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Systematic Review

Effectiveness of Combination of Leflunomide and Methotrexate Compared to Etanercept in the Treatment of Rheumatoid Arthritis: A Systematic Review and Meta-Analysis

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Abstract

Context: Rheumatoid arthritis (RA) is a chronic progressive systemic inflammatory condition, which affects mainly the joint synovial and does not have a definitive treatment. Data was collected using the American College of Rheumatology (ACR) score, and different levels of improvement were shown as ACR20, ACR50, and ACR70. The aim of this study was to compare the effectiveness of combination of leflunomide and methotrexate (LEF + MTX) to etanercept (ETN).

Methods: This systematic review was performed to evaluate the effectiveness of LEF + MTX in comparison with ETN. Electronic databases, including cochrane, PubMed, Scopus, and CRD, were searched up to December 2015. Quality assessment was conducted by the Jadad scale and the Cochrane Collaboration's tools. Meta-analysis was conducted for effective outcomes of the included studies. Effectiveness was measured by ACR. This review was updated up to January 2019.

Results: Overall, 2780 eligible articles were retrieved, five of which were eligible for inclusion. Effectiveness outcomes showed an improvement in ACR criteria. Differences in the improvement of ACR70, ACR50, and ACR20 criteria in LEF + MTX groups compared to placebo groups were reported 0.78%, 20%, and 27%, respectively, and these differences compared to ETN groups were respectively 0.003%, 21.93%, and 32%.

Conclusions: Combination of leflunomide and methotrexate is effective, and it can be used as before biomedical medications such as etanercept, as it is more cost-effective.

Keywords: Rheumatoid Arthritis; Leflunomide; Methotrexate; Etanercept

1. Context

Rheumatoid arthritis (RA) is an autoimmune chronic progressive systemic inflammatory condition in which joints are affected symmetrically. Swelling is the main and primary symptom in synovial joint, following which other joints and their structure are attacked. Rheumatoid arthritis is a chronic disease that causes pain, stiffness, swelling, and limited motion and function in various joints and leads to deformity through the stretching of tendons and ligaments and destruction of joints through the erosion of cartilage and bone (1, 2). According to the literature, 1% - 2% of the global population suffer from RA (3, 4). The exact reason for Rheumatoid Arthritis is unknown (5).

There are some scales to measure changes in RA, one of which is the American College of Rheumatology (ACR) score. Different levels of improvement are referred as ACR20, ACR50, and ACR70. Numbers indicate how many symptoms of RA have improved and decreased. The ACR score is represented as a percentage. ACR20 score means that the patient has improved by 20%, and ACR50 score means the patient has improved by 50%, and an ACR70 score means the patient has improved by 70% (3, 6, 7).

This criterion includes physical function, physician health assessment, patient health assessment, number of painful joints, number of swollen joints, and laboratory tests (including erythrocyte sedimentation rheumatoid arthritis (ESR), C-reactive protein (CRP), and rheumatoid factor) (8, 9).

The goal of treatment is reducing symptoms and improving function. Four main groups of drugs are used to treat RA, including painkillers, non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), and biopharmaceutical drugs (10, 11). Leflunomide and methotrexate are immunosuppressive disease-modifying antirheumatic drugs (DMARD). This group functions through inhibiting inflammation, suppressing the

immune system, reducing pain and swelling of the joints, improving joints performance, and decreasing the damage to them (10, 11). Etanercept is a biological medicine against inflammatory agents to reduce inflammation and prevent disease process. Tumor necrosis factor (TNF) inhibitors are the first line of treatment over other medications of biopharmaceutical group. It treats autoimmune diseases by interfering with tumor necrosis factor by acting as a TNF inhibitor (12, 13).

The objective of this study was to compare the effectiveness of leflunomide and methotrexate to of etanercept.

2. Evidence Acquisition

A primary review to assess the effectiveness was performed, and the structured question, the keywords, and the search strategy (Table 1) were chosen based on the review. The systematic review was performed using the electronic databases, including the Cochrane Library, Scopus, CRD, and PubMed, up to December 2015. Also, we updated this review up to January 2019.

Table 1. Search Strategy

Databases	Keywords	
PubMed	#1 = Methotrexate; #2 = Leflunomide; #3 = combination therapy; #4 = Rheumatoid arthritis; #5 = clinical trial; #6 = #1 AND #2 AND #3 AND #4 AND #5; #7 = Etanercept; #8 = #7 AND #4; #9 = #8 OR #6	720
SCOPUS	#1 = Methotrexate; #2 = Leflunomide; #3 = combination therapy; #4 = Rheumatoid arthritis; #5 = clinical trial; #6 = #1 AND #2 AND #3 AND #4 AND #5; #7 = Etanercept; #8 = #7 AND #4; #9 = #8 OR #6	1504
COCHRANE	#1 = Methotrexate; #2 = Leflunomide; #3 = combination therapy; #4 = Rheumatoid arthritis; #5 = clinical trial; #6 = #1 AND #2 AND #3 AND #4 AND #5; #7 = Etanercept; #8 = #7 AND #4; #9 = #8 OR #6	420

PICO of this study was as follows: Population: patients who suffer from RA, intervention: combination of leflunomide and methotrexate, comparison: etanercept, outcome: improvement in ACR criteria, design: RCT.

2.1. Inclusion Criteria Were the Following

Type of study: studies that compare the effectiveness of the combination of leflunomide and methotrexate with that of etanercept; participants: patients who suffer from RA; type of intervention: comparison of the effectiveness of the combination of leflunomide and methotrexate with that of etanercept in the treatment of RA; and type of outcome: improvement in ACR criteria.

The two coauthors extracted information independently, and in case of any disagreements, a third person made the decision according to the inclusion criteria. The extracted data were (1) type of study; (2) patients' attributes (number, age, and gender); (3) the characteristics of the disease; (4) intervention; and (5) outcomes. There was no limitation in our search strategy, but only English-language studies were included in our final selection.

The quality of the selected studies was assessed by the Jadad scale (Table 2) by the two coauthors independently. It consists of seven questions. Quality was not used as a criterion for excluding studies, but it was considered in the final result.

Table 2. Assessment of the quality of the selected studies

JADAD Scoring Criteria	Potential Score	Score Awarded
Was the study described as randomized?	+1	
Was the method of randomization appropriate	+1	
Deduct 1 point if the method of randomization is inappropriate	-1	
Was the study described as double blinded?	+1	
Was the method of blinding appropriate?	+1	
Was the method of blinding inappropriate?	-1	
Was there a description of withdrawals and dropouts?	+1	

[a]Keywords: #Methotrexate; # Amethopterin; # Mexate; # Methotrexate Sodium; #Sodium, Methotrexate; #Methotrexate, Disodium Salt; #Methotrexate, Sodium Salt; #Methotrexate Hydrate; #Hydrate, Methotrexate; # = Methotrexate, Dicesium Salt; # Dicesium Salt Methotrexate; ##1 OR #2 OR #3 OR #4 OR #5 OR #6 OR#7 OR #8 OR #9 OR #10 OR #11; #N-(4-trifluoromethyphenyl)-5-methylisoxazole-4-carboxamide; #HWA 486; #HWA-486; # SU101; # Arava; # Leflunomide; #combination therapy; #Rheumatoid arthritis; # Idiopathic arthritis; #chronic arthritis; #symetric poly-arthritis; #Chronic poly-arthritis; # clinical trial; #TNR-001; #TNR 001; # TNT receptor fusion protein; #TNTR-Fc; #TNF receptor type II-IgG fusion protein; #recombinant human dimeric TNF receptor type II-IgG fusion protein; # Enbrel; #Etanercept.

Meta-analysis was conducted by RevMan 5 for all of the effectiveness outcomes.

3. Results

Overall, 2780 articles were retrieved in this search; 325 records were removed due to being duplicates, and 2402 were excluded after screening the headlines and abstracts. The remaining 53 full-text articles were assessed for eligibility, and 48 studies were excluded in quality analysis because of different age groups, comparators, settings, types of study, or other criteria. Overall, 1369 patients in five records were eventually selected for analysis. In the updated search, we found 540 records, 399 were left after removing duplicates, then they were excluded by topic and abstract. Twenty-nine articles were studied fully, but none was added because of not meeting the inclusion criteria.

Prisma diagram is shown in Figure 1.

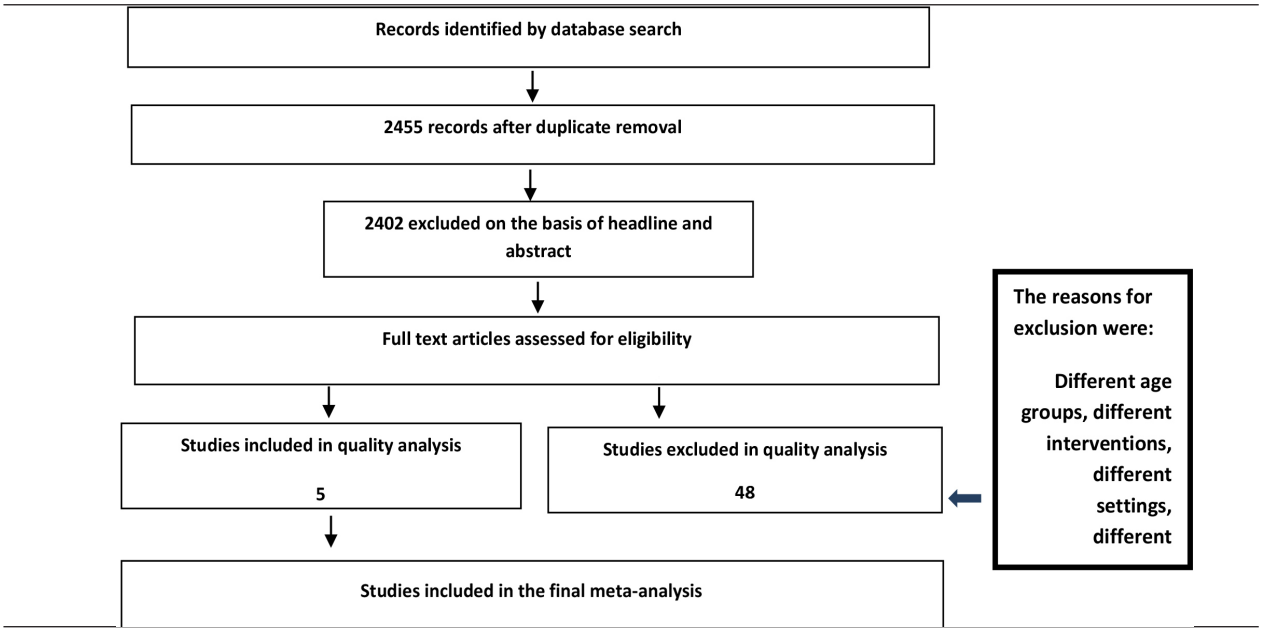

Figure 1. Flow diagram of the selection procedure

The summary of the characteristics of the studies is presented in Table 3.

All five studies were double-blind, randomized control trials, four studies evaluated ETN versus placebo, and one compared LEF + MTX with placebo. Effectiveness was measured by ACR, and the quality of all the included studies was high.

Table 3. Included Studies

Author	Topic	Country	Number of Patients	Jadad Score
Hobbs et al. (14)	Efficacy and safety of Etanercept (ETN) in patients with moderately active rheumatoid arthritis (RA) despite disease-modifying antirheumatic drug (DMARD) therapy	USA, Canada	210	5
Keystone et al. (15)	Once-weekly administration of 50 mg ETN in patients with active rheumatoid arthritis: Results of a multicenter, randomized, double-blind, placebo-controlled trial	USA, Canada	470	5
Kremer et al. (16)	Concomitant leflunomide therapy in patients with active RA despite stable doses of methotrexate: A randomized, double-blind, placebo-controlled trial	USA, Canada	263	5
Moreland et al. (13)	Etanercept therapy in RA. A randomized, controlled trial	USA	246	5
Moreland et al. (17)	Treatment of RA with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein	USA	180	4

3.1. Results of Effectiveness: Etanercept Versus Placebo

The aim of treatment was to reduce symptoms and pain. It should be noted that the effectiveness of these medications is an improvement in the ACR criterion.

3.2. Outcome: ACR20

ACR20 improvement after 24 weeks was extracted from four studies. The random-effects model was used to analyze the pooled data as there was notable heterogeneity ($I^2 = 80\%$).

The results of this meta-analysis confirmed that ETN was more efficacious than placebo. As the meta-analysis shows, ETN increased ACR20 by 2.77, and the forest plot displays (2.77 - 1 = 1.77) 1.77 improvement by ETN as compared with placebo (Figure 2).

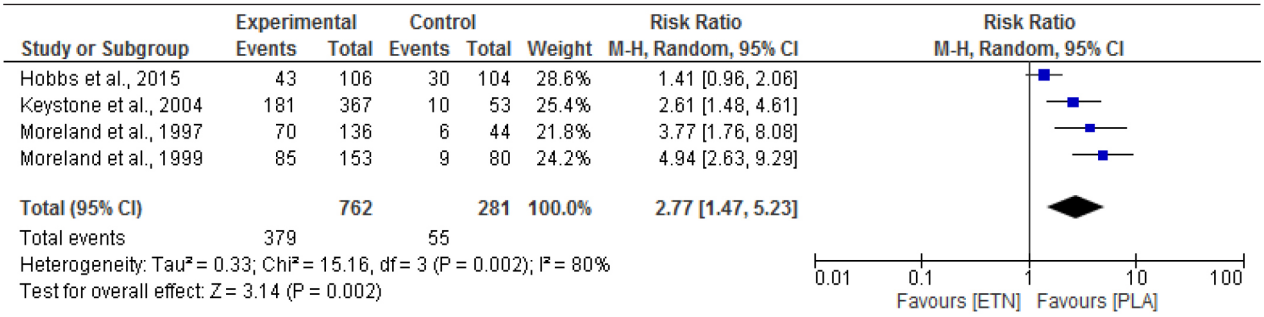

Figure 2. Analysis of efficacy comparison: Etanercept vs. placebo ACR20

The random-effects model showed a significant difference in ACR 20 for ETN compared to placebo and indicated ACR20 improvement by 1.77 in ETN groups rather than the placebo groups.

The effectiveness of ETN by ACR20 was evaluated in the two common doses of 25 and 50 mg. To measure the effectiveness of studies, subgroup analysis was performed, and then the overall effectiveness was examined (Figure 3).

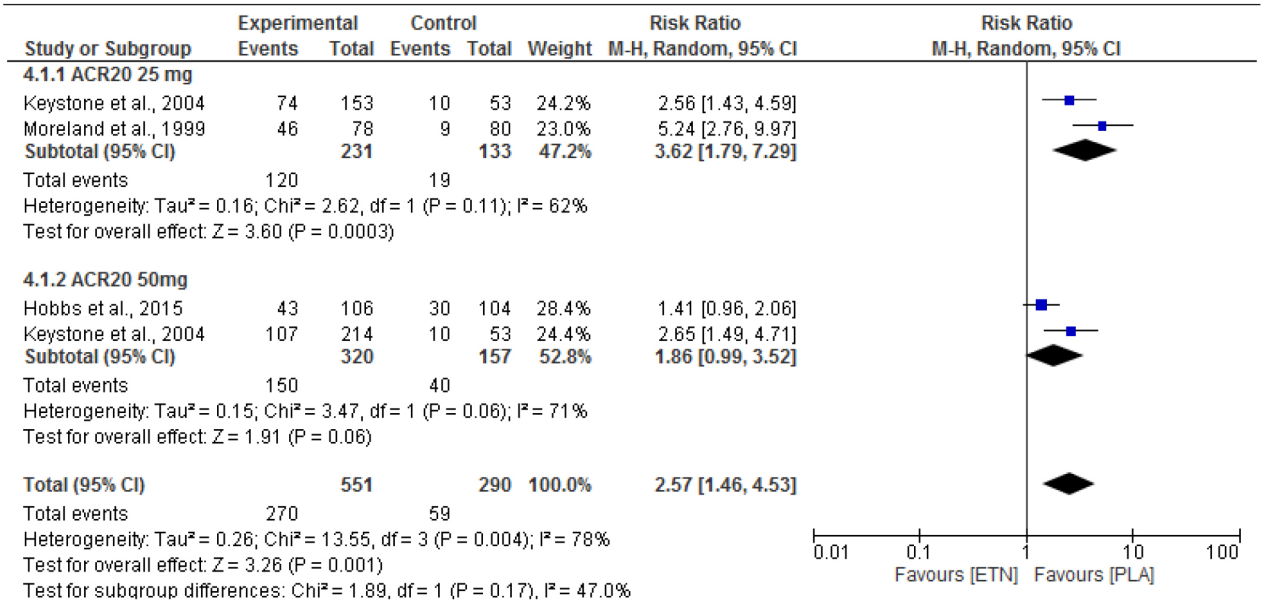

Figure 3. Analysis of efficacy comparison: Etanercept 25 mg and Etanercept 50 mg vs. placebo ACR20

This subgroup meta-analysis manifested 2.60 improvement in ACR20 in ETN 25 mg group rather than the placebo group. Also, this subgroup meta-analysis shows 0.86 improvement in ACR20 in ETN 50 mg groups rather than placebo groups; these results are statistically significant with 95% confidence interval.

Generally, the results showed that ETN was more efficacious than placebo (total effect is 1.57 improvement in ACR20).

Moreland's study in 1997 was excluded from subgroup meta-analysis because of different dose.

3.3. Outcome: ACR50

ACR50 improvement after 24 weeks was extracted from four studies. The random-effects model was used to analyze the pooled data as there was notable heterogeneity ($I^2 = 53\%$).

The results of this meta-analysis confirmed that ETN was more efficacious than placebo. As the meta-analysis exhibited, ETN increased ACR50 by 3.22, and the forest plot showed (3.18 - 1 = 2.18) 2.18 improvement by ETN as compared with placebo (Figure 4).

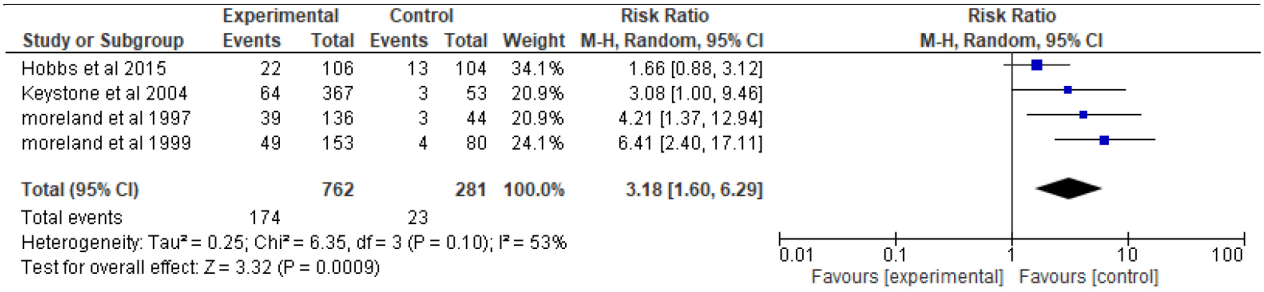

Figure 4. Analysis of comparison of the effectiveness of Etanercept vs. placebo ACR50

The random-effects model showed a significant difference in ACR50 for ETN compared to placebo and indicated 2.18 improvement in ACR50 in ETN groups rather than placebo groups.

The effectiveness of ETN by ACR50 was evaluated in the two common doses of 25 and 50 mg. To understand the effectiveness of studies, subgroup analysis was conducted and then the overall effectiveness was tested.

This subgroup meta-analysis indicates 4.32 improvement in ACR50 in ETN 25 mg groups rather than placebo group, and it is statistically significant with 95% confidence interval. Also, this subgroup meta-analysis revealed 0.93 improvement in ACR50 in ETN 50 mg groups rather than placebo groups, and it is statistically significant with 95% confidence interval.

Generally, the results revealed that ETN was more efficacious than placebo (total effect was 2.21 improvement in ACR50) (Figure 5).

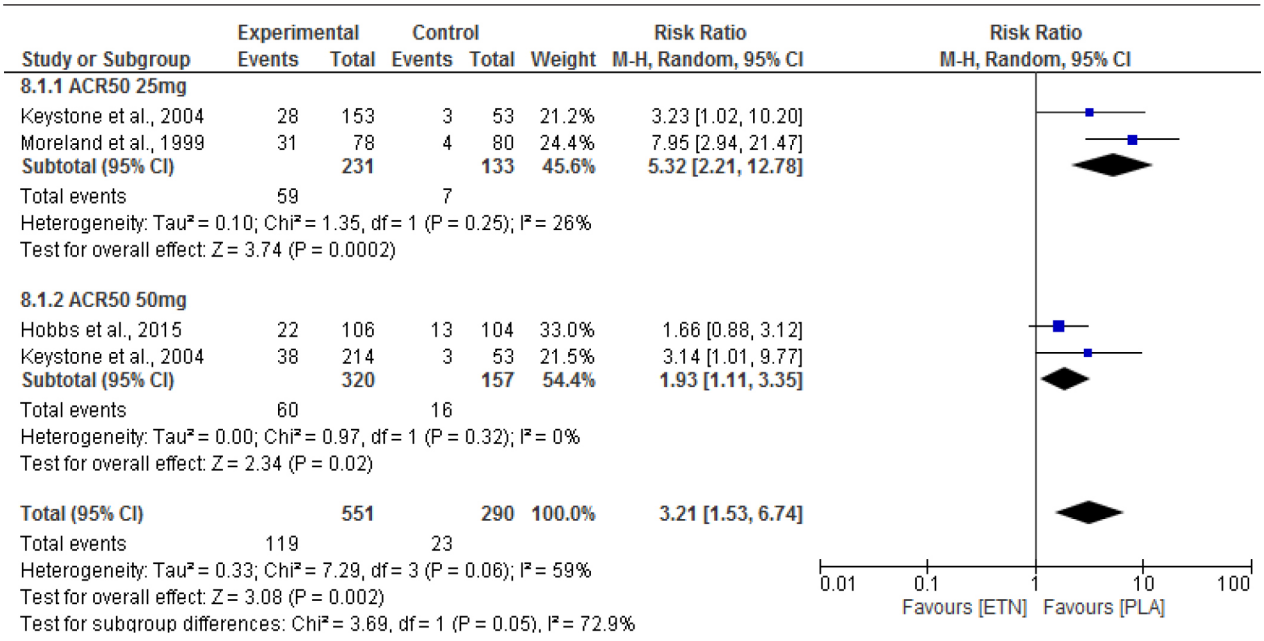

Figure 5. Analysis of efficacy comparison: Etanercept 25 mg and Etanercept 50 mg vs. placebo ACR50

3.4. Outcome: ACR70

ACR70 improvement after 24 weeks was extracted from four studies. The fixed-effects model was used to analyze the pooled data as there was not any heterogeneity ($I^2 = 0$).

The results of this meta-analysis confirmed that ETN was more efficacious than placebo. As the meta-analysis showed, ETN increased ACR70 by 5.41, and the forest plot exhibited (5.41 - 1) 4.41 improvement in ETN in compare with placebo (Figure 6).

The fixed-effects model showed a significant difference in ACR50 for ETN compared to placebo and indicated 4.41

improvement in ACR50 in ETN groups rather than placebo groups.

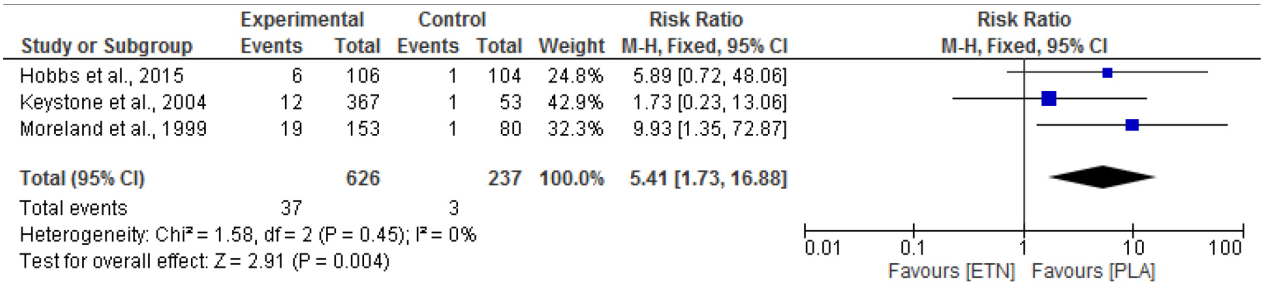

Figure 6. Analysis of efficacy comparison: Etanercept vs. placebo ACR70

Etanercept was significantly better than placebo, and ACR 20/50/70 improved in ETN respectively by 1.77, 2.18 and 4.41 rather than placebo.

The effectiveness of ETN by ACR70 was evaluated in the two common doses 25 and 50 mm. To assess the effectiveness of studies, subgroup analysis was performed, and then the overall effectiveness was tested.

This subgroup meta-analysis represented 5.37 improvement in ACR70 in ETN 25 mg groups rather than placebo groups, and it is statistically significant with 95% confidence. Also, this subgroup meta-analysis demonstrated 2.03 improvement in ACR70 in ETN 50 mg groups rather than placebo groups, and it is statistically significant with 95% confidence interval.

Generally, the results confirmed that ETN was more efficacious than placebo (total effect was 3.66 improvement in ACR70) (Figure 7).

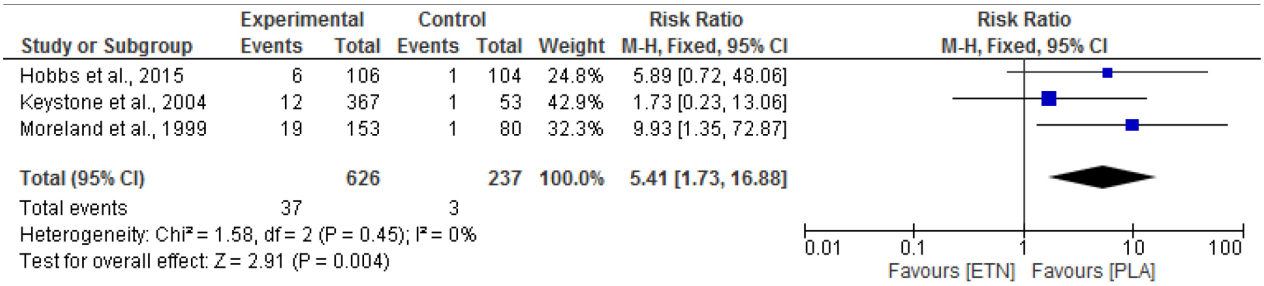

Figure 7. Analysis of Efficacy Comparison Etanercept 25 mg and Etanercept 50 mg vs. placebo ACR70

3.5. Results of LEF + MTX

Results of LEF + MTX therapy by the American College of Rheumatology (ACR) criteria scores (20,5 0, and 70) as end points are discussed below.

There was one study to compare the effectiveness of the combination of LEF + MTX with placebo. The open-label extension trial of Kremer et al. study (Kremer 2002) compared the effectiveness of combined LEF and MTX with a placebo group.

The following tables show frequently distribution of reducing symptoms and prevention of disease process. (Table 4).

Table 4. Frequency Distribution of Improving ACR20 Criteria in the Two Groups

Group	Number of Improvement Cases	Number of No Response	Total
Combination group	60	70	130
Placebo	26	107	133

It showed that 46% of the population had improved in ACR20 criteria in combination groups, while 19% of those who received placebo were recovered.

The frequency distribution of improved ACR50 criteria for AR in both groups was as the following table (Table 5).

Table 5. Frequency Distribution of Improved ACR50 Criteria in the Two Groups

Group	Number of Improvement Cases	Number of No Response	Total
Combination group	34	96	130
Placebo	8	125	133

It shows that 26% of population had improvement in ACR50 criteria in combination groups, while 6% of those who received placebo were recovered.

The frequency distribution of improved ACR70 criteria for AR of both groups was as the following table (Table 6).

Table 6. Frequency Distribution of Improved ACR70 Criteria in the Two Groups

Group	Number of Improvement Cases	Number of No Response	Total
Combination group	13	117	130
placebo	3	130	133

It shows that 1% of population had improvement in ACR70 criteria in combination groups, while 0.22%. of those who received placebo were recovered.

The findings of the meta-analysis show that a significant difference is between ETN and placebo and between the combination of LEF and MTX and placebo. Clearly, ETN is more effective than the combination of LEF and MTX. Although ETN is more effective, leflunomide combined with methotrexate would be an effective combination which can be prescribed before biomedical medication regarding their cost.

4. Discussion

These studies have shown that ETN and LEF + MTX are both effective therapies for AR, and they have a safety profile and can improve ACR criteria.

Etanercept is a powerful medication to significantly reduce the symptoms and improve ACR criteria. Etanercept is biologic medicine.

Numerous studies have shown a significant effect for ETN in the treatment of RA, but regarding its cost, it has not been used as the first or second line of therapy. The effects difference of ACR70, ACR50, and ACR20 criteria in ETN rather than placebo were respectively 0.003%, 21.93%, and 32%.

An 11 -year study was performed in North America by Weinblatt et al. in 2011 (18), where 163 patients in early stage and 264 patients in advanced stages were included. The study investigated the effectiveness and safety of ETN in RA. The outcomes showed improvement in ACR20, 50, and 70 criteria. In the first group, ETN improved ACR respectively by 77%, 52%, and 38%, and in the second group these rates were 71%, 51%, and 24%. The study confirmed the medication is effective (18).

Klareskog et al. (19) performed a multicenter study in 12 European countries during five years. The study included 549 patients, and ACR20, 50, and 70 were the outcomes, and improvement in these criteria was respectively 78%,51%, and 21%. The outcome of this study confirmed the effectiveness of ETN (19).

In 2006, a study was conducted by Dore et al. (20) in the United States among 222 patients with RA during 24 weeks. The type of complications developed included sinusitis, fatigue, headaches, diarrhea, nausea, respiratory tract infection, and pain (20).

This study revealed that LEF + MTX is effective in reducing the symptoms of RA and showed that effect differences between LEF + MTX and placebo in ACR70, ACR50, and ACR20 criteria were 78.0%, 20%, and 27%, respectively. Also, meta-analysis was not conducted because one study had been included.

Several studies have confirmed the effectiveness of the combination of leflunomide and methotrexate, including a review in 2012 that was conducted by the Drug Agency and Health Canada to investigate the effectiveness and safety of leflunomide and methotrexate combination.

In that study, two systematic reviews and four clinical trials were included, all of which showed that LEF + MTX was more effective than MTX alone. Also, the combination therapy reduced the signs and symptoms of RA and increased physical movement (21).

A 24-week multi-center study was performed in Colombia by Londono et al. (22) in 2009 among 88 patients. It investigated the effectiveness and safety of LEF + MTX in RA. The primary outcome was improvement of ACR20 criterion. The results at the end showed that this criterion rose by 76% (22).

5. Conclusions

Although etanercept is more effective than leflunomide combined with methotrexate, this combination can be prescribed before biomedical medication regarding their cost.

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