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Effects of leflunomide therapy on the serum lipid profile in patients with rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic, autoimmune disease, characterised by chronic, synovial inflammation, cartilage and bone degeneration, resulting in joint destruction. Both inflammation and destruction lead to functional impairment and disability. RA is also associated with enhanced morbidity and premature mortality of patients (pts) (1). The increased mortality is largely attributed to cardiovascular disease (CVD), primarily coronary heart disease (2). It might be due to increased prevalence of cardiovascular risk factors, such as atherogenic lipid profile. An accelerated atherosclerosis in RA pts is linked with the persistent inflammatory reaction. It has been reported that disease modifying antirheumatic drug (DMARD) treatment has a beneficial influence on the lipid profile and preventing CVD in RA pts (3).

Leflunomide (LEF) is a new DMARD, converted through the liver into its active metabolite A77 1726, which has antiinflammatory and immunomodulatory properties. LEF is a *de novo* pyrimidine synthesis inhibitor, by blocking the rate-limiting enzyme dihydrorotate dehydrogenase (4, 5). Its targets of action are lymphocyte proliferation and activation, cell migration and activation of transcription factor NF-κB. LEF is also *in vivo* and *in vitro* cyclooxygenase 2 (COX-2) inhibitor. (5, 6). Clinical observations demonstrated that LEF usually provides a distinct and early clinical improvement in RA therapy, which is connected with the significant reduction of acute phase proteins and pro-inflammatory cytokine concentrations (1, 4, 6). LEF is now an approved, safe and effective agent in long-term treatment of RA (4, 6).

The objective of the study was to investigate whether LEF treatment may modify the lipid profile and the atherogenic index in RA pts.

MATERIAL AND METHODS

The study group consisted of 76 RA pts treated in the Department of Rheumatology and Connective Tissue Diseases, Medical University of Lublin, and in the out-patients' clinic, between January 2005 and November 2006. All pts fulfilled the 1987 ACR criteria for RA (7) and were treated with LEF (20 mg/day) and observed prospectively for up to 24 months. Patients' charts were reviewed for demographic information and clinical diagnosis. Clinical and laboratory data were collected and used to determine the disease activity score, using 28 joints score (DAS28). DAS28 was calculated as a primary outcome measure. Serum samples to assess: total cholesterol (TC), high-density lipoprotein cholesterol (HDL), triglycerides (TG) and the atherogenic index (ratio TC/HDL

cholesterol) were taken at baseline and at month 3, 6, 12 and 18. Serum C reactive protein (CRP), erythrocyte sedimentation rate (ESR) were determined at the same time. Lipids were determined using the standard enzymatic technique. LDL-cholesterol (LDL-C) was calculated according to the Friedewald formula. Serum levels of CRP were measured by immunoturbidimetric assay, with the upper limit of the normal range at 5 mg/l.

The group consisted of 66 women (86.8%) and 10 men (13.2%). The mean (SD) age was 54.5 (10.8) (range 28–77 years); the mean (SD) disease duration was 135.4 (95.1) months (range 7– 420). Long-standing RA (disease duration >10 years) was observed in 34 pts (44.7%). The mean (SD) duration of LEF therapy was 13.5 (5, 8) months (range 3–24). LEF treatment is still continued in 52 pts (68.4%). The therapy was interrupted: in 9 pts (11.9%) due to adverse events; in 14 pts (18.4%) due to non-satisfactory clinical effect and in 1 patient (1.3%) due to planned conception.

Statistics. The χ^2 test was used for qualitative parameters. Correlation between quantitative variables was assessed by Spearman's correlation coefficients. To compare subgroups of pts with long-standing RA and with shorter disease duration, Student's test or non-parametric Mann-Whitney *U* test, respectively, were used. For all tests, *P* values less or equal to 0.05 were considered significant.

RESULTS

The mean (SD) DAS-28 at the baseline was 6.0 (1, 2) (range 3.2–8.3) and decreased significantly in consecutive months to: after 3 months: 4.7 (1, 2) (range 2.4–7.3); after 6 months: 4.4 (1, 3) (range 1.8–7.4); after 12 months: 4.2 (1, 2) (range 1.6–7.3); after 18 months: 3.9 (1.1) (range 2.0–6.1) ($p<0.01$) (Table 1). The mean values of CRP and ESR decreased significantly in consecutive months, as well (Table 1).

The mean levels of TC were 201.3 ± 40.2 mg/dl at the baseline and increased significantly after LEF treatment to: 211.1 ± 45 mg/dl in month 3; 217.6 ± 48.3 mg/dl in month 6; 220.8 ± 51.9 mg/dl in month 12; 226.9 ± 39.7 mg/dl in month 18 ($p<0.03$). However, also the mean levels of HDL cholesterol were significantly higher after LEF therapy: 58.3 ± 13.6 mg/dl at the baseline; 65.7 ± 16.5 mg/dl in month 3; 64.2 ± 22.2 mg/dl in month 6; 63.2 ± 15.3 mg/dl in month 12 ($p<0.01$) (Table 1). Only at the baseline HDL cholesterol levels were higher in pts with long-standing RA (63.2 ± 15.4 mg/dl vs 54.7 ± 11.0 mg/dl; $p<0.01$). There was a an inverse correlation at baseline between HDL levels and CRP and ESR values ($p<0.01$).

The atherogenic index at the baseline was 3.5 ± 0.8 and decreased significantly to 3.3 ± 0.9 in month 3 ($p<0.02$). In consecutive months the index increased and was not significantly changed in comparison to the baseline value (Table 1).

The mean TG baseline level was 125.2 ± 59.2 mg/dl and did not change significantly during the LEF therapy (Table 1). Levels of TG were significantly higher in pts with high disease activity (DAS28 ≥ 5.1) than in pts with moderate disease activity (DAS28 < 5.1) at the baseline (135.2 ± 62.3 mg/dl vs 90.5 ± 27.6 mg/dl; $p<0.02$) and in month 6 (152.0 ± 59.8 mg/dl vs 109.9 ± 41.8 mg/dl; $p<0.02$) (Fig. 1). The value of DAS28 at the baseline correlated positively with levels of TG at the baseline and at month 6 ($p<0.01$), as well as with TC at months 3 and 6 ($p<0.02$).

Table 1. Clinical and biochemical values of the studied patients

Value/Month	0	3	6	12	18
DAS28	6.0 ± 1.2	4.7 ± 1.2 p<0.01	4.4 ± 1.3 p<0.01	4.2 ± 1.2 p<0.01	3.9 ± 1.1 p<0.01
CRP (mg/l)	34.1 ± 29.9	17.6 ± 18.3 p<0.01	16.4 ± 20.4 p<0.01	16.8 ± 25.6 p<0.01	9.2 ± 8.3 p<0.01
ESR (mm/h)	51.9 ± 26.8	38.6 ± 25.3 p<0.01	39.1 ± 25.4 p<0.01	32.8 ± 23.5 p<0.01	33.2 ± 24.7 p<0.01
TC (g/dl)	201.3 ± 40.2	211.1 ± 45.0 p<0.04	217.6 ± 48.3 p<0.02	220.8 ± 51.9 p<0.01	226.9 ± 39.7 p<0.03
HDL (g/dl)	58.3 ± 13.6	65.7 ± 16.5 p<0.01	64.2 ± 22.2 p<0.02	63.2 ± 15.3 p<0.01	59.5 ± 79.8 NS
Index TC/HDL	3.5 ± 0.8	3.3 ± 0.9 p<0.03	3.6 ± 1.0 NS	3.6 ± 0.9 NS	4.1 ± 0.9 NS
TG (mg/dl)	125.2 ± 59.2	137.2 ± 74.8 NS	142.2 ± 58.3 NS	129.7 ± 50.5 NS	151.9 ± 53.7 NS

Values are: mean ± SD; NS: statistically non-significant

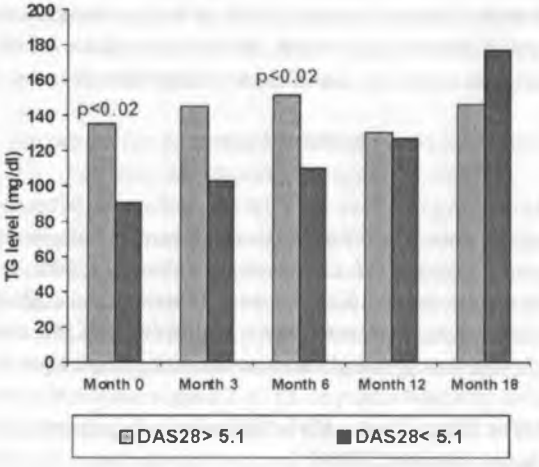

Fig. 1. TG levels in RA pts with high and moderate activity

DISCUSSION

Our results demonstrate clinical improvements in the signs and symptoms of RA as well as in laboratory parameters of disease activity, that were achieved with LEF treatment. Significant improvement, characterized by reduced values of DAS28, ESR and CRP, was observed in month 3 and was sustained during the whole follow-up.

Our results are consistent with the reports in the literature, which confirm effectiveness and safety of LEF treatment in RA pts (1, 6, 8). Smolen and Emery reported that LEF was significantly superior to placebo and comparable to sulphasalazine and methotrexate (MTX). They emphasized that LEF retarded radiographic progression and improved functional ability of RA pts (16). Clinical response to LEF occurred quickly and improvement was maintained for up to 5 years (4, 6, 8).

In our pts, the reduction of RA activity during the LEF therapy, was associated with changes in the lipid profile. The beneficial changes were observed mostly in the first few months of treatment.

The mean values of HDL and TC increased significantly in consecutive months, up to month 12. However, the best results were noticed in month 3, when atherogenic index decreased significantly in comparison to the baseline. In the following months the value of atherogenic index increased, which was due to the rise of TC level. Higher disease activity characterized by DAS28 was correlated positively with levels of TG and TC. Additionally we noted an inverse correlation between HDL levels and CRP and ESR levels.

RA pts in remission or with controlled disease show an increase in HDL levels and a reduction in the atherogenic index compared with pts with active disease (10. In the literature there are some reports concerning effects of antirheumatic therapy on serum lipid levels in RA pts (3, 9, 10). However, we did not find any reports concerning effects of LEF therapy. Georgiadis et al. reported a significant reduction of the atherogenic index, after treatment of early RA with MTX and prednisone. These changes were inversely correlated with values of CRP and ESR (10). Park et al. reported that in newly diagnosed RA, treatment with DMARDs (MTX in 93%) brought clinical improvement, associated with beneficial changes in the lipid profile, mainly in those with good response to the therapy (9). They suggested that lipid levels correlated with RA disease activity and effective control of RA can reverse adverse lipid profiles without using lipid-lowering drugs (9). We found that LEF treatment has, at least partially, beneficial effect on the lipid profile in RA pts. The effect was associated with decreased disease activity and clinical improvement. Better control of RA activity is associated with a better lipid profile, which may reduce the risk of cardiovascular disease.

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SUMMARY

Cardiovascular morbidity and mortality seems to be enhanced in rheumatoid arthritis (RA) patients (pts). Leflunomide (LEF) is a disease modifying antirheumatic drug (DMARD) that usually provides a distinct clinical improvement in RA therapy. The objective of the study was to investigate whether LEF treatment may modify the lipid profile in RA pts. The study group consisted of 76 RA pts. Pts were treated with LEF for 3–24 months. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL), triglycerides (TG) and the atherogenic index (ratio TC/HDL), C reactive protein (CRP), erythrocyte sedimentation rate (ESR) were measured at the baseline and at month 3, 6, 12 and 18. Disease activity 28 joints score (DAS28) was calculated as a primary outcome measure. The value of DAS-28 decreased significantly in consecutive months. The mean levels of TC and HDL increased significantly after LEF treatment. There was an inverse correlation at the baseline between HDL levels and CRP and ESR values. The atherogenic index decreased significantly in month 3, but in consecutive months it was not changed in comparison to the baseline. The mean TG levels did not change significantly during the LEF therapy. The value of DAS28 correlated positively with levels of TG at the baseline and at month 6, as well as with TC at months 3 and 6. LEF treatment was associated with decreased disease activity and significant increase in both TC and HDL levels. The atherogenic index did not change significantly. Before the treatment TG levels correlated positively and HDL correlated inversely with the disease activity.

Zmiany profilu lipidowego podczas leczenia leflunomidem
chorych na reumatoidalne zapalenie stawów

U chorych na reumatoidalne zapalenie stawów (RZS) obserwuje się zwiększone ryzyko zachorowania i umieralności z powodu chorób układu sercowo-naczyniowego. Leflunomid (LEF) jest lekiem modyfikującym przebieg choroby (LMPCh), który zwykle przynosi wyraźną poprawę kliniczną w leczeniu RZS. Celem pracy była ocena wpływu leczenia LEF na profil lipidowy u chorych na RZS. Oceniano grupę 76 chorych na RZS. Chorzy byli leczeni LEF przez 3–24 miesięcy. Podczas kolejnych wizyt w miesiącach 3, 6, 12, 18 przeprowadzono oznaczenia stężeń: cholesterolu całkowitego (TC), frakcji cholesterolu HDL (HDL), trójglicerydów (TG), białka C reaktywnego (CRP) oraz określono indeks aterogenny (stosunek TC/HDL) i szybkość opadania krwinek czerwonych (OB). Skuteczność leczenia oceniano za pomocą wskaźnika aktywności choroby dla 28 stawów (*disease activity score*, DAS-28). Aktywność choroby oceniana za pomocą DAS-28 zmniejszała się znacząco w kolejnych miesiącach leczenia. Średnie stężenia TC i HDL wzrosły istotnie podczas leczenia LEF. Zaobserwowano ujemną korelację pomiędzy wyjściowym stężeniem HDL i stężeniem CRP oraz wartością OB. Indeks aterogenny zmniejszył się znacząco w trzecim miesiącu, jednak w kolejnych okresach leczenia nie różnił się istotnie od wartości wyjściowej. Średnie stężenie TG nie zmieniło się istotnie podczas leczenia LEF. Wartości DAS-28 korelowały dodatnio ze stężeniem TG w miesiącach 0 i 6, jak również ze stężeniem TC w miesiącach 3 i 6. Leczenie LEF wiązało się ze zmniejszeniem aktywności choroby i znaczącym wzrostem stężeń TC i HDL. Indeks aterogenny nie zmienił się znacząco. Przed podjęciem leczenia LEF stężenie TG korelowało dodatnio, a HDL ujemnie z aktywnością choroby.