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Review article

Adalimumab in rheumatoid arthritis treatment: a systematic review and meta-analysis of randomized clinical trials

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ABSTRACT

Since the discovery of the role of tumor necrosis factor in the physiopathological process of rheumatoid arthritis, five drugs that block this cytokine have been used as therapeutic options. To evaluate the efficacy and safety of adalimumab in the treatment of rheumatoid arthritis we performed a systematic review and meta-analysis of randomized controlled trials. A search of relevant studies in Medline (through PubMed) and LILACS in June 2011 was carried out. Study selection, data collection and analysis were performed in pairs and independently by two reviewers and by a third reviewer in cases of disagreement. The meta-analysis was performed using the software Review Manager® 5.1 using the random effects model. Eleven articles related to adalimumab were included and considered nine studies with 3461 patients. Ten studies showed low risk of bias regarding the blinding of participants and personnel and blinding of outcome assessment. Patients who received the combination treatment of adalimumab and methotrexate showed better efficacy results and lower radiographic progression when compared to placebo + methotrexate in 24-104 weeks. Patients who received adalimumab as monotherapy showed better efficacy outcomes when compared to placebo in 24 and 26 weeks. The results of the meta-analyses of adverse events were not statistically significant, except for reactions at the injection site, which favored the control group. Adalimumab efficacy was demonstrated in monotherapy and when associated to a DMARD, but the evidence for combined use is more robust.

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Adalimumabe no tratamento da artrite reumatoide: uma revisão sistemática e metanálise de ensaios clínicos randomizados

R E S U M O

Palavras-chave:
Artrite reumatoide
Adalimumabe
Fator de necrose tumoral
Revisão sistemática
Metanálise

Desde a descoberta do papel do fator de necrose tumoral no processo fisiopatológico da artrite reumatoide, cinco medicamentos bloqueadores dessa citocina têm sido empregados como opção terapêutica. Para avaliar a eficácia e a segurança do adalimumabe no tratamento da artrite reumatoide foi conduzida uma revisão sistemática com metanálise de ensaios clínicos controlados e randomizados. Foi realizada busca de estudos relevantes nas bases de dados Medline (via PubMed) e LILACS em junho de 2011. A seleção dos estudos, coleta e análise de dados foram realizadas de forma pareada e independente por dois revisores e por um terceiro revisor em casos de discordância. A metanálise foi conduzida no software Review Manager® 5.1 usando o modelo de efeitos aleatórios. Onze artigos referentes ao adalimumabe foram incluídos e contemplaram nove estudos com 3461 pacientes. Dez estudos mostraram baixo risco de viés quanto ao cegamento dos participantes e pessoal e cegamento de avaliação de resultados. Os pacientes que receberam tratamento da associação de adalimumabe e metotrexato apresentam melhores resultados de eficácia e menor progressão radiográfica quando comparados ao grupo placebo + metotrexato em 24 a 104 semanas. Os pacientes que utilizaram adalimumabe em monoterapia apresentaram melhores resultados de eficácia em relação ao placebo em 24 e 26 semanas. Os resultados das metanálises de eventos adversos não foram estatisticamente significantes, exceto para reações no local de aplicação, na qual favoreceu o grupo controle. A eficácia do adalimumabe foi demonstrada em monoterapia e associado a algum MMCD, porém as evidências para o uso combinado são mais robustas.

Introduction

Evidence-based Medicine is the conscientious, explicit and sensible use of best evidence for decision-making in patient care. The practice of evidence-based Medicine integrates the individual experience of the physician with the best evidence available through systematic research.[1]

Systematic reviews are considered Level I evidence and have stringent methods that decrease the occurrence of biases when compared to narrative reviews.[2] The benefits of the monoclonal antibody adalimumab in the control of rheumatoid arthritis (RA) have been widely reported in the literature and, in Brazil, this is the second most used drug of this class of biological agents for the treatment of this disease.[3-5] The annual cost of this treatment is high, being estimated in Brazil at R$ 71,117.00 and with a ratio of incremental cost-effectiveness per quality-adjusted life year (QALY), when compared to therapy with methotrexate (MTX), of R$ 628.124,00.[6] This high cost emphasizes the importance of systematization of all the evidence available to aid decision-making in health care.

RA is a systemic inflammatory, chronic and progressive disease of unknown etiology that affects the synovial membrane of joints, leading to cartilage and bone destruction. This autoimmune disorder affects the joints, often in the hands and feet, on both sides equally and symmetrically.[3,7] The prevalence is estimated at 0.5-1.0% of the population and is more frequent in women, according to studies performed in the United States, Europe and Brazil.[8,9]

The care of patients with RA includes the use of disease-modifying antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, in addition to non-pharmacological treatment such as occupational therapy and physical therapy.[10] Biological DMARDs represent a breakthrough in therapy and RA and have been indicated in cases where patients do not respond to conventional treatment.

The tumor necrosis factor (TNF) blockers adalimumab, etanercept, infliximab, certolizumab and golimumab are included in this class.[3,10,11]

Aiming to contribute to the practice of evidence-based Medicine, we performed a systematic review and meta-analysis of randomized controlled trials to evaluate the efficacy and safety of Adalimumab in the treatment of RA.

Methods

This study is part of a systematic review of randomized controlled trials on the efficacy and safety of the drugs adalimumab, etanercept, infliximab and rituximab in the treatment of rheumatoid arthritis.

Eligibility criteria

Randomized controlled trials written in Portuguese, English and Spanish were selected for the review. We considered comparisons of Adalimumab 40 mg once every 15 days as monotherapy or combined with DMARDs vs. control group in patients with rheumatoid arthritis diagnosis according to the revised criteria of the American College of Rheumatology and active disease.[12]

Article search

The search for studies was carried out in the Medline database (through Pubmed) and LILACS in June 2011 and supplemented by manual searching in references of systematic reviews and the studies that were found. The search strategy consisted of the following words: rheumatoid arthritis, monoclonal antibodies, D2E7 antibody, Humira®. The search in Pubmed was structured from Mesh (Medical Subject Headings) terms and a sensitive search was performed for randomized controlled trials.

Study selection and data collection

Study selection was carried out by analysis of the titles and abstracts of studies selected by the search. Data were collected using a standardized form.

Two reviewers independently assessed and extracted data from each study and disagreements were resolved by consensus or by a third reviewer. Data on characteristics of the study design and the population, duration of disease, previous or concomitant use of DMARDs, intervention and outcomes were collected for each trial.

The primary outcome was the ACR20 response defined by the American College of Rheumatology (ACR). ACR20 response occurs when there is a decreased of 20% in the count of joints with pain and edema and improvement in 3 of the 5 variables: overall assessment by the patient and physician, pain, Health Assessment Questionnaire (HAQ) scale and acute phase inflammatory markers (C-reactive protein or erythrocyte sedimentation rate - ESR).[13] The secondary outcomes were ACR50 and ACR70 responses, in which there are 50% and 70% improvement in the same parameters, in addition to functionality, measured by the HAQ scale, radiographic outcomes, loss to follow-up and safety. The authors, if necessary, were contacted to provide additional information.

Methodological quality and risk of bias

The assessment of methodological quality and risk of bias was performed independently by two reviewers with access to the author's name, institution and the journal that published the study and disagreements were resolved by consensus. Quality assessment by the modified Jadad scale and risk of bias assessment proposed by the Cochrane Collaboration were employed. These tools assess methodological aspects, such as randomization, blinding and loss of participants. The modified Jadad scale scores clinical trials from 0-6 and the higher the score, the better the methodological quality.[14, 15]

Meta-analysis

The meta-analysis was performed using the Review Manager® 5.1 software. We used the weighted difference in means for continuous outcomes and relative risk for dichotomous data, both considering a confidence interval of 95%.

The presence of heterogeneity between studies was considered a premise and therefore the random effects model was applied. Statistical heterogeneity was considered if $P < 0.10$ for the chi-square test and $I^2 > 40\%$ and in those cases,

the potential factors that influenced this phenomenon were investigated.[16]

Results

The search for studies of the four drugs (Adalimumab, Etanercept, Infliximab and Rituximab) resulted in 3620 articles in Pubmed and 84 in LILACS, as well as nine articles found by manual search. Eleven articles related to Adalimumab were included and considered nine studies with 3461 patients (Fig. 1).

Study characteristics

Seven studies evaluated groups of patients treated with Adalimumab (ADA) 40 mg every 2 weeks combined with some DMARDs vs. DMARDs as monotherapy (plus placebo): in six studies patients used MTX and in the STAR study subjects received some DMARDs, among them MTX, chloroquine, hydroxychloroquine, leflunomide, parenteral gold, oral gold
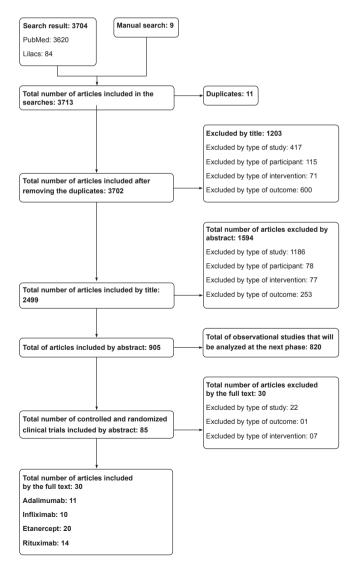

Fig. 1 – Diagram of the selection process for the inclusion of randomized controlled trials in the systematic review.

compounds, sulfasalazine, or any combination of these.[17] Most patients (82.1% group ADA + DMARDs and 84.9% group placebo + DMARDs) used one or more DMARDs during the study and MTX was the most common (56.0% group ADA + DMARDs and 62.6% group placebo + DMARDs). Two trials were performed in groups using ADA 40 mg every 2 weeks as monotherapy compared to placebo. Only the PREMIER study included arms of comparison between ADA monotherapy vs. MTX monotherapy.[18]

Patients had active RA in all studies. The study GUEPARD defined active disease by DAS28 (disease activity score) greater than or equal to 5.1.[19] The other studies defined it by counting the joints involved, ranging from 9 to 12 tender joints and 6 and 10 swollen joints. Furthermore, the PREMIER and DE019 studies included patients with positive rheumatoid factor or at least one joint with erosion.[18,20-22]

The GUEPARD and PREMIER studies evaluated treatment-naïve patients with MTX. [18,19,20] The STAR study included treatment-naïve patients or those who had failed MTX therapy, whereas others showed data from individuals with previous use or treatment failure with DMARDs.[17] The GUEPARD and PREMIER studies considered patients with short disease duration, with a mean ranging from 4-8 months in the randomized groups, while the mean in the remainder ranged from 7-11 years.[18,19,20] The number of swollen and tender joints at baseline was similar among trials, except in the GUEPARD study, which showed lower values for these measures (Table 1).[19]

No authors declared freedom from conflicts of interest. The GUEPARD study was funded by the French Society of Rheumatology and the treatment with Adalimumab was provided by the Abbott laboratory.[19] Chen et al. reported no source of funding and all other studies declared Abbott pharmaceutical industry support.[23]

Methodological quality and risk of bias

The GUEPARD study showed a value in the modified Jadad scale equal to three (low quality) by not being double-blind, two (11.1%) had a score equal to four (appropriate quality), while five studies (55.6%) showed score of five and one study, by van de Putte et al., had a score of six, indicating high quality.[19,24] The mean score was 4.66 (Table 2).

Only in the study by van de Putte et al., methods of randomization and allocation concealment for interventions after randomization were reported, even though all studies were described as randomized.[24] Therefore, as these methods were considered appropriate, only that study showed low risk of bias in allocation concealment (selection bias) and in the generation of random allocation sequences (selection bias). The allocation concealment is an important aspect in the design of a study, because when this procedure is appropriately carried out, one can prevent selection bias in the allocation of intervention, by protecting the allocation sequence until interventions are allocated (Table 2).[15]

The study of van de Putte et al. showed a high risk of bias in relation to incomplete reporting of outcomes, as the loss to follow-up was significantly different between the groups (56.4% in the placebo group and 28.3% in the ADA group).[24] The GUEPARD study, for not being double-blind, showed a high risk of bias in the criteria of blinding of participants and personnel (performance bias), and blinding of outcome assessment (detection bias).[19] The other studies showed low risk of bias in these two items (Table 2).

The inter-examiner agreement level showed an almost perfect agreement (kappa = 0.831, SD = 0.675) in the assessment of the methodological quality by the modified Jadad scale and substantial agreement (kappa = 0.654, SD = 0.571) in the analysis of risk of bias.[25]

Efficacy

Adalimumab 40 mg + DMARDs vs. placebo + DMARDs

Patients who used ADA + DMARDs were more likely to achieve ACR20, ACR50 and ACR70 responses at 24 weeks when compared to patients from the group placebo + DMARDs (Fig. 2). The relative risk (RR) with confidence interval (CI) of 95% to achieve ACR20 response was 1.92 (1.50; 2.47) with high heterogeneity (I^2 = 66%, P = 0.01). We excluded studies to assess which of them would be influencing heterogeneity and it was observed that after removing the ARMADA study [26] the RR (95%CI) was 1.73 (1.48; 2.02) with no statistically significant heterogeneity (I^2 = 24%, P = 0.26) (Fig. 2).[17,19,21,23,27]

In up to 24 weeks, the ACR50 response showed RR (95% CI) of 2.91 (2.00; 4.24), with high heterogeneity (I^2 = 59%, P = 0.03). The exclusion of the study by Chen et al.[23] increased the RR (95% CI) to 3.23 (2.35; 4.44) and statistical heterogeneity may not be significant (I^2 = 41%, P = 0.15).[17,19,21,26,27] In up to 24 weeks, the ACR70 response was 4.02 (2.77; 5.96), with no statistically significant heterogeneity (I^2 = 3%, P = 0.40) (Fig. 2).[17,19,21,23,26,27]

The sources of heterogeneity for the studies by Chen et al. and ARMADA are not clear.[23,26] The exclusion of the GUEPARD study, the only non-double-blind trial, from the three meta-analyses did not alter the level of heterogeneity and statistical significance of the results.[19]

In 52 weeks of treatment, the results of meta-analyses showed no statistical significance and showed high heterogeneity (I^2= 90-96% and P ≤ 0.001).[18,21] The isolated studies indicated statistically significant differences between the comparison groups, favoring ADA + MTX therapy. The magnitude of the response was greater in the DE019 study, when compared to PREMIER. This difference, as well as the high heterogeneity found in the meta-analyses, can be explained by the fact that the PREMIER study included patients with early disease (up to one year of diagnosis) and treatment-naïve patients with MTX, while the DE019 study evaluated patients with a mean of 11 years of disease and treatment failure with DMARDs.[18,21]

Jamal et al., in a continuation of the DE019 study, found that patients with early disease (≤ 3 years) and with established disease (> 3 years) showed the same response profile, always in favor of the intervention group.[22]

In the analysis of 104 weeks, only the PREMIER study was included.[18] The RR (95% CI) for ACR20 was 1.23 (1.08; 1.41), for ACR50 was 1.36 (1.15; 1.62) and for ACR70 was 1.68 (1.33; 2.12), favoring the ADA + MTX group.

The comparison of ADA monotherapy vs. MTX was performed only by the PREMIER study, which showed no statistical difference favoring the MTX group, only for ACR20 response at 52 weeks, although with a borderline confidence

Table 1 – Basal characteristics of the studies included in the systematic review.

Study (time of follow-up)	Patients (n)	Age (years) mean (SD)	Time of disease duration (years) mean (SD)	Patients that used DMARDs previously n (%)	Edematous joints mean (SD)	Painful joints mean (SD)	Patients using steroids n (%)	Patients using NSAIDs n (%)	HAQ mean (SD)
STAR (Furst et al., 2003) - 24 weeks[17]	636								
ADA 40 mg every 2 weeks + DMARDs	318	55.0(12.8)	9.3(8.8)	292(91.8)	20.9(11.0)	27.3(13.0)	162(50.9)	198(62.3)	1.37(0.62)
MMCD	318	55.8(12.4)	11.5(9.7)	295(92.8)	21.3(11.2)	27.6(13.8)	173(54.4)	203(63.8)	1.43(0.60)
ARMADA (Weinblatt et al., 2003) - 24 weeks[26]	271								
ADA 40 mg every 2 weeks + MTX	67	57.2(11.4)	12.2(11.1)	NI	17.3(8.6)	28.0(12.7)	NI	NI	1.55(0.61)
MTX	62	569(10.8)	11.1(8.0)	NI	16.9(9.5)	28.7(15.2)	36(58.1)	NI	1.64(0.63)
DE019 (Keystone et al., 2004)-52 weeks[21]	619								
ADA 40 mg every 2 weeks + MTX	207	56.1(13.5)	11(9.2)	NI	19.3(9.8)	27.3(12.7)	SI	NI	1.45(0.63)
MTX	200	56.1(12.0	10.9(8.8)	NI	19.0(9.5)	28.1(13.8)	99(49.5)	NI	1.48(0.59)
DE019 (Jamal et al., 2009) - 52 weeks[22]	407								
ADA 40 mg every 2 weeks + MTX≤3 years	41	49.7	1.8	NI	22.1	29.5	23(56.1)	NI	1.5
MTX ≤ 3 years	37	52.6	1.9	NI	19.2	30.1	13(35.1)	NI	1.5
ADA 40 mg every 2 weeks + MTX > 3 years	166	57	13.3	NI	18.7	26.9	74(44.6)	NI	1.4
MTX > 3 years	163	56.3	12.9	NI	19.1	28	58(35.6)	NI	1.5
Kim et al. (2007) - 24 weeks[27]	128								
ADA 40 mg every 2 weeks + MTX	65	48.5(10.2)	6.8(4.2)	65(100)	12.2(5.6)	19.2(9.2)	NI	NI	1.4(0.6)
MTX	63	49.8(10.5)	6.9(4.5)	63(100)	12.8(5.8)	20.3(8.6)	NI	NI	1.3(0.6)
PREMIER (Breedveld et al., 2006) - 104 weeks[18]	799								
ADA 40 mg every 2 weeks + MTX	268	51.9(14.0)	0.7(0.8)	87(32.5)	21.1 (11.2)	30.7 (14.2)	96(35.8)	NI	1.5(0.6)
ADA 40 mg every 2 weeks	274	52.1(13.5)	0.7(0.8)	91(33.2)	21.8 (10.5)	31.8 (13.6)	100(36.5)	NI	1.6(0.6)
MTX	257	52.0(13.1)	0.8(0.9)	81(31.5)	22.1 (11.7)	32.3 (14.3)	91(35.4)	NI	1.5(0.6)

Table 1 – Basal characteristics of the studies included in the systematic review (continued).

Estudo (tempo de acompanhamento)	Pacientes (n)	Idade (anos) média (DP)	Tempo de duração doença (anos) média (DP)	Pacientes que usaram MMCD prévio n (%)	Articulações edemaciadas média (DP)	Articulações dolorosas média (DP)	Pacientes em uso de esteroides n (%)	Pacientes em uso de AINES n (%)	HAQ média (DP)
PREMIER (Kimel et al., 2008) - 104 weeks [20]									
ADA 40 mg every 2 weeks + MTX	268	51.9(14.0)	0.7(0.8)	87(32.5)	21.1(11.2)	30.7(14.2)	96(35.8)	NI	1.6(0.6)
MTX	257	52.0(13.1)	0.8(0.9)	81(31.5)	22.1(11.7)	32.3(14.3)	91(35.4)	NI	1.5(0.6)
Chen et al. (2009) - 12 weeks [26]	47								
ADA 40 mg every 2 weeks + MTX	35	53.0(29.0-75.0)≠	6.2(0.3-19.1)≠	35(100)	21.9	32.5	NI	NI	1.7(1.5-1.9)≠
MTX	12	53(35.0-73.0)≠	8.3(1.3-15.6)≠	12(100)	24.1	37.2	NI	NI	1.8(1.5-2.1)≠
GUEPARD (Soubrier et al., 2009) - 52 weeks [19]	65								
ADA 40 mg every 2 weeks + MTX	33	46.3(16.3)	0.4(0.2-0.5)±	SI	9.5	13.8	NI	10(30.3)	1.69(0.59)
MTX	32	49.3(15.2)	0.4(0.3-0.4)±	NI	10.8	14.1	NI	10(31.3)	1.41(0.74)
Van de Putte et al. (2004) - 26 weeks [24]	544								
ADA 40 mg every 2 weeks	113	52.7(13.3)	10.6(6.9)	NI	20.5(10.6)	33.7(15.9)	77(68.1)	93(82.3)	1.83(0.59)
Placebo	110	53.5(13.2)	11.6(9.3)	NI	19.8(9.3)	35.5(14.2)	74(67.3)	92(83.6)	1.88(0.64)
CHANGE (Miyasaka et al., 2008) - 24 weeks [28]	352								
ADA 40 mg every 2 weeks	91	56.9(10.3)	9.9(7.9)	91(100)	19.1(7.3)	24.4(10.7)	NI	NI	1.64(0.70)
Placebo	87	53.4(12.8)	8.4(8.2)	87(100)	19.3(7.0)	23.7(8.8)	NI	NI	1.39(0.75)

ADA, adalimumab; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; HAQ, Health Assessment Questionnaire; DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate; NI, no information.

± median (interquartile interval).

≠ median (amplitude).

Study	Random generation of allocation sequence (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data	Selective reporting of outcomes	Modified Jadad scale
Van de Putte et al., 2004[24]	Low risk	Low risk	Low risk	Low risk	High risk	Uncertain	6
PREMIER (Breedveld 2006; Kimel 2008)[18,20]	Uncertain	Uncertain	Low risk	Low risk	Low risk	Low risk	5
DE019 (Keystone et al., 2004; Jamal et al.,2009)[21,22]	Uncertain	Uncertain	Low risk	Low risk	Low risk	Low risk	5
Kim et al., 2007[27]	Uncertain	Uncertain	Low risk	Low risk	Low risk	Low risk	5
ARMADA (Weinblatt et al., 2003)[16]	Uncertain	Uncertain	Low risk	Low risk	Low risk	Low risk	5
CHANGE (Miyasaka et al., 2008)[28]	Uncertain	Uncertain	Low risk	Low risk	Low risk	Low risk	5
Chen et al., 2009[23]	Uncertain	Uncertain	Low risk	Low risk	Low risk	Low risk	4
STAR (Furst et al., 2003)[17]	Uncertain	Uncertain	Low risk	Low risk	Low risk	Uncertain	4
GUEPARD (Soubrier et al., 2009)[19]	Uncertain	Uncertain	High risk	High risk	Low risk	Low risk	3

Table 2 – Risk of bias proposed by the Cochrane Collaboration[11] and modified Jadad scale score10 of the methodological quality of the studies included in the systematic review.

interval (RR = 0.86, 95% CI: 0.74; 0.99). ACR50 and ACR70 responses at 52 weeks, and ACR20, ACR50 and ACR70 responses at 104 weeks were not statistically significant. This was also the only study that compared the combination ADA + MTX with ADA as monotherapy and the first group showed better ACR20, ACR50 and ACR70 responses at 52 and 104 weeks.[18]

Patients undergoing combination therapy (ADA+ DMARDs) showed greater reduction in HAQ scale. The difference in means between groups at 24 weeks was -0.32 (-0.40; -0.24) and at 52 weeks of -0.32 (-0.39; -0.24).[18,19,21,26,27] There was no significant heterogeneity (I^2 = 0% P = 0.99 and 0.60 for 24 and 52 weeks, respectively) (Table 3). Only the PREMIER study reported HAQ outcome at 104 weeks and the difference in means (95% CI) was -0.10 with non-significant 95% CI (-0.21; 0.01).[18]

The comparison of ADA vs. MTX was performed only by PREMIER study, which showed a difference in HAQ scale of zero between the groups at 52 and 104 weeks. This was also the only study that compared the combination with ADA + MTX with ADA as monotherapy. At 52 weeks, the first group showed greater reduction in HAQ scale (difference in means of -0.30, 95% CI: -0.41; -0.19); however, this result was not maintained at 104 weeks (difference in means of -0.10, 95% CI: -0.22; 0.02).[18]

Jamal et al. showed that the difference between ADA + MTX and placebo + MTX in relation to HAQ scale was higher in patients with up to three years of disease, when compared to patients with established RA, albeit not significant (P > 0.05).[22]

Kimel et al. used data from the PREMIER study and reported that patients with RA treated with ADA + MTX and MTX monotherapy had lower scores on the physical component summary of the SF-36 when compared with the reference population of the United States at 12 weeks. At 104 weeks of treatment, there was a difference only for the MTX group.[20]

It was not possible to perform a meta-analysis for radiological outcomes, as the articles did not indicate standard deviation or other measure of variability that would allow combination of data. Keystone et al. showed that at 52 weeks, the patients who received ADA + MTX showed better radiographic progression measured by the modified Sharp score, when compared with the placebo + MTX group (increase of 0.8 vs. 2.7, P ≤ 0.001). Improvements were also found in the scores for erosion (increase of 0.4 *versus* 1.6, p ≤ 0.001) and joint space narrowing (increase of 0.1 vs. 1.0, P ≤ 0.01).[21]

In the PREMIER study, at 26 weeks, the increase in the modified Sharp index was 0.8, 2.1 and 3.5 for patients on the combination therapy, MTX and ADA, respectively (P < 0.05 for all comparisons). At 52 and 104 weeks of treatment, these values were 1.3 and 1.9 (ADA + MTX), 3.0 and 5.5 (ADA) and 5.7 to 10.4 (MTX, with P < 0.05 for all comparisons).[18]

The meta-analysis showed a greater risk of loss to follow-up for lack of efficacy for placebo + DMARDs group in up to 104 weeks (RR 0.31 95% CI: 0.21; 0.45) with no statistical heterogeneity, I^2 = 0% and P = 0,80.[17,18,21,27] Loss to follow-up due to adverse reactions showed RR of 1.55 (95% CI: 1.08; 2.21) in up to 104 weeks, favoring the placebo + DMARDs group, with no statistical heterogeneity, I^2 = 0%, P = 0.61 (Table 3).[17,18,21,23,26,27]

The PREMIER study showed no difference in the risk of loss to follow-up due to lack of efficacy and adverse reactions between groups ADA and MTX. On the other hand, when comparing the group ADA + MTX with ADA monotherapy, RR (95% CI) of 3.91 (2.18; 7.02) was observed for loss to follow-up due to lack of efficacy, favoring the combination.[18]

Study or Subgroup	ADA + MTX (DMARDs) Events	Total	Placebo + MTX (MMCD) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.1.1 ACR20							
STAR (Fusrt 2003) 17	168	318	111	318	39.4%	1.51 [1.26, 1.82]	
GUEPARD (Soubrier 2009)19	28	33	16	32	14.5%	1.70 [1.17, 2.47]	
DE019 (Keystone 2004)21	131	207	59	200	28.7%	2.15 [1.69, 2.72]	
Chen 2009 23	19	35	4	12	3.2%	1.63 [0.69, 3.83]	
ARMADA (Weinblatt 2003)26	45	67	9	62	0.0%	4.63 [2.47, 8.66]	
Kim 2007 27	40	65	23	63	14.3%	1.69 [1.15, 2.46]	
Subtotal (95% CI)		658		625	100.0%	1.73 [1.48, 2.02]	
Total events	386		213				
Heterogeneity: Tau² = 0.01; Chi² = 5.23, df = 4 (P = 0.26); I² = 24%							
Test for overall effect: Z = 6.86 (P < 0.00001)							
1.1.2 ACR50							
STAR (Fusrt 2003) 17	92	318	36	318	31.2%	2.56 [1.80, 3.64]	
GUEPARD (Soubrier 2009)19	22	33	9	32	17.9%	2.37 [1.30, 4.34]	
DE019 (Keystone 2004)21	81	207	19	200	24.6%	4.12 [2.60, 6.53]	
Chen 2009 23	12	35	4	12	0.0%	1.03 [0.41, 2.59]	
ARMADA (Weinblatt 2003)26	37	67	5	62	10.6%	6.85 [2.88, 16.31]	
Kim 2007 27	28	65	9	63	15.7%	3.02 [1.55, 5.87]	
Subtotal (95% CI)		690		675	100.0%	3.23 [2.35, 4.44]	
Total events	260		78				
Heterogeneity: Tau² = 0.05; Chi² = 6.74, df = 4 (P = 0.15); I² = 41%							
Test for overall effect: Z = 7.23 (P < 0.00001)							
1.1.3 ACR70							
STAR (Fusrt 2003) 17	47	318	11	318	33.8%	4.27 [2.26, 8.09]	
GUEPARD (Soubrier 2009)19	15	33	6	32	21.3%	2.42 [1.08, 5.46]	
DE019 (Keystone 2004)21	43	207	5	200	17.3%	8.31 [3.36, 20.55]	
Chen 2009 23	5	35	0	12	1.8%	3.97 [0.24, 66.96]	
ARMADA (Weinblatt 2003)26	18	67	3	62	10.4%	5.55 [1.72, 17.93]	
Kim 2007 27	14	65	5	63	15.4%	2.71 [1.04, 7.09]	
Subtotal (95% CI)		725		687	100.0%	4.07 [2.77, 5.96]	
Total events	142		30				
Heterogeneity: Tau² = 0.01; Chi² = 5.14, df = 5 (P = 0.40); I² = 3%							
Test for overall effect: Z = 7.20 (P < 0.00001)							

0.01   0.1   1   10   100
Favors Placebo   Favorece ADA

Test for subgroup differences: Chi² = 24.32, df = 2 (P < 0.00001), I² = 91.8%

Fig. 2 – Meta-analysis of ACR20, ACR50 and ACR70 responses in up to 24 weeks. Adalimumab 40 mg every two weeks + DMARDs vs. placebo + DMARDs.
DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate. ADA, adalimumab.
Statistics I² >40% indicates statistical heterogeneity between the studies. A P value < 0.10 in the Chi-square test indicates heterogeneity.

Adalimumab 40 mg versus placebo
The results of this comparison are shown for the period of 24/26 weeks. The combination of these studies resulted in RR (95% CI) of 2.67 (1.89; 3.77), 3.19 (1.81; 5.62) and 7.90 (2.42; 25.80) for ACR20, ACR50 and ACR70, respectively, favoring the ADA group. There was no statistical heterogeneity (I² = 0%, P = 0.45, 0.46 and 0.73 for ACR20, ACR50 and ACR70, respectively) (Table 3).[24,28]

The difference in means (95% CI) in HAQ scale between the ADA and placebo groups was -0.31 (-0.42; -0.19), I² = 0%, P = 0.93, favoring the ADA group. The RR (95% CI) for loss to follow-up due to adverse events was 3.34 (1.27; 8.80), favoring the placebo group and with no significant heterogeneity (I² = 0%, P = 0.55, Table 3).[24,28]

Safety

Adalimumab 40 mg + DMARDs vs. placebo + DMARDs
The results of meta-analyses of adverse events showed no statistical significance, except for the reaction at the injection site at up to 52 weeks, which favored the placebo + DMARDs group, but with borderline confidence interval (RR: 1.32; 95% CI: 1.02; 1.71).[17,21,23,26] All meta-analyses showed low statistical heterogeneity (Table 3).

Adalimumab 40 mg vs. placebo
Only reaction at the injection site showed a statistically significant result with RR (95% CI) of 12.45 (3.92; 39.52) at 24/26 weeks, with no statistical heterogeneity (I² = 0%, P = 0.86). The RR (95% CI) for serious adverse reactions was 1.24 (0.49; 3.13), with substantial heterogeneity (I² = 68% and P = 0.08, Table 3).[24,28]

The study by van de Putte et al. at 26 weeks, reported that more patients that used ADA, when compared to the placebo group, reported headache (18.6% vs. 10.9%), skin rash (20.4% vs. 5.5%) and pruritus (11.5% vs. 0.9%, P < 0.05 for all comparisons). Severe infections occurred at similar frequencies in both groups (2.3% ADA vs. 0.0% placebo).[24]

In the CHANGE study, at 24 weeks, the frequency of infections (45.1% vs. 36.8%) and severe infections (6.6% vs. 1.1%)

Table 3 – Results of the meta-analyses for HAQ, adverse events and loss to follow-up for comparisons ADA 40 mg every two weeks+ DMARDs vs. placebo + DMARDs and ADA 40 mg every two weeks vs. placebo.

Outcome	Period (weeks)	Studies	Participants	Measure of effect (95%CI) *	I² (%)[a]	P value[b]
ADA 40 mg + MMCD vs. placebo + MMCD						
HAQ	Up to 24	4[19,21,26,27]	729	-0.32 (-0.40; -0.24)	0	0.99
HAQ	52	2[18,21]	932	-0.32 (-0.39; -0.24)	0	0.60
Loss due to lack of efficacy	Up to 104	4[17,18,21,27]	1696	0.31 (0.21; 0.45)	0	0.80
Loss due to adverse reaction	Up to 104	6[17,18,21,23,26,27]	1872	1.55 (1.08; 2.21)	0	0.61
Adverse reactions	Up to 104	5[17,18,21,23,27]	1955	1.03 (1.00; 1.05)	0	0.67
Severe adverse reactions	Up to 24	3[17,23,27]	811	0.84 (0.58; 1.20)	0	0.54
Infections	Up to 24	3[17,23,27]	1171	1.07 (0.93; 1.24)	0	0.59
Severe infections	Up to 104	6[17,18,21,23,26,27]	2014	1.73 (0.72; 4.14)	27	0.23
Reaction at the injection site	Up to 52	4[17,21,23,26]	1219	1.32 (1.02; 1.71)	2	0.38
Tuberculosis	Up to 104	5[17,18,21,23,27]	1743	2.25 (0.46; 11.02)	0	0.96
Cancer	Up to 104	6[17,18,21,23,26,27]	2226	1.02 (0.30; 3.47)	0	0.53
Death	Up to 104	5[17,18,21,23,27]	1743	2.38 (0.52; 10.84)	0	0.88
ADA 40 mg vs. placebo						
ACR20	24/26	2[24,28]	401	2.67 (1.89; 3.77)	0	0.45
HAQ	24/26	2[24,28]	401	-0.31 (-0.42; -0.19)	0	0.93
Loss due to adverse reaction	24/26	2[24,28]	401	3.34 (1.27; 8.80)	0	0.55
Severe adverse reactions	24/26	2[24,28]	401	1.24 (0.49; 3.13)	68	0.08
Reaction at the injection site	24/26	2[24,28]	401	12.45 (3.92; 39.52)	0	0.68

ACR, American College of Rheumatology; ADA, adalimumab; DMARDs, disease-modifying antirheumatic drugs; HAQ, Health Assessment Questionnaire.

* Data on relative risk for dichotomous outcomes and difference of means for continuous outcomes with a confidence interval of 95%.

  Statistics I² > 40% indicates statistical heterogeneity between studies.

[b]P-value < 0.10 at the chi-square test indicates statistical heterogeneity between studies. Superscript numbers indicate the studies used in the meta-analyses.

showed no statistically significant differences between the ADA and placebo groups.[28]

Discussion

The results of the systematic review and meta-analysis showed that patients who were treated with ADA 40 mg every two weeks associated with MTX showed better efficacy results and lower radiographic progression when compared to patients receiving placebo + MTX. The risk of occurrence of loss to follow-up due to lack of efficacy was higher in the placebo + MTX group, while the loss due to adverse reactions was higher in the ADA + MTX group. However, these results are more robust for a follow-up of 24 weeks, as only two studies evaluated the patients for 52 and only one for 104 weeks.

There was no statistically significant difference regarding the efficacy and loss to follow-up due to lack of efficacy between the ADA monotherapy group with ADA 40 mg every two weeks and MTX monotherapy, whereas radiographic progression for the group that used ADA showed better results. The combination of ADA 40 mg every other week + MTX when compared to ADA 40 mg every two weeks as monotherapy showed better outcomes in ACR response and radiographic

progression, whereas in the HAQ scale the result was statistically significant only at 52 weeks and also favorable to the combination. The risk of loss to follow-up due to lack of efficacy was higher for the monotherapy. These comparisons were evaluated by only one trial.[18]

Patients that received ADA 40 mg every two weeks as monotherapy showed better efficacy outcomes when compared to placebo at 24/26 weeks, and loss due to adverse reactions favored the placebo group.

Meta-analyses of adverse events were not statistically significant when comparing "ADA 40 mg every two weeks + MTX *versus* placebo + MTX" and "ADA 40 mg every two weeks vs. placebo," with the exception of reactions at the injection site, which is expected to be higher in the group that used the anti-TNF agent. It is noteworthy that the RR in the comparison of "ADA 40 mg every two weeks + MTX *versus* placebo + MTX" showed borderline confidence interval for this event.

An inherent characteristic of clinical trials is that they are carried out in a carefully selected population and, therefore, do not represent the actual population. Furthermore, most of the studies included were performed for a short period of time (one study lasted two years). Thus, the results of clinical trials have low external validity and should be extrapolated to clinical practice with caution, especially

safety outcomes, as rare adverse events are often reported in post-marketing studies.

Therefore, it is important to consider the results of adverse events from studies with longer time of follow-up. An open label extension of five years of the PREMIER study showed that the rate of severe infections was 3.3 events per 100 patient-years, and that there were two cases of tuberculosis (0.1 / 100 patient-years), a case of lymphoma (< 0.1/100 patient-years) and one non-melanoma skin cancer (< 0.1/100 patient-years), in addition to 11 other reports of malignant tumors.[29] The open label phase of the DE019 study, which also lasted five years, reported a rate of severe infections of 4.4 per 100 patient-years and two cases of tuberculosis. The rate of non-melanoma skin cancer was 1.1/100 patient-years and other types of cancer, 1.5/100 patient-years.[30] In the early open-label stage of the two studies, all patients started using ADA 40 mg once every 15 days.

A meta-analysis of cohort studies indicated that patients with RA that used TNF antagonists showed a 40% increase in the risk of severe infections when compared with patients who used DMARDs (RR: 1.37, 95% CI: 1.18; 1.60).[31]

In clinical trials with TNF blockers, it is common to perform screening for latent TB infection and prophylactic treatment in positive cases. This is also recommended by the treatment guidelines and occurs in clinical practice.[11] Nevertheless, there have been cases of tuberculosis related to the use of these drugs. The Spanish registry of adverse events of biological therapy in rheumatic diseases reported that the incidence of tuberculosis before 2002 was 472 per 100,000 patient-years and, from 2002 to January 2006, when recommendations for screening and prophylactic treatment of patients with latent tuberculosis began to be disclosed, the incidence decreased to 172 cases per 100,000 patient-years.[32]

The British Society for Rheumatology reported in 2008 that the risk of tuberculosis in patients treated with adalimumab was 217/100.000 person-years, while the mean annual incidence of the UK population was 13.2 events/ 100.000 person-years. Almost half of the cases were diagnosed after the end of treatment, indicating that the surveillance for tuberculosis should continue even after therapy cessation.[33]

A systematic review of clinical trials and cohorts shows that the combination of adalimumab (or other biological agent, such as etanercept, infliximab, or rituximab) with MTX achieves better clinical responses than monotherapy with the biological agent alone.[34] Clinical trials that have shown the benefit of ADA monotherapy compared the biological agent with placebo and in the PREMIER study, in general, there was no difference between the ADA and MTX groups.[18,24,28]

The GUEPARD study showed that, although the ADA + MTX combination provides faster responses, it does not offer the best results of efficacy and radiological indices after one year, when compared with patients who started treatment with MTX as monotherapy, which would not justify initiating treatment of RA with the biological agent.[19]

Comparisons with other systematic reviews

Other systematic reviews corroborate the results shown here, demonstrating greater efficacy of ADA compared to control in the short and long term. However, caution is needed when interpreting long-term results, as studies lasting more than 52 weeks are scarce and the meta-analyses usually show high heterogeneity.[4,35-37]

Wiens et al. showed that the result of the meta-analysis for ACR responses at 52 weeks is statistically significant and favorable to the group using ADA, which differs from the results found in this review.[38] This difference regarding the direction of results may be related to the method used by the authors, using both arms with ADA of the DE019 study, counting the results of placebo group twice, in addition to combining groups with different doses of ADA, which may have skewed the results.[21]

Jamal et al. showed that there is no difference in ACR response when comparing patients with early and established disease.[22] On the other hand, systematic reviews of TNF blockers have found that the ACR response was better in patients with more than two years of disease and better results were seen in patients with previous MTX use.[33,37]

Limitations

The publication bias is a concern in any systematic review. It is possible that studies suggesting benefits of the intervention of interest are published, while those of which results point in another direction remain unpublished. In this situation, a systematic review of published studies can identify a spurious benefit of an important effect or fail to indicate important adverse events.[39]

Overall, the evidence can be considered strong, as the studies included in this review had good methodological quality and low risk of bias, except for the GUEPARD study, of which design was not double-blind.[19] It was observed that the results remain similar after the exclusion of this study.

Implications for research and clinical practice

No studies were found comparing Adalimumab with other biological agents, demonstrating a lack of knowledge in this area, as it would be important for clinical practice to know the comparative efficacy and safety profiles between biological agents, considering that in relation to placebo and MTX, they are already well established.

This study showed that Adalimumab at a dose of 40 mg every two weeks is effective in the treatment of RA and well tolerated in the short term. The efficacy of Adalimumab was demonstrated in monotherapy and associated to DMARDs, particularly MTX, although the evidence for combined use is more robust. The available scientific evidence corroborates the recommendations of the Brazilian Society of Rheumatology for RA treatment: the use of biological agents is indicated for patients who persist with disease activity despite treatment including at least two regimens with DMARDs, of which at least one is a combination of DMARDs. The use of biological agents must be performed associated to a DMARD, preferably MTX.[3]

Conflicts of interest

Financial support

Erratum

The article "Adalimumab in rheumatoid arthritis treatments: a systematic review and meta-analysis of randomized clinical trials" (Rev Bras Reumatol 2013;53(5):419-430) was wrongly classified as an original article, but should be considered a review article instead.

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