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Brief communication

Lipid profile and anti-TNF-α use

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ABSTRACT

The use of anti-TNF-α has been associated with several changes in lipid profile, although some study results are conflicting. The knowledge of this fact is of great importance when one observes at the association between rheumatic diseases and accelerated atherogenesis. The aim of this analysis was search for changes in lipid profile in anti TNF-α users in the population of Southern Brazil and its association with duration of use, indications, patient gender and type of anti-TNF. For this purpose, we studied the profiles of total cholesterol (TC), HDL cholesterol (HDLc), LDL cholesterol (LDLc), atherogenic index (ATI) and triglycerides (TGs) of 58 patients (42 with rheumatoid arthritis and 16 with spondyloarthritis) before and after using this drug for a median of 16.0 months. There were no changes in the levels of TC, HDLc, LDLc and ATI (P = NS). However, there was a significant increase in TG levels (P = 0.03). The median difference between first and second TG measurements was 16 mg/dL and this increase was not associated with gender, time of use, use indication or type of anti TNF-α (P = NS). It was concluded that the use of anti TNF-α is associated with increased values of TG.

Perfil lipídico e uso de anti-TNF-α

Palavras-chave:
Anti-TNF-alfa
Artrite reumatoide
Espondiloartrites
Aterogênese

RESUMO

O uso do anti-TNF alfa tem sido associado a várias alterações no perfil lipídico, embora o estudo dessas alterações tenha gerado resultados que ainda são conflitantes. O conhecimento desse fato é de grande importância quando se observa a associação entre doenças reumáticas e aterogenêse acelerada. Esta pesquisa foi feita com o intuito de verificar alterações no perfil lipídico de usuários de anti-TNF-α na população do sul do Brasil e sua associação com tempo de uso, indicações, gênero do paciente e tipo de anti-TNF. Para tanto, analisaram-se os perfis de colesterol total (TC), HDL colesterol (HDLc), LDL colesterol (LDLc), índice aterogênico (IAT) e triglicerídeos (TGs) de 58 pacientes (42 com artrite reumatoide e 16 com espondiloartrites) antes e depois do uso desse medicamento por um tempo mediano de 16,0 meses. Não se observaram alterações nos níveis de CT, HDLc, LDLc e IAT (P = NS). Todavia, houve um aumento significativo nos níveis de TGs (P = 0,03). A diferença mediana dos valores de TGs entre primeira e segunda medidas foi de 16 mg/dL, e esse aumento não estava associado ao gênero do paciente, tempo de uso, indicação de uso ou tipo de anti-TNF-α (P = NS). Concluiu-se que o uso de anti TNF-α está associado com aumento nos valores de TGs.

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Introduction

There is an increased cardiovascular risk in chronic inflammatory diseases such as rheumatic ones.[1] This is evident in patients with rheumatoid arthritis (RA), when one observes that patients have a 1.7-fold higher chance of having myocardial ischemia than the general population, a risk comparable to that shown by patients with type 2 diabetes mellitus.[2]

The knowledge that inflammation and atherogenesis are closely associated has generated a new way to approach these patients from the therapeutic point of view, aiming to control the inflammatory activity and reduce these complications. Thus, the aggressive use of traditional DMARDs or new drugs such as biological ones has been offered as an attractive option.[3,4] In a study of 49 patients with RA, in which 30 were treated satisfactorily with anti-TNF-α for 12 months, it was observed that the thickness of the carotid intima-media in subjects who received this medication and monitored the disease was significantly smaller than in those not receiving it.[4] This effect was attributed to the improvement in the inflammatory process. However, the anti TNF-α drugs also seem to have a direct effect on lipid metabolism.[5]

The administration of TNF-α to rodents is followed by an increase in hepatic synthesis of cholesterol and its blood concentrations, due to an increase in the activity of HMG-CoA reductase. [5] This increase is not higher only because HMG-CoA activity is partially offset by the production and synthesis of squalene synthase (also known as farnesyl-diphosphate farnesyltransferase), which is the first enzyme to act on the mevalonate pathway.[5]

However, in humans and other primates, the administration of this cytokine has not caused changes in the levels of total serum cholesterol (TC) and LDL-cholesterol (LDL-c).[5] Patients with cancer undergoing TNF-α infusion for five days showed a 7% reduction in TC and 43% reduction in HDL-cholesterol (HDL-c).[6] In addition to these changes, TNF-α increases levels of triglycerides (TGs) by a lipolytic action in adipose tissue, as well as by the increased hepatic synthesis of TGs, caused by an increase in the concentration of their precursors.[5] This cytokine also promotes decreased clearance of TG-rich lipoproteins.[5]

The study of the lipid profile after administration of anti TNF-α in patients with spondyloarthritis (SA) and RA has shown conflicting findings. Van Eijk et al.[7] studied 92 patients with SA and observed increase in TC, HDL-c and apolipoprotein A1, resulting in a better TC/HDL-c ratio. Castro et al.[8] studied 15 patients with psoriatic arthritis and observed increased levels of TGs after 3 months of infliximab. Results of a meta-analysis[9] of other 32 studies (13 of which were prospective) showed that inhibition of TNF-α in RA patients was associated with increased levels of TC and HDL-c, whereas LDL-c and the atherogenic index remained unchanged; the prolonged use resulted in increased levels of TGs and decreased Apo B/Apo A ratio.

In this context, the present study aims to analyze the lipid profile in the local population of patients with RA and spondyloarthritis (SA) treated with anti TNF-α.

Methods

This is a retrospective study, which was approved by the local Research Ethics Committee. Patients were included when they had used anti-TNF-α drugs (infliximab, etanercept and adalimumab) for more than three months, for the treatment of RA and SA, older than 18 years, of both genders, who had a lipid profile assessment performed immediately before the use of anti-TNF-α drugs and another after their introduction and had not undergone changes in basal medication doses (including corticosteroids), or introduction or withdrawal of agents with potential to alter the lipid profile, except for anti TNF-α, during the observation period between the assessment of the two lipid profiles.

Demographic data, as well as data on time of use and indication of the drug, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), TC, HDL-c, LDL-c and TG levels were collected and the atherogenic index (ATI = TC/LDL-c) was calculated. In our institution the lipid profile is assessed in fasting and TC, TGs, LDL-c and HDL-c are measured by enzymatic/colorimetric methods. Normal values were considered as TC up to 200 mg/dL, HDL-cholesterol levels above 40 mg/dL, LDL-cholesterol up to 110 mg/dL and TG up to 150 mg/dL.

The data were collected in spreadsheets and analyzed using the Graph Pad Prism program, release 5.0. Student's *t* test, Mann Whitney and Krukall Wallis tests were used for association studies, whereas Spearman's test was used for the correlation study. The significance level was set at 5%.

Results

Analyzing the medical records of 609 patients with RA and 134 patients with SA, 125 users of anti TNF-α were identified. Of these, 58 patients met the requirements described above for data analysis and constituted the sample that was studied. There were 31.0% of men and 68.9% women, mean age 47.1 ± 12.9 years and mean disease duration of 12.7 ± 7.4 years. The indication was RA in 72.4% (42/58) and SA in 27.5% (16/58); 50% (29/58) used etanercept, 6.8% (4/58) adalimumab and 43.1% (25/58) used infliximab. The duration of drug use ranged from 8.1-24.6 months (median of 16.04 months).

Prednisone was used by 70.68% (41/58) of patients, with a median dose of 10 mg/day; methotrexate was used by 37.93% (22/58) of patients, leflunomide by 29.31% (17/58); antimalarial drugs by 25.86% (15/58); sulfasalazine by 8.62% (5/58) and azathioprine by 3.44% (2/58) of patients.

The lipid profile values obtained before and after TNF-α use can be seen in Table 1, which showed there was a significant increase in TG values after the use of these drugs.

The median variability in TG values (ΔTGs) was 16.0 mg/dL. When analyzing this variation in relation to patient gender, type of anti TNF-α and disease indication, no differences were found, as seen in Table 2.

When analyzing the variability in TG values (ΔTGs) in relation to time of use, there was no correlation between these two variables (R = 0.008, 95%CI: -0.25 to +0.27, P = 0.94).

Table 1 – Variation in lipid profile values and inflammatory activity before and after the use of anti-TNF-α.

	Before	After	P
Total cholesterol (mg/dL)	Mean of 179.1 ± 38.12	Mean of 177.4 ± 32.3	1.00
HDL cholesterol (mg/dL)	Mean of 55.7 ± 16.5	Mean of 55.4 ± 14.86	0.90
LDL cholesterol (mg/dL)	Median of 102.4	Median of 95.8	0.31
Atherogenic index	Median of 3.1	Median of 3.2	0.96
Triglycerides (mg/dL)	Median of 90.5	Median of 105.0	0.03
ESR (mm /1st hour)	Median of 28.5	Median of 19.0	0.02
C-reactive protein (mg/dL)	Median of 1.35	Median of 0.12	0.03

ESR, erythrocyte sedimentation rate.

Table 2 – Variability of levels of triglycerides (ΔTG) according to gender, indication for use and type of anti TNF-α.

Gender	Median ΔTG in males of 10.0 mg/dL Median ΔTG in females of 21.5 mg/dL	P = 0.46
Type of anti-TNF-α	Median ΔTG of etanercept of 21 mg/dL Median ΔTG of infliximab of 19.5 mg/dL Median ΔTG of adalimumab of 4.5 mg/dL	P = 0.71
Indication for use	Median ΔTG in rheumatoid arthritis of 20.25 mg/dL Median ΔTG in spondyloarthritis of 10.5 mg/dL	P = 0.34

Discussion

The effect of anti-TNF-α on the lipid profile of its users is controversial. In the present study, there were no changes in the profile of TC, HDL-c, LDL-c or atherogenic index. In contradiction to what would be expected considering the known mechanisms of TNF-α effect on the lipid profile, there was an increase in TGs. These findings are in agreement with those by Castro et al.,[8] Stern et al.,[10] Kiortsis et al.[11] and Tam et al.[12] However, in at least two other studies[13-14] there were no significant changes in TG levels, while in two others[15,16] found a decrease in TG levels.

Although the contribution of hypertriglyceridemia to atherosclerotic disease has not been much appreciated in the past, it is known today that the increase in TG levels is independently associated with cardiovascular risk, particularly the coronary type.[17] However, to date, a causal link between these two variables has not been established, as the accumulation of TGs in atherosclerotic plaques is very small when compared to the accumulation of cholesterol.[17]

Notwithstanding these concerns, a study carried out in 2007 with 14,000 young men showed that hypertriglyceridemia was associated with increased coronary risk and that the increase in TG levels between two measurements increased this risk.[18] Furthermore, it is known that hypertriglyceridemia is associated with glucose intolerance and insulin resistance.[17]

No differences could be demonstrated between the several forms of TNF-α inhibition in the present study regarding TG levels. Garcês et al.[19] studied the effects of etanercept and infliximab on the lipid profile in a sample of patients with RA, psoriatic arthritis and SA, observed differences between the two agents, the first being associated with increases in TC and LDL-c and the second with increased HDL-c levels. These authors attributed a class-specific effect to these drugs, secondary to the different capabilities of blocking lymphotoxin-α, which would have a pro-atherogenic effect. Other studied variables, such as gender and time of use, did not influence the changes observed in the present study. Interestingly, Jacobsson et al.[20] found that the use of anti-TNF-α improves survival in women, but not in men with RA.

It is quite likely that the cardiovascular protective factor of anti-TNF was not due to changes in the lipid profiles of patients, given the pleomorphic actions of TNF-α in the cardiovascular system. However, further studies are necessary to clarify the importance of these metabolic changes, especially in cases of long-term use of this drug group.

Conflicts of interest

The authors declare no conflicts of interest.

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