Original Article

Efficacy of Leflunomide 100 mg Weekly Compared to Low Dose Methotrexate in Patients With Active Rheumatoid Arthritis. Double Blind, Randomized Clinical Trial

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ABSTRACT

Objective: To determine the clinical efficacy and safety of Leflunomide (LFN) 100 mg/week compared to low dose Methotrexate (MTX) 10 mg/week in a double-blind, randomized, controlled trial with 52 weeks of follow up in Rheumatoid Arthritis (RA) patients.

Patients and methods: Patients who met ARC1987 criteria for RA were included. All patients had medical records, including laboratory tests and hand X-rays. Clinical evaluations for improvement and ACR and EULAR response criteria were performed. Statistical analysis for independent’s samples between both groups defined a P value of ≤.05. Safety was evaluated by comparing the proportion of adverse events (AE) registered.

Results: Of the 90 patients screened, five were withdrawn and the remaining 85 patients were randomized: 43 LFN and 42 MTX. Sixty-three patients completed the study, 72% in the LFN group and 74.4% in the MTX group. ACR20 improvement criteria were achieved by LFN group in 90.3%, and in MTX 78.1% (P=0.14) at week 52. EULAR improvement criteria applied at the end point showed a DAS28 score for the LFN group of 3.45, and for the MTX group was 3.67 (P=0.43). Total withdrawals including loss during follow up, AE and lack of efficacy for each group was 12 patients in the LFN group, and 10 patients in the MTX group. Regarding safety, no serious AE of a life threatening nature were reported.

Conclusions: These outcomes confirm that LFN 100 mg/week offers an adequate and sustained improvement effect on the clinical manifestations of RA, similar to low dose treatment with MTX 10 mg/every week after 52 weeks of follow up; it may be a good therapeutic option alone or in combination with other anti-rheumatic drugs.

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Leflunomide (LFN) es un no-biológico enfermedad-modificando antirreumático (DMARD), un inhibidor de la síntesis de purina, que es indicado para el tratamiento de artritis reumatoide (RA). Se han realizado varios estudios clínicos que han demostrado su beneficio y seguridad, considerado equivalente al tratamiento con sulfasalazina (SFA) o metotrexato (MTX).1-3

Una problemática común en el tratamiento de RA es la adherencia (respectando la dosis de prescripción) y el mantenimiento (mantener el tratamiento durante un largo período de tiempo) del DMARD, una dificultad que se debe a múltiples factores, como polifarmacia, eventos adversos de medicamentos y el costo de tratamiento, especialmente en aquellos pacientes que no tienen una seguridad social, todo lo cual dificulta obtener un buen resultado a largo plazo.

Buscando alternativas de tratamiento que favorezcan la adherencia y el cumplimiento del tratamiento, desarrollamos un estudio descriptivo abierto con criterios y recogida de datos de pacientes tratados con LFN, con una dosis semanal de 100 mg. Se excluyeron a aquellos pacientes con DMARD durante un mes antes de la inclusión, y más de 3 meses antes de la inclusión de LFN o MTX. Se excluyeron a los pacientes que tenían al menos 6 o más articulaciones dolorosas (SJ) y dolorosas (PJ) articulaciones, ADAS 28 al final del estudio fue de 3,45, y para MTX de 3,67, no existiendo diferencias significativas (p = 0,43). Los pacientes excluidos para LFN fueron 11, y 10 para MTX. La falla terapéutica se definió en 5,2% para LFN, y 12,1 en el caso de MTX. No se reportaron eventos adversos graves que pusieran en riesgo la vida de los pacientes.

Conclusión: Los resultados confirman que LFN usada en dosis semanales de 100 mg, ofrece una adecuada y sostenida mejoría de las manifestaciones clínicas de RA, al compararlo con una dosis baja de MTX. Pudiendo ser una opción terapéutica en algunos pacientes como monoterapia o en combinación con otros antirreumáticos.

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Development study

 Patients evaluated: 90
 Excluded: 5
 Randomized:

 LFN
 100 mg/w
 43
 Total exclusions: 12
 Loss to follow up: 4
 Adverse events: 6
 Treatment failure: 2
 Final: 31

 MTX
 10 mg/w
 42
 Total exclusions: 10
 Loss to follow up: 4
 Adverse events: 2
 Treatment failure: 4
 Final: 32

Fig. 1. This Flowchart shows the progression of the patients evaluated and included in the study. Patients were excluded if they did not meet inclusion criteria, two were lost to follow-up, and one withdrew informed consent before randomization. Twelve patients withdrew from the LFN group and 10 from the MTX. The reason for exclusion is explained in detail in the text. End of the study was achieved in 74% for both groups, 31 patients in the LFN and 32 in the MTX.

Assigning Treatment Groups

Patients were randomized into 2 blocks using a table of random numbers, without the intervention of the research group (1:1): the target for the LFN group and a control group of MTX. For the target LFN group, a loading dose of 100 mg/day for 3 consecutive days was given, based on the average half-life of the drug, and administered at a weekly dose of 100 mg. For the MTX group, a fixed low dose of 10 mg weekly was administered; for both groups, placebos were administered in numerical form in an equivalent manner to achieve the blinding of patients and medical researchers.

Statistical Analysis

The primary objective of the study was to compare the efficacy and safety of a weekly dose of 100 mg LFN compared to the effect achieved with low dose of MTX 10 mg weekly. The efficacy was measured by ACR 20 improvement criteria as a study endpoint at 52 weeks of treatment. Variables also included were ACR 50 and 70 improvement, EULAR improvement criteria, and an independent evaluation of the ESR and HAQ-Di variables.

Results

Of the 90 patients evaluated for study entry, 5 were excluded, and the 85 remaining were randomized into 2 groups as follows: a group of 43 patients were assigned to LFN and 42 to MTX (Fig. 1). Both groups of patients were assessed at least once during follow up from the baseline visit. The demographics and disease characteristics were similar for both groups (Table 1). Three patients were treated with DMARDs prior to enrollment, 2 for the LFN group. One of them who received LFN 20 mg/day and hydroxychloroquine for 2 months discontinued treatment for 7 months before being randomized to the LFN group. A second patient, with an irregular treatment, took MTX for a month, 3 months after being randomized to the LFN group. Finally, in a patient receiving conventional LFN, diffuse alopecia developed after 2½ months and treatment was suspended; the patient was sent to our hospital and included in pre-randomization, after no treatment was given for 3 months, to the MTX group. Sixty-three patients completed 52 weeks of treatment, 31 in the LFN (72%) and 32 in the MTX group (74.4%). Early discontinuation of patients at week 16 occurred more often in the LFN than in the MTX group (19.4 vs 5%), respectively. At the end of the study, the total of patients who left were 21, either by loss to follow up or adverse events. Twelve cases occurred (27.9%) in the LFN and 10 patients (23.8%) in the
Table 1
Disease Characteristics and Demographic Data.

<table>
<thead>
<tr>
<th></th>
<th>Leflunomide Group±SD</th>
<th>Methotrexate Group±SD</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (No.)</td>
<td>43</td>
<td>42</td>
<td>–</td>
</tr>
<tr>
<td>Age, years</td>
<td>42.8 (±11.7)</td>
<td>42.1 (±10.8)</td>
<td>.76</td>
</tr>
<tr>
<td>Female, %</td>
<td>88.3</td>
<td>85.7</td>
<td>.56</td>
</tr>
<tr>
<td>Duration of the disease, months</td>
<td>25.2 (±6.8)</td>
<td>20.9 (±3.5)</td>
<td>.57</td>
</tr>
<tr>
<td>Tender joint count, 0–28</td>
<td>11.1 (±5.1)</td>
<td>11.5 (±6.1)</td>
<td>.74</td>
</tr>
<tr>
<td>Swollen joint count, 0–28</td>
<td>8.9 (±4.8)</td>
<td>7.5 (±4.9)</td>
<td>.17</td>
</tr>
<tr>
<td>Global disease score by the patient (activity), 0–100 mm, VAS*</td>
<td>43.1 (±15.1)</td>
<td>44.5 (±15.1)</td>
<td>.67</td>
</tr>
<tr>
<td>Global disease score by the physician (activity), 0–100 mm, VAS*</td>
<td>52.2 (±12.3)</td>
<td>52.1 (±15.2)</td>
<td>.95</td>
</tr>
<tr>
<td>Pain score, 0–100 mm, WAS &amp;</td>
<td>70.7 (±26.2)</td>
<td>70.6 (±20.5)</td>
<td>.98</td>
</tr>
<tr>
<td>HAQ-Di</td>
<td>0.96 (±0.09)</td>
<td>0.83 (±0.07)</td>
<td>.27</td>
</tr>
<tr>
<td>DAS 28</td>
<td>5.8 (±0.96)</td>
<td>5.6 (±0.88)</td>
<td>.24</td>
</tr>
<tr>
<td>Rheumatoid factor presence, %</td>
<td>41 (±95.3)</td>
<td>39 (±90.7)</td>
<td>.53</td>
</tr>
<tr>
<td>Erythrosedimentation rate, mm/h</td>
<td>35.4 (±13.5)</td>
<td>30.2 (±15.0)</td>
<td>.10</td>
</tr>
<tr>
<td>Prior DMARD treatment</td>
<td>2 (4.6%)</td>
<td>1 (2.3%)</td>
<td>.27</td>
</tr>
</tbody>
</table>

SD: standard deviation; VAS: visual analog scale; DMARD: disease modifying antirheumatic drugs.

* P: no statistically significant differences were seen between groups; P≤.05.

MTX group. Discontinuation due to lack of efficacy was found in 2 patients in the LFN group (5.2%) and in 4 cases with MTX (12.1%) (Fig. 1).

The ACR improvement criteria were assessed at weeks 8, 24, and 52. In patients assigned to LFN, 28 (80%) achieved ACR 20 at week 24 and in 29 cases (93.5%) at week 52. For the MTX group the results showed that 30 patients (83%) achieved ACR 20 at week 24 and 25 (78.1%) at week 52; comparing the two groups, there was no statistically significant difference (Fig. 2). Evaluating the results of the study end point for ACR 50 and ACR 70 we found no significant differences by comparing the groups for these variables (Fig. 3).

The independent variables were evaluated and the results of the HAQ-Di at baseline scored 0.96 for the LFN group and 0.83 for MTX (P=.27). The final evaluation of study data showed a score of 0.23 for LFN and 0.39 for MTX, with a reduction of 0.7 and 0.43, respectively for each study group, with a marginal difference when evaluating this data (P=.05) in the LFN group.

EULAR criteria for improvement and remission were evaluated at week 52 of the study. Initial DAS 28 results of the LFN group were 5.83 and 3.45 at 52 weeks (2.38 reduction points). For the MTX group a baseline score of 5.60 was seen, 3.67 at study end, with a net reduction of 1.93 points. There were also no statistically significant differences when comparing results between the two groups (P=.43). The standard cutoffs to define improvement in EULAR DAS 28 were as follows: <3.2 points=good response, from 3.2 to 5.1 moderate response >5.1 points no response (Fig. 4). Applying the EULAR remission criteria (<2.6 points), 7 patients of the LFN group and 6 of the MTX group achieved remission.
Table 2
Infectious Diseases Registered.

<table>
<thead>
<tr>
<th></th>
<th>LFN=43</th>
<th>MTX=42</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infections</td>
<td>6 13.9</td>
<td>12 28.5</td>
</tr>
<tr>
<td>Urinary infection</td>
<td>3 6.9</td>
<td>3 7.1</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>1 2.3</td>
<td>1 2.4</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>0 0</td>
<td>1 2.4</td>
</tr>
<tr>
<td>Vulvovaginitis</td>
<td>1 2.3</td>
<td>3 7.1</td>
</tr>
</tbody>
</table>

A greater number of upper respiratory tract infections were seen in the MTX than in the LFN group.

Safety

Serious adverse events were considered by investigators in 9 cases, 2 dermatological reactions occurred in patients in the LFN group, one of them developing severe rash, another erythema multiforme on the trunk. Six patients had elevated liver enzymes 2.5 times above the normal range, four of them received LFN and 2 belonged to the MTX group and they were all withdrawn from the study (Fig. 1).

Less important events recorded for both groups included vasculitis, pruritus, alopecia, and headache. Presence of infections was observed in both groups, with a slightly higher percentage in patients with MTX treatment (Table 2). Gastrointestinal adverse events (GI) are described in Table 3, where episodes of diarrhea were more often present in the LFN group. The data recorded regarding alterations in liver function tests were as follows: 7 and 17 cases had elevated liver enzymes in the LFN and MTX groups. Four (9.3%) in the LFN group remained >2.5 times the normal range, so patients were withdrawn from the study. In 3 other patients, despite the high values referred to above, these returned to normal levels during the study. For the MTX group, 2 patients had elevations for which they were eliminated, another 7 returned to normal baseline levels without recurrence at study end; there were no statistically significant differences when comparing both groups (P=.02) (Fig. 5). Three cases of hypertension were detected, 2 in the LFN and one in the MTX group for both groups and classified as a minor event. Finally hematologic abnormalities documented in the LFN group consisted of leukopenia in 4 patients, 2 with anemia and one with thrombocytopenia; in the case of MTX there were 2 cases of leukopenia, 2 with anemia and one with mild thrombocytopenia.

There were no adverse events that would jeopardize the lives of patients in any of the 2 groups.

Table 3
Non-liver Gastrointestinal Effects.

<table>
<thead>
<tr>
<th></th>
<th>LFN=43</th>
<th>MTX=42</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
</tr>
<tr>
<td>Gastritis</td>
<td>12 27.9</td>
<td>11 26.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 20.9</td>
<td>1 2.3</td>
</tr>
<tr>
<td>Abdominal Distension</td>
<td>2 4.6</td>
<td>6 14.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 6.9</td>
<td>6 14.2</td>
</tr>
<tr>
<td>Other</td>
<td>2 4.6</td>
<td>1 2.3</td>
</tr>
</tbody>
</table>

Gastrointestinal events such as gastritis and diarrhea were more frequently reported in the LFN than in the MTX group, as seen in the literature; however, abdominal distension was more common in the MTX group.

Discussion

In daily practice, rheumatologists have a need for RA treatment regimens that are effective and safe, in addition to being flexible in their administration, in order to maintain adherence and compliance to treatment and thus achieve the goals and objectives of clinical improvement or remission of disease.9

LFN is a non-biological DMARDs belonging to the isoxazole class; after administration it is rapidly converted to its active metabolite A77 1726; this metabolite induces its therapeutic effect by inhibiting the enzyme dihydrorotate dehydrogenase. This is an important key enzyme in pyrimidine de novo production in T lymphocytes. This molecule has a long plasma life of about 2 weeks (14–18 days).10

Published studies indicate that the ACR 20 improvement criteria in patients with RA treated with MTX monotherapy ranges from 40% to 60% at 6 and 12 months of follow up.11 On the other hand, it is well known that treatment of RA patients at doses of 20 LFN mg/day has shown benefit in clinical response similar to MTX and other DMARDs as SSZ.11-13 Jakez-Ocampo et al. published a pilot study using LFN as an open treatment at 100 mg weekly in patients with refractory RA.14 This study included 16 patients, 8 of them in treatment with LFN 100 mg/week and another 8 with the regular dose of 20 mg daily followed by a period of one year. The base treatment of patients was not changed, including at least the combination of 2 or 3 DMARDs in association with different doses of steroids. The results showed benefits in the initial treatment group of LFN 20 mg/day; however, at the end of the study, no statistically significant differences between the 2 groups, including the development of ACR 20 improvement, was seen. Minor events were reported more frequently in the LFN 20 mg/day group. A second study was conducted by the same authors15 this time in 3 groups with a diagnosis of early RA (less than one year since onset). Thirty patients were divided into 3 groups: the first group of 10 patients treated with LFN 100 mg/week, the second group of 10 patients treated with LFN 20 mg/day and a third group treated with MTX at a dose of 7.5–15 mg/week, with a one year of follow up. By the eighth week of the study, response was observed in all 3 groups, noting again the fastest response in the LFN 20 mg/day group compared to LFN 100/week and MTX/week with a P=.001 and P=.03, respectively. The variables assessed at the end of the study showed no significant differences in any of the 3 groups. In relation, the presence of adverse events was more frequent in the LFN 20 mg/day and MTX/week groups compared to LFN 100 mg/week.
In addition, our group previously performed an open 6 month clinical trial at LFN weekly dose of 100 mg in patients with active RA. Fifty patients were enrolled in the study, starting treatment with a loading dose of 100 mg/day for 3 days followed by a weekly dose of 100 LFN mg for a period of 6 months. After 12 weeks, 75% of patients had achieved ACR 20 improvement response and 58% achieved an ACR 50. At study end, 74% achieved ACR 20, 64% of patients achieved ACR 50 and ACR 70 28% improvements.

Adverse events reported in the study ranged from 2% to 16%, which included headache, rash, hair loss, elevated liver enzymes and diarrhea. It was concluded that clinical benefit in response to a weekly regimen of 100 mg of LFN is associated with minor adverse events already reported previously.

The results obtained in this study show that both drugs, at doses lower than those recommended, help compliance and adherence to treatment in a very acceptable percentage, emphasizing that the low dose of MTX of 10 mg/week is only presently recommended at baseline, increasing it if tolerated quickly and in a stepwise fashion. We observed that at week 52, retention of patients was 31 patients (72%) and 32 cases (76%) for the LFN and MTX groups, respectively, with an overall retention of 74%, a situation that differs from reports by other authors, which present more than a 50% loss in studies to LFN at a standard dose; a similar number is reported in patients with long-term treatment with MTX.

The results of ACR improvement, HAQ-DI and ESR did not differ between groups, stressing that the dose of MTX used is currently considered suboptimal and not comparable for assessment of the efficacy of MTX in this study, as the current recommendations of EULAR point out, where a rapid increase up to 20 or 25 mg/week is indicated in order to reduce clinical activity. Of patients who completed the study in the LFN group, 28 achieved an ACR 20 response (90.3%) at week 52 (Fig. 2); however, applying the calculation of patients intended to treat (ITT), the ACR 20 response was 67.4%. Two patients were eliminated from the LFN group for not achieving ACR 20 improvement, compared to MTX where 4 cases did not achieve it.

Regarding adverse events, those seen in the LFN group were similar to those reported in the literature, affecting the skin with erythematous urticaria, alopecia and diarrhea. Liver toxicity was less frequent, randomized, controlled trial of treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. Arthritis Rheum. 2001;44:1984–92.


