Leflunomide as an alternative csDMARD for rheumatoid arthritis in a resource-constrained setting: A real-life experience

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Background. Early treatment with methotrexate (MTX) remains the mainstay of rheumatoid arthritis (RA) treatment. In patients with inadequate response to MTX, the European Alliance of Associations for Rheumatology (EULAR) recommends the addition of a biological disease-modifying antirheumatic drug (bDMARD) if poor prognostic factors are present. Despite patients in Africa frequently having poor prognostic factors, bDMARDs are often not available. Leflunomide (LEF) has been shown to be a potent DMARD, leading EULAR to question whether its efficacy is equivalent to MTX as a first-line agent.

Objective. To review LEF's use and safety profile in a low-resource setting, and its usefulness in patients with inadequate response to MTX.

Methods. A retrospective record review was done of all patients with RA who received LEF for at least 6 months between 2018 and 2020 at the Division of Rheumatology, Tygerberg Academic Hospital, Cape Town, South Africa. Patients in whom LEF was discontinued within the first 6 months were also included when assessing the discontinuation rate and side-effects. Demographic information, reasons for initiation, side-effects and treatment discontinuation were recorded. Efficacy data were recorded using the clinical disease activity index (CDAI) at 6-month intervals up to 24 months.

Results. A total of 210 patients who were on LEF were included. Most (n=177) patients were females from low-income backgrounds, with a mean age of 56.51 years and a mean (standard deviation) disease duration of 6.9 (1.0 - 13.8) years. Almost all patients (n=209; 99.52%) had poor prognostic factors, mainly high disease activity (mean CDAI 26.68) and previous exposure to ≥2 conventional synthetic DMARDs (csDMARDs). Most patients initiated LEF owing to loss of efficacy and poor response to triple therapy. After initiation of LEF, treatment targets were achieved by 98 (53%) patients, with 22 (11.9%) and 76 (41.1%) patients achieving clinical remission and low disease activity, respectively (p<0.001, confidence interval (CI) 9.90 -12.29). The mean CDAI decreased to 11.17 (p<0.001, CI 9.59 - 12.74). Most disease control was achieved within the first 6 - 12 months, and was sustained for 24 months. A total of 16 (7.62%) patients experienced side-effects, necessitating treatment discontinuation. Two pregnancies exposed to LEF in the first trimester resulted in healthy babies.

Conclusion. LEF has been demonstrated to be an effective alternative csDMARD for patients with inadequate response to MTX-based therapies, reducing the mean CDAI from 26 to 11. It adds a viable alternative for RA patients with poor prognostic factors and lack of access to bDMARDs.

Keywords: leflunomide, csDMARDs, rheumatoid arthritis, CDAI, methotrexate

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Early disease-modifying antirheumatic drug (DMARD) therapy remains the mainstay of rheumatoid arthritis (RA) treatment, with methotrexate (MTX) being the drug of choice when initiating patients on management. In their 2022 updated recommendations, the European Alliance of Associations for Rheumatology (EULAR) recommended MTX be part of first-line treatment for managing RA.[1] EULAR further recommended that patients with an inadequate response to MTX should be prognosticated based on the risk-factor profile for disease progression. In the absence of poor prognostic factors, another conventional synthetic DMARD (csDMARD) may be used to try and achieve disease control.

EULAR includes the following as poor prognostic factors: persistently moderate or high disease activity (after csDMARD therapy), according to composite measures including joint counts, despite csDMARD therapy, high acute-phase reactant levels, high swollen joint count, presence of rheumatoid factor (RF) and/or anti-citrullinated protein autoantibodies (ACPA), presence of early joint erosions and failure of ≥2 csDMARDs.[1] If poor prognostic factors are present, they recommend adding a biological DMARD (bDMARD) if there is inadequate response to MTX. The latter is problematic in settings where the availability of bDMARDs is limited owing to economic constraints.[2]

Leflunomide (LEF) has been shown to be an effective csDMARD, comparable to MTX regarding efficacy and side-effect (SE) profile in multiple studies.[3-6] Whether LEF is equivalent to MTX as first-line csDMARD therapy is, however, still unclear, and therefore EULAR included this as a research question in their 2022 update.[1] Given the restricted availability of bDMARDs in some settings, this remains an important question.

The reality is that most patients with RA in low- and middle-income countries have advanced disease and multiple poor prognostic factors at the time of diagnosis.[7] This has been attributed

to the lack of and delayed access to trained rheumatologists, as well as disease-specific therapeutic strategies.[2,8,9] Given that we practise in such a resource-constrained setting, we decided to review LEF use in our hospital, focusing on its efficacy and SEs, to evaluate it as an alternative for patients with inadequate response to MTX and other csDMARDs in this setting, and to add to the available data.

Methods

Tygerberg Academic Hospital is a publicly funded academic hospital in Cape Town, South Africa (SA), providing tertiary healthcare to 2 million people, mainly from a low-income population. It therefore represents an appropriate site to explore the research question.

A retrospective record review of Tygerberg Academic Hospital's rheumatology outpatient department was undertaken. Patients were identified using the pharmacy database, and all RA patients aged ≥18 years who received LEF for at least 6 months between 2018 and 2020 were included in the study.

Demographic information (age, gender and comorbidities), prognostic factors, reasons for LEF initiation, combinations of DMARDs used, SEs and reasons for treatment discontinuation were recorded.

Poor prognostic factors include persistent disease activity, high acute-phase reactant levels, high swollen joint count, presence of RF and/or ACPA, early joint erosions and failure of ≥2 csDMARDs. Given the retrospective nature of our study and the low-income setting, we did not have inflammatory markers and radiological data available for all patients, therefore we used persistent disease activity and failure of ≥2 csDMARDs for prognostication.

Patients with incomplete medical and drug history were excluded, except where they had stopped LEF in <6 months because of SEs; these were included when reviewing tolerability and retention-rate data.

SEs were classified as significant if ≥1 of the following factors were present: association with increased risk of morbidity or mortality; necessitated treatment discontinuation; warranted in-hospital management; and resulted in impaired quality of life; or, since this is a retrospective review, if the treating physician deemed an effect significant, recorded it in the notes as such and potentially adjusted management because of it.

Due to its validity, cost-effectiveness and feasibility in a resource-constrained setting, the clinical disease activity index (CDAI) was used as a composite measure to evaluate response to treatment.[10] Considering that this was a retrospective review, CDAI scores were calculated in 6-month intervals and not at a specific time. Therefore, CDAI values were extracted at initiation, 6 - 12, 12 - 18 and 18 - 24 months. CDAI values <2.8, ≤10, between >10 and ≤22 and >22 were considered as clinical remission (CR), low disease activity (LDA), moderate disease activity (MDA) and high disease activity (HDA), respectively.

Statistical analysis was done using the SPSS version 25 (IBM, USA) statistical software package. Missing data were not replaced. A bar graph was used to depict the categorical variables of interest. Descriptive statistics such as mean and standard deviation (SD) were reported for continuous variables. A paired *t*-test was used to assess efficacy, using the CDAI over time. A percentage of reduction or increase was derived from the absolute CDAI at initiation, comparing it with CDAI at 6-month intervals. Pearson's χ^2 test was used to assess the association between variables and outcomes. $P<0.05$ was considered statistically significant.

Ethical approval was obtained from the Stellenbosch University Health Research Ethics Committee (ref. no. S22/03/035).

Results

Demographics

A total of 258 medical records were reviewed. Twenty patients were excluded because LEF was used for conditions other than RA. A further 28 patients were excluded because of incomplete medical and drug history, leaving 210 patients to be included in the study (Fig. 1).

Most (84%) patients were female, with a mean age of 56.5 years. The mean (standard deviation (SD)) duration of their disease before receiving LEF was 6.9 (1.0 - 13.8) years. Males and females had similar disease activity levels at the initiation of LEF. Male patients demonstrated a slightly better, but not statistically significant, response than females, with the mean CDAIs decreasing from 26.4 to 11.3 and 26.8 and 12.5, respectively. However, all patients who achieved CR were female, and the odds ratio for achieving remission was 4.06 for females compared with males.

The most common comorbidities were cardiovascular disease, mainly hypertension and heart failure, at a staggering 77%. Chronic obstructive pulmonary disease (COPD) secondary to smoking was the second most common comorbidity at 21%. Twelve percent of patients suffered from concomitant diabetes mellitus. Despite 32% of patients being recorded as having gastro-oesophageal reflux, this probably reflects multifactorial causes including reflux, gastritis secondary to chronic nonsteroidal anti-inflammatory drug and steroid use, etc. Five patients (2.4%) developed malignancies, and one patient had chronic hepatitis B infection but received treatment for it and was stable despite the immune suppression.

All patients who initiated LEF were previously exposed to a combination of csDMARDs, and were on concomitant low-dose (≤7.5 mg/day) oral corticosteroid therapy tapered in <3 months, except for one already in CR when LEF was started. Before LEF was adopted as an alternative csDMARD, the protocol as per the SA Rheumatism and Arthritis Association (SARAA) recommendations was to use combination therapy with MTX, sulfasalazine (SSZ) and chloroquine (CLQ) (referred to as triple therapy) for patients not achieving LDA on MTX, and who were unable to access bDMARDs.[11] If triple therapy was ineffective or had to be changed owing to SEs, then azathioprine (AZA) or ciclosporin (CSP) were the alternative csDMARDs.[12,13] As a result, 158 (75%) patients were on triple therapy before LEF initiation, while 52 (24.8%) were on different MTX, SSZ, AZA and CSP combinations.

The patients who had previously been on triple therapy (MTX, SSZ and CQ) had on average a shorter disease duration than those on a regimen containing AZA or CSP. This is, however, not surprising, since AZA and other medicines would have been the third line, therefore the mean disease duration is expected to be longer. The interesting fact in these subgroups, however, was that despite the longer duration of disease in the AZA+CSP group, they had a similar response to LEF. The mean CDAIs at initiation, 12 and 24 months for the triple therapy group were 27.5, 16.4 and 13.3, respectively, while the AZA+CSP group's mean CDAIs were 24.2, 12.8 and 9, respectively.

Indication for the initiation of LEF

Failure to achieve remission or LDA, as well as SEs from other csDMARDs, were the main reasons LEF was initiated. There was a mixture of indications for LEF initiation, with some frequently overlapping. These could, however, be simplified into four general indications: failure of triple therapy; SEs from MTX; SEs from SSZ; and failure of other combinations (Fig. 2).

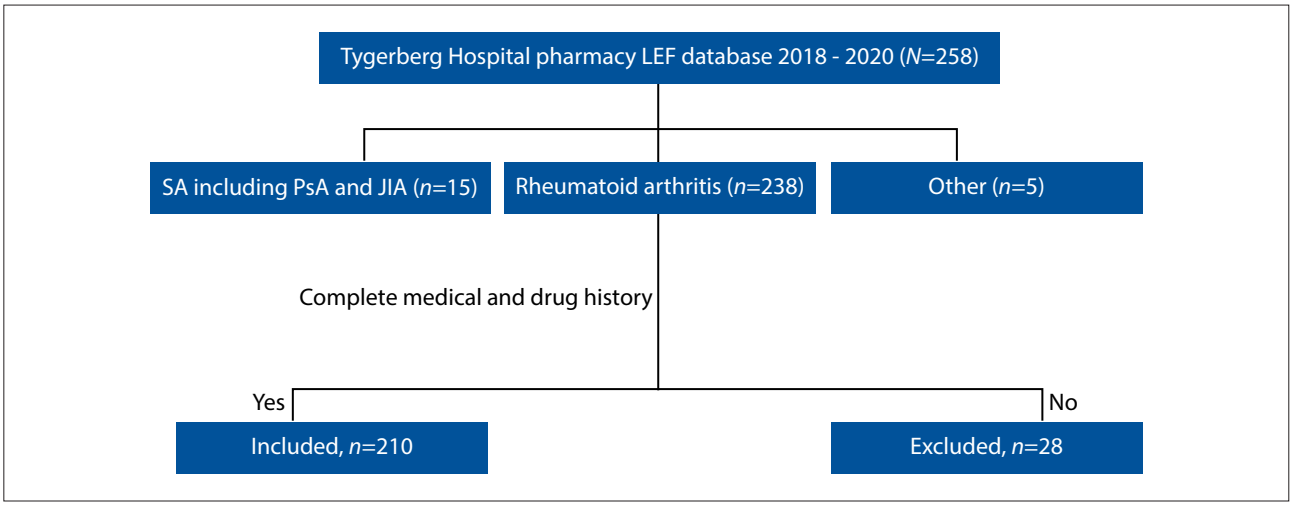


Fig. 1. Inclusion criteria for adult patients receiving leflunomide between 2018 and 2020. (LEF = leflunomide; SA = spondylarthritis; PsA = psoriatic arthritis; JIA = juvenile idiopathic arthritis.)

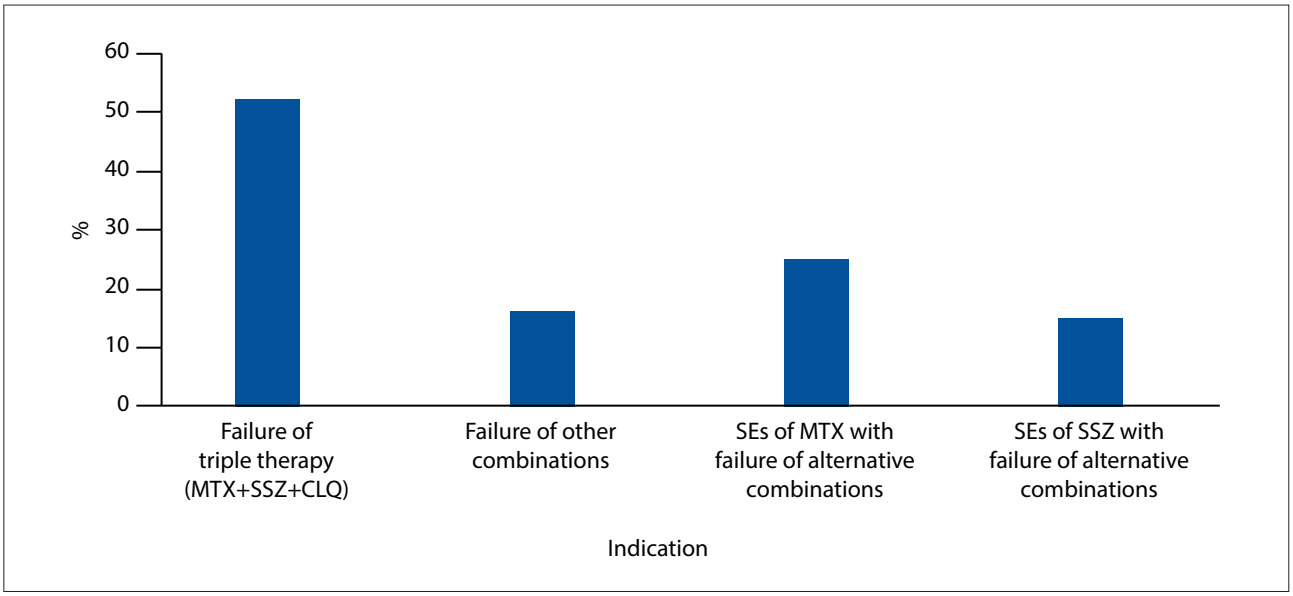


Fig. 2. Indications for leflunomide initiation (N=210). (MTX = methotrexate; SSZ = sulfasalazine; CLQ = chloroquine, SEs = side-effects.)

Efficacy and retention rates

Most patients (75%) were failing triple therapy (MTX+SSZ+CLQ), with a mean CDAI for all patients before LEF initiation of 26.68. One hundred and twenty (58.3%) patients had HDA, while 81 (39.3%) patients had MDA when switched to LEF. Within the first 6 - 12 months on LEF-based combinations, the mean CDAI decreased from a mean of 26.68 to 11.17 ($p<0.001$, CI 9.59 - 12.74). This was achieved through a significant reduction (70.83%) in the number of patients with HDA. Although the number of patients with MDA at 6 - 12 months increased from 81 to 93 (12.9%), this increase can be attributed to the patients with HDA improving to MDA. The mean CDAI of 11.17 consisted of 55 (28.5%) patients who improved to LDA, and 10 (5.2%) patients who achieved CR. Thirty-five (18.1%) patients had refractory disease, and still had HDA.

This pattern of improvement was sustained as the number of patients with high and moderate disease activity reduced further by 18 and 24 months, while the number with LDA and CR increased further. Also, of the patients who still had MDA at 24 months, 143 (68%) had a >50% reduction in their CDAI. On the negative side, 27 (14.6%) patients still had HDA.

The csDMARD used before LEF initiation influenced what patients were started on LEF as a replacement. Given that the use of triple therapy was frequent, and that it became the practice to replace MTX with LEF, the combination of LEF+CLQ+SSZ was the most commonly used (44.28%) combination in patients where LEF was introduced. Another 59 (28.09%) patients were initiated on LEF+CLQ, 19 (9%) patients on LEF+SSZ, 16 (7.62%) on LEF monotherapy, and 20 (9.5%) on some combination with MTX.

There were similar trends between the different combinations in which LEF was used. Initially, there was high to moderate disease activity, with a significant response in the first 6 - 12 months, and subsequently a slower improvement towards 24 months. Interestingly, the group on LEF+CLQ showed a better response than the LEF+CLQ+SSZ group. Fifty-nine (28.09%) patients initiated on LEF+CLQ demonstrated rapid response at 6 - 12 months, with 50 - 75% reductions in CDAI, translating to 23 (38.18%) patients achieving LDA and 4 (7.27%) patients achieving CR, while only 15 (15.78%) and 5 (5.26%) patients on LEF+CLQ+SSZ achieved LDA and CR, respectively. Patients who failed to show rapid response on LEF+CLQ and still had MDA after 6 - 12 months demonstrated

improvement after the addition of SSZ. However, this improvement was not rapid, and was limited to those with MDA.

The predictors of rapid disease control and remission at 12 months were female sex, not having previously been on >2 csDMARD combinations, and initiation on LEF+CLQ.

The continuation of LEF-based therapy in patients who still had HDA after 6 - 12 months of treatment offered very little increase in efficacy; the numbers of patients with HDA were 35 (18.1%) and 36 (19%) at 6 - 12 months and 12 - 18 months, respectively (Figs 3 and 4).

Safety profile and discontinuation rate

LEF was retained for 24 months for most patients (*n*=172, 82.38%). The mean duration of LEF use was 42.34 months. Of those who discontinued LEF-based csDMARD therapies, 19 (9.04%) demonstrated failure to achieve disease control, and 30 (14.28%) patients reported SEs secondary to LEF, but only 16 (7.62%) had significant SEs necessitating LEF discontinuation. In 2 (0.95%) patients, LEF was stopped because they conceived while on LEF.

The mean onset of SEs was 7.83 months, with nausea and vomiting, followed by hepatotoxicity, with raised alanine aminotransferase levels not explained by other factors being the earliest SEs to be detected. Of the 5 patients who developed hepatotoxicity, 3 developed an elevation of serum aminotransferase two times the upper limit of normal, necessitating treatment discontinuation. No patient needed admission, and all liver functions returned to normal after discontinuation. Of the patients who developed hepatotoxicity requiring LEF discontinuation, one was on the LEF+MTX combination. As only 20 (9.5%) patients were on this combination, there is uncertainty about how to interpret this, and whether it is statistically significant.

Considering that infections are always a concern when on immune suppression, while on LEF there were 10 patients with infections significant enough to need physician input. Four cases of tuberculosis (TB) were recorded, and two fungal skin infections. Two patients had their LEF discontinued, and three passed away due to the combination of sepsis and other comorbidities.

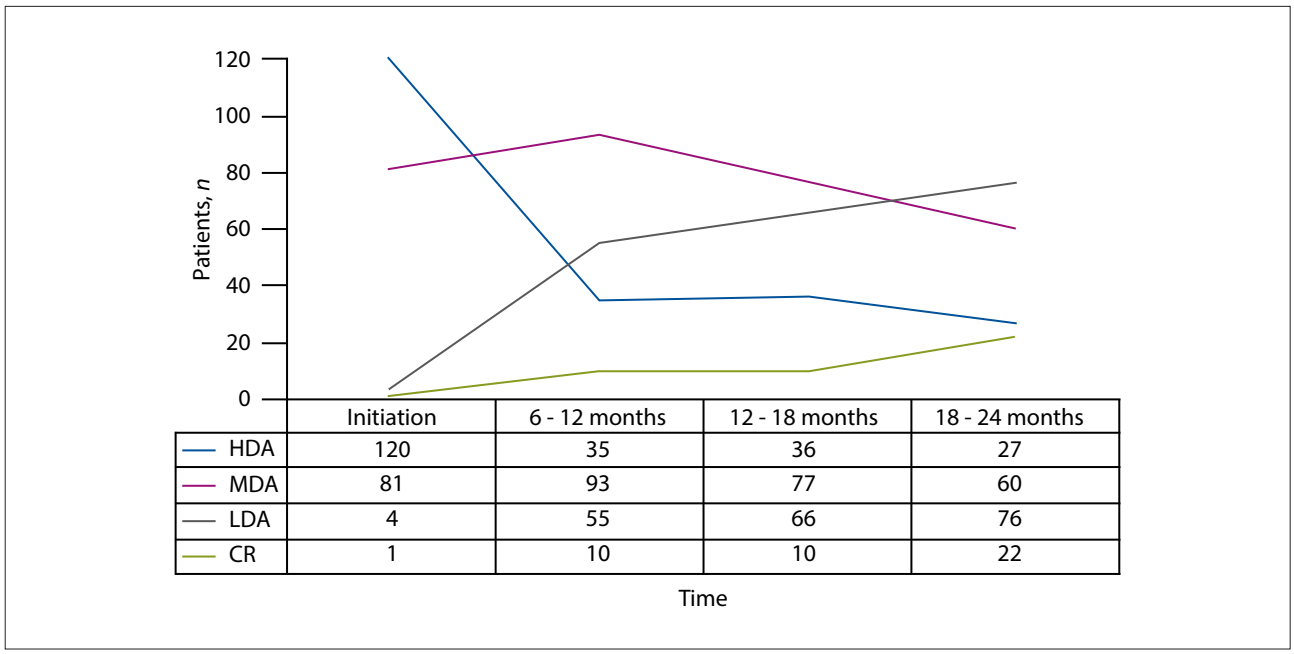
Among those who discontinued LEF, one developed TB and then had a drug-induced liver injury (DILI) due to concomitant LEF and TB therapy. TB therapy is quite a common reason for DILI;[14] therefore, it is debatable as to what part the LEF contributed, but given the need for 6 months of TB therapy, it was deemed safer to discontinue the LEF. The second patient had extensive chronic disease, and had already had bilateral hip replacements. He then needed ankle surgery with external fixation, and developed significant cellulitis 1 month later. Given the metallic hardware *in situ*, it was deemed safer to discontinue the LEF (Table 1).

All three patients who died while on LEF-based csDMARD therapy had longstanding disease (>8 years); two patients had severe interstitial lung disease (ILD), and one required home oxygen. They both died during the SARS-COV-2 pandemic owing to acute exacerbations of ILD secondary to COVID-19 pneumonia. The third patient had a longstanding, complicated cardiovascular disease that necessitated an above-knee amputation due to peripheral vascular disease, and then died due to wound sepsis.

Discussion

Over the past two decades, the paradigms of treating RA have changed significantly. This can be partly attributed to the increased understanding regarding pathogenesis, leading to more directed therapies such as bDMARDs and targeted synthetic DMARDs (tsDMARDs). Together with newer medications, improved disease monitoring instruments and goal-directed therapeutic strategies such as the CDAI and a treat-to-target (T2T) approach are improving management.[15] Combined, all of these are assisting in achieving early disease control, sustained remission and improved quality of life for RA patients.

The achievement of these treatment targets is influenced by the early initiation of DMARDs, the absence of poor prognostic factors and the availability of targeted therapies. EULAR recommends the introduction of a bDMARD if disease control is not achieved with the first csDMARD in the presence of poor prognostic factors.[1] However, since this is not always practical in resource-constrained settings, the results of our study show great promise, demonstrating



	Initiation	6 - 12 months	12 - 18 months	18 - 24 months
HDA	120	35	36	27
MDA	81	93	77	60
LDA	4	55	66	76
CR	1	10	10	22

Fig. 3. Clinical disease activity for patients initiated on leflunomide-based regimens over time (N=201). (HDA = high disease activity; MDA = moderate disease activity; LDA = low disease activity; CR = clinical remission.)

LEF to be an effective and well-tolerated alternative in these settings.

As Mody[7] explains, patients in low-income countries frequently present late and with poor prognostic features. He also points out that constraints on the availability of newer bDMARDs predispose patients to worse outcomes. Our study was a good representation of this population, since they had poor prognostic features, with most (98%) having high to moderate disease activity at the start, and all having failed multiple other csDMARD combinations, with limited access to bDMARDs.

After the introduction of LEF, there was a rapid improvement in disease control, with the mean CDAI improving from 26 to 11, and the number of patients with HDA reducing by 70%. Much of the improvement was achieved within 6 - 12 months, followed by gradual but sustained improvement up to 24 months. Given the retrospective nature of our study, the LEF-based combinations used depended on what csDMARDs the patients had been exposed to previously. The responses, however, were consistent between the different regimens, as were the trends of slight but ongoing improvement.

Our results correspond with what Hodkinson *et al.*[16] found in a study in a similar resource-constrained setting in Soweto, SA. They also looked at patients who had inadequate response to csDMARDs but could not access bDMARDs. They, however, focused on patients going onto a LEF+MTX regimen, whereas we looked at all LEF combinations. Similar to our results, they found a significant improvement in the first few months, with slower but sustained improvement later. Their results were slightly better than others, with 56.70% of patients achieving LDA or remission, compared with our 46.67%. Our study and that of Hodkinson *et al.*[16] complement each other, in that their results show that a LEF+MTX combination is safe and efficacious, and probably the preferred choice for these patients, while our results show similar success in other combinations of csDMARDs with LEF, and therefore offer an alternative if there is a contraindication for MTX.

In the current study, the main contributing factor to LEF-based therapy discontinuation was the failure to achieve treatment targets. Twenty-three percent of patients either discontinued LEF because of non-response, or still experienced HDA after 2 years. This, however, corresponds with what we expect from any regimen. In a Cochrane review of 158 trials looking at all DMARDs, including biologics and tofacitinib, Hazlewood *et al.*[17] found that the American College of Rheumatology (ACR) 50% response (50% reduction in the number of swollen and tender joints, and a reduction of 50% in three of the following five parameters: physician global assessment of disease, patient global assessment of disease, patient assessment of pain, C-reactive protein or erythrocyte sedimentation rate, and degree of disability in Health Assessment Questionnaire score) ranged between 27 and 64%. Aletaha and Smolen[6] acknowledge that 60% of patients may require up to a third regimen, and only 75 - 80% will eventually reach the target of LDA or CR. The reality is that, with any drug, there may potentially be non-responders. Therefore, in our study, patients who did not reach LDA are treatment failures, but also markers of the resource-constrained nature of our environment, since, in a perfect world, they would have moved onto a bDMARD or a tsDMARD.

In their recommendations from their 2022 update,[1] EULAR accepts that remission may not be a realistic target in all patients, and that in some, LDA may be acceptable.[15] Many of the patients in our study fell within this group, having had the disease for multiple years,

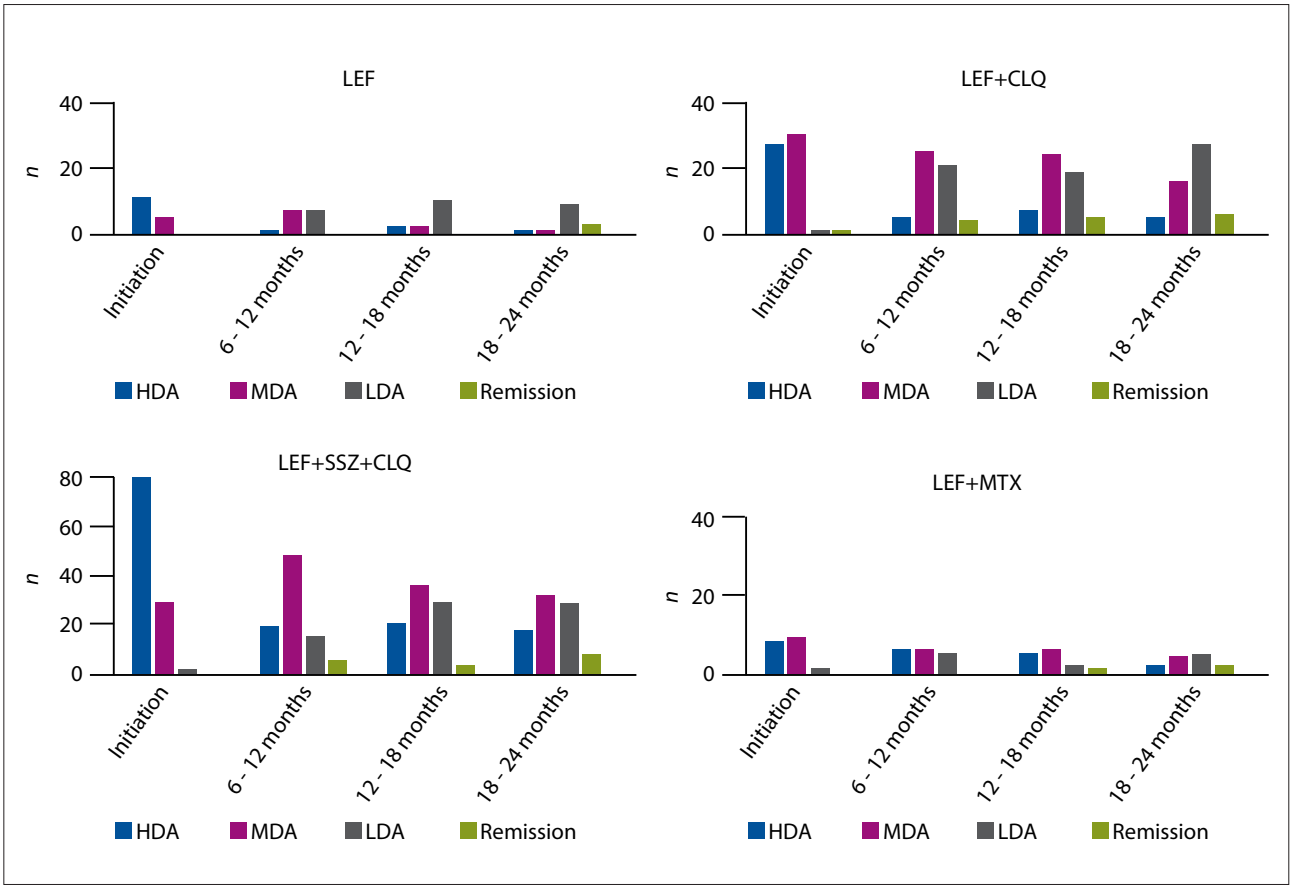


Fig. 4. Response rates to leflunomide (LEF) monotherapy and LEF-based conventional synthetic disease-modifying antirheumatic drug combinations. (CLQ = chloroquine; SSZ = sulfasalazine; MTX = methotrexate; HDA = high disease activity; MDA = moderate disease activity; LDA = low disease activity.)

Table 1. Leflunomide adverse events and associated discontinuation rates (*N*=54)

Reason for discontinuation	*n* (%)	
Drug failure	19 (9.04)	
Side-effects	16 (7.62)	
Pregnancy	2 (0.95)	
Death	3 (1.42)	
Side-effect	**Reported/detected (*n*=30), *n***	**Discontinued (*n*=16), *n***
Nausea and vomiting	9	6
Hepatotoxicity*	5	3†
Alopecia	1	1
Infection		
PTB	4	1
Skin infection	2	
MSK infection	1	1
Oral ulcers	1	1
Leukopaenia	3	2
Other	4	1

PTB = pulmonary tuberculosis; MSK = musculoskeletal.
*Mild elevation of serum aminotransferase.
†Elevation of serum aminotransferase 2× above upper limit of normal.

with multiple risk factors for severe disease in the form of high joint counts, and having previously failed ≥2 csDMARDs. Therefore, despite only 22 (11.9%) patients achieving CR and a further 76 (41.1%) achieving LDA, this translates to half of the patients (53%) reaching acceptable targets within a group of patients who had previously failed multiple regimens, which points to LEF being a viable alternative.

It is also remarkable that these were patients with established disease (mean (range) time from disease onset to initiation of LEF = 6.9 (1 - 13) years), and despite this, they had a fair response to LEF, and it sustained efficacy.

Hepatotoxicity has been one of the most commonly reported adverse events of LEF, leading to discontinuation. Previously, Emery *et al.*[4] demonstrated the incidence of associated transaminase elevation to be 5.4% in the first year and 2.7% in the second year of using LEF. This corresponded with the low level (2.4%) of hepatotoxicity observed in our study.

In patients with RA, the risks of infections are influenced by factors such as higher disease activity, DMARDs and concomitant corticosteroids, which significantly contribute to serious infections.[18] In our study, TB infections were the most common infections, occurring in four cases. Of the four patients diagnosed with pulmonary TB (PTB) while on LEF, one had to stop LEF because of compounding hepatotoxicity due to a concurrent TB regimen and LEF. Some case reports suggest that there is an increased risk of TB reactivation with LEF,[19] while other opinions are conflicting.[20] Considering LEF's mode of action and the fact that it does influence the tumour necrosis factor (TNF) signature in patients, and considering the proven risk of anti-TNF medications in TB, the link should at least be considered. Furthermore, since SA is one of 30 high-burden TB countries listed by the World Health Organization, note should be taken of this signal, and vigilance employed when using LEF.

The comorbidity profile of the four patients who developed PTB consisted of COPD, which was treated with bronchodilators and inhaled corticosteroids (ICS). In two of the four patients, the bridging corticosteroid therapy was tapered over 3 months. Considering the nature of duration- and dose-dependent corticosteroid risk factors for TB infection, the low-dose bridging corticosteroid therapy probably had no causal relationship beyond the underlying ICS-treated COPD and refractory RA.[18] It was also deemed safe to cautiously continue LEF in three patients, as all four patients had other predictable risk factors for TB infection.

Two pregnancies were recorded while on LEF. Patients in their reproductive years were given counselling regarding the effects of LEF during pregnancy, based on the available data. If they consented to initiate LEF, they were advised to use reliable contraceptives. In our series, both pregnancies were unplanned. After receiving counselling, the mothers decided against termination. The recommended cholestyramine wash-out procedure was done promptly at diagnosis, and both pregnancies resulted in healthy babies with no congenital abnormalities. The average gestational age at diagnosis was 14 weeks. Pfaller[21] reported 13 studies of 222 women exposed to LEF during pregnancy. Despite resulting in 8 babies with congenital defects, this was reported to be comparable with unexposed pregnancies. Pfaller is supported in her findings by a study by Chambers *et al.*[22] in which they compared pregnant women with RA who were exposed to LEF with a matched control group not exposed to LEF.[22] They found the rate of congenital defects to be 5.4% and 4.2%, respectively. Despite these reports, it needs to be highlighted that most exposed patients stopped the drug as soon as pregnancy was diagnosed (on average at 3.1 weeks, in the case of Chambers), and underwent the recommended cholestyramine wash-out procedure. It may be argued that our study's number of pregnancies exposed to LEF does not carry significant statistical value. However, it is reassuring that healthy pregnancy outcomes are still possible despite exposure. While pregnancies do not necessarily need to be terminated, it remains essential to follow precautions and prevent exposure as much as possible.

Study limitations

The study was conducted as a retrospective review, which presented certain limitations. Among these, incomplete data on 11.76% of the cases, resulting in their exclusion, merits questioning, as these exclusions may introduce a degree of bias into the study. Additionally, owing to the resource constraints in the system, laboratory tests were kept to a minimum, and therefore data such as inflammatory markers and X-ray evaluations for early joint erosions in prognostication were not consistently available. However, clinical prognostication data such as joint counts were well documented, enabling adequate assessment of efficacy at treatment reviews. The use of the CDAI as a composite measure may be viewed as a limitation, since most research uses the ACR 20/50/70% response criteria. However, CDAI has been validated and is accepted by Smolen and his international task team[15] as one of the accepted composite measures in the treatment of RA.

Conclusion

In our study, LEF is demonstrated to be a statistically significant and effective alternative csDMARD for patients who had an inadequate response to MTX-based therapies, reducing the mean CDAI from 26 to 11. It delivered considerable improvement, even in patients with longstanding disease (mean 6.9 years) who had failed treatment with multiple combinations of csDMARDs. Our population was high risk, with high joint counts and failure of previous regimens, but despite this, LEF showed rapid disease control, with a significant improvement at 6 months in a large number of patients. It also demonstrated tolerable SEs, comparable with studies using other csDMARDs.[23,24] Therefore, LEF is shown to be useful in low-resource settings where MTX is ineffective and the availability of bDMARDs is limited.

Data availability. Upon reasonable request to the authors and with permission from the Stellenbosch University Health Research Ethics Committee, data used in this study will be made available.

Declaration. None.

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Conflicts of interest. None.

1. Smolen JS, Landewé RBM, Bergstra SA, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis 2022;82(1):3-18. https://doi.org/10.1136/ard-2022-223356
2. Kolou M. Challenges of rheumatoid arthritis management in sub-Saharan Africa in the 21st century. Open J Rheumatol Autoimmune Dis 2023;13(1):17-40. https://doi.org/10.4236/ojra.2023.131003
3. Kalden JR, Schattenkirchner M, Sörensen H, et al. The efficacy and safety of leflunomide in patients with active rheumatoid arthritis: A five-year followup study. Arthritis Rheum 2003;48(6):1513-1520. https://doi.org/10.1002/art.11015
4. Emery P, Breedveld FC, Lemmel EM, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. Rheumatology 2000;39(6):655-665. https://doi.org/10.1093/rheumatology/39.6.655
5. Smolen JS, Emery P. Efficacy and safety of leflunomide in active rheumatoid arthritis. Rheumatology 2000;39(Suppl 1):S48-S56. https://doi.org/10.1093/oxfordjournals.rheumatology.a031495
6. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: A review. JAMA 2018;320(3):1360-1372. https://doi.org/10.1001/jama.2018.13103
7. Mody GM. Rheumatology in Africa-challenges and opportunities. Arthritis Res Ther 2017;19(1):17-19. https://doi.org/10.1186/s13075-017-1259-3
8. Rudan I, Sidhu S, Papana A, et al. Prevalence of rheumatoid arthritis in low- and middle-income countries: A systematic review and analysis. J Glob Health 2015;5(1):010409. https//doi.org/10.7189/jogh.05.010409
9. Nicholas A, Alare K, AbdulBasit Opeyemi M, Oluwatosin A. The outlook of rheumatological care in Africa: Current state, challenges, and recommendation. Ann Med Surg 2022;82(September):4-6. https://doi.org/10.1016/j.amsu.2022.104689
10. Anderson J, Caplan L, Yazdany J, et al. Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. Arthritis Care Res 2012;64(5):640-647. https://doi.org/10.1002/acr.21649
11. Hodkinson B, van Duuren E, Pettipher C, et al. South African recommendations for the management of rheumatoid arthritis: An algorithm for the standard of care in 2013. S Afr Med J 2013;103(8):577-585. https//doi.org/10.7196/samj.7047.
12. Wells G, Haguenauer D, Shea B, Suarez-Almazor ME, Welch VA, Tugwell P. Cyclosporine for rheumatoid arthritis. Cochrane Database Syst Rev 2000;1998(2):CD001083. https://doi.org/10.1002/14651858.CD001083
13. Suarez-Almazor ME, Spooner C, Belseck E. Azathioprine for treating rheumatoid arthritis. Cochrane Database Syst Rev. 2000;(4):CD001461.
14. https://doi.org/10.1002/14651858.CD001461
15. Jiang F, Yan H, Liang L, et al. Incidence and risk factors of anti-tuberculosis drug induced liver injury (DILI): Large cohort study involving 4 652 Chinese adult tuberculosis patients. Liver Int 2021;41(7):1565-1575. https//doi.org/10.1111/liv.14896
16. Smolen JS, Aletaha D, Bijlsma JWJ, et al. Treating rheumatoid arthritis to target: Recommendations of an international task force. Ann Rheum Dis 2010;69(4):631-637. https://doi.org/10.1136/ard.2009.123919
17. Hodkinson B, Magomero KR, Tikly M. Combination leflunomide and methotrexate in refractory rheumatoid arthritis: A biologic sparing approach. Ther Adv Musculoskelet Dis 2016;8(5):172-179. https://doi.org/10.1177/1759720X16664324
18. Hazlewood GS, Barnabe C, Tomlinson G, Marshall D, Devoe DJA, Bombardier C. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis: A network meta-analysis. Cochrane Database Syst Rev 2016;8: CD010227. https://doi.org/10.1002/14651858.CD010227.pub2
19. Riley TR, George MD. Risk for infections with glucocorticoids and DMARDs in patients with rheumatoid arthritis. RMD Open 2021;7(1):1-7. https://doi.org/10.1136/rmdopen-2020-001235
20. Sundbaum JK, Arkema EV, Bruchfeld J, Jonsson J, Askling J, Baecklund E. Tuberculosis in biologic-naïve patients with rheumatoid arthritis: Risk factors and tuberculosis characteristics. J Rheumatol 2021;48(8):1243-1250. https://doi.10.3899/jrheum.201251
21. Hočevar A, Rozman B, Praprotnik S, et al. Leflunomide-associated tuberculosis? Rheumatology 2006;45(2):228-229. https://doi.org/10.1093/rheumatology/kei173
22. Pfaller B. A critical review of the reproductive safety of Leflunomide. Clin Rheumatol 2020;39(2):607-612. https://doi.org/10.1007/s10067-019-04819-4
23. Chambers CD, Johnson DL, Robinson LK, et al. Birth outcomes in women who have taken leflunomide during pregnancy. Arthritis Rheum 2010;62(5):1494-503. https://doi.org/10.1002/art.27358
24. Adas MA, Allen VB, Yates M, et al. A systematic review and network meta-analysis of the safety of early interventional treatments in rheumatoid arthritis. Rheumatology 2021;60(10):4450-4462. https://doi.org/10.1093/rheumatology/keab429
25. O'Dell JR, Mikuls TR, Taylor TH, et al. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med 2013;369(4):307-318. https://doi.org/10.1056/NEJMoa1303006

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