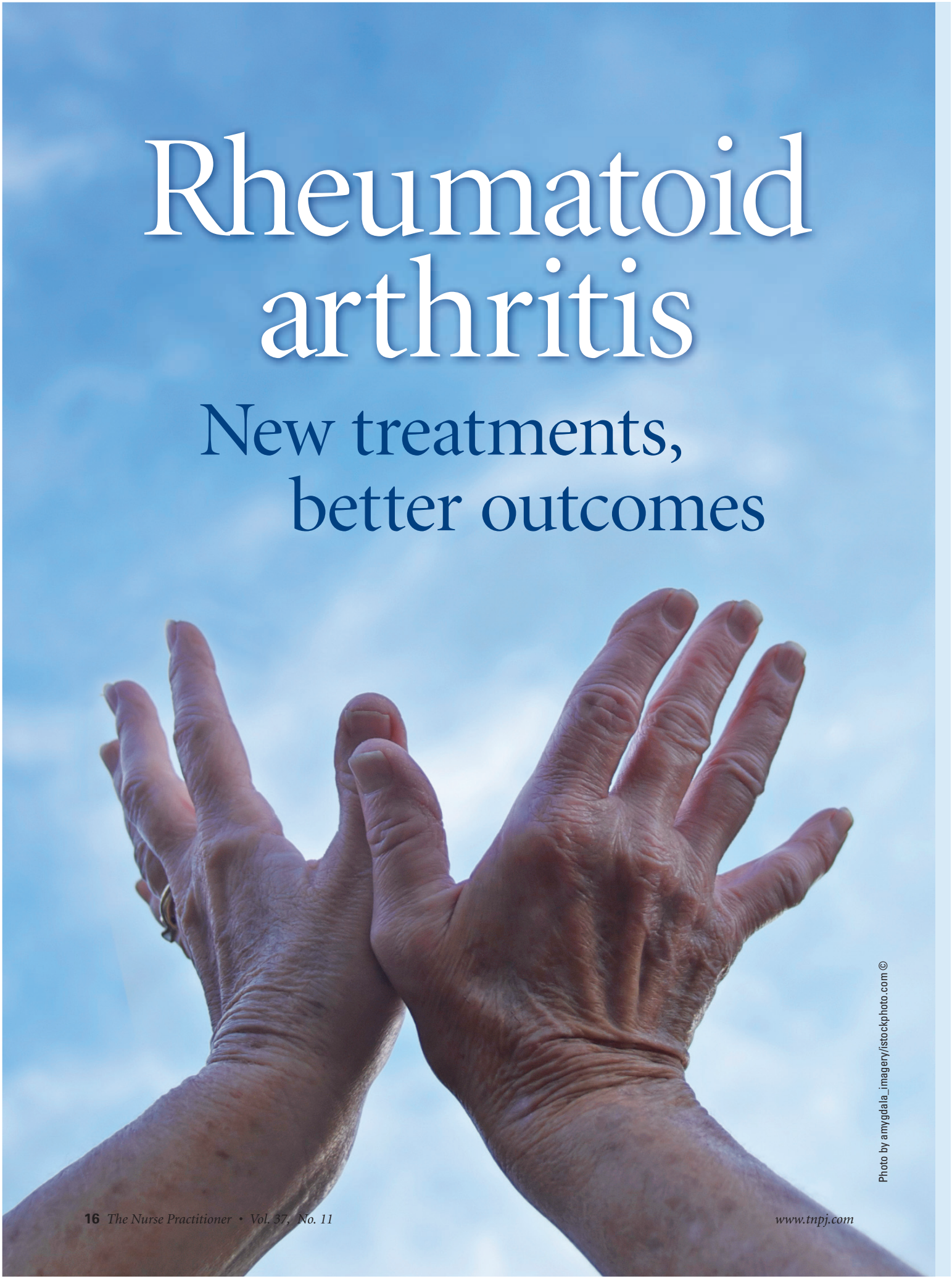
Rheumatoid arthritis

New treatments, better outcomes



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Abstract: There have been numerous changes regarding evidence-based care of patients with rheumatoid arthritis, a costly, chronic, autoimmune disease. This article provides an update on the factors that affect the safe use of biologic medications in this patient population.

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Rheumatoid arthritis (RA) is a chronic, autoimmune disease characterized by inflammation of the synovial tissues.[1] Left untreated, the disease can result in destruction of articular cartilage and the juxtaarticular bone.[1] There are approximately 1.5 million adults in the United States with RA, and the prevalence is higher in women and older people.[2-4] The difference in the mortality between those with RA and the general population is increasing.[5] The direct and indirect costs attributed to RA have been estimated at $19.2 billion.[6]

Updates on the classification criteria for RA

In 2010, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) revised the RA classification criteria with the purpose of improving upon the 1987 criteria in classifying early disease (see *2010 ACU/EULAR classification criteria for rheumatoid arthritis*).[7] The revised criteria take advantage of a new understanding of the importance of antibodies to citrullinated proteins in the pathogenesis of RA.[7] They are measured as anticyclic citrullinated peptide (CCP) antibodies that are highly specific for RA. In a comparison of the two classification criteria (n = 265), Cader and colleagues concluded that the 2010 criteria improved sensitivity by 24% but reduced specificity by 15%[8]; otherwise stated, far fewer patients with RA are left unclassified, but there are a slightly increased number of patients without the disease who are classified as having RA. A study conducted by van der Linden and colleagues found that delayed rheumatologic evaluation can result in exacerbated rates of disease remission and increased rates of joint destruction, thus emphasizing the importance of early diagnosis.[9] With the availability of treatments that are effective at relieving inflammation and preventing structural joint damage, early diagnosis and treatment is critical to achieving optimal outcomes for patients with RA.

Updates on the determination of disease activity

In 2011, the ACR and EULAR defined disease remission for the purposes of clinical trials. The Boolean-based definition states that the patient must have less than or equal to one tender joint, swollen joint, patient global assessment (0 to 10 scale), and less or equal to 1 mg/dL value reported for the C-reactive protein.[10] The index-based definition is that a patient must have a score on a measure of disease activity (includes tender joint count, swollen joint count, patient global assessment of disease activity, physician global assessment of disease activity, and C-reactive protein level) of less than or equal to 3.3.[10]

RA treatment overview

To prevent damage to joints, maintain functional status, and decrease pain, treatment guidelines recommend the use of nonbiologic and/or biologic disease-modifying antirheumatic drugs (DMARDs) within 3 months of diagnosis.[1,7] Appropriate use of biologic and nonbiologic DMARDs can result in remission of disease as evidenced by lack of joint swelling and pain, normal tests of inflammation, and lack of erosive radiographic progression.[1,7] The early initiation of biologic and nonbiologic DMARDs results in a cost-effectiveness ratio of $4,849 per quality-adjusted life-year—a figure accounting for the quality and quantity of life by adjusting the number of life-years via quality.[11]

Over the past 24 years, significant advances have been made in the medications used to treat moderate-to-severe RA.[12] In 2010, an international task force set forth the recommendation to treat RA to target (see *RA treat to target recommendations*).[13] Treating RA until low-disease activity or disease remission is attained is the key concept of the treat-to-target recommendations.[13] The recommendations state that measures of disease activity should be used, and adjustments to medications should be made every 3 months until this goal is met.[13]

Key words: biologic medications, chronic autoimmune disease, evidence-based management of rheumatoid arthritis, rheumatoid arthritis

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Recommendations for the use of nonbiologic and biologic DMARDS were made in 2008 and then updated in May of 2012.[14,15] In the 2012 recommendations, nonbiologic DMARDs can be used as monotherapy for low, moderate, and high disease activity when the patient does not have features suggesting a poor prognosis.[15] Erosions on radiograph, functional limitations, positive rheumatoid factor/anti-CCP antibodies, and extra-articular disease were factors used to determine the potential for a patient's poor prognosis.[15] In the presence of poor prognostic features in patients with moderate disease activity (or in those with high disease activity but without features of poor prognosis), combinations of nonbiologic DMARDs should be used. In patients with high disease activity and poor prognostic indicators, antitumor necrosis factor (anti-TNF) alpha agents with or without methotrexate (except infliximab, which should not be used as monotherapy), or combinations of nonbiologic DMARDs should be started.[15]

Singh and colleagues provide guidelines for switching between biologic agents: when there is a lack of clinical response, or clinical response is lost and the patient experiences an adverse event.[15] Those recommendations specify that patients with moderate-to-high disease activity should be switched from an anti-TNF alpha agent after 3 months if there is no benefit. Non-TNF biologic agents should be monitored for benefit for 6 months before switching therapy. Anti-TNF alpha agents and non-TNF biologic agents should be switched based on the agent used when the adverse event occurred and its severity.[15]

Methotrexate remains the first-line medication for moderate-to-severe RA.[14] An estimated 45.6% of patients with RA taking methotrexate as monotherapy meet ACR response rates 20% (20% improvement in multiple measures of disease activity); 22.8% meet ACR response rates 50% (50% improvement in multiple measures of disease activity); and 9.4% meet ACR response rates 70% (70% improvement in multiple measures of disease activity).[16] Most biologics should be started ideally with methotrexate (unless contraindicated) in those with high disease activity and poor prognostic features.[14]

2010 ACR/EULAR classification criteria for RA[7]*

Testing should be conducted on those with clinical synovitis or joint swelling that is not reasonably explained by another diagnosis.

Classification criteria	
A. Joint involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints (with or without large joint involvement)	2
4-10 small joints (with or without large joint involvement)	3
>10 joints, at least one of which is a small joint	5
B. Serology	
Negative rheumatoid factor (RF) and negative anticyclic citrullinated protein antibody (ACPA)	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute phase reactant	
Normal C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)	0
Abnormal CRP or ESR	1
D. Duration of symptoms	
<6 weeks	0
≥6 weeks	1

Scores from A to D are summed and a score of ≥ 6 indicates diagnostic classification of RA

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Introduction to biologics

There are currently nine genetically engineered biologic medications with indications to treat RA; four of these have been FDA approved over the past 5 years.[12] Two of these medications (certolizumab and golimumab) belong to the TNF alpha class; one is a B-cell inhibitor (rituximab), and the other is an interleukin (IL)-6 inhibitor (tocilizumab) (see *Biologics used in RA*).[12] Biologic agents (excluding anakinra, which is discussed below) effectively treat RA as evidenced by the biologics having ACR response rate 20% (20% improvement in multiple measures of disease activity) ranging from 85% to 48%;[16,17] ACR response rate 50% (50% improvement in multiple measures of disease activity) ranging from 21% to 69%;[16,17] and ACR response rate 70% (70% improvement in multiple measures of disease activity) ranging from 11% to 47%.[16,18] Although effective in treating disease, these medications are costly.[19] In their recent study evaluating RA treatment cost-effectiveness (as opposed to clinical effectiveness), Finckh and colleagues reported that there is inconclusive fiscal evidence to support the early (less than 3 months) use of biologic agents.[11]

Anakinra, an IL-1 receptor antagonist, was FDA approved for use in the treatment of RA in 2001.[12] This drug has limited effectiveness at improving symptoms of RA and therefore will not be discussed in further detail.[16]

Anti-TNF alpha agents

Three anti-TNF alpha agents have been used for over 10 years for the treatment of RA.[12] TNF alpha is a proinflammatory cytokine found to play a key role in the synovial inflammation seen in RA.[20] Infliximab, one of the first anti-TNF alpha agents, was FDA approved for use in patients with RA in 1999.[12] Infliximab is a chimeric IgG1κ monoclonal antibody specific for human TNF alpha.[16] Adalimumab,

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an anti-TNF alpha agent FDA approved for use in the treatment of RA in 2002,[12,21] is a recombinant human immunoglobulin G monoclonal antibody specific for human TNF alpha.[21] Infliximab offers a chimeric monoclonal antibody versus adalimumab, which offers a humanized monoclonal antibody—a clear differentiation between these two agents. A third, early anti-TNF alpha agent, etanercept, inhibits TNF alpha via a differing mechanism. Etanercept is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kDa (p75) TNF receptor linked to the Fc portion of human immunoglobulin G1.[22]

Predictors of clinical response to biologics are an ongoing topic under investigation. A recent study was conducted to determine if antibodies to adalimumab and infliximab are formed and what effect this potential antibody formation has on clinical response.[23] Radstake and colleagues found that a nonresponder to these two anti-TNF alpha agents had high levels of serum antibodies to the drug;[23] this suggests that antibody formation may play a significant role in individual patient response to biologic agents.

In 2009, two additional anti-TNF alpha agents were FDA approved for the treatment of RA.[12] One of these agents, certolizumab pegol, is a humanized antibody Fab fragment conjugated to an approximate 40 kDa polyethylene glycol (PEG) with specificity for human TNF alpha.[24] Because of pegylation, the half-life of this medication is increased by 14 days when compared to other anti-TNF alpha agents. An additional unique property of this agent is that its structure may prevent complement, antibody-dependent cytotoxicity, or cell death.[24]

Golimumab, the second recently approved anti-TNF alpha agent, is described as a human IgG1κ monoclonal antibody specific for human TNF alpha. Lower concentrations of golimumab are required to neutralize TNF alpha when compared to infliximab.[25]

T-cell costimulation inhibitor

Abatacept was FDA approved to treat RA in 2005.[12] This agent is a soluble fusion protein consisting of cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) linked to the modified Fc portion of human immunoglobulin G1. CTLA4 is an inhibitory molecule that has a greater affinity for CD28 than CD80 or CD86. In normal physiologic functioning, the binding of CD80 or CD86 (on the antigen presenting cell) to CD28 (on the T-cell) results in T-cell activation. T-cell activation is selectively modulated when abatacept outcompetes CD80 and CD86 for CD28 binding.[26]

IL-6 receptor inhibitors

Tocilizumab is a humanized monoclonal antibody that exerts its effect by binding to IL-6 receptors. IL-6 is proinflammatory cytokine seen in excess in patients with RA.

RA treat to target recommendations[13]*

1. Goal of treatment is clinical disease remission.
2. The absence of signs and symptoms of significant inflammatory disease is the definition of clinical disease remission.
3. Although remission is the ultimate goal, it may be necessary with long-standing disease, to establish the treatment goal of low disease activity.
4. Drug therapy should be adjusted at least every 3 months until treatment goals are reached.
5. Disease activity should be measured monthly in those patients high/moderate disease activity and every 3 to 6 months in those with low disease activity.
6. Validated composite disease activity measures should be used.
7. Along with the composite disease activity measure, structural changes and functional abilities should be considered when making clinical decisions.
8. Low disease activity to disease remission should be maintained.
9. Comorbidities, patient factors, and drug-related risk should be considered when determining treatment goals and measures of disease activity.
10. Rheumatologists should supervise care and provide patients with information about the treatment goals and strategy.

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There are two IL-6 receptors (CD126 and IL6R alpha) on cell surfaces that mediated the effects of IL-6.[27] Tocilizumab, which exerts an effect on both receptors, was FDA approved for the treatment of RA in 2010.[12]

B-cell inhibitor

Rituximab is a chimeric monoclonal antibody exerting its effect on CD20+ B cells. Although historically used for a longer duration in patients with non-Hodgkin lymphoma, rituximab was FDA approved in 2009 for use in patients with RA who have had an inadequate response to anti-TNF alpha agents.[12,28] Rituximab binds to CD20, which depletes B cells possibly by promoting cell death and cell-mediated/complement-dependent cytotoxicity.[28]

Safety concerns with newer biologic agents

Certolizumab pegol and golimumab

According to the FDA label, there are no contraindications for use of either of these anti-TNF alpha agents in patients with RA. However, drug manufacturers state that there are a number of warnings including the risk of serious infections similar to older anti-TNF alpha agents. Both certolizumab pegol and golimumab should be used cautiously in those with an active infection. Similarly, opportunistic infections and serious fungal infections have been reported with the use of these medications. Signs and symptoms of infections

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Biologics used in RA[12,21,22,29-33, 36-39]

Drug	Class	Route of administration/ use with methotrexate	Cost	Pregnancy category/ excretion in breast milk
Abatacept	T-cell costimulation inhibitor	Subcutaneous (SC) or I.V.*/optional	$1,828 per month	C/not known
Adalimumab	Anti-TNF agent	SC*/optional	$1,800 per month	B/not known
Etanercept	Anti-TNF agent	SC*/optional	$1,700 per month	B/not known
Certolizumab pegol	Anti-TNF agent	SC*/optional	Initial $5,400 Maintenance $1,800 per month	B/not known
Golimumab	Anti-TNF agent	SC*/yes	$1,900 per month	B/not known
Infliximab	Anti-TNF agent	I.V.*/yes	$3,000 per infusion	B/not known
Rituximab	B-cell inhibitor	I.V.*/yes	$1,940 (twice yearly dosing)—$2,910 (three times per year)	C/not known
Tocilizumab	IL-6 inhibitor	I.V.*/optional	$1,060 to $2,125 per month, depending on the dose	C/not known

*Refer to manufacturer's prescribing information for the most current routes of administration, dosage and precautions.

should be carefully monitored in patients taking these anti-TNF alpha agents; there is also the risk of reactivation of tuberculosis (TB) and hepatitis B. Patients should be screened before and periodically throughout treatment for the presence of these infectious diseases. For patients taking either of these agents, a tuberculin skin test with an induration area greater than or equal to 5 mm is considered positive. Drug manufacturers also state that those taking certolizumab pegol and golimumab are 2 to 3.8 times as likely to develop lymphoma when compared to the general population, respectively. They also state that an association between leukemia and anti-TNF alpha agents has been reported. Worsening and new onset heart failure, hypersensitivity, hematologic (pancytopenia), neurologic conditions (demyelinating disease, optic neuritis, seizure disorders, peripheral neuropathies), and lupus-like syndromes have been reported with the use of anti-TNF alpha agents. Prescribers are advised that autoantibodies to certolizumab pegol can develop; certolizumab pegol and golimumab should be used cautiously with other biologic agents. According to FDA labeling, no live or attenuated vaccinations should be given while a patient is taking these medications.[29,30] The ACR's 2012 updated guidelines for the use of biologic medications in RA are presented below and cover much of the safety information addressed in FDA labeling.[15]

Abatacept

Similar to certolizumab pegol and golimumab, the FDA labeling states there are no absolute contraindications to taking abatacept. However, there are warnings about using abatacept with anti-TNF alpha agents because there were increased rates of infections seen in those taking both agents concomitantly. The risk of serious infection continues to exist in those patients taking abatacept without the use of anti-TNF alpha agents. Chronic obstructive pulmonary disease exacerbations have been reported in those taking abatacept in addition to increased reported cases of lung cancer and lymphoma. The risk of lymphoma has been reported by manufacturers to be 3.5 times higher in patients taking abatacept when compared to the general population; hypersensitivity reactions have been observed with the use of this medication. Manufacturers recommend screening for latent TB and hepatitis B infections.[31]

Rituximab

According to FDA labeling, there are no contraindications to the use of rituximab. The manufacturer's prescribing information warns that patients using rituximab for RA or other indications may experience infusion reactions, severe mucocutaneous reactions, and/or tumor lysis syndrome. Progressive multifocal leukoencephalopathy, serious infections, and reactivation of hepatitis B have also been reported by those taking this medication. Manufacturers recommend screening before starting therapy and monitoring throughout treatment. The medication has also been associated with cardiac dysrhythmias, renal toxicity, and bowel obstruction/perforation. To identify potential cytopenias, laboratory monitoring before therapy and weekly-to-monthly therapy is recommended.[32]

Tocilizumab

The FDA label states that the only contraindication to taking tocilizumab is a hypersensitivity reaction to the medication. The manufacturer has provided warnings that the medication

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has been associated with serious infections, hypersensitivity reactions, and gastrointestinal perforation. Demyelinating conditions are also possible with drugs used in the treatment of RA according to tocilizumab manufacturers. Reactivation of viruses such as hepatitis and herpes zoster may occur with the use of this medication; it may also reactivate latent TB. Appropriate screening for these infections should occur before and periodically throughout treatment. Patients should also avoid live vaccinations while they are taking this medication.[33] Manufacturers recommend monitoring patients' neutrophil counts, platelets, and transaminases.[33] An additional FDA label recommendation is to monitor lipid levels while a patient is taking tocilizumab.[33] Kume and colleagues conducted a 24-week trial investigating lipid levels along with other cardiovascular risk factors in patients taking tocilizumab, etanercept, and adalimumab. There were no significant differences found in the primary outcome cardioankle vascular index; however, there were significant increases in the fasting total serum cholesterol in the tocilizumab group.[34] An additional 5-year trial comparing cardiovascular events in patients with RA who are taking tocilizumab and etanercept is being conducted.[35]

ACR's 2012 recommendations

In their 2012 recommendations, the ACR described the safe use of biologics.[15] Authors suggested that etanercept may be used in patients with RA and coexisting hepatitis C infection, and patients with untreated and treated (Child-Pugh class B or higher) chronic hepatitis B infection should not be treated with biologics. No recommendations were made about biologic use in patients with RA who have a history of a positive hepatitis B core antibody.[15] The recommendations specify that biologic agents can be used in RA patients who have a history of solid tumor or nonmelanoma skin cancer treated more than 5 years ago.[15] Rituximab is a treatment option for persons with RA and a history of malignancy not meeting these criteria.[15] Patients with class III/IV heart failure or with an ejection fraction less than 50% should not take anti-TNF alpha agents according to these recommendations.[15] The 2012 recommendations continue to advise that all patients should be screened for latent TB before initiating therapy with biologic agents via tuberculin skin tests or interferon-gamma release assays (IGRAs). In patients with a history of bacillus Calmette-Guerin vaccination, IGRA should be used. Annual TB screening should be based on risk of exposure.[15] Based on age and risk factors, patients with RA should receive killed, recombinant, and live attenuated vaccinations before initiating therapy with biologic and nonbiologic DMARDs.[15] Recommended nonlive vaccinations for RA patients taking biologic and nonbiologic DMARDs include pneumococcal, influenza, hepatitis B, and human papillomavirus.[15] For those taking only nonbiologic DMARDs, the herpes zoster vaccination is recommended.[15]

Biologic agents under investigation

Thirteen Phase III trials representing seven classes of medications are being conducted to investigate. new biologic medications for use in the treatment of RA.[35]

Advancements in treating RA

Significant advances have been made in the diagnosis/treatment of RA in recent years, and treatment effectiveness has greatly improved with the use of biologic medications.[15] However, the proportion of patients not reaching remission in RA remains high, necessitating further research. Thirteen Phase III clinical trials are being conducted to investigate seven drug classes used to treat RA.[35] NP

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