Therapeutic efficacy and safety of methotrexate + leflunomide in Colombian patients with active rheumatoid arthritis refractory to conventional treatment

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ABSTRACT

Introduction: The combination of methotrexate (MTX) + leflunomide (LFN) has been shown to be effective in the treatment of RA. Its safety has been questioned. **Objective:** To evaluate the effectiveness and safety of the combination of MTX + LFN in patients with active RA. **Methods:** This was a 24-week multicenter study, which included 88 patients with active disease despite consistent treatment with methotrexate and prednisolone. **Results:** We included 78 women (88%) and 10 men. The age was 51.3 ± 12.4 years, and the evolution of disease was 8 ± 6.8 years. Patients had active disease, which was indicated by a median of IQR of 10.0 (7.0-13.0) for swollen and of 14.0 (18.0–10.0) for tender joints for the whole group. The ACR responses achieved at week 24 were: ACR20: 76.0%; ACR50: 67.1%; ACR70: 23.9%. There was improvement in the activity of disease: DAS-28 score: 5.8 ± 1.2 at baseline vs. 3.8 ± 1.6 at week 24 (P = 0.000). The most significant adverse event was elevation of transaminases in eight patients (26%). Eight patients were withdrawn due to adverse events: four due to the elevation of transaminases, and one each due to diabetes insipidus, rash, diabetes mellitus and osteomuscular pain. **Conclusion:** The combination of MTX + LFN is effective for treating RA in patients for whom conventional treatment has failed. Strict medical and laboratory control is to be enforced for safety.

Keywords: rheumatoid arthritis, methotrexate, drug toxicity.

INTRODUCTION

Rheumatoid arthritis (RA) is a symmetric, polyarticular, chronic inflammatory disease. Progression over time leads to the destruction of joints, deformity, different levels of functional incapacity, and deterioration in the quality of life.[1] Its prevalence varies with the population studied.[2] In Colombia, there is no real estimate of the prevalence of RA, except among the Afro-American population in the Pacific region, with a measured prevalence of 0.01%,[3] Although data on the prevalence of RA are scarce in Latin America, there is information in several countries in the region. Spindler et al.[4] found a 0.2% rate in Tucuman, Argentina. In Brazil, Senna et al.[5] estimated the prevalence at 0.5%. Cardiel[6] reported a prevalence of 0.3% in Mexico City. Based on these data, the overall prevalence in the region has been estimated conservatively at 0.4%.[7]

It has been shown that proper control of inflammation reduces the damage shown on X-rays and prevents the destruction of joints. Treatment with disease-modifying anti-rheumatic drugs (DMARDs), analgesics, and anti-inflammatory drugs has been shown to be effective for controlling symptoms and reducing the progression of joint damage. Results published in recent years have shown that the combination of methotrexate (MTX) with other DMARDs is more effective than MTX monotherapy.[8]

Leflunomide (LFN) is a DMARD that has been approved for the treatment of RA since 1996. Like MTX, it has

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antimetabolite effects, inhibiting the synthesis of pyrimidines,[9] and has been shown to be effective for treating RA in various studies.[10,11] It has been suggested that the combination of MTX + LFN is effective for controlling the disease; however, this combination has not been included in any treatment protocols, due to the possibility of an increased frequency of hematological and hepatic adverse events.[12]

The efficacy of this combination for controlling RA has been previously demonstrated in various studies of patients with inadequate MTX response. The adverse effects reported in these studies have not been consistent, although the majority of the side effects seem to be minor and disappear with the reduction of the dose or withdrawal of the medication.[13–15]

The Brazilian consensus on RA treatment greatly emphasizes the need to try a second DMARD before starting a biologic agent.[16] Although the cost is a very relevant issue in decision-making on the treatment of RA, this is not the main reason to use MTX + LFN. The use of these DMARDs, isolated or in combination, is probably safer regarding long term use, when compared to biologics, though there are no strict data to support this assumption.

The results of the present study could help to establish the true potential of this combination among the current possible RA treatments in Colombia and elsewhere in Latin America.

MATERIALS AND METHODS

Design of the study

This was an open, non-controlled, multicenter, 24-week study. It was conducted between January and December 2009 at 10 Colombian centers that provide rheumatological treatment. The principal objective was to evaluate the efficacy and safety of adding LFN to the treatment regimens of RA patients who continued to have inflammatory activity despite combined therapy with MTX, glucocorticoids, and non-steroidal anti-inflammatory drugs (NSAIDs).

Population

We included 88 patients older than 18 years of age who had established ACR-criteria RA diagnoses[17] made at least 12 months prior to the start of the study and fewer than 15 years of disease evolution and whose disease remained active despite receiving regular treatment in the last three months. We considered regular treatment a combination of low-dose glucocorticoids (≤ 10 mg/day of prednisone), MTX at a dose of ≥ 12.5 mg/week, and oral NSAIDs and/or acetaminophen at 2 g/day. We included patients who, in addition to these treatments, had also used stable doses of 250 mg/day chloroquine over the last three months.

We defined disease activity by the American College of Rheumatology recommendations.[18] We included only those patients with the ability to understand and fill out various forms related to quality of life (Short Form 12, SF-12), functional capacity (Health Assessment Questionnaire, HAQ-DI), disease activity (Visual Analog Scale, EVA 0–10 cm), therapeutic efficacy, and safety related to treatment.

We excluded patients with important comorbidities, including active peptic ulcer disease, consumption of alcohol in amounts greater than 30 cc/week, viral hepatitis, obstructive liver disease, immunodeficiency, treatment with rifampicin, chronic kidney disease, and congestive heart failure. We also excluded patients with transaminase levels greater than 1.5 times the control, serum creatinine levels > 1.5 mg/dL, a calculated creatinine excretion < 55% and a WBC count < 3500/mm^3. We excluded pregnant or nursing women.

We added LFN to the previously described protocols of all the patients. The initial dose was 100 mg for three days, after which it was maintained at 20 mg/day. We recorded the laboratory information at each visit as part of the evaluation of adverse effects. In the present study we used LFN produced by PROCAPS Laboratories in the form of soft gelatin capsules, which are approved for use in Colombia by the Instituto Nacional de Vigilância de Medicamentos y Alimentos (INVIMA) with sanitary record number 2006M-005987.

Evaluation of clinical efficacy

The principal outcome evaluated comprised the ACR20 results. We also considered the ACR50 and ACR70 results.

Evaluation of safety

Safety was measured by the number of adverse events reported at each visit, the physical evaluation, and the laboratory data, which included blood count, erythrocyte sedimentation rate (ESR), transaminases, nitrogen urea (BUN), creatinine, and urinalysis.

A greater than 3-fold elevation in the transaminase levels led to removal from the study. A persistent elevation of ≥ 2 but ≤ 3 times the normal value required a reduction of the MTX dose to 7.5 mg weekly or a reduction of the LFN dose to 10 mg/day. The regimens were modified sequentially at the discretion of the investigator, who indicated which drug to reduce first. If the elevation persisted at this level (≥ 2 but ≤ 3 times the normal value) despite the dose modification for the two medications, then the patient was withdrawn from the study at the discretion of the investigator.

Statistical analysis

We used measures of dispersion and central trend for the quantitative variables and frequencies and percentages for the qualitative variables. For comparisons of the quantitative variables with parametric distribution, we used the Student's *t*-test for related samples and the Wilcoxon signed-rank test for variables with nonparametric distribution. For the qualitative variables, we used a χ^2 test with the Fisher's correction when appropriate. We used a significance level of $P \leq 0.05$ and 95% confidence intervals.

Ethical aspects

The study followed the norms established by the Helsinki Declaration, The Guidelines for Good Clinical Practice, and Resolution 8430 (1993) of the Colombian Ministry for Social Protection. It was approved by the Central Committee on Ethics in Clinical Investigations of the Department of Medicine at the Universidad de La Sabana. All of the patients signed an informed consent form, and confidentiality was strictly maintained.

Operative aspects

The Clinical Investigation Unit of the Universidad de La Sabana is a site for clinical and pharmacological investigations that has been authorized by the INVIMA to develop this type of investigation, as were all the participating sites. It complies with the procedures and regulations established in 2008 by Resolution 2378 of the Colombian Ministry for Social Protection. The study was approved and overseen by the subdivision of Biological Medications of INVIMA, and it complied with all of the Colombian legal requirements applicable to this type of trial.

RESULTS

Demographic characteristics

We included a total of 88 patients: 78 women (88.6%) and 10 men (11.3%). The general characteristics of the population and the disease histories are summarized in (Table 1).

In relation to the background of patients: 24 (37.5%) had family history of RA, 18 (22%) arterial hypertension, nine (11.2%) peptic ulcer disease, 11 (13.7%) alcohol, and six (7.5%) smoking. The drugs received by the beginning of the study were as follow: methotrexate, 88 (100%), 15.6 ± 3.4 mg/week; prednisolone, 49 (55%), 7.8 ± 4.3 mg/day; and chloroquine, 29 (32%), 225.9 ± 52.9 mg/day.

Change in activity for the disease

Beginning at week 6 and continuing until week 24, there were significant (P = 0.000) differences from baseline in the number of painful joints, number of inflamed joints, duration of morning stiffness in minutes, global evaluation of activity of the disease both by the patient and the physician, and fatigue. Three patients remained on a high count of swollen and painful joints throughout follow-up, but continued in the study by researcher decision, because of the improvement in other parameters, including physical functioning and quality of life (Table 2).

Change in functional capacity and quality of life

The physical functioning of the patients as measured by the HAQ-DI showed significant and sustained improvement from week 6 when compared with the baseline measurement; and this improvement was maintained until the end of the study (baseline: 0.91 ± 0.53; week 6: 0.43 ± 0.42; week 12: 0.39 ± 0.44; week 18: 0.35 ± 0.27; and week 24: 0.32 ± 0.41). On the individual level, eight (11.3%) patients did not improve, 26 (36.6%) improved by less than 0.5 point, and 37 (52%) improved by more than 0.5 point. Seventeen (24%) patients achieved an HAQ-DI score of 0 by the end of the study.

The quality of life, as measured by the SF-12, showed a significant improvement in all domains, beginning at week 6 and continuing until the final evaluation (Table 3).

ACR response

After week 6 of the combined MTX and LFN treatment, 50.7% reached ACR20, 22.5% reached ACR50, and 5.6% reached

Table 1
General information

Variable	n (%)
Population	88
Gender M/F	10/78 (11–89)
Age, mean ± SD (years)	51.3 ± 12.4
Age at onset, mean ± SD (years)	43 ± 12.4
Time of evolution mean ± SD (years)	8 ± 6.8
Delay of dx, mean ± SD (months)	21 ± 32
Visits to the rheumatologist in the last year	3 (0–12)
Educational level	
High School	60 (69%)
Professional	27 (31%)
Extra-articular manifestations	
Sicca	12 (14%)
Nodules	21 (24%)
Disease markers	
Positive anti-CCP test	67 (77%)
Positive test for RA	63 (72.5%)

Table 2
Improvement in the activity of the disease

Activity	Baseline	Week 6	Week 12	Week 18	Week 24
Painful joints, median (IQR)	14.0 (18–10)	7.0 (2–10)	4.0 (2–6)	4.0 (1–6)	3.0 (0–5)
Swelling joints, median (IQR)	10.0 (7–13)	4.0 (1–8)	4.0 (1–6)	2.0 (1–5)	2.0 (0–4)
Morning stiffness (min)	72.6 ± 57.5	29.0 ± 34.2	22.8 ± 30.4	26.6 ± 41.4	15.6 ± 22.3
Activity by the patient	6.9 ± 2.1	4.4 ± 2.2	3.8 ± 2.2	3.7 ± 2.2	3.4 ± 2.1
Activity by the doctor	6.4 ± 1.8	4.0 ± 1.9	3.6 ± 1.6	3.4 ± 1.9	2.9 ± 1.8
Fatigue	5.6 ± 2.7	4.3 ± 2.4	3.6 ± 2.5	3.7 ± 2.5	2.9 ± 2.0
Pain	6.9 ± 2.1	4.5 ± 2.2	4.0 ± 2.3	3.4 ± 2.3	3.3 ± 2.0

P = 0.000 beginning from week 6 in all variables.

Table 3
Evaluation of the change in quality of life

	Baseline	Week 6	Week 12	Week 18	Week 24
Physical functioning	30.6	53.5	54.6	57.6	60.8
Role-physical	22.9	52.8	58.2	59.4	65.7
Bodily pain	39.1	66.2	70.0	67.8	71.3
General health	23.9	44.4	45.9	48.6	51.1
Vitality	48.5	61.1	63.1	67.1	74.8
Social functioning	49.0	62.3	65.4	67.8	69.0
Role-emotional	22.5	60.6	67.5	60.9	66.8
Mental health	43.4	62.0	65.0	61.6	64.6
Physical health total	26.5	54.2	57.1	58.2	62.3
Mental health total	41.0	61.5	65.1	64.3	66.2
SF-12 total	33.9	58.1	61.1	61.4	64.2

P = 0.000 beginning from week 6 in all components.

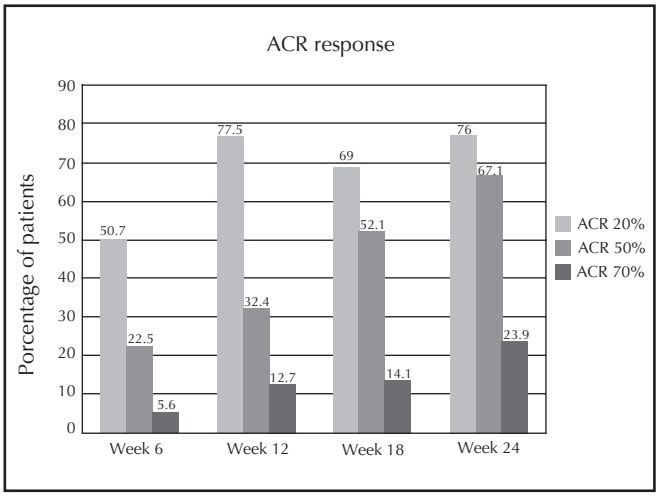

Figure 1
ACR response.

ACR70. At 24 weeks of treatment, 76% of the patients reached ACR20, 67.1% reached ACR50, and 23.9% reached ACR70 (Figure 1).

Although the score on the Disease Activity Score with respect to 28 joints (DAS-28) was not considered the primary variable for evaluating the improvement in disease activity, there was a significant reduction that began at week 6 and was maintained until the end of the study: 5.8 ± 1.2 at baseline; 4.3 ± 1.3 at week 12; and 3.8 ± 1.6 at week 24 (P = 0.000).

Safety

A total of 72 out of 88 patients completed the study. Four patients withdrew voluntarily, and four were lost during the tracking. Thirty adverse events were reported: gastrointestinal complaints (pyrosis, dyspepsia, and diarrhea) in 12% of the patients; elevation of transaminase levels in 10% of the patients; respiratory complaints (common cold and pneumonia acquired in the community) in 6% of the patients; and alopecia in 13% of the patients. In the patients with elevated transaminases, we adjusted the doses of MTX and/or LFN in accordance with the protocol.

The most common laboratory abnormalities were elevated hepatic enzymes. Four patients were withdrawn from the study due to persistently elevated transaminase levels. Follow-up with these patients showed normalization of the elevated enzyme levels after discontinuation of the medications. Four other patients were withdrawn due to diabetes insipidus, diabetes mellitus, osteomuscular pain, or a skin eruption. One patient experienced a reduction in the WBC count to below 1500 mm^3 but recovered with a reduction of the LFN dose to 10 mg/day (Table 4).

Table 4
Adverse events

Events	n (%)
Elevated transaminase levels	8 (26%)
Alopecia	4 (13%)
Rash	2 (6.6%)
Dyspepsia	2 (6.6%)
Leukopenia	1 (3%)
Myalgias	1 (3%)
Oral ulcers	1 (3%)
Pneumonia	1 (3%)
Osteomuscular pain	1 (3%)
Diabetic decompensation	1 (3%)
Diabetes insipidus	1 (3%)
Mild respiratory infection	1 (3%)
Trauma	1 (3%)
Arthritis	1 (3%)
Trigger finger	1 (3%)
Abdominal pain	1 (3%)
Slight elevation of creatinine	1 (3%)
Diarrhea	1 (3%)

Table 5
Patients with elevated transaminases

IU/dL	AST	ALT	FA
Normal	48 (65%)	38 (52%)	56 (76%)
> 1.2 to ≤ 2	17 (23.2%)	26 (35.6%)	12 (16.4%)
> 2 to ≤ 3	3 (4.1%)	6 (8.2%)	2 (2.73%)
> 3	5 (6.8%)	3 (4.1%)	0

*ALT: alanine aminotransferase; *AST: aspartate aminotransferase; *FA: alkaline phosphatase.

Increases in the AST and/or ALT levels to between 1.2 and two times the normal value were observed in 43 patients (48%); 17 patients (23%) showed AST elevations, and 26 patients (35%) showed ALT elevations (Table 5).

DISCUSSION

Despite increased information on the use of the combination of MTX + LFN in the treatment of RA being available in recent years,[19,20] no previous study has evaluated the therapeutic efficacy and safety of this alternative in the Colombian or other Latin American populations.

In the present study, we included patients with established RA who had not responded adequately to treatment with MTX or to a combination of MTX and antimalarial drugs. In Colombia, these two medications are frequently used by rheumatologists as first-line treatments, along with low doses of glucocorticoids and NSAIDs.[21]

The initial clinical studies of therapies combining MTX with other DMARDs showed disappointing results, probably due to the low MTX doses that were used; however, later studies have shown better therapeutic efficacy, without a significant increase in adverse events.[22,23]

LFN is a DMARD the primary action of which is inhibition of the biosynthesis of pyrimidines, thus limiting the proliferation of activated T lymphocytes.[24] MTX works through multiple mechanisms, including the inhibition of the biosynthesis of purines, inhibition of cellular polyamine synthesis, modulation of the cytokine activity, release of adenosine, and activation of cellular apoptosis. The potential synergy that has been observed in *in vitro* studies suggests that the combination of MTX + LFN may be useful in the treatment of RA.[25]

Over the course of time, some questions have arisen regarding the use of LFN, particularly in combination with MTX. Despite conflicting opinions, however, it has been shown by Weinblatt that the combination is more effective and safer than treatment with MTX or LFN alone.[12] Fifty-seven percent of the patients achieved an ACR20 response after nine months of treatment, and this response was maintained for three months, until the termination of the study. Similar results have been reported by Van Riel.[26]

The results from a randomized study by Kremer have shown that the combination of MTX + LFN is superior to treatment with MTX alone. A total of 46.2% of the patients who received the combination reached an ACR20 response after 24 weeks of treatment, compared to 19.5% of the patients that received MTX alone. ACR50 was achieved in 26.2% and 6% of the patients, respectively, and the ACR70 responses were 10% and 2.3%, respectively.[14]

The following ACR responses were seen at weeks 6, 12, 18, and 24 of the present study: 50.7%, 77.5%, 69.0%, and 76.0%, respectively, for ACR20; 22.5%, 32.4%, 52.1%, and 67.1%, respectively, for ACR50; and 5.6%, 12.7%, 14.1%, and 23.9%, respectively, for ACR70. The percentage of patients who reached an ACR20 response increased rapidly and was maintained during the tracking period. The ACR50 and ACR70 responses showed increases as the study continued. Likely due to the short tracking time, no patient experienced remission, although there was a significant improvement in the variables related to the inflammatory activity of the disease, beginning with the first weeks of tracking.

The percentages of ACR20, ACR50, and ACR70 responses in our study were greater than those reported by previous studies. It is important to emphasize that the patients included

had, on average, 8 ± 6.8 years of disease evolution and had demonstrated that they were refractory to stable treatment with a combination of MTX, low-dose glucocorticoids, NSAIDs, and antimalarials. Lee et al.[19] have reported ACR20, ACR50, and ACR70 responses greater than those we found, which seems to be related to the time of disease evolution and a lack of previous DMARD use.

With regard to the DAS-28 responses, which are considered to indicate a clinically significant improvement when there is a change from the previous value ≥ 1.2, there was an improvement above this threshold from week 12 to week 48 in our study, indicating movement from a state of severe activity to a state between light and moderate activity. These results were correlated with those found by measuring functional capacity with the HAQ-DI.

The HAQ-DI results showed a significant functional improvement in the patients that began in the initial weeks and was maintained until the end of the study. A total of 35 patients (52%) had a reduction greater than 0.5 at week 24. Four of them reached an HAQ-DI score of zero.

Until the end of the study, the distribution of base HAQ-DI values showed how the MTX and LFN therapy reduced, to a great degree, the functional deterioration and incapacity produced by RA .

The effectiveness of the combination was also evident in the change in quality of life, as evaluated by the SF-12. There was improvement in all of the components from week 6 until the end of the study. All these differences were statistically significant. These results were consistent with those obtained in other studies. These studies have reported the same phenomenon from the first week of LFN treatment, although without clarifying the reasons for the change.[12,14,27]

With respect to safety, the combination of MTX + LFN was reasonably well tolerated. Of the 88 patients who began the study, 72 (81.2%) completed the tracking period of 24 weeks, three patients withdrew their informed consent, and four were lost during tracking due to changes in insurance companies. In Colombia, on average, patients change their insurance company every 18 months, which causes problems in continuity when treating patients with chronic diseases.

In the present study there were no serious adverse effects related to treatment with LFN, as previously reported, such as deaths, prolonged hospitalization, sepsis, severe infections or liver failure.[28–30] It is possible that the sample size and the relatively short follow-up period did not permitted the detection of these complications.

There were significant elevations in transaminase levels (more than three times the normal limit) in eight patients (9%), four of whom withdrew from the study. The adverse clinical events reported were gastrointestinal disorders, respiratory symptoms, and symptoms related to the skin and skin appendages. The adverse events found were consistent with those reported in previous studies.[12,31–33]

The hepatotoxic potential of the combination of MTX + LFN is certainly a concern. In a study by Kremer, the patients who changed from placebo to LFN with no loading dose showed elevations in AST of 13.7% and in ALT of 14.6%, although these elevations were less frequent than in those patients who received LFN from the outset with a loading dose (AST 16.9% and ALT 31.5%).

In these studies, all of the elevated transaminase levels reversed themselves without intervention upon a reduction of the dose or suspension of the medication. In our study, the protocol called for the suspension of MTX if there was a 3-fold transaminase elevation, and in the case of an elevation ≥ 2 but ≤ 3, the protocol required a reduction of the MTX dose to 7.5 mg weekly or a reduction of the LFN dose to 10 mg/day, at the discretion of the investigator. After the reduction or removal of the MTX and/or LFN doses, there was normalization of the levels of hepatic enzymes compared to the laboratory controls at 4 and 8 weeks, as was the case in other studies.[33,34]

Alves recently published the results of monitoring of 71 patients with RA for eight months: 36.6% were using 20–25 mg/week of MTX alone and 63.4% were using 20–25 mg/week of MTX plus 20 mg/day of LFN. Of the patients on the combination therapy, 11.1% had abnormal levels of liver enzymes *versus* 11.5% of the patients on monotherapy. There was no difference between patients being treated with MTX alone or in combination with LEF. The authors concluded that the combination of MTX + LFN in RA patients generally is safe and well tolerate.[13] Nevertheless, we emphasize the risk of liver toxicity from the combination and the need for strict monitoring of transaminase levels when using this combination. This monitoring is necessary from the outset and for the entire treatment period. Similarly, physicians should avoid this combination in patients with previous liver disease or with additional risk factors for hepatotoxicity.

Dyspepsia is another adverse effect that has been frequently reported among patients who receive this combination, with an incidence that can reach 16.7%.[14] In the present study, we used the pharmaceutical form of a soft gelatin capsule, which has been approved for use in Colombia since 2006 by the INVIMA under record number M-0005987. Although the sample size did not allow us to confirm it, there seems to be a relationship between adequate gastrointestinal tolerance and pharmaceutical presentation.

In the present study we used a loading dose of LFN when starting treatment. Loading doses are associated with a higher incidence of side-effects, particularly nausea and diarrhea. It is now common in the practice (in some countries) to omit the loading dose and this seems to have increased acceptability by the patients. Although it is necessary to validate these findings, omitting the loading dose may improve the tolerability of the combination of MTX + LFN.[35]

Our study did not track the progression of the disease with radiography, due to the difficulties of standardizing the radiography readings in our study environment. Nevertheless, a reduction in damage on the radiography has been previously shown in a convincing manner for treatment with MTX or LFN as monotherapies.[10,34]

The combination of MTX + LFN can be considered a treatment option for patients who have had an incomplete response to monotherapy with MTX or to other combinations of MTX with DMARDs that have been ineffective or not well-tolerated. The economic impact on the health system that this combination could have, as a previous step to the addition of biological agents in patients who are refractory to conventional treatment requires validation in studies with more patients and longer tracking. However, a previous study published on the direct medical costs of RA in Colombia suggested that the combination of MTX + LFN may be an alternative to more costly regimens, with an average annual cost of US$1,381.[36] Recently, our group has published data on the annual costs of RA patient care relative to the severity of the disease and the drugs used. A patient who is moderately active and requires the use of MTX + LFN has an annual expense that varies between US$1,821 and US$7,716, while this same patient treated with anti-TNF-α biological agents has an annual expense of between US$31,931 and $US123,661.[37] Using a combination of MTX + LFN could be a more economical treatment alternative for patients with moderate to severe RA.

The efficacy results from the present study suggest that the combination of MTX + LFN provides a potential clinical benefit with acceptable tolerability, although the elevation of hepatic enzymes requires strict and frequent monitoring of transaminase levels. However, when interpreting the results obtained in this study it is necessary to consider that the sample size and follow-up time is insufficient to bring out all the possible serious adverse events that the combination of MTX + LFN could produce.

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