Biologic Disease-Modifying Antirheumatic Drugs

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Learning Objectives

1. Distinguish between biologic DMARD use and nonbiologic DMARD use in the treatment of rheumatoid arthritis (RA).
2. Assess the differences between classes of biologic disease-modifying antirheumatic drug (DMARD) therapy.
3. Based on individual patient characteristics, construct a treatment and monitoring plan for a patient with RA and, when appropriate, include biologic DMARD therapy.
4. Justify switching agents or usingcombination therapy with nonbiologic DMARDs when treatment with DMARD monotherapy fails.
5. Evaluate the need for tuberculosis screening and vaccinations in patients either starting or currently receiving biologic DMARDs.
6. Evaluate the precautions, contraindications, and warnings involving the use of biologic DMARDs in high-risk patients.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that may result in significant disability. The management of RA has seen significant advances during the past 2 decades. Although some patients with RA experience mild illness with minimal joint destruction, disease progression can lead to significant deformity of the affected joints.

Rheumatoid arthritis is systemic in nature and often affects joints in a symmetric manner. The primary symptoms of RA include joint pain or stiffness, weakness, and muscle aches. Joint deformity typically occurs late in disease progression. Extra-articular manifestations of RA may also be present.

Epidemiology

Rheumatoid arthritis affects about 1% of the world's population with relatively low variation in incidence among countries. When matched for age, 2–3 times more

Baseline Knowledge Statements

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of pathophysiology that leads to rheumatoid arthritis (RA)
- Diagnosis of RA
- General drug knowledge of nonbiologic DMARDs
- Consequences of uncontrolled RA
- Extra-articular manifestations of RA

Additional Readings

The following free resources are available for readers wishing additional background information on this topic.

- Singh JA, Furst DE, Bharat A, et al. 2012 Update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res 2012;64:625-39.

Abbreviations in This Chapter

ACR	American College of Rheumatology
ACPA	Anti–citrullinated protein antibody
DAS28	Disease Activity Score in 28 Joints
DMARD	Disease-modifying antirheumatic drug
DTM	Disease therapy management
EULAR	European League Against Rheumatism
HBV	Hepatitis B virus
HCV	Hepatitis C virus
JAK	Janus kinase
LTBI	Latent tuberculosis infection
RA	Rheumatoid arthritis
TB	Tuberculosis
TNF	Tumor necrosis factor

women are affected with RA than men. The prevalence of RA increases with age in both sexes and is greatest in patients aged 40–70 years. Heritability analysis and genetic markers suggest a genetic link to RA.

The cause of RA remains to be fully elucidated but likely involves both genetic and environmental factors. In a joint affected with RA, there is chronic pain and inflammation of the synovial tissue lining the joint capsule. The inflammatory process involves stimulation of T lymphocytes and B cells and, ultimately, the formation of autoantibodies by way of plasma cells. Autoantibodies such as rheumatoid factor and anti–citrullinated protein antibodies (ACPAs) may be detected before clinical disease is apparent. Rheumatoid factor is generally a polyclonal immunoglobulin (Ig) M antibody and is present in 85%–90% of patients. Although not specific to RA, higher levels of rheumatoid factor are associated with more severe RA. Inflammation of the synovium results in tissue proliferation (referred to as pannus) and may lead to invasion of cartilage and erosion of bone.

The progression of the disease is variable for each patient but is usually insidious versus abrupt. Patients at risk of developing joint abnormalities or disability include those with a high number of inflamed joints, high erythrocyte sedimentation rate, presence of rheumatoid factor or ACPA, and persistent inflammation.

The systemic nature of RA results in extra-articular disease in an estimated 40% of patients. These patients may experience higher rates of vasculitis, rheumatoid nodules, keratoconjunctivitis sicca, pericarditis, pleural effusions, and pulmonary fibrosis than patients without RA. The disease is also associated with higher mortality; this is primarily from an increase in cardiovascular disease, which likely is related to the chronic inflammation caused by RA (Pieringer 2011). It is unclear if extra-articular disease increases mortality because studies assessing this question have had conflicting results (Gabriel 2003; Turesson 2002).

Nonbiologic DMARDs

The most recent edition of the American College of Rheumatology (ACR) recommendations includes five nonbiologic disease-modifying antirheumatic drugs (DMARDs): methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, and minocycline (Singh 2012). These "nontargeted" immunosuppressive DMARDs have the capacity to significantly alter the course of RA. Table 1-1 summarizes nonbiologic agents used to treat RA.

Agents other than DMARDs that may be used for RA include nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. Although they may be used as "bridge therapy" until the DMARD provides relief, NSAIDs are not considered disease-modifying agents and should not be used as monotherapy. Corticosteroids are used in RA for anti-inflammatory properties in addition to immunosuppressive effects. Corticosteroids are primarily used in short courses for flares or during the initiation of DMARD therapy. Some evidence suggests that corticosteroids slow bone erosion and damage (Bakker 2012).

Methotrexate is the preferred nonbiologic DMARD for treatment of RA. In clinical trials, methotrexate significantly decreases symptoms of RA and slows joint destruction on radiography. Methotrexate may require dose reduction in patients with liver disease, and it must be used with caution in renal dysfunction, with literature suggesting a 50% dose reduction when the CrCl is below 50 mL/minute (Aronoff 2007). When oral methotrexate is titrated past the starting dose of 7.5 mg, bioavailability decreases by about 30%, which may be caused by a saturation effect (Hamilton 1997). The weekly dosage of oral methotrexate may be given in two doses separated by 12 hours to allow for absorption of higher doses. Subcutaneous administration of methotrexate may improve bioavailability and also avoid gastrointestinal toxicity. Methotrexate is often used in combination with biologic DMARDs, which are discussed later.

Biologic DMARDs

Several classes of biologic DMARDs are available for the treatment of RA. Biologic agents are targeted to alter a specific step in the pathogenesis of the inflammatory response associated with RA. Specifically, these agents inhibit proinflammatory cytokines such as tumor necrosis factor (TNF) or interleukin (IL) molecules, among other mechanisms. These agents carry specific safety warnings. Table 1-2 provides a summary of the available biologic DMARDs and tofacitinib.

The ACR criteria have become widely used in clinical trials as a marker for efficacy for the treatment of RA.

Trials commonly cite ACR 20, ACR 50, and ACR 70 response when discussing clinical efficacy. For example, an ACR 20 response is defined as a 20% improvement in specific clinical variables such as tender and swollen joint counts, patient or physician global assessments, and laboratory acute phase reactants. The Disease Activity Score (DAS) is also commonly referenced in RA trials; this composite index quantifies RA disease activity.

TNF Inhibitors

Tumor necrosis factor is a pleiotropic cytokine that plays a key role in the inflammatory process of RA. The TNF inhibitors work by binding to TNF-α and blocking its activity on cell surface receptors. The U.S. Food and Drug Administration (FDA) has given five TNF inhibitors label approval for the treatment of RA: etanercept, infliximab, adalimumab, golimumab, and certolizumab. Each agent has shown efficacy in improving clinical response, reducing damage assessed on radiography, and improving quality of life while decreasing disability. Several TNF inhibitors are approved for use as monotherapy, although combination with methotrexate improves response in both early and established RA (Scott 2006).

Limited head-to-head trials of the anti-TNF agents have been performed. A recent meta-analysis found an overall greater ACR 50 response to TNF inhibitors than placebo at 6 months; however, this significant improvement was seen only with adalimumab, etanercept, and certolizumab. Although there were no significant differences in discontinuation rates between each TNF inhibitor versus placebo, this meta-analysis found that

Table 1-1. Nonbiologic Agents to Treat RA

Agent	Dose	Adverse Effects	Comments
Hydroxychloroquine	200–300 mg twice daily orally Adjust dose for severe renal dysfunction	GI complaints, skin reactions, headaches, retinal damage (rare)	Antimalarial drug Low toxicity profile but moderate clinical effect
Leflunomide	100 mg daily orally for 3 days; then 20 mg daily Not recommended with pre-existing liver disease	GI complaints, reversible alopecia, rash, elevated transaminases, peripheral neuropathy	Clinical efficacy is considered equivalent to methotrexate Alternative to methotrexate if patient is unable to tolerate methotrexate Teratogenic – avoid in pregnancy
Methotrexate	7.5–15 mg orally weekly (up to 20–30 mg weekly) ; may divide weekly dose into 2 doses given 12 hours apart 10–25 mg once weekly IM or SC Hepatic impairment: use with caution Renal dysfunction: use with caution; consider a dose reduction of 50% with CrCl < 50 mL/minute	Nausea, vomiting, stomatitis, thrombocytopenia, increased LFTs, chronic hepatotoxicity, photosensitivity	Nonbiologic DMARD of choice Teratogenic – avoid in pregnancy Bioavailability decreases with oral doses exceeding 7.5 mg SC administration may improve bioavailability and avoid GI toxicity
Minocycline	100 mg twice daily orally Hepatic impairment: use caution Renal dysfunction: use with caution; max 200 mg daily when CrCl < 80 mL/minute	Nausea, vomiting, anorexia, hepatotoxicity	Moderate reduction in RA progression compared with other nonbiologic agents
Sulfasalazine	500–1000 mg daily orally; titrate to 1000 mg twice daily	Headache, rash, gastric distress, myelosuppression (i.e., agranulocytosis, neutropenia, and leukopenia), increased liver enzymes	May be used as monotherapy or as part of combination therapy

DMARD = disease-modifying antirheumatic drug; GI = gastrointestinal; IM = intramuscular; LFT = liver function tests; RA = rheumatoid arthritis; SC = subcutaneous.

adalimumab, certolizumab, and infliximab had a higher rate of discontinuation than etanercept (Aaltonen 2012).

The adverse effect profile of the TNF inhibitors is fairly consistent across the class. One of the most common adverse effects is either injection site or infusion reactions, depending on route of administration. Because the anti-TNF agents modulate immune response, serious infections are also a concern. To reduce the risk of infection, vaccines should be administered before anti-TNF agent initiation. Patients should also be screened for tuberculosis. Live vaccines should not be administered during treatment. Tumor necrosis factor inhibitors may induce or exacerbate multiple sclerosis and reactivate hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Heart failure exacerbation and increased risk of cancer are described in anti-TNF prescribing information; however, new insights on these risks, developed on the basis of new data, are discussed in the following.

Etanercept

Etanercept is a dimeric fusion protein that consists of an extracellular portion of human p75 TNF receptor linked to an Fc fragment of human IgG. Etanercept is self-administered by subcutaneous injection and can be used as either monotherapy or in combination with methotrexate.

Etanercept efficacy has been demonstrated in patients whose disease previously failed to respond to methotrexate (Moreland 1999). At 24 weeks, ACR-20

Table 1-2. Biologic Agents to Treat Rheumatoid Arthritis

Agent	Class	Dose	Frequency
Abatacept	T-cell costimulation modulator	IV: < 60 kg: 500 mg 60–100 kg: 750 mg > 100 kg: 1000 mg	Weeks 0, 2, 4, then monthly
		SC: 125 mg	Weekly May be initiated with or without single IV loading dose If using loading dose, use weight-based dose above and start SC injection within 24 hours of the initial IV infusion
Adalimumab	TNF-α inhibitor	40 mg SC	Every 14 days May increase dose to 40 mg every week in patients not taking methotrexate
Anakinra	IL-1 receptor antagonist	100 mg SC	Daily
Certolizumab	TNF-α inhibitor	400 mg SC, followed by 200 mg SC	400 mg SC weeks 0, 2, and 4, followed by 200 mg SC every 2 weeks
Etanercept	TNF-α inhibitor	50 mg SC; 25 mg SC	Weekly; twice weekly
Golimumab	TNF-α inhibitor	50 mg SC	Monthly Combine with methotrexate[a]
Infliximab	TNF-α inhibitor	3 mg/kg IV infusion	Weeks 0, 2 and 6; then every 8 weeks[a] Combine with methotrexate[a]
Rituximab	Anti–CD 20	1000 mg IV plus	Days 1 and 15 may retreat every 24 weeks (no sooner than every 16 weeks) Combine with methotrexate[a]
Tocilizumab	IL-6 receptor antagonist	IV: 4 mg/kg; may increase to 8 mg/kg	Every 4 weeks
		SC: 162 mg	< 100 kg: every other week; increase to every week based on clinical response ≥ 100 kg: every week
Tofacitinib	Janus kinase enzyme inhibitor	5 mg PO	

[a]Dose of infliximab may be increased up to 10 mg/kg or administered as often as every 4 weeks in patients with disease that does not respond to lower doses.

IL = interleukin; IV = intravenously; PO = by mouth; SC = subcutaneously; TNF = tumor necrosis factor.

response rates were 51% in the etanercept 10-mg twice-weekly group, 59% in the etanercept 25-mg twice-weekly group and 11% in the placebo group. Etanercept efficacy has also been demonstrated in the treatment of early RA in methotrexate-naive patients (Bathon 2000). In the ERA trial, patients at risk of rapidly progressive joint damage were randomized to either twice-weekly etanercept monotherapy or weekly oral methotrexate for at least 1 year (Genovese 2002). The study showed etanercept more rapidly decreased symptoms and joint damage, but after 12 months of therapy, clinical response was similar to the methotrexate group. Etanercept can be given subcutaneously once weekly (50-mg injection) or twice weekly (two 25-mg injections given 3–4 days apart).

Infliximab

Infliximab is a chimeric antibody that combines murine and human IgG. Infliximab is approved in combination with methotrexate to reduce signs and symptoms, stall progression of joint damage, and improve physical functioning in patients with moderate to severe RA. To prevent the formation of antibodies to this foreign protein, methotrexate must be administered concomitantly with infliximab for the duration of treatment. Infliximab is administered by intravenous infusion by a health care professional.

The efficacy of infliximab was demonstrated in the pivotal phase III ATTRACT trial. In this randomized controlled trial, patients with inadequate response to methotrexate were randomized to receive infliximab or placebo add-on therapy to methotrexate. After 30 weeks, the cohort receiving infliximab achieved an ACR 20 response rate of 51.8% versus only 17% from methotrexate plus placebo (Maini 1999). Infliximab efficacy has also been demonstrated in the treatment of early RA and methotrexate-naïve patients. In the ASPIRE trial, infliximab plus methotrexate provided significantly greater clinical, radiologic, and functional improvement than methotrexate alone (St. Clair 2004).

Adalimumab

Adalimumab is a fully human monoclonal antibody specific to TNF and is produced using recombinant DNA technology. Adalimumab is self-administered as a subcutaneous injection and is approved for use as monotherapy or in combination with methotrexate.

The efficacy of adalimumab was demonstrated in the ARMADA trial in patients with an inadequate disease response to methotrexate (Weinblatt 2003). At 24 weeks, ACR 20 responses were 47.8%, 67.2%, and 65.8% in the adalimumab 20 mg, 40 mg, and 80 mg groups, respectively, versus 14.5% in the placebo group. Methotrexate background therapy was continued in each of the treatment arms. The efficacy of adalimumab in early methotrexate-naïve RA patients was demonstrated in the Premier study (Breedveld 2006). Patients were assigned to adalimumab or methotrexate monotherapy or adalimumab plus methotrexate combination therapy. The study had a 2-year follow-up and found that combination therapy was more effective than monotherapy, but no difference was found between adalimumab and methotrexate monotherapy.

Golimumab

Golimumab is a fully human anti-TNF Ig G monoclonal antibody produced using recombinant DNA technology. The agent binds to both soluble and transmembrane TNF, which allows for both receptor binding and inhibition of cytokine activity (Nam 2010). Golimumab is also indicated for use in combination with methotrexate.

The efficacy of golimumab was demonstrated in the phase III GO-FORWARD trial (Keystone 2009). In this study, 444 patients with active RA (despite stable dose methotrexate) were randomized to either continue methotrexate monotherapy, receive golimumab monotherapy, or receive golimumab plus methotrexate therapy. At 24 weeks, significantly more patients in the combination therapy group reached ACR 20 than the methotrexate group (59.6% vs. 27.8%). Golimumab efficacy has also been demonstrated in the treatment of early RA for methotrexate-naive patients (Emery 2009). In the phase III GO-BEFORE trial, a modified intention-to-treat analysis showed golimumab plus methotrexate therapy achieved a statistically significant disease improvement over methotrexate alone. Additionally, golimumab has been shown to be efficacious in patients who have not responded to other anti-TNF agents (e.g., etanercept, adalimumab, infliximab) (Smolen 2009). At 24 weeks, ACR 20 was achieved in 43.8% of patients receiving golimumab therapy versus 16.8% in the placebo group.

Certolizumab

Certolizumab is a pegylated Fab fragment of humanized anti-TNF monoclonal antibody and can be administered with or without methotrexate. Efficacy of certolizumab was demonstrated in methotrexate nonresponders in the RAPID-1 and RAPID-2 trials (Keystone 2009; Smolen 2009). In the RAPID-1 trial, ACR 20 was achieved in a significantly greater number of patients than those in the placebo group (all patients received methotrexate). In the RAPID-2 trial, certolizumab demonstrated inhibition in radiographic progression. Efficacy of certolizumab monotherapy in patients whose previous DMARD therapy had failed was demonstrated in the FAST4WARD trial (Fleischmann 2009). At 24 weeks, ACR 20 rates were 45.5% in the certolizumab arm versus 9.3% in the placebo group ($p<0.001$).

Costimulation Modulators (Abatacept)

Abatacept is a selective T-cell costimulation modulator approved for the treatment of moderate to severe RA. To become activated, T cells (specifically, the CD20 receptor)

require costimulation with CD 80/86 on antigen-presenting cells (APCs). Abatacept inhibits inflammation associated with RA by preventing the interaction between APCs and T cells.

The efficacy of abatacept has been demonstrated in several clinical studies. In one trial, abatacept given in combination with methotrexate improved remission rates and reduced radiographic progression of early RA versus methotrexate monotherapy (Westhovens 2009). Abatacept in combination with methotrexate was also effective in increasing ACR 20, 50, and 70 responses (compared with placebo) when given to patients with an inadequate response to methotrexate monotherapy (Kremer 2006). In addition, in patients with an inadequate disease response to anti-TNF therapy, 50% treated with abatacept experienced ACR 20 response versus 20% treated with placebo (Genovese 2005). Similarly, abatacept demonstrated a greater reduction in RA disease activity than infliximab in a 12-month trial (Schiff 2008). Initially, abatacept was approved only for monthly intravenous administration according to a weight-based dosing regimen. Recently, subcutaneous administration of abatacept proved noninferior to intravenous therapy (Genovese 2011). As a result, the subcutaneous administration of abatacept is now also approved for the treatment of RA.

Abatacept can be given in combination with nonbiologic agents such as methotrexate, but combination with biologic agents (especially anti-TNF agents) should be avoided. In a clinical trial, adverse events, serious adverse events, and discontinuations were higher when abatacept was combined with other biologic DMARDs but not nonbiologic DMARDs. Patients with underlying chronic obstructive pulmonary disease (COPD) developed adverse effects related to the respiratory system (e.g., COPD exacerbations, cough, rhonchi, dyspnea) more often than patients who received placebo (Weinblatt 2006). Common adverse effects with abatacept include infections, infusion-related events, headache, and dizziness.

Anti-CD 20 Agents (Rituximab)

Rituximab is a genetically engineered chimeric monoclonal antibody that treats RA by depleting peripheral B cells. Originally approved for the treatment of certain types of cancer, rituximab is approved in combination with methotrexate for moderate to severe RA in patients whose disease has failed to respond to anti-TNF therapy. The role of B cells in the inflammatory process of RA is multifaceted and includes the production of proinflammatory cytokines (e.g., TNF-α, IL-1, IL-6) and disrupting antigen presentation by T cells. Plasma cells, which are derived from B cells, produce antibodies (e.g., rheumatoid factor, ACPA) that promote the autoimmune process of RA.

Rituximab is given as two 1000-mg intravenous infusions separated by 2 weeks. Although this dosing has not been directly compared with other biologic DMARDs in a randomized controlled trial, there is evidence to support its use when anti-TNF agents have failed. In this patient population, one course of rituximab improved ACR 20, 50, and 70 response compared with placebo, and also improved the Disease Activity Score in 28 Joints (DAS28), a validated instrument for the assessment of disease activity in RA (Cohen 2006). An extension of this trial showed that rituximab decreased radiographic structural joint damage for up to 5 years (Keystone 2012). A longitudinal cohort study assessed patients treated with either rituximab or an alternative anti-TNF agent after initial treatment with an anti-TNF agent. Rituximab was more effective than the alternative anti-TNF agent if the patient switched drug classes because of ineffectiveness but not if the switch was because of adverse effects (Finckh 2010). Additionally, in an observational study of patients with an inadequate response to an initial anti-TNF agent (SWITCH-RA), rituximab was better at reducing RA symptoms than an alternative anti-TNF agent (Emery 2014).

As a result of B cell depletion, rituximab could theoretically decrease the concentration of circulating Ig (e.g., IgG, IgM, IgA); however, concentrations generally remained within normal limits in clinical trials (Cohen 2006). After the initial treatment, patients can be retreated with rituximab after 24 weeks (or no sooner than 16 weeks), which is consistent with clinical trials and generally coincides with the return of peripheral B cells (Cohen 2006).

Infusion reactions (e.g., pruritus, fever, urticaria/rash, chills, hypotension, hypertension) are common with rituximab, and patients should be pretreated with a corticosteroid, acetaminophen, and an antihistamine. Rituximab may increase the rate of infections compared with placebo. However, most infections in clinical trials were mild and included upper respiratory tract infections, nasopharyngitis, and sinusitis. In clinical trials, retreatment with rituximab did not increase the incidence of infusion-related events and did not pose additional safety concerns (Mease 2010).

IL-6 Receptor Antagonists (Tocilizumab)

In RA, chronic joint inflammation increases the production of IL-6, which furthers the inflammatory response by stimulating B- and T-cell development. Tocilizumab is a humanized monoclonal antibody that binds to IL-6 and inhibits its anti-inflammatory effects. Tocilizumab is approved as an intravenous formulation to be given as 4 mg/kg or 8 mg/kg every 4 weeks and as a subcutaneous formulation given as 162 mg every week or every other week based on patient weight. Notable adverse effects of tocilizumab include increased liver enzymes, increased cholesterol, and decreased neutrophil and platelet counts. Tocilizumab induces cytochrome P450 (CYP) 3A4 and may decrease the serum concentration of drugs metabolized by this enzyme. Patients treated with tocilizumab were at increased risk of infections, which increased the discontinuation rate of tocilizumab overplacebo in clinical trials.

Tocilizumab is indicated for treatment of RA in patients who have not responded to at least one DMARD. Tocilizumab has been effective as monotherapy in clinical trials in patients whose disease failed to respond to nonbiologic DMARDs (Dougados 2013; Jones 2010). Tocilizumab is approved for use without concomitant methotrexate; however, it has been used in combination with methotrexate in clinical practice, a practice supported by data from randomized controlled trials (Emery 2008). Because many biologic DMARDs are used in combination with methotrexate, tocilizumab may be an alternative for patients who cannot tolerate methotrexate or for whom methotrexate use is inappropriate.

Although clinical use of tocilizumab typically follows treatment failure with an anti-TNF agent, there is evidence to suggest that tocilizumab is superior to adalimumab, a commonly used anti-TNF agent (Gabay 2013). This randomized controlled trial compared tocilizumab monotherapy (8 mg/kg every 4 weeks) with adalimumab (40 mg subcutaneously every 2 weeks). Patients treated with tocilizumab had a greater decrease in DAS28 and ACR response rates. However, more patients treated with tocilizumab required dose modification or interruption because of adverse effects.

IL-1 Receptor Antagonists (Anakinra)

Of agents in the IL-1 receptor antagonist class, only anakinra has label approval for use in RA; it is approved for patients whose disease has failed to respond to other DMARDs. Interleukin-1 is a cytokine that is increased in response to inflammation and contributes to cartilage degradation and bone resorption. The daily dosage of anakinra is 100 mg given as a subcutaneous injection. For patients with renal impairment (i.e., CrCl less than 30 mL/minute), the recommended dosage is 100 mg every other day.

Anakinra may be used as monotherapy or in combination with other DMARDs with the exception of anti-TNF drugs. In a clinical trial, the combination of anakinra plus etanercept increased the rate of adverse effects (Genovese 2004). In addition, the combination produced no benefit in clinical outcomes as measured by ACR20 after 24 weeks of therapy. The risk of this combination is deemed to outweigh any benefit.

Anakinra is not included in the most recent ACR recommendations because of its infrequent use compared with other biologics and because there is a lack of strong data to support its use (Singh 2012). Although a significant number of patients in clinical trials achieved symptomatic relief with anakinra versus placebo, the benefit was modest compared with other biologics (i.e., the anti-TNF agents adalimumab, infliximab, and etanercept) (Mertens 2009). In a systematic review of biologic agents, anakinra's lack of efficacy resulted in treatment discontinuation rates higher than those of most other biologics (Desai 2012). Additional adverse effects with anakinra include injection site reactions (up to 71% of patients), serious infections, and decreased neutrophil counts.

Janus Kinase Enzyme Inhibitors

Tofacitinib is a member of the newest class of agents approved to treat RA, the Janus kinase (JAK) enzyme inhibitors. Inhibition of JAK modulates the inflammatory process by interrupting cytokine signaling and immune cell function, specifically by preventing the phosphorylation and activation of signal transducers and activators of transcription. In contrast to biologic agents, the small size of the tofacitinib molecule allows for oral administration and intracellular action. The typical dosage of tofacitinib is 5 mg twice daily. However, this should be reduced to 5 mg daily in patients who have moderate to severe renal insufficiency, moderate hepatic impairment, or who are taking potent inhibitors of CYP3A4, which extensively metabolizes tofacitinib.

Clinical studies support the use of tofacitinib both as monotherapy and in combination with other DMARDs such as methotrexate, but not with other biologic agents. At approved doses, tofacitinib improved symptoms of RA according to ACR response and also improved physical function according to the Health Assessment Questionnaire-Disability Index, but improvements in remission and radiographic changes were variable at 3 and 6 months. In one trial comparing tofacitinib monotherapy with placebo, tofacitinib improved ACR response rates and physical function but did not improve disease remission, although more patients met criteria for low disease activity (Fleischmann 2012). In another trial, tofacitinib showed improvements in ACR 20 criteria, physical function, and disease remission in combination with methotrexate in patients who had experienced treatment failure with an anti-TNF agent (Burmester 2013). When given in combination with methotrexate, tofacitinib was similar to adalimumab in efficacy, physical function, and disease remission, although formal noninferiority analysis was not completed because of study design (Van Vollenhoven 2012). Twelve-month data from a 24-month study showed that tofacitinib improved signs and symptoms of RA and physical function more than placebo; however, it did not decrease radiographic progression of the disease at the approved dosage of 5 mg twice daily (Van der Heijde 2013).

The most common adverse effects in clinical trials were headache, diarrhea, nasopharyngitis, upper respiratory infection, and hypertension (Burmester 2013; Van der Heijde 2013; Van Fleischmann 2012; Vollenhoven 2012). Tofacitinib may contribute to neutropenia and may also increase liver enzymes and lipid parameters. As with other biologics, infections, including serious infections, were increased with tofacitinib.

RA Treatment

Goals and Principles

Principles for the treatment of RA are rapidly changing as new agents are approved and additional trials are conducted. In addition, the course of RA and resulting disability,

joint damage, and inflammation are highly variable for each patient. In general, the 2012 ACR recommendations support early and aggressive treatment of RA based on individual patient circumstances. Treatment for RA with DMARDs may reverse joint damage and preserve physical function and health-related quality of life (Singh 2012).

The goal of RA treatment is complete remission, although low disease activity may be a more acceptable target for some patients (Singh 2012). According to a recent consensus provided by the ACR and European League Against Rheumatism (EULAR), RA remission can be defined as no more than one tender or swollen joint, C-reactive protein less than 1 mg/dL, and positive patient global assessment. Alternatively, remission may be defined by a Simplified Disease Activity Index score of 3.3 or less (Felson 2011). In clinical trials, remission is commonly defined as a score of less than 2.6 on the DAS28. Low, moderate, or high disease activity may also be determined by use of these validated scales.

Clinical recommendations may be based on the length of time that a patient has had RA. A disease duration of less than 6 months is termed *early RA*, whereas RA of at least 6 months is considered *established RA*. Of note, although the ACR/EULAR changed the RA classification criteria in 2010, these terms remain in the current guidelines because clinical data are based on the old criteria. Another important distinction when choosing treatment is the presence or absence of poor prognostic features. Features of poor prognosis include functional limitation, extra-articular disease, positive rheumatoid factor or ACPA, or bony erosions on radiography (Singh 2012).

Early RA

Options for treating early RA are based on the level of disease activity and the presence or absence of poor prognostic features (Table 1-3). The panel of experts that created the ACR guidelines for RA treatment recommend the use of nonbiologic DMARD monotherapy in early RA for patients without poor prognostic factors for any degree of RA disease activity (i.e., low, moderate, or high). Monotherapy with DMARDs includes methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, and minocycline. In patients with high disease activity and absence of poor prognostic features, the panel recommends the use of methotrexate plus hydroxychloroquine as initial therapy. Combination therapy with methotrexate plus either hydroxychloroquine, leflunomide, or sulfasalazine is recommended for patients with moderately or highly active disease and poor prognostic features. Triple therapy with methotrexate, hydroxychloroquine, and sulfasalazine may also be used in these patients. There is a role for the use of anti-TNF agents with or without methotrexate as initial therapy for patients with early RA. This approach is appropriate for patients with high disease activity and poor prognostic features. Infliximab, however, should be used with methotrexate and not as monotherapy (Singh 2012).

Established RA

The guidelines for treating established RA address the concepts of switching among nonbiologic DMARDs, switching from nonbiologic DMARDs to the biologic agents, and switching among biologic agents. For a patient with established RA who is taking DMARD monotherapy, therapy should be reassessed after 3 months of treatment. At that point, the patient may benefit from either adding a nonbiologic agent to current therapy or switching to another nonbiologic DMARD, based on prognosis and disease activity. Patients with moderate to high disease activity after 3 months of treatment with methotrexate monotherapy or DMARD combination therapy can add or switch to an anti-TNF biologic agent. Other candidates for adding or switching to an anti-TNF biologic agent include patients with moderate to high disease activity who have already been treated with intensified DMARD combination therapy or after a second DMARD.

When treatment with a biologic agent is necessary, anti-TNF agents are typically selected before other biologic agents

Table 1-3. Treatment of Early RA[a]

	Absence of Poor Prognosis	Presence of Poor Prognosis
Low disease activity	DMARD monotherapy[b]	Not addressed
Moderate disease activity	DMARD monotherapy[b]	DMARD combination therapy[c]
High disease activity	DMARD monotherapy[b] or MTX + HCQ	DMARD combination therapy[c] or anti-TNF agent with or without MTX[d]

[a]Early RA = disease duration less than 6 months.
[b]DMARD monotherapy includes methotrexate, minocycline, hydroxychloroquine, sulfasalazine, and leflunomide.
[c]DMARD combination therapy includes methotrexate plus hydroxychloroquine, methotrexate plus leflunomide, methotrexate plus sulfasalazine, sulfasalazine plus hydroxychloroquine, and sulfasalazine plus hydroxychloroquine plus methotrexate.
[d]Options include etanercept with or without methotrexate, infliximab with methotrexate, adalimumab with or without methotrexate, golimumab with or without methotrexate, and certolizumab with or without methotrexate.
Anti-TNF = anti-tumor necrosis factor; DMARD = disease-modifying antirheumatic drug; HCQ = hydroxychloroquine; MTX = methotrexate; RA = rheumatoid arthritis..

Patient Care Scenario

A female patient (height 66 inches, weight 81 kg) with RA has been taking adalimumab 40 mg subcutaneously weekly for 6 months. Before that was taking 40 mg subcutaneously every 14 days. The patient's disease activity has steadily increased since the dose adjustment. She has not tried other therapies to treat RA. The patient's medical history includes hypertension, type 1 diabetes mellitus, hyperlipidemia, and depression. Her laboratory values include BUN 23 mg/dL, SCr 1.1 mg/dL, glucose 158 mg/dL (random), potassium 5.1 mmol/L, sodium 138 mmol/L, hemoglobin A1C 7.2%, TC 304 mg/dL, HDL cholesterol 36 mg/dL, LDL cholesterol 190 mg/dL, and TG 390 mg/dL. Which one of the following would be best to recommend for treatment of this patient's RA?

- Abatacept 750 mg intravenously weeks 0, 2, 4, then monthly.
- Certolizumab 400 mg subcutaneously every 2 weeks.
- Tocilizumab 4 mg/kg intravenously every 4 weeks.
- Rituximab 1000 mg intravenously days 1 and 15.

Answer

Patients taking an anti-TNF agent for RA for at least 3 months who continue to experience at least moderate disease activity may benefit from either switching to another anti-TNF agent or switching to a non-TNF biologic DMARD. Certolizumab is another anti-TNF agent. Guidelines support trying a different anti-TNF agent when one anti-TNF agent does not adequately control RA symptoms. However, the certolizumab dose of 400 mg subcutaneously every 2 weeks is higher than the recommended dose of 400 mg subcutaneously weeks 0, 2, and 4 followed by 200 mg subcutaneously every 2 weeks. Tocilizumab is an IL-6 receptor antagonist (non-TNF option). The dose is appropriate; however, tocilizumab would not be recommended in this case because of uncontrolled hyperlipidemia. Rituximab is an anti-CD20 agent that depletes B cells. In a clinical trial, rituximab was found more effective than switching to an alternative anti-TNF agent if the reason for the switch in medication classes was ineffectiveness. The proposed dose of rituximab is appropriate; however, it is to be given in combination with methotrexate, which is not included as part of the proposed option. The first option, abatacept, is a T-cell costimulation modulator that is a non-TNF biologic DMARD option. This patient weighs 81 kg, and the proposed dose of abatacept 750 mg is appropriate for patients weighing 60–100 kg. Of the available choices listed above, abatacept is the most appropriate option for this patient.

1. Finckh A, Ciurea A, Brulhart L, et al. Which subgroup of patients with rheumatoid arthritis benefits from switching to rituximab versus alternative anti-tumor necrosis factor (TNF) agents after previous failure of an anti-TNF agent? Ann Rheum Dis 2010;69:387-93.
2. Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res 2012;64:625-39.

because of their high efficacy and the preference given to them in the guidelines and in clinical practice. Patients taking an anti-TNF agent may benefit from switching to a non-TNF agent if disease activity remains moderate to high after 3 months or if adverse events occur. If the adverse event experienced with an anti-TNF agent is not considered serious, the patient may want to try a different anti-TNF agent. Because of the variability in the role of proinflammatory cytokines (e.g., TNF-α, IL-1, IL-6) that mediate the RA disease process among patients, those who have tried anti-TNF agents without achieving adequate disease control may benefit from switching to another class of biologics that target a different aspect of the inflammatory cascade.

In clinical practice, patients commonly are switched between anti-TNF agents because of a lack of complete remission. This is supported by the guidelines, although only limited controlled clinical trials have investigated the concept. Patients may respond to one anti-TNF agent and not another because of drug resistance, which is linked to the development of antibodies to the drug (Emery 2012)

Additional time may be necessary to determine the success of treatment of RA with non-TNF biologic agents. Compared with anti-TNF agents, a 6-month trial of non-TNF agents should be considered before reassessing therapy and providing adjustments (Singh 2012). If a patient experiences inadequate disease response or adverse effects after 6 months of treatment with a non-TNF agent, a switch to a different class of drugs is recommended. Options include either another non-TNF agent or an anti-TNF agent, if appropriate. Non-TNF agents specifically included in the latest ACR guidelines include abatacept, rituximab, and tocilizumab. Anakinra is not included because of low clinical use and little perceived clinical benefit. Tofacitinib was not approved at the time the guidelines were published; however, on the basis of clinical trial data and pharmacodynamics, a 6-month trial is appropriate to determine if tofacitinib will be efficacious for a particular patient. Figure 1-1 describes recommendations for switching among biologic agents in the treatment of established RA.

Safety Considerations of Biologic DMARDs

Tuberculosis Screening

Tuberculosis (TB) infections were documented in patients with RA even before the biologic DMARDs were on the market. An increased number of cases occurred after the release of anti-TNF agents (Gardam 2003). Because TNF-α regulates host defense against mycobacterial infections, inhibition of this cytokine increases the risk of new-onset TB infection and reactivation of latent tuberculosis infection (LTBI). Tuberculosis infection has been documented with all of the anti-TNF agents, although some studies suggest the risk is lower with etanercept (Tubach 2009; Gomez-Reino 2003). In contrast to the anti-TNF agents, no causal link has been

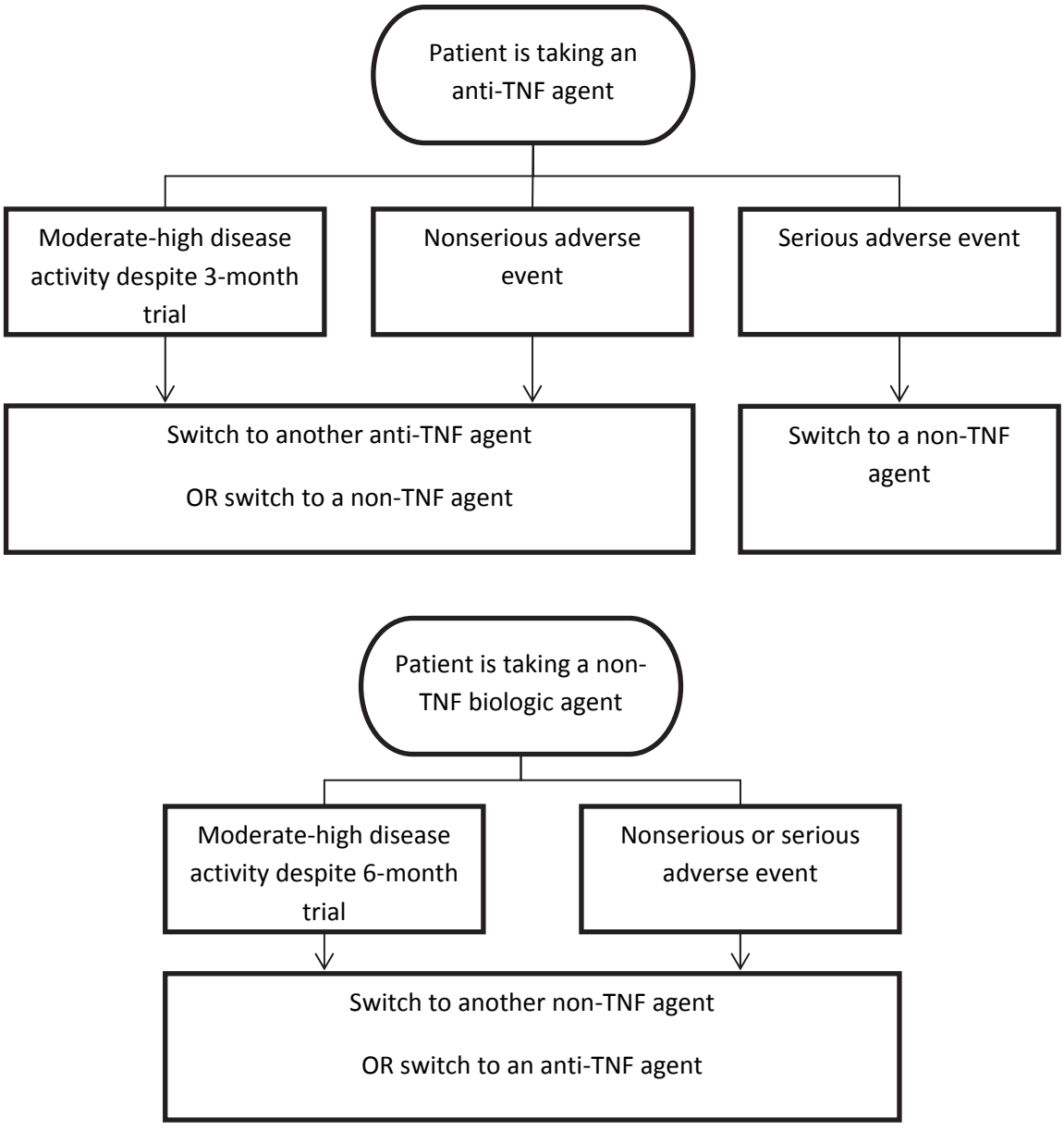

Figure 1-1. Recommendations for switching among biologic agents for the treatment of established rheumatoid arthritis.

Anti-TNF = anti-tumor necrosis factor.
Information from: Singh JA, Furst DE, Bharat A, et al. 2012 Update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res 2012;64:625-39.

established between anakinra, abatacept, rituximab, or tocilizumab and either new-onset TB infection or reactivation of LTBI, although experience with tocilizumab in patients with LTBI is limited (Rubbert-Roth 2012).

Screening for LTBI has been shown to reduce the risk of reactivation. The ACR guidelines recommend screening for LTBI with a thorough assessment of the patient's medical history and with either the tuberculin skin test or interferon-gamma-release assay (IGRA). This screening should take place before initiation of any biologic DMARD therapy (not just the anti-TNF agents) regardless of a patient's risk factors for LTBI. Risk factors for TB infection include intravenous drug use, prison or health care occupation, homelessness, and a history of travel or residence in an area with high prevalence of the infection.

The optimal test for TB screening is unclear. The tuberculin skin test may be limited by the potential for false-negative results in patients with RA receiving immunosuppressant therapy or with immunocompromising comorbidities (Smith 2011). The IGRA has similar sensitivity but improved specificity over the tuberculin skin test in patients with a history of Bacille Calmette-Guerin vaccine or past infection with a non-TB mycobacterium. The IGRA is more costly than the tuberculin skin test and may have reduced sensitivity in patients without intact immune systems (Smith 2011) The ACR endorses use of the IGRA in patients with a history of Bacille Calmette-Guerin vaccination. The guidelines caution that a negative TB screen should not be interpreted as excluding the possibility of infection, especially iwhen clinical suspicion exists because of concomitant risk factors. A second screening can be considered 1–3 weeks after the initial negative screen to confirm results.

The 2012 ACR guidelines recommend a stepwise approach to TB screening. Any positive tuberculin skin test (induration of greater than 5 mm in the immunocompromised patient) or IGRA should be followed by chest radiography. If chest radiography is suggestive of active TB, a subsequent sputum examination is indicated to check for active TB infection. Anti-TB therapy should be started in any patient with RA having active TB, and prophylactic therapy should be initiated in a patient with LTBI. According to the ACR guidelines, biologic therapy can begin or resume after complete treatment of active TB and after 1 month of anti-TB prophylaxis in a patient with LTBI.

The value of repeated TB screening in patients treated with long-term biologic therapy is unknown (Fuchs 2009). However, the 2012 ACR guidelines recommend annual screening for patients receiving long-term biologic therapy who live, work, or travel where TB exposure is likely to occur.

Vaccination Recommendations

Patients with RA are more susceptible to vaccine-preventable infections. One study estimated the risk of infectious complications to be 2-fold higher in patients with RA than in the general population (Gluck 2008). This increased susceptibility is not likely dependent on treatment with immunomodulating biologic therapies alone. Other factors that may contribute to an increased risk of infection in patients with RA include immune system dysfunction attributable to the disease itself, comorbidities, nonbiologic immunosuppressive RA therapies, and RA disease activity (Au 2011; Kapetanovic 2006). Biologic therapy clearly plays a role in increased risk of infection. Specifically, the anti-TNF drugs block important signaling processes in the immune response, leading to greater susceptibility to bacterial and fungal pathogens.

Regardless of cause, the morbidity and mortality in patients with RA make vaccination screening and administration important. Unfortunately, vaccination status in the population with RA is low. A study of Irish patients with RA found that only 42% were up to date on their influenza vaccination, and just 19% had received a pneumococcal vaccination (McCarthy 2011).

The ACR guidelines recommend that before biologic therapy initiation, the inactivated influenza vaccine, recombinant pneumococcal vaccine, recombinant human papillomavirus vaccine, and live attenuated herpes zoster vaccine be administered to patients deemed appropriate by the current Center for Disease Control and Prevention (CDC) vaccination schedule. Additionally, the HBV vaccination should be considered before biologic therapy for any patient with risk factors for the disease. Risk factors for HBV include intravenous drug abuse, multiple sexual partners in the previous 6 months, and occupational setting such as health care or the prison system.

The 2013 CDC schedule recommends annual influenza vaccinations in adults, a three-dose series of the human papillomavirus vaccine in men and women 19–26 years of age, herpes zoster vaccination once after age 60, and a three-dose series of HBV vaccination in at-risk individuals. The pneumococcal polysaccharide (PPSV23) vaccination should be given to adults (older than 19 years) with RA followed by a one-time revaccination 5 years after the first dose. The CDC also recommends that individuals at least 65 years of age receive a one-time revaccination if they were vaccinated more than 5 years previously and the primary vaccination was given before age 65 (CDC 2013).

According to the ACR guidelines, live vaccines are contraindicated during biologic therapy; however, the guidelines do not address the minimum interval to wait after administration of a live vaccine before biologic therapy initiation. Guidelines from three countries (i.e., Great Britain, India, and Canada) recommend waiting 4 weeks between administration of a live vaccine and initiation of biologic therapy (Bombardier 2012; Misra 2008; Devlin 2005; Ledingham 2005).

Inactivated vaccines are generally considered acceptable for patients taking immunosuppressive drugs. The ACR guidelines recommend concomitant administration

of biologic therapy with the inactivated influenza vaccine, pneumococcal vaccine, human papillomavirus vaccine, and HBV vaccine for appropriate patients. Although not discussed in the ACR guidelines, data suggest the risk of infection is higher in patients with high RA disease activity (Au 2011). Based on this information, it may be prudent to vaccinate patients when their maximal immune response is anticipated, which is just before initiation of biologic therapy or during a time of stable disease (Van Assen 2011).

Immunosuppression and Opportunistic Infections

In addition to increased risk of vaccine-preventable infections, biologic agents pose an increased risk of opportunistic bacterial and fungal infections. A boxed warning about the risk of serious, sometimes fatal *Legionella* and *Listeria* infections was recently added to the label of each of the TNF inhibitors. The FDA adverse effect reporting system contained 80 cases of *Legionella* pneumonia in patients receiving TNF inhibitors between 1999 and 2010 (FDA 2011). Of the 80 cases, 65% were receiving their respective anti-TNF agent for RA for a median of 10.4 months. All TNF inhibitors except certolizumab were linked with the incidence of Legionnaire's disease. The FDA has also received reports of *Listeria monocytogenes* in patients taking TNF inhibitors and identified 26 published cases of *Listeria* infections in anti-TNF treated patients (FDA 2011). Data from the French registry RATIO report the annual incidence rate of nontuberculosis opportunistic infections including *Legionella* and *Listeria* to be 151.6 per 100,000 patient years (Salmon-Ceron 2011). The same study found that monoclonal anti-TNF antibodies (specifically infliximab and adalimumab) rather than soluble TNF receptor therapy (specifically etanercept) and steroid use greater than 10 mg per day are independently associated with increased risk of opportunistic infection.

Opportunistic fungal infections, particularly histoplasmosis, have been identified in patients treated with adalimumab, etanercept, infliximab, and certolizumab pegol. In 2008, the FDA required a strengthened label warning for opportunistic fungal infections on these drugs (FDA 2008). This was prompted by several cases of histoplasmosis that were not initially recognized by health care professionals, thereby delaying treatment. Twelve of 21 of these cases were fatal (FDA 2008). Unfortunately, histoplasmosis infections often present atypically in anti–TNF treated patients. Once acquired, this population is at greater risk of more severe or disseminated disease (Smith 2009), Special care should be taken in assessing for and recognizing these infections in patients taking biologic agents.

Cardiovascular Disease

Inflammatory diseases such as RA increase cardiovascular risk. The increased risk of cardiovascular disease (CVD) morbidity is estimated to be 2-fold higher than that of the general population (Avina-Zubieta 2012). In addition to a higher prevalence of traditional CVD risk factors in patients with RA, the disease itself seems to confer additional risk factors (Barbhayiya 2013). These disease-specific risk factors include immune dysregulation, plaque instability, elevated thrombotic markers (fibrinogen, D-dimer), systemic inflammation, and impaired coronary reserve (Barbhayiya 2013),

An array of human and animal studies have suggested an association between TNF inhibitors with vascular instability, progression of atherosclerosis, and negative inotropic and cardiac remodeling effects on the myocardium (Barbhayiya 2013; Danila 2008). Because of the presumed deleterious effects of TNF-α within the cardiovascular system, it has been postulated that treatment with anti-TNF agents actually confers a cardioprotective effect; however, data are conflicting.

Biologic DMARDs in High-Risk Patients

Heart Failure

Concern with the use of anti-TNF agents in heart failure stems from several randomized clinical trials as well as postmarketing case reports. A 2001 report from the American College of Cardiology identified several large-scale clinical trials that were stopped early because etanercept treatment failed to demonstrate a benefit on heart failure or mortality (Louis 2001). In addition, a study of 150 patients with New York Heart Association (NYHA) class III and IV heart failure found treatment with infliximab increased mortality and hospitalization from heart failure exacerbation after just 28 weeks of treatment (Chung 2003). Postmarketing case reports of new and worsening heart failure in patients receiving anti-TNF therapy have also been documented. In 2003, a study from the FDA MedWatch program reported 38 new cases of heart failure and nine cases of heart failure exacerbation in patients receiving anti-TNF therapy (Kwon 2003). Thirty-eight of these cases were in patients with RA; of the incident heart failure cases, 50% occurred in patients with no identifiable risk factors. Ten of the 38 cases occurred in patients younger than 50 years.

This worrisome clinical data influenced the ACR guidelines for use of anti-TNF agents in patients with heart failure. The guidelines recommend avoiding any anti-TNF biologic in patients with NYHA class III or IV heart failure or in those with an ejection fraction of 50% or less. New York Heart Association class III patients have marked limitation of physical activity because of their heart condition but are comfortable at rest. New York Heart Association class IV patients are unable to carry out any physical activity without discomfort and may experience discomfort at rest. The ACR guidelines do not address the use of non-TNF biologics in the patient with RA and concomitant heart failure.

Not all data regarding anti-TNF biologics and heart disease are unfavorable. A recent study of more than 20,000 U.S. veterans with RA found that use of TNF

inhibitors was not associated with increased risk of heart failure and was associated with a decreased risk of stroke (Al-Aly 2011). This study is further supported by a second study of patients with RA that found the use of anti-TNF agents was not associated with a greater risk of hospitalization for heart failure than nonbiologic DMARD use (Solomon 2012). Lastly, a review and meta-analysis found that anti-TNF therapy is associated with a reduced risk of all cardiovascular events, myocardial infarction, and stroke (Barnabe 2011). The study did not look at the risks of anti-TNF agents in heart failure specifically. Because of conflicting evidence in this high-risk population, more research is needed to determine best practices for use of anti-TNF biologics in heart failure.

Hepatitis

It is well established that immunosuppression increases viral replication, although much of the existing data come from patients receiving chemotherapy for malignancy or long-term immunosuppression after transplant rather than in the RA setting. Both rituximab and the anti-TNF agents have been implicated in viral replication and reactivation of hepatitis infections, whereas extremely limited data exist in the setting of HBV or HCV with the other biologic agents (Hoofnagle 2009; Koo 2009; Vassilopoulos 2007).

Although the risk of viral replication exists, the current ACR guidelines do not recommend universal HBV or HCV testing at baseline for patients initiating biologic therapy. The guidelines do suggest that if risk factors for hepatitis are present, evaluation may include hepatitis B surface antigen (HBsAG), antibody (anti-HBs), or core antibody (HBcAb) testing and/or HCV antibody testing; however, no formal recommendation for specific screening procedures are made. In contrast, the CDC recommends every patient starting immunosuppressive therapy be screened for HBV with the HBsAG, anti-HBs, and HBcAb tests (Weinbaum 2008). A survey of U.S. rheumatologists found 69% practiced universal HBV screening before initiating immunosuppressive therapy (Stine 2010).

In 2012, the ACR guidelines were updated regarding biologic use in patients with hepatitis; these changes are shown in Table 1-4. In contrast to the 2008 guidelines, which relied predominantly on Child-Pugh classification, the new guidelines include both disease severity and concurrent treatment in therapeutic decision-making. Now biologic agents are not recommended in untreated chronic HBV regardless of the Child-Pugh classification. Research shows that the rate of HBV reactivation in patients receiving immunosuppression therapy without antiviral prophylaxis ranges widely from 24%–88%. The risk of liver-related mortality in this population is high at 5%–30%. Specific to anti-TNF agents, the rate of HBV reactivation in HBsAg-positive patients not receiving antiviral prophylaxis is 38% (Vassilopoulos 2011). When chronic HBV is being treated, biologic therapy can be used in mild disease (defined as Child-Pugh class A). Biologic therapy is contraindicated in patients with Child-Pugh class B or C because of HBV, regardless of treatment status.

Current guidelines recommend etanercept as a treatment option for patients with RA having HCV. This is in contrast to the 2008 guidelines, in which biologic therapy is contraindicated in active HBV or HCV infection. Of note, the 2012 guidelines do not distinguish acute HCV from chronic HCV, nor do they discuss HCV Child-Pugh

Table 1-4. ACR Guidelines on the Use of Biologic Agents to Treat RA in Patients with a History of Hepatitis

	2008 Recommendations	2012 Recommendations
Active hepatitis B	Contraindicated	Not discussed
Active hepatitis C	Contraindicated	Etanercept
Chronic hepatitis C (Child-Pugh class A)	Any biologic agent	Etanercept
Chronic hepatitis C (Child-Pugh class B or C)	Contraindicated	Etanercept
Untreated chronic HBV (Child-Pugh class A)	Any biologic agent	Contraindicated
Treated chronic HBV (Child-Pugh class A)	Any biologic agent	Any biologic agent
Untreated/treated HBV (Child-Pugh class B or C)	Contraindicated	Contraindicated

RA = rheumatoid arthritis.

Patient Care Scenario

A 53-year-old woman (weight 84 kg) with medical history of HCV has a new diagnosis of RA. Her allergies include sulfa medications (severe swelling of tongue, lips and throat). She is experiencing a moderate degree of functional limitation as a result of the RA. The rheumatologist notes the presence of rheumatoid nodules and joint erosions on a recent radiograph. She also has a positive rheumatoid factor. Her disease activity is considered high by the rheumatologist, who prefers to use a biologic agent as initial therapy. What would be best to recommend for this patient?

Answer

Early treatment in a patient with RA is based on disease severity and the presence or absence of poor prognostic features. The patient has high disease activity based on an assessment by the rheumatologist and features of poor prognosis including functional limitation, extra-articular disease (manifesting as rheumatoid nodules), positive rheumatoid factor, and erosions present on radiography. Therapy options for this patient include traditional DMARD combination therapy or an anti-TNF agent with or without concurrent methotrexate.

Because the patient has a life-threatening allergy to sulfa, she is not a candidate for any DMARD combination therapy that contains sulfasalazine. Additionally, the patient is not a candidate for any combination therapy that includes methotrexate because of her history of HCV. These two factors eliminate each of the traditional combination DMARD therapy options and leave therapy with an anti-TNF inhibitor as first choice. This patient is considered at high risk when taking biologic therapy because anti-TNF agents have been implicated in viral replication and reactivation of HCV infection. Of the anti-TNF agents, etanercept has the greatest amount of evidence supporting its use in the setting of HCV. Etanercept is also the preferred biologic agent in the treatment of RA in patients with HCV according to the 2012 ACR guideline update.

Unlike biologic therapy in patients with HBV, biologic treatment in patients with HCV is not based on Child-Pugh classification or concomitant antiviral therapy. Therefore, no additional hepatic disease assessments need to be completed, and the patient can be considered for biologic therapy. Whereas the guidelines call for anti-TNF therapy with or without methotrexate for early initial RA, this patient has a clear contraindication to methotrexate because of her history of HCV. Etanercept monotherapy should therefore be initiated at a weekly subcutaneous injection of 50 mg.

1. Brunasso MG, Puntoni M, Fulia A, et al. Safety of anti-tumor necrosis factor agents in patients with chronic hepatitis C infection: a systematic review. Rheumatology 2011;50:1700-11.

2. Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res 2012;64:625-39.

class differences. The ACR recommendation is supported by randomized controlled data as well as findings from a systematic review (Brunasso 2011; Zein 2005). A phase II,randomized controlled trial found improved biochemical and virologic response with etanercept add-on therapy in 50 patients infected with chronic HCV (Zein 2005). More recently, a systematic review described the findings of 153 patients with concomitant HCV receiving anti-TNF treatment for various indications (Brunasso 2011). Of the 153 patients assessed, 110 received treatment with etanercept therapy. Of those receiving etanercept, only one confirmed case and five suspected cases of worsened HCV were reported.

Malignancy

Because TNF-α plays an important role in host defense, there is concern that therapy with TNF inhibitors may predispose patients to adverse effects related to impaired immunity, including an increased incidence of neoplasm.

Only one study to date found the risk of malignancy to be significantly higher in patients with RA who were treated with anti-TNF agents (Bongartz 2006). Of note, doses of anti-TNF agents studied in this review were often higher than those recommended in clinical practice for treatment of RA. Recent meta-analyses and systematic reviews refute this finding (Le Blay 2012; Solomon 2012; Askling 2011; Mariette 2011). A pooled analysis of randomized controlled trials from 2011 found anti-TNF therapy did not significantly increase the risk of short-term malignancy, except for nonmelanoma skin cancer, in which anti-TNF therapy doubled the risk of occurrence (Askling 2011). This finding was supported by two additional studies (Solomon 2012; Mariette 2011).

The labeling for malignancy in most non-TNF biologics is vague, largely because of the lack of postmarketing data to inform the risk in tocilizumab, abatacept, and anakinra (Ruderman 2012). Tofacitinib, however, carries a boxed warning for increased risk of lymphoma and other

malignancies, especially in patients receiving concomitant immunosuppressive therapies.

The 2012 ACR guidelines recommend rituximab for treatment of RA in patients with any solid or nonmelanoma malignancy treated within the past 5 years and any skin melanoma or lymphoproliferative malignancy history, regardless of time since treatment. Of note, this recommendation is not supported by clinical trial data; however, rituximab is indicated for treatment of lymphoma and other hematologic cancers and may be a safer alternative in patients with a recent history of malignancy. Any biologic therapy, including the anti-TNF agents, can be used in patients with solid malignancy or nonmelanoma skin cancer that was treated more than 5 years previously, according to the guidelines. The guidelines panel rated the level of evidence for these recommendations a "C" based on consensus opinion of experts, case studies, or standards of care. Additionally, the literature search for the 2012 guideline update ended February 26, 2010, and did not include many of the reviews discussed earlier.

Patient Education

With the introduction of synthetic DMARDs, and now the biologic DMARDs, treatment goals for RA have shifted from simply treating symptoms to trying to control or halt disease activity. Ensuring the appropriate DMARD is being used with good adherence is important to achieving low disease activity or remission. Inadequate treatment and poor adherence are both issues in patients with RA (Schmajuk 2011).

Several studies have shown that interdisciplinary, patient-centered care in RA produces clinical and functional outcomes superior to the traditional rheumatologist-centered model (Engen 2011; Esselens 2009). One study showed that pharmacists can improve patient medication adherence and quality of life through an RA disease therapy management (DTM) program (Stockl 2010). In the study, patients were flagged for participation in the DTM program by the pharmacy benefits manager if they had a diagnosis of RA and a pharmacy claim for an injectable RA drug. The DTM program offered pharmacist- and nurse-directed patient education and resources to self-manage pharmacotherapy and symptoms. Special attention was given to education on medication adherence. Counseling sessions included information on management of injection site reactions, the consequences of missed doses, patient assistance programs, and financial aid for injectable RA drugs. A proportion of days covered of at least 0.80 is considered high adherence and is the benchmark most commonly reported in the literature (Andrade 2006). The results of the study showed that proportion of days covered was significantly higher for patients enrolled in the DTM program than for patients receiving biologic therapy from a traditional community pharmacy (0.83 vs. 0.60). The patients in the DTM program also showed significantly greater physical health-related quality of life than their community pharmacy comparators.

Another role for pharmacists in the management of RA lies in the importance of vigilant safety monitoring. As discussed earlier, biologic DMARD therapy is not without risks. Although prevention strategies have been developed to minimize or mitigate the adverse reactions of biologic therapy, they are not always incorporated into practice.

Practice Points

In considering treatment of RA:

- Medication selection between nonbiologic DMARDs, biologic DMARDs, and tofacitinib is based on RA disease activity, presence or absence of features of poor prognosis, and therapy that has been tried previously.
- The biologic agents are typically tried after trials with other DMARD agents and rarely as initial therapy. When treatment with a biologic agent is necessary, TNF inhibitors are typically selected before other biologic agents because of their high efficacy and preference given in the guidelines and clinical practice.
- Patients taking a TNF inhibitor who experience significant disease activity after 3 months of treatment may consider switching to another TNF inhibitor or a non-TNF agent.
- Patients taking a non-TNF biologic agent who experience significant disease activity after 6 months of treatment may consider switching to another non-TNF agent or an anti-TNF agent.
- Although adalimumab, certolizumab, and etanercept can be used as monotherapy, each of the TNF inhibitors shows improved response when given in combination with methotrexate in early and established RA. Golimumab and infliximab are indicated only in combination with methotrexate.
- Anti-TNF agents should be avoided in patients with NYHA class III-IV heart failure.
- Because anti-TNF agents modulate immune response, serious infection is a concern. Vaccinations and TB screening should occur before initiation of these agents, and live vaccines should be avoided during treatment.
- Any biologic therapy can be used in patients with a history of solid malignancy or nonmelanoma skin cancer treated more than 5 years previously. Rituximab is recommended for solid and nonmelanoma malignancy treated within the past 5 years and any skin melanoma or lymphoproliferative malignancy history, regardless of time since treatment.
- Biologic therapy can be used in mild HBV (Child-Pugh class A) when a prophylactic antiretroviral agent is being used concomitantly. Etanercept is recommended in patients with HCV.

A study team set out to determine whether implementation of system-wide clinical care guidelines for biologic response modifiers increased the rate of compliance with safety monitoring recommendations (Hanson 2013). The guidelines recommended a TB test, HBsAg test, liver function test (LFT), complete blood cell count (CBC), up-to-date vaccination status, cancer assessment, pregnancy test, and evaluation of all other contraindications to therapy occur before initiation of a biologic agent. A process was developed to flag biologic hospital orders or outpatient prescriptions for an assessment of guideline compliance. Guideline compliance was defined as completion of four safety screenings (TB, HBsAg, LFT, and CBC) before initiation of biologic therapy. During this evaluation process, pharmacists assisted clinical staff in ordering laboratory tests before biologic initiation, when necessary.

Before implementation of the clinical care guidelines, only 31% of outpatient biologic prescription orders were preceded by completion of the safety monitoring guidelines. After implementation of the guidelines, a statistically significant improvement occurred in 60% of cases compliant with the guidelines.

Conclusion

The increased availability of biologic DMARD agents to treat RA provides expanded drug therapy options for patients. Clinical studies for the biologic DMARDs often enroll patients who have already tried and not responded to methotrexate or other DMARD therapy. In clinical practice, the biologic agents are typically tried after trials with other DMARD agents and rarely as initial therapy. There are limited data comparing biologic DMARD agents. Several classes of biologic agents are available, and patient-specific characteristics and adverse effect profiles of the agents should be considered when selecting among the biologic agents. Additionally, the ACR guidelines provide algorithms to aid the clinician in the decision. The pharmacist plays an important role in patient education and drug selection for these patients with progressing RA.

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Self-Assessment Questions

1. A patient with a history of severe chronic obstructive pulmonary disease, depression, and hyperlipidemia presents to the rheumatology clinic for a follow-up visit related to rheumatoid arthritis (RA). The patient has been taking an anti-tumor necrosis factor agent, adalimumab 40 mg subcutaneously, for the past year and has not achieved satisfactory control of RA symptoms. Which one of the following is best to recommend for this patient?

   A. Increase adalimumab to 80 mg subcutaneously weekly.
   B. Stop adalimumab and start abatacept 125 mg subcutaneously weekly.
   C. Stop adalimumab and start etanercept 25 mg subcutaneously weekly.
   D. Stop adalimumab and start golimumab 50 mg subcutaneously monthly plus methotrexate 7.5 mg orally every week.

2. A 46-year-old woman with RA was started on intravenous tocilizumab at her last appointment 3 months ago. Today, she presents for follow-up. She states that her joint pain and stiffness have not improved since starting tocilizumab. Her medical history is significant for hypothyroidism, hypertension, and chronic constipation. Which one of the following is best to recommend for this patient?

   A. Add etanercept 50 mg subcutaneously every week.
   B. Add methotrexate 7.5 mg orally daily.
   C. No change in therapy.
   D. Stop tocilizumab and initiate infliximab.

Questions 3–5 pertain to the following case.

L.P. is a 58-year-old woman (height 66 inches, weight 76 kg) with a new diagnosis of RA. Her disease activity is considered high. In addition, L.P. has features of poor prognosis including positive rheumatoid factor and bony erosions by radiography. She lives in a rural area that is a significant distance from the city where her clinic appointments are located. Her laboratory data include BUN 23 mg/dL, SCr 1.4 mg/dL, glucose 148 mg/dL, potassium 5.0 mmol/L, and sodium 139 mmol/L.

3. Which one of the following is the best initial therapy for L.P.?

   A. Anakinra 100 mg subcutaneously daily plus methotrexate 7.5 mg orally weekly.
   B. Adalimumab 40 mg subcutaneously every other week plus methotrexate 7.5 mg orally weekly.
   C. Leflunomide 20 mg orally daily.
   D. Methotrexate 7.5 mg orally weekly.

4. Which one of the following is most likely to pose medication administration challenges for L.P.?

   A. Abatacept.
   B. Certolizumab.
   C. Infliximab.
   D. Tofacitinib.

5. L.P. refuses an injectable medication. Which one of the following is best to recommend for L.P.?

   A. Hydroxychloroquine 200 mg twice a day.
   B. Leflunomide 100 mg for 3 days. Then 20 mg daily plus sulfasalazine 500 mg three times a day.
   C. Methotrexate 7.5 mg weekly plus sulfasalazine 500 mg twice daily.
   D. Tofacitinib 5 mg twice daily.

6. A 23-year-old woman presents to the clinic to initiate biologic therapy for RA. She was vaccinated with the inactivated influenza, recombinant pneumococcal, and human papillomavirus vaccines 2 weeks ago. Which one of the following is best to recommend for this patient?

   A. Start biologic therapy immediately.
   B. Start biologic therapy in 2 weeks.
   C. Start biologic therapy in 4 weeks.
   D. Do not start biologic therapy.

7. A patient was given a diagnosis of RA 3 years ago. Her medical history includes hypothyroidism. Initially, therapy with methotrexate plus sulfasalazine adequately controlled her RA symptoms. However, she has recently experienced an increase in tender and swollen proximal joints of the hands. Today, at the follow-up appointment, a change in therapy is being considered. Which one of the following is best to recommend for this patient?

   A. Anakinra 100 mg subcutaneously daily.
   B. Etanercept 50 mg subcutaneously weekly.
   C. Golimumab 50 mg subcutaneously weekly.
   D. Rituximab 1000 mg intravenous days 1 and 15 plus methotrexate 7.5 mg orally every week.

8. A 32-year-old woman has a new diagnosis of RA. She is planning to become pregnant in the next year and questions whether RA will affect her chances of becoming pregnant. Her medical history includes type 2 diabetes mellitus. Which one of the following is best to recommend for this patient?

   A. Adalimumab 40 mg subcutaneously every other week.
   B. Golimumab 50 mg subcutaneously every week.
   C. Leflunomide 20 mg orally daily.
   D. Methotrexate 7.5 mg orally every week.

9. A 56-year-old man (height 70 inches, weight 98 kg) has had RA for 5 years. He is currently taking disease-modifying antirheumatic drug (DMARD) combination therapy with methotrexate 15 mg orally every week plus hydroxychloroquine 400 mg orally daily. In the past year, his disease activity has progressed to moderate despite the combination therapy. His current laboratory values include BUN 22 mg/dL, SCr 2.2 mg/dL, glucose 190 mg/dL, potassium 4.8 mEq/L, and sodium 136 mEq/L. Which one of the following is best to recommend for this patient?

   A. Switch to methotrexate intramuscularly and continue hydroxychloroquine.
   B. Switch to tocilizumab 4 mg/kg intravenously monthly plus methotrexate 7.5 mg orally daily.
   C. Switch to tofacitinib 5 mg orally daily.
   D. Switch to etanercept 50 mg subcutaneously weekly.

10. Which one of the following education points is most appropriate for a patient taking tofacitinib for RA?

    A. Increased risk of infection while taking the medication.
    B. Monitoring for medication-induced myalgia.
    C. Need for frequent blood glucose testing.
    D. Tofacitinib not to be taken in combination with simvastatin.

Questions 11–13 pertain to the following case.

L.S. is a 62-year-old woman who presents with uncontrolled RA and complaints of fatigue and weight loss. Her rheumatologist would like to convert her therapy from oral methotrexate to etanercept. L.S. has the following vaccination history: tetanus/diphtheria/acellular pertussis (TDaP) vaccine, annual inactivated influenza vaccine, Bacille Calmette-Guerin vaccine, and the recombinant pneumococcal vaccine (with one-time revaccination). She is employed in a correctional facility.

11. Which one of the following would be best option to screen for tuberculosis (TB) in L.S.?

    A. Tuberculin skin test at baseline.
    B. Interferon-gamma-release assay (IGRA) at baseline.
    C. Tuberculin skin test at baseline and annually.
    D. IGRA at baseline and annually.

12. L.S. was screened for TB infection and the results returned negative. Which one of the following would be the best next step in the treatment of L.S.'s RA?

    A. Begin etanercept therapy.
    B. Rescreen for TB.
    C. Obtain chest radiography.
    D. Collect sputum culture for examination.

13. If L.S. were to start etanercept therapy, which one of the following vaccines would be most appropriate to administer during treatment?

    A. Hepatitis B vaccine.
    B. Human papillomavirus vaccine.
    C. Pneumococcal vaccine.
    D. Zoster vaccine.

14. In which one of the following patients with RA would it be most appropriate to recommend biologic therapy?

    A. A patient with untreated Child-Pugh class A hepatitis B.
    B. A patient with treated Child-Pugh class A hepatitis B.
    C. A patient with untreated Child-Pugh class B hepatitis B.
    D. A patient with treated Child-Pugh class B hepatitis B.

15. A 43-year-old man has a medical history of RA, heart failure, diabetes, and hyperlipidemia. His current laboratory values are as follows: A1C 7.3%, LDL cholesterol 148 mg/dL, TG 445 mg/dL, and an ejection fraction of 48%. Which one of the following biologic agents would be best to treat this patient's RA in combination with methotrexate?

    A. Adalimumab.
    B. Etanercept.
    C. Rituximab.
    D. Tocilizumab.

16. A 43-year-old man has a medical history of RA, testicular cancer (diagnosed 3 years ago, currently in remission), and New York Heart Association (NYHA) class II heart failure. He presents to initiate

his first biologic DMARD. Which one of the following is best to recommend for this patient?

A. Abatacept.
B. Anakinra.
C. Etanercept.
D. Rituximab.

Questions 17 and 18 pertain to the following case.

T.T. is a 54-year-old man (height 70 inches, weight 86 kg) who has moderate RA disease activity and no features of poor prognosis. T.T. has been taking oral methotrexate 25 mg weekly for 2 years. He feels that his RA symptoms are well controlled on his current regimen, but he has heard of newer injectable biologic DMARDs to treat RA and wants to know if he should switch. He is tolerating methotrexate well and denies adverse effects. Although he does not have a history of renal dysfunction, routine laboratory monitoring now shows moderate renal dysfunction. T.T.'s pertinent laboratory values and vital signs include: sodium 140 mEq/L, potassium 4.2 mEq/L, BUN 18 mg/dL, SCr 1.8 mg/dL, and glucose 178 mg/dL.

17. Which of the following would be most advantageous when switching this patient from oral methotrexate to a biologic DMARD?

A. Ease of administration.
B. Slowing joint destruction on radiography.
C. Increased bioavailability.
D. Minimizes risk of reactivation of tuberculosis.

18. Which one of the following is best to recommend for this patient?

A. Make no change in therapy.
B. Reduce methotrexate to 15 mg orally.
C. Stop methotrexate and initiate etanercept 50 mg subcutaneously weekly.
D. Switch to methotrexate 30 mg intramuscularly weekly.

Questions 19 and 20 pertain to the following case.

A 2006 meta-analysis by Bongartz et al. assessed the risk of malignancy from the anti-TNF agents. Data from the nine randomized controlled trials showed 29 cases of malignancy in patients treated with at least one dose of anti-TNF therapy (n=3493) and three cases of malignancy in the control group (n=1512).

19. Based on the results from the meta-analysis, which one of the following best represents the number needed to harm, for malignancy in patients treated with anti-TNF inhibitors?

A. 120.
B. 159.
C. 196.
D. 380.

20. Based on the results from the meta-analysis, which one of the following best represents the odds ratio for developing malignancy from therapy with an anti-TNF agent?

A. 2.3.
B. 4.2.
C. 6.4.
D. 9.6.