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EDUCATIONAL OBJECTIVES

GOAL: To discuss the role of the pharmacist and pharmacy technician in collaborating with patients to improve understanding of, and adherence to, medications used to treat rheumatoid arthritis.

After participating in this activity, pharmacists will be able to:

- > Describe current American College of Rheumatology (ACR) treatment guidelines, the Choosing Wisely recommendations, and treat-to-target approaches to the management of RA
- > Discuss screening mechanisms to identify RA patients with medication adherence problems
- > Discuss ways to improve adherence to RA therapies
- > Describe new and emerging therapies for RA and their potential roles in therapy

After participating in this activity, pharmacy technicians will be able to:

- > Recall basic signs and symptoms of RA
- > Identify medications that are commonly used to treat RA
- > Recall ways to help RA patients with adherence to therapy
- > List the goals of patient education and adherence counseling



The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in the knowledge-based activity, and will receive up to 0.2 CEUs (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission.

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Rheumatoid arthritis: Partnering for optimal care

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Abstract

Rheumatoid arthritis (RA) is an autoimmune disease that may have articular and extra-articular manifestations. Management can be achieved through nonpharmacologic and pharmacologic means. Pharmacologic therapy traditionally consists of either traditional or biologic disease-modifying antirheumatic drugs. Recent literature supports close monitoring of the disease through use of composite disease activity measures, and treating to a target to achieve remission. Adherence to RA therapy is essential to help decrease disease progression and increase the chance to achieve remission. Pharmacists play a critical role in helping patients understand, and adhere to, RA medications.

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RHEUMATOID ARTHRITIS:

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation of the joints. Certain patient populations may be at increased risk of developing RA based on demographics, genetics, environmental factors, and infectious processes. RA can lead to the development of extra-articular manifestations of an ocular, oral, pulmonary, renal, neurologic, or cardiovascular nature.¹ Without appropriate treatment, chronic inflammation and joint destruction progress, impairing the patient's quality of life (QOL) and ability to perform activities of daily living (ADLs). Early treatment and patient adherence are important to preserve the patient's physical function.²

Epidemiology

RA's prevalence is estimated at about 1%, increasing with age until the 7th decade of life. Although incidence rates are similar between sexes during the first 10 years of life and over age 60 years, women between ages 15 and 45 years are 6 times more likely to have RA than men.¹

Studies performed in families and twins have demonstrated a genetic component. In monozygotic (identical) twins, the correlation is 4 times greater than in dizygotic (fraternal) twins.³ Inheritance of certain alleles of HLA-DR, expressed in the major histocompatibility complex (MHC) locus, is associated with increased risk and severity of RA. White patients with HLA-DR4 have more than a 3 times greater risk of developing RA. In Native American patients, RA is correlated with HLA-DR9 genotype, while a strong HLA-DR associated correlation has not been determined in African American patients. Not all patients with RA have an identifiable genetic component.⁴

Additionally, certain environmental factors (eg, smoking, pulmonary disease) and infectious agents (eg, *Escherichia coli*, *Porphyromonas gingivalis*, Epstein-Barr virus) have been associated with an increased risk of RA.¹

Pathophysiology

In RA, the body's immune system is unable to distinguish between self-tissue and foreign tissue. Therefore, the immune system attacks the body's own synovial and connective tissues. Interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF) are the main pro-inflammatory cytokines involved in RA's inflammatory process. The inflammation leads to proliferation of synovial tissue, also known as pannus. Pannus invades surrounding tissue, causing joint destruction and erosion of bone and cartilage. CD4 T cells produce cytotoxins within the synovial membrane, causing further bone and cartilage erosion. Production of cytotoxins by activated T cells results in additional inflammatory activity. Prostaglandins and histamine are released causing increased blood flow that contributes to some RA symptoms such as pain, warmth, and redness. Additionally, antibodies are formed due to B-cell activation. The antibodies contribute to further damage of both the bone and synovium.¹

Clinical presentation

The classic signs and symptoms of RA include joint involvement. The most commonly affected joints include small joints located within the wrists, feet, and hands, but the jaw, shoulders, spine, elbows, hips, knees, and ankles can also be affected. Although generally symmetrically distributed, some patients with early disease may experience asymmetrical distribution. Usually symptoms appear over weeks to months, but some patients may experience a sudden onset, presenting with systemic symptoms (eg, anxiety, depression, loss of appetite, fever).

Additional RA symptoms include pain, myalgias, tenderness, joint stiffness, and swelling. Joint stiffness tends to be worse in the morning but may last all day. Fatigue may be worse in the afternoon, with earlier onset during RA flares. On physical examination, affected joints may feel swollen, tender, and/or warm. Chronic inflammation may lead to deformity, muscle atrophy, and a decrease

in ability to move, decreasing QOL and impairing the patient's ability to perform ADLs. Patients may also develop hammer toe deformities, bunions, and calluses, which can further impact ambulation. Therefore, early treatment to prevent progression of inflammation is important.¹

Due to RA's systemic nature, extra-articular involvement may occur. One possible manifestation, rheumatoid nodules, may develop in a variety of locations, most commonly in the extensor areas of the forearms, elbows, and hands, and less commonly in the feet, lungs, and meninges. Other complications may be pulmonary: pleura within the lungs, pulmonary fibrosis, and less commonly, interstitial pneumonitis. Ocular manifestations (eg, keratoconjunctivitis sicca, scleritis) and oral manifestations (eg, salivary gland swelling, xerostomia) are also possible. Furthermore, RA increases risk of atherosclerosis and myocardial infarction. Other manifestations include but are not limited to: vasculitis, renal disease, and hematologic and neurologic manifestations.⁵

Treatment recommendations

RA can be stratified by duration of disease. Early RA is defined as having symptoms for less than 6 months' duration. Established RA is defined as either meeting the 1987 American College of Rheumatology (ACR) RA classification criteria or having symptoms for 6 months or longer. RA also can be stratified by level of disease activity as low, medium, or high based on validated scales. These further classifications assist in the clinical decision-making process for therapy.⁶

RA cannot be cured, but it can be treated with nonpharmacologic and pharmacologic management. As such, treatment is focused on prevention of long-term complications including destructive joint changes and maintenance of function and QOL.¹ The primary goal of therapy is disease remission, which can be defined a number of ways.⁶

Nonpharmacologic management

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includes resting joints, weight reduction, surgery, physical therapy, and occupational therapy.¹ Pharmacologic management can include nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, disease-modifying antirheumatic drugs (DMARDs), and biologic therapy.¹ NSAIDs have a role as needed in symptomatic relief.¹ Glucocorticoids can be classified as low or high dose, with prednisolone 10 mg/day or higher indicating high dose, and can also be classified as short-term (<3 months) or long-term therapy.⁶ Glucocorticoids have many potential roles in therapy including management of RA flares, bridge therapy to manage symptoms while waiting for DMARDs to begin working, and low-dose add-on therapy to DMARDs in patients who remain symptomatic.¹

DMARDs are the backbone of therapy for RA management and can be biologic or nonbiologic in nature (**Table 1**).^{1,7} Nonbiologic DMARDs include methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, and minocycline (referred to as DMARDs hereafter). Others include azathioprine, cyclophosphamide, cyclosporine, and gold salts. Tofacitinib is a newer agent approved by FDA in 2012. Of these agents, most patients are initially started on methotrexate unless otherwise indicated.¹

Biologic DMARDs (referred to as biologics hereafter) are newer agents targeted against specific portions of the pathophysiology of RA. Many of these agents, including adalimumab, certolizumab, etanercept, golimumab, and infliximab, demonstrate activity through inhibition of TNF- α . Other agents demonstrate activity against different portions of the inflammatory process including IL-1 (anakinra) and IL-6 (tocilizumab). Abatacept works through binding to CD80/86 on T cells and antigen-presenting cells and rituximab binds to the CD20 protein on B cells.¹

Multiple treatment recommendations for management of RA include treat to target (T2T), "Choosing Wisely," and ACR recommendations. The T2T principle postulates that treating patients to a specific

goal confers a better outcome. This concept is not exclusive to RA, being found in other disease states.⁸ In cardiovascular disease, specific blood pressure goals are demonstrated to have superior outcomes in patient care, and in diabetes care, certain blood glucose goals have been associated with prevention of late complications. In RA management, T2T goals promote disease remission or lowering of disease activity, thereby preventing late complications such as joint damage and physical disability, which can lower QOL.^{8,9} Disease activity can be measured by acute-phase reactants, composite indices of disease activity, or swollen joint counts.⁹ One difficulty with application of T2T in the RA population is the lack of a uniform measurement of disease activity and identification of target compared to other disease states applying the principle.¹⁰

Currently, the ACR endorses 6 disease activity and functional status assessments to measure disease activity and make clinical decisions. These include the Simple Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Patient Activity Scale (PAS), Patient Activity Scale-II (PAS-II), Routine Assessment of Patient Index Data (RAPID-3), and the Disease Activity Score 28 (DAS28).^{11,12} DAS28, for example, is a composite scored from 4 component measures: number of swollen joints out of 28, number of tender joints out of 28, either blood CRP or erythrocyte sedimentation rate, and a patient global assessment of health.¹³ This validated composite assessment can produce a score associated with the different levels of disease activity in RA, with a possible range of 0 to 9.4.¹⁴ This tool requires adequate training for reliable joint count assessment and takes approximately 10 seconds for patients and 3 to 5 minutes for providers to complete, excluding time

delay for lab results.¹⁴

T2T includes 10 specific recommendations and 4 principles of care:¹⁰

- The rheumatologist and patient must share in the decision-making process for the management of RA;
- The primary goal for the management of RA is to improve QOL long term;
- Cessation of inflammation is important for achievement of this goal; and
- T2T optimizes disease outcomes in RA through adjusting therapeutic management to the measured disease activity.

T2T recommendations identify clinical remission as the primary goal for management, with low disease activity recommended as an alternative. In patients with established disease, prior treatment failure, and joint damage, complete remission may not be feasible, making secondary recommendation of low disease activity an appropriate alternate goal.⁹ Definition of clinical remission should include absence of signs and symptoms indicative of inflammatory disease activity. Drug therapy should be adjusted every 3 months until treatment target is reached. Disease activity should be regularly assessed and documented, with the frequency of assessment increasing with disease severity. In patients with moderate-to-high disease activity, assessments should be made monthly, with less-frequent monitoring in sustained low disease activity. Validated composite measures of disease activity, such as DAS28 and CDAI, are needed to direct treatment decisions. These composite disease activity measures can be used to classify a patient's disease activity as low, moderate, high, or in remission. This is important for determining appropriate initial therapy as well as for assessing treatment efficacy regarding need for therapy alterations. No specific composite

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PAUSE AND PONDER

How can a pharmacist help apply Choosing Wisely to practice?

RHEUMATOID ARTHRITIS:

TABLE 1

Medications for the Management of Rheumatoid Arthritis

Medication		Mechanism of Action	Side Effects	Monitoring
Nonbiologic	Hydroxy-chloroquine	Exact mechanism unknown	Diarrhea, rash, retinopathy	Ophthalmologic examinations at baseline and every 3 months
	Leflunomide	Converted to active metabolite, teriflunomide, which inhibits dihydroorotate dehydrogenase to inhibit pyrimidine synthesis and modulate inflammation	Alopecia, rash, diarrhea	Baseline CBC, LFT, SCr, and repeat every 2-12 weeks (frequency dependent on duration of therapy)
	Methotrexate	Folate antimetabolite that inhibits dihydrofolate reductase to interfere with DNA synthesis and repair	Myelosuppression, interstitial pneumonia, hepatic fibrosis, rash	Baseline CBC, LFT, SCr, and repeat every 2-12 weeks (frequency dependent on duration of therapy)
	Sulfasalazine	Exact mechanism unknown	Rash, myelosuppression, GI upset	Baseline CBC, LFT, SCr, and repeat every 2-12 weeks (frequency dependent on duration of therapy)
	Tofacitinib	JAK inhibitor	Headache, UTI, URI, diarrhea, nasopharyngitis	Screen for TB, hepatitis B, and hepatitis C prior to use. CBC at baseline and throughout therapy. FLP 4–8 weeks after starting therapy. LFTs during therapy.
Biologic	Abatacept	Binds to CD80/86 receptors of antigen-presenting cells to prevent T-cell activation through binding to CD28	Infections, nasopharyngitis, headache	Screen for TB, hepatitis B, and hepatitis C prior to use
	Adalimumab	TNF-alpha inhibitor	Injection site reactions, URI	Screen for TB, hepatitis B, and hepatitis C prior to use
	Anakinra	IL-1 antagonist	Injection site reactions	Screen for TB, hepatitis B, and hepatitis C prior to use
	Certolizumab	TNF-alpha inhibitor	Injection site reactions, URI, UTI	Screen for TB, hepatitis B, and hepatitis C prior to use
	Etanercept	TNF-alpha inhibitor	Injection site reactions, URI	Screen for TB, hepatitis B, and hepatitis C prior to use
	Golimumab	TNF-alpha inhibitor	Injection site reactions, infections, nasopharyngitis	Screen for TB, hepatitis B, and hepatitis C prior to use. CBC prior to use and during use.
	Infliximab	TNF-alpha inhibitor	Injection site reactions, URI, rash, nausea, abdominal pain, headache	Screen for TB, hepatitis B, and hepatitis C prior to use
	Rituximab	Peripheral B-cell depletion through binding to CD20.	Injection site reaction, rash, hypertension, infection	Screen for TB, hepatitis B, and hepatitis C prior to use
	Tocilizumab	IL-6 receptor antagonist	Injection site reactions, rash, nasopharyngitis	Screen for TB, hepatitis B, and hepatitis C prior to use

Abbreviations: CBC, complete blood count; FLP, fasting lipid panel; GI, gastrointestinal; IL, interleukin; JAK, Janus kinases; LFT, liver function tests; SCr, serum creatinine; TB, tuberculosis; TNF, tumor necrosis factor; URI, upper respiratory infections; UTI, urinary tract infections.
Source: Refs 1,6,7

outcome is recommended over another. Composite measures of disease activity, functional changes, and structural impairment should be considered in the clinical decision-making process.

Throughout the whole disease management process, the treatment target, such as disease remission or low disease activity, should be maintained as the goal of therapy. Once goal disease

activity level has been achieved, it should be maintained to halt damage. For example, cessation of DMARD therapy during remission has been associated with RA flares and heightened disease activity.

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So, once remission has been achieved, medications should be continued to maintain the patient in remission. Another recommendation is that comorbid conditions, patient-specific factors, and drug-related risks may affect the choice of composite measure of disease activity as well as the target value.⁹ For example, in patients with ankle or forefeet involvement in RA, the DAS28 assessment does not include these joints, making it less ideal.⁸ As one of the overarching goals pertains to involving the patient in their care, the final recommendation is to ensure the patient is appropriately informed about the targets and strategies being used in their disease management.⁹

The American Board of Internal Medicine Foundation started the Choosing Wisely campaign in 2012. As also recommended for other disease states, it invited medical professional societies to create a list of 5 commonly used tests, treatments, or services in the management of diseases that should be questioned and discussed by physicians and patients as to their necessity or use, with the idea of helping to combat rising healthcare costs by possibly excluding these from disease management.¹⁵ Choosing Wisely recommendations from ACR seek to facilitate open communication between patients and providers to prevent potentially wasteful healthcare spending in RA.¹⁶ Estimates of the cost of healthcare waste to the US healthcare system in 2011 were between 21% and 47% of total healthcare expenditures, or \$558 to \$1263 billion annually, indicating a need to cut waste.¹⁷ Sources of waste can include overtreatment, failures in pricing, failures in delivery of care, and fraud.¹⁷

Thus, ACR recommends against magnetic resonance imaging of the peripheral joints to monitor arthritis or using dual x-ray absorptiometry scans more than every 2 years. Although patients are at high risk for osteoporosis from corticosteroid use, changes in bone density are often small when measured over short intervals. Lyme disease may also present with arthritis or arthralgia in single or mul-

tipale joints. In patients with musculoskeletal symptoms, testing for Lyme disease without exam findings or history suggestive of it should be avoided due to both healthcare waste and potential for harm. In addition, ACR recommends against antinuclear antibodies (ANA) subserologies in patients without a positive ANA or clinical suspicion of immune-mediated disease, because the subserologies are often negative when ANA is negative. For the management of RA, Choosing Wisely recommends prescribing nonbiologic DMARDs, such as methotrexate, before using biologic agents. These nonbiologics should be given for adequate trials of at least 3 months before changing to biologic treatment for most patients. This recommendation is due to cost of therapy and the availability of generic nonbiologic agents. In addition, side effects associated with biologic agents, although rare, are serious. Patients with poor prognostic factors would, however, potentially benefit from initial biologic therapy for RA.¹⁶

Components of both Choosing Wisely and T2T can be found in the newest ACR guidelines for the management of RA updated in 2015.⁶ In general, ACR guidelines recommend using a T2T approach regardless of disease intensity or duration. In patients with low disease activity, initial therapy with DMARD monotherapy, preferably methotrexate, is recommended over combination therapy with other DMARDs. In patients with moderate or high disease activity, use of DMARD monotherapy, with or without glucocorticoids, is preferred to combination therapy. Should the disease activity remain elevated despite therapy, intensification of therapy is preferred with specific recommendations dependent on the baseline treatment regimen, disease duration (early compared to established RA), and history of treatment responses.⁶ For patients with low disease activity and established RA, continuation of therapy is recommended. De-escalation of therapy can be considered in patients with established RA in remission. This involves tapering off 1 medication at a time through reductions in dose or fre-

quency; however, patients should not be tapered off of all RA therapies. The decision to taper should involve patient preference after discussion of risks, and a monitoring plan for disease activity, including flares, should be in place. In patients who experience an RA flare despite therapy, addition of a low-dose, short-duration glucocorticoid regimen can be considered.⁶

Patient-specific factors including comorbid conditions, presence of poor prognostic factors, disease activity, and cost of therapy may guide treatment decisions. For example, TNF-alpha inhibitors should be avoided in patients with congestive heart failure. ACR guidelines do include a number of disease-specific recommendations for comorbid conditions including malignancy, infections, hepatitis B, and hepatitis C.⁶ In addition, cost of therapy and convenience of use may affect treatment decisions when more than 1 appropriate option is available.⁶ The therapy selected has additional implications on required monitoring parameters and vaccinations. Traditional DMARDs like leflunomide, methotrexate, and sulfasalazine, for example, require monitoring of liver function and serum creatinine, as well as complete blood counts. Tofacitinib and biologic therapy require screening for tuberculosis prior to initiation of therapy (**Table 1**). The guidelines recommend all RA patients age 50 years or older receive the herpes zoster vaccine prior to initiation of tofacitinib or biologic therapy.⁶

New and emerging therapies

Despite currently available treatment agents, not all patients with RA achieve desired clinical outcomes, so various mechanisms and agents are being explored as potentially new options.¹⁸ Regulatory T cells (Tregs) help preserve homeostasis of the immune system. Treg function in patients with RA is abnormal but can be stabilized with TNF-alpha inhibitor therapy. Clinical trials are ongoing, and no serious adverse events have been discovered thus far. In patients with an irregular Treg phenotype, antagomirs might be used to affect microRNAs con-

RHEUMATOID ARTHRITIS:

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TABLE 2
Medication Adherence Challenges in RA and Strategies for Improvement

MEDICATION ADHERENCE CHALLENGES	FACTORS IMPACTING ADHERENCE	HOW TO HELP IMPROVE ADHERENCE
MEDICATION RELATED	<ul style="list-style-type: none"> ▶ Total of pills and/or doses daily ▶ Route of administration 	<ul style="list-style-type: none"> ▶ Make recommendations to patient's provider to simplify regimen and/or convert to regimen with patient's preferred route of administration ▶ Recommend medication adherence apps to help patients remember to take their medications
PATIENT RELATED	<ul style="list-style-type: none"> ▶ Beliefs about RA ▶ Beliefs about efficacy, safety, and necessity of RA treatment ▶ Beliefs about patient's input in health-related decisions and ability to carry out health-related behaviors ▶ Perceived social/healthcare team support 	<ul style="list-style-type: none"> ▶ Provide individualized counseling based on patient's beliefs and preferences ▶ Refer patients to RA support groups
PROVIDER RELATED	<ul style="list-style-type: none"> ▶ Degree of collaboration with patient ▶ Communication style ▶ Continuity of care 	<ul style="list-style-type: none"> ▶ Utilize SIMPLE strategy to improve adherence
HEALTH-SYSTEM RELATED	<ul style="list-style-type: none"> ▶ Access to care ▶ Availability of educational and supportive resources ▶ Patient engagement 	<ul style="list-style-type: none"> ▶ Engage patients, offer counseling at each visit to the pharmacy

Source: Refs 19,21,24,26,32

tributing to inflammation. Regulatory B cells (Bregs) can produce immunosuppressive cytokines. As RA is an autoimmune disease, suppression of the immune system could be beneficial.¹⁸

Biologics that target IL-17 have been associated with beneficial results in patients with RA. Use of ixekizumab and long-term use of secukinumab have demonstrated a decrease in signs and symptoms associated with the disease. TNF-alpha blockers, however, appear to have greater clinical efficacy than these agents.¹⁸ Conversely, biologics that target IL-6 appear to have similar clinical efficacy to TNF-alpha blockers in patients with certain receptors. Tocilizumab is now on the market and can be considered an alternative treatment option. Similar results and side effects have been observed in clinical trials with clazakizumab, olokizumab, sarilumab, and sirukumab. Biologics that

target IL-20 may also prove beneficial in treatment of RA.¹⁸

Another investigational drug, mavrilimumab, has demonstrated an increase in the improvement of signs and symptoms in patients with RA following subcutaneous administration for 12 weeks. Ocrelizumab and ofatumumab, monoclonal antibodies against the CD20 antigen, are being studied for use in RA. Approval for use is pending. Baricitinib, a kinase inhibitor, is currently in phase 3 trials but has demonstrated safety and efficacy in patients with RA who had an inadequate response to TNF-alpha blockers.¹⁸ In general, for all new and emerging therapies, additional studies are required to ensure safety and efficacy.

Identifying medication nonadherence

As with many chronic diseases, medica-

tion adherence is critical to limit symptoms and delay progression of RA. Unfortunately, the World Health Organization estimates that only 50% of patients in developed countries with chronic diseases are adherent to their treatment(s).¹⁹ A recent meta-analysis evaluated medication adherence in patients with RA and found the rate to be 66%.²⁰ Although this is slightly better than other chronic diseases, there is still much room for improvement. Increased adherence leads to better RA management, including decreased RA progression, increased disease remission, decreased need for additional therapy, and perhaps most importantly, greater functional ability.²¹ Pharmacists and pharmacy technicians are uniquely positioned to identify nonadherence and collaborate with patients to modify adherence behaviors (Table 2).

Measuring patient adherence is notoriously challenging. One rheumatology-specific medication adherence questionnaire, the Compliance Questionnaire Rheumatology, has been validated against electronic tracking of medication vial cap removal, which is currently considered the gold-standard in adherence measurement.²² Although this tool can be used to detect nonadherence reliably and highlight potential adherence barriers, it is a 19-item survey that takes patients about 12 minutes to complete. This tool may be useful in clinical rheumatology settings, but it is simply not built for the fast-paced environment of community pharmacy. Pharmacists and pharmacy technicians are often limited to less precise assessments of adherence, including asking the patient about his or her medication-taking behaviors, or reviewing refill histories. Neither of these measures is ideal, as patients may under or over report adherence, and the act of refilling a medication on time does not guarantee the patient is truly taking the medication as prescribed.

To assist pharmacists and other healthcare providers with identifying nonadherence, studies have evaluated factors

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that may contribute to RA-specific medication adherence. Factors associated with increased adherence include positive patient perception of medication efficacy and necessity, patient understanding of the adverse effects associated with their regimen, patient perception of RA severity, and a collaborative and supportive patient-provider relationship.^{20,21,23} One recent survey indicates that route of administration is the most important medication-related determinant of adherence among RA patients who prefer oral administration to injection.²⁴ In contrast, a study comparing adherence rates of RA medications showed that infliximab, administered intravenously, has the best adherence, compared to etanercept administered by subcutaneous injection and the oral medications sulfasalazine and methotrexate.²⁰ This may be partly due to the fact that infliximab is administered by a healthcare provider rather than self-administered by the patient.

Conversely, factors associated with nonadherence include increased weekly medication cost to the patient and longer duration of illness, possibly due to decreased perception of treatment necessity over time.^{20,21} In regard to biologics, out-of-pocket cost is the most prohibitive factor. A recent study found that 18.2% of RA patients never pick up their first biologic prescription, and this rate increases with out-of-pocket cost of the medication, with a significantly increased risk of nonadherence at or above \$250 per prescription per month.²⁵

Role of pharmacists/pharmacy technicians in improving adherence

Clearly, an individualized approach is required to improve RA medication adherence consisting of these elements: developing a rapport with the patient by learning and respecting the patient's preferences and beliefs, collaborating with the patient to identify specific barriers to adherence and explore potential solutions, and utilizing a multidisciplinary approach

to treatment including a plan for continuous follow-up. Pharmacy technicians play a key role in this process, as they frequently interact with patients at the point of prescription refill and pick up. Technicians should take note of patients with an inconsistent RA medication refill history, patients who have high copays for their RA medications, and patients who may express displeasure or confusion regarding their RA medication regimen, and offer these patients a consultation with the pharmacist. Technicians and pharmacists should be mindful that not just newly diagnosed patients need this attention. All patients, even those with a long history of RA, should be routinely monitored to prevent declining adherence over time.

During consultation, pharmacists may wish to use the SIMPLE strategy for improving medication adherence.²⁶ This acronym reminds pharmacists of 6 key ways to assist patients: **S**implifying regimen characteristics as clinically appropriate to make it easy for patients to be adherent; **I**mparting knowledge to patients about the efficacy and adverse effects associated with, and necessity of, their medications; **M**odifying patient beliefs on medication-taking behaviors by addressing adherence barriers; **P**atient communication, providing care in a way that incorporates patient preferences and builds trust between patient and pharmacist; **L**eaving the bias of preconceived notions and biases and delivering individualized counseling; and **E**valuating adherence on a regular basis.

Resources

Pharmacists may refer to websites such as www.arthritis.org, www.rheumatology.org, and www.rheumatoidarthritis.org, which contain comprehensive resources including medication information, lifestyle recommendations, support groups, and blogs for patients who may be struggling with their diagnosis of RA, as well as detailed information about patient assistance programs and organizations that may be able to help with out-of-pocket

prescription costs.²⁷⁻²⁹

For patients who use smartphones, pharmacists may recommend applications (apps) to improve adherence (**Table 2**). A recent review assessed 367 medication adherence apps.³⁰ Authors downloaded and evaluated 100 apps they believed most likely to improve adherence and be user friendly. The summation of their evaluations was used to design a searchable database at www.medappfinder.com.³¹ Patients may search for apps based on attributes they desire, including cost, ability to record doses taken or not taken and to order refills, language availability, and more. The website includes a separate search function for providers such as pharmacists, with over 30 searchable attributes, including several that may be useful to patients with RA, such as setting dose reminders for complicated regimens like once-weekly or once-monthly dosing schedules. The database may be utilized by pharmacists to recommend a specific app to a patient based on individualized adherence barriers identified during motivational interviewing.

Conclusion

RA is a chronic autoimmune disease characterized by joint inflammation that can progressively worsen to limit physical function, thereby decreasing patient's QOL and ability to perform ADLs. Nonpharmacologic and pharmacologic treatments are needed to prevent these complications. Pharmacologic treatment should be individualized to limit both disease progression, as well as cost, as appropriate. RA medication adherence is critical in achieving these goals, and pharmacists can promote adherence through individualized counseling and recommending resources, including apps. New agents are currently being explored for the treatment of RA, and pharmacists will need to stay informed so that they may educate patients as these come to market.

» **References** are available online at www.drugtopics.com/cpe.

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RHEUMATOID ARTHRITIS:

TEST QUESTIONS

FOR PHARMACISTS

1. The validated, 19-item rheumatology-specific medication adherence assessment tool is known as:
 - a. Rheumatoid Arthritis Compliance Questionnaire
 - b. Medication Adherence in Rheumatology Questionnaire
 - c. Morisky Questionnaire
 - d. Compliance Questionnaire Rheumatology
2. Which of the following is a predictor of adherence in patients with rheumatoid arthritis (RA)?
 - a. Patient understanding of the adverse effects associated with his/her medication
 - b. Authoritative provider-patient relationship
 - c. Subcutaneous route of administration
 - d. Long duration of RA
3. Which of the following is a predictor of nonadherence in patients with RA?
 - a. Patient understanding of the adverse effects associated with his/her medication
 - b. Authoritative provider-patient relationship
 - c. Subcutaneous route of administration
 - d. Long duration of RA
4. What percentage of patients with RA are adherent to medications?
 - a. 50%
 - b. 88%
 - c. 66%
 - d. 34%
5. Which of the following is not a component of the SIMPLE strategy to improve medication adherence?
 - a. Imparting knowledge to patients about efficacy/adverse effects associated with medications
 - b. Making the patient feel guilty for being nonadherent
 - c. Evaluating adherence on a regular basis
 - d. Simplifying regimen characteristics as clinically appropriate
6. Which website contains a searchable database that allows pharmacists to identify medication adherence apps for patients based on over 30 attributes?
 - a. www.medadherence.com
 - b. www.medappfinder.com
 - c. www.adherenceapp.com
 - d. www.medappsearch.com
7. Which of the following describes the most important role of the pharmacist in improving adherence in patients with RA?
 - a. Providing continuous counseling and education to all patients with RA, regardless of disease duration
 - b. Directing patients with RA to websites where they can locate additional resources
 - c. Recommending medication adherence apps to all patients with RA
 - d. Setting up automatic monthly prescription refills for all RA medications
8. Which of the following describes the ideal relationship in which the pharmacist can assist a patient with RA to improve medication adherence?
 - a. An authoritative relationship in which the pharmacist reiterates all of the prescriber's instructions
 - b. A paternalistic relationship in which the pharmacist chastises the patient for nonadherence
 - c. A collaborative relationship in which the pharmacist respects and values the patient's preferences and beliefs
 - d. A sympathetic relationship in which the pharmacist validates the patient's reasons for nonadherence
9. Which of the following agents demonstrated an improvement in the signs and symptoms of RA following subcutaneous administration for 12 weeks?
 - a. Bortezomib
 - b. Mavrilimumab
 - c. Baricitenib
 - d. Sarilumab
10. Ixekizumab targets which of the following?
 - a. GM-CSF
 - b. IL-6
 - c. IL-17
 - d. IL-20
11. Which of the following is a monoclonal antibody active against the CD20 antigen that is being studied for potential use in RA?
 - a. Ocrelizumab
 - b. Mavrilimumab
 - c. Tocilizumab
 - d. Olokizumab
12. Which biologic disease-modifying antirheumatic drug that targets IL-6 is already available on the market?
 - a. Sirukumab
 - b. Clazakizumab
 - c. Olokizumab
 - d. Tocilizumab
13. Which of the following most accurately describes the current role of emerging therapies in RA?
 - a. These agents are considered first-line agents.
 - b. A majority are ineffective in the treatment of RA.
 - c. These agents have an established role in the treatment of RA.
 - d. Additional studies are required to ensure safety and efficacy.
14. TR is a 65-year-old female with newly diagnosed RA being initiated on therapy today. Her DAS28 today was 2.8 (low activity), and she has no contraindications for use of any agents. Which of the following would be the most appropriate agent for TR to be initiated on based on ACR 2015 guidelines?
 - a. Methotrexate
 - b. Tofacitinib
 - c. Infliximab
 - d. Sulfadiazine
15. Which of the following is true regarding de-escalation of therapy per ACR 2015 recommendations?
 - a. In patients with established disease, consideration for de-escalation of therapy can occur with low disease activity.
 - b. In patients with established disease, consideration for de-escalation of therapy can occur with remission.
 - c. In patients with established disease in remission, RA therapy can be titrated to remove all agents.
 - d. In patients with established disease with low disease activity, RA therapy can be titrated to remove all agents.
16. Which of the following agents should be avoided in a patient with heart failure?
 - a. Infliximab
 - b. Hydroxychloroquine
 - c. Sulfasalazine
 - d. Anakinra
17. Which of the following is not among the Choosing Wisely recommendations for RA?
 - a. Do not prescribe biologics before a trial of methotrexate.
 - b. Do not repeat dual x-ray absorptiometry scans > every 1 to 2 years.
 - c. Do not test for subserologies of antinuclear antibodies (ANA) without positive ANA.
 - d. Do not prescribe methotrexate before a trial of biologics.
18. Which of the following best describes the purpose of the Choosing Wisely campaign?
 - a. To identify best practice therapies we should all be using

TEST QUESTIONS

- b. To identify which lab tests are the most appropriate for use
- c. To foster conversations between patients and providers about waste and harm from unnecessary tests and therapy
- d. To identify spending gaps in care, and where we should focus more of the cost of therapy

19. Which of the following is an overarching principle of the treat-to-target (T2T)

recommendations for RA?

- a. The rheumatologist makes the best decisions for patient care.
- b. Increasing inflammation is the best way to manage RA.
- c. An optimization of outcomes occurs by measuring disease activity and adjusting therapy to it.
- d. The treatment of RA is solely based on the decisions of the patient.

20. Which of the following are appropriate comprehensive measures of disease activity for applying T2T to RA except?

- a. SDAI
- b. CDAI
- c. DAS28
- d. All of the above

FOR PHARMACY TECHNICIANS

1. Which of the following is the most likely reason that a patient with RA may be nonadherent to therapy?

- a. Patient fully understands necessity of the medication.
- b. Patient pays a monthly copay of \$250 for the medication.
- c. Patient fully understands adverse effects of the medication.
- d. Patient believes the medication works well to treat RA.

2. Which of the following is the most appropriate recommendation to improve adherence for the patient from question 1?

- a. Recommend a medication adherence app with dose reminders
- b. Recommend discontinuing the medication
- c. Recommend a patient assistance program
- d. Recommend setting up automatic monthly refills

3. Which of the following patients is in the most need of referral to the pharmacist for medication adherence counseling today?

- a. Patient who consistently fills all RA medications each month
- b. Patient who has a low monthly copay for all RA medications
- c. Patient who complains at checkout that he doesn't feel his RA medications are

controlling his symptoms

- d. Patient who mentions at checkout that she has a strong understanding of her RA medications thanks to previous counseling by the pharmacist

4. What is the most important goal of medication adherence counseling for the patient from question 3?

- a. Provide the patient with resources to decrease medication cost.
- b. Help the patient to choose a medication adherence app that offers dose reminders.
- c. Explaining the potential adverse effects associated with the medication
- d. Exploring the patient's perception of the efficacy and necessity of the medication and providing education where needed

5. Which of the following are most commonly affected in patients with rheumatoid arthritis?

- a. Shoulders, wrists, elbows
- b. Feet, wrists, hands
- c. Ankles, hips, the spine
- d. Hands, shoulders, feet

6. Which of the following is most consistent with the typical presentation of RA?

- a. Symmetrical distribution with an insidious onset
- b. Asymmetrical distribution with an abrupt onset

- c. Symmetrical distribution with an abrupt onset
- d. Asymmetrical distribution with an insidious onset

7. When is joint stiffness typically worse in patients with RA?

- a. During the day
- b. During the night
- c. In the morning
- d. No general pattern

8. Which of the following is a biologic agent approved for the management of RA?

- a. Methotrexate
- b. Tofacitinib
- c. Omalizumab
- d. Adalimumab

9. Which of the following is a biologic DMARD that works as a TNF-alpha inhibitor?

- a. Azathioprine
- b. Anakinra
- c. Abatacept
- d. Golimumab

10. Which of the following is a nonbiologic DMARD for the management of RA?

- a. Rituximab
- b. Certolizumab
- c. Hydroxychloroquine
- d. Infliximab

RHEUMATOID ARTHRITIS:

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