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Effects pf Biological Response Modifiers on the Prevalence pf Autoantibodies to Vascular Injury in Agroup of Iraqi Patients with Autoimmune Disease

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Abstract

Background; .biological disease modifiers mainly those targeting tumor necrosis factor (Etanercept), (Infliximab), together with (Adalimumab) are currently an important part of the treatment plan for seropositive poly-articular arthropathy. Since these drugs greatly affect the course of the disease, they alter the treatment of this condition and significantly slow down X-ray progression of the aforementioned condition. Some biologics are designed to precisely suppress tumor necrosis factor (TNF), a key regulator of joint pain and damage. Tumor necrosis factor is a predominant inflammatory interleukin which synchronizes the release of other soluble mediators [1]. Purpose: to assess the changes in P-ANCA an indicator of vascular injury after treatment with the biologic Etanercept (anti-TNFα) in patients with refractory seropositive polyarticular arthropathy. Methods: patients with refractory and classically unrelieved seropositive poly-articular arthropathy received a biological modulator (Etanercept) for 3 months. Participants' sera were collected and examined consecutively for P-ANCA at baseline as well as post-dosing. Statistical analysis was performed using the SPSS 10 .Results: after 3 months, there was a significant decrease in serum anti-lactoferrin level of nearly 97%, and a concomitant increase of anti-lysozyme, with an increase of 551.6%. However, other autoantibodies are elevated, non-importantly. Conclusion: Etanercept had variable effects on P-ANCA in patients with refractory seropositive poly arthropathy after 3 months of therapy.

Keywords

autoantibodies, vascular injury, Iraqi patients , autoimmune disease

Etanercept, Infliximab, and Adalimumab are TNF inhibitors authorized for management of a variety of rheumatic conditions. Biological disease-modifying agents have dramatically changed the course of drug therapy in the case of seropositive poly arthropathy, due to their ability not only to slow down disease course decisively, but also to severely impede radiographic escalation of joint lesions. These drugs are made specifically to curb TNF which is the main trigger of joint destruction. Tumor necrotic factor is a critical mediator in promoting inflammation by triggering the release of other inflammatory interleukins. [1] This mediator is found in Huge amount in the joint and appears to be synthesized by synovial and tissue – infiltrating macrophages. It is the main harmful cytokine that causes tissue damage. TNF-α has been observed suppressing functions of Treg in persons suffering from seropositive polyarticular arthropathy. [2]

in addition, tumor necrotic factor is a key mediator that amplifies associated cytokine milieu along with regulating chemokine and cytokine receptors, as well as other fundamental processes of tissue damage [3] Interleukin-17A interacts synergistically with TNF-α, contributes to the stimulation of fibroblast and chondrocytes , as experimentally verified .[4]

Etanercept is a genetically engineered hybrid consists of two proteins, the receptor of tumor necrotic factor together with fragment crystallizable moiety of gamma globulins, an is prescribed either alone or along with MTX .it interacts with circulatory along with locally produced tumor necrotic factor in affected joints ,and then prevents its binding to the TNF receptor and interrupting its action [5] Anti-TNF treatment had achieved significant curative goals in patients with seropositive polyarticular arthropathy [6]

biological disease modifiers (Anti−TNF-α agents) corrected the functional defects and triggered production of new competent Treg lineage which balanced the deficient ones in patients with seropositive polyarticular arthropathy .[7,8] . Etanercept (TNF-α blocker) synergistically, improves disease activity by restoring TH17, Treg count and the mediators they release in synergy with MTX, whilst simultaneously suppressing other inflammatory cytokines. [9]

Similar results had been observed, where Treg were able to reduce Th17 and improves disease outcome by blocking the activity of IL-6 in the joints. [10] Furthermore, biological disease modifiers markedly increased Treg abundance, with concomitant decrease in CRP. [11]
Therefore, manipulation and alteration of Treg count and function is likely to be potential mode of action of biological disease modifiers. in refractory seropositive polyarticular arthropathy. [8, 12, 13]
Biological therapeutics promote the generation of a superior and robust Treg lineage, thereby reducing IL-17 production. [14]

Neutrophil cytoplasmic antibodies represent antibody systems that target various cytoplasmic components of neutrophil and monocytes. .researchers had identified two different patterns: C-ANCA (staining throughout the neutrophil cytoplasm), along with P-ANCA (staining around the cell nucleus) using an immunofluorescent microscope on ethanol-fixed neutrophils. [15] .PR3 together with MPO were identified as potential targets of the aforementioned autoantibodies [16]

These c-ANCAs are an important diagnostic marker in Wegener's granulomatosis, whilst p-ANCA showed diagnostic value in microscopic polyangiitis and pauci-immune crescentic glomerulonephritis consequently. [17] in addition , C-ANCA(atypical) with an unknown antigen target has been demonstrated .many papers and articles have announced the existence of ANCA in several other autoimmune inflammatory diseases as inflammatory bowel diseases and seropositive polyarticular arthropathy [18] although no specific antigen has been identified in those conditions , several enzymes and proteins inside granules of neutrophils may be responsible .[19] the range of distribution of ANCA is 0% to 72% in subjects with seropositive polyarticular arthropathy .[20]
Thus, our aim was to investigate the changes in P-ANCA (anti-lactoferrin, anti-cathepsin, anti-elastase, and anti-lysozyme) after administration of biological disease modifiers (Etanercept) in patients with refractory seropositive polyarticular arthropathy.

Materials and Methods

Eighteen patients with refractory seropositive polyarticular arthropathy patients, 17 female, 1 male (94%/6%), with average participants age of 47.6 year, and their average disease period equals 10.7 years were consecutively chosen for the purpose of this research . The study plan consisted of the administration of Etanercept along with MTX for three months (July to November 2012) under the guidance of aboard-certified physician from department of rheumatology/ Baghdad hospital (Medical City).

Eight cases ended the treatment regimen as planned, ten of whom deliberately refused to continue. Exclusion criteria involved any infectious, chronic and other concomitant diseases that may affect results.

All participants had already failed classic medications involving DMARD (hydroxychloroquine, azathioprine, cyclosporine, and MTX). 25 mg of Etanercept was administrated subcutaneously two times a week in each case for 3 months.
Two serum samples were collected from each case, the first at base line, and the second after completing the treatment regimen.

All samples were then stored at -20 centigrade and thawed for testing only. Twenty healthy subjects participated in the study and serum samples were collected and tested for comparison. ELIZA was utilized to calculate the ANCA for study participants, as recommended by the supplier.

An ELISA microplate reader, and a plate washer (Biotech ELX 800, ELX 50, USA) were used for detection of ANCA. The below kits had been selected for ANCA evaluation; Anti elastase, anti-cathepsin, anti-lactoferrin and anti-lysozyme Abs screening by (immuchem, Belgium). Statistical analysis accomplished utilizing the SPSS 10 statistical package. Descriptive statistics metrics (Mean, SD) reveal variables, whilst T test calculated the variation of the mean between two continuous numeric variables. $P < 0.005$ was considered important.

Study findings

Table (1) illustrates the variation of the P-ANCA serological parameters before and after

treatment with Etanercept. A Significant decrease in serum anti-lactoferrin levels was observed from base line of 13.5±11.0 (Mean± SD) to 0.4±0.1, a reduction of almost 97%. Other p-ANCA autoantibodies were found to be elevated in seropositive polyarticular arthropathy patients after 3 months of drug treatment. Anti cathepsin increased from 16.4±8.6 to 20.1±33.1 with a rate of increase ↑25.7%, p>0.05.
Anti elastase increased from 5.7±4.3 to 10.4±11.2, rate ↑82.5%, p>0.05.and Anti-lysozyme from 3.1±2.5 to 20.2±15.6, rate ↑551.6%, p<0.05.

Table (1). Values of study parameters before and after treatment with the biologic Etanercept in comparison to health subjects

Parameters	patients				Controls	
	Mean± SD before therapy (n= 36)	Mean± SD after therapy (n= 16)	Change %	p value	Mean± SD	p value
Anti cathepsin (U/ml)	16.4±8.6	20.1±33.1	↑25.7%	0.664*	3.1±0.6	0.005**
Anti lactoferrin (U/ml)	13.5±11.0	0.4±0.1	↓97.0%	0.000**	2.4±1.6	0.000**
Anti elastase (U/ml)	5.7±4.3	10.4±11.2	↑82.5%	0.122*	9.0±5.2	0.042**
Anti-lysozyme (U/ml)	3.1±2.5	20.2±15.6	↑551.6%	0.001**	2.4±1.2	0.000**

*=Not significant, **=Significant.

Discussion

In this study, significant reductions in anti-lactoferrin levels were seen, with a reduction rate approaching 97% for the sera tested. Other p-ANCA autoantibodies showed high levels in the aforementioned after 3 months of drug treatment. This increase was either negligible for anti-elastase and anti-cathepsin G, or significant for anti-lysozyme.

The study results were consistent with several studies that have observed an increase in non-specific autoantibodies anti-TNF treatment , which is considered a transient phenomenon [21, 22]. The increase in these non-specific autoantibodies is not well defined, but, several mechanisms have been proposed.
It was hypothesized that treatment with biological agents mainly the inhibitors of tumor necrotic factor dramatically lowers circulating CRP levels; a protein with a well-known function of apoptotic body clearance. [23]

apoptosis is one of the predominant players in autoimmunity, and tumor necrotic factor has indispensible function in apoptosis. [24]Finally, suppressing TNF- α, a dominant Th1 cytokine promotes a shift to a Th2 response with increased autoantibody production. [21] The situation is different with anti-LF. In several studies, [25, 26, and 27] it have been reported to be the predominant p-ANCA with pathogenic implications in seropositive polyarticular arthropathy. Anti-LF antibodies have been found more frequently in patients with seropositive polyarticular arthropathy with vasculitis than in others, and may be used as diagnostic marker in the above condition. [28] The decrease in anti-LF after treatment with Etanercept is consistent with several studies reporting anti-TNFα is a potentially effective treatment for persons suffering from vasculitis [29] apparent improvement in disease outcome.

The accumulated data indicates that tumor necrotic factor is essential for systemic vasculitis development, so recovery mechanism may be related to the decrease in TNF. heightened up regulation of TNF ,its receptors, as well as TNF blood levels were observed at sites of vasculitis damage ,[30] during disease flare up, which returns to normal with diminished disease activity .[31] additionally , treatment with tumor necrotic factor modulators reversed inflammatory renal vasculitis experimentally .[32]

Conclusion

the Etanercept effect on P-ANCA in refractory seropositive polyarticular appeared controversial and needs to be clarified ; one hand ,it significantly reduced one of the main pathogenic autoantibodies ,namely anti-lactoferrin, on the other side ,it didn't significantly increase other P_ANCA like anti-cathepsin and anti-elastase.

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