ANTI-TUMOR NECROSIS FACTOR ALPHA BIOLOGIC THERAPY DOSE ADJUSTMENT NECESSITY IN PATIENTS WITH RHEUMATOID ARTHRITIS. A CASE PRESENTATION.

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ABSTRACT

Rheumatoid arthritis is an inflammatory disease characterized by chronic joint erosive processes, affecting approximately 1% of the population. [1] The pathogenic mechanisms processes involve the activation of pro-inflammatory cytokines, including TNF alpha. [2]

The purpose of this case presentation is to elucidate a possible correlation between the high level of blood TNF alpha and the apparent lack of response to biologic therapy directed against this molecule.

A female patient, aged 55 years, diagnosed with rheumatoid arthritis in 2006, presents an increased inflammatory biological syndrome. The patient was being treated biologically (adalimumab, and two years of etanercept previously. One year ago, the patient presents the elevation values of the blood tests commonly used to monitor the status of patients with inflammatory rheumatoid arthritis up to 2.5-3 x than normal values. Initially, this increase is considered to be due to a respiratory seasonal condition. We continued monitoring the status, after subsequent remission of these respiratory disorders, and we observed the persistence of those elevated test, this time without an obvious possible causing comorbidity.

We decided to evaluate the current patient status and we obtained the following information:

Biological syndrome currently moderately exceeds the maximum normal values. ESR was 47 mm/h and CRP 1.5 than the normal value.

TNF alpha value determined by immunochemical methods with detection by chemiluminescence (CLIA) is 67.2 pg / mL

Biological confirmation by determining serum TNF alpha and increased observation that the current level may be one explanation for the possible reactivation of the disease prompted us to continue the study in patients receiving

anti-TNF alpha biologic. This study is ongoing. We can imagine this correlation between the level of TNF alpha and the degree of disease activity at least in the case of a group of patients treated with biological drugs. If this could be demonstrated, then perhaps we can expect a change in the curative approach of these patients, meaning that dose adjustment can be considered depending on the level of TNF alpha, and why not, depending on other cytokines that may be included in future studies.

Keywords: *rheumatoid arthritis, Tumor Necrosis Factor alpha, biological therapy*

INTRODUCTION

Rheumatoid arthritis is an inflammatory disease characterized by chronic joint erosive processes, affecting approximately 1% of the population. The pathogenic mechanisms processes involve the activation of pro-inflammatory cytokines, including TNF alpha (tumor necrosis factor-alpha), which plays an important role. TNF alpha is a cell-signaling protein involved in systemic inflammation and in the acute phase reaction. It is produced chiefly by activated macrophages, although it can be produced by many other cell types, such as CD4+ lymphocytes, NK cells, neutrophils, mast cells, eosinophils, and neurons. TNF promotes the inflammatory response, which, in turn, causes many of the clinical problems associated with autoimmune disorders such as rheumatoid arthritis

Inhibition of cytokines, and especially of TNF alpha, resulted as a natural conclusion for chronic disease control, but how these treatments succeed to do so is debatable.

This is in question because the immune system comprises many mechanisms, uncertain involved in each patient, even in the same condition. The "mapping" of these immune mechanisms involved can probably give us an image of them and implicitly on the most effective methods of treatment.

OBJECTIVE

The purpose of this case presentation is to elucidate a possible correlation between the high level of blood TNF alpha and the apparent lack of response to biologic therapy directed against this molecule.

To achieve this, we compared the biological parameters of this patient, especially the TNF alpha level, and the current clinical status.

CASE REPORT INFORMATION

A female patient, aged 55 years, diagnosed with rheumatoid arthritis in 2006, presents an increased inflammatory biological syndrome (both the ESR, and the

CRP serum levels are increased). The patient was being treated biologically (adalimumab) from May 2016, prior to performing two years of treatment with another anti-TNF biologic agent (etanercept), discontinued treatment due to inefficiency. She attended various DMARD (disease modifying anti-rheumatic drugs) regimens, currently following treatment with methotrexate 20 mg/week.

The patient uses non-steroidal anti-inflammatory about 3-4 times a week, the substance generally administered being 90 mg etoricoxibum per day.

The current status shows no significant comorbidities, the patient smokes, does not drink alcohol, and lives in an urban area. The patient demonstrated compliance to recommended treatments, as there were no interruptions or delays in administration for personal reasons.

In February-March 2018 the patient presents the elevation values of the blood tests commonly used to monitor the status of patients with inflammatory rheumatoid arthritis up to 2.5-3 x than normal values. Initially, this increase is considered to be due to a respiratory seasonal condition. We continued monitoring the status, after subsequent remission of these respiratory disorders, and we observed the persistence of those elevated test, this time without an obvious possible causing comorbidity.

The persistence of the biological values of inflammation aroused the suspicion of a treatment inefficiency and qualified the patient as eligible for the study.

PRELIMINARY DISCUSSION

Although little studied in the literature, a possible association between serum levels of TNF alpha and the effectiveness of biological treatment was brought to attention in 2005 by Edrees AF et al. which showed that "RA patients who responded well to infliximab and had the inactive disease at the time of the study have lower levels of serum TNF-alpha which could be suppressed by the time further recommended doses of infliximab. RA Patients with active disease had higher serum levels of TNF-alpha which could not be suppressed after the recommended doses of infliximab infusion. " [1] Thus, patients in the study group (55 patients) were divided into two subgroups, according to the response to treatment after 6 months. Patients resistant to treatment, which the authors called "active group", had averaged values of serum TNF alpha of 76.1 pg / mL from stable to treatment group - 38.0 pg/ml ($P < 0.02$). [3]

In 2011 Tsutomu Takeuchi et al. confirm this idea, pointing out that "baseline tumor necrosis factor-alpha levels predict the necessity for dose escalation of infliximab therapy in patients with rheumatoid arthritis". [4]

RESULTS

We decided to evaluate the current patient status and we obtained the following information:

Her laboratory tests on admission revealed normal values for hemoleucogram test (WBC of 8.4 × 10^3/μL, a hemoglobin level of 12.1 g/dL, and platelets 240 × 10^3/μL. She also had a normal urinalysis.

Biological syndrome currently moderately exceeds the maximum normal values. ESR was 47 mm/h and CRP 1.5 than normal value. Her rheumatoid factor was high at 67 IU/mL.

TNF alpha value determined by immunochemical methods with detection by chemiluminescence (CLIA) is 67.2 pg / mL.

The normal value of TNF alpha is according to the determination kit <8.1pg / ml.

Clinical examination revealed a number of 4 painful joints (right hand 1-4 metacarpophalangeal joints) and one swollen joint (2nd metacarpophalangeal joint at the same hand). Fatigue has been a symptom repeatedly reported by the patient, including at this visit, above the average expected.

There were not any significant changes in other parameters of blood tests (liver function tests, kidney, etc.).

She had no recent trauma and showed no clinically obvious infection. Biological parameters reinforced this conclusion.

The visual analog scale (VAS) was 50 mm, and we calculated a Disease Activity Score (DAS28-ESR) of 4.8.

CONCLUSIONS AND FUTURE CONCERNS

We can imagine this correlation between the level of TNF alpha and the degree of disease activity at least in the case of a group of patients treated with biological drugs. If this could be demonstrated, then perhaps we can expect a change in the curative approach of these patients, meaning that dose adjustment can be considered depending on the level of TNF alpha, and why not, depending on other cytokines that may be included in future studies.

Biological confirmation by determining serum TNF alpha and increased observation that the current level may be one explanation for the possible

reactivation of the disease prompted us to continue the study in patients receiving anti-TNF alpha biologic. This study is ongoing.

At the same time, the appearance on a proportion of patients of adverse events is supposed to occur in the context of insufficient inhibition of this cytokine because the benign, protective effects by triggering the autoimmune mechanisms of these molecules are known. This is also a topic of concern for us in the future.

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