Azaïs et al. J Rheum Dis Treat 2016, 2:032
Volume 2 | Issue 1
ISSN: 2469-5726

Journal of
Rheumatic Diseases and Treatment

Research Article: Open Access

Meta-Analysis of the Clinical Efficacy of the Placebo Effect from Tumour-Necrosis-Factor Inhibitors to Treat Rheumatoid Arthritis after Methotrexate Failure

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Abstract

Introduction: Tumour-necrosis-factor (TNF) inhibitors, used to treat rheumatoid arthritis (RA), have non-specific (placebo effect) and specific effects. This meta-analysis appraises these effects within the first 3 months of treatment. Data were collected from ACR 20, 50 and 70 scores at week-24 from RA patients receiving TNF-blockers or a placebo after methotrexate (MTX) failure.

Methods: A systematic literature review evaluated RCTs of TNF-blockers vs. placebo given to patients after MTX failure (10 mg/week during 6 months), published until October 2015. RA patients were naive to biotherapies.

Results: Twenty-two RCTs (out of 1,388) were evaluated: six studied infliximab, five etanercept, four adalimumab, three certolizumab and four golimumab. Thirteen RCTs were available for the ACR 20 score at week-24. The overall placebo effect was 24.7% (CI95% [0.192;0.301] p = 0), the adalimumab one was 26.7% ((CI95% [0.161;0.373]) p = 0.001), certolizumab 16.4% ((CI95% [0.068;0.26]) p = 0), and infliximab 31.9% ((CI95% [0.154;0.485]) p = 0.001). Subgroup analyses showed the i.v. route generated a 31.90% placebo effect vs. 23.30% via the subcutaneous route (95%CI [0.154;0.485] p = 0.001). The placebo ACR-50 response was 10.90% ((CI95% [0.074;0.144]) p = 0) for 14 RCTs: only adalimumab was significant (15.40%, (CI95% [0.026;0.281]) p = 0). The ACR-70 placebo effect was 3.40% (95% (CI [0.019; 0.049]) p = 0) in 13 studies (NS).

Conclusions: Even though TNF-blockers had greater efficacy, placebo effect should be considered. Indeed, it is estimated at ~20% even treatment failure. Adalimumab, certolizumab and infliximab had higher placebo effects, as did the i.v route. The greater the stringency of ACR criteria, the more the placebo effect was decreased.

Keywords

Rheumatoid arthritis, Placebo effect, TNF-blockers, MTX failure, Meta-analysis

Introduction

Rheumatoid arthritis (RA) is the most frequent cause of chronic inflammatory rheumatism, and occurs in ~0.8% of the population [1]. The medium age of onset is 40-60 years, and more women develop RA than men. To aid diagnosis of RA, the ACR (American College of Rheumatology) criteria were initiated in 1987 and re-reviewed in 2010: these criteria have great specificity (93.5%) and sensibility (89.3%) [1,2]. A score of at least 6 items (serology, joints symptoms, during of the symptoms and acute phase reactants) defines RA. Early diagnosis, using the ACR criteria, can reduce the risks of developing structural defects and achieve more rapid remission [3,4]. However, it could persist, in the diagnosis of especially early RA, some mistake with fibromyalgia or non-inflammatory rheumatisms like chondrocalcinosis or gout. ACR 20, 50 and 70 quantify the RA activity and were described by the OMERACT (Outcome Measure in Rheumatoïd Arthritis Clinical Trial). They respectively correspond to 20%, 50% and 70% of amelioration on the number of painful joints, the number of swollen joints, and at least 3 items between decreases of global activity evaluated by the patient himself, pain scale (evaluated by practitioners or patients themselves), functional handicap, and blood inflammation.

Methotrexate (MTX) is the cornerstone-treatment for RA: international rheumatologic societies recommend it a primary treatment [5]. However, if MTX fails after 3 months and above all after 6 months (at a minimal dose of 10 mg/week, with an optimal dose of 20 mg/week), new biologics, such as tumour-necrosis factor (TNF) inhibitors [4-6]: i.e., infliximab, adalimumab, etanercept, golimumab, or certolizumab, or other drugs in addition to MTX (hydroxychloroquine and sulfasalazine) need to be prescribed. In certain cases, these can be initially used in association with MTX, but only for patients who have a poor prognosis [5,7].

TNF-inhibitors generate specific and non-specific effects. The latter include the placebo effect, the regression to the mid, and the natural evolution of the disease. Psychosocial and physiological effects are linked with the placebo effect [8,9]. Regarding the neurobiological effects, the placebo effect uses the same neuronal systems as opioid drugs (i.e., the regions identified by TEP -TDM and magnetic resonance imaging) with activation of the cingulate, frontal cortices and the nucleus accumbens-core areas [10-14].

The placebo effect is more efficacious during the first 3 months

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Citation: Azaïs J, Vergne-Salle P, Bonnet C, Dufauret-Lombard C, Treves R, et al. (2016) Meta-Analysis of the Clinical Efficacy of the Placebo Effect from Tumour-Necrosis-Factor Inhibitors to Treat Rheumatoid Arthritis after Methotrexate Failure. J Rheum Dis Treat 2:032

Received: January 20, 2016: **Accepted:** March 29, 2016: **Published:** March 31, 2016

of treatment even though it can occur at any time during treatment. However, there is a paucity of information on this within the literature. It is reported that > 30% of patients are responders [15].

In this meta-analysis, we assess the placebo effect in double-blind randomized trials comparing TNF-inhibitors plus methotrexate (MTX) and MTX plus placebo, after MTX failure in rheumatoid arthritis patients. The criteria of efficacy were the ACR 20, 50 and 70 clinical scores. We hypothesize that the patients in the arm with MTX plus placebo, who have previously failed to MTX therapy, allow a good evaluation of the placebo effect.

Methods

Patients

Patients within the selected studies had to be aged ≥ 18 years and had suffered from RA for at least 3 months after consulting a rheumatologist (according to the 1987 ACR criteria). These latter have been listing in the chart (Table S1), drawn thanks to 2010 ACR/EULAR classification and recommendations: a score ≥ 6 defines RA. The disease had to be active, with a disease-activity score evaluated by a DAS-28 score of ≥ 3.2 despite potentially efficacious doses of MTX (10 mg/week for 3 months minimum). As patients were in failure of MTX, they could not be in low disease activity or in remission (respectively DAS-28-VS score between 2.6 and 3.2 and < 2.6). The DAS-28 score lists 28 tender and swollen joint counts, the VS rate (reflect of blood inflammation) and disease global activity evaluated by the patients themselves. So, each patient suffers from tender and swollen joints for at least 6 weeks, with inflammatory schedule pain (awakenings and morning stiffness > 30 minutes), with some degree of blood inflammation.

The patients had to be naive to biotherapies such as TNF inhibitors (infliximab, certolizumab, adalimumab, golimumab, etanercept). In each study, corticosteroids could be only used if their doses were <10 mg/day and had been stable for 2 weeks before inclusion of the patients in the trial.

We noted the age, gender, concomitant treatments, average duration of RA disease, MTX doses, DAS 28, and rates of ACR 20, 50, 70 scores.

Because MTX treatment had failed, its pharmacological clinical efficacy was the same in both groups: thus, the non-specific effect was studied in the placebo + MTX group only. The primary goal in our meta-analysis was to assess the responders' ACR 20, 50 and 70 scores from each study. The second goal was to assess the impact of the different TNF inhibitors and their administration routes.

Methods

A systematic review of the literature was conducted (ending in October 2015) using PubMed, Embase and Cochrane databases. Randomized controlled trials were selected that included RA patients treated for the first time by any one of five TNF inhibitors after failure of MTX therapy (at a minimum dose of 10 mg/week for a minimum of 3 months).

Patients were divided into two groups according to their received treatment. The 1st group corresponds to patients who received placebo plus MTX, whereas the 2nd group corresponds to patients who were treated by TNF-inhibitors active drug plus MTX. It is important to notice that each group continued to take their MTX therapy. As MTX treatment was considered inefficient: thus, the first group demonstrated the non-specific effect and so, the placebo effect.

The following keywords were searched for in the databases using Boolean criteria ('and', 'or', 'not'): rheumatoid arthritis, MTX failure, and tumour-necrosis inhibitors (commercial and non-commercial drug names). The specific MESH terms were, first, 'rheumatoid arthritis' AND 'infliximab' OR 'Remicade®, 'etanercept' OR 'Enbrel®', 'golimumab' OR 'Simponi®', 'adalimumab' or 'Humira®', 'certolizumab' or 'Cimzia®', and secondly 'placebo effect', 'MTX failure'. There were no geographic or demographic restrictions, but we only considered reports written in English and French.

After selecting these potential papers, we chose eligible trials according to our criteria. These had to include name of the first author, year of publication, study design, geographic zone, number of patients in the two groups, ACR 20, 50, and 70 scores at week 24, drug-administration routes, and name of the TNF inhibitor (s). The choose of selecting articles at week 24 corresponded to the patients' clinical evaluation after 6 months of treatment by MTX and TNF inhibitors, as it is usually done in current clinics (in fact, as usual, the decision to change the biotherapy occurs at 6 months in case of treatment failure, not at 3 months because it is too early to judge of treatment efficacy, excepted for the drug certolizumab).

Statistical analyses

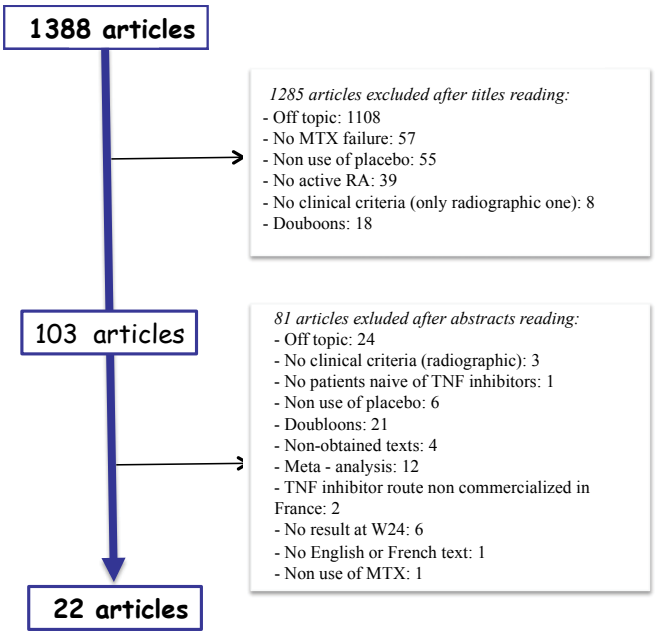
This meta-analysis used Methodomics software to identify the ACR 20, 50 and 70 response rates and Excel software was used to check each data into tables. Heterogeneity tests were conducted by a specific statistician to choose between random or fixed-effect models. Fix models were chosen if the heterogeneity was too important in order to decrease bias. Confidence intervals were set at 95% and statistical significance was $p < 0.05$.

Deontology

All trials included in our meta-analysis had been approved by a deontological committee.

Results

Twenty-two RCTs (out of 1388) were included in the systematic review and meta-analysis as it showed in this flow chart.



Flow chart 1: Systemic review and meta-analysis.

Six articles were on infliximab, five etanercept, four adalimumab, three certolizumab, and four golimumab. These included a total of 9649 patients: 2953 in the MTX + placebo group (group 1) and 6696 to those that received TNF-inhibitor therapy + MTX (group 2). The RCTs which studied infliximab included 3206 patients (994 placebo, 2212 TNF-inhibitors), the etanercept studies included 1693 patients (537 placebo, 1156 TNF-inhibitors), the adalimumab studies included 1573 patients (592 placebo, 981 TNF-inhibitors), those that reported certolizumab included 1848 patients (445 placebo, 1403 TNF-inhibitors), and the golimumab included 1329 patients (385 placebo, 944 TNF-inhibitors).

Patients had suffered from RA for at least 3 months: median duration was 7.92 years for infliximab, 8.8 years for etanercept, 10.23 years for adalimumab, 7.3 years for certolizumab, and 7.6 years for golimumab. Overall the mean patient age was 52.3 years: 52.1 years for infliximab (one missing value), 50.1 years for etanercept (2 missing data), 55.1 years for adalimumab, 52.7 years for certolizumab, and 51.5 years for golimumab.

Women were 80% of cases: of these, 78% represented the patients who received infliximab (one missing value) 81% who received etanercept (2 missing values), 79% who received adalimumab, 78% who received certolizumab, and 81% who received golimumab. Of the total, 82% were Caucasian. There were 13 studies that included different regions of the world, 3 that only included Japanese patients, 4 that only included American and Canadian patients, and 2 that only included European patients.

In all selected studies, MTX doses were 10-25 mg/week for at least 3 months.

Among all studies, DAS-28-VS activity scores were estimated on overage at 6.19 for all patients on TNF-inhibitors active drug +MTX, and 6.11 for all patients in the MTX + placebo group.

The different routes of medication included in this meta-analysis were those recommended by medical authorities (SFR, EULAR and ACR committees): the IV route for infliximab and subcutaneously (SC) for the other TNF-inhibitor drugs. MTX was administered by SC or orally.

ACR-20 criteria

ACR-20 scores at week-24 were available for 13 of the RCTs: two for infliximab [16,17], three for etanercept [18-20], three for adalimumab [21-23], three for certolizumab [24-26] and two for golimumab [27,28]. Two trials reported using the IV route [16,17] and 10 reported the SC route.

The overall non-specific effect was 24.7% (CI95% [0.192;0.301] p = 0). The random model was used (Table 1).

The non-specific effect was different for each drug (Table 2). It was higher for infliximab at 31.9% ((CI95% [0.154; 0.495]), p = 0.001) and 29.7% for golimumab ((CI95% [0.237; 0.358]), p = 0.418 not significant).

Heterogeneity tests were significant for adalimumab: 26.7% ((CI95% [0.161;0.373]), p = 0.001), for certolizumab: 16.4% ((CI95% [0.068;0.260]), p = 0), and for infliximab: 31.9% ((CI95% [0.154;0.485]), p = 0.001). Subgroup analyses for the method of injection showed 31.9% vs. 23.3% for the IV route non-specific effect response vs. the SC route ((CI95% [0.154;0.485]), p = 0.001) (Table 3).

ACR-50 criteria

The ACR-50 responses were studied in 14 RCTs: two for infliximab [16,17], three for etanercept [18-20], three for adalimumab [21-23], three for certolizumab [25-27] and three for golimumab [28,29]. Two trials reported using the IV route [16,17] and 12 used the SC route [18-23, 25-29].

The ACR-50 non-specific response, at week-24, was 10.90% ((CI95% [0.074;0.144]), p = 0) for the 14 RCTs from the random model (Table 4). It was only significant for adalimumab: 15.4% ((CI95% [0.026;0.281]), p = 0), etanercept: 11% ((CI95% [0.026;0.195]), p = 0.008) and infliximab: 14% ((CI95% [0.033;0.246]), p = 0.008) (Table 5). The poorest result was obtained for certolizumab: 5% ((CI 95% [0.017; 0.084]), p = 0.062) (Table 5). Even though heterogeneity tests were not statistically different with regards to golimumab and certolizumab studies, heterogeneity increased up to 94.1% for adalimumab and was 64.0% for certolizumab.

The non-specific effects for the ACR-50 scores were not associated with increased use of IV or SC routes, although responses generated by the IV route were 14% ((CI95% [0.033; 0.246]), p = 0.008) versus 10.5% for the SC ((CI95% [0.064; 0.145]), p = 0).

ACR-70 criteria

The ACR-70 response, at week-24, included 13 RCTs: two for infliximab [16,17], three for etanercept [18-20], three for adalimumab [21-23], three for certolizumab [24-26] and two for golimumab [27,28]. Two studies reported using the IV route [16,17] and 11 reported the SC route.

The ACR-70 non-specific effect at week-24 was 3.4% ((CI95% [0.019;0.049]), p = 0), using the random model (Table 6).

For each type of TNF-inhibitor, the placebo effect was increased by 6.1% with infliximab (fixed model, ((CI95% [0.017; 0.105]), p = 0.112)) and was decreased at maximum by 1.6% with certolizumab (fixed model, ((CI95% [0.003; 0.028]), p = 0.3)), but neither result was statistically significant.

Table 1. Over-all results for the ACR-20 scores according to statistical fixed and random models.

Model	Prevalence	95%CI	Heterogeneity	*p*-value-het	Q-het	I^2
Fixed	0.219	(0.202; 0.237)	12	0	100.621	88.07
Random	0.247	(0.192; 0.301)	12	0	100.621	88.07

Table 2. TNF-inhibitor and placebo effects for ACR-20 scores according to the statistical random model.

TNF-inhibitor	Prevalence	95%CI	Q-het	Df-het	*p*-value het??	I^2
Adalimumab	0.267	0.161; 0.373	14.256	2	0.001	85.97
Certolizumab	0.164	0.068; 0.260	16.971	2	0	88.22
Etanercept	0.215	0.129; 0.302	4.125	2	0.127	51.52
Golimumab	0.297	0.237; 0.358	0.656	1	0.418	0
Infliximab	0.319	0.154; 0.485	10.633	1	0.001	90.59

Table 3. Placebo effect according to type of drug administration: intravenous (i.v.) or subcutaneous (SC).

Route	Prevalence	95%CI	Q-HET	Df-het	*p*-value-het	I^2
i.v.	0.319	0.154; 0.485	10.633	1	0.001	90.59
SC	0.233	0.173; 0.293	81.754	10	0	87.77

Table 4: Overall results for the ACR-50 score according to the statistical fixed and random models.

Model	Prevalence	95%CI	Heterogeneity	*p*-value-het	Q-het	I^2
Fixed	0.09	0.078; 0.101	13	0	101.653	87.21
Random	0.109	0.074; 0.144	13	0	101.653	87.21

Table 5: TNF-inhibitor and placebo effects for the ACR-50 score according to the statistical random model.

TNF-inhibitor	Prevalence	95%CI	Q-het	Df-het	*p*-value het	I^2
Adalimumab	0.154	0.026; 0.281	33.941	2	0	94.11
Certolizumab	0.05	0.017; 0.084	5.562	2	0.062	64.04
Etanercept	0.11	0.026; 0.195	9.604	2	0.008	79.17
Golimumab	0.107	0.053; 0.161	5.878	2	0.053	65.97
Infliximab	0.14	0.033; 0.246	7.074	1	0.008	85.86

Table 6: Overall results for the ACR-70 score according to the statistical fixed and random models.

Model	Prevalence	95%CI	Heterogeneity	*p*-value-het	Q-het	I^2
Fixed	0.0	**0;0**	12	0	87.929	86.35
Random	0.034	0.019; 0.049	12	0	87.929	86.35

The chosen route of drug administration (IV or SC) did not significantly change the results with only a 6.1% non-specific effect response with IV ((CI95% [0.017; 0.105]), p = 0.112) versus a 2.9% with SC ((CI95% [0.014; 0.044]), p = 0).

Discussion

The aim of this meta-analysis was to estimate the placebo effect *via* the non-specific effect as scored by clinical ACR 20, 50 and 70 responses after the 24th week of treatment with one of the five TNF-inhibitors in patients with RA and who had a failed MTX treatment. They also had to be biotherapy naive. The demographic data showed that the two groups (placebo + MTX and TNF-inhibitor + MTX) were homogeneous and comparable, and representative of RA patients treated at hospital. The mean age of patients was 52.3 years with mid disease duration of 8.52 years. Of the total, 80% were women.

Every patient included in this meta-analysis had a failed MTX treatment and had been randomized into the two groups. The meta-analysis was conducted with the MTX + placebo group. The placebo effect was the most important for the ACR-20 scores with a top of was 24.7%. Overall, the more stringent the ACR criteria, the lower the placebo effect.

Heterogeneity was a factor because of the variation in MTX and TNF-blocker dosages and administration frequencies. The rates were analysed using the statistical random model. Response to placebo seemed to vary depending even if the results were no significant on the type of administration with a higher placebo effect when the drug was administered via the IV route.

This study shows that the non-specific effect can provide therapeutic benefits even though the treatment used has been a failure. Thus, this needs to be taken into account when considering medical prescriptions and therapeutics.

However, this study was limited because of heterogeneity of drug therapies and their different doses and pharmacological effects even though the patients' criteria at inclusion had been fulfilled. Neither the numbers of Caucasian or female patients, or the dose rates used for MTX, glucocorticoids, or TNF-blockers, provided an adequate explanation for the observed heterogeneity. Nevertheless, the doses of TNF-blockers used in different countries and the administration route selected (particularly the IV route) could account for these variations. Baseline characteristics may influence the 'placebo effect', and a meta-regression could help in exploring heterogeneity.

Learned societies as EULAR, ACR and SFR societies, consider that 6 months TNF-inhibitors is sufficient to evaluate the efficacy of TNF inhibitors [4-6]. Many studies show, as it was mentioned in introduction, that non-specific effect as the placebo effect, have a higher potential of acting during the third first months, even though it could occur at any time during treatment [15]. However, the evaluation at 6 months of treatment could be difficult on certain points.

Firstly, because it could exist pharmacokinetics variability between patients, explaining the better or worse efficacy of active drug on RA activity [30]. Indeed, many studies focused on the potential polymorphism impact on TNF-inhibitors efficacy. They demonstrated that it could exist a better clinical response when there are important residual rates of TNF-inhibitors in blood [31-36]. A few clinical patients' characteristics appear to influence TNF-inhibitors efficacy like the higher serology positivity, patient's weight, and FcγRIIIa polymorphism (patients having one 'F' allele have a less response to infliximab whereas them who have 'V/V' genotype [37]. However, the studies included in the meta-analysis are all randomized allowing the same repartition of these characteristics in the two groups. As for sure, TNF-inhibitors efficacy results on their action on the immune system.

Secondly, it could be difficult to *stricto sensu* compare each TNF-inhibitors between them because their half-life times are not the same (9-12 days for infliximab, 9-15 days for golimumab, 14 days for certolizumab, 4-5 days for etanercept, and 10-20 days for adalimumab), as their ways of administration (IV vs. SC routes with so not the same residual rates in patients' blood) and their way of acting (chimeric IgG1 with a murine fab portion for infliximab, human recombinant IgG1 for adalimumab and golimumab, recombinant fusion protein with soluble receptor for etanercept, humanized fab fragment antibody for certolizumab).

Moreover, the dose of MTX in some trials was about 10 mg/week, which is not the optimal dose: the diagnosis of MTX failure could be wrong. Indeed, MTX optimal dose is about 20 mg/week, and it could be even more in some patients.

The choice of focussing on the change in ACR criteria rather than DAS 28 or PRO's (Patient Reported Outcome) scores like HAQ would appear open to criticism in a number of respects. Indeed, ACR criteria could appear less sensitive to the real placebo effect estimation than PRO's score because it is not submitted to patients' suggestiveness and feelings (it only depends on the physician's assessment) and it is not a continuous variable. However, after checking ACR, DAS 28, and HAQ changes in our 22 included trials, data were only homogenous and statistically analysable for ACR criteria.

Furthermore, it is difficult to only talk about placebo effect because, as we said in introduction, the placebo effect is a component of the non-specific effect. The improvement noticed between baseline to endpoint could be more linked to a combination of regression to the mid, natural improvement and willingness to please the investigators than to placebo effect.

To conclude, the placebo effect must be taken into account in all clinical therapeutic responses, despite treatment failure of MTX, even though new biotherapies more increase the chance of remission from RA in addition to MTX.

Conflict of Interest

There is no conflict of interest.

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Table S1: Patients within the selected studies suffered from RA.

Symptoms	Points
Joint distribution	**(0-5)**
1 large joint	0
2-10 large joints	1
1-3 small joints (large joints not counted)	2
4-10 small joints (large joints not counted)	3
> 10 joints (at least one small joint)	5
Serology	**(0-3)**
Negative	0
Low positive ACPA (or RF)	2
High positive ACPA (or RF)	3
Symptoms duration	**(0-1)**
< 6 weeks	0
> 6 weeks	1
Acute phase reactants	**(0-1)**
Normal CRP and normal VS	0
Abnormal CRP or abnormal VS	1