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EFFICACY AND TOXICITY OF LEFLUNOMIDE IN PSORIATIC ARTHRITIS (INFLUENCE ON THE CLINICAL ACTIVITY AND LEVEL OF INFLAMMATION AND CONNECTIVE TISSUE DESTRUCTION MARKERS).

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Abstract

Objectives: To determine the features of Leflunomide (LF) use in combination with DMARDs and to evaluate impact of LF on the level of MMP-3 and pyridinoline in adults with psoriatic arthritis (PsA).

Methods: 63 PsA pts received LF alone (31 pts) or in addition to Methotrexate or Sulfasalazine (32 pts – COMBI group) were evaluated according to PsARC, PASI50, DAS response criteria, matrix metalloproteinase-3 (MMP-3) and pyridinoline levels before and after 3 months of the treatment.

Results: The efficacy in COMBI group was significantly higher on DAS (1.4 times), PASI (2.3 times) and MMP-3 dynamics (1.9 times) vs LF alone. Decrease of MMP-3 and pyridinoline was more striking in PsARC responders vs non-responders (by 28.6% and 10.9% vs 0% and 3.6%).

Conclusions: The efficacy of LF COMBI is higher vs LF alone in PsA. Reduction in MMP-3 and pyridinoline shows the ability of LF to lower inflammation and bone destruction levels in pts with PsA.

Key words: *leflunomide, psoriatic arthritis, matrix metalloproteinase-3, pyridinoline.*

Psoriatic arthritis (PsA) is a common, usually seronegative, inflammatory disease of the joints associated with psoriasis (Ps). About 7% of patients (pts) with arthritis are patients (pts) with PsA (Gladman et al 2005) and around 20–30% (range of prevalence estimates 6 to 39%) of patients with Ps develop PsA (Mease et al 2010). After 10 years of PsA 55% of pts have deformity more than 5 joints (Gladman 1994). Only the prompt diagnosis and prescribing of adequate therapy can prevent progression of disease and disability of pts. It is known that activation of T cells plays a key role in the immunopathogenesis of PsA (Kaltwasser et al 2007). Leflunomide (LF) acts precisely on this link of immunity. But until now remain under-explored the efficacy and toxicity of LF combination therapy (COMBI) with non-biological disease-modifying antirheumatic drugs (DMARDs) compared with LF alone in PsA. Furthermore conventional laboratory markers of inflammation (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)) in PsA worse correlate with the severity of lesions of the musculoskeletal system than in rheumatoid arthritis (RA) (Mease 2005), and that complicates the assessment of response to therapy in PsA.

On the role of a new marker of inflammation can be proposed matrix metalloproteinase-3 (MMP-3), which level is significantly higher in pts with RA and ankylosing spondylitis who have a lesion of peripheral joints (Ishiguro et al 1996, Vandooren et al 2004). In another study studied the effectiveness of TNF-α inhibitors in PsA pts was found correlation between dynamics of MMP-3 levels and Disease Activity Score (DAS)28 dynamics (van Kuijk et al 2010). The results of this study allowed the authors to suggest the possibility to use MMP-3 as a marker to identify potential new drugs for the treatment

in small groups of PsA pts because (of) CRP and ESR in these patients are not always elevated, even in the presence of active arthritis. It should be noted that the decrease in MMP-3 under the influence of golimumab treatment was also correlated with response to treatment (ACR20, ACR50 and DAS28) in patients with RA (Visvanathan et al 2010).

Determination of pyridinoline level in biological fluids is widely used to assess bone resorption in various diseases (Hubert et al 2001), because its serum level correlates with the most objective histomorphometrical indices of bone resorption (Ureña 1995). Increased level of pyridinoline before treatment is a predictor of intensive radiological progression in patients with RA receiving synthetic (Hashimoto et al 2009) and biological DMARDs (Hashimoto et al 2011). Prognostic significance of pyridinoline serum level is proved for patients with PsA - pyridinoline is more sensitive and specific to predict ACR20 and DAS28 responses in comparison with CRP in pts receiving golimumab (Wagner et al 2012).

The purpose of this study was: (1) to determine the features of LF use in combination therapy with non-biological DMARDs (Methotrexate (MTX) and Sulfasalazine (SS)); and (2) to evaluate the impact of LF on the level of MMP-3 and pyridinoline in adults with PsA.

MATERIALS AND METHODS

Patients

63 PsA pts with peripheral arthritis received LF (20 mg/day) alone (32 pts – MONO group) or in addition to MTX (mean dose 12.7±3.0 mg/week) (19pts) or SS (mean dose 2.0 g/day) (13pts) – COMBI group. LF administered in addition to the DMARDs because of insufficient treatment effect of SS or MT (saving or recurrence of clinically apparent synovitis, dactylitis, involvement of new joints). Duration of SS receiving ranged from 9 months to 5 years (average – 28.8 ± 18.4 months), MTX - from 6 months to 7 years (average – 34.8 ± 20.5 months.). Despite DMARDs use pts had number of tender and swollen joints ≥ 3 at screening visit. 60 PsA pts who achieved the end of the study (25 men and 35 women, mean age 49.7±10.7 years, mean arthritis duration 101.9±86.0 months) were assessed before and 3 months after changes in treatment (biological agents were not used, doses of corticosteroids (CS) and NSAIDs were not changed during study period). Three pts with PsA dropped out of the study early (2 weeks) because of LF discontinuation caused by its side effects. Pts of COMBI and MONO groups were comparable (Table 1).

Table 1

Demographic and clinical characteristic of PsA patients included in the study (M ±SD)

	MONO	COMBI	Total
male (%)	12 (40)	13 (43.3)	25 (41.6)
female (%)	18 (60)	17 (56.7)	35 (58.4)
age, years	49.4±12.3	49.9±9.1	49.7±10.7
PsA duration, months	92.5±91.5	111.3±80.54	101.9±86.0
CS use, pts (%)	2 (6.6)	8 (26.7)*	10 (16.7)
NSAID use, pts (%)	16 (53.3)	16 (53.3)	32 (53.3)
HAQ	1.20±0.51	1.08±0.48	1.14±0.50
ESR, mm/h	20.5±9.20	22.9±14.0	21.7±11.8

CRP, mg/l	9.63±4.39	10.0±4.32	9.84±4.32
MMP-3, ng/ml	14.6±6.28	19.8±9.22	17.2±8.28
pyridinoline, nM/l	2.06±0.71	2.06±0.57	2.06±0.63
DAS	4.07±0.89	4.49±0.97	4.28±0.95
DAS(CRP)	3.94±0.85	4.36±0.90	4.15±0.91
PASI	11.1±9.95	17.2±15.8	14.1±13.4

* $p<0.05$ vs MONO.

The only anamnestic index which differed was frequency of CS receiving: it was probably greater in COMBI group - 26.7% of pts compared with 6.6% in MONO.

Assessments

Joint tenderness score (228 max.) (JTS), joint swelling score (222 max.) (JSS), 44 swollen joint count, Ritchie index, duration of morning stiffness (minutes), Health Assessment Questionnaire (HAQ), Disease Activity Score (DAS) and DASCRP, ESR, serum levels of CRP (mg/l), MMP-3 (ng/ml) and pyridinoline (nM/l) were evaluated. Response was evaluated according to PsARC, DAS and DASCRP criteria, and PASI50 criteria for skin lesions, serum levels of CRP, ESR. Serum levels of CRP, MMP-3 and pyridinoline were conducted by enzyme-linked immunosorbent assay (ELISA) using test systems by "Biosource" (USA) and "Quidel" (USA).

Statistical analysis

All statistical analyses were performed on data collected through each patient's week 12 visit. Clinical efficacy analysis was performed using the modified intent-to-treat population, which included patients in the intent-to-treat population who had both a baseline assessment and at least one postbaseline assessment. The safety population comprised all patients who received any study treatment and at least one safety assessment.

The baseline demographics, disease activity and severity measures were compared between the two groups by Wald-Wolfowitz runs test, Δ of parameters absolute values significance were calculated by T-test, linear relationship between variables – by Pearson's correlation. The proportions of patients achieving PsARC, DAS, DASCRP and PASI50 responses at week 12 were analysed using a Fisher's exact test for comparing group differences. A p value <0.05 was considered significant.

RESULTS

LF alone vs LF in addition to MTX or SS

Among 63 pts with PsA included in the study completion rate after the 3-month observation was 95.2% (60 pts): 30pts in the MONO group and 30 – in COMBI respectively. After treatment in both groups took place positive changes in the basic clinical and laboratory parameters (Table 2): decreased number of swollen and tender joints - by 72.6% and 63.1%, almost three times shorter duration of morning stiffness, significantly improved functional ability of patients - HAQ fell by 37.8%, decreased of the ESR and CRP (by 20.6% and 11%), DAS and DASCRP - by 38.2% and 10.7%. All changes in both groups were statistically significant.

Table 2

Changes of clinical and laboratory parameters after 12 weeks of treatment in COMBI and MONO groups (M ±SD of absolute values Δ)

Characteristic	MONO	COMBI	All pts
joint tenderness score (228 max.)	-21.5±25.5**	-28.7±29.6**	-25.1±27.6**
joint swelling score (222 max.)	-6.33±7.67**	-12.3±11.1**§	-9.30±9.93**
morning stiffness, min	-46.7±79.2**	-133.6±175.3**§	-90.1±141.8**
HAQ	-0.38±0.45**	-0.26±0.34**	-0.32±0.40**
DAS	-1.08±0.70**	-1.52±1.08**§	-1.30±0.93**
DASCRP	-1.06±0.66**	-1.50±1.06**§	-1.28±0.90**
PASI	-3.96±6.31**	-8.97±10.0**§	-6.47±8.67**
ESR, mm/h	-2.70±7.35	-3.80±10.2*	-3.25±8.81**
CRP, mg/l	-1.36±3.52*	-1.35±4.17	-1.35±3.83**
MMP-3, ng/ml	-1.89±5.52	-4.83±7.69**§	-3.36±6.80**
pyridinoline, nM/l	-0.17±0.35**	-0.18±0.28**	-0.18±0.31**

* p<0.05, ** p<0.01 vs baseline values; § p<0.05 vs MONO.

The efficacy in COMBI group was significantly higher on the score of swollen joints (1.9 times), duration of morning stiffness (2.8 times), DAS and DASCRP (1.4 times for both) and PASI (2.3 times) compared with MONO group. Among the laboratory parameters only reduction of MMP-3 after treatment was significantly greater in COMBI group - 24.4% versus 13.0% compared with pts receiving LF alone.

Analysis of the results regarding to the skin lesions was conducted on the basis of data obtained in the survey of 59 pts because one patient was not detected psoriatic skin lesions at the start of treatment and during the study.

After 3 months of treatment PASI decreased in MONO and COMBI groups by 36.0% and 53.5% respectively (p <0.01, p between groups <0.05). PASI50 after a 3-month of treatment achieved 44.0% of pts: 51.7% in COMBI group comparing with 36.7% of responders among pts who receive LF alone (p <0.05).

The number of PsARC responders constituted 60.0% in MONO group vs 70.0% in COMBI (p>0.05). There was also no difference between 2 groups according to DAS response. But the number of pts who have had good and moderate response according to DASCRP and achieving PASI50 was significantly higher in COMBI group compared with MONO: 86.7% and 51.7% vs 63.3% and 36.7% respectively (p <0.05).

Markers of connective tissue destruction and clinical response

Highly probable changes in the basic clinical and laboratory parameters accompanied by decrease of MMP-3 (19.6%) and pyridinoline (8.6%) levels. More striking changes were in the group of PsARC responders (65% of pts). Levels of MMP-3 in this group decreased by 28.6%, pyridinoline - by 10.9% in comparison with 0% and 3.6% in the group of non-responders respectively (Table 3).

Table 3

Clinical and laboratory parameters before and after 12 weeks of treatment in PsARC responders and non-responders groups (M ±SD)

	PsARC non-responders		PsARC responders	
	Week 0	Week 12	Week 0	Week 12
joint tenderness score (228 max.)	31.3±15.1	27.7±18.0	58.0±32.5$^{\#}$	21.4±19.3**§§
joint swelling score (222 max.)	8.67±5.82	5.86±4.88*	17.6±12.5$^{\#}$	4.82±5.45**§
morning stiffness, min	92.7±153.5	51.7±62.7**	179.0±213. 6	62.4±80.0**§
HAQ	0.89±0.48	0.83±0.52	1.19±0.50	0.74±0.51**§§
DAS	3.74±0.70	3.25±0.82*	4.58±0.94$^{\#}$	2.83±0.85**§
DASCRP	3.61±0.61	3.09±0.80*	4.44±0.92$^{\#}$	2.75±0.84**§
ESR. mm/h	22.3±14.4	21.2±12.3	21.4±10.3	17.0±7.61*
CRP, mg/l	9.39±4.71	7.52±4.04**	10.1±4.14	9.00±4.05*
MMP-3, ng/ml	15.3±6.90	15.3±5.74	18.2±8.80	13.0±4.59**§§
pyridinoline, nM/l	1.96±0.56	1.89±0.46	2.11±0.67	1.88±0.65**§

* p<0.05, ** p<0.01 vs baseline values; §p<0.05, §§ p<0.01 vs PsARC non-responders.

At the same time a significantly difference in the dynamics of ESR and CRP between the groups of PsARC non-responders and responders was not registered.

Positive dynamics of inflammation and connective tissue destruction markers accompanied by highly probable changes in key clinical parameters in pts achieving PsARC response: decreased JSS and JTS - by 72.6% and 63.1%, there was almost three times shorter duration of morning stiffness, significantly improved functional ability of patients - HAQ index fell by 37.8%, also reduced the value of DAS and DASCRP - by 38.2% and 10.7%. In pts who did not meet the PsARC response criteria also observed decrease in the number of swollen joints (11.3%), duration of morning stiffness (by 44.3%), lower DAS and DASCRP (13.0% and 14.3% respectively).

Prior to treatment the levels of pyridinoline and MMP-3 in PsARC responders were 2.11 nM/l and 18.2 ng/ml and were significantly higher compared with a group of PsARC non-responders by 7.6% and 18.9% respectively.

In the correlation analysis revealed that changes in MMP-3 positively correlated with the dynamics of the number of swollen joints ($r = 0.29$, $p < 0.03$) and duration of morning stiffness ($r = 0.52$, $p < 0.001$). It should be noted that these clinical indicators were traditionally considered the most sensitive marker of severity (prevalence and activity) of inflammatory joint damage. The dynamics of any other

laboratory parameters (ESR, CRP, pyridinoline) was not correlated with changes in MMP-3 level or the dynamics of joint and skin damage.

Safety

During the study 3 pts prematurely (up to 4 weeks of treatment) discontinued the drug because of side effects (one patient because of dermatitis, sensory neuropathy, and by increasing the level of ALT more than 3 times above the ULN). In 14 pts (23.3%) were observed adverse events (dyspepsia, alopecia, dermatitis, increased ALT/AST less than 2 times above the ULN, cardialgia, neuropathy) that did not require discontinuation. Among all 17 cases of adverse events 58.8% occurred in COMBI group and 41.2% in group of LF MONO ($p > 0.05$). The treatment tolerability was good (adverse events not observed or observed single mild adverse event that does not affect the physical activities or quality of life) in 73% of cases.

DISCUSSION

We present the first study to investigate the efficacy of LF in adults with PsA with evaluation of LF impact on the level of MMP-3 and pyridinoline. Decrease in levels of these parameters under the influence of treatment may indicate the ability of therapy to slow down the rate of destruction of connective tissue including bone tissue. Ability to use pyridinoline as a marker of bone resorption has been demonstrated for patients with RA, its serum levels changes correlate with changes in intensity of osteoporosis (based on computed X-ray densitometry of hands) and radiographic progression (Jensen et al 2004). It also should be noted that according to the literature there are grounds for MMP-3 use not only as a marker of connective tissue inflammation, but also as a marker of bone destruction. It is particularly known about correlation between lower levels of MMP-3 and radiological progression in RA pts (Young-Min et al 2007). The possibility of such connection has genetic basis. In RA study was revealed the association of polymorphism of the gene encoding the synthesis of MMP-3 with radiographic progression (Nemec et al 2007).

Mechanism of LF action on the intensity of bone destruction is pathogenetically substantiated - in RA pts LF (unlike MTX) increases transendothelial migration of peripheral blood mononuclear cells (Grisar et al 2004), which produce the vast majority of pro-inflammatory cytokines and are precursors of osteoclasts. As a result of their actions occurs joint destruction (Firestein et al 1990). In addition, there was described clinical case when in PsA pt under the influence of LF within 1 year slowed radiographic progression and even partial bone erosions repair was observed (Cuchacovich & Soto 2002).

In our study clinical response was fairly high as for non-biological DMARDs, but 60.0% of PsARC responders among LF alone pts are virtually identical to the results obtained in a randomized placebo-controlled multicenter study - 59% of pts achieved PsARC response after 6 months of LF treatment (Kaltwasser et al 2004). Even greater was PsARC response according to the results of the recently completed European prospective observational study that evaluated the effectiveness of LF in 514 PsA pts. After 24 weeks of treatment the number of PsARC responders was 86.4% (Behrens et al 2012).

In the current study we found that combination therapy with adding of LF should be used in pts with PsA who have inadequate response to treatment with MTX or SS. The use of the combination therapy in our study was more efficiently compared with LF alone. There were no striking differences between the toxicity of the combination therapy and LF monotherapy.

It is worth mentioning that among the PASI50-responders was significantly less the number of pts receiving CS - 11.5% compared with 21.2% in the "non-responders" group ($p < 0.05$).These

differences may be associated with the development of CS-induced psoriatic skin lesions (Ritchlin et al 2003).

Among the laboratory parameters serum level of MMP-3 in the best way reflects the dynamics of the clinical parameters of joint inflammation in PsA pts. The dynamics of traditional laboratory parameters (ESR, CRP) was not correlated with changes in MMP-3. Such correlation interaction is typical for other spondylarthropathies. It is known that the level of MMP-3 correlated with the severity of inflammatory infiltration and does not correlate with ESR and CRP in patients with ankylosing spondylitis (Vandooren et al 2004).

In summary, significant reduction in levels of MMP-3 and pyridinoline under the influence of treatment shows the ability of LF to lower levels of inflammation and bone destruction in patients with PsA, and greater anti-destructive effect should be expected in pts who receive combination therapy compared with LF alone. Larger studies with comparison of MMP-3 and pyridinoline dynamics with changes in results of imaging techniques (e.g. CT scans with high resolution) under the influence of DMARDs are indicated to determine whether MMP-3 and pyridinoline could be a useful addition to the diagnostic armamentarium in this disease.

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