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Severe hypertriglygeridemia in a rheumatoid arthritis patient treated with leflunomide

Sirs,

Leflunomide (LEF) is a well-established treatment for rheumatoid arthritis (RA). We describe an interesting case of a patient exhibiting severe hyper-triglyceridimia, attributed to LEF.

A 54-year-old male, with a diagnosis of RA for 11 years, was treated with methotrexate (MTX) from 1996 to 2005, and since 2002 in combination with infliximab. For several years he was also on enalapril, hydrochlorothiazide, carvedilol, digitalis and acenocoumarol because of hypertension and chronic atrial fibrillation. On June 2005, MTX was switched to LEF due to RA exacerbation (DAS28 = 6,5). From that time, triglyceride (TG) levels started to rise (Table I), despite specific instructions for dietary and lifestyle modifications. Additionally, at several time points, our patient denied the addition of a lipid lowering drug, due to polypharmacy. On March 2006, TG were 1200 mg/dl and he complained of diarrhea, bloating, insomnia and dizziness, symptoms that although not specific enough, could be attributed to LEF. As a result, a diagnosis of LEF induced hypertriglyceridemia was suggested, LEF was immediately discontinued and a wash out procedure was performed (cholestyramine 8 gr, three times daily for 11 days). On the follow up visits, TG started to decline gradually, reaching normal values 8 months later (Table I).

Table I.

	5/05	6/05	7/05	12/05	3/06	5/06	9/06	11/06
Glu	96	98	117	106	104	101	123	99
Ur	25	46	28	27	40	34	27	25
Cr	0.7	1.0	0.8	0.8	0.9	0.8	0.8	0.7
UA	8.8	9.0	6.5	5.5	6.8	8.7	6.9	5.3
TC	222	222	240	255	339	249	187	146
LDL	154	153	153	126	84	132	111	94
HDL	31	27	30	30	13	28	29	29
TG	187	212	283	496	1210	445	234	115
CRP	1.61	2.42	1.53	0.43	0.31	0.5	0.31	1.54

Glu: Glucose (70-110 mg/dl); Ur: Urea (15-55 mg/dl); Cr: Creatinine (0.6-1.2 mg/dl); UA: Uric acid (3.0-8.2 md/dl); TC: Total Cholesterol (150-220 mg/dl); LDL: Low Density Lipoprotein (<130 mg/dl); HDL: High Density Lipoprotein (<40 mg/dl); TG: Triglycerides (<150 mg/dl); CRP: C- Reactive Protein (0.08-0.8 mg/dl).

Cholestyramine, a bile acid sequestrant (BAS), serves as an antidote in LEF toxicity presumably by interrupting the excessive enterohepatic circulation of LEF. It is also known as a lipid lowering drug. Thus someone could argue that the decline of TG in our patient is principally through the hypolipidemic action of cholestyramine than lowering of LEF levels. However, it is known that BAS, even though they are able to decrease LDL cholesterol levels, they also tend to increase VLDL production and therefore raising TG levels (1). Additionally, our patient was also receiving specific antihypertensive drugs (thiazide diuretics and beta blockers) that can also raise TG levels. Therefore, one could support the view that the LEF induced hyper-triglyceridemia was indirect, by increasing the levels of those antihypertensive drugs. However, hydrochlorothiazide is able to increase TG levels but it also increases uric acid levels. On the contrary, our patient had a decline in uric acid levels after LEF initiation, probably due to the ability of LEF to reduce serum uric acid concentrations by increasing urate renal excretion (2, 3). Additionally, although beta-blockers in general increase serum TG levels, carvedilol decreases TG levels or has no effect at all (4, 5). Finally, the strongest evidence that our patient hypertriglyceridemia should be attributed to LEF is that upon discontinuation of LEF, TG levels started to decline and reached normal values 8 months later.

To the best of our knowledge, there is only one case report in the literature describing a case of increased TG levels, attributed to LEF (6). Concerns about LEF discontinuation rates are currently rising (9, 10) and although several clinical studies have been published examining the efficacy and safety of LEF in various diseases, none of them had shown any side effect on triglycerides levels. In two of them (7, 8), 1 patient in each study developed hypercholesterolemia, *i.e*., an increase in total cholesterol levels. As severe hypertriglyceridemia is a well-described cause of pancreatitis, a disease with significant mortality, we recommend lipid profile examination at least every 3 months, for the first year after the initiation of LEF.

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Competing interests: none declared.

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