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INFLUENCE OF LEFLUNOMIDE ON THE CLINICAL ACTIVITY, LEVEL OF INFLAMMATION AND BONE DESTRUCTION MARKERS IN PSORIATIC ARTHRITIS

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

Background: About 7% of patients (pts) with arthritis are pts with psoriatic arthritis (PsA) [1] and around 20–30% (range of prevalence estimates 6 to 39%) of pts with psoriasis (Ps) develop PsA [2]. After 10 years of PsA 55% of pts have deformity of more than 5 joints [3]. The activation of T cells plays a key role in the immunopathogenesis of PsA [4]. 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) in PsA. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) in PsA correlate worse with the severity of lesions of the joints than in RA [5]. As a new marker of inflammation and bone resorption can be proposed matrix metalloproteinase-3 (MMP-3) and pyridinoline.

Objectives: To evaluate the impact of LF combination therapy with DMARDs on the clinical activity and level of MMP-3 and pyridinoline in adults with PsA.

Methods: 63 PsA pts with peripheral arthritis received LF (20 mg/day) alone (32 pts – MONO group) or in addition to Methotrexate (mean dose 12,7±3,0 mg/week) (19) or Sulfasalazine (mean dose 2.0 g/day) (13) (COMBI group). Response was evaluated according to PsARC and PASI criteria, Health Assessment Questionnaire (HAQ), Disease Activity Score (DAS) and DAS CRP, serum levels of CRP, ESR, MMP-3 and pyridinoline (test systems by "Biosource" (USA) and "Quidel" (USA)) at baseline and after 3 months of the treatment.

Results: Among 63 pts with PsA completion rate after the 3-month observation was 95.2% (60 pts): 30pts in the MONO group and 30 – in COMBI. After treatment in both groups took place positive changes in the basic clinical and laboratory parameters (Table 1): 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 – HAQ fell by 37.8%, decreased of the ESR and CRP (by 20.6% and 11%), DAS and DAS CRP – by 38.2% and 10.7%. All changes in both groups were statistically significant.

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. The number of PsARC and PASI50 responders constituted 60.0% and 51.7% in MONO group vs 70.0% and 36.7% in COMBI respectively ($p > 0.05$). The number of pts who have had good and moderate response according to DASCRP was higher in COMBI group compared with MONO: 86.7% vs 63.3% (ц = 2.15, $p < 0.05$). That was 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% vs 3.6% and 0% in the group of non-responders respectively (Table 2).

Table 1

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

Characteristic	MONO	COMBI	All pts
Tender joints score (228 max.)	-21,5±25,5**	-28,7±29,6**	-25,1±27,6**
Swollen joints 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**
DAS CRP	-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, мм/h	-2,70±7,35	-3,80±10,2*	-3,25±8,81**
CRP, мg/l	-1,36±3,52*	-1,35±4,17	-1,35±3,83**
MMP-3, нgr/мl	-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 COMBI.

Table 2

Laboratory parameters before and after 12 weeks of treatment in PsARC responders and non-responders groups (M ±σ)

	PsARC responders		PsARC non-responders	
	Week 0	Week 12	Week 0	Week 12
ESR, мм/h	21,4±10,3	17,0±7,61*	22,3±14,4	21,2±12,3
CRP, мg/l	10,1±4,14	9,00±4,05*	9,39±4,71	7,52±4,04**
MMP-3, нгг/мl	18,2±8,80	13,0±4,59**§§	15,3±6,90	15,3±5,74
Pyridinoline, nM/l	2,11±0,67	1,88±0,65**§	1,96±0,56	1,89±0,46

* – p<0,05, ** – p<0,01 – significance of changes compared with baseline values??; § – p<0,05, §§ – p<0,01 compared with PsARC non-responders.

Significant difference in the dynamics of ESR and CRP between the groups of PsARC non-responders and responders was not registered and significant decrease of CRP level in PsARC non-responders was 19.9%. Before the treatment the levels of pyridinoline and MMP-3 in PsARC responders were higher compared with a group of PsARC non-responders by 7.6% and 18.9%. The 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). Reduction of MMP-3 was significantly greater in COMBI group – 24.4% vs 13.0% in MONO.

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%) observed adverse events 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 in 73% of cases.

Conclusions: In pts with PsA who have inadequate response to treatment with Methotrexate or Sulfasalazine combination therapy with adding of LF should be used. The use of the combination therapy is more efficiently compared to monotherapy. There were no striking differences between the toxicity of the COMBI and MONO groups. Among the laboratory parameters serum level of MMP-3 more fully reflects the dynamics of the clinical parameters of joint inflammation. 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.

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ВПЛИВ ЛЕФЛУНОМІДУ НА КЛІНІЧНУ АКТИВНІСТЬ, РІВЕНЬ МАРКЕРІВ ЗАПАЛЕННЯ ТА КІСТКОВОЇ ДЕСТРУКЦІЇ У ХВОРИХ З ПСОРІАТИЧНИМ АРТРИТОМ

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Резюме: Вивчено вплив лефлуноміду (ЛФ) в складі комбінованої базисної терапії (КБТ) та як монотерапії у 63 хворих з псоріатичним артритом (ПсА). Ефективність ЛФ в комбінації з сульфасалазином чи метотрексатом є вищою порівняно з монотерапією ЛФ стосовно ураження суглобів (вища частота досягнення доброї та задовільної відповіді за DAS(СРБ)), шкіри (більша кількість хворих – "відповідачів" за PASI 50) та зниження рівня матриксної металопротеїнази-3. Суттєвих відмінностей у переносимості ЛФ як монотерапії та у складі КБТ немає

Ключові слова: лефлуномід, псоріатичний артрит, матриксна металопротеїназа-3, піридинолін.

ВЛИЯНИЕ ЛЕФЛУНОМИДА НА КЛИНИЧЕСКУЮ АКТИВНОСТЬ, УРОВЕНЬ МАРКЕРОВ ВОСПАЛЕНИЯ И КОСТНОЙ ДЕСТРУКЦИИ У БОЛЬНЫХ С ПСОРИАТИЧЕСКИМ АРТРИТОМ

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Резюме: Изучено влияние лефлуномида (ЛФ) в составе комбинированной базисной терапии (КБТ) и в качестве монотерапии у 63 больных с псориатическим артритом (ПсА). Эффективность ЛФ в сочетании с сульфасалазином или метотрексатом выше в сравнение с монотерапией ЛФ относительно поражения суставов (выше частота достижения хорошего и удовлетворительного ответа по DAS(СРБ)), кожи (большее количество больных – "ответчиков" по PASI 50) и снижения уровня матриксной металлопротеиназы-3. Существенных различий в переносимости ЛФ в качестве монотерапии и в составе КБТ нет.

Ключевые слова: лефлуномид, псориатический артрит, матриксная металлопротеиназа-3, пиридинолин.