

New Approaches for the Treatment of Rheumatoid Arthritis

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Goals and Objectives

Goals:

- 1) To provide the pharmacist with information regarding abatacept and rituximab, two recently approved therapies for the treatment of rheumatoid arthritis
- 2) To provide the pharmacist with an understanding of how these agents can be used in the current treatment paradigm for rheumatoid arthritis

Objectives

After completing the article, the pharmacist should be able to:

- 1) Describe the actions and side-effects of each agent
- 2) List the approved indications for each agent
- 3) Discuss the recommended dosing regimens for each agent
- 4) Describe the pharmacokinetic properties of each agent
- 5) Determine the appropriate use of these agents in the management of rheumatoid arthritis

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Introduction

Traditional therapeutic approaches for rheumatoid arthritis (RA) have centered on non-biologic disease-modifying antirheumatic drugs (DMARDs), the most prescribed being methotrexate (MTX).¹ More recently, biologic DMARDs have been developed that target inflammatory mediators, which are important in the immunopathogenesis of RA (Figure 1). The earliest biologic DMARDs approved for the treatment of RA were the anticytokine agents, three of which act against tumor necrosis factor (TNF)- α : infliximab (Remicade®; Centocor Incorporated, Malvern, PA), etanercept (Enbrel®; Immunex Corporation, Thousand Oaks, CA) and adalimumab (Humira®, Abbott Laboratories, Abbott Park, IL); and one against interleukin (IL)-1: anakinra (Kineret®; Amgen Incorporated, Thousand Oaks, CA).

Figure 1

Targets of biologic therapies for rheumatoid arthritis (footnotes)

MHC=major histocompatibility complex;

TCR=T cell receptor; IL=interleukin;

TNF=tumor necrosis factor;

RF=rheumatoid factor

While these biologic DMARDs have provided notable clinical benefits to many patients with RA, a substantial number of individuals do not respond to cytokine antagonist therapy, or their response diminishes over time. Until recently, these individuals had no proven alternative treatment options.² Novel therapies to meet the needs of these patients have recently been launched in the US, and many are in development.

New approaches to treating rheumatoid arthritis

The activation of T cells is an early event in RA immunopathology, followed by the stimulation of other immune cells such as B cells and macrophages. This leads to cytokine release and ultimately to joint destruction.³ The recent approval of two new biologic RA therapies ó abatacept (ORENCIA®; Bristol-Myers Squibb, Princeton, NJ), which targets T-cell activation, and rituximab (Rituxan®; Genentech Incorporated, San Francisco, CA), which depletes CD20+ B cells ó has opened the door to a wider

selection of treatment options for patients with RA who have had an inadequate response to their current treatment regimen.

Abatacept

Abatacept is the first RA therapy to be specifically approved for the treatment of RA in patients with an inadequate response to either traditional DMARDs or TNF antagonist therapy. Abatacept is indicated for reducing signs and symptoms, inducing a major clinical response, slowing the progression of structural damage and improving physical function in adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs, such as MTX or TNF antagonists. Abatacept may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.⁴

Mechanism of action of abatacept

Abatacept is a soluble fusion protein that consists of the extracellular domain of human cytotoxic lymphocyte-associated antigen-4 (CTLA-4) linked to the modified Fc (hinge, CH2 and CH3 domains) portion of human immunoglobulin G1. Abatacept acts by binding to CD80/CD86 on antigen presenting cells and preventing interaction with CD28 on T cells,⁵ thereby modulating one of the key co-stimulatory pathways required for full T-cell activation.⁶

Administration of abatacept

Following the initial administration, abatacept should be given 2 and 4 weeks after the first infusion, and every 4 weeks thereafter. Abatacept should be administered as a 30-minute intravenous (IV) infusion at a fixed dose approximating 10 mg/kg, according to weight range, as specified in Table 1. No premedication is required.⁴

Clinical efficacy with abatacept

Abatacept treatment results in marked reductions in the signs and symptoms of RA in a broad range of patients, demonstrating significant efficacy both for the treatment of patients with RA who have had an inadequate response to MTX⁷⁻⁹ and for the treatment of those not responding adequately to TNF antagonists.¹⁰

Pharmacokinetics of abatacept

Abatacept has a mean (range) half-life of 13.1 (86 25) days in patients with RA, as assessed after multiple 10 mg/kg IV infusions.⁴ At 10 mg/kg, serum concentration appeared to reach a steady state by Day 60 with a mean (range) trough concentration of 24 (1666) mcg/mL. No systemic accumulation of abatacept occurred upon repeated treatment with 10 mg/kg IV at monthly intervals.⁴ Concomitant MTX, non-steroidal anti-inflammatory drugs, corticosteroids and TNF blocking agents have been found not to influence abatacept clearance.⁴ The main pharmacokinetic properties of abatacept are summarized in Table 2.

The pharmacokinetics of abatacept have not been studied in children or adolescents and no formal studies have been conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of abatacept. Formal drug interaction studies have not been conducted to date.

Safety and tolerability of abatacept

In clinical trials, abatacept was found to be generally safe and well tolerated when added to non-biologic background DMARDs. Acute infusion-related events (adverse reactions occurring within 1 hour of the start of the infusion; assessed specifically in Phase III trials only) were more common in the abatacept-treated patients than in placebo recipients (9% for abatacept, 6% for placebo). The most frequently reported events (162%) were dizziness, headache and hypertension.⁴

Warning and precautions with abatacept

Because a higher rate of infections has been seen when abatacept is added to a background of biologic therapy^{11, 12} abatacept is not recommended for use concomitantly with TNF antagonists or anakinra.⁴

The manufacturers advise that the use of abatacept in patients with RA and chronic obstructive pulmonary disease should be undertaken with caution and that such patients should be monitored for worsening of their respiratory status.

Abatacept is a pregnancy category C drug, and should be used during pregnancy only if clearly needed and, as such, nursing mothers should discuss with their healthcare practitioner the

risk/benefit of continued breastfeeding or discontinuation of the drug.⁴

The manufacturer also advises that patients be evaluated for signs of infection prior to each dose of abatacept and when being transitioned to abatacept from another biologic agent. As yet, no data are available on the secondary transmission of infection from patients receiving live viral vaccines to patients receiving abatacept, and the efficacy of vaccination in patients receiving abatacept is not known. Based on its mechanism of action, abatacept may blunt the effectiveness of some immunizations. These considerations have led to the recommendation that live viral vaccines should not be given concurrently with abatacept, or within 3 months of its discontinuation.⁴

Prior to initiating immunomodulatory therapies, including abatacept, patients should be screened for latent tuberculosis infection with a tuberculin skin test. Patients testing positive in tuberculosis screening should be treated by standard modality prior to therapy with abatacept.⁴ However, abatacept has not been studied in patients with a positive tuberculosis screen, and the safety of abatacept in individuals with latent tuberculosis infection is unknown.

Rituximab

Rituximab is indicated in combination with MTX to reduce signs and symptoms in adult patients with moderately to severely active RA who have had an inadequate response to one or more TNF antagonists.¹³

Mechanism of action of rituximab

Rituximab is a genetically engineered chimeric murineóhuman monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes, and the Fc domain recruits immune effector functions to mediate B-cell lysis in vitro. Administration of rituximab results in the rapid and sustained depletion of circulating and tissue-based B cells.¹³

Administration of rituximab

Rituximab is given as a 1000 mg IV infusion, followed by a second 1000 mg IV infusion after 2

weeks. Rituximab should be administered only by IV infusion at an initial rate of 50 mg/hr. Administration of a glucocorticoid (such as methylprednisolone 100 mg IV on Days 1 and 15 plus oral prednisone 60 mg on Days 2-7 and 30 mg on Days 8-14) 30-60 minutes prior to each infusion has been shown to reduce the frequency and severity of infusion reactions.¹⁴ In addition, premedication consisting of acetaminophen and an antihistamine should be considered before each infusion of rituximab.¹³

Transient hypotension may occur during rituximab infusion, so consideration should be given to withholding antihypertensive medications 12 hours prior to rituximab infusion.¹³

Clinical efficacy with rituximab

Rituximab is effective in patients with active RA,¹⁵ specifically in those patients with active RA and an inadequate response to one or more TNF antagonists.¹⁶ A single course of rituximab, given as two infusions 2 weeks apart, is also effective for at least 24 weeks in the treatment of active RA in rheumatoid factor-positive patients who have had an incomplete response to MTX.¹⁴

Pharmacokinetics of rituximab

Following the administration of two doses of rituximab in patients with RA, the mean maximum serum concentration values were 183 mg/L (coefficient of variation [CV]=24%) for the 2 x 500 mg dose; and 370 mg/L (CV=25%) for the 2 x 1000 mg dose. Following the 2 x 1000 mg rituximab regimen, mean volume of distribution at steady state was 4.3 L (CV=28%).¹³ Mean systemic serum clearance of rituximab was 0.01 L/hour (CV=38%), and mean terminal elimination half-life after the second dose was 19 days (CV=32%).¹³ The pharmacokinetics of rituximab have not been studied in children or adolescents. No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of rituximab.¹³ The pharmacokinetic parameters of rituximab are shown alongside those of abatacept in Table 2.

Safety and tolerability of rituximab

The most common adverse events were infusion associated; 32% of patients with RA who were treated with rituximab experienced an adverse event during or within 24 hours following their

first infusion, compared with 23% of placebo-treated patients receiving their first infusion. Rituximab has caused severe infusion reactions, some of which have proved fatal. The administration of an IV glucocorticoid prior to rituximab infusions reduced the frequency and severity of infusion reactions. However, in clinical trials there was no clear benefit from the administration of an oral glucocorticoid for the prevention of acute infusion reactions. In RA clinical studies, 39% of patients in the rituximab group experienced an infection of any type compared with 34% of patients in the placebo group. The frequency of serious infections was 2% and 1%, respectively.¹³

Precautions and contraindications with rituximab

The use of rituximab is contraindicated in several patient populations, including those with hypertension and those with previous cardiovascular disease. The use of rituximab for RA in patients without a prior inadequate response to one or more TNF antagonists is not recommended,¹³ and the safety and efficacy of retreatment has not been established in controlled trials. Consequently, the long-term side effects of continuous retreatment with B-cell depletion therapies such as rituximab in patients with RA are yet to be determined. Patients that require close monitoring during infusions include those with pre-existing cardiac and pulmonary conditions, and those with prior clinically important cardiopulmonary adverse events.¹³

The safety of immunization with live viral vaccines following rituximab therapy has not been studied and vaccination with live virus vaccines is not recommended. The ability to generate a primary or anamnestic humoral response to vaccination is currently being studied.¹³ Because rituximab targets all CD20+ B lymphocytes (malignant and non-malignant), complete blood counts and platelet counts should be obtained at regular intervals during rituximab therapy, and more frequently in patients who develop cytopenias. The duration of cytopenias caused by rituximab can extend well beyond the treatment period.¹³

Conclusion

New therapies that selectively target events involved upstream in RA immunopathology offer valuable alternatives for patients who have failed standard DMARD therapy. The approval of rituximab in combination with MTX for the treatment of patients with an inadequate response to TNF antagonists provides a further option for patients who have experienced inadequate responses to all other treatment options. The indication of abatacept for reducing signs and

symptoms, inducing a major clinical response, slowing the progression of structural damage, and improving physical function suggests that abatacept will have a considerable impact on the RA treatment paradigm. Abatacept can be used either as monotherapy or in combination with non-biologic DMARDs in patients with an inadequate response to MTX as well as those with inadequate responses to TNF antagonist therapy, providing a valuable therapeutic option with a novel mechanism of action.

Table 1
Abatacept dosage according to weight range

Body weight of patient	Dose	Number of vials*
<60 kg	500 mg	2
60-100 kg	750 mg	3
>100 kg	1 g	4

*Each vial provides 250 mg of abatacept for administration

Table 2
Pharmacokinetic properties of abatacept and rituximab

Pharmacokinetic parameter (Means)	Abatacept in RA (after 10 mg/kg multiple doses*)	Rituximab (after 2 x 1000 mg doses)
Peak concentration (mg/L)	295	370
Terminal half-life (days)	13.1	19.0
Systemic clearance	0.22 mL/hour/kg	0.01 L/hour
Volume of distribution	0.07 L/kg	4.3 L

*Multiple intravenous infusions were administered at Days 1, 15 and 30, and monthly thereafter.

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