Effect of anti-TNF-α tumor necrosis factor therapy on lipid profile in a sample of patients attending Baghdad teaching hospital

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Abstract:

Background: Anti-tumor necrosis factor drugs (biological agents) are a class of drugs that are used worldwide to treat inflammatory conditions "these drugs are able to reduce inflammation and stop disease progression".

Objectives: To evaluate lipid profile changes after anti-TNF therapy in patients with psoriatic, rheumatoid arthritis and ankylosing spondylitis

Patients &methods: A prospective study included 90 patients presenting with 30 Psoriatic arthritis (n=30), ankylosing spondylitis (n=30) rheumatoid arthritis (n=30) who were treated with anti-TNF therapy (infliximab, rituxmab etanercept) and assessed during follow-up period after 6month of therapy.

Results: Regarding lipid profile, significance differences (P<0.000) were seen after biological therapy with infliximab infusion in patients with psoriatic arthritis. The current study had significant differences regarding TG and HDL after 6 month of treatment of rheumatoid arthritis patients with rituximab., Significance differences were seen regarding TG and LDL in ankylosing spondylitis patients treated with etanercept

Conclusion: Significance differences were seen regarding lipid profile and antitumor necrosis factor alpha therapy regarding psoriatic, Rheumatoid arthritis and ankylosing spondylitis

Key words: Dyslipidemia, Psoriatic arthritis, Rheumatoid arthritis, AntiTNF

Introduction:

Tumor necrosis factor-alpha (TNF-α) is a "multifunctional pro-inflammatory cytokine" that had a major role in the etio-pathogenesis of "psoriasis" and 'psoriatic arthritis", "rheumatoid arthritis', "inflammatory bowel disease" and other dermatologic and rheumatologic conditions". [1].

"Anti-tumor necrosis factor drugs (biological agents)" are a class of drugs that are used worldwide to treat inflammatory conditions "These drugs are able to reduce inflammation and stop disease progression". "There are five biologic agents that target TNF: infliximab., a chimeric human-murine monoclonal antibody; adalimumab and golimumab, "fully human anti-TNF-α monoclonal antibodies" (IgG1); etanercept, a fusion protein composed of a dimer of the extracellular portions of human TNFR2 (p75) fused to the Fc domain of human IgG1; and "certolizumab", "a pegylated, humanized Fab fragment of an anti-TNF-α monoclonal antibody".[2]. "A new era in the treatment of rheumatic diseases began with the development of "TNF-*α*-inhibitors", where "TNF-*α* is a cytokine that performs an important role in inflammatory diseases", which have shown satisfactory results for both joint and skin diseases" [3]. "Adverse effects, including infections and lipid profile changes, have been related to this treatment for rheumatoid arthritis and ankylosing spondylitis." [4, 5]."The published studies on the association of TNF-α inhibitors with dyslipidemia in rheumatic diseases report inconsistent results", due to variety of reason like small sample size, variable study duration, and lack of adjustment for co-variables such as age, co morbidities, and relevant disease-modifying anti-rheumatic drugs; very few studies include a comparative group of patients not using these biologic modifiers. Most of the studies exclusively examined the relationship between infliximab use and changes in lipid profile pre- and post-drug exposure, and they invariably showed an increase in TC with treatment; the majority also showed an increase in HDL but no changes in TC:HDL".,. "Other reports including patients receiving "etanercept and adalimumab" show either an increase in HDL or no changes in lipids" [6, 7], "but the results were not reported specifically for each TNF-α inhibitor except for 1 study" [8] "They observed no association of either etanercept or monoclonal TNF-α inhibitor use versus nonuse with lipid levels in patients with rheumatoid arthritis."

The objective of the study is to evaluate lipid profile changes after anti-TNF therapy in patients with psoriatic, rheumatoid arthritis and ankylosing sopondylitis"

Patients and methods:

Patients: A prospective study was carried out in "Baghdad teaching hospital" (biological unit and outpatient clinic of rheumatology) for a period of six months which included 90 patients (30 "Psoriatic arthritis", 30 "ankylosing spondylitis" and 30 of rheumatoid arthritis) who were treated with anti-TNF therapy (infliximab, etanercept & rituximab) respectively and assessed during follow-up period after 6 months of therapy

Infliximab; (Remicade®) is presented as: a vial containing 100 mg of lyophilised powder. The dose for adult patients is 5 mg per kg given intravenously. Initially patients are to be treated at week zero, week 2 and week 6. Subsequent infusions are at 8-week intervals"

Rituximab; (Rituxan ®) Administer as two 1000-mg intravenous infusions separated by 2 weeks (2 infusions separated by 2 weeks is 1 course).

Repeat course every 6 months or based on clinical evaluation "

Etanercept; (Enbrel®) 50 mg is presented as a set of 4 prefilled syringes of solvent 1 mL. The dose for adult patients is 1 subcutaneous injection once weekly."

The exclusion criteria: included: previous diagnoses of dyslipidemia, diabetes mellitus, renal failure, liver disease, and use of medications that could interfere with lipid metabolism "

Methods:

Serum was separated and total cholesterol, triglycerides, high density lipoproteins cholesterol were measured directly by special Reagents (Bio-systems, Spain) by enzymatic colorimetric method after 12 hours over night fasting by using analyzer (MICRO Germany). LDL–Cholesterol was calculated mathematically from the total cholesterol, triglycerides and HDL–Cholesterol concentrations.

LDL Cholesterol=Total Cholesterol–[HDL Cholesterol+TG/5]

Statistical analysis; Analysis of data was carried out using the available statistical package of SPSS-20 (Statistical Packages for Social Sciences-version 20). Data were presented in simple measures of mean, standard deviation. Using paired t-test for difference between two means, statistical significance was considered whenever the P value was equal or less than 0.05.

Results:

The results of the study regarding the total cholesterol, Triglycerides, High Density Lipoprotein & Low density Lipoprotein (TC, TG, HDL and LDL) had significance differences (P<0.000) were seen after biological therapy with "infliximab infusion" in patients with psoriatic arthritis (Tab 1).

Results in table 2 showed that the current study had significance differences regarding "Triglycerides (TG)" and "High Density Lipoprotein (HDL)" after 6 months of treatment of rheumatoid arthritis patients with "rituximab". Significance differences were seen regarding "Triglycerides (TG)" and "low Density Lipoprotein (LDL)" regarding "ankylosing spondylitis" patients treated with "etanercept" (Tab 3).

Table 1: The distribution of study sample according to infliximab and lipid profile

Lipid profile	Infliximab		p-value
	Before	After 6 months	
	Mean±SD	Mean±SD	
TC	174.13±19.97	223.93±31.15	0.0001*
TG	171.00±34.28	383.77±87.26	0.0001*
HDL	48.30±7.62	30.50±9.95	0.0001*
LDL	117.20±48.34	197.00±7.09	0.0001*

*Significant

Table 2: The distribution of study sample according to rituximab and lipid profile

Lipid profile	Rituximab		p-value
	Before	After 6 months	
	Mean±SD	Mean±SD	
TC	209.33±55.74	223.60±46.67	0.287
TG	194.60±27.36	247.83±111.41	0.014*
HDL	30.77±9.79	26.40±5.48	0.037*
LDL	197.33±7.46	199.43±.50	0.129

*Significant

Table 3: The distribution of study sample according to etanercept and lipid profile

Lipid profile	Etanercept		p-value
	Before	After 6 months	
	Mean±SD	Mean±SD	
TC	176.93±43.43	194.83±46.04	0.127
TG	211.80±32.05	335.73±100.54	0.0001*
HDL	30.63±9.42	30.23±9.99	0.874
LDL	122.03±52.32	197.33±7.46	0.0001*

* Significant

Discussion:

Hypertriglyceridemia, is a well-known factor of cardiovascular risk: high TG levels predict the subsequent occurrence of coronary artery disease [9]. The current study shed light on a significant increase in TC,TG and LDL levels after six months

of anti-TNF therapy (inflximab) used in patients with Psoriatic arthritis this is in accordance with previously conducted studies by "Antoniou *et al*. who observed a significant increase in the TG levels and a decrease in HDL-c concentrations in eight patients with Psoriatic Arthritis after infliximab therapy" [10]. Conversely, "Sparnakis *et al*. found a significant increase in HDL-c levels during the evaluation and only a significant increase in TC in the first month of evaluation." [11]. "It is clinically evident that Psoriatic arthritis patients without cardiovascular risk factors or cardiovascular disease have an elevated prevalence for macro- vascular disease, which is represented by an increased carotid intima-media thickness" [12]. "This thickness independently correlates with activity parameters in Psoriatic arthritis and traditional risk factors for atherosclerosis "[13]. These data corroborate the idea that special attention and strict control of the risk factors for atherosclerotic diseases in patients with Psoriatic arthritis are necessary [14]. Regarding rheumatoid arthritis and anti-TNF factor(rituximab) significance differences regarding TG and HDL after 6 months of treatment of rheumatoid arthritis patients with rituximab. "Another study evaluated 34 patients with rheumatoid arthritis, using the three TNF blockers, and found an increasing of TC, HDL-c, and LDL-c levels, with no changes in TG levels or the atherogenic index after approximately six months of anti-TNF treatment" [15]." Soubrier *et al*. investigated the lipid profiles of 29 rheumatoid arthritis patients before and after anti-TNF treatment for 14 weeks and did not show any lipid profile change in these patients" [16]. "In other study, Popa *et al*. investigated the effects of anti-TNF treatment on the lipid profiles of 55 rheumatoid arthritis patients after one year of treatment. They could demonstrate that the treatment modified the plasma concentrations in the lipoproteins of these patients. There was an increase in HDL-c concentrations and no changes in the atherogenic index during the first two weeks of treatment. Nevertheless, the beneficial effects were not sustained over time; there were eventually TC and LDL-c increases even though the HDL-c levels did not change for twelve months. This finding suggested a worsening of the lipid profiles and an increase in the atherogenic index of these patients, which could increase their cardiovascular risk [17]. "Regarding ankylosing spondylitis significance differences were seen regarding TG and LDL only treated with etanercept this results is similar to other reported study done by Hussein et., al. in Egypt who found that significantly higher LDL-C levels in AS patients receiving anti-TNF than those are not receiving anti-TNF [18] this finding parallels other conducted research by Graces *et al*. they found that in patients with Rheumatoid arthritis or ankylosing spondylitis treated with anti-TNF blockers, infliximab treatment increased the total cholesterol and LDL-C levels, but had no effect on HDL-C and TGs production, "whereas etanercept increased HDL-C significantly but had no effect on total cholesterol or LDL-C levels". [19]

Conclusion:

Significant differences were seen regarding lipid profile and antitumor necrosis factor type alpha therapy regarding psoriatic, Rheumatoid arthritis and ankylosing spondylitis.

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