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Managed Care Strategies for Improving Patient Outcomes in Rheumatoid Arthritis

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Target Audiences

Managed care pharmacists, pharmacy directors, medical directors, and nurses who manage patients with rheumatoid arthritis.

Overall Goal

The overall goal of the supplement is to provide managed care professionals with information and practical strategies to guide sound decisions about appropriate medication therapies and management strategies for patients with rheumatoid arthritis.

Learning Objectives

1. Summarize current research evidence regarding the efficacy, safety risks, and adherence rates associated with traditional disease-modifying antirheumatic drugs (DMARDs) and biologic agents for rheumatoid arthritis
2. Describe applications of comparative effectiveness research to the managed care of patients with rheumatoid arthritis
3. Evaluate the strengths and potential shortcomings of collaborative, multidisciplinary models of managed care in rheumatoid arthritis

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Core Management Principles in Rheumatoid Arthritis to Help Guide Managed Care Professionals

Sandeep K. Agarwal, MD, PhD

ABSTRACT

BACKGROUND: Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disease that affects approximately 1% of the population. Initial symptoms include joint swelling, stiffness, and tenderness, which are all causes of disability. The diagnosis of RA is based on patient history of joint pain and stiffness, the documentation of symmetric polyarticular joint synovitis, and laboratory measures including radiographs, inflammatory markers, and autoantibodies. As the disease progresses, synovial inflammation leads to cartilage damage, bone erosions, and joint destruction, the major causes of long-term disability. RA is associated with many comorbidities and complications, including cardiovascular disease, which is responsible for higher rates of mortality among patients compared with the general population. Over the past 2 decades, advances in the development of synthetic disease-modifying antirheumatic drugs (DMARDs) and biologic agents for RA have markedly changed treatment goals and management strategies.

OBJECTIVES: To review recent updates in the diagnosis and treatment of RA, as well as the importance of early and aggressive treatment and management strategies.

SUMMARY: Borrowing from other medical fields, a paradigm of "tight control" of RA has been supported by evidence and is gaining wide acceptance in rheumatology. In 2010, the American College of Rheumatology and the European League Against Rheumatism (EULAR) published revised classification criteria for RA, which will assist in the diagnosis of early RA and facilitate appropriate treatment intervention. Over the last decade, many patients on biologic agents have demonstrated that early and aggressive treatment of RA is beneficial in treating synovial inflammation, delaying joint damage, and improving patient outcomes. Contemporary management strategies based on early diagnosis, aggressive treatment, and regular monitoring have helped a significant number of patients with RA achieve current treatment goals of low levels of disease activity and, in some cases, clinical remission.

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Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory arthritis that affects approximately 1% of the population.[1] The disease affects people of all ages but is most common from the ages of 40-70 years.[1] Initially polyarticular synovial inflammation, leading to joint swelling, stiffness, and tenderness, is the major cause of disability. Over time synovial inflammation leads to cartilage damage, bone erosions, and joint destruction, the major causes of long-term disability. In addition, patients with RA have increased mortality compared with the general population, largely attributed to an increased risk of cardiovascular disease.[2] The burden of illness of RA not only impacts patients and families but also society through sick leave, loss of work productivity, and utilization of health care, stressing the importance of effective management of RA.[3]

Over the past 2 decades, optimal use of synthetic disease-modifying antirheumatic drugs (DMARDs) and/or biologic agents has proven highly effective in treating inflammation, delaying joint damage, and improving patient outcomes. The goals of treatment have expanded from the treatment of inflammation and achievement of a low disease activity state, to the realistic goal of achieving and maintaining clinical remission in a significant number of patients. In addition to treating inflammation, the inhibition of progressive joint destruction is also an important goal. Finally, by using DMARDs and biologic agents, physicians and their patients are striving to decrease pain and stiffness associated with inflammation, retard progressive structural joint damage, reduce RA comorbidities, restore function and quality of life, and help patients to maintain their societal roles.

It is commonly accepted that early intervention leads to improved patient outcomes. This paradigm is supported by a number of clinical trials. Therefore, it is critical that patients with symptoms of RA are identified early and referred to specialists with experience in treating RA, which will facilitate initiation of disease-modifying therapy that can be systematically modified in the pursuit of the treatment goals. In this article, we will review recent updates in the diagnosis and treatment of RA as well as the importance of early and aggressive treatment.

Diagnosing Rheumatoid Arthritis

The diagnosis of RA is a clinical diagnosis that combines the patient history of joint pain and stiffness, the physical examination documentation of symmetric polyarticular joint swelling (synovitis), and the laboratory tests including radiographs, inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]), and autoantibodies (rheumatoid factor [RF] and anti-cyclic citrullinated peptide antibodies

TABLE 1 2010 Rheumatoid Arthritis Classification Criteria[a]

Criteria	Score
Joints	
1 large joint	0
2–10 large joints	1
1–3 small joints (large joints excluded)	2
4–10 small joints (large joints excluded)	3
>10 joints (at least 1 small joint)	5
Serology	
Negative RF *and* negative anti-CCP	0
Low-positive RF *or* low-positive ACPA (≤3 times the upper limit of normal)	2
High-positive RF *or* high-positive ACPA (>3 times the upper limit of normal)	3
Symptom duration	
<6 weeks	0
≥6 weeks	1
Acute phase reactants	
Normal CRP and ESR	0
Abnormal CRP or ESR	1

[a]*Source: Aletaha D, Neogi T, Silman AJ, et al. Arthritis Rheum. 2010;62(9):2569-81.*[5]

ACPA = anti-citrullinated protein antibody; CCP = cyclic citrullinated peptide; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor.

[anti-CCP]). Physicians often use the 1987 American College of Rheumatology (ACR) Classification Criteria of RA to assist in making the diagnosis.[4] One study reported that 49% of surveyed rheumatologists would initiate disease-modifying therapy only after patients fulfilled these criteria.[4,5] However, these are not diagnostic criteria and are not sensitive in identifying patients with early RA.[6,7] Furthermore, since 1987, the discovery of anti-CCP and the possibility of using magnetic resonance imaging (MRI) has made improvements in our ability to diagnose early RA.[8-10] Given the importance of early detection and intervention, there was a need to develop criteria that will facilitate early diagnosis of RA.

Accordingly, a joint working group of ACR and the European League Against Rheumatism (EULAR) was formed to develop new classification criteria for RA (Table 1).[11] The criteria incorporate 4 domains including the types of joints involved, presence of autoantibodies, laboratory markers of inflammation, and symptom duration. These criteria are intended for patients with at least 1 joint with definite clinical synovitis (swelling, not just tenderness), and in whom the synovitis is not explained by another disease such as psoriasis, systemic lupus erythematosus, or gout. Patients are considered to have RA if they have a score of at least 6. Since these criteria are targeting early RA diagnoses, patients with long-standing disease that has become inactive or less active who previously satisfied these criteria or have erosions on radiographs will still be classified as having RA.

The new criteria are an important step forward to assist in the diagnosis of RA early in the disease course, thereby facilitating early intervention. However, it should be noted that these criteria are not intended to be a primary care screening or referral tool. They are classification criteria and not diagnostic criteria. It remains to be determined if these newer classification criteria are able to be used as diagnostic criteria and if they are successful in identifying patients with early RA. Indeed several recent reports have demonstrated that the 2010 classification criteria are slightly more sensitive than the 1987 ACR criteria.[12-14] Finally, as imaging techniques such as MRI and ultrasound improve and/or become more affordable, it will be important to adapt these criteria to include these modalities.

Benefits of Aggressive Treatment in Early RA

Treatment of RA has clearly been shown to be effective in not only minimizing short-term disability by treating inflammation, pain, and stiffness, but also in preventing long-term disability through the slowing of radiographic progression in RA patients with established disease. Treatment with synthetic DMARDs (sulfasalazine, methotrexate, or leflunomide) is not only effective in treating joint inflammation,[15-20] but also in slowing radiographic progression.[19,21] Furthermore, it has been shown that biologics are also effective in decreasing clinical symptoms of RA and reducing radiographic progression.[22-25]

Current paradigms now support the early and aggressive treatment of RA compared with delayed treatment. The Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo) study compared combination synthetic DMARD therapy with single DMARD therapy in a cohort of early RA patients.[26] At 2 years, 71% of the combination DMARD group achieved a 50% clinical response (ACR 50) compared with 58% using single-drug therapy.[26] Interestingly, at 5 years (years 3-5 treatment was per physician discretion), both groups had similar improvement in clinical activity scores, but the combination group had significantly better radiographic scores than the single DMARD group.[27] In addition, a meta-analysis comparing early (less than 2 years of disease duration) with delayed use of synthetic DMARDs demonstrated a significant reduction in long-term radiographic progression for RA patients treated early with DMARDs.[28]

With the introduction of biologics, it has become more evident that early and aggressive treatment of RA is beneficial for some patients. Clinical studies have demonstrated that treatment of early RA patients with a combination of a tumor necrosis (TNF) inhibitor and methotrexate results in better clinical outcomes.[29,30] The Behandel Strategieen (BeSt) study was a single-blind clinical trial where RA patients with less than 2 years of disease duration were randomized to 1

of 4 arms: (1) sequential DMARD monotherapy substitution, (2) step-up combination DMARD therapy, (3) combination DMARD therapy plus corticosteroids, and (4) combination therapy with DMARD plus infliximab (TNF inhibitor).[29] Patients treated with infliximab combination therapy had faster clinical improvement (Disease Activity Score [DAS] in 44 Joints, Health Assessment Questionnaire [HAQ]) and less radiographic progression using the Sharp/Van der Heijde radiographic joints score than the monotherapy or step-up combination DMARD therapy. A 5-year follow-up report of the BeSt trial demonstrated that all groups had good clinical outcomes, but the infliximab combination group had less joint damage as assessed by radiographs.[31] In the PREMIER study, patients with less than 3 years of disease duration were randomized to methotrexate alone, adalimumab alone, or methotrexate/adalimumab combination therapy. Early treatment with combination therapy proved superior to methotrexate alone or adalimumab alone in clinical treatment responses as well as radiographic progression of joint damage.[30] Interestingly, methotrexate alone and adalimumab alone had similar clinical responses in treatment-naïve patients, but adalimumab alone had less radiographic progression. Finally, the Combination of Methotrexate and Etanercept in Active Early Rheumatoid Arthritis (COMET) trial tested methotrexate monotherapy versus methotrexate and etanercept in methotrexate-naïve RA patients with early moderate-to-severe disease of 3-24 months duration.[32] At 1 year, 50% of patients in the combination group achieved remission compared with 28% in the methotrexate alone group. Furthermore, 80% of patients in the combination group achieved radiographic nonprogression, compared with 59% in the methotrexate alone group. In total, these studies suggest an advantage of treating patients early in the disease course, emphasizing the importance of early diagnosis, referral, and intervention.

Goal-Directed Therapy in RA

In the past, many of the decisions made by physicians for initiation and changes in treatment relied on an informal assessment of disease activity and functional status of the patient by the physician and patient. Subsequently, many clinical assessment tools have been developed and validated to quantify disease activity and patient functional status. Borrowing from other medical fields such as type 1 diabetes, a paradigm of "tight control" of RA has emerged. Indeed several studies have provided important data showing improved clinical outcomes in RA patients who had treatment decisions partially based on quantitative measurements and goals.[26,29,33,34] In the Tight Control of Rheumatoid Arthritis (TICORA) study, patients in the "tight control," or intensive, group had treatment augmented if the disease activity was higher than a specific cut-off. The routine therapy group was seen every 3 months and treatment decisions were based on physician judgement, not a specific target or disease activity measure. The intensive group had lower disease activity scores and higher disease remission rates than the routine therapy group. In the Computer Assistant Management in Early Rheumatoid Arthritis (CAMERA) trial, patients in the intensive group came to the clinic monthly where the dose of methotrexate was tailored to a predefined quantitative response level using a computer decision program. The result was a significant improvement in clinical responses relative to the conventional group. Therefore, multiple studies have now confirmed that goal-directed therapy in RA using quantitative measurements of disease activity results in improved clinical outcomes.

TABLE 2 Disease Activity Levels Using Various RA Disease Activity Instruments[a]

Instrument	Low Activity	Moderate Activity	High Activity
DAS28	≤3.2	3.2–5.1	>5.1
SDAI	≤11	11–26	>26
CDAI	≤10	10–22	>22
RADAI	<2.2	2.2–4.9	>4.9
PAS	<1.9	1.9–5.3	>5.3
RAPID	<6	6–12	>12

[a]*Source: Saag KG, Teng GG, Patkar NM, et al. Arthritis Rheum. 2008;59(6):762-84.*[35]

CDAI = Clinical Disease Activity Index; DAS28 = Disease Activity Score using 28 joint counts; PAS = Patient Activity Scale; RA=rheumatoid arthritis; RADAI = Rheumatoid Arthritis Disease Activity Index; RAPID = Routine Assessment Patient Index Data.

Medical Treatment of Rheumatoid Arthritis

In 2008, the ACR updated the recommendations for the medical treatment of RA.[35] The guidelines discuss use of synthetic DMARDs that are commonly used including hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide, as well as biologic agents. Currently, in the United States, there are 9 biologics approved for the treatment of RA, including TNF inhibitors (infliximab, etanercept, adalimumab, certolizumab pegol, and golimumab), anakinra (IL-1 receptor antagonist), abatacept (CTLA4-Ig fusion protein), rituximab (antiCD20 antibody), and tocilizumab (anti-IL-6 receptor antibody). Rituximab and tocilizumab are currently approved for RA patients who have failed treatment with at least 1 TNF inhibitor. Use of nonsteroidal medications and corticosteroids can be considered in all RA patients as adjunctive therapy but are not primary forms of therapy due to their lack of disease-modifying effects or long-term side effects.

Three clinical factors are important to help in clinical decision making: disease duration, RA disease activity assessment, and prognostic factors of poor outcomes. Disease duration is divided into less than 6 months, 6-24 months, and greater

than 24 months. RA disease activity could be assessed as high, medium, or low based on several validated instruments to measure RA disease activity (Table 2): Disease Activity Score in 28 joints (DAS28), simplified disease activity index (SDAI), clinical disease activity index (CDAI), rheumatoid arthritis disease activity index (RADAI), patient activity scale (PAS) or routine assessment patient index data (RAPID). Finally, the prognostic factors that should be considered in the treatment decision are functional limitation (HAQ Disability Index), extra-articular disease, seropositivity for RA or anti-CCP, and/or bony erosions by plain film radiography.

According to these most recent guidelines, synthetic DMARDs should be considered for all patients with RA. In patients with low disease activity who do not have features of poor prognosis and have less than 2 years of disease duration, monotherapy may be appropriate. In patients with long-standing disease, moderate to high disease activity, and/or features of poor prognosis, combination synthetic DMARD therapy was suggested. Interestingly, based on the growing literature demonstrating benefits of early aggressive therapy for patients with less than 6 months of disease duration and with high disease activity, the combination of methotrexate and a TNF inhibitor should be strongly considered. Otherwise, use of biologics is reserved for patients who have persistent disease activity (moderate to high) despite methotrexate or similar synthetic DMARDs.

The guidelines do not sufficiently address whether patients who fail methotrexate or similar synthetic DMARDs should be given a second synthetic DMARD. The best path for the patient who fails a single TNF inhibitor also has not been sufficiently addressed. Should this patient switch to another TNF inhibitor or change classes of biologics? Indeed the literature is conflicting in this regard with some studies suggesting that patients can respond to a second TNF inhibitor.[36,37] Other studies suggest that the response to the second TNF inhibitor is less, and 1 study even suggested that the response to another class of biologics may be better than a second TNF inhibitor.[38-40] Furthermore, the guidelines do not address whether the dose of infliximab should be increased and/or the dosing interval decreased. Both have been commonly used by physicians and can increase the duration of treatment but may not alter the ultimate discontinuation of the medication.[41,42] These issues need to be studied and clarified to help patients, physicians, and health care providers make the best treatment decisions.

Finally, a critical part of the medical management of the RA patient is screening patients for comorbidities that might contraindicate specific treatments prior to treatment initiation. Leflunomide, methotrexate, and biologic agents should not be used in patients with active bacterial infections, active herpes zoster infections, or life-threatening fungal infections. Leflunomide and methotrexate are contraindicated in patients with white blood cell counts less than 3,000 per cubic millimeter (mm^3) or a history of a hematologic malignancy in the past 5 years. Patients with liver function abnormalities should not receive all 3 drugs (sulfasalazine, leflunomide, and methotrexate), and patients with renal insufficiency should not be prescribed methotrexate. Leflunomide and methotrexate should not be used in patients with active or chronic hepatitis B and C. Finally, methotrexate and leflunomide should not be used in pregnant or lactating women.

All patients being considered for a biologic agent should be screened before, and annually thereafter, for exposure to tuberculosis. This can be performed with a tuberculin skin test or the interferon serum tuberculosis assays. The TNF inhibitors are contraindicated in patients with hepatitis B. Furthermore, patients with a history of multiple sclerosis or demyelinating disorders or congestive heart failure (New York Heart Association class III-IV) should not be prescribed TNF inhibitors.

The treatment of RA with synthetic DMARDs and biologics is effective but carries potential risks. Therefore, all patients should be routinely monitored for side effects with regular physician visits and blood tests. Blood counts, serum transaminases, serum albumin, and serum creatinine should be monitored frequently in all patients taking methotrexate, leflunomide, and sulfasalazine. Initially the testing should be done monthly, but once a stable dose has been achieved for over 6 months, every 8-12 weeks is considered sufficient, and it is reasonable to obtain a complete blood count and liver function tests in patients on TNF inhibitors every 6 months. Patients on hydroxychloroquine should receive routine ophthalmologic examinations as well. All patients being treated should receive annual influenza vaccinations (injections of killed virus, not inactivated live virus nasal spray), routine pneumococcal vaccination, and hepatitis B vaccination. Finally, in patients on biologics, all live vaccinations should be avoided in patients and household contacts.

Conclusions

The treatment of RA has undergone several paradigm shifts, resulting in vastly improved patient outcomes. The armamentarium of medications that is effective in treating inflammation as well as slowing joint damage and destruction has greatly expanded. Low disease activity, and occasionally remission, as well as the prevention of joint damage are realistic goals for all patients. All patients with RA should receive disease-modifying treatments including synthetic DMARDs and possibly biologics early in the disease course. With aggressive but judicious use of medications and careful monitoring of disease activity and side effects, the health and quality of life in patients with RA will be vastly improved.

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Assessment of Disease Activity and Treatment Outcomes in Rheumatoid Arthritis

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ABSTRACT

BACKGROUND: Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease which primarily causes a symmetric polyarthritis. Clinical manifestations of the disease include joint pain, stiffness, and swelling. Unless treated, this debilitating disease can progress into long-term disability. Medications for RA include synthetic disease-modifying antirheumatic drugs (DMARDs) and biologic agents. The rapid expansion of new RA drugs into the market has led to a need for health care practitioners to understand the effectiveness of each medication and the indications of use including when to initiate and stop therapies. Clinical assessment tools, including biomarkers used to indicate RA and the progression of the disease, have been proven effective for making a diagnosis and determining effective treatment regimens. Disease activity scales are also useful for guiding diagnoses and monitoring patients to assess treatment effectiveness.

OBJECTIVES: To review the various clinical assessment tools that have been designed to confirm an early diagnosis of RA, measure disease progression, and assist in determining the most optimal treatment regimens for patients with RA.

SUMMARY: The diagnosis of RA combines the patient history of joint pain and stiffness and the physical examination documentation of symmetric polyarticular joint swelling (synovitis). Laboratory tests including radiographs and blood tests for biomarkers can provide useful information to confirm the diagnosis of RA. Various autoantibodies have been reported in the blood of RA patients, but only the rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP) have been incorporated as diagnostic measures in routine clinical practice. Monitoring and assessment instruments for RA include the Disease Activity Score 28 (DAS28), the Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI). Although these clinical assessment tools have limitations, health care providers can use them as measures of disease progression and to assist in planning treatment strategies to modify disease activity and improve the quality of life for the patient.

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Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease which primarily causes a symmetric polyarthritis, clinically manifesting joint pain, stiffness, and swelling.[1] Untreated, most patients have a progressive course resulting in short- and long-term disability. Fortunately, the number of effective medications for the treatment of RA has rapidly expanded and includes synthetic disease-modifying antirheumatic drugs (DMARDs) and biologic agents such as tumor necrosis factor inhibitors (TNF inhibitors).[2,3] It is now clear that early diagnosis, referral, and treatment of patients with RA results in improvement in clinical signs and prevention of joint destruction.[4,5]

Due to the increasing number of medications for the treatment of RA, physicians and other health care providers involved in the care of RA patients must decide which medications to use, when to start them, and when to change the therapeutic regimen. In 2008, the American College of Rheumatology (ACR) published updated guidelines for the use of synthetic DMARDs and biologic agents for the management of RA.[6] The goal of treatment is not only improvement in clinical signs of inflammation, pain, and function, but also in the prevention of structural joint damage and long-term functional disability. To achieve these goals, the guidelines depend on the ability of the health care team to determine the level of disease activity and the response or lack of response that a patient may have had to a particular intervention. Accordingly, various clinical assessment tools have been validated to measure disease activity and treatment efficacy.[7] These tools can be used by health care providers to assist with clinical decisions including when to use medications, add a medication, switch medications, or even stop a medication. It is now appreciated that incorporating these clinical tools and treating to a goal can improve clinical outcomes for RA patients.[8,9]

Multiple studies also have demonstrated that aggressive treatment of early RA results in better clinical outcomes than delayed therapy.[4,5] To facilitate the treatment of RA patients early in the disease course, it is essential to diagnose and refer patients efficiently. In 2010, the ACR and European League Against Rheumatism (EULAR) developed new classification criteria for RA aimed at early diagnosis.[10] While intended for use in clinical trials, physicians often use similar criteria for diagnostic guidelines. Included in these criteria are serum biomarkers that help confirm the diagnosis. In this article, we will briefly review biomarkers that assist in the diagnosis of RA. Furthermore, we will review biomarkers and clinical assessment tools of disease activity that can be incorporated into the care of the patient with RA. Together these clinical tools are important to help physicians and other health care providers

rapidly diagnose and effectively manage RA to provide patients with markedly improved clinical outcomes.

Biomarkers Used in Diagnosis

The diagnosis is a clinical diagnosis that combines the patient history of joint pain and stiffness and the physical examination documentation of symmetric polyarticular joint swelling (synovitis). Laboratory tests including radiographs and blood tests can provide useful information that confirms or leads to the diagnosis of RA. In the past, many autoantibodies have been reported in the blood of RA patients, but only the rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP) have been incorporated into routine clinical practice.

Rheumatoid Factor. Rheumatoid factor (RF) is an autoantibody (IgM, IgA, or IgG) directed against the Fc portion of IgG. RF is found in up to 75%-80% of patients with RA (seropositive RA). The specificity of the RF for RA increases with a higher serum titer, particularly in the context of a patient with an inflammatory arthritis. However, RF is not a diagnostic marker for RA. RF also occurs in other diseases including Sjögrens syndrome, cryoglobulinemia, systemic lupus erythematosus and certain infections including hepatitis C, rubella, and subacute bacterial endocarditis. Finally, RF can also be found in healthy adults as they age.

Although the titers of RF do not reliably change with disease activity, the presence of RF provides the physician with prognostic information. Seropositive RA patients and patients with high titers of RF are more likely to develop joint erosions than seronegative patients.[11] Accordingly, the most recent treatment guidelines consider the presence of RF as a marker of poor prognosis that can help guide physicians to more aggressive treatment.[6]

Anti-Cyclic Citrullinated Peptide Antibodies. Anti-CCPs are autoantibodies directed against proteins that contain the amino acid citrulline. Citrulline is an amino acid formed from arginine when proteins undergo certain forms of post-translational modification. While the sensitivity of anti-CCP for the diagnosis of RA is similar to that of RF (50%-70%, depending on the test used), it has a higher specificity than RF (95-98%).[12] Unlike RF, anti-CCPs are not commonly found in infectious diseases and do not occur with aging.[13] Anti-CCP is also uncommon in other rheumatic diseases although it can be seen in patients with palindromic rheumatism.[13,14]

Similar to RF, the presence of anti-CCP at early diagnosis predicts more radiographic progression, as demonstrated by many studies showing a strong association between anti-CCP positivity and the development of bone erosions.[15,16] Furthermore, anti-CCP titers do not reliably change with disease activity. Therefore, like RF, anti-CCP can help identify patients prone to more severe disease, who might benefit from more aggressive treatment.[6]

Clinical Tools for Goal-Directed Treatment

Previously physician decisions for initiation and treatment modification have essentially relied on an informal assessment of disease activity and functional status of the patient. During the patient visits, physicians will often determine the number of swollen joints (SJC) and tender joints (TJC) and use this information to change therapy in the absence of clear goals. However, there are a number of limitations to using SJC and TJC as main criteria for modifying therapy, including poor reproducibility and failure to predict progressive joint damage and functional disability.[17] Fortunately, many clinical assessment tools have been developed and validated to quantify disease activity and patient functional status.[7]

Multiple studies have now confirmed that goal-directed therapy in RA using quantitative measurements of disease activity results in improved clinical outcomes.[8,9] In the TICORA (Tight Control of Rheumatoid Arthritis) study, 111 patients with less than 5 years of RA disease activity were randomly assigned to an intensive management program, where treatment decisions were changed according to a target, or routine care.[8] Patients in the "tight control," or intensive group, had treatment augmented if the disease activity was higher than 2.4 using the Disease Activity Score in 28 joints (DAS28). The study examined combinations of synthetic DMARDs. The primary outcome was to decrease disease activity scores. In the end, the intensive group had lower disease activity scores and higher disease remission rates than the routine therapy group. Furthermore, patients in the intensive group had greater improvement in function and quality of life. Finally, early and more aggressive management of the disease activity in the intensive group led to slower radiographic progression and less joint damage.

The Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) trial was a study of 299 RA patients with early RA treated (defined as symptoms less than 1 year) with methotrexate.[9] The goal was to look at remission outcomes by randomly assigning patients to an intensive, goal-directed group versus a conventional therapy group. The intensive treatment group was seen monthly with adjustment to the methotrexate dose, which was dictated by a computer program targeting a predefined quantitative response level. The conventional group was seen every 3 months with treatment adjustments driven per routine clinical care. As hypothesized, more patients in the intensive treatment group achieved remission and sustained it for a longer period of time than the conventional treatment group. Together the TICORA study and the CAMERA study support the paradigm that goal-directed treatment of RA results in improved clinical outcomes.

Biomarkers for RA Disease Activity

The erythrocyte sedimentation rate (ESR) is an acute phase reactant that increases during a variety of physiological states including inflammation, and most physicians monitor ESR as a biomarker of RA disease activity. Acute phase reactants are a result of increased protein synthesis by hepatocytes or liver cells induced by inflammatory cytokines as a result of tissue injury. ESR is an indirect way of measuring for elevation in the concentration of acute phase plasma proteins, particularly fibrinogen. These acute phase proteins lead to the aggregation of erythrocytes, which causes them to descend into a test tube more rapidly. The ESR is elevated during inflammatory states such as active RA, but also from inflammation that can occur with infections or malignancies. Aberrant results in the ESR may occur during noninflammatory states where the erythrocyte morphology is altered, including anemia, older age, or a stored blood sample.

C-reactive protein (CRP) is another acute phase reactant that is increased during inflammation. CRP is present in trace concentrations in the plasma of all humans and binds to constituents of cell membranes and nuclei which are exposed at sites of tissue damage, and CRP may target the sites for clearance. Following acute inflammatory stimulus, the concentration of CRP rapidly increases for 2 or 3 days to peaks that generally reflect the extent of tissue injury, and in the absence of continuing stimulus, serum levels decrease rapidly. However, persistently elevated levels are seen in chronic inflammatory states such as active RA. Similar to the ESR, inflammation from infections and malignancies can increase the CRP; however, anemia, older age, and storage of blood samples do not significantly alter the CRP.

ESR and CRP have little use as a specific test in the diagnosis of RA, although they are part of the new ACR/EULAR Classification Criteria for RA.[10] These tests may be used to follow disease activity and monitor response to therapy. Treatment of joint inflammation in RA is usually accompanied by a decrease in the ESR and CRP. Failure to suppress the CRP is a predictor of a poor response to TNF inhibitors.[18] However, the ESR and CRP are not sufficient to determine treatment responses. Despite improvement of acute phase reactants, some patients will have progression of joint damage.[19] Therefore, the ESR and CRP should only be used in combination with other parameters by the clinician to determine disease activity.

Overview of Assessment Instruments

The development of a disease index that adequately reflects the disease activity by both subjective and objective criteria is a complicated task. Fortunately, extensive efforts have been dedicated to the development of multiple instruments that have been validated to follow disease activity in RA patients (Table 1). The incorporation of some of these tools into routine clinical care will likely improve treatment outcomes in RA patients.

TABLE 1 Characteristics of Selected Assessment Tools Used in RA

Tool	Formula	Low Disease Activity	Moderate Disease Activity	High Disease Activity
DAS28[20]	$(0.56\times\sqrt{TJC})+(0.28\times\sqrt{SJC})+(0.70\times\text{lognESR})+(0.014\times PGA)$	<2.6	<3.2	<5.1
SDAI[23]	SJC + TJC + PGA + PhGA + CRP	<3.3	<11	<26
CDAI[24]	SJC + TJC + PGA + PhGA	<2.8	<10	<22
GAS[26]	TJC + mHAQ + pain	4-7	8-20	>20

CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; DAS28 = Disease Activity Score 28 joints; ESR = erythrocyte sedimentation rate; GAS = Global Arthritis Score; logn = log-normal; mHAQ = modified Health Assessment Questionnaire; PGA = Patient Global Assessment; PhGA = Physician Global Assessment; RA = rheumatoid arthritis; SDAI = Simplified Disease Activity Index; SJC = swollen joint count of 28 joints; TJC = tender joint count of 28 joints.

Disease Activity Score (DAS28). DAS28 is a weight multidimensional instrument that uses a physician's assessment of the joints, the patient's overall self-assessment of disease activity, and a laboratory marker of inflammation (CRP or ESR).[20] During the examination, physicians determine the number of swollen and tender joints in 28 joints including the small joints in the hands, wrists, elbows, shoulders, and knees. The score is derived from a complicated formula, but fortunately, several online tools can easily be accessed to calculate the score. The DAS28 score can quantify disease activity at the first clinic visit and be used in subsequent visits for comparison. The scoring system has been validated for use in clinical trials as well as routine patient care.[21,22] One limitation of the DAS28 is the need to have the ESR or CRP on the day of the examination. The results of these tests may not be immediately available to the physician during the patient encounter.

Simplified Disease Activity Index (SDAI). The SDAI is another instrument that has been validated in clinical practice to assess RA disease activity.[23] The SDAI is calculated by adding up the SJC and the TJC in the same 28 joints used in the DAS28. These are added to the patient's global assessment, the physician's global assessment, and CRP. The SDAI has the advantage over the DAS28 in that the calculations are not as cumbersome, yet the performance of the SDAI is similar to the DAS28.[24]

Clinical Disease Activity Index (CDAI). The CDAI is an even more simplified score than the SDAI.[24,25] The CDAI is determined by the summation of the SJC, TJC, patient's global assessment, and the physician's global assessment.[24,25] Unlike the DAS28 and the SDAI, the CDAI does not include the ESR or CRP. This enables the physician to immediately know the disease activity score and make treatment decisions during

the patient encounter. Similar to the SDAI, the CDAI has been reported to perform well in clinical practice.[24,25]

Global Arthritis Score (GAS). The GAS uses the 28 tender joint count, modified Health Assessment Questionnaire (HAQ) score, and patient's self-reported pain. The GAS has also been shown to correlate with other measures like DAS28 and SDAI.[26] It also does not involve inflammatory markers and therefore can be readily calculated during the patient encounter.

Health Assessment Questionnaire – Disability Index (HAQ-DI). The HAQ-DI was among the first instrument based on generic, patient-centered dimensions.[27,28] It is composed of 20 items in 8 categories: dressing and grooming, hygiene, arising, reaching, eating, gripping, walking, and common daily activities. The HAQ-DI also has a visual pain scale that assesses the presence or absence of arthritis-related pain and its severity over the past week. Although not a disease activity marker, the HAQ-DI can provide important information for the physician about the patient's functional status that may not readily become apparent through the routine patient encounter.

Limitations of Disease Activity Instruments

While the literature supports that goal-directed treatments using validated instruments to assess disease activity results in improved patient outcomes, there are some limitations that should be recognized. First, the SJC and TJC in the above instruments assess only 28 joints. Notable exceptions to the joint evaluation are the feet, ankles, and hips, which are commonly affected in RA. An additional limitation to be considered are potential confounders in the patient self-reported assessments of disease activity. For example, RA patients may have concomitant osteoarthritis, fibromyalgia, or depression that could increase their self-assessment of disease activity, while not reflecting true activity of the inflammatory arthritis. Having other objective measures such as the ESR or CRP or the joint counts may help counter this potential bias. Finally, the consistency with which physicians derive their global assessments can also vary. The limitations may be overcome by using more than 1 assessment tool and educating the patient on how other diseases could impact perceptions of pain and function.

Conclusions

With the growing number of medications available for the treatment of RA, physicians and patients are faced with difficult decisions pertaining to initiation and discontinuation of medications. Multiple studies support early, aggressive treatment that is goal directed. Many instruments have been validated that can be incorporated into routine clinical practice to aid in treatment decisions with the goal of optimizing clinical responses and reducing joint damage from RA.

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Biologic Agents in Rheumatoid Arthritis: An Update for Managed Care Professionals

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ABSTRACT

BACKGROUND: Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory arthritis that clinically manifests as joint pain, stiffness, and swelling. If left untreated, persistent synovial inflammation can progress to cartilage and bone destruction and ultimately to major long-term disability and mortality. Synthetic disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, leflunomide, and sulfasalazine, have markedly improved clinical symptoms and slowed joint damage in RA patients. However, despite the effectiveness of synthetic DMARDs, many patients who use them continue to have clinical symptoms of inflammation and progressive joint destruction. Recent advances in our understanding of the pathogenesis of RA have led to the identification of novel cellular and molecular therapeutic targets. Biologic agents aimed at these targets have provided some evidence of effectiveness that is transforming the management of RA.

OBJECTIVE: To inform health care providers about some of the recent advances in RA pathogenesis and innovative biologic therapies that have shown effectiveness in improving clinical outcomes and inhibiting radiographic progression.

SUMMARY: Although the specific trigger of the autoimmune response in RA is not known, pathogenesis is generally believed to be associated with the generation of autoantibodies through interactions of antigen-presenting cells with the adaptive immune system (CD4+ T cells and B cells). The main inflammatory mediators of joint inflammation and destruction in RA are tumor necrosis factor (TNF)-alpha, interleukin-1 (IL-1), IL-6, chemokines, and proteases. Advances in our understanding of the key cells and inflammatory cytokines have led to the development of targeted biologic agents. As of 2011, 5 TNF-alpha inhibitors are approved for use by the FDA: infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol. In randomized clinical trials, all of these agents have been shown to be effective in reducing clinical signs of inflammation in RA patients who have failed synthetic DMARDs. Multiple studies have demonstrated significant benefits of early treatment with TNF-alpha inhibitors combined with methotrexate. Other FDA-approved biologic agents for treating moderate-to-severe RA include abatacept, rituximab, and tocilizumab. All biologic agents carry an increased risk of infections. Additional potential side effects include infusion and injection site reactions for intravenous and subcutaneously administered agents, respectively. All patients being considered for biologic agents should be screened annually for tuberculosis and should receive pneumococcal, influenza, and hepatitis B vaccinations.

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Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory arthritis that clinically manifests as joint pain, stiffness, and swelling.[1] Without treatment, persistent inflammation leads to cartilage damage, bone erosions, and joint destruction, the major causes of long-term disability. Treatment with synthetic disease modifying antirheumatic drugs (DMARDs) such as methotrexate, leflunomide and sulfasalazine represented an important paradigm shift that resulted in marked improvement in clinical symptoms and slowing joint damage.[2-8] However, despite the effectiveness of these medications in the treatment of RA patients, a significant number of patients continue to have clinical symptoms of inflammation and progressive joint destruction. Fortunately, recent advances in our understanding of the pathogenesis have led to the identification of novel therapeutic targets. Biologic agents aimed at these cellular and molecular targets have further transformed the management of RA. In this article we will provide a focused update on the biologic agents that are used in the treatment of RA.

Pathophysiology of Joint Inflammation in Rheumatoid Arthritis

RA is an inflammatory arthritis that results from a systemic autoimmune response. Although the specific trigger of the autoimmune response is not known, it is commonly believed that the generation of autoantibodies through interactions of the innate immune system (antigen-presenting cells) with the adaptive immune system (CD4+ T cells and B cells) is central to the pathogenesis.[1,9] The systemic autoimmune response subsequently targets the synovial membrane. The normal synovial membrane lines the joint capsule of diarthrodial joints and is characterized by a thin lining layer made up of synovial fibroblasts and macrophages that rests upon a relatively hypocellular sublining layer, containing blood vessels, connective tissue, and a few immune cells such as mast cells and neutrophils. The inflamed synovial membrane in rheumatoid arthritis demonstrates cellular hyperplasia and activation in the lining layer and pronounced infiltration of inflammatory cells, including CD4+ T cells, B cells, plasma cells, macrophages, and neutrophils, into the sublining layer. The inflammatory infiltrate secretes large amounts of inflammatory cytokines, such as tumor necrosis factor (TNF)-alpha, interleukin-1 (IL-1), IL-6, chemokines (chemoattractant cytokines that recruit additional cells), and proteases.[10] These factors further activate the synovial lining macrophages and fibroblasts to secrete additional inflammatory cytokines and proteases. The end result is the formation of an inflamed and invasive synovial membrane called the pannus. The invasive pannus instigates joint destruction through cartilage degradation and activation

TABLE 1 *Biologic Agents in the Treatment of RA*

Medication	Type of Biologic Agent	Target	Route of Administration	Loading Protocol	Maintenance Dosage
Infliximab[a]	Mouse/human chimeric antibody	TNF alpha	Intravenous	Yes	3-10 mg per kg every 4-8 weeks
Etanercept[b]	Receptor fusion protein	TNF alpha	Subcutaneous	No	50 mg weekly
Adalimumab[c]	Human antibody	TNF alpha	Subcutaneous	No	40 mg monthly
Certolizumab pegol[d]	Pegylated Fab' fragment of humanized antibody	TNF alpha	Subcutaneous	Yes	200 mg every other week or 400 mg monthly
Golimumab[e]	Human antibody	TNF alpha	Subcutaneous	No	50 mg per month
Abatacept[f]	Receptor fusion protein	CD28/B7 T-cell costimulation	Intravenous	Yes	500-1,000 mg every 4 weeks according to weight
Rituximab[g]	Mouse/human chimeric antibody	CD20+ B-cells	Intravenous	No	2 separate 1,000 mg doses 2 weeks apart every 6 months
Tocilizumab[h]	Humanized antibody	IL-6 receptor	Intravenous	No	4-8 mg per kg every 4 weeks
Anakinra[i]	Interleukin-1 receptor antagonist	IL-1 receptor	Subcutaneous	Yes	100 mg daily

[a]*Remicade (infliximab) prescribing information. February 2011. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103772s5281lbl.pdf.*
[b]*Enbrel (etanercept) prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/103795s5415lbl.pdf.*
[c]*Humira (adalimumab) prescribing information. February 2011. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125057s0215lbl.pdf.*
[d]*Cimzia (certolizumab pegol) prescribing information. July 2010. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/125160s111lbl.pdf.*
[e]*Simponi (golimumab) prescribing information. October 2010. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/125289s0029lbl.pdf.*
[f]*Orencia (abatacept) prescribing information. August 2009. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125118s0086lbl.pdf.*
[g]*Rituxan (rituximab) prescribing information. April 2011. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103705s5344lbl.pdf.*
[h]*Actemra (tocilizumab) prescribing information. April 2011. http://www.gene.com/gene/products/information/actemra/pdf/pi.pdf.*
[i]*Kineret (anakinra) prescribing information. December 2009. http://www.kineretrx.com/professional/pi.jsp.*
kg = kilograms; mg = milligrams; RA = rheumatoid arthritis; TNF = tissue necrosis factor.

of osteoclasts in the bone to cause bone erosions.[11] Advances in our understanding of the key cells (T cells, B cells) and inflammatory cytokines (TNF and IL-6) have provided therapeutic opportunities, which are now directly targeted by biologic agents approved for the treatment of RA (Table 1).

Measuring Treatment Responses in Clinical Trials

Clinical trials seeking to demonstrate the efficacy of a potential therapeutic in RA utilize several common outcomes.[12] Clinical improvements in the symptoms of inflammation are usually documented using relative change in the American College of Rheumatology (ACR) 20 response and absolute change the Disease Activity Score (DAS28).[13,14] The ACR 20 is defined as a reduction by 20% or more in the number of tender and swollen joints plus a 20% improvement in 3 of 5 of the following measures: pain, patient global assessment of disease activity, physician global assessment of disease activity, self-assessed physical disability, and acute phase reactants (erythrocyte sedimentation rate or C-reactive protein).[13] Some studies will also report the ACR50 or ACR70, which are 50% and 70% improvements in the above measures. The DAS28 score is a weighted score of swollen joints count, tender joint counts, patient global assessment of disease activity, and acute phase reactants.[14]

Since the treatment of RA not only seeks to decrease symptoms of inflammatory arthritis, but also to prevent the joint damage that can ensue, many clinical trials seek to report indices of joint damage.[15,16] Using plain film radiographs of the hands, there are several validated measures of joint damage in RA. The most commonly used tool in clinical trials is the Sharp Score, where higher scores indicate greater joint damage.[15]

Tumor Necrosis Factor Inhibitors

TNF-alpha is a key cytokine in the inflammatory process in RA.[10,17] Biologic agents targeting TNF-alpha, called TNF inhibitors, were the first approved and most broadly used biologics for the treatment of RA. Currently, 5 TNF inhibitors are approved for use by the U.S. Food and Drug Administration (FDA): infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol. In randomized clinical trials RCTs, all of these agents have been shown to be effective in reducing clinical signs of inflammation in RA patients who have failed therapy with synthetic disease-modifying agents by measures such as ACR20 and DAS28.[18-25] Impressively, a significant number of patients in these RCTs also achieve ACR50 and ACR70 responses, and in some cases can achieve remission. Furthermore, TNF inhibitors are effective in reducing radiographic progression. Although the different TNF inhibitors have structural differences, no head-to-head clinical trials have been performed comparing the individual agents; therefore at this time, no conclusions can be made with regards to whether one TNF inhibitor is superior to another.

Per the FDA approval, infliximab should be used in combination with methotrexate. Multiple clinical trials have demonstrated that TNF inhibitors are more effective when combined

with methotrexate.[19,21,26] Multiple studies have demonstrated a significant benefit of early treatment with TNF inhibitors and methotrexate, suggesting that there may be a window of opportunity for early intervention that has lasting benefits to patients with regards to disease progression.[26,27] Although these agents are clearly effective, some patients either do not respond or stop responding to a TNF inhibitor.[28,29] Fortunately, multiple other biologic agents are also approved for treatment of RA patients.

Abatacept. Abatacept is a biologic agent that blocks T-cell activation through inhibition of CD28-B7 mediated costimulation of the T-cell. Structurally, abatacept is a recombinant, fully human fusion protein of human CTLA-4 and the Fc domain of human IgG1. Abatacept has been shown to be effective in treating clinical symptoms (improvement in ACR20, ACR50, and ACR70) in RA patients who have previously had an inadequate response to TNF inhibitors.[30] Subsequent studies have also demonstrated that abatacept is effective in RA patients who have previously had an inadequate response to methotrexate (TNF inhibitor naïve patients).[31,32] Abatacept has also been shown to slow radiographic progression in RA patients.[30,33] Abatacept is approved by the FDA for treatment of patients with moderate to severe RA that have had an inadequate response to methotrexate or TNF inhibitors. More recently, a subcutaneous form of abatacept has been shown to have comparable efficacy and safety with the intravenous formulation in a noninferiority trial and has been approved by the FDA.[34]

Rituximab. Rituximab is a human/mouse chimeric antibody that targets CD20, a molecule that is found on the surface of B-cells. The expression pattern of CD20 changes as B-cells differentiate from stem cells to B-cells and plasma cells.[35] CD20 is found on pre B-cells, immature B-cells, activated B-cells, and memory B-cells but not plasma cells.[35] The pilot studies demonstrating effectiveness of rituximab in RA rekindled the appreciation of the importance of the B-cell lineage in the pathogenesis of RA.[36] The DANCER study and the REFLEX study are important RCTs that have demonstrated a clinical benefit in RA patients with an inadequate response to methotrexate or TNF inhibitors, respectively.[37,38] Furthermore, it has been demonstrated that rituximab delays radiographic progression in RA patients.[38] Subsequent studies have demonstrated the feasibility of administering repeated courses of rituximab at 6-month intervals.[39] Accordingly, the FDA has approved rituximab for the treatment of patients with moderate to severe RA that have had an inadequate response to TNF inhibitors.

Tocilizumab. Tocilizumab is a humanized antibody directed against the IL-6 receptor, an inflammatory cytokine that is produced by and targets a large number of cells relevant to RA pathophysiology.[40] Macrophages, B-cells, T-cells, fibroblasts, and other cells are capable of producing IL-6. Osteoclasts, B-cells, T-cells, hematopoietic stem cells, and hepatocytes are capable of responding to IL-6 through the IL-6 receptor.[40] The OPTION trial demonstrated the efficacy of tocilizumab in treating clinical symptoms of RA in patients with an inadequate response to methotrexate, and the RADIATE trial demonstrated the efficacy of tocilizumab in treating clinical symptoms of RA in patients with an inadequate response to TNF inhibitors.[41,42] Lastly, the LITHE trial also confirmed the clinical benefit of tocilizumab in RA treatment, demonstrating that tocilizumab also delays radiographic progression in RA patients.[43] Accordingly, the FDA has approved tocilizumab for the treatment of patients with moderate to severe RA that have had an inadequate response to TNF inhibitors.

Adverse Events

The biologic agents approved for the treatment of RA result in rapid improvement in clinical symptoms, and all delay radiographic progression. However, biologic agents must be used judiciously and with consideration of the potential adverse effects that may occur. All biologic agents carry an increased risk of infections. RA patients using these medications who present with fevers should be evaluated by a physician to determine the source of the fever, and antibiotics should be administered, if appropriate. Given the risks of infections by all of these agents, it is not recommended that patients be treated with simultaneous combinations of biologic agents. Additional potential side effects include injection site reactions in subcutaneously administered agents. Furthermore, the intravenous biologic agents can have infusion reactions ranging from minor to life-threatening. All patients being considered for biologic agents should be screened annually for tuberculosis (TB) using a tuberculin skin test or the interferon-gamma release TB blood tests. All patients on biologic agents should receive a pneumococcal vaccination, annual influenza vaccination, and hepatitis B vaccination. Finally, for patients on biologics, all live vaccinations should be avoided in patients and household contacts.

Other considerations differ depending on the class of biologic agents. TNF inhibitors are contraindicated in patients with hepatitis B, multiple sclerosis or demyelinating diseases, or congestive heart failure (New York Heart Association class III-IV). It remains controversial as to whether TNF inhibitors are associated with an increased risk of malignancies. Rituximab has been associated with transient neutropenia and hypogammaglobulinemia.[44] While opportunistic infections have been reported in case reports with all the biologic agents, progressive multifocal leukoencephalopathy, due to JC virus, has been reported in rheumatic patients receiving rituximab at the case report level.[45] Finally neutropenia, liver function abnormalities, thrombocytopenia, and elevated lipids have been observed in patients treated with tocilizumab in clinical trials.[41,42] Long-term adverse effects of the biologic agents are not known, and RCTs are not optimal for the identification of rare adverse events. As we gain additional experience with biologic agents, physicians and other health care providers

must remain alert to look for additional, previously unknown adverse events not identified in clinical trials.

Conclusions

Biologic agents directed at TNF-alpha, T-cell costimulation, B-cells, and IL-6 are efficacious in clinical trials for the treatment of RA patients with an inadequate response to synthetic DMARDs. Furthermore, all of the biologic agents can delay radiographic progression, indicating the potential benefits in preventing long-term disability from joint damage in addition to the short-term disability from symptoms of inflammatory arthritis. The biologic agents are an important addition to the growing list of medications available for the treatment of RA, and when used judiciously are effective and relatively safe. However, these are potent medications with the potential for serious side effects. Therefore, patients being prescribed these agents should be carefully followed by physicians and other health care providers. By combining synthetic DMARDs and the available biologic agents, the management of RA has been transformed over the past 10 years offering RA patients great hope that they will experience clinical benefit and maintain productive, functional lives.

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DISCLOSURES

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Comparative Effectiveness Research (CER): A Summary of AHRQ's CER on Therapies for Rheumatoid Arthritis

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ABSTRACT

BACKGROUND: In recent years, the U.S. government has designated funding of several large-scale initiatives for comparative effectiveness research (CER) in health care. The American Recovery and Reinvestment Act (ARRA) of 2009 apportioned more than $1 billion to support CER programs administered by the Department of Health and Human Services (DHHS), the National Institutes of Health (NIH), and the Agency for Healthcare Research and Quality (AHRQ). CER is generally defined as the undertaking of original research or systematic reviews of published literature in order to compare the benefits and risks of different approaches to preventing, diagnosing, or treating diseases. These approaches may include diagnostic tests, medications, medical devices, and surgeries. The overall goals of CER are to support informed health care decisions by patients, clinicians, payers, and policy makers and to apply its evidence to ultimately improve the quality, effectiveness, and efficiency of health care.

OBJECTIVES: To (a) provide managed care professionals with general definitions of CER, specifically as it is administered by AHRQ; (b) discuss the importance of CER to clinical and managed care pharmacists; and (c) summarize key methods and findings from AHRQ's 2007 comparative effectiveness review on therapies for rheumatoid arthritis (RA).

SUMMARY: As supported by AHRQ, CER is conducted in order to synthesize comprehensive evidence on the comparative benefits and harms of treatment interventions. The findings from comparative effectiveness reviews can thus contribute to informing therapeutic strategies and treatment decisions. In 2007, a multitude of RA treatment options and studies motivated AHRQ to commission a systematic comparative effectiveness review. Conducted by investigators at the RTI-University of North Carolina Evidence-Based Practice Center, the review included comparisons of synthetic disease-modifying antirheumatic drugs (DMARDs), biologic agents, synthetic DMARDs versus biologic agents, and various combination therapies. Head-to-head comparisons of synthetic DMARDs generally revealed no significant differences in long-term clinical and radiographic outcomes, or in functional capacity or health-related quality of life. Two nonrandomized prospective cohort studies and 1 open-label effectiveness trial reported no differences in ACR20 and ACR50 response rates in patients treated with the tissue necrosis factor (TNF)-alpha inhibitors etanercept and infliximab. Comparisons of TNF-alpha inhibitors generally indicated no significant differences in rates of adverse events, including serious infections, and no increases in rates over time. In comparisons of a biologic agent combined with methotrexate versus a biologic agent alone, combination therapies were generally associated with better clinical response rates and better outcomes of functional capacity and quality of life. The most common adverse events observed in studies on biologic agents were diarrhea, headache, nausea, rhinitis, injection site reactions, and upper respiratory tract infections.

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The U.S. government has invested over $1 billion in comparative effectiveness research (CER) since President Obama signed the American Recovery and Reinvestment Act (ARRA) in February 2009.[1] Before this time, the limited amount of funding provided by the federal government was administered by the Agency for Healthcare Research and Quality (AHRQ). The $1.1 billion dollar ARRA investment was almost 37 times the annual amount previously devoted to CER by the federal government.[1]

The key question for CER is "…which treatment works best, for whom, and under what circumstances?"[2] This question led to the development of AHRQ's Effective Health Care Program, which was originally funded by Congress as part of the Medicare Prescription Drug Improvement and Modernization Act. The legislation included 3 components: priority setting, authority for research, and a mandate that the results be made available to multiple audiences.[3] Since 2005, AHRQ has invested $125 million on systematic reviews, observational studies, methods development and training, and a library of guides for clinicians and patients on 14 priority conditions.[3] AHRQ products related to rheumatoid arthritis (RA) are discussed later in this article.

What Is Comparative Effectiveness Research?

The ARRA assigned the Federal Coordinating Council for Comparative Effectiveness Research the responsibility to enhance coordination of CER conducted or supported by federal departments and agencies. In one of its initial activities, the Council defined CER as follows:

> "Comparative effectiveness research is the conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat and monitor health conditions in "real world" settings. The purpose of this research is to improve health outcomes by developing and disseminating evidence-based information to patients, clinicians, and other decision-makers, responding to their expressed needs, about which interventions are most effective for which patients under specific circumstances."[4]

According to the Council's conceptualization of CER, it must target diverse patient populations and wide-ranging diseases and health conditions. The interventions investigated in CER may include medications, diagnostic procedures, medical and assistive devices and technologies, behavioral therapies, and delivery system strategies.

There are a number of important components to established definitions of CER. The first and most obvious is that the research is *comparative*. The intent is that meaningful

comparisons will be made between interventions, instead of comparisons of interventions with placebo, which is common in randomized controlled trials (RCTs). The second component is that the universe being compared is much broader than just looking at drug therapy. The Institute of Medicine developed a list of the 100 highest priorities for CER.[5] Of these, only 36 involved either direct comparisons of drug therapy or a comparison of drug therapy with other treatment options.

In looking at CER, one must distinguish *effectiveness* from *efficacy*. In 1962, Congress passed the Kefauver-Harris amendments requiring sponsors to demonstrate the safety and efficacy of a drug to be licensed for sale in the United States. Efficacy is proven through RCTs. These trials enroll relatively small numbers of subjects, hundreds or a few thousand, who meet rigorous inclusion and exclusion criteria related to the disease state of interest, comorbid conditions, and additional drug therapy. These trials demonstrate efficacy, or whether the drug *can* work in a very select group of patients. These studies lack the external validity to determine whether the drug *actually* works in a "real-world" group of patients who have multiple complicating disease states, take a variety of other drugs, and may or may not be adherent to therapy. Studies that look at "real-world" data measure effectiveness or how well the drug works in a broad group of patients outside of a clinical trial.

Does CER really mean just effectiveness, or will clinical trial data be used as well? At present this issue is not clear; however, an attractive alternative, called pragmatic clinical trials, has been described by Sullivan and Goldmann (2011), as well as others.[6] Pragmatic clinical trials are prospective in nature but address the issue of external validity by enrolling the full range of patients that clinicians in practice will see as potential candidates to use the drug of interest. A component of CER will include primary studies which develop new evidence through original studies that make head-to-head comparisons of treatment alternatives for a condition or a disease. Additionally, an important option is to look at retrospective database studies for CER. These studies either use claims data, which include medical and pharmacy claims for a large population of patients, electronic medical record data, or both. Claims data have the advantage of being able to determine which drugs and treatments were actually used and when. However, claims data lack many meaningful clinical outcomes. Electronic medical record (EMR) data are an excellent source of clinical outcome information, including data on which drugs were prescribed. Nonetheless, EMR data do not generally indicate whether prescriptions were actually filled. The Holy Grail for these types of studies is a combination of both types of data, which characterizes some limited data sets in closed systems such as the U.S. Department of Veterans Affairs and Kaiser Permanente. There is a significant need for comparative effectiveness studies to investigate beyond the scope of placebo-controlled clinical trials used for licensing. For example, CER conducted as systematic reviews and meta-analyses of published studies affords the potential to include head-to-head trials, clinical trials that enroll a broader group of patients, and observational studies containing claims and EMR data.

AHRQ Methods for Conducting CER Systematic Reviews

Comparative effectiveness reviews are comprehensive reports that use published data to make head-to-head comparisons of products. These reviews are conducted by AHRQ's 14 Evidence-Based Practice Centers (EPC). Established in 2007, the EPCs are listed as follows:[7]

- Blue Cross and Blue Shield Association, Technology Evaluation Center
- Duke University
- ECRI Institute
- Johns Hopkins University
- McMaster University
- Minnesota Evidence-Based Practice Center
- Oregon Evidence-Based Practice Center
- RTI International—University of North Carolina
- Southern California
- Tufts—New England Medical Center
- University of Alberta
- University of Connecticut
- University of Ottawa
- Vanderbilt University

AHRQ has established 3 key principles for conducting comparative effectiveness reviews:[8]

- Reviews must be relevant and timely for decision makers
- Reviews must be objective and scientifically rigorous
- Public participation in the reviews and transparency in the review process are critical to increase public confidence and credibility

AHRQ further points out that interpretation of the data is critical and that there are limits of interpretation. Drugs may be shown to be equivalent for an average group of patients, but that does not necessarily imply that they are equivalent for all individuals. As the EPCs conduct reviews, they are further guided by principles for the Effective Health Care Program, which include:

- Approaching the evidence from a clinical, patient-centered perspective
- Fully exploring the clinical logic underlying the rationale for a service
- Casting a broad net with respect to types of evidence, which includes placing a high value on effectiveness and applicability, in addition to internal validity
- Presenting benefits and harms for different treatments and tests in a consistent manner

As part of the transparency, topics are nominated in a public

process. AHRQ contracts with 1 of the EPCs to complete each review. This process includes an expert panel of researchers and clinicians who guide the selection of key clinical questions for the topic. The EPC conducts an extensive literature search and selects studies according to rigorous inclusion criteria. For example, studies are generally screened for whether patient samples represent prespecified populations and conditions of interest, appropriateness of blinding methods, and sufficiency of patient follow-up. From the studies that meet the inclusion criteria, the EPC extracts data relevant to the key clinical questions, evaluates the strength of evidence, compiles the data and performs meta-analyses, and prepares a draft technical report that undergoes peer review, public commentary, and a revision process before the report is published on the Effective Health Care Program website.

Why Is CER Important for Pharmacists?

Therapeutic decisions are often made through anecdote and personal experience with individual patients. In many cases pharmacists need to make decisions based on limited information from placebo-controlled clinical trials when they really need head-to-head data. CER will provide pharmacists with evidenced-based data that compares therapeutic agents used on real-world patients. Comparisons of head-to-head trials will allow pharmacists to determine the most effective and safe drug for patients and to apply that information to an individual patient. The data can be used by pharmacists to make clinically informed decisions for patients and to communicate that information to other practitioners.

AHRQ's 2007 CER on Rheumatoid Arthritis Therapies

In 2007, AHRQ published a systematic review of research on the comparative benefits and risks of synthetic and biologic disease-modifying antirheumatic drugs (DMARDs) for RA and psoriatic arthritis in adults.[9] Conducted by the RTI-University of North Carolina EPC, the review included 42 head-to-head trials and 58 observational studies on RA therapies.[10] Published studies were identified and obtained through comprehensive database searches covering the period from 1980 through September 2007. The key clinical questions that guided the review are summarized as follows:

1. Do RA therapies differ in their ability to reduce patient-reported symptoms, to slow or limit progression of radiographic joint damage, or to maintain remission?
2. Do RA therapies differ in their ability to improve functional capacity or quality of life?
3. Do RA therapies differ in harm, tolerability, adherence, or adverse effects?
4. What are the comparative benefits and harms of RA therapies in patient subgroups specified by stage of disease, history of prior therapy, demographics, concomitant therapies, or comorbidities?

In the studies that met the EPC researchers' inclusion criteria, analyses involved various comparisons among and between synthetic DMARDs (corticosteroids, hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine) and biologic agents (abatacept, adalimumab, anakinra, etanercept, infliximab, and rituximab) used as monotherapy or in combination therapy. The researchers evaluated the strength of study evidence using a modified version of the GRADE method (Grading of Recommendations, Assessment, Development, and Evaluation).[11] The strength of evidence for each treatment comparison was graded as *high*, *moderate*, or *low*, reflecting the reviewers' level of confidence in whether the evidence reflected the true effects of the study interventions.

Most of the studies included in the AHRQ systematic review evaluated clinical improvement using American College of Rheumatology (ACR) 20/50 criteria and disease activity scores (DAS). Radiographic progression was most often evaluated with Sharp or Sharp–van der Heijde scores. Functional capacity and health-related quality of life outcomes were evaluated with the Health Assessment Questionnaire (HAQ) or the Medical Outcomes Study Short Form 36 (SF-36). Analyses of comparative risks of RA therapies were based on 1 or more of the following adverse effects: hepatic events, interstitial lung disease, respiratory infection, hospitalization due to infection, and malignancies. In addition, the systematic review analyzed the comparative risks of serious infections, including tuberculosis, pneumonia, osteomyelitis, progressive multifocal leukoencephalopathy, and sepsis. Addressing key questions 1-3, notable findings regarding the comparative benefits and risks of RA therapies are summarized as follows.

Comparisons of Synthetic DMARDs Used as Monotherapy. With few exceptions, head-to-head comparisons revealed no significant differences in long-term clinical and radiographic outcomes or in functional capacity or health-related quality of life among patients treated with various synthetic DMARDs used as monotherapy. Unless noted otherwise in the following summaries, rates of adverse events and discontinuations did not differ in comparisons of synthetic DMARDs.

Comparison of leflunomide versus methotrexate was based on 1 publication that reported a meta-analysis of 2 RCTs conducted over 2 years.[12] After 1 year, the proportion of patients meeting ACR20 criteria was significantly greater in the methotrexate versus leflunomide arms (odds ratio [OR] = 1.43, 95% confidence interval [CI] = 1.15-1.77, $P = 0.001$). At the 2-year endpoint, there was no significant difference in ACR20 outcomes between the treatment groups (OR = 1.28, 95% CI = 0.98-1.67). However, for the 2-year measures of functional capacity and health-related quality of life, significantly less improvement was reported for patients using methotrexate versus leflunomide (SF-36 physical component: 4.6 vs. 7.6, $P < 0.01$; HAQ Disability Index: −0.26 vs. −0.45, $P < 0.01$). Radiographic outcomes did not differ significantly between the treatment

groups. For all of the above comparisons, the EPC researchers judged the strength of evidence as moderate.

Based on 3 RCTs that lasted up to 1 year (N = 479), the EPC researchers concluded that there were no significant differences in clinical outcomes and functional capacity in patients treated with methotrexate versus sulfasalazine.[13-15] For this comparison, a difference in treatment persistence was reported in 1 meta-analysis of 71 RCTs and 88 observational studies.[16] After 5 years, a greater proportion of patients reported continuing methotrexate (36%) versus sulfasalazine (22%, *P* value not reported).

Comparisons of Biologic Agents Used as Monotherapy. In their literature search, the EPC researchers did not identify any RCTs with head-to-head comparisons of biologic agents. Two nonrandomized prospective cohort studies[17,18] and 1 open-label effectiveness trial[19] compared the tissue necrosis factor (TNF)-alpha inhibitors etanercept and infliximab. Based on ACR20 and ACR50 response rates, there were no differences in efficacy outcomes between treatment groups; the strength of evidence in these 3 studies was judged as moderate. As a class, tissue necrosis factor (TNF)-alpha inhibitors were significantly more effective than anakinra based on ACR20 response rates.[20] Reported as incidence rates, the most common adverse events observed in observational studies on biologic agents were diarrhea (7%-18%), headache (12%-18%), nausea (8%-20%), rhinitis (8%-18%), injection site reactions (19%-56%), and upper respiratory tract infections (9%-24%).[10] Comparisons of TNF-alpha inhibitors generally indicated no significant differences in rates of adverse events, including serious infections, and no increases in rates over time. A systematic review indicated higher rates of injection site reactions in patients using anakinra compared with adalimumab or etanercept.[20] A retrospective cohort study reported higher overall discontinuation rates for anakinra (41%) compared with etanercept (31%; $P = 0.004$) or infliximab (35%; $P = 0.03$).[21] Pooled results from 3 observational studies revealed that the incidence of granulomatous infections was higher in patients treated with infliximab (239 infections per 100,000 patients) versus etanercept (74 infections per 100,000 patients).[22-24]

Synthetic DMARDs Versus Biologic Agents Used as Monotherapy. The EPC researchers identified 3 RCTs that compared the effectiveness of methotrexate versus the TNF-alpha inhibitors adalimumab or etanercept. In 2 of these trials, all patients had early RA and were methotrexate-naïve.[25,26] The other trial included methotrexate-naïve patients as well as patients who had not responded to a synthetic DMARD other than methotrexate. In all 3 studies, there were no significant treatment-group differences in clinical response, quality of life, or functional capacity. However, radiographic outcomes were significantly better among patients treated with a biologic agent versus methotrexate. For example, as reported in the ERA (Early Rheumatoid Arthritis) study, over a 1-year follow-up period a lack of radiographic progression was observed in 72% of patients on etanercept versus 60% of patients on methotrexate ($P = 0.007$).[27] In a 1-year prospective cohort study, subjects who had failed initial RA treatment had a markedly higher probability of achieving functional independence on a biologic agent than on a synthetic DMARDs (OR = 3.88, 95% CI = 1.71-8.79).[28] In addition, this study reported that patients using biologic agents were more likely to achieve remission (OR = 1.95; 95% CI = 1.20-3.19). In the ERA study, significantly higher rates of mouth ulcers (14% vs. 5%; $P < 0.50$) and nausea (29% vs. 17%, $P < 0.50$) were reported for the methotrexate versus etanercept groups.[26] Otherwise, the AHRQ systematic review indicated no differences in incidences of adverse events between biologic agents and synthetic DMARDs; however, in the studies on which comparisons were based, small sample sizes may have limited the statistical power necessary to detect differences.

Monotherapy Versus Combination Therapy. Two 4-year trials were identified that compared sulfasalazine-methotrexate to monotherapy with 1 of these medications in patients with early RA.[14-15] The findings for both studies indicated no differences in ACR response rates or radiographic changes across the combination therapy verus monotherapy groups. However, over an 18-month period, another study reported a significantly greater improvement in DAS measures for patients treated with combination therapy (–0.67) versus methotrexate alone (–0.26, $P = 0.023$).[29]

In 3 RCTs, synthetic DMARD plus corticosteroid therapy was compared to synthetic DMARD monotherapy.[29-32] These studies reported significantly fewer eroded joints and lower radiographic progression in patients on the combination therapy. In 1 study, patients on combination therapy (corticosteroid combined with sulfasalazine or methotrexate) had significantly higher remission rates than patients on DMARD monotherapy (DAS28 < 2.6: 55.5% vs. 43.8%, $P < 0.001$).[29] Studies included in this analysis reported similar discontinuation rates due to adverse events.

In the few trials that have compared combination therapy comprising 2 biologic agents with biologic monotherapy, the most common finding is that combination therapy is associated with higher rates of adverse events.[33-34] In 1 study comparing etanercept alone versus a combination of etanercept and anakinra, the combination therapy group experienced significantly more adverse events (14.8% vs. 2.5%).[33] Likewise, another study reported more adverse events among patients treated with combinations of abatacept plus various other biologic agents versus abatacept alone (22.3% vs. 11.7% to 12.5%, *P* value not reported).[34]

One of the more consistent and robust findings of the AHRQ systematic review involved comparisons of a biologic agent combined with methotrexate versus a biologic agent alone. The combination therapies included methotrexate plus adalimumab, etanercept, infliximab, or rituximab. Compared with a biologic agent alone, combination therapy was generally associated with better clinical response rates. For example, 1 trial reported that significantly more patients on adalimumab plus methotrexate compared with adalimumab monotherapy met ACR50 criteria after 2 years of treatment (59% vs. 37%, $P < 0.001$).[25] Similarly, the TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study also identified higher DAS28 remission rates for the combination therapy compared with etanercept alone (35% vs. 16%, $P < 0.001$).[35-37] Combination therapy was also associated with significantly better outcomes of functional capacity and quality of life.

Conclusions

For managed care professionals, comparative effectiveness research offers value through its focus on making meaningful comparisons *between* health care interventions instead of comparing interventions with placebo, which is common in RCTs. In addition, comparative effectiveness reviews, like the AHRQ review on RA therapies, offer the advantage of pooling findings from numerous studies and grading the quality of evidence to guide treatment and management decisions. In December 2010, AHRQ published a protocol for conducting an update to its 2007 comparative effectiveness review on RA therapies.[38] The updated review, to be based on the same key clinical questions that guided the original study, will evaluate outcomes of RCTs and observational studies that have been published since 2007. In addition to the synthetic DMARDs and biologic agents that were compared in the 2007 review, the update encompasses 3 biologics—certolizumab pegol, golimumab, and tocilizumab—that were approved in 2009 or 2010.

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Potential Advantages of Interprofessional Care in Rheumatoid Arthritis

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ABSTRACT

BACKGROUND: Rheumatoid arthritis (RA) affects over 1 million people in the United States. Although the emergence of new medications has substantially improved treatment options and outcomes for patients with RA, the disease is still a major cause of morbidity and mortality. In addition, significant barriers to adherence characterize RA medication management. A reasonable approach to improving RA patient outcomes entails interprofessional, multidisciplinary models of care. Working with rheumatology specialists, RA multidisciplinary care teams may comprise case managers, pharmacists, physical and occupational therapists, social workers, physiatrists, orthopedists, or other health professionals. Experience and evidence have supported the value of interprofessional, coordinated care models for patients with various chronic diseases. However, potential drawbacks include the costs associated with implementation of such approaches, the extra time required for their administration, and the lack of incentives for clinicians to adopt collaborative care approaches.

OBJECTIVES: To summarize the arguments and evidence for interprofessional, multidisciplinary care programs in RA.

SUMMARY: Various multidisciplinary models of RA care have been described in the literature. Whereas the case for implementing such models is underscored by the chronic nature of the disease, by its comorbidities and complications, and by barriers to patient medication adherence, cost-effectiveness analyses to document benefits of coordinated interprofessional RA care are lacking. Most studies on interprofessional care in RA are relatively old and have been conducted outside of the United States. Nonetheless, the findings are still relevant and may shed light on potential avenues for the development of new models in this country.

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With recent advances in the treatment of rheumatoid arthritis (RA), including the development of biologic agents, primary therapeutic goals and strategies have shifted from relieving symptoms to reducing disease activity and progression. Today, expert rheumatologists generally view low disease activity states or, in some cases, clinical remission as attainable goals for people with RA. Nonetheless, due to a number of challenging barriers, including lack of access, low income, low health literacy, and perceived lack of efficacy, many patients unfortunately do not receive appropriate medications and/or achieve these goals.[1-3] To address this issue from the managed care perspective, it is necessary to evaluate the effectiveness of structural and procedural models of health care delivery. Given the fact that RA is associated with multiple comorbidities and complications, managed care professionals must be especially attentive to the potential for awkward and unsafe care transitions, lack of communication among the patient's care providers, and ineffective utilization of resources in this population. As discussed in this article, an alluring alternative to the standard rheumatologist-centered care model is the development of interprofessional coordinated care models.

Potential Advantages of Interprofessional Care Models

Interprofessional care models are defined by the nature of interactions among health providers serving individual patients. According to the authors of a large-scale technical review of interprofessional care models, these interactions are ideally based on shared power and authority, along with mutual respect for each participant's professional abilities.[4] By transforming this textbook definition into a working practice, health professionals engage in cooperative problem solving and shared decision making. Given effective cooperation among the patient, providers, health systems, and employers, coordinated care approaches offer promise for improving outcomes and minimizing waste and duplication of services. The potential exists for patients to experience greater satisfaction with their health care, more appropriate care in less intensive settings, and more timely and accessible care. Providers may benefit from less variance in care strategies and from supplementary resources to assist with more intensive patients—resources such as disease and medication therapy management programs. In addition, health systems and employers may benefit from less variation in care, controlled costs, and improvement in patient adherence to plans of care.

Optimal care coordination models vary by patient population, payer organization, and program goals.[4] Ideally, models should be designed to reduce hospital readmission rates

specific to medication errors, to improve compliance with treatment plans, and to provide formal follow-up care. For members with high average length of stay (ALOS), the model should promote adherence to medication regimens, resolve access issues, provide disease- and medication-related education, and offer medication assessment at discharge in order to minimize complications of illness.

One example of an interprofessional coordinated care model comprises the patient, pharmacist, and nurse case manager. This patient-centered model is especially pertinent for patients in transition and those who may have access issues. More specifically, this model may ideally serve patients in transition who have complex discharge needs, multiple providers, and multiple medications that have been prescribed by different providers. In addition, the model may be especially appropriate for complex cases, including patients who are experiencing fragmentation or gaps in care, frail elderly patients with multiple chronic conditions, high users of health care, and at-risk populations (e.g., dual-eligible Medicare beneficiaries with disabilities).

In the collaborative model described above, the pharmacist should be highly integrated into case management activities. Pharmacists can serve this role by providing access to real-time pharmacy utilization data for appropriate case management staff; by relaying potential medication therapy concerns, when raised by case management staff to appropriate pharmacy staff; and by providing medication therapy management services. The nurse case manager would be responsible for integrating the pharmacist's recommendations into existing case management programs that can help close the loop in assessing and managing a given patient population. The joint responsibility of case managers and pharmacists in this model may improve clinical, economic, and quality-of-care outcomes; moreover, the model offers the potential to increase the likelihood that patients will adhere to their prescribed medications.

Of course, the promise of interprofessional coordinated care models must be weighed against potential drawbacks and system barriers. As it stands, physicians currently do not have sufficient incentive to integrate diagnosis, therapy, and medication management. This is clearly an important system barrier to the effectiveness of the coordinated care model. Current systems also tend to foster limited communication among primary care providers, specialty physicians and clinicians, pharmacists, and case managers. Insufficient education among treating providers regarding the interprofessional processes and tools available in the managed care organization also provides challenges. Costs of these programs, cost sharing, and funding would also need to be addressed, especially in systems in which care is provided by different companies. When evaluating outcomes, providers may disagree on the assessment framework and on who should get credit for coordinated care interventions. Considerable systematic and evidence-based planning is required to identify populations to be served and to establish the specific roles and functions of the various health care providers involved in the coordinated care model. Moreover, the framework for outcomes reporting must be agreed upon early on in the process, before care is provided to the patient. In short, successful interprofessional care programs depend on minimizing role confusion and breaking down barriers of working in silos.

Our present health care system certainly presents challenges to implementing an effective interprofessional care model. We still have boundary issues within our industry, such as confusion about how to coordinate various payer entities. We also have confidentiality issues that have not been resolved. As an industry, we have not yet developed standardized tools that are widely accepted, thus creating difficulties when working with many different entities. An important premise for addressing these issues is that coordination of the team working with a specific patient population is as important as coordination of individual patients themselves.

Applying Interprofessional Care Models to RA Management

Interprofessional care models have been a hallmark of case management and are gaining wide recognition in the industry as a way to maximize patient outcomes in various populations and health care settings. Such models may indeed be intuitively pertinent for patients with chronic diseases, such as RA, that are associated with multiple complications and comorbidities. Given the focus on RA in this educational supplement, it is appropriate to review the literature on interprofessional care models in this field. Although most studies on interprofessional care in RA are relatively old and have been conducted outside of the United States, the findings are still relevant and may shed light on potential avenues for the development of new models in this country.

Variations on Multidisciplinary Care Models in RA. Toward the goal of ensuring optimal patient care, efforts to form collaborative teams of rheumatologists along with other health care professionals have been documented over at least the last 5 decades.[5] What are the characteristics, strengths, and weakness of current models of care in RA? This question was central to a study conducted by MacKay et al. (2008) in which 74 opinion leaders in arthritis were interviewed about the structures and processes of their health care organizations.[6] The key informants, most of whom worked in Canada or the United Kingdom, represented physiotherapists, nurses, and rheumatologists who specialized in RA. Upon analysis of the qualitative data derived from these interviews, MacKay et al. identified 5 main types of care models, designated as (a) specialized arthritis programs, (b) ongoing management, (c) triage, (d) rural consultation support, and (e) telemedicine.

In the model designated as *specialized arthritis programs*, a

primary care physician refers the patient to a specialist, and the patient is subsequently referred to other health care practitioners in an effort to deliver high-quality care, provide educational benefits, and allow for access to a comprehensive range of services. This model is consistent in structure and process with common approaches in the United States. In the *ongoing management model*, health care providers expand their clinical roles, working with the specialist. Patients are also referred to extended role providers (ERPs), nurse practitioners, clinical nurse specialists, and other health professionals in order to facilitate the maintenance of care. In addition, addressing psychosocial issues and continuity of care, patient education and self-management are considered integral components of the ongoing management model.[6]

According to the classification format described by MacKay et al., the *triage model* is designed to accommodate the needs of patients with musculoskeletal conditions such as arthritis by providing a primary care physician for consultation purposes, in addition to an ERP to conduct assessments.[6] The approach varies, with some teams led by physiotherapists while others are led by primary care physicians or other members of the health care team. MacKay et al. identified 2 models focusing on the provision of local access to specialist care in rural and remotely geographic regions. First, the *rural consultation support model* facilitates the provision of health care resources to rural communities through patient referrals to a specialist. Patients visit the primary care physician in their local area, who makes referrals to a specialist. The referrals may be conducted through a centralized coordinating system, and the specialist travels to the rural location. Since the visits by the specialist can be brief or infrequent, a liaison is often incorporated in order to ensure ongoing patient monitoring. In the *telemedicine model*, health information is shared via telecommunication of the health care services. Once the patient is referred to a specialist, a health care professional will accompany the patient to the remote facility where the musculoskeletal assessment is performed while the specialist views the examination.[6]

According to MacKay et al., the strengths of multidisciplinary, collaborative care models are characterized by their access to several health care service providers in a single location, including specialists, and facilitation of care continuity.[6] The models also tend to decrease waiting times and allow for the rationing of specialist resources. However, the provision of this broad range of health care services and coordination of the multidisciplinary team present both time and fiscal constraints. Informants of the study identified many challenges, including a lack of coordination in networking among providers, poorly defined roles of health practitioners, deficiencies in standardized billing procedures, and a lack of communication between providers.

Effectiveness of Multidisciplinary Approaches to RA Care. The case for multidisciplinary care programs in RA is supported by the chronic nature of the disease and by patients' unique needs.[5] As reviewed in the previous articles in this supplement, over the last several decades the documented clinical and radiographic effectiveness of synthetic disease-modifying antirheumatic drugs (DMARDs), and more recently the biologic agents for RA, has substantially shifted treatment goals and management strategies, which now largely focus on achieving low disease activity states and remission. However, inadequate receipt of appropriate DMARD therapies and low adherence rates are not uncommon among individuals with RA.[1,2] Adherence can be undermined by patients' naïve perceptions and lack of education about the disease as well as by its negative functional consequences, which include pain, fatigue, physical disability, and depression.[5,7] Accordingly, a logical hypothesis is that the standard rheumatologist-centered approach to care may not be sufficient to address the multidimensional needs of all RA patients.[8]

A cross-sectional study conducted by Esselens et al. (2009) in Belgium compared clinical and functional outcomes in RA patients who received multidisciplinary outpatient care (n = 89) or standard rheumatologist-centered care (n = 102).[5] Disease duration for all patients was less than 5 years. The study authors reported that the distribution of treatment regimens, which included monotherapy or combination therapy with biologic agents and/or synthetic DMARDs, was comparable across the 2 study groups. Under the supervision of a rheumatology nurse specialist, patients in the multidisciplinary group attended an outpatient clinic where their nonpharmacological care comprised patient education and visits with a physiotherapist, an occupational therapist, and/or a social worker. Through weekly meetings, the nurse specialist facilitated communication among members of the care team. The multidisciplinary team discussed individual patient cases at least once per month. When specific medical, psychosocial, or vocational problems were identified for a given patient, he or she was contacted for follow-up by the appropriate member of the care team.

Esselens et al. found that clinical and functional outcomes were significantly better among patients who received multidisciplinary outpatient care versus standard rheumatologist-centered care. Disease activity was measured by the Disease Activity Score using 28 joints (DAS28) instrument, with low disease activity scores and clinical remission cutoffs set at < 3.2 and < 2.6, respectively. Disease activity was relatively low in both groups. However, significantly more patients achieved low disease activity (80% vs. 60%, $P = 0.01$) and clinical remission criteria (69% vs. 39%, $P = 0.001$) in the multidisciplinary outpatient versus standard rheumatologist-centered groups, respectively. Group differences in functional outcomes were evaluated by the Health Assessment Questionnaire (HAQ) and the Short Form-36 instrument (SF-36). The percentage of patients with no

functional impairment on the HAQ was significantly greater in the multidisciplinary group (38%) than in the standard care group (15%, $P = 0.000$). The multidisciplinary group also had significantly better scores on various SF-36 indices, including measures of general health, physical function, social function, physical pain (less pain), vitality, and mental health.[5] However, in addition to the limitations of its cross-sectional design, this study did not address the differences in costs between the 2 care programs.

The most comprehensive analysis of multidisciplinary approaches to RA care was a 1997 systematic review conducted by Vliet Vlieland and Hazes.[9] Although dated, the review findings reflect many of the issues that one might expect in contemporary multidisciplinary approaches to RA care. The review included studies comparing the effectiveness of inpatient multidisciplinary team care approaches with regular outpatient care. For this analysis, the review authors identified 6 randomized controlled trials (RCTs) that included RA patients between 50 and 65 years with a disease duration of 3 to 14 years. The studies were conducted in the United States, Canada, The Netherlands, and the United Kingdom. In addition to rheumatologists and rheumatology nurse specialists, the composition of multidisciplinary team members included occupational therapists and social workers. The overall findings from this review indicated that compared with regular outpatient care, inpatient multidisciplinary team care was generally associated with better clinical outcomes but higher costs. For example, in 1 RCT, self-reported pain (assessed on a visual analogue scale) was reduced by 24% in the inpatient multidisciplinary group versus 0% in the regular outpatient care group ($P < 0.05$).[10] Directly following treatment, significantly greater reductions in articular joint tenderness on the Ritchie Index were also reported for the multidisciplinary inpatient group (28% improvement) versus the regular outpatient care group (0% improvement; $P < 0.05$). Reductions in pain intensity and articular joint tenderness, both indicators of disease activity, provided evidence for the efficacy of inpatient multidisciplinary team care group compared with standard outpatient care directly following treatment. However, these differences were not found after a 1-year follow-up. Although the studies included in the systematic review by Vliet Vlieland and Hazes did not include detailed data on cost differences between the 2 treatment approaches, the review authors concluded that inpatient multidisciplinary RA care was more expensive than the standard approach and that the difference was mainly attributed to hospitalization costs.[10]

The systematic review by Vliet Vlieland and Hazes also included 6 studies that compared outpatient multidisciplinary team care versus regular outpatient care.[11-17] In these studies, the multidisciplinary team usually comprised a rheumatologist, nurses, physical and occupational therapists, and a social worker. In several of the studies, multidisciplinary care included telephone interviews or regular home visits by a nurse. Over intervention periods of 1 to 2 years, the studies measured outcomes of disease activity as well as functional and psychosocial status. With regard to clinical outcomes, the RCTs in this analysis had mixed results. In 1 study that assessed functional capacity with the Sickness Impact Profile, functional status and overall health were better among patients who received outpatient multidisciplinary care versus regular outpatient care.[15] However, other studies revealed no significant differences in disease activity and functional outcomes for this comparison of care models.[11,12,17] The systematic review by Vliet Vlieland and Hazes did not address the comparative costs of multidisciplinary versus standard approaches to RA care. To our knowledge, no systematic study has been published that compares the economic costs of multidisciplinary RA care with other care models in the United States.

Conclusions

Whereas multidisciplinary, coordinated care approaches to managing patients with RA seem intuitively appropriate, a lack of contemporary research on cost-effectiveness outcomes precludes conclusions about their utility. In addition to RCTs that focus on these outcomes in patients who receive care through different interprofessional models, new studies are needed to identify best practices and strategies for implementing and administering such models, for enhancing communication among members of the care team, and for resolving issues of provider compensation and patient outcomes assessment.

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Supplement