ORIGINAL ARTICLE

Leflunomide in monotherapy of rheumatoid arthritis: meta-analysis of randomized trials

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KEY WORDS

leflunomide, methotrexate, placebo, rheumatoid arthritis, sulfasalazine

ABSTRACT

INTRODUCTION Rheumatoid arthritis (RA) is a chronic systemic disease of the connective tissue that leads to progressive joint destruction, disability, withdrawal from occupational activity, and premature death.

OBJECTIVES The aim of the paper was to evaluate the efficacy and safety of leflunomide compared with placebo, methotrexate, and sulfasalazine in monotherapy of RA.

PATIENTS AND METHODS A systematic search of databases (MEDLINE, EMBASE, Cochrane CENTRAL) was performed. Only randomized blind trials were included into the analysis. The quality of the trials was assessed by the Jadad scale. A quantitative synthesis of the results was performed (meta-analysis).

RESULTS The analysis included 7 trials involving 2861 patients (1432 on leflunomide, 312 on placebo, 922 on methotrexate, and 133 on sulfasalazine). Leflunomide, compared with placebo, increased the probability of the American College of Rheumatology 20% improvement (ACR20) response 2-fold (relative risk [RR], 2.02; 95% CI, 1.46–2.80) and the probability of ACR50 response 4-fold (RR, 4.36; 95% CI, 2.33–8.17), after 1 year of treatment. Efficacy of leflunomide did not differ from that of methotrexate with reference to the majority of endpoints. Leflunomide showed partial superiority over methotrexate in the percentage of patients obtaining ACR50 and ACR70 response, doctor's assessment of the disease activity, reduction in C-reactive protein (CRP) levels, and improvement of the quality of life (assessed with the modified health assessment questionnaire [HAQ]). Sulfasalazine showed partial superiority in the reduction of erythrocyte sedimentation rate, while leflunomide was superior to sulfasalazine the ACR20 and ACR50 clinical response, quality of life (assessed with the HAQ), doctor's and patient's assessment of the disease activity, and reduction in CRP levels.

CONCLUSIONS There were no significant differences between the effects of treatment with leflunomide and methotrexate or sulfasalazine, but leflunomide monotherapy proved more effective than placebo in relieving symptoms and signs of RA.

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Conflict of interest: D. Golicki and M. Niewada received funding from Sanofi-Aventis Sp. z o.o. J. Lis and K. Pol are employees of Sanofi-Aventis Sp. z o.o.
Received: October 15, 2011.
Revision accepted: January 10, 2012.
Published online: January 11, 2012.
Pol Arch Med Wewn. 2012; 122 (1-2): 22-32

INTRODUCTION Rheumatoid arthritis (RA) is a chronic, inflammatory systemic autoimmune disease of the connective tissue. It is characterized by nonspecific symmetrical arthritis, extra-articular lesions, and organ complications. It is a chronic disease and despite treatment and episodes of remission, it leads to progressive joint destruction, deformation, disability, and premature death.[1] It is estimated that every fourth RA patient requires replacement of a large joint; after 5 years, 50% of the patients become unable to work and after 10 years – 100%. Incidence of RA varies from 0.5% to 2% of the population. Morbidity varies from 31 to 50 persons per 100,000.[1,2]

All RA patients should receive disease-modifying antirheumatic drugs (DMARDs).[1,3] These

agents may prevent or reduce joint damage, help maintain regular structure and function of the joints, reduce the overall health care costs, and ensure occupational activity of RA patients. DMARDs should be introduced within 3 months from diagnosis.

Leflunomide is a DMARD with immunomodulating, immunosuppressive, and antiproliferative properties. Its active metabolite, A771 726, blocks the dihydroorotate dehydrogenase enzyme, thereby inhibiting the de novo synthesis of pyrimidines.[4] Leflunomide relieves the signs and symptoms of RA. Evidence of clinical efficacy of leflunomide was summarized in a few systematic reviews[5,6] and meta-analyses[7-10]; however, these publications were based on rather old database searches and had different inclusion criteria with marked heterogeneity of the included studies.[8]

The aim of the paper was to evaluate clinical efficacy and safety of monotherapy with leflunomide in RA patients, compared with placebo, methotrexate, and sulfasalazine, on the basis of a systematic review and meta-analysis of randomized clinical trials (RCTs).

PATIENTS AND METHODS

A systematic review and meta-analysis was conducted according to the QUOROM guidelines[11] and Cochrane Collaboration standards.[12]

Inclusion and exclusion criteria

A systematic review included prospective single- or double-blind RCTs involving adult patients with active RA and comparing the efficacy of leflunomide against placebo or any other active treatment. Only full-text papers published in English, German, French, or Polish in peer-reviewed journals were considered. Nonrandomized clinical trials, open-label clinical trials, reviews, reports concerning only laboratory findings, underlying disease mechanisms, and treatment mechanisms, as well as trials published only as abstracts were excluded. Endpoints of the review included: clinical improvement according to the American College of Rheumatology criteria (ACR20, ACR50, ACR70),[13] clinical improvement according to the European League Against Rheumatism (EULAR) criteria[14,15] or the Paulus criteria,[16] tender and swollen joint count, general patient's and doctor's assessment of disease activity, change of acute phase markers – erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), patient's pain assessment, duration of morning stiffness, functionality assessment according to the health assessment questionnaire (HAQ),[17] quality-of-life assessment according to the Short Form-36 (SF-36) questionnaire,[18] radiographic changes according to the Sharp[19] or Larsen[20] scores. All safety data were analyzed as desrcibed by the authors.

Search strategy

The following databases were searched for RCTs: MEDLINE (PubMed), EMBASE (Ovid), and the Cochrane Central Register of controlled trials (Issue 4, 2011). The most recent search was conducted independently by 2 persons (D.G. and M.N.) on December 9, 2011. The search included the following MeSH terms: "Arthritis, Rheumatoid", "leflunomide"; and key words: "rheumatoid", "arthritis", "leflunomid*", "arava", and "isoxazole". We also applied the Highly Sensitive Search Strategy (HSSS) filter recommended by the Cochrane Collaboration and designed to search for RCTs.[12] Details concerning search strategies used for particular databases may be provided upon request. We also used the references from the reports, clinical trial registers (ClinicalTrials.gov, Current Controlled Trials), and Internet browsers. Moreover, we consulted the drug manufacturer about the published and possibly unpublished clinical data.

Trial selection and data extraction

The titles and abstracts of the trials were assessed independently by 2 authors (D.G. and M.N.). All publications that potentially qualified for the review were assessed in full text version in detail for meeting the inclusion and exclusion criteria. Data extraction was performed independently by 2 investigators (D.G. and M.N.) on the basis of a form developed prior to the study. The extracted data were compared. The protocol assumed that in case of discrepancies between the investigators, another investigator would act as an arbiter until consensus was achieved.

Assessment of trial quality

Methodology of trials included into the review was assessed with the Jadad scale.[21] Description of randomization procedure (0–2 points), description of a blinding method (0–2 points), and description of patients withdrawn from the trial (0 or 1 point) were taken into account. The trials were also assessed for the size of trial population, number of participating centers, and duration of follow-up.

Statistical methods

The meta-analysis was conducted using the RevMan software, version 5.0.[22] We calculated the weighted mean difference for continuous data and the relative risk (RR) for binary data. RR >1 meant that patients from the experimental group had higher probability of achieving endpoint than those from the control group.

By default, a fixed data model (fixed effect) was applied. Heterogeneity of the trials was assessed by means of the χ^2 and I^2 tests. When compared trials had high heterogeneity ($P < 0.1$ or $I^2 > 50\%$), the random effect model was applied. The results were considered statistically significant at the level of $P < 0.05$.

RESULTS

Description of trials

On the basis of the title and abstract, 60 papers were identified and analyzed in full-text versions. The scheme of search process is presented in FIGURE 1. Eventually, 17 publications including 7 double-blind RCTs[23-29] and 10 articles supplementing data from clinical trials were included in the systematic review. The original publication by Strand et al.[25] was

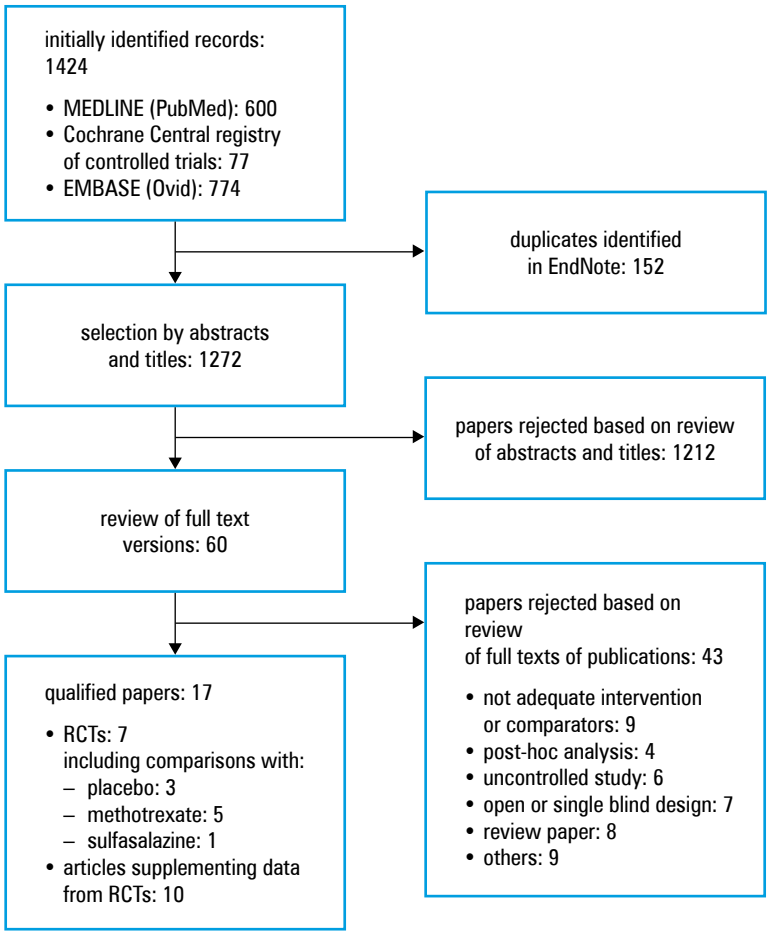

FIGURE 1 QUOROM flow diagram
Abbreviations: RCTs – randomized control trials

supplemented with the results from the second year of double-blind follow-up[30] and additional data on the quality-of-life improvement within this trial.[31-33] Similarly, the original publication from the trial by Smolen et al.[24] was supplemented with additional information on the second year double-blind follow-up[34,35] and radiographic disease progression.[36] The results of all 3 major phase III trials – Strand et al.,[21] Smolen et al.,[24] and Emery et al.[26] were separately summarized for radiographic changes[37] and separately for 2-year changes in the quality of life, physical functions, and productivity.[38] Finally, the publication by Reece 2002[39] provided supplementary data from the trial by Kraan et al.[27]

Efficacy of leflunomide (n = 1432 patients) was compared with placebo (n = 312) in 3 trials,[23-25] methotrexate (n = 922) in 5 trials,[25-29] and sulfasalazine (n = 133) in 1 trial.[24] All the included trials were conducted as double-blind RCTs. The trials differed in scope: from one-country (Netherlands,[28] China),[29] to large multinational research programs[24-26]; in the number of participating centers: from 2[27,28] to 117,[26] in the number of subjects: from 15[28] to 999[26]; and in duration of follow-up – from 12[29] to 104 weeks[24-26] (TABLE 1). The trials differed also in the quality of methodology: from 2[28] to 5 points[24,25] in the Jadad scale, with the average score of 3.86 points.

The review included only trials that involved patients with diagnosed RA in the active phase. In most studies, women constituted from 66% to 88% of the patients, the average age of patients was over 50 years, and the mean duration of RA was from 3 to 6 years,[26-29] 5 to 8 years,[24,25] or 7 to 9 years.[23] Over 60% of the subjects in all trials had the rheumatoid factor in the blood.

Almost all trials included in the review studied the same intervention, namely, treatment with oral leflunomide at a dose of 20 mg daily. The only exception was the paper by Mladenovic et al.[23] concerning phase II trial where the safety and efficacy of 3 doses of leflunomide (5 mg, 10 mg, and 25 mg) were compared with placebo in 3 parallel groups. Only the group with registered dose of 10 mg was included into the meta-analysis. In all trials, an increased intiation dose of leflunomide was administered (50 to 100 mg) to accelerate the achievement of steady state serum concentration of the drug. In the clinical trials included in this meta-analysis, methotrexate was administered at a target dose of 15 mg per week,[25-29] and sulfasalazine at an initial dose of 0.5 g daily, gradually increased to 2 g daily.[24]

Efficacy of leflunomide vs. placebo Leflunomide, compared with placebo, proved highly efficient in relieving the signs and symptoms of RA. The following observations were made: a reduction in tender joint count by 47%–52% (vs. 18%–26% for placebo), reduction in swollen joint count by 42%–49% (vs. 20%–27%), improvement in the general patient's assessment by 30%–38% (vs. worsening by 2%, improvement by 7%), improvement in the doctor's assessment by 32%–46% (vs. 9%–16%), reduction in the ESR by 13%–16% (vs. elevation by 2%–7%), reduction in CRP levels by 30%–51% (vs. reduction by 5%, elevation by 19%), reduction in pain by 37%–43% (vs. 6%–15%), reduction in the duration of morning stiffness by 65% (vs. 7%) were observed. Also, improvement in patients' functioning assessed using the various versions of the health assessment questionnaire (HAQ) by 35%–45% (vs. worsening by 8%, improvement by 5% in the placebo group) or using the problem elicitation technique (PET top 5) by 35% (vs. 3%) was observed. Furthermore, an increase in the productivity of patients taking leflunomide by 18% (vs. 0.5% among placebo patients), increase in total physical component of the SF-36 questionnaire by 25% (vs. 3%), and slower progression of joint degenerative changes, as assessed on hand and feet X-rays by the Sharp scoring, by 2.3% after 1-year follow-up (vs. 8.5%) were observed. After 6 months of leflunomide treatment, response criterion by the American College of Rheumatology, ACR20, was achieved by 55% patients (vs. 29% in the placebo group), and the response was maintained in 52% patients during 1-year follow-up (vs. 26%; FIGURE 2). Superiority of leflunomide was also apparent when more stringent criteria were applied: ACR50 – 34% patients after 1 year of treatment (vs. 8%),

TABLE 1 Characteristics of included trials

Trial	Number and localization of centers	Population size	Duration of follow-up (weeks)	Population	Type of intervention (n)	Comparator (n)	Trial design	Assessment of trial quality by Jadad (points)
Mladenovic et al.[23]	6 Yugoslavia, Croatia, Slovenia	402	24	RA, active phase	LEF 5 mg/d (95) LEF 10 mg/d (101) LEF 25 mg/d (104)	placebo (102)	RCT, DB	4 (2/1/1)[a]
Smolen et al.[24]	36 Europe, Australia, New Zealand, South Africa	358	104	RA, active phase	LEF 20 mg/d (133)	placebo (92) sulfasalazine (133)	RCT, DB	5 (2/2/1)
Strand et al.[25]	47 United States, Canada	482	104	RA, active phase	LEF 20 mg/d (182)	placebo (118) MTX 7.5–15 mg/w (182)	RCT, DB	5 (2/2/1)
Emery et al.[26]	117 Europe, South Africa	999	104	RA, active phase	LEF 20 mg/d (501)	MTX 10–15 mg/w (498)	RCT, DB	4 (1/2/1)
Kraan et al.[27]	2 The Netherlands, United Kingdom	39	16	RA, active phase, early phase	LEF 20 mg/d (18)	MTX 15 mg/w (21)	RCT, DB	3 (1/1/1)
Kraan et al.[28]	2 The Netherlands	15	52	RA, active phase	LEF 20 mg/d (7)	MTX 7.5–15 mg/w (8)	RCT, DB	2 (1/1/0)
Bao et al.[29]	9 China	566	12	RA, active phase	LEF 20 mg/d (323)	MTX 15 mg/w (243)	RCT, DB	4 (1/2/1)

a summary Jadad scale depends on 3 factors: randomization (0–2 points; 1st figure in parentheses), blinding (0–2 points; 2nd figure in parentheses), and description of patients excluded from the study (0–1 point; 3rd figure in parentheses).

Abbreviations: DB – double-blind, LEF – leflunomide, MTX – methotrexate, RA – rheumatoid arthritis, others – see FIGURE 1

and ACR70 – 20% (vs. 4%). In the clinical trials included in the meta-analysis, leflunomide was statistically significantly more efficacious than placebo in all analyzed endpoints (TABLE 2).

Efficacy of leflunomide vs. methotrexate The compared trials were highly heterogeneous in quality. No significant differences were noted between lefflunomide and methotrexate in the reduction of most signs and symptoms of RA. The meta-analysis of trial results focused on such endpoints as the percentage of patients achieving ACR50 response after 1 year of treatment (FIGURE 3), percentage of patients achieving ACR70 response after 1 year of treatment, general doctor's assessment of RA activity after 12–16 weeks of treatment, reduction in CRP levels after 12–16 weeks of treatment, patient's pain assessment after 12–16 weeks of treatment, and improvement in the quality of life assessed by the modif HAQ questionnaire after 2 years of treatment indicated superiority of leflunomide over methotrexate (TABLE 3). No statistically significant differences in the efficacy of the compared drugs in the remaining endpoints were found.

Efficacy of leflunomide vs. sulfasalazine In a trial by Smolen et al.,[24] during a long follow-up, a significantly higher number of patients taking leflunomide achieved ACR20 response (82%) compared with patients taking sulfasalazine (60%; $P < 0.01$). Leflunomide also proved superior when more stringent criterion, i.e., ACR50, was applied (52% vs. 25%; $P = 0.04$). In the comparison of leflunomide and sulfasalazine, a transient superiority of sulfasalazine in ESR reduction was observed. The effect was not permanent and tended to disappear after 12 months of treatment. Simultaneously, a long-term superiority of leflunomide in the improvement of the quality of life assessed by the HAQ questionnaire (relative improvement from baseline: 45% vs. 29%; $P < 0.01$) was observed, which persisted after 2 years of treatment (59% vs. 39%; $P < 0.05$). Also, both the general patient's assessment of disease activity (reduction by 46% vs. reduction by 29%) and doctor's assessment (reduction by 50% vs. reduction by 32%) indicated that the therapeutic effect of leflunomide was maintained after 2 years of treatment, which was not observed for sulfasalazine. The efficacy of leflunomide vs. sulfasalazine is summarized in TABLE 4.

Study or subgroup	Leflunomide events	Leflunomide total	Placebo events	Placebo total	Weight	Risk ratio M-H, fixed, 95% CI
2.1.1 ACR20 – after 6 months of tratment						
Mladenovic et al.[23]	60	101	31	102	30.8%	1.95 [1.40–2.73]
Smolen et al.[24]	71	130	26	92	30.4%	1.93 [1.35–2.77]
subtotal (95% CI)		**231**		**194**	**61.3%**	**1.94 [1.52–2.49]**
total events	131		57			
heterogeneity: $\chi^2 = 0.00$, df = 1 ($P = 0.96$); $I^2 = 0\%$						
2.1.2 ACR20 – after 1 year of treatment						
Strand et al.[25]	95	182	33	128	38.7%	2.02 [1.46–2.80]
subtotal (95% CI)		**182**		**128**	**38.7%**	**2.02 [1.46–2.80]**
total events	95		33			
heterogeneity: not applicable						
test for overall effect: Z = 4.25 ($P < 0.0001$)						
total (95% CI)		**413**		**322**	**100%**	**1.98 [1.62–2.40]**
total events	226		90			
heterogeneity: $\chi^2 = 0.04$, df = 2 ($P = 0.98$); $I^2 = 0\%$						
test for overall effect: Z = 6.78 ($P < 0.00001$)						
test for subgroup differences: not applicable						

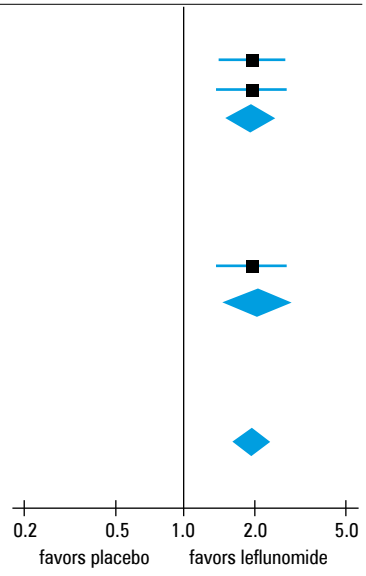

FIGURE 2 Meta-analysis of efficacy of leflunomide vs. placebo: ACR20 responders
Abbreviations: ACR – American College of Rheumatology, CI – confidence interval

Study or subgroup	Leflunomide events	Leflunomide total	Methotrexate events	Methotrexate total	Weight	Risk ratio M-H, fixed, 95% CI
1.1.1 ACR50 – after 4 months of treatment						
Kraan et al.[28]	3	7	2	8	100%	1.71 [0.39–7.48]
subtotal (95% CI)		**7**		**8**	**100%**	**1.71 [0.39–7.48]**
total events	3		2			
heterogeneity: not applicable						
test for overall effect: Z = 0.72 ($P = 0.47$)						
1.1.2 ACR50 – after 1 year of treatment						
Kraan et al.[28]	5	6	5	7	9.5	1.17 [0.65–2.10]
Strand et al.[25]	65	190	44	190	90.5%	1.48 [1.07–2.05]
subtotal (95% CI)		**196**		**197**	**100%**	**1.45 [1.07–1.96]**
total events	70		49			
heterogeneity: $\chi^2 = 0.53$, df = 1 ($P = 0.47$); $I^2 = 0\%$						
test for overall effect: Z = 2.40 ($P = 0.02$)						
1.1.3 ACR50 – after 2 years of treatment						
Strand et al.[28]	65	190	53	190	100%	1.23 [0.91–1.66]
subtotal (95% CI)		**190**		**190**		**1.23 [0.91–1.66]**
total events	65		53			
heterogeneity: not applicable						
test for overall effect: Z = 1.33 ($P = 0.19$)						

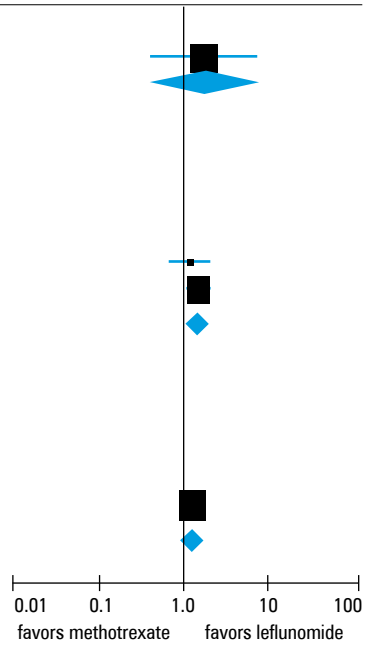

FIGURE 3 Meta-analysis of efficacy of leflunomide vs. methotrexate: ACR50 responders
Abbreviations: see FIGURE 1

Safety Meta-analysis of safety data showed that patients treated with leflunomide had higher risk of alopecia, elevation of liver enzymes, diarrhea, and allergic reactions, compared with placebo. Moreover, patients treated with leflunomide were more frequently withdrawn from the study due to adverse events compared with placebo (TABLE 5). Compared with methotrexate monotherapy, treatment with leflunomide resulted in a higher risk of pruritus, hypertension, diarrhea, and alopecia. However, the risk of mouth ulceration and elevated liver enzymes, exceeding 3 times the upper normal limit, was lower for leflunomide than for methotrexate. In 1 trial (n = 266) patients treated with leflunomide had a higher risk of back pain and diarrhea than those receiving sulfasalazine.

TABLE 2 Efficacy of leflunomide vs. placebo: summary of a meta-analysis

Endpoint	Number of trials	Number of patients	RR (95% CI)	Heterogeneity I^2
percentage of patients with ACR20 response				
– after 6 months	2[23,24]	425	1.94 (1.52–2.49)	0
– after 1 year	1[25]	310	2.02 (1.46–2.80)	–
– total	3	735	1.98 (1.62–2.40)	0
percentage of patients with ACR50 response				
– after 6 months	1[24]	222	2.34 (1.34–4.10)	–
– after 1 year	1[25]	310	4.36 (2.33–8.17)	–
– total	2	532	3.14 (1.70–5.81)	53.3
percentage of patients with Paulus 20 response	2[23,24]	425	2.47 (1.86–3.29)	0
Endpoint	**Number of trials**	**Number of patients**	**WMD (95% CI)**	**Heterogeneity I^2**
reduction in tender joint count				
– after 6 months	1[24]	221	–5.40 (–7.44 to – 3.36)	–
– after 1 year	1[25]	300	–4.70 (–6.59 to –2.81)	–
– total	2	521	–5.02 (–6.41 to –3.64)	0
reduction in swollen joint count				
– after 6 months	1[24]	221	–3.80 (–5.55 to –2.05)	–
– after 1 year	1[25]	300	–2.80 (–4.25 to –1.35)	–
– total	2	521	–3.21 (–4.32 to –2.09)	0
patient's assessment of RA activity	2[23,24]	424	–0.61 (–0.81 to –0.40)	0
doctor's assessment of RA activity	2[23,24]	424	–0.65 (–0.95 to –0.36)	57.3
reduction in ESR value				
– after 6 months	2[23,24]	424	–9.46 (–13.65 to –5.28)	0
– after 1 year	1[25]	300	–8.90 (–13.68 to –4.12)	–
– total	3	724	–9.22 (–12.37 to –6.07)	0
reduction in CRP levels				
– after 6 months	1[24]	221	–4.30 (–5.27 to –3.33)	–
– after 1 year	1[25]	300	–1.09 (–1.62 to –0.56)	–
– total	2	521	–2.67 (–5.81 to 0.48)	96.9
patient's assessment of pain				
– after 6 months	2[23,24]	424	–1.34 (–1.57 to –1.12)	40.3
– after 1 year	1[24]	300	–1.80 (–2.40 to –1.20)	–
– total	3	724	–1.40 (–1.61 to –1.19)	44.4
duration of morning stiffness	2[23,24]	421	–36.05 (–58.05 to –14.05)	0
quality of life (HAQ)	2[24,25]	521	–0.43 (–0.51 to –0.34)	0

Abbreviations: CRP – C-reactive protein, ESR – erythrocyte sedimentation rate, HAQ – health assessment questionnaire, RA – rheumatoid arthritis, RR – relative risk, WMD – weighted mean difference, others – see **FIGURE 1**

DISCUSSION Our study confirmed the findings of other meta-analyses in a set of high-quality and homogenous studies found in most up-to-date publication search. According to the data, leflunomide efficacy is not significantly different from that observed for other older and well-established DMARDs such as methotrexate or sulfasalazine.

The quality of any meta-analysis depends on methodological correctness of the included trials. Two trials included into our analysis[27,28] had low quality, obtaining 3 and 2 points in the Jadad scale, respectively. However, the effect of these trials on the final results was negligible due to low sample sizes (n = 39, n = 15, respectively). Patients from these studies constituted less than 2% of the whole patient population included into the meta-analysis. The remaining 5 trials were large (over 350 participants), had high quality (4 or 5 points in the Jadad scale), and had substantially long-term follow-up (3 trials of 2-year duration). The meta-analysis of leflunomide efficacy as compared with methotrexate revealed significant heterogeneity (I^2 >80%). This was mainly caused by the differences in the results of 2 phase III trials, Strand et al.[25] and Emery et al.,[26,40] which were essential for leflunomide registration. The main difference in the study protocols concerned the use of folic acid. In the US-based study, in which folic acid supplementation was used, the results were poorer than in the international study, in which it was not used.[41] The trials qualified for the review differed in the duration of follow-up: from 12 weeks to 2 years. More than once, it was impossible to present, within a meta-analysis, the trial results determined at different time points. However, the most important

TABLE 3 Efficacy of leflunomide vs. methotrexate: summary of a meta-analysis

Endpoint	Number of trials	Number of patients	RR (95% CI)	Heterogeneity I^2
percentage of patients with ACR20 response				
– after 12–16 weeks	3[26,28,29]	558	1.04 (0.91–1.18)	0
– after 1 year	3[25,26,28]	1377	0.98 (0.73–1.32)	82.6
– after 2 years	2[25,26]	799	1.01 (0.77–1.32)	85.5
percentage of patients with ACR50 response				
– after 12–16 weeks	1[28]	15	1.71 (0.39–7.48)	–
– after 1 year	2[25,28]	393	1.45 (1.07–1.96)	0
– after 2 years	1[25]	380	1.23 (0.91–1.66)	–
percentage of patients with ACR70 response				
– after 1 year	1[25]	380	2.00 (1.20–3.34)	–
– after 2 years	1[25]	380	1.39 (0.85–2.29)	–
Endpoint	**Number of trials**	**Number of patients**	**WMD (95% CI)**	**Heterogeneity I^2**
reduction of tender joint count				
– after 12–16 weeks	2[27,29]	543	–1.42 (–3.96 to 1.12)	36.2
– after 1 year	2[25,26]	1346	0.21 (–2.24 to 2.66)	87.2
– after 2 years	2[25,26]	770	–0.16 (–1.87 to 1.54)	48.5
reduction of swollen joint count				
– after 12–16 weeks	2[27,29]	543	–0.40 (–1.17 to 0.38)	0
– after 1 year	2[25,26]	1346	0.99 (–1.46 to 3.44)	90.1
– after 2 years	2[25,26]	770	0.48 (–1.17 to 2.12)	57.8
patient's assessment of RA activity				
– after 12–16 weeks	2[27,29]	543	–0.23 (–0.72 to 0.27)	49.7
– after 1 year	2[25,26]	1346	0.03 (–1.15 to 1.20)	92.7
– after 2 years	2[25,26]	770	–0.30 (–1.37 to 0.78)	85.3
doctor's assessment of RA activity				
– after 12–16 weeks	2[27,29]	543	–0.35 (–0.67 to –0.02)	10.3
– after 1 year	2[25,26]	1346	0.13 (–0.84 to 1.11)	90.0
– after 2 years	2[25,26]	770	–0.01 (–1.28 to 1.26)	90.6
reduction in ESR				
– after 12–16 weeks	2[27,29]	543	1.60 (–6.42 to 9.62)	46.7
– after 1 year	2[25,26]	910	7.05 (–6.28 to 20.37)	95.0
– after 2 years	2[25,26]	747	7.51 (–3.74 to 18.76)	86.6
reduction in CRP levels				
– after 12–16 weeks	2[27,29]	543	–0.44 (–0.78 to –0.09)	0
– after 1 year	2[25,26]	907	0.03 (–0.37 to 0.44)	57.8
– after 2 years	2[25,26]	744	0.16 (–0.51 to 0.84)	28.3
patient's assessment of pain				
– after 12–16 weeks	2[27,29]	543	–0.38 (–0.74 to –0.01)	0
– after 1 year	2[25,26]	932	0.16 (–1.10 to 1.43)	91.9
– after 2 years	2[25,26]	769	–0.18 (–1.52 to 1.16)	89.5
duration of morning stiffness				
– after 12–16 weeks	2[27,29]	543	–16.59 (–43.99 to 10.80)	0
– after 1 year	2[25,26]	759	0.75 (–15.30 to 16.79)	66.8
– after 2 years	2[25,26]	759	8.28 (–8.72 to 25.28)	63.0
quality of life (HAQ) questionnaire				
– after 1 year	1[26]	530	0.06 (–0.02 to 0.14)	–
– after 2 years	1[26]	530	0.05 (–0.04 to 0.14)	–
quality of life (modified HAQ)				
– after 1 year	1[25]	362	–0.10 (–0.20 to 0.00)	–
– after 2 years	1[25]	199	–0.15 (–0.29 to –0.01)	–
progression of radiographic changes				
– after 1 year	2[25,26]	893	–0.03 (–0.85 to 0.78)	40.7
– after 2 years	1[25]	137	0.40 (–0.94 to 1.74)	–

Abbreviations: see **FIGURE 1** and **TABLE 2**

TABLE 4 Efficacy of leflunomide vs. sulfasalazine: summary of the trial by Smolen et al.[24] and supporting publication – Scott et al.[35]

Endpoint	Number of patients	RR (95% CI)
percentage of patients with ACR20 response		
– after 0.5 year of treatment	262	0.99 (0.80–1.23)
– after 1 year of treatment	152	0.97 (0.78–1.20)
– after 2 years of treatment	117	1.37 (1.07–1.75)
percentage of patients with ACR50 response		
– after 0.5 year of treatment	262	0.98 (0.64–1.51)
– after 1 year of treatment	152	1.08 (0.74–1.59)
– after 2 years of treatment	117	2.10 (1.25–3.53)
percentage of patients with ACR70 response		
– after 0.5 year of treatment	262	1.52 (0.64–3.60)
– after 1 year of treatment	152	0.88 (0.44–1.75)
– after 2 years of treatment	117	1.43 (0.70–2.91)
Endpoint	**Number of patients**	**WMD (95% CI)**
reduction of tender joint count	262	–1.60 (–3.44 to 0.24)
reduction of swollen joint count	262	–13.40 (–14.89 to –11.91)
patient's assessment of RA activity	262	0.00 (–0.25 to 0.25)
doctor's assessment of RA activity	262	–0.10 (–0.32 to 0.12)
reduction in ESR		
– after 0.5 year of treatment	261	9.20 (3.47 to 14.93)
– after 1 year of treatment	150	8.10 (–0.13 to 16.33)
– after 2 years of treatment	114	–1.10 (–11.03 to 8.83)
reduction in CRP levels		
– after 0.5 year of treatment	260	–1.20 (–1.98 to –0.42)
– after 1 year of treatment	150	–1.10 (–2.17 to –0.03)
– after 2 years of treatment	111	–1.40 (–2.77 to –0.03)
patient's assessment of pain		
– after 0.5 year of treatment	262	–7.50 (–14.21 to –0.79)
– after 1 year of treatment	151	–11.40 (–20.35 to –2.45)
– after 2 years of treatment	117	–15.10 (–25.16 to –5.04)
duration of morning stiffness		
– after 0.5 year of treatment	262	–51.00 (–101.73 to –0.27)
– after 1 year of treatment	152	–76.00 (–135.49 to –16.51)
– after 2 years of treatment	165	–50.00 (–87.72 to –12.28)
quality of life (HAQ)		
– after 0.5 year of treatment	229	–0.21 (–0.34 to –0.08)
– after 1 year of treatment	128	–0.17 (–0.34 to 0.00)
– after 2 years of treatment	96	–0.29 (–0.49 to –0.09)
progression of radiographic changes		
– after 0.5 year of treatment	168	0.00 (–0.01 to 0.01)
– after 1 year of treatment	113	0.00 (–0.01 to 0.01)
– after 2 years of treatment	55	–0.04 (–0.19 to 0.11)

Abbreviations: see **TABLE 2**

and numerous phase III studies had the longest follow-up (2 years). Finally, it should be noted that the efficacy of leflunomide vs. sulfasalazine was confirmed only in 1 clinical trial.[24] The safety analysis was limited to RCTs and aimed at quantitative evaluation of the risk of leflunomide adverse events compared with placebo, methotrexate, and sulfasalazine. A comprehensive safety analysis should also include other clinical data and comparators, and as such is presented in a separate report.[42]

These disadvantages of the meta-analysis should be confronted with the advantages: relatively high number of trials (n = 7) and patients (n = 2861), methodological homogeneity of the trials (parallel groups instead of cross-over design), and the use of double-blind method.

The results of our study are consistent with those reported in other systematic reviews[5,6] and meta-analyses.[7-10] Contrary to the Cochrane review, we included only RCTs performed in a single- or double-blind manner and excluded open RCTs, nonrandomized clinical trials, and cohort studies.[8] We also concentrated on monotherapy and use of leflunomide in the recommended doses. The final set of studies is less numerous but homogeneous in terms of the study design and quality. Our study search is also more up-to-date than that performed in other recently published systematic reviews (June 2008,[8] January 2009[10]).

As our paper aimed to include only English, German, French or Polish full-length articles published in peer-reviewed journals, there is a potential for publication bias. The number of included studies was too low to perform formal publication bias assessment using the funnel plot or other widely accepted statistical methods. Nevertheless, we can expect that studies excluded from the analysis were small and of low quality. As low-quality studies comprised less than 2% of the whole patient population included into the meta-analysis, the potential effect of lacking studies should be very low.

The position of leflunomide in the current treatment of RA was defined in the 2008 guidelines by the ACR[3] and 2010 EULAR recommendations.[43,44] The ACR Task Force Panel recommended the initiation of methotrexate or leflunomide monotherapy for patients with all disease durations and for all degrees of disease activity, irrespective of poor prognosis. Leflunomide reduces the disease activity and inhibits progression of radiographic changes to the same extent as medium doses of methotrexate. It is also efficacious in combination with methotrexate in patients, in whom methotrexate alone in full dose did not result in complete remission.[3] According to the EULAR recommendations, when methotrexate contraindications or intolerance are present, the following DMARDs should be considered as part of first-line treatment: leflunomide, sulfasalazine, or parenteral gold.[43] The above drugs have the best evidence for efficacy of all synthetic DMARDs.

The above recommendations have recently been considered in the Polish drug reimbursement system. From 2011, leflunomide is available for patients with RA and methotrexate intolerance or contraindications.

Conclusions Leflunomide, compared with placebo, proved highly efficient in relieving the signs and symptoms of RA. There were no significant

TABLE 5 Summary of safety meta-analysis (only statistically significant comparisons showed)

Adverse event	Number of trials	Number of patients	RR (95% CI)	Heterogeneity I^2
leflunomide vs. placebo				
alopecia	3[23-25]	832	5.79 (2.09–16.08)	0
elevation of liver enzymes	2[23-25]	607	3.36 (1.71–6.63)	0
withdrawal due to adverse events	3[23-25]	832	2.69 (1.64–4.41)	0
diarrhea	2[24,25]	525	2,21 (1.48–3.32)	0
allergic reactions	1[25]	300	1.68 (1.01–2.79)	–
leflunomide vs. methotrexate				
pruritus	2[26,29]	1503	3.40 (1.72–6.74)	0
hypertension	2[25,26]	1363	2.75 (1.76–4.29)	0
diarrhea	3[25,26,29]	1867	2.01 (1.60–2.54)	0
alopecia	3[25,26,29]	1867	1.62 (1.21–2.17)	0
mouth ulceration	2[25,26]	1363	0.61 (0.38–0.96)	0
elevation of liver enzymes >3 × ULN	1[26]	999	0.26 (0.18–0.37)	–
leflunomide vs. sulfasalazine				
back pain	1[24]	266	3.67 (1.05–12.85)	–
diarrhea	1[24]	266	1.92 (1.00–3.69)	–

Abbreviations: UNL – upper normal limit, others – see **TABLE 1**

differences between treatment with leflunomide and with methotrexate or sulfasalazine. Leflunomide, methotrexate, and sulfasalazine are pharmaceutical agents with a complex safety profile. Close monitoring of adverse reactions during each individual treatment is recommended.

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ARTYKUŁ ORYGINALNY

Leflunomid w monoterapii reumatoidalnego zapalenia stawów: metaanaliza badań z randomizacją

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SŁOWA KLUCZOWE

leflunomid, metotreksat, placebo, reumatoidalne zapalenie stawów, sulfasalazyna

STRESZCZENIE

WPROWADZENIE Reumatoidalne zapalenie stawów (RZS) jest przewlekłą chorobą systemową tkanki łącznej prowadzącą do postępującej destrukcji stawów, niepełnosprawności, wycofywania się z aktywności zawodowej oraz przedwczesnej śmierci.

CELE Celem pracy była ocena skuteczności i bezpieczeństwa leflunomidu w porównaniu z placebo, metotreksatem i sulfasalazyną w monoterapii RZS.

PACJENCI I METODY Przeprowadzono przegląd systematyczny baz danych (MEDLINE, EMBASE, Cochrane CENTRAL). Do analizy kwalifikowano badania z randomizacją ze ślepą próbą. Jakość zakwalifikowanych badań oceniono w skali Jadad. Przeprowadzono syntezę ilościową wyników badań (metaanalizę).

WYNIKI Do analizy włączono 7 badań klinicznych, w których wzięło udział 2861 chorych (1432 otrzymujących leflunomid, 312 – placebo, 922 – metotreksat, 133 – sulfasalazynę). Leflunomid w porównaniu z placebo dwukrotnie zwiększał prawdopodobieństwo osiągnięcia odpowiedzi według kryterium 20%-towej poprawy zdefiniowanego przez American College of Rheumatology (ACR20) (ryzyko względne [*relative risk* – RR] 2,02; 95% CI: 1,46–2,80) i czterokrotnie szansę osiągnięcia odpowiedzi ACR50 (RR 4,36; 95% CI: 2,33–8,17), po rocznym okresie leczenia. Skuteczność leflunomidu i metotreksatu nie różniły się znacząco w odniesieniu do większości punktów końcowych. Leflunomid wykazał częściową przewagę nad metotreksatem pod względem: odsetka pacjentów osiągających odpowiedź ACR50 i ACR70, oceny aktywności choroby według lekarza, zmniejszenia stężenia białka C-reaktywnego (*C-reactive protein* – CRP) i poprawy jakości życia (ocenianej za pomocą zmodyfikowanego kwestionariusza oceny stanu zdrowia [*health assessment questionnaire* – HAQ]). Wykazano przewagę sulfasazyny pod względem redukcji poziomu OB, a leflunomidu – pod względem odpowiedzi klinicznej ACR20 i ACR50, poprawy jakości życia (według kwestionariusza HAQ), oceny aktywności choroby według lekarza i pacjenta oraz zmniejszenia stężenia CRP.

WNIOSKI Nie stwierdzono istotnych różnic w skuteczności terapii pomiędzy leflunomidem a metotreksatem lub sulfasalazyną, udowodniono natomiast większą skuteczność monoterapii leflunomidem w porównaniu z placebo w zmniejszaniu objawów przedmiotowych i podmiotowych RZS.

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Praca wpłynęła: 15.10.2011.
Przyjęta do druku: 10.01.2012.
Publikacja *online*: 11.01.2012.
Zgłoszono sprzeczność interesów: D. Golicki i M. Niewada otrzymywali wynagrodzenie od firmy Sanofi-Aventis Sp. z o.o. J. Lis i K. Pol są zatrudnione przez firmę Sanofi-Aventis Sp. z o.o.
Pol Arch Med Wewn. 2012; 122 (1-2): 22-32