B Lymphocytes in Rheumatoid Arthritis and the Effects of Anti–TNF-α Agents on B Lymphocytes: A Review of the Literature

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ABSTRACT

Purpose: The aim of this article was to review published research related to B lymphocytes in rheumatoid arthritis, their role in the pathogenesis of the disease, the effects of tumor necrosis factor (TNF)-α inhibitors on B lymphocytes, the risk for infection, and responses to vaccines.

Methods: A PubMed search was conducted to review recent advances related to B lymphocytes and the effects of anti–TNF-α on B lymphocytes in rheumatoid arthritis.

Findings: B lymphocytes play an important role in the pathogenesis of rheumatoid arthritis. In this review, we summarize the major mechanisms by which B lymphocytes play a pathologic role in the development and propagation of the disease, as B lymphocytes are recruited to the synovial fluid, where they contribute to local inflammation through the secretion of pro-inflammatory mediators (cytokines, chemokines, micro-RNAs) and present antigens to T cells. We discuss the effects of TNF-α, either direct or indirect, on B lymphocytes expressing receptors for this cytokine. We also show that total B-cell numbers have been reported to be reduced in the blood of patients with rheumatoid arthritis versus healthy controls, but are significantly increased up to normal levels in patients undergoing anti–TNF-α therapy. As for B-cell subsets, controversial results have been reported, with studies showing decreased frequencies of total memory B cells (and memory subsets) and others showing no differences in patients versus healthy controls. Studies investigating the effects of anti–TNF-α therapy have also given controversial results, with therapy found to increase (or not) the frequency of memory B lymphocytes, in patients with rheumatoid arthritis versus healthy controls. Those highly variable results could have been due to differences in patient characteristics and limited numbers of subjects. Finally, we summarize the effects of blocking TNF-α with anti–TNF-α agents on possible infections that patients with rheumatoid arthritis may contract, as well as on responses to vaccination.

Implications: B lymphocytes play a significant role in the pathogenesis of rheumatoid arthritis, and B cell–depletion therapy has a major effect on the course of the disease. The advances in treatment of rheumatoid arthritis include the development of targeted therapies. Anti–TNF-α therapies are widely used despite potentially serious adverse events. The data on the effects of anti–TNF-α therapies on B lymphocytes are limited and conflicting. There is a need for larger studies to better understand the effects of newly discovered therapies on the different cells of the immune system. (*Clin Ther*. 2018;▮:▮▮▮–▮▮▮)

Key words: anti–TNF-α agents, B lymphocytes, rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis is a common autoimmune disease that is associated with progressive disability, systemic complications, early death, and socioeconomic costs.[1] Rheumatoid arthritis is characterized by synovial inflammation and hyperplasia (swelling); autoantibody production (rheumatoid factor [RF] and anti–citrullinated protein antibody [ACPA]);

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cartilage and bone destruction (deformity); and systemic features, including cardiovascular, pulmonary, psychological, and skeletal disorders.[2] Cardiovascular disease and infections represent the leading causes of disability and mortality in patients with rheumatoid arthritis,[3] which may result from compromised humoral immune response.[4,5] Patients treated with anti–tumor necrosis factor (TNF)-α, alone or with methotrexate (MTX), seem to be at further risk.[6,7] Slightly elevated risks for lymphoma and lymphoproliferative malignant disease,[8] lung cancer,[9] or skin cancer[10] have been associated with rheumatoid arthritis. Nonmelanoma skin cancer also appears to be increased in patients with rheumatoid arthritis in the setting of treatment with anti–TNF-α agents.[10]

The disease results from a complex interaction between genes and the environment, leading to a breakdown of immune tolerance and increased synovial inflammation in a characteristic symmetric pattern. Distinct mechanisms regulate inflammation and matrix destruction, including damage to bone and cartilage.[11] The inflammatory infiltrate in rheumatoid arthritis includes T lymphocytes, B lymphocytes, monocytes, and dendritic cells,[12–14] and in ~20% of patients lymphoid neogenesis develops with the formation of ectopic germinal centers (GCs).[15–18] The pathogenic role of chronic inflammation in rheumatoid arthritis is due to persistent immune response during the preclinical and clinical phases of the disease. Chronic inflammation in rheumatoid arthritis has recently been shown to be linked to immunometabolic requirements of innate and adaptive immune cells, as the chronic stimulation of the immune system requires a reliable supply of nutrients, oxygen, and biosynthetic precursors. Recent work has clearly indicated that the functional commitment of rheumatoid arthritis T cells in driving persistent synovial inflammation is mechanistically connected to inefficient DNA repair/chromosome instability (shorter telomeres) and metabolic reprogramming.[19–22] Abnormal metabolic pathways and increased oxidative stress in monocytes/macrophages also seem to be involved in altered T-cell activity and in the development of rheumatoid arthritis through the generation of autoantigens, as suggested by studies in both mice[22] and humans.[19–22]

The purpose of this review was to summarize the published research on B lymphocytes in rheumatoid arthritis, their role in the pathogenesis of the disease, the effects of blocking TNF-α with TNF-α inhibitors on B lymphocytes, the risk for infection, and responses to vaccines.

MATERIALS AND METHODS

Search of the Literature

We conducted a literature search using the PubMed (MEDLINE) database. We initially selected several appropriate key words (examples are *rheumatoid arthritis, inflammation, B lymphocytes,* and *anti–TNF-α agents*). The timeframe used was 1970 to 2018. We retrieved only the citations in English in which the selected key word was the major focus. There were no limitations on the type of study (experimental, clinical). References cited in our review are primary papers, as well as review articles, published in peer-reviewed journals. All references cited by the articles were also searched and analyzed.

RESULTS

A total of [360] articles were identified in the database search. After the exclusion of [260] articles that were [reporting results not reproduced in other studies], data from [102] articles (N = >10,000) were included in the present review.

Role of B Lymphocytes in the Pathogenesis of Rheumatoid Arthritis

B lymphocytes produce autoreactive pathogenic antibodies, such as RF and ACPA, which are well-established indicators of disease and disease severity, as they were shown to enhance tissue injury in a preclinical model of autoimmune arthritis.[23] Autoreactivity to malondialdehyde was recently reported in patients with rheumatoid arthritis and is also linked to disease activity and synovial pathogenesis.[24] Malondialdehyde is a naturally occurring aldehyde, produced under oxidative stress and associated with excessive generation of reactive oxygen species, which catalyze membrane lipid peroxidation. These autoreactive pathogenic antibodies in some patients can be detected many years before disease onset, suggesting that, in predisposed individuals, autoantibodies develop before the establishment of the inflammatory state that leads to clinically detected rheumatoid arthritis.