend towards improving the ACR response rate. Due consideration has to be given to the dose used in order to achieve an optimal response. Despite a decline in the response rate over time, biologicals are significantly better at all time points up to 96 weeks. In this meta-analysis, we analyzed 5 different biologicals acting on different protein targets. Combining these studies, biologicals, irrespective of the pathophysiological target they act on, are effective in the treatment of RA and improved the ACR 20, 50 and 70 response rates at 24, 52 and 96 weeks.

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