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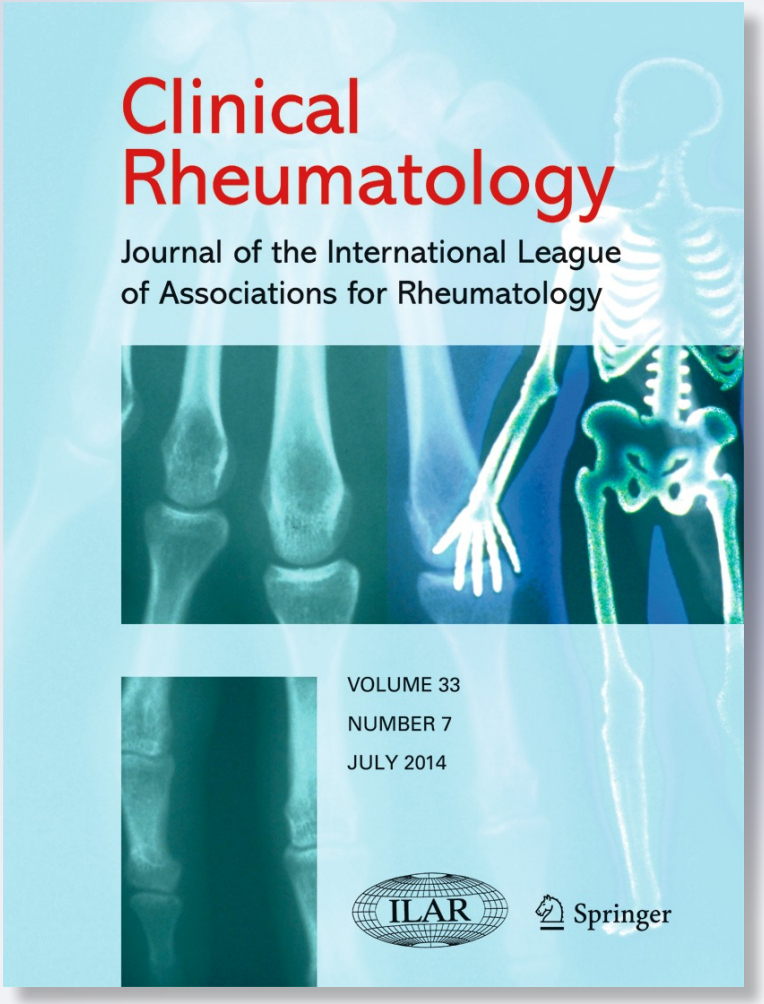

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ORIGINAL ARTICLE

The effect of leflunomide on the eye dryness in secondary Sjögren's syndrome associated with rheumatoid arthritis and in rheumatoid arthritis patients

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Abstract The aim of this work was to clarify the effect of leflunomide (LEF) on the eye dryness in patients with secondary Sjögren's syndrome associated with rheumatoid arthritis (RA-sSS) and in patients with rheumatoid arthritis (RA). Seventy-five female patients, 45 with RA-sSS (group A) and 30 with RA (group B), taking methotrexate at a dose of 20 mg/week for more than 6 months were enrolled in this study. They all had a loading dose of leflunomide then were maintained at a dose of 20 mg/day in addition to methotrexate for another 3 months. The modified disease activity score (DAS28) was calculated and modified Schirmer's-I test was performed. Assessment of disease parameters was done to all patients before and after 3 months of taking LEF. The mean modified Schirmer's-I test showed a significant decrease after 3 months of taking LEF in group A (3±1.6 before versus 1.9±1.6 after 3 months, $P<0.001$), while this difference was non-significant in group B (21.3±10 versus 19.9±11). One patient (group A) developed peripheral ulcerative keratitis (PUK) with exacerbation of disease activity (DAS-28=6.9) that improved by taking corticosteroids. Three patients (group A) had aggravation of punctate keratocojunctivitis sicca with punctate erosions without PUK. The condition improved dramatically by stopping LEF and using topical lubricants. We report in this study a significant deterioration of the eye dryness in patients with sSS-RA after 3 months of receiving LEF inspite of the significant improvement of their DAS28. This finding was not clearly detected in RA patients. Close monitoring of eye dryness changes by special tests in patients using LEF is recommended, especially in cases with sSS-RA having very low baseline values.

Keywords Eye dryness · Leflunomide · Peripheral ulcerative keratitis · Punctate keratoconjunctivitis sicca · Rheumatoid arthritis · Secondary Sjögren's syndrome

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Introduction

Sjögren's syndrome (SS) is an autoimmune exocrinopathy characterized by the infiltration of salivary and lacrimal glands by mononuclear cells with secondary destruction of the parenchymal tissue resulting in oral and ocular dryness [1]. It may occur alone as primary SS (pSS), or as secondary SS in association with other connective tissue diseases, including rheumatoid arthritis (RA) as (RA-sSS) [2].

Leflunomide (LEF) is an oral immunomodulatory agent. Its mechanism of action in suppressing inflammation is based on its inhibition of dihydroorotate dehydrogenase, an enzyme responsible for de novo synthesis of pyrimidine-containing ribonucleotides. It is used as a therapy for RA and for the systemic manifestations of SS [3]. Its combination with methotrexate is considered safe [4].

To our knowledge, the studies about the effect of LEF on the eye dryness either in RA patients or in SS patients are very few. A study, made by Woerkom et al. [5], reported modest improvement in eye and mouth dryness in pSS patients taking LEF. They found that the increment in Schirmer's test values might be of little clinical significance given the fact that baseline values may be very low.

Mucosal ulcers have been reported as a side effect with LEF in clinical trials. Allergic cutaneous reactions (rash,

purpura) were common (>10 %). These reactions were of mild to moderate severity. The hypothesis of that these side effects were due to the action of LEF on the cell cycle of the epithelium was suggested in addition to the possibility of being allergic cutaneous reactions [6].

The effect of LEF on the eye dryness in RA-sSS and RA patients is still not well described. This study was made to investigate the degree of eye dryness in RA-sSS and RA patients before and after 3 months of taking LEF.

Patients and methods

Seventy-five female patients with RA-sSS or RA, aged 21–70 years old, attending the outpatient clinic of the department of Rheumatology and Rehabilitation, College of medicine, Cairo University, over a 3-month period (1st October 2012–31st December 2012) were recruited in this study. All of them fulfilled the classification criteria for RA [7], and 45 patients of them were diagnosed in addition as having RA-sSS as they fulfilled the classification criteria for SS [8]. They met two of the following three features: (1) positive serum anti-SSA (Ro) and/or anti-SSB (La) (in 32 patients), or positive rheumatoid factor (RF) and ANA≥1:320) (in 14 patients); (2) labial salivary gland biopsy exhibition focal lymphocytic sialadenitis with a focus score ≥1 focus/4 mm^2 (in 21 patients); and (3) keratoconjunctivitis sicca with ocular staining score ≥3 (in 27 patients).

The inclusion criteria were patients aged >18 years with active disease [defined as a 28-joint disease activity score (DAS28) >1.6]. All patients with RA-sSS and RA had been taking methotrexate at a dose of 20 mg/week for more than 6 months before enrollment in the study.

All patients received a loading dose of LEF then were maintained at a dose of 20 mg/day in addition to methotrexate 20 mg/week for another 3 months. No other DMARDs were used by all patients. Patients with RA-sSS maintained using their local lubricants for eyes when needed.

The medical records of the patients were reviewed. All patients had full clinical examination and laboratory investigations. The modified disease activity score (DAS28) was calculated and modified Schirmer's-I test was performed. Assessment of all parameters was done to all patients before and after 3 months of taking LEF.

Exclusion criteria were patients with hepatic or renal impairment, severe infection (including hepatitis B or C or HIV), malignancy, significant cytopenias, concomitant heart and inflammatory bowel disease, and pregnancy or breastfeeding.

The protocol of the research was approved by the institution within which the work was undertaken and it conforms with the provisions of the world association's Declaration of Helsinki. All patients gave informed consent.

The modified disease activity score (DAS28) was calculated which considered 28 tender and swollen joint counts, general health (GH; patient assessment of disease activity using a 100-mm visual analogue scale (VAS) with 0=best, 100=worst), plus levels of an acute phase reactant. We used the erythrocyte sedimentation rate (ESR) measured in millimeters per hour. The reading of the first hour was taken. DAS28 values were calculated as follows:

$$DAS28(ESR)=0.56\times\sqrt{(TJC28)}+0.28\times\sqrt{(SJC28)}+0.014\times GH+0.70\times\ln(ESR)$$

where TJC=tender joint count and SJC=swollen joint count [9].

Modified Schirmer's-I test was performed for all patients before taking LEF and 3 months after adding it. Patients had not used tear substitutes for at least 1 h before examination. Patients dried their eyes carefully with a soft paper tissue; then the test strips—always starting with the right eye—were placed between the medial and lateral parts of the lower eyelid, and removed after 5 min. Anesthesia was not used. A positive result for reduced tear production was recorded if the strips were wetted 5 mm or less in one or both eyes, starting from the notch of the test strip corresponding to the inferior lid margin [10].

Statistical methods

The means and standard deviation (SD) were computed for the continuous variables. The difference between the means was tested by standard *t* test and *t* test for paired observations was used to compare the results before and after leflunomide use. For comparison of percentages chi-squared test ($\chi 2$) was applied. Differences were considered to be significant when *P* value was less than 0.05.

Results

Seventy-five female patients with RA were recruited in this study. All patients were Egyptians of Middle Eastern ethnicity. Forty-five patients had RA-sSS (group A), and 30 patients had RA (group B). The mean age of all patients was 48±11.8 (with range 21–70 years). Mean age of onset was 42.7±12.7 (with range 17–70 years). Mean disease duration at the time of enrollment in the study was 63.2±63.4 (with range 6–264 months). Keratoconjunctivitis sicca with ocular staining score ≥3 had been recorded previously in 27 patients. Labial salivary gland biopsy had been taken previously in 21 patients, and showed focal lymphocytic sialadenitis.

The general characteristics and the serological tests of all patients, patients with RA-sSS (group A), and patients with RA (group B) are shown in Tables 1 and 2.

The mean modified Schirmer's-I test in group A before having LEF was 3±1.6 compared to 1.9±1.6 after 3 months with $P<0.001$. The mean modified Schirmer's-I test in group B before having LEF was 21.3±10 compared to 19.9±11 after

Table 1 The general characteristics of all patients, patients with RA-sSS (group A), and patients with RA (group B)

	All patients *N*=75	Group A *N*=45	Group B *N*=30	Sig.
Age (years) (mean±SD)	48±11.8	50.1±12.2	44.8±10.5	NS
Age of onset (years) (mean±SD)	42.7±12.7	45.5±13.4	38.5±10.3	NS
Duration (months) (mean±SD)	63.2±63.4	54.7±61.8	76.1±64.6	$P<0.05$
Subcut. nodules (%)	6 (8)	3 (6.7)	3 (10)	NS
IPF (%)	1 (1.3)	1 (2.2)	0	NS
Pulmonary nodules (%)	1 (1.3)	0	1 (3.3)	NS
Morning stiffness (min)	24.6±38.3	19.5±38.2	29.3±36.3	NS
T 28	9.2±7.9	10.5±8	7.8±7.9	NS
E 28	4±5.9	5.2±6.9	2.7±4.5	NS
VAS	5±3	5.2±3	4.8±3	NS
ESR	59±30.4	60.2±30.8	58.1±29.4	NS
DAS28 (mean±SD)	4.7±1.4	4.9±1.5	4.5±1.4	NS

$P<0.05$ is considered significant

Subcut. nodules subcutaneous nodules, *IPF* interstitial pulmonary fibrosis, *T 28* tenderness in 28 joints, *E 28* effusion in 28 joints, *VAS* visual analogue scale, *ESR* erythrocyte sedimentation rate in first hour, *DAS 28* disease activity score 28, *sig.* significance

3 months of taking LEF with $P=0.053$ which approached statistical significance.

DAS28 in group A was 4.9±1.5 compared to 3.6±1.1 after 3 months ($P<0.001$), and in group B it was 4.5±1.4 compared to 3.6±1.3 after 3 months ($P<0.001$).

The data of group A and group B before and after having LEF with methotrexate for 3 months are shown in Table 3.

The side effects related to LEF were limited to headache in two patients (one in group A and one in group B) and diarrhea in one patient (group B) at the start of LEF intake, and those symptoms improved spontaneously while on continued drug intake.

After having LEF for 3 months, three patients (group A) had aggravation of keratocojunctivitis sicca with punctate erosions without actual peripheral ulcerative keratitis (PUK; Fig. 1a and b). Disease activity in those three patients was better controlled. DAS28 at the start of LEF was 4.36, 7.36, and 6.42 and became 3.6, 2.1, and 4.2 respectively after 3 months. Their main complaint was severe photophobia and blurred vision. The condition improved dramatically by stopping LEF and using topical lubricants.

One patient (group A) had the same complaint with DAS28 6.9 and was found to have PUK, denoting an exacerbation of disease activity (Fig. 2a). The condition did not improve by stopping LEF and improved only by taking corticosteroids 30 mg/day (Fig. 2b). Steroids were withdrawn gradually after improvement.

Table 2 RF, ANA, anti-SSA (Ro), and anti-SSB (La) in all patients, group A and group B

	All patients *N*=75	Group A *N*=45	Group B *N*=30	Sig.
RF *n* (%)	73 (97.3)	43 (95.6)	30 (100)	NS
ANA *n* (%)	18 (24)	14 (31.1)	4 (13.3)	NS
Anti-SSA (Ro) *n* (%)	32 (42.7)	32 (71.1)	0	$P<0.05$
Anti-SSB (La) *n* (%)	28 37.3)	28 (62.2)	0	$P<0.05$

$P<0.05$ is considered significant

RF rheumatoid factor, *ANA* antinuclear antibody, *sig.* significance

Discussion

This study was made to investigate the degree of eye dryness in RA-sSS and RA patients before and after 3 months taking LEF. The safety profile of LEF in the treatment of RA has been documented [6], as well as in pSS [5].

Leflunomide is an isoxazol derivate structurally unrelated to other immunomodulatory drugs, which can block the cytokine dependent T-cell growth [11]. The primary mode of action is arresting the cell cycle of stimulated lymphocytes by selective inhibition of de novo pyrimidine synthesis by blocking the enzyme dihydro-orotate dehydrogenase; thereby inhibiting B cell proliferation and cell cycle progression [12].

Sjögren's syndrome, an autoimmune disease characterized by exocrine gland dysfunction leading to dry mouth and dry eye diseases, is typified by progressive leukocyte infiltrations of the salivary and lacrimal glands [13].

Histologically, SS is characterized by extensive lymphocytic infiltration of the salivary glands [5], and the majority of infiltrating cells are T cells, predominantly $CD4^+$ T cells but also $CD8^+$ T cells, B cells, plasma cells, and macrophages [14].

Table 3 Modified Schirmer's-I test and DAS28 before and after taking leflunomide for 3 months in all patients, group A and group B

		All patients N=75	Group A N=45	Group B N=30
Modified Schirmer's (mean±SD)	Before leflunomide	10.4±11.1	3±1.6	21.4±10
	After leflunomide	9.1±11.3	1.9±1.6	19.9±11
Sig.		NS	P<0.001	NS
DAS 28	Before leflunomide	4.7±1.4	4.9±1.5	4.5±1.4
	After leflunomide	3.6±1.1	3.7±1	3.6±1.3
Sig.		P<0.001	P<0.001	P<0.001

P<0.05 is considered significant, P<0.001 is considered highly significant

Sig. significance

When patients with SS, either primary or secondary, are treated with LEF, it might ameliorate constitutional symptoms and halt ongoing damage in exocrine glands with residual function, resulting in improvement of function. Woerkom et al. reported by administration of LEF in patients with pSS modest improvements in dry eyes and mouth. However, they found that the increment in Schirmer's test values or parotid sialometry values might be of little clinical significance, given the fact that baseline values may be very low [5].

In the present study, there was a significant difference between the values of modified Schirmer's-I test in patients with RA-sSS before and 3 months after receiving LEF (P<0.001), and it approached statistical significance in the RA group. The disease activity assessed by DAS-28 showed a significant improvement in both patient groups (P<0.001).

By using LEF, improvements of the lacrimal gland function and of the eye dryness are expected, but this expectation is probably getting less when LEF is used with a non-functioning lacrimal gland. In other words, the lower the modified Schirmer's-I test values at the beginning of LEF intake, the less the improvement of the test value is expected to occur.

The very low baseline values of modified Schirmer's test was the finding presented by Woerkom et al. [5] as an explanation for the reported modest improvement in eye dryness in his pSS patients taking LEF.

The deterioration detected in our patients can be explained by the known effect of LEF on the skin and mucous

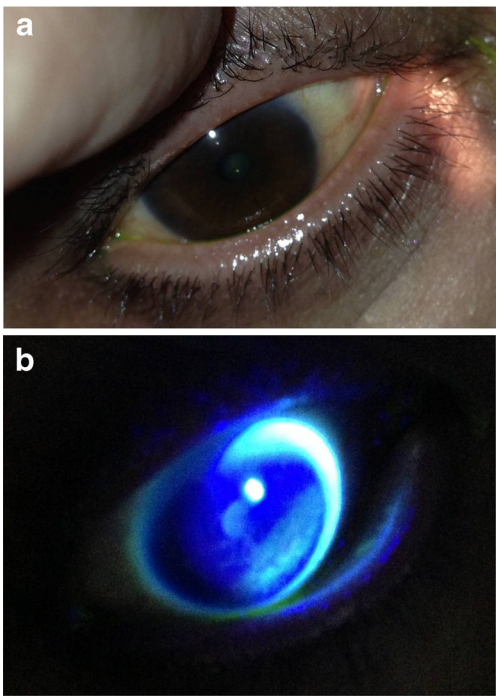

Fig. 1 **a** Keratoconjunctivitis sicca. Note the absence of evident corneal or conjunctival lesions, despite symptoms of photophobia and foreign body sensation. **b** The same eye as in **a**. Fluorescein dye has been instilled into the conjunctival sac, and the eye is examined with cobalt blue light. The inferior cornea shows confluent punctate corneal erosions staining green with fluorescein

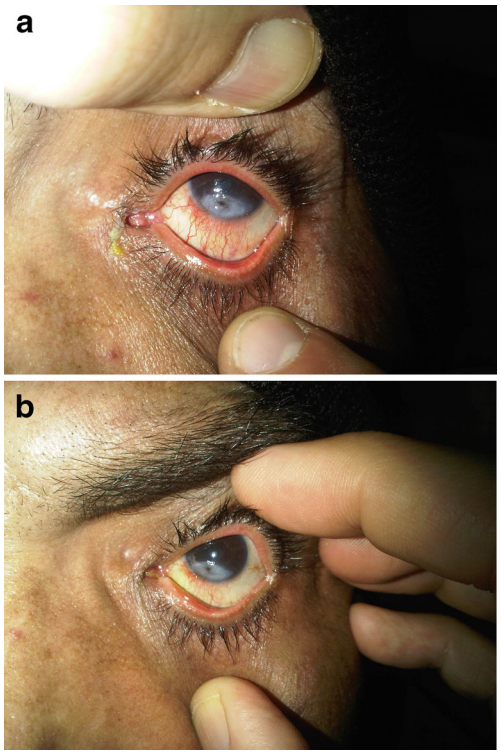

Fig. 2 **a** Peripheral ulcerative keratitis. Note the peripheral corneal infiltration (*white*), with thinning in the center (*brown*), with neighboring hyperemia of the conjunctiva and sclera. **b** The same eye as in **a** after 3 weeks of steroid therapy. There is decreased infiltration, decrease in the size of the thinned area, and marked resolution of the neighboring hyperemia

membrane. The main adverse effects of LEF include allergic skin reactions in addition to diarrhea, nausea, liver enzyme elevation, hypertension, and alopecia. A few cases of severe skin reactions such as toxic epidermal necrolysis have been reported [15].

Eight cases with skin necrosis due to LEF were reported in the literature [16]. Ulcerations may occur anywhere. Potentially life-threatening glomerulonephritis with mesangial deposits may be associated. Discontinuation of LEF followed by wash-out with cholestyramine allows healing. Corticosteroids or cyclophosphamide are sometimes necessary. Gros et al. [16] explained the occurrence of ulcerations as the result of excessive immunomodulation in the skin or from an inhibiting role of LEF on the epidermal growth factor receptor.

Leflunomide inhibits nitric oxide (NO) production in patients with active RA. Inhibition of NO synthesis may be one of the mechanisms responsible for the immunomodulatory activity of LEF [17]. It is present in tear and aqueous humor and is suspected of having an important physiological role in maintaining normal homeostasis of the ocular surface [18]. This possibility remains speculative, since we did not examine NO levels in the tears of the studied patients.

Three RA-sSS patients had an aggravation of keratocojunctivitis sicca with punctate erosions without actual PUK which improved dramatically by stopping LEF and using topical lubricants. The withdrawal of the drug once the keratitis was detected might have had a crucial effect in aborting the pathological condition before affecting the visual acuity of the patients catastrophically.

Punctate keratitis with keratinization of the cornea was reported in a patient with RA taking LEF by Hassikou et al. [15] and led to complete loss of vision.

This pattern of corneal affection, i.e. the punctate erosion without PUK, should be differentiated from the other pattern of the corneal affection known to occur in RA patients which is the PUK that denotes an exacerbation of disease activity. One RA-sSS patient in the recent study showed this disease complication and did not improve except by receiving steroids.

One limitation of this study is that it did not include another group of RA-sSS using methotrexate and placebo instead of methotrexate and leflunomide to clarify whether the deterioration seen is related to leflunomide rather than a natural disease progression over time.

In conclusion, we reported in this study a significant deterioration of eye dryness in patients with RA-sSS after 3 months of receiving LEF inspite of the significant improvement of their disease activity. This finding was not clearly detected in RA patients. Close monitoring of eye dryness changes by special tests in patients using LEF is recommended, especially in cases with RA-sSS having very low baseline values.

Disclosures None.

Conflicts of interest None.

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