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## Biologics for Treating Rheumatoid Arthritis: Review of Abatacept and Rituximab

### Learning Objectives

- 1) Describe the epidemiology of rheumatoid arthritis.
- 2) Become familiar with criteria for diagnosing rheumatoid arthritis and criteria to determine efficacy of treatment.
- 3) Understand the role of biologics in the treatment of rheumatoid arthritis.
- 4) Understand the most important benefits and risks associated with abatacept and rituximab.
- 5) Describe the mechanisms by which abatacept and rituximab affect the pathogenesis of rheumatoid arthritis.

### Abatacept and Rituximab: New Biologics for Rheumatoid Arthritis

#### Introduction

Rheumatoid arthritis (RA) afflicts about 0.5%-1% of the US population and about 1%-2% of the world's population, representing up to 3 million Americans and 60-120 million people worldwide.<sup>1</sup> RA is a chronic, painful and crippling disease for which there is no known cure, resulting in a decreased life expectancy and reduced quality of life. The lifetime cost for RA has been estimated at over \$93,000, and higher costs are associated with more severe disease.<sup>2</sup> Treatment for RA has traditionally focused on reducing inflammation and pain, and preserving joint function.<sup>1,3,4</sup> New biologic agents are now available that specifically target the underlying causes of inflammation in RA. Two of the newer biologics are abatacept, a costimulation blocker, and rituximab, a chimeric anti-CD20 monoclonal antibody. While several studies have shown the efficacy of rituximab in treating RA, there have also been several reports recently of very serious side effects, including deaths, attributed to rituximab. The FDA has issued a warning concerning the possible adverse effects of rituximab.<sup>5</sup> So far, with relatively limited use, these severe adverse events have not been reported for abatacept.

#### Epidemiology and Pathophysiology

The exact cause of RA is not known. It is a systemic autoimmune disease, characterized by flares and remissions, and it is thought to be partly genetic in origin, as well as having environmental triggers. Genetically, RA is associated with polymorphisms of the major histocompatibility complex II (MHC II) that encodes human leukocyte antigens (HLAs). The specific HLAs implicated in RA are HLA-DR1, HLA-DR4, HLA-DR6 and HLA-DR10.<sup>6</sup> RA affects 2-3 times the number of women as men, and more frequently af-

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fects women at a younger age. Onset of the disease is usually between 30-50 years old, though it can occur at any age and tends to increase in frequency from 60-85 years of age.<sup>6,7</sup>

RA is believed to be initiated when CD4+ T lymphocytes recognize arthritis-inducing antigens in the synovial tissue. A process is then set in motion in which the CD4+ T cells stimulate monocytes, macrophages and synovial fibroblasts. These then produce enzymes, matrix metalloproteinases, which are partially responsible for the destruction of cartilage and bone in the affected joints. T cell activation appears to be dependent on the presence of B cells. The exact role of B cells in the pathogenesis of RA is not yet clear, however, it is known that B cells are stimulated to produce rheumatoid factor antibody, as well as other immunoglobulins. Cytokines are also produced, including interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)-alpha. These are the major cytokines that perpetuate the inflammatory process in RA.<sup>8</sup>

Together, these processes lead to inflammation of the synovium, which becomes thickened. This locally invasive inflammatory tissue is called pannus, and over time, it penetrates and causes the destruction of the cartilage and bone.<sup>1,8</sup>

## Diagnosis and Goals of Treatment

The signs and symptoms of RA vary between patients, and are often similar to those of other musculoskeletal disorders, sometimes making diagnosis difficult. Some of the early signs of RA are fever, malaise, weight loss, symmetric joint tenderness, warmth, swelling and pain, and morning stiffness lasting 30 minutes to several hours.<sup>4</sup> Patterns of affected joints (symmetry and location) are important in diagnosing RA. According to the 1987 revised classification criteria for rheumatoid arthritis, diagnosis of RA is based on 1) morning stiffness, 2) arthritis of 3 or more joint areas, 3) arthritis of hand joints, 4) symmetric arthritis, 5) rheumatoid nodules, 6) serum rheumatoid factor (RF), and 7) radiographic changes.<sup>9</sup>

Serum RF, evaluated at baseline, has a specificity of about 90% and is found in over 75% of RA patients, making it a useful marker in early disease.<sup>4</sup> The American College of Rheumatology (ACR) Guidelines recommend that laboratory tests at baseline should include measurements for RF, erythro-

cyte sedimentation rate (ESR) or C-reactive protein (CRP) levels, and a complete blood cell count. ESR and CRP are among the acute-phase reactants used to measure clinical improvement. Renal and hepatic function tests are also recommended due to the possible toxicities of many drugs used in RA.<sup>10</sup>

An important method for tracking changes to the affected joints is through imaging, although it is likely that the x-rays will appear normal during the first 6 months after symptoms appear. Imaging has shown that about 30% of patients have joint damage at the time that RA is diagnosed, but this number increases to about 60% within 2 years.<sup>11</sup>

Criteria for defining improvement and remission in RA have been developed by the ACR. These criteria are now widely used in clinical practice and in clinical studies. The ACR criteria for 20% clinical improvement (ACR20) require a 20% improvement in the number of tender and swollen joints, as well as a 20% improvement in 3 out of 5 of the following: patient's global assessment, physician's global assessment, patient's assessment of pain, degree of disability, and level of acute-phase reactant.<sup>10</sup> Based on the same parameters, there are also criteria for 50% improvement (ACR50) and 70% improvement (ACR70).

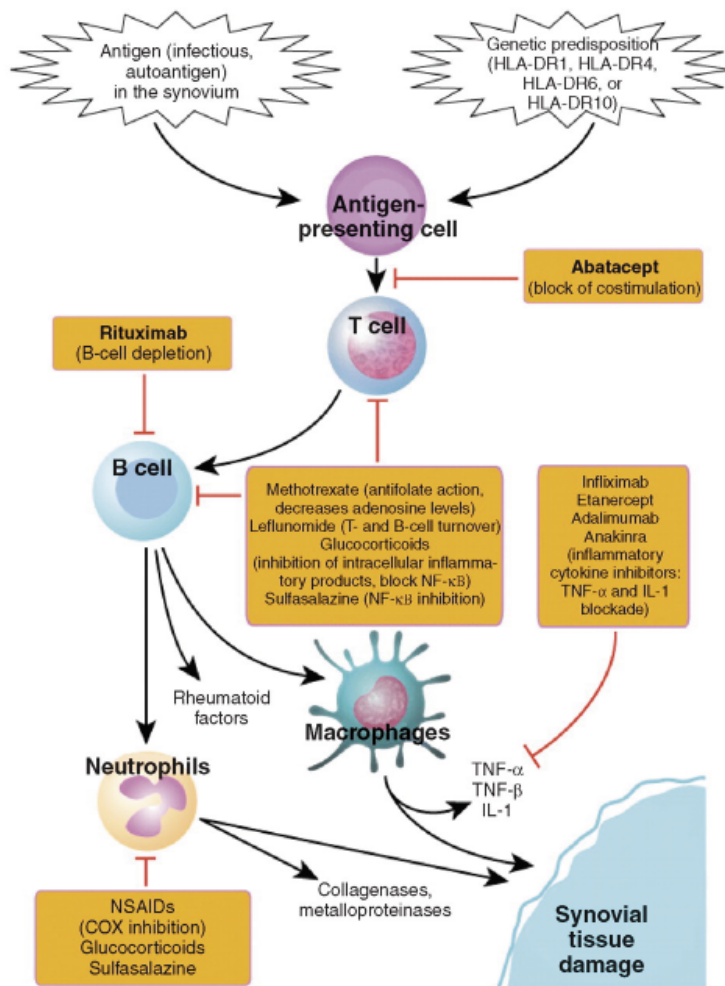
## RA Therapy

While diagnosis can be difficult, once the disease is diagnosed it is extremely important to start therapy as quickly as possible to prevent joint damage.<sup>11,12</sup> The goal of drug therapy for RA is to reduce inflammation, pain and joint destruction, and to preserve function. Ideally, the goal would be to induce complete remission, though this is seldom achieved. Drug therapy for RA generally consists of a combination of NSAIDs, glucocorticoids, disease-modifying antirheumatic drugs (DMARDs), and more recently, the biologics.

Although NSAIDs do not help to slow progression of disease, they are often given even before RA is diagnosed to reduce the pain and stiffness.<sup>11,12</sup> Side effects of concern with NSAIDs are gastrointestinal ulcers, perforation and hemorrhage, and these concerns increase with increased patient age.<sup>11</sup> COX-2 selective NSAIDs, such as rofecoxib (Vioxx<sup>®</sup>), celecoxib (Celebrex<sup>®</sup>) and valdecoxib (Bextra<sup>®</sup>) were used to help alleviate the gastrointestinal side effects

**Overview of the inflammatory process in the synovium and mechanism of action of drugs used to treat rheumatoid arthritis.** An infectious or environmental epitope in combination with a susceptible genetic background initiates the inflammatory cascade. The interaction between T and B cells often results in the production of rheumatoid factor and other autoantibodies. B cells also stimulate the activation of neutrophils and macrophages. Neutrophils secrete enzymes that directly mediate tissue damage. Macrophages are responsible for the production of inflammatory mediators (e.g., TNF- $\alpha$ , TNF- $\beta$ , IL-1). HLA=human leukocyte antigen, NF- $\kappa$ B= nuclear factor  $\kappa$ B, TNF=tumor necrosis factor, IL= interleukin, NSAIDs = nonsteroidal antiinflammatory drugs, COX = cyclooxygenase.

Figure 1. From Gaffo A, Saag KG, Curtis JR. Treatment of rheumatoid arthritis. *Am J Health-Syst Pharm.* 2006;63:2451-2465.



until rofecoxib, and then valdecoxib, were voluntarily removed from the market in 2004 and 2005 due to the possibility of serious cardiovascular adverse events.<sup>10,11</sup> Whatever NSAID is used, once RA has been diagnosed, DMARDs should be added to the regimen.

Among the drugs known as DMARDs are methotrexate, sulfasalazine, hydroxychloroquine, intramuscular gold, minocycline, azathioprine, cyclosporine and leflunomide. Of these drugs, methotrexate has become the standard of care.<sup>10</sup> Benefits of DMARDs are that they improve symptoms, reduce inflammation and slow disease progression, resulting in improved functional status. Among the drawbacks of these drugs are that dosing is sometimes complicated and there are multiple toxicities requiring close monitoring. However, perhaps the most important drawback is that approximately 50%

of patients taking methotrexate discontinue the drug after 5 years due to toxicity or lack of efficacy.<sup>12,13,14</sup> When patients fail methotrexate or other DMARDs due to lack of response or toxicity, biologics are the next step in therapy.

### Biological Agents in RA

The most recent therapies for RA are the biologics, or biologic DMARDs. In the last 10 years a great deal has been learned about the inflammatory process that is the underlying cause of pain and joint destruction in RA. Biological agents target specific areas of the inflammatory process, thus slowing the disease. Tumor necrosis factor (TNF) inhibitors, etanercept and infliximab were the first of the biologics approved by the US Food and Drug Administration (FDA) for treatment of RA, in 1998 and 1999, respectively. The third TNF inhibitor,

Table 1. Comparison of ACR response rates for abatacept and rituximab.

| Study                  | Duration of Treatment (weeks) | Number of patients | Treatment                             | ACR20 | ACR50 | ACR70 |
|------------------------|-------------------------------|--------------------|---------------------------------------|-------|-------|-------|
| Genovese <sup>19</sup> | 24                            | 256                | Abatacept ~10 mg/kg + DMARD           | 50.4% | 20.3% | 10.2% |
|                        |                               | 133                | Placebo                               | 19.5% | 3.8%  | 1.5%  |
| Kremer <sup>17</sup>   | 52                            | 115                | Abatacept 2 mg/kg + methotrexate      | 41%   | 23%   | 12%   |
|                        |                               | 105                | Abatacept 10 mg/kg + methotrexate     | 62.6% | 41.7% | 20.9% |
|                        |                               | 119                | Placebo + methotrexate                | 36.1% | 20.2% | 7.6%  |
| Kremer <sup>18</sup>   | 52                            | 433                | Abatacept ~10 mg/kg + methotrexate    | 73.1% | 48.3% | 28.8% |
|                        |                               | 219                | Placebo + methotrexate                | 39.7% | 18.2% | 6.1%  |
| Cohen <sup>26</sup>    | 24                            | 311                | Rituximab 1,000 mg + methotrexate     | 51%   | 27%   | 12%   |
|                        |                               | 209                | Placebo + methotrexate                | 18%   | 5%    | 1%    |
| Edwards <sup>27</sup>  | 24                            | 40                 | Rituximab 1,000 mg                    | 65%   | 33%   | 15%   |
|                        |                               | 41                 | Rituximab 1,000 mg + cyclophosphamide | 76%   | 41%   | 15%   |
|                        |                               | 40                 | Rituximab 1,000 mg + methotrexate     | 73%   | 43%   | 23%   |
|                        |                               | 40                 | Methotrexate                          | 38%   | 13%   | 5%    |
| Edwards <sup>27</sup>  | 48                            | 40                 | Rituximab 1,000 mg                    | 33%   | 15%   | 10%   |
|                        |                               | 41                 | Rituximab 1,000 mg + cyclophosphamide | 49%   | 27%   | 10%   |
|                        |                               | 40                 | Rituximab 1,000 mg + methotrexate     | 65%   | 35%   | 15%   |
|                        |                               | 40                 | Methotrexate                          | 20%   | 5%    | 0%    |
| Emery <sup>28</sup>    | 24                            | 124                | Rituximab 500 mg + methotrexate       | 55%   | 33%   | 13%   |
|                        |                               | 192                | Rituximab 1,000 mg + methotrexate     | 54%   | 34%   | 20%   |
|                        |                               | 149                | Placebo + methotrexate                | 28%   | 13%   | 5%    |

adalimumab, was approved in 2002. Anakinra, an interleukin-1 (IL-1) receptor antagonist, was approved to treat RA in 2001. The biologics most recently FDA approved for treating RA are abatacept in 2005, and rituximab in 2006, although rituximab was approved in 1997 for treatment of non-Hodgkin's lymphoma. Like most treatments for RA, biologics act by interrupting the inflammatory process in the synovium. (Figure 1)

## Abatacept

The FDA approved abatacept (Orencia<sup>®</sup>, Bristol-Meyers Squibb)<sup>15</sup> in 2005 for “reducing signs and symptoms, inducing major clinical response, slowing the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease Modifying Anti-Rheumatoid Drugs (DMARDs), such as methotrexate or TNF antagonists.” The FDA approved abatacept to be used as monotherapy or in combination with DMARDs, with the exception of TNF antagonists. Abatacept binds to CD80 and CD86, which prevents their interaction with CD28. By preventing this interaction, abatacept stops the costimulatory signal necessary to fully activate T lymphocytes involved in the pathogenesis of RA.<sup>16</sup> Administration of abatacept is by 30-minute intravenous (IV) infusion. After the initial administration, abatacept should be given at 2 and 4 weeks, then every 4 weeks thereafter. Dosing is determined by body weight: <60 kg=500 mg, 60 to 100 kg=750 mg, and >100 kg=1,000 mg. Among the most common side effects of abatacept are headache, nausea, sore throat and upper respiratory tract infection. The more serious side effects include increased risk of infection, allergic reactions and malignancies, although how abatacept possibly contributes to the development of cancer is not known.

Kremer and associates<sup>17</sup> evaluated abatacept in a randomized double-blind, placebo-controlled study, known as the AIM trial (Abatacept in Inadequate responders to Methotrexate), to determine safety and efficacy. This 12-month trial randomized 339 RA patients meeting specific ACR criteria to compare the efficacy of their ongoing methotrexate treatment plus placebo (n=119) to methotrexate plus either abatacept 2 mg/kg (n=105), or abatacept 10 mg/kg (n=115). The study drug was given by IV infusions at baseline, then every 2 weeks for the first month, and then monthly for the remainder of the trial. The mean age of patients was 55 years (range 17-83), 87% were Caucasian and 68% were female. The primary end point was based on ACR20 responses, and the secondary end points were ACR50 and ACR70 responses.

At the completion of the trial, patients were assigned to 4 different groups based on the ACR improvement responses. At 12 months, patients in

the abatacept 10 mg/kg group showed an ACR20 response of 62.6% compared with 36.1% for placebo (p<0.001). The abatacept 10 mg/kg group also had significant response rates for ACR50 at 1 year of 41.7% versus 20.2% for placebo (p<0.001), and ACR70 response rates of 20.9% versus placebo 7.6% (p=0.003). (Full results are given in Table 1).

Adverse events (AEs) were low in both abatacept groups, and similar to placebo. The most common AEs in all groups were headache, nausea and nasopharyngitis. The frequency of serious AEs was also similar between the 10 mg/kg abatacept group and placebo, 1.7% each. Serious AEs included myocardial infarction, chest pains and gastrointestinal disorders.

In a 12-month pivotal study with 652 RA patients, Kremer and associates<sup>18</sup> evaluated the efficacy of abatacept given once monthly as an IV infusion at a dose of approximately 10 mg/kg of body weight (n=433), compared with placebo (n=219). Mean age for these patients was 51 years, 78% were women and 86% were Caucasian. Primary end points were ACR20, clinically important improvement in Health Assessment Questionnaire Disability Index (HAQ-DI) score, and radiographic progression of joint erosion at one year. The Medical Outcomes Study Short Form-36 Health Survey (SF-36) was used to evaluate changes in HRQOL. Secondary end points included ACR50 and ACR70 responses at 6 months, as well as all ACR responses after 1 year.

Results in clinical efficacy of the trial showed significant improvement in ACR20 responses at 6 months in the abatacept group compared with placebo 67.9% vs 39.7% (p<0.001), in ACR50 responses 39.9% vs 16.8% (p<0.001), and in ACR70 responses 19.8% vs 6.5% (p<0.001). The results at 1 year showed even greater responses, ACR20 73.1% vs 39.7%, ACR50 48.3% vs 18.2%, and ACR70 28.8% vs 6.1% (p<0.001 for each). The physical function scores reflected a similarly significant improvement in the abatacept group.

The incidence of adverse events was similar in the active treatment group and the placebo group, 87.3% and 84.0%, respectively. Serious adverse events, including infections, occurred more frequently in the abatacept group; however, discontinuation due to serious infection was similar in both groups, 2 in the abatacept group (0.5%) and 1 in the placebo group

(0.5%). Six patients showed antibody reactivity to abatacept, but none experienced a hypersensitivity reaction.

A second pivotal study was conducted by Genovese and associates<sup>19</sup>, in which RA patients from 89 different sites were randomly assigned to either abatacept (n=258) at a dose of approximately 10 mg/kg of body weight, or to placebo (n=133). Study drug or placebo was given on days 1, 15 and 29, and then once every 28 days for 6 months. Patients had a mean age of 54 years, 96% were Caucasian and 77% were women. All patients were also taking at least one DMARD and were not allowed any TNF inhibitors. Primary end points were based on ACR20 response rates and patient improvement as measured by the HAQ-DI at 6 months. Secondary end points were ACR50 and ACR70 response rates at 6 months, and Disease Activity Score in 28 joints (DAS28) scores.

The ACR20 responses at 6 months were significantly greater in the abatacept group compared with placebo, 50.4% vs 19.5% (p<0.001). At 6 months, ACR50 and ACR70 results were also significantly improved with abatacept, 20.3% vs 3.8% (p<0.001) and 10.2% vs 1.5% (p=0.003), respectively. Physical function improvements were also significantly greater in the abatacept group at 6 months. The HAQ-DI for abatacept vs placebo was 47.3% vs 23.3% (p<0.001). Significant improvements were seen at day 15 and thereafter in the abatacept group. Abatacept also showed significant improvement over placebo in HRQOL scores in both physical and mental components (p<0.001 and p<0.01, respectively).

Adverse events causing discontinuation were low in both groups; abatacept 3.5%, serious events 2.7%, and placebo 3.8%, serious events 1.5%. The rates of any adverse events and serious adverse events were 79.5% and 10.5% respectively for abatacept, and 71.4% and 11.3% for placebo, respectively. Infections were not significantly different in the abatacept group compared with placebo, 37.6% vs 32.3% (p=0.30), while serious infections occurred at a rate of 2.3% in both groups. Infusion reactions were not significantly different between abatacept and placebo, 5.0% vs 3.0% (p=0.35), and were generally mild to moderate reactions. No severe reactions occurred in either group.

## Rituximab

Rituximab (Rituxan<sup>®</sup>) was FDA approved in 2006 for use in combination with methotrexate to treat adults with moderate to severe RA that did not have adequate response to TNF antagonist therapy.<sup>20</sup> Rituximab is a genetically engineered chimeric anti-CD20 monoclonal antibody that causes lysis of CD20 B cells.<sup>21</sup> Dosing for rituximab in RA is two 1,000 mg IV infusions which are separated by 2 weeks. To reduce the incidence and severity of infusion reactions, it is recommended that methylprednisolone 100 mg IV, or its equivalent, be given ½ hour before each rituximab infusion. Adverse reactions associated with rituximab include hematologic, cardiac, immune/autoimmune, infections, skin and gastrointestinal.<sup>22</sup> Early in 2006 the FDA issued a black box warning that rituximab had caused fatalities due to infusion reactions, tumor lysis-syndrome, and severe mucocutaneous reactions.<sup>23</sup> In December of 2006, the FDA issued a warning about 2 cases of fatal progressive multifocal leukoencephalopathy (PML) viral infection in lupus patients taking rituximab off-label.<sup>24</sup> Post-marketing surveillance has shown that there have been over 730,000 documented non-Hodgkin's lymphoma patients taking rituximab over the last 7 years with 23 cases of PML reported in these patients.<sup>25</sup> The usual dosing regimens for rituximab in treating hematologic malignancies consisted of 375 mg/m<sup>2</sup> IV given once a week for 4 weeks, or 8 weeks, in combination with chemotherapy. However, the results of several randomized, controlled trials have shown rituximab to be both safe and effective in treating RA.

Cohen and associates<sup>26</sup> conducted a 2-year multicenter, double-blind, placebo-controlled randomized trial that evaluated the use of rituximab in the treatment of RA. This was one of the pivotal studies used by the FDA in awarding rituximab its indication for RA. The investigators found rituximab to be safe and effective after one course, consisting of two 1,000 mg IV infusions, one on day 1 and the other on day 15, during the 24 week trial. All patients in both groups also received oral or IV methotrexate, at dosages of 10-25 mg/week. The study consisted of 520 RA patients, mean age 53 years, with an intent-to-treat (ITT) population of 499 patients, 201 patients randomized to the placebo arm and 298 to the study drug. All patients had active RA and all patients had

received anti-TNF agents, with 91% of the patients having had inadequate response to those agents. The primary end point for efficacy was based on ACR20 improvement criteria at 24 weeks. Secondary end points consisted of ACR50 and ACR70 improvement criteria, DAS28 scores, and the European League Against Rheumatism (EULAR) response criteria at 24 weeks.

The results showed that rituximab was significantly more effective than placebo, with values of  $p < 0.0001$  in all comparisons; ACR20 (rituximab 51% vs placebo 18%), ACR50 (rituximab 27% vs placebo 5%), and ACR70 (rituximab 12% vs placebo 1%). EULAR responses were also significantly improved in rituximab treated patients, 65% vs 22% ( $p < 0.0001$ ). DAS28 scores were significantly reduced from baseline in rituximab patients compared to placebo treated patients (-0.4 vs -1.9,  $p < 0.0001$ ). Rituximab was also associated with a 55% mean decrease in RF levels, while placebo showed a mean increase of 37%.

Safety data showed that 88% of placebo treated patients reported AEs, and 85% of patients taking the study drug. Less than 40% of all AEs were considered to be related to study treatment. In the placebo group, 2 patients left the study due to AEs, 1 with gastric cancer, and 1 with thrombocytosis. In the rituximab group, 8 patients withdrew from the study due to AEs, 5 had infusion related reactions, 1 because of cardiac tamponade, 1 experienced spontaneous abortion, and 1 had progressive RA. Urinary tract infection was reported in 8% of the placebo group and in 3% of the rituximab group, while nausea was reported more frequently in the rituximab group, 7% vs 2%.

Rituximab was also found to be effective in a 24-week, randomized, controlled, double-blind study conducted by Edwards and associates.<sup>27</sup> One hundred-sixty-one RA patients, with a mean age of 54 years, experiencing active disease were randomized to one of 4 dosage groups: methotrexate  $\geq 10$  mg/week orally, plus placebos (for rituximab and cyclophosphamide) as the control group; rituximab 1,000 mg IV on days 1 and 15, plus placebos (for methotrexate and cyclophosphamide); rituximab plus cyclophosphamide 750 mg IV on days 3 and 17, plus placebo (for methotrexate); or rituximab plus methotrexate, plus placebo (for cyclophosphamide). Dosing was the same in all groups. The

primary end point was based on the proportion of patients having an ACR50 response at 24 weeks. The secondary end points were ACR 20 and ACR70 responses as well as the EULAR response criteria.

At 24 weeks, the dosing schedules of rituximab combined with either methotrexate or cyclophosphamide showed significantly higher levels of response ( $p = 0.005$ ) than the control group, as measured by the ACR50 criteria. Response in the group that received rituximab alone was numerically higher than the control group (ACR50 criteria), but the difference did not reach statistical significance ( $p = 0.059$ ). Results for the secondary end points revealed that proportions of patients with ACR20 responses at 24 weeks were significantly greater in all rituximab groups ( $p \leq 0.025$ ) compared with the control group, and ACR70 responses were significantly higher in rituximab plus methotrexate than in the control group, ( $p = 0.048$ ). Statistically significant outcomes evaluated at 48 weeks for ACR20 responses were: methotrexate 20%, rituximab plus methotrexate 65% ( $p < 0.001$ ); ACR50 responses for methotrexate 5%, rituximab plus methotrexate 35% ( $p = 0.002$ ); ACR70 responses for methotrexate 0%, rituximab plus methotrexate 15% ( $p = 0.03$ ).

At the 24 week evaluation, the incidence of adverse events was similar in all treatment groups, with at least one adverse event reported by 73-85% of patients. Adverse events associated with the first infusion were 30-45% in each group. A total of 16 serious adverse events were reported in 14 patients, with patients receiving rituximab plus cyclophosphamide reporting the highest incidence. One patient in the control group and 4 patients in the rituximab groups reported serious infections. One of the 4, in the rituximab alone group, developed fatal bronchopneumonia. At 48 weeks, 6 additional serious adverse events were reported in the rituximab groups, including 2 serious infections.

Safety and efficacy of rituximab were evaluated by Emery and associates<sup>28</sup> in a 24-week, double-blind, placebo-controlled trial in which 465 RA patients were randomized into 9 different treatment groups. Twenty-one RF-positive patients, mean age 51 years, were given either placebo or rituximab 500 mg or 1,000 mg IV on days 1 and 15. The RF-positive group also got either placebo or methylprednisolone 100 mg IV on days 1 and 15, or methylprednisolone 100 mg IV on days 1 and 15 plus prednisone 60 mg

orally on days 2-7 and 30 mg on days 8-14. RF-negative patients were given either placebo or 2 doses of rituximab 1,000 mg IV, with or without glucocorticoids, and methotrexate 10-25 mg/week.

The primary end point was the proportion of RF-positive patients who met the ACR20 response criteria at 24 weeks. Secondary end points were to evaluate group differences in ACR50 and ACR70 responses, as well as DAS28 assessment and EULAR responses.

The intent-to-treat population for efficacy consisted of 367 RF-positive patients. Results at 24 weeks showed that the proportion who achieved an ACR20 response was significantly higher in all rituximab groups compared with placebo ( $p < 0.0001$ ). The proportion of patients with an ACR50 response was also greater in all rituximab groups ( $p \leq 0.001$ ), and an ACR70 response was significantly greater than placebo in the 500 mg rituximab group ( $p = 0.029$ ) and in the 1,000 mg rituximab group ( $p \leq 0.001$ ). DAS28 and EULAR outcomes were also significantly greater than placebo in all rituximab groups ( $p < 0.0001$ ).

Evaluation of safety measures showed that 70% of patients in the placebo groups reported at least one adverse event, compared to 81% in the 500 mg rituximab group, and 85% in the 1,000 mg group. Most events in all groups were rated mild to moderate, and most were associated with the first infusion. Of 26 total serious adverse events, serious infections occurred in 2 patients in the placebo group (1%), and 4 patients (2%) in the 1,000 mg rituximab group. The remaining 20 serious events occurred in: placebo, 2 AEs (1%), rituximab 500 mg, 9 AEs (7%), and rituximab 1,000 mg, 9 AEs (5%). Five of these events were nervous system related and the remaining events were widely distributed throughout the body systems. One fatal event occurred. A 73 year-old woman in the 500 mg rituximab group, with a history of atrial fibrillation, hypertension, diabetes and hyperlipidemia, died of a cerebral infarction 23 weeks after her first rituximab infusion.

## Conclusion

Traditional management of RA has focused on controlling pain and inflammation with NSAIDs and, more recently, with DMARDs, but these agents have often not been tolerated due to toxicities, or patients have had inadequate responses. After many years of research, the past few years have seen major progress in deciphering the molecular

pathogenesis of RA, and with that knowledge have come the biologic agents for treating RA. Randomized controlled trials have proven the efficacy of abatacept and rituximab in treating RA, and the side effects in trials have been largely mild to moderate. Based on limited experience, abatacept has been shown to induce fewer and milder adverse effects. However, clinicians should keep in mind the potential dangers of these new biologics. In addition to the warnings issued by the FDA for rituximab concerning tumor lysis syndrome, severe mucocutaneous reactions and severe infusion reactions, biologics increase the potential for malignancies and severe, even fatal, infections.

When dealing with a disease as painful and crippling as RA, clinicians and patients are looking for agents that show better results than have been available thus far. Biologics have improved the treatment of RA by slowing the progression of joint destruction in ways not possible before, and no doubt will have a growing place in the treatment of RA. In a recent position statement, the American College of Rheumatology indicated that, when appropriate, biologics should be made available to all patients suffering from serious RA. The issue of cost was also addressed, indicating that it may be cost effective to use biologics due to the reduced costs of complications associated with progressive RA.<sup>29</sup>

Patients must be well informed as to the benefits and risks involved with biologics, and clinicians should remain alert to signs of severe adverse effects. Hopefully, over time these biologics will prove to be as safe as they are effective.

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**ACPE# 107-999-07-039-H01 (0.1 CEU/1 Hr.)**

**Volume: 18 Issue: 1 MARCH 2007**

**Title of Educational Activity (Article)**

**BIOLOGICS FOR TREATING RHEUMATOID ARTHRITIS:  
REVIEW OF ABATACEPT AND RITUXMAB**

Name \_\_\_\_\_

Address \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_ Zip \_\_\_\_\_

Social Security Number (optional) \_\_\_\_\_

Pharmacy License Number(s) \_\_\_\_\_

I hereby certify that I have taken this test:

Signature/Date \_\_\_\_\_

1. Rheumatoid arthritis affects approximately how many people worldwide?
  - a. 0.5-1 million
  - b. 3-5 million
  - c. 60-120 million
  - d. 250-300 million
2. The mechanism of action for abatacept is:
  - a. depletion of beta cells
  - b. inhibition of the costimulation signal
  - c. inhibition of tumor necrosis factor alpha
  - d. interleukin-1 receptor antagonism
3. Rheumatoid arthritis affects women:
  - a. about as frequently as it does men
  - b. more severely than it does men
  - c. 2-3 times more frequently than it does men
  - d. at an older age of onset compared to men
4. The mechanism of action for rituximab involves:
  - a. interleukin-6 inhibition
  - b. lysis of CD20 B cells
  - c. interleukin-1 inhibition
  - d. inhibition of CD80 and CD86
5. Abatacept is indicated for use in rheumatoid arthritis patients who have had an inadequate response to one or more:
  - a. NSAIDs.
  - b. glucocorticoids
  - c. DMARDs
  - d. biologics
6. ACR20, ACR50 and ACR70 refer to criteria for measuring:
  - a. clinical improvement
  - b. quality of life
  - c. number of rheumatoid nodules
  - d. all of the above
7. The correct dose for one course of rituximab in treating rheumatoid arthritis is:
  - a. one 600 mg dose per week for 4 weeks
  - b. a single dose of 10 mg/kg per month
  - c. two 1,000 mg doses given 2 months apart
  - d. two 1,000 mg doses given 2 weeks apart
8. According to the 1987 revised classification criteria, diagnosis of rheumatoid arthritis is based on all of the following except:
  - a. asymmetric arthritis
  - b. arthritis of 3 or more joint areas
  - c. serum rheumatoid factor
  - d. rheumatoid nodules

9. The primary end point of the AIM trial found:
  - a. abatacept 10 mg/kg plus methotrexate was superior to placebo plus methotrexate by an ACR50 response of 41.7% versus 20.2%
  - b. abatacept 10 mg/kg plus methotrexate was superior to placebo plus methotrexate by an ACR20 response of 62.6% versus 36.1%
  - c. abatacept plus methotrexate was superior to placebo plus methotrexate by an ACR50 response of 20.3% versus 3.8%
  - d. abatacept ~10 mg/kg plus methotrexate was superior to placebo plus methotrexate by an ACR20 response of 73.1% versus 39.7%
10. Serious side effects associated with rituximab include all of the following except:
  - a. tumor lysis syndrome
  - b. infusion reactions
  - c. rhabdomyolysis
  - d. severe mucocutaneous reactions

**Please Note: The CE processing fee is \$7.50 USD. Forms should be mailed to: Kristen K. Dearden**

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**PROGRAM EVALUATION**

|                                     | Excellent |   |   | Poor     |   |
|-------------------------------------|-----------|---|---|----------|---|
|                                     | 5         | 4 | 3 | 2        | 1 |
| Overall quality                     | 5         | 4 | 3 | 2        | 1 |
| Relevance to practice               | 5         | 4 | 3 | 2        | 1 |
| Value of content                    | 5         | 4 | 3 | 2        | 1 |
|                                     | Agree     |   |   | Disagree |   |
|                                     | 5         | 4 | 3 | 2        | 1 |
| Important to pharmacists            | 5         | 4 | 3 | 2        | 1 |
| Increased my knowledge              | 5         | 4 | 3 | 2        | 1 |
| Achieved stated objectives          | 5         | 4 | 3 | 2        | 1 |
| Was educational and not promotional | 5         | 4 | 3 | 2        | 1 |

It took me \_\_\_\_\_ hours and \_\_\_\_\_ minutes to read this article and complete the assessment questions.

# New Molecular Entities & Biologicals

*FDA Approvals*  
November 2006 – February 2007

An *IDIS* search retrieved articles relevant to the new drugs and their approved uses. These articles provide a selection of key critical studies and reviews. Additional information on these newly approved drugs will be available in the FDA Approval Package (an official United States Food and Drug Administration [FDA] document) that is compiled for new drugs following approval. The FDA Approval Package includes reviews of the pivotal and supportive clinical studies conducted during the approval process. These studies are often not published elsewhere. FDA Approval Packages are selectively indexed and included as part of the *IDIS* database as they become available. Use the descriptor *155 FDA APPROVAL PACKAGE* in combination with the valid drug term to retrieve these documents from the *IDIS* database.

| Generic Name<br>Trade Name<br>(Therapeutic Potentials)                   | Sponsor<br>(Approval Date)                                     | Valid <i>IDIS</i> Drug Term<br>Drug Number<br>( <i>IDIS</i> Citations)                                     | Indication/Use<br>Dosage Form   | Valid <i>IDIS</i> Disease Term<br>Modified ICD-9-CM Number                                    |
|--|--|--|---|---|
| Paliperidone<br><i>Invega</i><br>(S)                                     | Janssen LP<br>(Dec. 19, 2006)                                  | PALIPERIDONE<br>28160861<br>(1 citation)   | Schizophrenia.<br>Oral Tablet   | Schizophrenia NEC<br>295.   |
| Human Papillomavirus<br>Recombinant Vaccine<br><i>Gardasil</i><br>(BIOL) | Merck<br>(June 8, 2006)<br>1/30/2007<br>Supplement<br>Approval | HUMAN PAPILOMAVI-<br>RUS VACCINE<br>80120056<br>(78 citations)   | Prevent cervical cancer, pre-<br>cancerous genital lesions and<br>genital warts due to human<br>papillomavirus (HPV) types 6,<br>11, 16 and 18. | Neop, MGN-Cervix Uteri<br>180.<br>War, Viral<br>078.1<br>Innoculation and Vaccination<br>99.3 |
| Lisdexamfetamine Dimesyl-<br>ate<br><i>Vyvanse</i><br>(S)                | New River<br>(Feb. 23, 2007)                                   | (0 citations) No published<br>human studies have been<br>found for entry into the <i>IDIS</i><br>database. | Treatment of attention<br>deficit hyperactivity disorder<br>(ADHD).<br>Capsule  | Syn-Hyperkinetic, Childhood<br>314.   |

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### Paliperidone

Kramer M, Simpson G, Maciulis V, Kushner S, et al. Paliperidone extended-release tablets for prevention of symptom recurrence in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol*.2007; 27: 6-14. (*IDIS* Article Number 568784)

*In a randomized, double-blind, placebo-controlled, multicenter study of 113 patients with schizophrenia, investigators evaluated the efficacy of paliperidone extended release tablets, 3-15 mg once daily, starting at 9 mg/day. Time to first recurrence of schizophrenia symptoms was the primary efficacy parameter, and the study was stopped early, at the preplanned interim analysis, due to positive efficacy. At interim analysis, investigators found that 14 patients taking the study drug (25%) had recurrence of symptoms, compared to 29 placebo patients (53%), and there was a significantly greater time to recurrence of symptoms, 83 days in the paliperidone group versus 23 days for placebo (p=0.005). Adverse events were similar in both the paliperidone and placebo groups.*

### Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine

Mao C, Koutsky LA, Ault KA, Wheeler CM, et al. Efficacy of human papillomavirus-16 vaccine to prevent cervical intraepithelial neoplasia: a randomized controlled trial. *Obstet Gynecol*.2006; 107:18-27. (*IDIS* Article Number 546914)

*Investigators conducted this 48-month, randomized, double-blind, placebo-controlled trial with 2,391 women aged 16-23 years who received intramuscular injections of 40µg human papillomavirus (HPV)16 L1 virus-like particle (VPL) vaccine or placebo on day 1, month 7 and then every 6 months through month 48. Results showed that 12 out of 750 women who received placebo developed HPV16-related cervical intraepithelial neoplasia (CIN) lesions, while there were no cases among the 755 women who received the HPV vaccine (efficacy 100%, 95% confidence interval [CI] 65-100%). Persistent HPV16 infection was reported in 111 of the placebo group, and by 7 in the vaccine group (efficacy 94%, 95% CI 88-98%).*

### Therapeutic Potentials:

S = Standard Review, the drug appears to have therapeutic qualities similar to those of one or more already marketed drugs

AA= Accelerated Approval

FT=Fast Track

P = Priority Review, significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease

BIOL= Biological

O = Orphan drug



Nicola Sarrazin is a 1984 graduate of the University of Iowa (B.A. in Anthropology and Asian Studies) and a 1997 graduate of the University of Iowa College of Pharmacy (Pharm.D.). Since that time she has been a pharmacist in the College of Pharmacy's Division of Drug Information Service. Nickie's responsibilities include indexing articles for the *IDIS* database, overseeing the Drug vocabulary and contributing articles for the *World of Drug Information* newsletter.

# 2007 DDIS MEETING SCHEDULE

*Come join us at the following meetings...*

American Association of Colleges of Pharmacy  
(AACCP)  
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July 14-18, 2007

American College of Clinical Pharmacy  
(ACCP)  
Denver, CO  
October 14-17, 2007

American Society of Health-System Pharmacists  
Midyear Clinical Meeting and Exhibits  
(ASHP-MYCM)  
Las Vegas, NV  
December 2-6, 2007

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