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ORIGINAL ARTICLE

Therapeutic potential of hydroxychloroquine on serum B-cell activating factor belonging to the tumor necrosis factor family (BAFF) in rheumatoid arthritis patients

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KEYWORDS

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Abstract *Objective:* To assess the serum B-cell activating factor belonging to the tumor necrosis factor family (BAFF) level in rheumatoid arthritis (RA) patients in view of different treatment regimens received and evaluate its relation with disease activity.
Patients and methods: Ninety female RA patients were included. Sixty were on disease modifying anti-rheumatic drugs (DMARDs); 34 on hydroxychloroquine (HCQ) plus methotrexate (MTX), 26 on leflunomide (LFN) plus MTX and 30 newly diagnosed cases not yet on any treatment. Thirty age and gender matched healthy subjects served as controls. Full history taking, clinical examination and relevant laboratory investigations were performed. Disease activity score, in 28 joints (DAS-28), was calculated.
Results: Serum BAFF level was significantly higher in patients (1.82 ± 0.91 ng/ml) compared to control (0.71 ± 0.33 ng/ml; $p < 0.001$). There was a significantly lower BAFF and disease activity in patients receiving DMARDs (1.55 ± 0.73 ng/ml and 3.08 ± 0.73) compared to new cases (2.36 ± 1.02 ng/ml and 3.46 ± 0.82) ($p < 0.001$ and $p = 0.036$, respectively). Those receiving HCQ + MTX had a lower BAFF level (1.29 ± 0.51 ng/ml) compared to those receiving

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LFN + MTX (1.94 ± 0.85 ng/ml; $p = 0.002$). The BAFF level significantly correlated with the presence of anti-CCP antibodies, DAS28 and MTX dose in all RA patients ($r = 0.24$, $p = 0.02$; $r = 0.504$, $p < 0.001$; $r = 0.51$, $p < 0.001$, respectively). Only DAS28 and MTX dose would highly influence the BAFF level ($p = 0.015$ and $p = 0.001$, respectively).

Conclusion: Elevated level of BAFF in RA has been confirmed with a notable relation to disease activity making it a promising marker. The beneficial effect of hydroxychloroquine in dampening BAFF level throws light on the importance of considering it in combination among the newly developed biologics that also target B-cells.

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory rheumatic disease, in which autoantibodies are part of the early disease manifestations. A pathogenic involvement of B cells is implicated in RA.[1] It is a systemic autoimmune arthritis that clinically manifests as joint pain, stiffness and swelling. If left untreated, persistent synovitis can progress to cartilage and bone destruction; ultimately to major long-term disability and mortality. Disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX), leflunomide (LFN) and hydroxychloroquine (HCQ), have markedly improved clinical symptoms and slowed joint damage. Despite their effectiveness, some patients continue to have clinical manifestations and progressive joint destruction. Advances in the understanding of the pathogenesis of RA have led to the identification of novel cellular and molecular therapeutic targets. Biologic agents aimed at these targets have provided some evidence of effectiveness that is transforming the management of RA.[2] Current strategic regimens which concentrate on systematic ways to bring patients into remission all include MTX as the first choice.[3]

Although the specific trigger of the autoimmune response in RA is not known, pathogenesis is generally believed to be associated with the generation of autoantibodies through interactions of antigen-presenting cells with the adaptive immune system (T and B cells). The main inflammatory mediators of joint inflammation and destruction in RA are tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), IL-6, chemokines, and proteases.[2] Interest in B-cells has been revived due to the description of new functions. Supporting a role for B-cells in the genesis of autoimmune diseases is the fact that the B-cell activating factor of the TNF ligand family (BAFF) is essential in their physiology. Based on experiments in mice, and validated in humans, this new cytokine has been highlighted. Excessive production of BAFF alters immune tolerance by rescuing self-binding B-cells. Overexpression in mice leads to autoimmune manifestation, and BAFF levels are elevated in the serum of autoimmune patients.[4] Since BAFF has been identified as a critical and major regulatory factor for B cell maturation and survival, convincing evidence indicates that deregulation of BAFF is involved in the pathogenesis of B-cell related autoimmune diseases including RA,[5–7] Juvenile idiopathic arthritis (JIA),[8] SLE,[9,10] Systemic sclerosis (SSc)[10] and Behcets disease.[11] Blockade of BAFF activity significantly improves the symptoms of autoimmune diseases such as systemic lupus erythematosus (SLE) and RA both in animal models and clinical trials.[5] Advances in our understanding of the BAFF system offer the opportunity to improve our therapeutic approach.[4]

During the past century, many immunosuppressive drugs have been described. Often their mechanisms of action were established long after their discovery.[12] Advances in our understanding of the key cells and inflammatory cytokines have led to the development of targeted biologic agents.[2] Biologic therapies have profoundly changed the course of RA, but factors that predict response, which could be used to optimize the use and selection of these costly agents that have potentially severe side effects, have not been identified. Because B-cells play critical roles in RA, developing serum biomarkers of B cell activation are potential predictive factors for the efficacy of biologic agents targeting B cells.[13]

The management of RA has entered a new era with the arrival of biologic agents. However, the tools needed to predict response to these drugs to allow tailoring of the treatment regimens are still lacking. This apparent gap in knowledge may lead to the serial use of several immunosuppressive drugs, which may expose patients to an elevated risk of adverse side effects.[13]

Biologic agents are effective in reducing clinical signs of inflammation in RA patients who have failed DMARDs and significant benefits of their combination with MTX have been documented. All biologic agents carry an increased risk of infections with an additional potential side effect of site reactions. Patients being considered for biologic agents should be screened annually for tuberculosis and should receive pneumococcal, influenza, and hepatitis B vaccinations.[2]

Methotrexate (MTX) is currently the most frequently used drug in the treatment of RA. The drug had been synthesized in 1948 and first tests to treat patients with psoriasis and RA were published in 1951. However, until the 1980s there was only limited use of MTX in the treatment of RA. Since the 1990s MTX is the DMARDs of first choice for the treatment of RA in most countries worldwide. By definition, DMARDs in RA are those compounds for which an inhibiting effect on radiographic progression has been demonstrated. Several combinations of DMARDs have been tested, most commonly with MTX as the anchor drug. There are now three main combinations that are playing an important role: MTX + HCQ, MTX + LFN and MTX + biologics such as anti-TNF and other new compounds which block IL6 receptor or T-cell activation and delete B cells.[3] Emerging data from further studies provide critical insight regarding the role of B cells and autoantibodies in various autoimmune conditions and will guide the development of more efficacious therapeutics and better patient selection.[14]

The aim of the present study is to assess the serum BAFF level in RA patients in view of different treatment regimens received and evaluate its relation with the disease activity.