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Review article

Infliximab, methotrexate and their combination for the treatment of rheumatoid arthritis: a systematic review and meta-analysis☆

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ABSTRACT

We performed a systematic review to evaluate the efficacy and safety of infliximab + methotrexate (IFX + MTX) regimens versus MTX alone or in combination with other disease-modifying anti-rheumatic drugs (DMARDs). We searched through major databases, the grey literature and did a manual search. Two independent reviewers conducted the selection, data extraction and analysis of the quality of the studies. Meta-analysis was conducted using Review Manager® 5.1 software. Nine trials were included. The mean modified Jadad score was 4.4, but only one study showed low risk of bias. IFX + MTX regimen presented better responses in clinical outcomes of ACR and DAS28 by up to 54 weeks, and of radiographic progression by up to 104 weeks. Withdrawals due to lack of efficacy was lower in the IFX + MTX group. No significant difference in adverse events was observed. The IFX + MTX combination is more effective than treatment with MTX alone or DMARDs combination. This regimen presented good tolerability in patients previously treated with DMARDs, not treated with MTX or with insufficient responses to MTX. The efficacy of IFX + MTX is noted primarily during initial periods of treatment. High doses of IFX were as effective as the standard dose, but with possible higher risk of serious infections. Therefore, we advise clinicians to use the standard dose of IFX 3 mg/kg every 8 weeks.

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Infliximabe, metotrexato e sua combinação no tratamento da artrite reumatoide: revisão sistemática e metanálise

Palavras-chave:
Infliximabe
Revisão sistemática
Metanálise
Artrite reumatoide
Eficácia

RESUMO

Foi feita uma revisão sistemática para avaliar a eficácia e a segurança do esquema infliximabe + metotrexato (IFX + MTX) *versus* MTX isoladamente ou em combinação com outros medicamentos modificadores do curso da doença (MMCD). Pesquisou-se nas principais bases de dados eletrônicas e na literatura cinzenta e fez-se uma busca manual. Dois revisores independentes fizeram a seleção, extração de dados e análise da qualidade dos estudos. A metanálise foi feita com o software Review Manager® 5.1. Incluíram-se nove estudos. O escore médio na escala de Jadad modificada foi de 4,4, mas somente um estudo mostrou baixo risco de viés. O esquema IFX + MTX apresentou melhores respostas nos desfechos clínicos do escore ACR e do DAS28 por até 54 semanas e na progressão radiográfica por até 104 semanas. Os abandonos decorrentes da falta de eficácia foram menores no grupo IFX + MTX. Não foi observada diferença estatisticamente significante nos eventos adversos. A combinação IFX + MTX é mais eficaz do que o tratamento com MTX isolado ou em combinação com MMCD. Esse esquema apresentou boa tolerabilidade em pacientes previamente tratados com MMCD, não tratados com MTX ou com respostas insuficientes ao MTX. A eficácia do regime IFX + MTX é observada principalmente durante os períodos iniciais do tratamento. Altas doses de IFX foram tão eficazes quanto a dose padrão, mas com a possibilidade de "um" maior risco de infecções graves. Recomenda-se, portanto, que os médicos utilizem a dose padrão de IFX de 3 mg/kg a cada oito semanas.

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterised by peripheral, symmetric polyarthritis with potential for joint deformity that can cause functional disability, premature mortality and reduced quality of life. It is estimated that 0.3–1.0% of the population worldwide is affected by RA, which is most frequently observed in developing countries and in women.[1]

The treatment of RA patients combines educational, preventive and non-pharmacological interventions with pharmacological treatment and surgical procedures. First-line therapy includes the early use of a synthetic disease-modifying anti-rheumatic drug (DMARD), such as methotrexate (MTX), which is the drug of choice.[2] However, only 20–40% MTX monotherapy-treated patients show a satisfactory clinical response.[3] Drug combinations are a valid strategy in non-responsive patients, which may include the addition of another synthetic DMARD or the biological DMARD agents, such as tumour necrosis factor α blockers (anti-TNFα).[4] Infliximab (IFX) is a chimeric monoclonal antibody (murine) of the anti-TNFα class that represents approximately 40% of biological agent prescriptions.[5,6]

Second-line treatment strategies show similar rates of success and the choice among them is based primarily on the presence or absence of a poor prognosis and in the disease activity.[4,7] The benefits of adding sulfasalazine (SSZ) and hydroxychloroquine (HCQ),[8–11] leflunomide[12] or cyclosporin[13] to MTX therapy have been demonstrated. The IFX + MTX combination has been assessed in numerous systematic reviews[14–19] but their control groups included only placebo or MTX treatment. Key issues, including the effect of disease duration, dose and patient profile, were not sufficiently addressed in most of these reviews.

With this systematic review and meta-analysis we aimed to assess the efficacy and safety of IFX + MTX compared to MTX in monotherapy or in combination with other synthetic DMARDs considering treatment-relevant clinical outcomes.

Methods

A systematic review with meta-analysis was performed according to the Cochrane Handbook for Systematic Reviews of Interventions. The results were reported according to the "Preferred Reporting Items for Systematic Reviews and Meta Analyses: The PRISMA statement".[20] This review is part of another project entitled "Evaluation of the effectiveness and safety of biological agents adalimumab, etanercept, infliximab and rituximab used in the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, Brazil and Minas Gerais", which was performed by the Research Group on Pharmacoepidemiology and Research Group on Health Economics at the UFMG.

Search strategy

The online search was performed in EMBASE (until April 2012), CENTRAL (until June 2012), PubMed (until July 2012) and LILACS (until October 2012) databases. Different combinations of keywords, mesh terms and filters were applied, and the full search strategy for each database was provided online in Appendix 1. We performed a manual search in the

references of all included studies and previously published systematic reviews. We also searched the grey literature in the Annals of the American College of Rheumatology (ACR, 2011, 2012), the European League Against Rheumatism (EULAR, 2010–2012) meetings and the thesis and dissertation databases of the Coordination for the Improvement of Higher Education Personnel, Brazilian Digital Library of Theses and Dissertations, the Digital Library of Theses and Dissertations of USP and the ProQuest Dissertation and Theses Database. Ongoing Randomised Clinical Trials (RCT) were surveyed in the International Clinical Trials Registry Platform Search Portal, Brazilian Registry of Clinical Trials and at *clinicaltrials.gov*.

Eligibility criteria

We included phase III RCTs that evaluated RA patients diagnosed according to the American College of Rheumatology (ACR) criteria 1987[21] regardless of disease duration. We considered eligible studies comparing IFX + MTX versus MTX as a monotherapy or in combination with other synthetic DMARDs. The minimal follow-up period was two months.

The following exclusion criteria were applied: studies that were not performed exclusively on RA patients; changes in therapy over time; drug-conversion studies; pilot studies; editorials/reviews/letters/comments; and studies published in languages other than Portuguese, Spanish or English.

Study selection

Two reviewers independently evaluated the titles, abstracts and full text of all identified studies to assess their eligibility. A third reviewer resolved disagreements.

Assessment of methodological quality and risk of bias

Methodological quality was assessed using the modified Jadad scale,[22] which evaluates randomisation, blinding and loss to follow-up using seven dichotomous questions that are worth one point each. Studies with inadequate randomisation lose one point. The final score ranges from 0 to 6: 0–2 indicate a low-quality study, 3 or 4 indicates adequate quality, and 5 or 6 indicates high quality. The risk of bias was assessed using the Cochrane Collaboration tool,[23] which considers six dimensions: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting of outcomes. The study was classified as having low risk of bias when all criteria were reported and were adequate, a high risk of bias when at least one of the criteria was inadequate, and an uncertain risk of bias when one or more items were not reported. The inter-rater reliability was measured using the Kappa statistic according to Landis and Kock[24] and calculated using SPSS® 17.0 software. Inter-rater reliability was substantial for the modified Jadad scale ($0.70 \pm$ DP 0.73) and moderate for the risk of bias assessment (0.55 ± 0.78).

Data collection

Two independent reviewers collected data on study design, methodological quality, risk of bias, patient profile, efficacy and safety outcomes using an electronic form that was designed in Excel® 2007. A consensus resolved all disagreements.

The primary outcome was the measurement of ACR20, which is defined as 20% improvement in swollen joints and joint pain in combination with a 20% improvement in three of five criteria: patient's global assessment of pain; patient's global assessment of disease activity; physician's global assessment of disease activity; patient's assessment of physical function; and C-reactive protein levels.[25] Secondary outcomes included the ACR50 and ACR70, clinical remission (defined as a DAS28 [Disease Activity Score 28] < 2.6), radiographic data, loss to follow-up and adverse events.

Statistical analysis

A random effects model was used for all meta-analyses due to the clinical heterogeneity of the included studies. Relative risk (RR) was used as a measure of treatment effect, and it was calculated using the Mantel–Haenszel method for binary data. Mean differences and the inverse variance method were used for continuous data. Confidence intervals of 95% were presented for both measures. Heterogeneity was assessed using the χ^2 test for heterogeneity and the I^2 index and was considered statistically significant when p value was lower than 0.10 and I^2 value higher than 40%.[26] We identified the source of heterogeneity through a sensitivity analysis, in which studies were removed from the meta-analysis one by one to investigate possible causes related to patients and study characteristics. Subgroup analysis was also performed to evaluate the effects of pre-treatment, study length, dosage and the IFX administration regimen. In the meta-analysis we included results from the longest available follow-up, unless indicated otherwise. We used Review Manager® software version 5.1 for statistical tests (Copenhagen: The Cochrane Collaboration, 2011).

Results

We identified 5782 articles, of which 249 were considered for full reading and 74 articles were selected. A total of 11 articles, representing multiple publications of nine studies, evaluated IFX and met the inclusion criteria for this review (Fig. 1). We found one completed phase III clinical trial with unpublished results (Table 1, online resource). We have not found any thesis or dissertations. Abstracts found in the annals of meetings had their respective full articles collected by manual search. The characteristics of the nine included trials are presented in Table 1. The studies were published between 1998 and 2012, and the follow-up periods ranged from 14 to 104 weeks. Patients profile included individuals previously treated with DMARDs, not treated with MTX or those that had insufficient responses to MTX.

Most studies defined active RA by the presence of six or more swollen joints and six or more tender joints in combination with the additional criteria of morning stiffness, C-reactive protein levels and erythrocyte sedimentation rates. ASPIRE[27] and ATTEST[28] defined active RA as 10 or more swollen joints and 12 or more tender joints. Zhang[29]

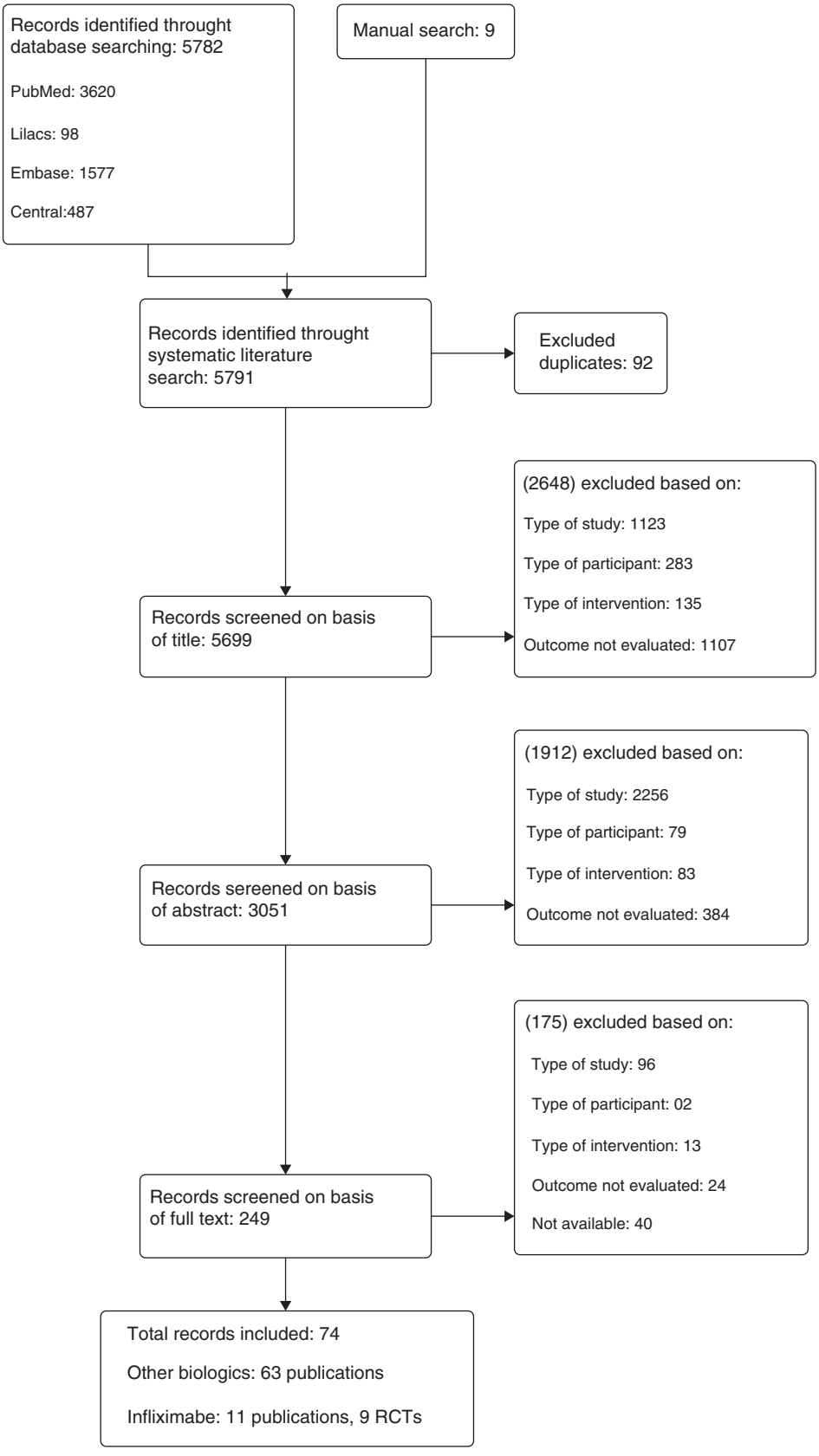


Fig. 1 – Diagram of included studies.

Table 1 – Population baseline characteristics of the included studies.

Study – follow-up	Patients (*n*)	Age (years) mean (SD)	Duration of disease (years) mean (SD)	Number of previous DMARD mean (SD)	Number of swollen joints mean (SD)	Number of tender joints mean (SD)	Patients on oral steroid therapy %	Patients on NSAID therapy %
Maini et al.[33] – *26 weeks*								
Placebo + MTX	14	48.8 (12.3)	7.6 (4)	2 (1–3)[b]	17 (12–25)[b]	28 (22–47)[b]	50	NI
IFX IV 3 mg/kg each 4 weeks + MTX	15	58.9 (10)	12.1 (9)	2 (2–4)[b]	16 (13–22)[b]	21 (12–31)[b]	60	NI
IFX IV 3 mg/kg each 4 weeks	14	47 (15)	7.8 (4.3)	2.5 (2–3)[b]	17 (11–32)[b]	31 (23–39)[b]	50	NI
IFX IV 10 mg/kg each 4 weeks + MTX	14	50.4 (13.4)	11.1 (7.4)	2 (2–4)	20 (14–31)[b]	26 (23–37)[b]	28	NI
IFX IV 10 mg/kg each 4 weeks	15	56.3 (9.1)	9.7 (7.4)	2 (1–4)	19 (11–22)[b]	23 (16–35)[b]	60	NI
ATTRACT[35,36] – *30 weeks*								
Placebo + MTX	88	51 (19.0–75.0)[b]	8.9 (0.8–35.0)[b]	2.5 (1.4)	19	24	64	72
IFX IV 3 mg/kg each 8 weeks + MTX	86	56 (25.0–74.0)[b]	8.4 (0.7–45.0)[b]	2.8 (1.5)	19	32	63	79
IFX IV 3 mg/kg each 4 weeks + MTX	86	51 (19.0–78.0)[b]	7.2 (0.5–33.8)[b]	2.6 (1.5)	20	31	53	76
IFX IV 10 mg/kg each 8 weeks + MTX	87	55 (19.0–80.0)[b]	9.0 (0.5–49.9)[b]	2.5 (1.4)	20	30	57	77
IFX IV 10 mg/kg each 4 weeks + MTX	81	52 (23.0–74.0)[b]	8.7 (0.6–47.0)[b]	2.5 (1.3)	23	35	65	68
ASPIRE[27] – *52 weeks*								
Placebo + MTX	282	50 (13)	0.9 (0.7)	NI	22 (11)	34 (15)	38	82
IFX IV 3 mg/kg each 8 weeks + MTX	359	51 (12)	0.8 (0.7)	NI	21 (10)	32 (15)	37	85
IFX IV 6 mg/kg each 8 weeks + MTX	363	50 (13)	0.9 (0.8)	NI	22 (11)	33 (15)	39	82
START[34] – *22 weeks*								
Placebo + MTX	363	52.0 (44–61)[b]	8.4 (4–15)[b]	NI	15 (10–21)[b]	22 (15–32)[b]	59.2[b]	39.4[b]
IFX IV 3 mg/kg each 8 weeks + MTX	360	53.0 (45–61)[b]	7.8 (3–15)[b]	NI	15(11–21)[b]	22 (15–31)[b]	59.2[b]	43.3[b]
IFX IV 10 mg/kg each 8 weeks + MTX	361	52.0 (43–60)[b]	6.3 (3–14)[b]	NI	15 (10–21)[b]	22 (15–30)[b]	59.0[b]	41.3[b]
Abe et al.[32] – *14 weeks*								
Placebo + MTX	47	55.1 (7.6)	7.5 (5.0)	NI	13.5 (7.6)	17.8 (8.7)	89.4	95.7
IFX IV 3 mg/kg each 8 weeks + MTX	49	55.2 (10.9)	9.1 (7.4)	NI	15.1 (9.0)	19.0 (11.8)	85.7	89.8
IFX IV 10 mg/kg each 8 weeks + MTX	51	56.8 (10.5)	7.1 (5.1)	NI	13.2 (6.2)	18.7 (12.3)	92.2	94.1
Zhang et al.[29] – *18 weeks*								
Placebo + MTX	86	48.9 (8.0)	96.0 (74.6)[c]	NI	NI	NI	NI	NI
IFX IV 3 mg/kg + MTX	87	47.9 (10.1)	85.6 (74.0)[c]	NI	NI	NI	NI	NI
Durez et al.[30] – *52 weeks*								
Placebo + MTX	14	53.8 (15.2)	0.45 (0.29)	NI	10.3 (5.5)	11.6 (7.5)	NI	0
IFX IV 3 mg/kg each 8 weeks + MTX	15	50.0 (9.9)	0.36 (0.31)	NI	12.5 (5.4)	15.9 (8.0)	NI	0
ATTEST[28] *52 weeks*								
Placebo + MTX	110	49.4 (11.5)	8.4 (8.6)	NI	20.1 (7.0)	30.3 (11.7)	70.0	84.5
IFX IV 3 mg/kg + MTX[a]	165	49.1 (12.0)	7.3 (6.2)	NI	20.3 (8.0)	31.7 (14.5)	71.5	86.1
SWEFOT[3,31] – *104 weeks*								
SSZ 1000 mg bid + HCQ 400 mg/day + MTX	130	52.9 (13.9)	6.3 (3.6)[c]	NI	NI	NI	8	NI
IFX IV 3 mg/kg each 8 weeks + MTX	128	51.1 (13.3)	6.2 (3.5)[c]	NI	NI	NI	6	NI

NSAID, nonsteroidal anti-inflammatory drugs; IFX, infliximab; HCQ, hydroxychloroquine; MTX, methotrexate; SSZ, sulfasalazine; DMARD, disease-modifying anti-rheumatic drug; IV, intravenously; SD, standard deviation; BID, twice a day; NI, not informed.

[a] Infliximab at days 1, 15, 43, 85 and each 56 days.

[b] Median.

[c] In months.

defined active RA as three or more swollen and eight or more tender joints in addition to further criteria. Non-steroidal anti-inflammatory drugs (NSAIDs) at stable doses and low doses of oral glucocorticoid (≤10 mg/day prednisolone) were allowed in all trials except in Durez et al.[30] This study[30] and SWEFOT[31] evaluated only patients with initial RA, defined as disease duration of less than 12 months. The ASPIRE[27] and Durez et al.[30] studies evaluated MTX-naive patients, but the other studies evaluated patients with insufficient responses to MTX. The mean weekly dose of MTX was 7.2 ± 2.0 mg in Abe et al.,[32] 7.5 mg in Maini et al.[33] and ranged from 7.5 to 20 mg in Durez et al.[30] and Zhang[29] studies. MTX dose ranged from 15 to 20 mg in the other studies.[3,27,28,31,34–36]

Methodological quality and risk of bias

Nine trials were classified as randomised, but only two of these studies reported the methods of randomisation.[27,35] The Jadad scale score was generally good (ranging from moderate to high). The pharmaceutical industry funded six studies.[27,28,30,31,34,35] We identified a potential source of bias in three trials,[30,31,33] and only one study[35] was classified as low risk of bias (Table 2).

ACR response

Infliximab standard dose (3 mg/kg every eight weeks) per follow-up period

Eleven studies were included in this analysis. Six of them included 1470 patients and presented results of up to 30 weeks of follow-up,[28–30,32,34,35] four studies with 1086 patients presented results of 52 weeks[27,30,31,36] and one study of 258 patients presented results of 104 weeks.[3] Patients who received combination therapy with IFX showed a better ACR response than patients treated with MTX alone or in combination with DMARDs until 30 and 52 weeks of treatment. However, no significant difference between groups was observed after 104 weeks of follow-up. The heterogeneity of ACR20 and ACR50 was significant and moderate for the 30 weeks of follow-up studies (Table 3). Heterogeneity at 52 weeks of follow-up was assessed using the stratification between MTX-naive patients and patients with insufficient responses to MTX (see Section "Heterogeneity assessment and subgroup analysis").

Infliximab standard dose per patient profile

The patient's previous treatments, regardless of follow-up period, revealed that the IFX + MTX combination achieved better results than synthetic DMARDs in patients who had previously failed to MTX treatment, compared to MTX-naïve patients (Table 3).

Infliximab standard dose according to disease duration

Combination therapy with IFX showed better ACR responses than MTX alone or in combination with synthetic DMARDs in patients with established RA. This result was not observed in patients with early RA (Table 3).

High-dose infliximab

Patients that used IFX regimens with doses higher than 3 mg/kg or in shorter intervals showed better ACR responses than patients treated with MTX alone or in combination. Meta-analysis of high-dose IFX versus standard dose of 3 mg/kg every eight weeks did not show difference in ACR20 and ACR50 outcomes within 54 weeks of follow-up. Despite being statistically significant, difference in ACR70 response was boarder line favouring IFX high-doses (Table 3).

Clinical remission

Two studies assessed clinical remission at 28[28,34] and 54 weeks of follow-up[27,30] in patients using the standard dose of IFX. Meta-analysis favoured IFX + MTX combination in all follow-up periods and in the overall analysis, with no statistically significant heterogeneity observed. The RR up to 28 weeks of treatment was 2.57 ([1.44; 4.60]; $I^2 = 30\%$; $p = 0.23$). The RR at 52 weeks was 1.48 ([1.07; 2.05]; $I^2 = 0\%$; $p = 0.62$), and the overall analysis, which assessed 1569 patients, produced an RR = 1.92 ([1.35; 2.74]; $I^2 = 49\%$; $p = 0.12$).

Radiographic progression

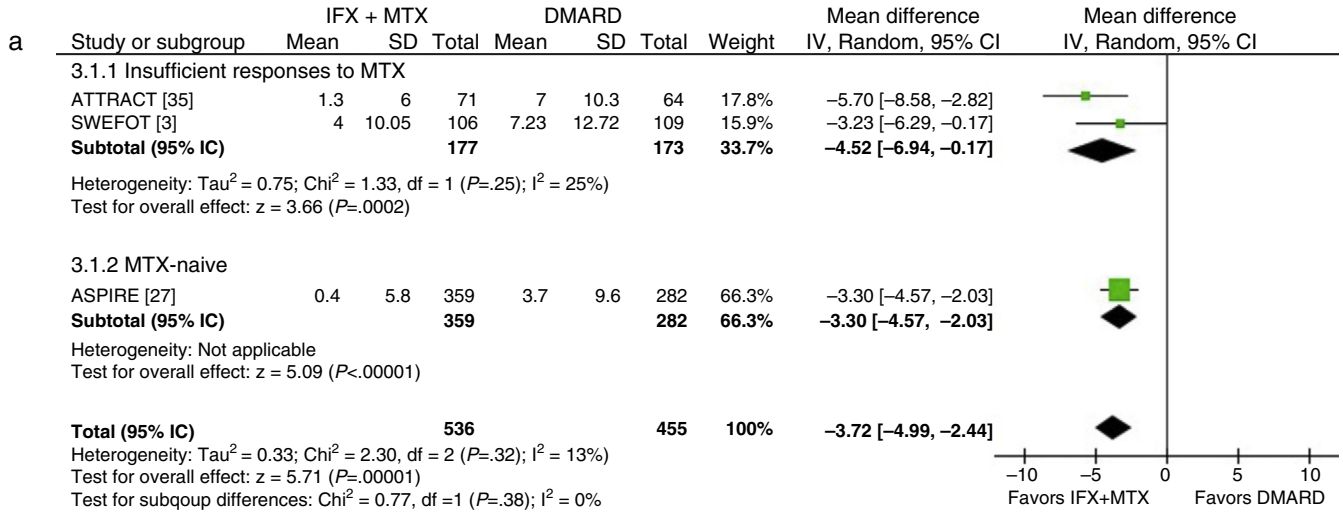
A meta-analysis of three studies[3,27,36] revealed lower radiographic progression in patients who were treated with IFX + MTX at a standard dose than in patients who were treated with other synthetic DMARDs at 52 and 104 weeks. Statistically significant differences were observed in patients with an insufficient response to MTX and treatment-naive patients (Fig. 2).

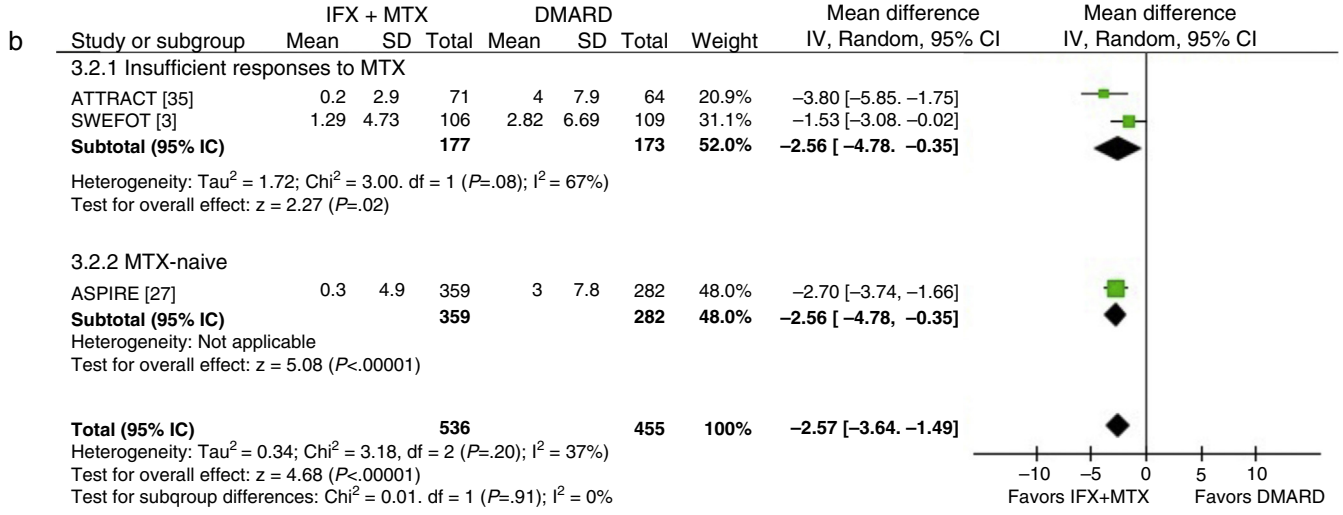
Withdrawals

A meta-analysis of five studies,[3,27,28,32,36] comprising 1474 patients, revealed a lower risk of withdrawals due to lack of efficacy in the group treated with IFX + MTX (RR = 0.33 [0.17; 0.63]; $I^2 = 45\%$; $p = 0.12$). Meta-analysis of eight studies,[3,27–30,32,34,36] which assessed 2399 patients, revealed no difference between groups in withdrawals due to adverse events (RR = 1.59 [0.96, 2.65]; $I^2 = 40\%$; $p = 0.11$). After removal of SWEFOT[3] study, in which the control group included patients who received HCQ and SSZ in combination with MTX, the overall risk of withdrawals due to adverse events was higher in the IFX + MTX group (RR = 2.05 [1.33; 3.16]; $I^2 = 0\%$; $p = 0.43$). Analysis of withdrawals due to adverse events by patient profile revealed an increased risk for MTX-naive patients (RR = 3.01 [1.49; 6.06]; $I^2 = 0\%$; $p = 0.97$) but not in patients with an insufficient response to MTX. Regimens with high-dose IFX were as safe as the standard regimen regarding discontinuation due to adverse events (RR = 1.12 [0.80; 1.57]).

Safety

Safety meta-analyses revealed no statistically significant differences between the IFX standard dose + MTX and DMARD groups in the outcomes of infection, serious infections, serious adverse events, tumours and death. Infusion reactions occurred more frequently in the IFX + MTX group (RR = 2.21 [1.63; 2.99]). However, serious infections and infusion reactions





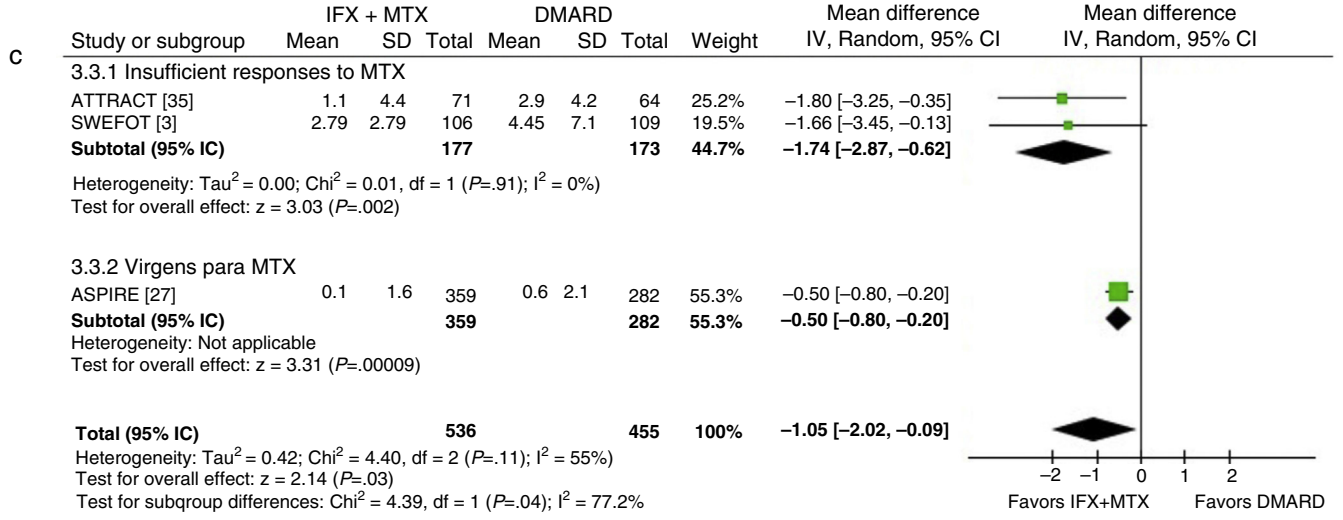


Fig. 2 – Meta-analysis of radiological progression according to the Van der Heijde modified Sharp score 2a –Total Score; 2b – Erosion score; 2c- Joint-space narrowing.

Table 2 – Within-study quality and risk of bias assessment.

Study	Modified Jadad scale								Risk of bias						
	Randomisation	Appropriate randomisation method	Inappropriate randomisation method	Concealment	Appropriate Concealment method	Losses to follow-up	ITT analysis	Score	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Overall risk of bias
ATTRACT[35,36]	1	1	0	1	1	1	1	6	L	L	L	L	L	L	L
Maini et al.[33]	1	0	0	1	1	1	1	5	U	L	L	L	L	H	H
ASPIRE[27]	1	1	0	1	1	1	0	5	L	L	L	L	U	L	U
START[34]	1	0	0	1	1	1	1	5	U	U	L	L	L	L	U
ATTEST[28]	1	0	0	1	1	1	1	5	U	U	L	L	L	L	U
Zhang [29]	1	0	0	1	0	1	1	4	U	U	U	U	L	U	U
SWEFOT[3,31]	1	1	0	0	0	1	1	4	U	H	H	H	L	L	H
Abe et al.[32]	1	0	0	0	0	1	1	3	U	U	U	U	L	L	U
Durez et al.[30]	1	0	0	0	0	1	1	3	U	U	H	L	L	L	H

U, unclear risk of bias; L, low risk of bias; H, high risk of bias.

Table 3 – Meta-analysis of the efficacy of infliximab compared to control.

Comparison [study]	ACR 20 (RR, 95% CI)	I^2 (%)[a]	*p*-Value[b]	ACR 50 (RR, 95% CI)	I^2 (%)[a]	*p*-Value[b]	ACR 70 (RR, 95% CI)	I^2 (%)[b]	*p*-Value[b]
Infliximab standard dose according time to follow up									
30 weeks[28–30,32,34,35]	1.99 (1.56; 2.55)	68	0.009	2.45 (1.73; 3.48)	54	0.05	2.64 (1.78; 3.91)	12	0.34
52 weeks [27,30,31,36]	1.48 (1.11; 1.96)	70	0.02	1.47 (1.25; 1.74)	0	0.49	1.66 (1.31; 2.09)	0	0.48
104 weeks[3]	1.20 (0.87; 1.67)	–	–	1.38 (0.90; 2.10)	–	–	1.18 (0.66; 2.12)	–	–
Infliximab standard dose per patient profile									
Insufficient responses to MTX[3,28,29,32,34,36]	1.77 (1.38; 2.26)	74	0.002	2.13 (1.53; 2.97)	61	0.003	2.18 (1.43; 3.34)	43	0.12
MTX-naive[27,30]	1.40 (0.84; 2.34)	64	0.10	1.44 (1.18; 1.76)	0	0.51	1.56 (1.19; 2.04)	0	0.58
Infliximab standard dose according to disease duration									
Early RA, disease duration < 1 year[3,30]	1.45 (0.89; 2.36)	51	0.15	1.47 (1.02; 2.14)	0	0.15	1.30 (0.76; 2.23)	0	0.40
Established or late RA, disease duration > 1 year[27–29,32,34,36]	1.75 (1.30; 2.34)	87	<0.00001	2.11 (1.48; 3.01)	74	0.002	2.18 (1.50; 3.15)	45	0.10
Infliximab high doses									
Doses higher than 3 mg/kg each 8 weeks versus DMARD[27,32,34,36]	2.41 (1.56; 3.73)	92	<0.00001	3.46 (2.01; 5.96)	85	<0.00001	4.56 (2.20; 9.46)	75	=0.001
High doses versus standard dose IFX[27,32,34,36]	1.07 (0.97; 1.17)	22	0.28	1.17 (1.00; 1.36)	27	0.25	1.19 (1.01; 1.41)	0	0.46

CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug; IFX, infliximab; RA, rheumatoid arthritis; RR, relative risk; –, not estimable.

[a] $I^2 > 40\%$ indicate heterogeneity between studies.

[b] *p*-Value < 0.10 of χ^2 indicates heterogeneity between studies.[1]

showed moderate heterogeneity. Subgroup analysis revealed that MTX-naive patients who received IFX + MTX had more serious infections than the MTX group (2.80 [1.14; 6.84]). Still, this result was obtained from a single study[27] (Table 4).

Regimens with high-dose IFX were as safe as the standard regimen regarding serious adverse events (1.15 [0.77; 1.71]) and serious infections (1.84 [0.71, 4.79]). However, the heterogeneity of serious infections was moderate and significant (68%; 0.04), the study ASPIRE[27] being the source of this heterogeneity. The risk of serious infections became higher in patients who received high-dose IFX than patients who received the standard IFX dose when the ASPIRE study was excluded, and no significant heterogeneity was observed (RR = 3.07 [1.42; 6.64]).

Heterogeneity assessment and subgroup analysis

The heterogeneity of ACR20 and ACR50 was significant and moderate for the studies with up to 30 weeks of follow-up (Table 3). Heterogeneity became non-significant and the results remained favourable to IFX + MTX (1.74 [1.32; 2.29]) when the ATTRACT[35] and START[34] studies were excluded from the ACR20 meta-analysis of 30 weeks. Heterogeneity became non-significant and the results still favoured the group receiving IFX + MTX (1.74 [1. 32; 2.29]) when the START study[34] was excluded from the ACR50 meta-analysis of 30 weeks. No reasonable explanation for the source of heterogeneity could be established. The cause of heterogeneity of ACR analysis at 52 weeks was the difference in patient profile with respect to previous experience with DMARs. Therefore, we conducted a subgroup analysis, in which ACR20 showed no statistical significance between the groups who received IFX + MTX or DMARDs in patients with an insufficient response to MTX (1.72 [0.92; 3.22]) and in MTX-naive patients (RR = 1.40 [0.84; 2.34]). For ACR50, IFX + MTX regimen was superior in MTX-naive patients (1.44 [1.18; 1.76]) but not in patients who had an insufficient response to MTX (1.72 [0.98; 3.00]). In contrast, IFX + MTX was statistically superior to DMARD therapy in MTX-naive patients (1.56 [1.19; 2.04]) and in patients with an insufficient response to MTX (2.20 [1.06; 4.56]) in ACR70 meta-analysis.

Discussion

This systematic review and meta-analysis included nine randomised controlled clinical trials and one ongoing study, and showed superior results of efficacy as evaluated by ACR and DAS28, and of radiographic progression for IFX + MTX compared to MTX monotherapy or in combination with other DMARDs, regardless of disease duration, dose and patient profile.

The efficacy of the IFX + MTX regimen was assessed from 14 weeks of treatment[32] to 104 weeks[3] in patients with an insufficient response to MTX and in MTX-naive patients. IFX + MTX use began early after RA diagnosis[30,31] or after 10 years of disease duration[32,35,36] on average. The therapeutic regimen was variable and included the administration of 3 or 10 mg/kg IFX every four or eight weeks[33,35,36] or 6 mg/kg IFX every eight weeks.[27] The control group included placebo + MTX or a combination of synthetic DMARDs.

These differences affected the size and direction of the effect, which favoured IFX + MTX especially during shorter periods of follow-up in patients with established RA and an insufficient response to MTX. These results support the treatment with synthetic DMARDs, reserving the IFX + MTX regimen for cases of a failure of the first-line regimen. This approach is corroborated by Du Pan et al.,[37] who performed a systematic review that specifically evaluated patients with early RA and recommended the use of IFX + MTX for cases with rapid radiographic progression, insufficient response to MTX or other clinical and biological signs of aggressive disease, since there is no robust evidence that supports the efficacy, safety and cost of the early use of IFX.

The results of efficacy and safety also encourage the use of the recommended standard regimen of 3 mg/kg IFX at weeks 0, 2 and 6 and then every eight weeks in combination with MTX, instead of increased dose or shorter intervals of IFX administration, as described in individual studies.[4,7]

Clinical remission favoured the use of IFX + MTX after 24 and 54 weeks of treatment and the ACR response after 52 weeks. However, the high heterogeneity of the analysis of ACR20 and ACR50 for up to 30 weeks of treatment and the lack of effect of ACR20 at 52 weeks in the subgroup analysis by past DMARD exposure were notable. Wiens et al.[18] also reported inconsistent results in the ACR20 and 50 responses after 30 weeks, and considered the high number of patients who achieved the therapeutic response in the test and control groups on the START[34] study as a possible explanation. The ACR20 response may be more sensitive to the use of some treatments because it is less strict. However, differences between treatments became more evident with more strict ACR responses because in this case these responses were directly related to the efficacy of the biological agent use.

Furthermore, only the SWEFOT study[3,31] assessed efficacy outcomes for up to 104 weeks of follow-up, and this study reported no difference in the ACR responses between IFX + MTX and DMARD combination groups. This affected also the meta-analysis of our study, because when it was excluded the result of efficacy outcomes was favourable for the IFX + MTX. In contrast, the prevention of radiographic progression using IFX + MTX was confirmed, despite the control group (i.e., with DMARD combination or MTX monotherapy).

Withdrawals due to adverse events were especially affected by the exclusion of the SWEFOT study.[3,31] With the exclusion of this study the analysis became statistically significant favouring IFX + MTX. This result was expected because the addition of a higher number of drugs to a therapeutic regimen increases the probability of adverse events and decreases the differences between strategies. Other systematic reviews that did not include this study also reported a greater loss to follow-up as a result of adverse events in the IFX + MTX group.[16,18] Considering withdraw due to adverse events according to patients' past experience with DMARDs, the results of our meta-analysis showed higher risk of loss in the IFX + MTX group for MTX-naive patients, but not for patients with an insufficient response to MTX, as reported by Chen et al.[15] These results suggest that previously treated patients exhibit a higher tolerance to adverse events.

Table 4 – Safety meta-analysis of standard dose IFX 3 mg/kg each 8 weeks.

Outcome	Number of evaluated studies [study]	Patients (*n*)	RR (IC 95%)	I^{2a}	*p*-Value[b]
Infections	4	658	1.04 (0.73; 1.47)	66%	0.03
Insufficient responses to MTX	3[3,28,32]	629	1.21 (0.75; 1.98)	57%	0.10
MTX-naïve patients	1[30]	29	0.81 (0.61; 1.06)	–	–
Serious infections	6	2128	1.19 (0.48; 2.93)	56%	0.08
Insufficient responses to MTX	4[3,28,34,36]	1428	0.83 (0.33; 2.06)	31%	0.24
MTX-naïve patients	2[27,30]	700	2.80 (1.14; 6.84)	–	–
Serious adverse events	8	2397	1.02 (0.79; 1.33)	0%	0.57
Insufficient responses to MTX	6[3,28,29,32,34,36]	1697	0.86 (0.61; 1.21)	0%	0.57
MTX-naïve patients	2[27,30]	700	1.32 (0.87; 1.98)	0%	0.63
Tumours	7	2369	1.87 (0.42; 8.35)	0%	0.92
Insufficient responses to MTX	6[3,28,29,32,34,35]	1698	1.87 (0.42; 8.35)	0%	0.92
MTX-naïve patients	1[27]	671	–	–	–
Tuberculose	5	1928	4.12 (0.47; 36.07)	0%	0.78
Insufficient responses to MTX	4[28,29,32,34]	1265	2.97 (0.12; 71.81)	–	–
MTX-naïve patients	1[27]	663	5.48 (0.28; 105.67)	–	–
Death	6	2052	1.05 (0.20; 5.42)	0%	0.55
Insufficient responses to MTX	4[3,28,32,34]	1352	2.47 (0.26; 23.61)	0%	0.86
MTX-naïve patients	2[27,30]	700	0.40 (0.04; 4.38)	–	–
Infusion reactions	3	1042	2.21 (1.63; 2.99)	72%	0.03
Insufficient responses to MTX	2[28,32]	371	1.52 (1.02; 2.26)	0%	0.40
MTX-naïve patients	1[27]	671	3.16 (1.98; 5.03)	–	–

CI, confidence intervals; RR, relative risk; MTX, methotrexate; –, not estimable.

[a] $I^2 > 40\%$ indicate heterogeneity between studies.

[b] *p*-Value < 0.10 of χ^2 indicates heterogeneity between studies.

No differences in safety were observed in this or previous systematic reviews,[15,18,19] but other evidence sources have reported that the use of anti-TNFα increases patients' risk of developing tuberculosis (TB) and other infections.[38–40] An evaluation of the biological products database of the Spanish Society of Rheumatology revealed incidence rates of 1113 per 100,000 in 2001, which was significantly higher than national rates.[38] A meta-analysis of safety from observational studies[40] related an increased risk of infections of approximately 40% for RA patients who were treated with anti-TNFα (RR = 1.37 [1.18; 1.60]). These risks support the use of TB screening for all patients who might receive anti-TNFα treatment, and these patients should be followed using new tests for the signals and symptoms of infections, especially during the first year of treatment.[7,41]

Regarding the comparison of high-dose IFX and the standard dose of 3 mg/kg every 8 weeks, we did not find significant differences in ACR outcomes after 54 weeks of follow-up. Therefore, the lower dose of 3 mg/kg IFX every eight weeks was as effective as the other doses in isolated studies[32,34,35] and in the meta-analysis of this review. However, the results of the meta-analysis on serious infections showed significant heterogeneity. The ASPIRE[27] study, which included MTX-naive patients, was excluded, and the risk of infections became higher with high doses of IFX + MTX, showing that MTX-naive patients may be more susceptible to infections. Therefore, the group that received high doses of IFX had high infection rates compared to the standard dose IFX group. These results were consistent with Aaltonen et al.[19] and Alonso-Ruiz et al.[16] who reported no differences in efficacy between high and standard doses of IFX. However, no difference in safety between the dose regimens was described,[19] although this study did not analyse heterogeneity or perform a subgroup analysis by patient DMARD exposure. An IFX induction regimen using 10 mg/kg is not indicated by the manufacturer, and it is discouraged by the results of clinical trials and this systematic review, since it provides no additional benefits. Besides, this strategy can increase the risk of infections compared to placebo + MTX group.[34,35]

One RCT that was not included in our systematic review because of the dose escalation analysed the increase in IFX dose from 3 to 5 mg/kg every 8 weeks and revealed no additional benefit to the primary outcome (DAS28 after 28 weeks) or secondary outcomes (e.g., number of swollen and tender joints, C-reactive protein and erythrocyte sedimentation rate) within 52 weeks. Furthermore, an increase in the incidence of adverse events was observed, but these adverse events did not include serious adverse events or serious infections.[42]

Ollendorf et al.[43] also demonstrated that patients using IFX increased the dose more frequently over shorter periods of time than patients using etanercept and adalimumab (32.1%, 8.5% and 4.7%, respectively). Consequently, the cost of IFX treatment was approximately 30% higher than other anti-TNFα agents. These results suggest that increasing IFX dose in patients who do not adequately respond to the standard dose of 3 mg/kg IFX every eight weeks in combination with MTX is not the best strategy.[42,44]

Limitations

A random effects model was used, and the results of the subgroup analyses lost part of its inference value due to the clinical heterogeneity of trials in the evaluated outcomes, patient profile, period of follow-up, dose and administration period. However, the results were consistent with the literature, and although not entirely reflective of reality, they demonstrate the direction of the effect. Other limitation is that only three of the published RCTs were not funded by the pharmaceutical industry. Studies funded by the pharmaceutical industry are more likely to report favouring outcomes to their products[45] and therefore, the results of these studies should be interpreted cautiously. Because of that, the assessment of risk of bias became more pertinent, and only one study in this review was classified as a low-risk of bias in all assessed domains. Also, we could not assess the publication bias of the outcomes because the recommended number of clinical trials to perform this analysis with robustness is 10 studies. However, we conducted the manual search and search through the grey literature to minimise this effect. Evidence on the IFX + MTX regimen versus MTX is well established, but other types of comparison must be explored. Only one published study[3,31] assessed the regimen INF + MTX versus a DMARD combination. Because of that, this systematic review could not establish the best strategy for patients in whom first-line therapy fails. Clinical trials that compare the efficacy of IFX + MTX to combinations of DMARDs are required to cover this knowledge gap.

Implications for clinical practice

The use of IFX + MTX promoted radiographic and clinical benefits that were less significant in early RA patients, which suggests that early treatment with any synthetic DMARD is more important than early treatment using a biological agent. The combination of IFX + MTX may be a better strategy for the prevention of radiographic progression than MTX alone. The choice between INF + MTX over combination DMARDs should consider their ability to reduce functional loss over time (i.e., radiographic progression) balanced with the small clinical differences that are observed over long periods of follow-up, and the higher cost of anti-TNFα treatment.

Conclusions

IFX + MTX therapeutic regimens showed better results of clinical efficacy evaluated by ACR and DAS28 than MTX monotherapy or combined DMARDs, regardless of disease duration, dose and patient past experience with DMARD. The efficacy of IFX + MTX was more evident in shorter periods of follow-up, patients with established RA and patients with insufficient response to MTX. Radiographic progression was averted in longer follow-up periods. The lowest dose, 3 mg/kg IFX every eight weeks, was as effective as the other IFX doses. The data on safety suggest that increases in IFX doses were related to an increased incidence of infections, and therefore should not be used.

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Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material associated with this article can be found in the online version available at doi:10.1016/j.rbre.2014.10.009.

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