Is It Possible to Withdraw Biologics From Therapy in Rheumatoid Arthritis?

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ABSTRACT

Background: Biologic agents targeting tumor necrosis factor (TNF) have revolutionized the treatment of rheumatoid arthritis (RA). Clinical remission is perceived as a realistic primary goal, and its maintenance leads to structural and functional remission.

Objective: This study reviews whether discontinuation of biologic agents is possible after sustained remission and discusses its significance from the risk/benefit point of view (including safety and health economic considerations).

Methods: Using a strategic PubMed search, 45 original research articles regarding discontinuation of biologic agents were identified; 7 were selected that had an obvious focus on discontinuation of biologic agents. These articles included the TNF20, BeSt (Behandel Strategieen), and RRR (Remission Induction by Remicade in RA) studies. However, because of the limitations of the original search, we also review here some articles that did not focus mainly on discontinuation of biologic agents but that presented data regarding biologic-free control. These studies included OPTIMA (Optimal Protocol for Treatment Initiation With MTX and Adalimumab), PRESERVE, and CERTAIN, as well as some recent findings in the HONOR (Humira Discontinuation Without Functional and Radiographic Damage Progression Following Sustained Remission) study from our department.

Results: In BeSt and OPTIMA, clinical remission was sustained without functional progression by discontinuing TNF inhibitors, after reducing disease activity by using TNF inhibitors and methotrexate (MTX), in patients with early RA and who were MTX naive. In some studies (including RRR and HONOR), the discontinuation of TNF inhibitors after sustained remission was possible in some patients with long-standing RA who had an inadequate response to MTX. When disease activity flared up after treatment discontinuation, re-treatment with infliximab or adalimumab was highly effective and safe in the majority of patients. It is also clear that tight control with TNF inhibitors and MTX seems to be a prerequisite for having a better chance of biologic-free remission.

Conclusions: Intensive treatment with TNF inhibitors may change the disease process of RA and potentially offers the possibility of a "treatment holiday" from biologic agents. (*Clin Ther*. 2013;35:2028–2035) © 2013 Elsevier HS Journals, Inc. All rights reserved.

Key words: biologic, discontinuation, remission, rheumatoid arthritis, treatment.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammation and joint destruction that causes significant morbidity and mortality. To prevent joint damage, disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX) should often be started after patients are diagnosed. However, the use of MTX monotherapy often fails to control disease activity and to prevent structural damage, and more effective treatment strategies are thus needed. TNF plays a pivotal role in the pathologic processes of RA through the accumulation of inflammatory cells and the self-perpetuation of inflammation, which leads to joint destruction. The combination of MTX and biologic agents targeting tumor necrosis factor (TNF) has revolutionized the treatment of RA, producing significant improvements in clinical, radiographic, and functional outcomes that were not previously observe. The combination has produced the emerging outcome and upcoming end

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point for the treatment as the followings.[1–5] Clinical remission is perceived as an appropriate and realistic primary goal in many patients, and its maintenance leads to structural and functional remission.

The possibility of discontinuation of biologic agent treatment after achievement of remission or low disease activity must be considered because of the long-term safety issues found by inhibiting a particular cytokine and the economic burden associated with expensive biological products. The decision to discontinue synthetic DMARDs should be made with caution; such discontinuation results in twice as many flare-ups, difficulties in reintroducing remission, and a halt in damage.[6] However, similar studies are not available for the biologic agents it remains unclear whether treatment strategies with biologics targeting induction and/or maintenance of clinical remission can potentially lead to subsequent discontinuation of the TNF inhibitors. The goal of the present article was to determine if discontinuation of biologic agents targeting TNF is possible in RA patients, after obtaining low disease activity or clinical remission during certain periods of use with TNF inhibitors. The content is based on results of a systemic literature review as well as new information.

METHODS

A search of PubMed was conducted by using a search strategy that combined terms for *rheumatoid arthritis, biological agent*, and *discontinuation, discontinuing,* or *cessation*. The systematic literature search strategy was as follows: #1, arthritis, rheumatoid [MeSH]; #2, biological agents OR biologics OR TNF inhibitor OR infliximab OR etanercet OR golimumab OR abatacept OR tocilizumab OR certolizumab pegol; #3, clinical trial [Filter]; #4, English [Filter]; #5, discontinuation OR discontinuing OR cessation; #6, review [Filter]; #7, juvenile idiopathic arthritis; and #8, #1 AND #2 AND #3 AND #4 AND #5 NOT #6 NOT #7.

The titles and abstracts of the citations were screened, and relevant articles were retrieved. The following selection criteria were used: (1) clinical trials of biologic agents in patients with RA, followed by discontinuation of the biologic agents due to preferable effectiveness but not to adverse events or to insufficient efficacy; (2) patients with RA aged >18 years; and (3) data available on 1 or more of the following prespecified outcomes: ratio of remission or low disease activity after at least 12 weeks of discontinuation or ratio of re-administration of the biologic agents.

Forty-five original research articles were identified from the PubMed search; 7 articles were selected as candidate studies, and 38 articles were excluded from our analysis. All of the included and excluded articles were published since 1998. The reasons for exclusion were categorized into 3 groups: (1) no description of discontinuing biologic agents; (2) reasons for discontinuing biologic agents were not specified; and (3) no description of discontinuing biologic agents due to preferable effectiveness. Characteristics of the candidate studies are summarized in the **Table**.[7–13]

The majority of the excluded articles focused on the efficacy and safety of certain biologic or synthetic DMARDs but not on discontinuation after attaining preferable disease control. The 7 included articles focused on discontinuation of biologic agents. However, those studies were published from a limited number of nations or institutes, and 4 were subanalyses of the BeSt (Behandel Strategieen) study and 2 were subanalyses of the RRR (Remission Induction by Remicade in RA) study. In addition, published evidence regarding biologic-free disease control is limited in cases of infliximab. We therefore reviewed some articles that did not mainly focus on discontinuation of biologic agents but that included data regarding biologic-free control, including the OPTIMA (Optimal Protocol for Treatment Initiation With MTX and Adalimumab), PRESERVE, and CERTAIN studies. We also included recent findings from the HONOR (Humira Discontinuation Without Functional and Radiographic Damage Progression Following Sustained Remission) study from our department.

RESULTS

Can We Discontinue Infliximab?

Infliximab is an anti-TNF chimeric monoclonal antibody that was approved for the treatment of RA in 1999 in the United States and the European Union. The study regarding biologic-free treatment in RA patients was first reported by a British group as a TNF20 study.[9,14] Patients with early RA who had <12 months of symptoms were treated with a combination of infliximab and MTX. Patients who initiated treatment with infliximab and MTX achieved higher American College of Rheumatology 50% and 70% improvement