Management of osteoarthritis and rheumatoid arthritis in adults

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Author Disclosures: Brittany Hoffmann-Eubanks and the *DSN* editorial and continuing education staff do not have any actual or potential conflicts of interest in relation to this lesson.

Universal program number: 0401-0000-16-011-H01-P
CE Broker tracking number: 20-583784
Activity type: Knowledge-based
Initial release date: Dec. 19, 2016
Planned expiration date: Dec. 19, 2019
This program is worth two contact hours (0.2 CEUs).

Target Audience
Pharmacists in community-based practice.

Program Goal
To review epidemiology, etiology, pathophysiology, diagnosis and treatment of osteoarthritis and rheumatoid arthritis in adults.

Learning Objectives
Upon completion of this program, the pharmacist should be able to:

1. Describe the prevalence and clinical presentation of osteoarthritis and rheumatoid arthritis in the U.S. population.
2. Identify common risk factors for the development of osteoarthritis and rheumatoid arthritis.
3. Evaluate current treatment options for osteoarthritis to make appropriate drug therapy recommendations.
4. Evaluate current treatment options for rheumatoid arthritis to make appropriate drug therapy recommendations.
5. Design a therapeutic plan for a patient with osteoarthritis or rheumatoid arthritis using patient specific data.

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INTRODUCTION

It is estimated that 52.5 million adults, or approximately 1-in- 5 U.S. adults has clinically diagnosed arthritis.[1] Arthritis is a general term that includes more than 100 different rheumatic diseases and conditions. Arthritis is a disease that commonly is thought to target the elderly; however, it affects individuals of all ages. Risk of arthritis increases with age; however two-thirds of people with arthritis actually are younger than 65 years of age.[1-2] Arthritis is more common in women than men (29% versus 19%, respectively) and includes all racial and ethnic groups. The number of adults with arthritis is expected to increase to 78 million by the year 2040.[2] Arthritis is more common in patients with other conditions, such as heart disease, diabetes, high blood pressure and obesity [1-2] (see Figure 1). For example, about 49% of adults with heart disease and 47% of adults have arthritis. Patients who have comorbid conditions along with arthritis experience more complicated disease-state management that often results in lower quality of life.

Arthritis is the most common cause of disability among U.S. adults. [1-4] Approximately 22.7 million U.S. adults report limitations in their activities due to arthritis.[3] For example, 6 million adults report an inability to walk a quarter mile, 14 million report limitations in bending or kneeling and 8 million have difficulty climbing stairs. In addition to the physical limitations, patients also report less socialization with friends and family as a result of their mobility concerns.

As mentioned above, arthritis is a large general term that includes more than 100 different rheumatic diseases. This lesson will focus on two of the most common rheumatic conditions — osteoarthritis, or OA, and rheumatoid arthritis, or RA.

EPIDEMIOLOGY

Osteoarthritis

Osteoarthritis is the most prevalent joint disease in the United States, affecting approximately 27 million Americans.[4-7] Overall, OA affects 13.9% of U.S. adults ages 25 years and older, and 33.6% of those ages 65 years and older. [4] Further prevalence data can be broken down based upon the definition of OA, specific joints involved and characteristics of the patient population (see Table 1). Osteoarthritis is a progressive disorder that often develops over years in patients whose symptoms may remain stable for long periods during this time.[7] Osteoarthritis can occur in any joint of the body; however, most commonly it is found in the small joints of the hands, knees, spine, hips or feet. After 50 years of age, women become more likely than men to be affected by OA. [4]

Rheumatoid arthritis

Rheumatoid arthritis is the most common systemic inflammatory autoimmune disease in the United States.[8-9] The most recent prevalence data in the United States comes from the Rochester Epidemiology Project in Minnesota.[10] From 1995 to 2007, 41 per 100,000 people were diagnosed with RA yearly. Incidence rose with age — 8.7 per 100,000 of people ages 18 years to 34 years, and 54 per 100,000 of people ages 85 and older.[10] Data also showed a peak from ages 65 years to 74 years, with 89 per 100,000 people of all estimated ages adjusted to the 2000 U.S. population.[10] Another study from the Minnesota data estimated a lifetime risk for RA at 4% for women and 3% for men.[11] It is impor-

tant to note that due to the demographics of the population area containing Minnesotan adults, the data cannot be generalized beyond Caucasians. Globally, rheumatoid arthritis affects about 1% of the population.[12] Rheumatoid arthritis has a significant impact on a patient's ability to perform activities of daily living, such as work and home activities; also, it increases mortality.[13-15] Approximately one-third of patients are work-disabled within two years of disease onset, and approximately 50% are work-disabled after 10 years.[12] In 1997, RA accounted for 22% of all deaths due to arthritis and other rheumatic conditions in the United States.[8] Notably, cardiovascular mortality appears to be 1.5-fold higher in patients with RA compared with the general population as a result of CV risk factors and RA disease-related risk factors.[12] Rheumatoid arthritis is a complicated exchange between chance, genes and the environment.[16] Twin studies, for example, have revealed a strong genetic disposition for RA with concordance rates of 15% to 30% in monozygotic twins and 5% in dizygotic twins.[12,16-17] The concordance rates among twins can only be applied in the context of prevalence of disease related to heritability. Data from another study suggest that 50% to 60% of disease among twins is related to the environmental and genetic sharing that takes place among twins.[18] There is a well-documented association between RA susceptibility and differences in human leukocyte antigen, or HLA,-DRB1 alleles, particularly among those positive for certain autoantibodies, such as rheumatoid factor, or RF, and anti-citrullinated protein antibody, or ACPA.[12,16-17]

Table 1
Average annual prevalence of osteoarthritis in the ambulatory healthcare system in the United States from 2001 to 2005

OSTEOARTHRITIS CLASSIFICATION	AUTHOR	AGE IN YEARS	MILLIONS AFFECTED	GENDER AFFECTED IN MILLIONS
Knee	Dillon et al 1994	≥ 60	37.4	42.1 female; 31.2 male
	Leyland et al 2012	≥ 60	47.8	-
	Felson et al 1987	≥ 45	19.2	19.3 female; 18.6 male
	Jordan et al 2007	≥ 45	37.4	42.1 female; 31.2 male
	Felson et al 1987	≥ 26	4.9	4.9 female; 4.6 male
Hip	Jordan et al 2009	≥ 45	28	25.9 female; 25.4 male
Symptomatic radiographic OA in the hand (per 100)	Zhang et al 2002	≥ 26	6.8	9.2 female; 3.8 male
	Dillon et al 2007	≥ 60	8 overall	-
Radiographic knee OA (per 100)	Dillon et al 1994	≥ 60	12.1	10 female; 13.6 male
	Felson et al 1987	≥ 45	6.7	7.2 female; 5.9 male
	Jordan et al 2007	≥ 45	16.7	18.7 female; 13.5 male
	Felson et al 1987	≥ 26	4.9	4.9 female; 4.6 male
Radiographic hip OA (per 100)	Felson et al 1987	≥ 45	8.7	9.3 female; 9.2male

Information from resource 4: Centers for Disease Control and Prevention. Arthritis: Osteoarthritis (OA). Available from: http://www.cdc.gov/arthritis/basics/osteoarthritis.htm. Accessed 17 July 2016. OA=osteoarthritis

ETIOLOGY AND PATHOLOGY

Osteoarthritis

Osteoarthritis is commonly referred to as a "wear and tear" disorder of the joints focusing on the loss of cartilage; however, now it is widely accepted that the disease process involves the entire joint.[19] In addition to loss of cartilage, there is remodeling of subarticular bone, ostephyte formation, ligamentous laxity, weakening of periarticular muscles and, in some cases, synovial inflammation.[20] It has been suggested that these changes may occur due to an imbalance between the breakdown and repair of joint tissue.[19-20] Osteoarthritis is categorized into two major classes— primary (idiopathic) OA in which there is no identifiable cause, and secondary OA, which is associated with a known etiologic cause. Development of OA is a complex multifactorial process that includes both modifiable and nonmodifiable risk factors (see Table 2).

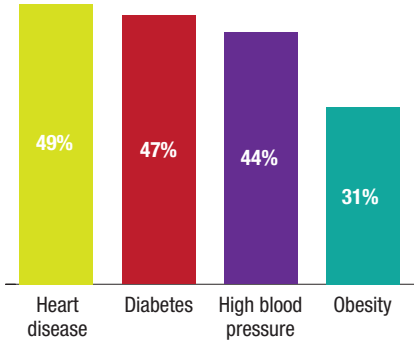
Obesity

Obesity is one of the most important preventable risk factors for the development of OA.[5-6] In early analysis, questions arose as to whether obesity preceded osteoarthritis development and was indeed confirmed with a greater risk found in women compared with men.[5] More recently, a 2010 meta-analysis showed that those who were obese or overweight had a 2.96 higher risk of knee OA compared with those of normal weight (95% CI 2.56 to 3.43).[21] Additionally, from the same meta-analysis, those in the "overweight" body mass index, or BMI, category had double the risk of developing incident knee OA compared with the population with normal weight. Risk of incident knee OA increases with increasing BMI regardless of knee alignment.[22] The Framingham study showed that women who lost about 5 kg had a 50% reduction in risk of developing symptomatic knee OA,[6,22] and was confirmed in a more recent meta-analysis.[23] Weight loss also has shown to decrease pain and disability in patients with already-established incident knee OA.[23-24]

Age

Age is one of the strongest risk factors for OA of all joints.[5-6,22,25] The exact mechanism is not known but may be a consequence of cumulative exposure to biomechanical stresses and biological changes making the joint and surrounding tissues less resilient.[22] It is important to note that while OA occurs from a combination of factors, including excessive mechanical stress, it is not a guaranteed outcome of aging.[26] For example, an

FIGURE 1: PREVALENCE OF OTHER CHRONIC CONDITIONS IN ADULTS WITH ARTHRITIS



Adapted from resource 1: Centers for Disease Control and Prevention. "At a Glance 2015: Arthritis." Available from: http://www.cdc.gov/chronicdisease/resources/publications/aag/arthritis.htm. Accessed 17 July 2016.

Table 2
Risk factors for the development of osteoarthritis in adults

OA RISK FACTOR CATEGORY	OA-SPECIFIC RISK FACTORS	
Non-modifiable	Age	Increases with age
	Gender	Women > men
	Race/ethnicity	Varies among racial/ethnic groups
	Genetics	Strong genetic role
Modifiable	Diet	Area for future study
	Obesity	No. 1 risk factor
	Injury/surgery	Knee has strongest risk
	Occupation/sports	Repetitive use of joints increases risk
Other factors	Estrogen deficiency	Complex role of estrogen
	High bone-density	Inverse relationship observed between OA and osteoporosis
	Vitamins C, D and E	Conflicting supplementation evidence
	C-reactive protein	Appear to correlate with pain and stiffness

Information from resources 5,6,7

individual who is more susceptible to OA due to modifiable and nonmodifiable risk factors may not actually experience OA until an injury occurs.

Gender

The female sex is associated with higher prevalence and greater severity of disease.[6,22,27] An observed increase in OA in women during menopause has led to speculation that decreasing estrogen levels may have a role. However, observational studies and clinical trials have resulted in conflicting evidence.[28-30] For example, in the Heart and Estrogen/Progestin Replacement Study, a randomized controlled trial of older postmenopausal women with heart disease, there was no significant difference found in the prevalence of knee pain or disability between the treatment groups (estrogen replacement and placebo).[6,22,29] In contrast, the Women's Health Initiative showed a borderline significance in women using estrogen replacement therapy who were less likely to require total knee or hip arthroplasty, but this association was not seen with estrogen plus progestin compared to placebo. [6,22,30]

Genetics

Several studies have shown an inheritable component to OA (~40% to 65%) with strongest evidence for hand and hip OA compared to knee OA.[6,22,31-33] There have been three loci GDF5, 7q22 and MCF2L that have been linked to OA at genome-wide significance levels. [22,34-36] An additional study identified five new susceptibility loci for OA-implicating chromosomes three, six, nine and 12.[22,37] Pain severity related to OA also is an area of study in which a cohort study found an association with the COMT gene and pain sensitivity in hip OA. Other genes also have been studied, such as TRPV1 and PACE 4 gene Pcsk6, which were associated with knee pain in two meta-analyses.[22,38-39]

Occupation/Injury

Occupations that require repetitive use of joints have been associated with increased risk of OA. A 2011 meta-analysis showed a 1.6-fold increase in risk of knee OA related to occupational activities with the most risk related to activities other than standing.[40] There have been numerous studies that have shown knee injuries are a strong risk factor for OA. Further, two meta-analyses found a four–fold increased risk of developing OA when a knee injury occurred.[41-42]

Rheumatoid arthritis

Rheumatoid arthritis is a common systemic inflammatory autoimmune disease where the exact etiologic cause is unknown. More recently, RA has been regarded as a clinical syndrome with several disease subsets that involve multiple inflammatory cascades that converge into a final pathway leading to characteristic RA damage.[43] It is postulated that RA results from two potential blows —an environmental trigger and genetic susceptibility.[12,44] The first physiologic structure affected by rheumatoid arthritis is the synovium (synovial joint membrane that lines joint capsules and creates synovial fluid for the hands and feet).[12] Such additional inflammatory changes and influx of inflammatory mediators as T-cells and cytokines lead to cartilage and bone destruction and potentially may lead to systemic involvement of multiple organs and tissues.[12,16,45] There are several risk factors associated with the development of RA.

Genetics

Genetic factors account for 50% of risk associated with RA development.[17,43] There are more than 30 genetic regions that have been associated with RA with no major pathogenic insights at this time, excluding HLA and PTPN22.[43]

Female sex

RA is three times more frequent in women than men and highest among women older than 65 years of age.[43] Pregnancy often has been shown to cause remission of RA.[54] Recent data also suggests that postpartum women are less likely to be diagnosed with RA when compared with their nulliparous counterparts.[46] In addition, breastfeeding decreases the risk of RA in women who have breastfed for at least 24 months.[47]

Environmental

Smoking increases the risk of RA by twofold, especially in ACPA-positive disease; the gastrointestinal microbiome also has been shown to be involved in autoantibody production (bacteria dependent).[12, 43,48] Such infectious triggers as Epstein-Barr virus, parvovirus, mycoplasma and proteus have been studied and reviewed, but data has largely been disappointing.[17] Other risk factors that may play a role but in which strong evidence is lacking include alcohol and coffee intake, oral contraceptive use and vitamin D status.[43]

The above-mentioned gene and environment interactions result in the loss of self-tolerance driving the influx of inflammatory mediators and the characteristic destructive processes seen in rheumatoid arthritis. It is important to consider the roles of the adaptive and humoral immune system components in the pathogenesis of RA to understand current and future treatment options for RA.

The adaptive immune system

T-lymphocyte normal creation and development in the thymus leading to activation is very specific and important to the normal process of preventing infection and harm in organisms.[49] Activation of t-helper, or Th, cells requires two steps: The Th cell must recognize cognate antigen displayed by antigen-presenting cells, such as T-cell receptor, or TCR, and IL-2; and a second co-stimulatory signal between CD80/86 via dendritic antigen-presenting cell and CD28 on T-cell.[12,16] Th-cells then begin recruitment, such as Th17, which leads to production of IL-17A, IL-17F, IL-21, IL-22 and TNF-α.[12,16] A pro-inflammatory state is then supported by secretion of growth factors (e.g., IL-1β, IL-6, IL-21 and IL-23) by dendritic cells and macrophages and proliferation of Th17 cells. IL-17A also works

PATIENT SCENARIO 1: OSTEOARTHRITIS

SP is a 78-year-old Caucasian female who presents to the pharmacy with her daughter complaining of hip pain when walking. The patient is wheelchair-bound but can walk short distances with assistance and a transfer belt. The patient and daughter are looking for a recommendation as she is experiencing stiffness in the morning and after prolonged sitting, making her transfers difficult and painful. Patient reports the pain is "achy" when sitting and "sharp" when walking. She states it feels different than the nerve pain in her legs, which is more like "pins and needles." She denies the pain lasting longer than 30 to 60 minutes, but says it "comes and goes" when sitting or transferring. Patient reports she is allergic to penicillin (hives).

History of present illness
- Polio as a child: Unsure of year
- Diabetes: 2000
- Hypertension: 2000
- Dyslipidemia: 2000
- Diabetic neuropathy: 2005
- Status Post Brain Aneurysm: 1995
- Status Post hemorrhagic stroke: 1995
- Left side paralysis s/p hemorrhagic stroke: 1995
- Intermittent aphasia s/p hemorrhagic stroke: 1995

Subjective and objective findings reported
- Weight: 210 lbs.
- Height: 5'5
- BMI: 34.9
- Blood Pressure: 132/82 mmHg, left, sitting
- Pulse: 70 bpm, RRR
- A1c: 6.8%
- Pain: 5 a.m. to 6 a.m., 7 p.m. to 8 p.m. when transferring

Current prescription medications
- Lisinopril: 20 mg daily
- Valsartan: 160 mg daily
- Metformin: 500 mg twice daily
- Gabapentin: 600 mg three times daily
- Aspirin: 325 mg daily
- Atorvastatin: 40 mg at bedtime
- One touch Ultra® test strips: Test twice daily

Current nonprescription medications
- Vitamin B complex: Daily
- Acetaminophen-diphenhydramine: 500-25 mg, two at bedtime

Current orthopedic devices in use
- Four-prong cane to assist with transfer
- Full left leg brace and partial right leg brace
- Right heel lift (leg length discrepancy) s/p polio as a child

Discussion

Current 2012 ACR OA guidelines recommend the combination of nonpharmacologic and pharmacologic interventions in patients with osteoarthritis.

Nonpharmacologic: The patient should receive patient education regarding osteoarthritis. In addition, due to this patient's limited mobility after suffering from a hemorrhagic stroke, a referral to a physical therapist is necessary to create an appropriate exercise and/or strength-building program. Weight loss also should be considered in this patient, as SP's BMI is 34.9. A referral to a registered dietitian also may be appropriate to assist with weight loss due to the patient's limited mobility. The patient should be assessed for psychosocial interventions as warranted.

Pharmacologic: In patients with hip OA, initial first-line management may consist of acetaminophen, oral NSAIDs, tramadol or intraarticular corticosteroid injections per the 2012 ACR OA guidelines. This patient's previous stroke history excludes the use of NSAIDs due to the risk of a future heart attack and/or stroke. Furthermore, this patient has additional risk of cardiovascular events due to her diabetes status. Recent data also suggests that acetaminophen may not be helpful in the treatment of OA pain. A practitioner may choose to start with adding on additional acetaminophen during the day (max of 4000 mg/day total) due to its safety profile and low cost. If SP has a suboptimal response to acetaminophen, the practitioner may then escalate therapy by stepping up to intraarticular injections or tramadol. Duloxetine also may be a preferred adjunctive agent in this patient due to her neuropathic pain. The patient should be counseled on the importance of not exceeding 4000 mg total per day of acetaminophen, including her acetaminophen-diphenhydramine she uses at bedtime. Appropriate follow-up should occur to assess efficacy of nonpharmacologic and pharmacologic interventions with the goal of minimizing pain and preventing advanced joint damage.

with TNF-α to promote activation of fibroblasts and chondrocytes.[12,16] Interestingly, direct T-cell targeting by cyclosporine or T-cell-depleting mechanisms has not been shown to be a very effective treatment.[16,50] However, there currently is an effective treatment that utilizes cytotoxic-lymphocyte-associated antigen 4 with the Fc fragment of IgG1 to disrupt the presentation of antigen by blocking the co-stimulatory signal mediated through CD28 with CD80/86.[16] Another pathway is the activation of macrophages and fibroblasts via contact by T-cells involving CD40, CD40 ligand, CD200, CD200 ligand, intracellular adhesion molecule 1 and leukocyte-function-associated antigen.[16]

The humoral immune system

Humoral immune system cells also play an important role, including macrophages, mast cells and natural killer cells.[12,16] Macrophages are activated by granulocyte colony stimulating factor and granulocyte-macrophage colony stimulating factor via toll-like receptors and nucleotide-binding oligomerization domain-like receptors.[12,16] TNF-α, IL-1, 6,12,15,18 and 23 are secreted and involved in the release of degradation enzymes, phagocytosis, antigen presentation and reactive oxygen intermediates that further the inflammatory cascade in RA.[12] TNF-α and IL-6 are the two primary focus areas of the pathogenesis of RA. TNF-α has a wide variety of functions, including activation of cytokines, chemokine expression, endothelial-cell adhesion molecules, protects fibroblasts, promotes angiogenesis, suppresses regulatory T-cells and promotes pain[12]. IL-6 also is widely utilized and promotes leukocyte activation and autoantibody production, and contributes to anemia, cognitive dysfunction and dysregulation of lipid metabolism.[12,16] Further, both factors are implicated in osteoclast activation and differentiation.[12,16]

CLINICAL PRESENTATION AND DIAGNOSIS

Osteoarthritis presentation

OA most commonly presents in patients ages 50 years and older, and has an insidious onset over a period of many months to years.[7] Since the primary symptoms of OA are joint pain, stiffness and limitation of movement, pain is usually the first symptom that leads patients to seek out their primary care physician, or PCP.[7, 10-11] Pain is generally characterized by patients as deep and aching, and the stiffness or pain usually resolves in less than 30 minutes,

unlike rheumatoid arthritis. OA pain may be weather related and can result in severe limitations of activities of daily living. OA pain typically affects one to a few joints at a time, develops over a long period of time, is increased by joint use and impact and can worsen after rest ("gelling"), with variable intensity throughout the day and week.[51] In advanced disease, pain may be consistent even during periods of rest. Moreover, patients who seek out their PCP also report difficulty or limitations in activities of daily living, such as walking, climbing stairs and completing household chores.[7] In addition to pain, physical manifestations of OA that can be observed are crepitus with movement (grating sound or sensation produced by friction between bone and cartilage), joint-line tenderness, bony swelling, deformity (late disease), joint space narrowing and presence of osteophytes.[51]

Osteoarthritis diagnosis

Patients with OA are evaluated based upon their history, physical examination, radiographic findings and extent of joint involvement. The joints most commonly affected are the hands, knees, hips and spine, but nearly any joint can be involved (see Table 3).[52,59]

OA is commonly asymmetric, affecting one joint severely, such as the hip, with practically normal function of the other. OA is primarily a clinical diagnosis that can be made by healthcare providers based upon a history and physical examination.[7,51-52] Laboratory tests and radiographic examinations are not routinely required for diagnosis if presentation is typical with respect to signs and symptoms based upon the following criteria:[51]

- Persistent usage-related joint pain in one or a few joints;
- Age 45 years and older; and
- Only brief morning stiffness (≤ 30 minutes).

Clinicians may feel confident of an OA diagnosis in the presence of other risk factors mentioned above (i.e., obesity and age). However, clinical judgment should be exercised, along with appropriate imaging and laboratory assessments, if patients present with atypical signs and symptoms (e.g., pain for 45 minutes or longer and significant joint inflammation), weight loss or are ages 45 years or younger and absent any major joint trauma.[51] Laboratory testing may be conducted in some cases to rule out other diseases, such as rheumatoid arthritis (e.g., ACPA or RF) and gout (uric acid).[7] Additionally, markers of inflammation, such as erythrocyte sedimentation rate, or ESR, and C-reactive protein, or CRP, are generally within normal limits in patients with OA, synovial fluid lacks crystals and white blood cell counts are less than 1500 cells/μL.[7, 52]

False-positive results may be possible; thus, it is important for healthcare providers to consider the purpose of the test and the potential for unnecessary confusion due to results in patients who have a low probability of gout or autoimmune arthritis.[7]

Table 3
Signs, symptoms and examination findings of osteoarthritis

JOINT	SIGNS AND SYMPTOMS	JOINT EXAMINATION FINDINGS	RADIOLOGIC EVALUATION
Knee	Pain with climbing stairs Genu varum ("bow-legged") Transient joint effusion	Deformity Local tenderness Bony proliferation Occasional synovitis Limited motion	Early mild OA: • Radiographic changes often absent Progressive OA: • Joint space narrowing • Subchondral bone sclerosis • Marginal osteophytes Late OA: • Abnormal alignment of joints • Effusions
Hip	Groin pain with weight-bearing exercises Stiffness after activity Limited joint movement		
Hand	Pain with movement Crepitus with movement Limited movement		
Feet	Typically involves the first metatarsophylangeal joint (big toe) Additional joints also may be affected		

Adapted from resources 52 and 59

Rheumatoid arthritis presentation

The pathogenic process of RA development is complex and multifactorial. The hallmark characteristics include presence of pannus (synovial hyperplasia), cartilage damage and bony erosion.[12,16-17,53] Approximately 80% of patients are affected with these hallmark issues within one year of diagnosis.[12] Patients typically present with pain and stiffness in multiple joints. The most common areas involved in the body are the wrists, proximal interphalangeal joints and metacarpophalangeal joints.[54] Morning stiffness that lasts longer than one hour is a defining characteristic of RA. Patients often present with visible "boggy" swelling or subtler synovial hyperplasia that can be palpated upon examination.[54] Patients also may complain of such systemic symptoms as fatigue, weight loss and low-grade fever with active disease. RA also is associated with several systemic complications that, for the purpose of this lesson, will not be discussed in detail but have been reviewed elsewhere.[12] It appears that prolonged inflammatory mediators due to the loss of tolerance contributes to the extra-articular involvement. Further, extra-articular involvement appears to increase mortality with men being affected higher than woman.[12,55] As discussed earlier in this lesson, the majority of deaths in patients with RA seem to be related to cardiovascular disease that isn't otherwise explained by traditional risk factors (e.g., hypertension, diabetes and dyslipidemia).[12,16,56]

Rheumatoid arthritis diagnosis

The diagnosis of RA is primarily based upon physical examination findings.[12,16,54] In 2010, the American College of Rheumatology, or ACR, and the European League Against Rheumatism, or EULAR, worked collaboratively to update the current RA classification criteria.[57] The purpose of the new 2010 criteria was to address the gap of the 1987 ACR classification criteria, which poorly identified patients with early arthritis that may develop into RA.[12,43,54,56] Patients who are identified earlier in the disease process have been shown to have better outcomes, specifically with respect to erosive joint damage and extra-articular disease, which may be prevented or delayed with proper therapeutic treatment.[43] The new criteria are intended to be used to identify clinical trial patients, differentiate patients with synovitis and determine the group at highest risk for developing persistent or erosive RA.[12,57] In addition, the ACR/EULAR criteria authors also developed an algorithm for practitioners to classify definite RA.[57]

Diagnostic tests also may aide in the diagnosis of RA due to the common presence of such autoantibodies as rheumatoid factor, or RF, and anti-citrullinated protein antibody, or ACPA.[54] ACPA is more specific to RA and when present may be prognostic for increased joint disease and lower remission rates.[43,54] Approximately 50% to 80% of patients with RA have RF, ACPA or both.[43] Additionally, CRP and ESR, both of which are inflammatory markers, have been added to the new ACR/EULAR classification criteria since they are frequently elevated in RA patients and useful for disease activity and therapeutic monitoring.[54,57] Additional tests that may be ordered prior to treatment include a complete blood cell count with differential, assessment of renal and hepatic function, assessment of hepatitis C, hepati-

PATIENT SCENARIO 2: RHEUMATOID ARTHRITIS

KP is a 63-year-old male who presents to his primary care physician complaining of swelling and stiffness in his fingers, especially by "his knuckles," that is prolonged and painful. He states he has tried acetaminophen without relief for the last six weeks but his hands still hurt and don't seem to be getting better. He reports that tasks that used to be easy, such as writing with a pen, now are difficult and painful. The stiffness he experiences lasts several hours every day. The patient states he is worried he has rheumatoid arthritis as his mom does. The patient denies any allergies to any medications.

History of present illness
- Hypertension: 2010
- Hyperlipidemia: 2012
- Depression: 2005

Objective data obtained at today's visit:
- Weight: 180 lbs.
- Height: 6'0"
- BMI: 24.4
- Blood pressure: 150/89 mmHg, sitting, right
- Pulse: 75 bpm, RRR
- Pain: 7 bilateral MTC joints
- Smoker: 1/2 pack per day

Current prescription medications
- Citalopram: 40 mg daily
- Rosuvastatin: 20 mg daily
- Amlodipine: 5 mg daily

Current nonprescription medications
- Men's multivitamin: Daily
- Garlic: Daily
- Acetaminophen: 500 mg, one to two tablets every six hours as needed

Discussion

KP is presenting with common symptoms of OA and/or RA. The patient's pain lasts longer than 30 minutes and is not reported to improve with rest, suggesting that osteoarthritis may not be the correct diagnosis. The patient's age, smoking status (environmental trigger) and family history (genetic susceptibility) are all risk factors for the development of RA. Further evaluation of KP should take place to determine if the patient has RA or another condition with a similar presentation. The 2010 ACR/EULAR Criteria may be used to determine if the patient fits the early or defined RA classification, and additional laboratory tests may be conducted to aid in diagnosis. For example, such autoantibodies as RF and ACPA may be present in up to 50% of patients with RA. Additional inflammatory markers, such as ESR and CRP, also may be evaluated to determine diagnosis and/or prognosis. Once a proper RA diagnosis has been established, the updated 2015 ACR RA guidelines recommend a treat-to-target strategy regardless of the patient's disease activity. Patients with low disease activity naïve to DMARDs are recommended to receive monotherapy with a DMARD, such as methotrexate. The patient's response to therapy and disease status should be monitored frequently in the beginning (every two to four weeks). If the patient has a suboptimal response to treatment with continued disease activity (moderate to high), they can then be escalated on a treat-to-target strategy, and such additional agents as hydroxychloroquine, leflunomide or sulfasalazine may be added. The patient is again assessed for response and disease activity and, if still suboptimal, will be escalated in therapy utilizing biologics. Traditional DMARDs and biologics have a wide variety of serious adverse effects associated with them, and selection of therapy should be initiated on a case-by-case basis with the practitioner and the patient involved in the decision-making process. Patients should receive proper counseling on prescribed disease-modifying anti-rheumatic drugs adverse effect profile(s) and any necessary pretreatment tests.

tis B and tuberculosis.

TREATMENT AND MANAGEMENT -OA

In 2007, the FDA published a request for proposals to conduct analysis of various clinical issues related to OA.[58] The Osteoarthritis Research Society International, or OARSI, was selected to respond, and in 2008 formed several committees and working groups to answer the FDA's questions.[59] One of the major areas of opportunity identified with respect to treatment is the heterogeneity of OA and subsequent difficulty in classifying patients into subgroups based upon phenotypes.[59] As a result, targeting of clinical trials with respect to pharmacologic therapies has been challenging, leading to modest effect sizes of current drug therapies. According to the OARSI-FDA collaboration group, future advances in OA phenotypes and evaluation mechanisms — beyond pain and disability — will help increase the specificity of treatment selection.[59] In 2012, the ACR published updated guidelines for the use of nonpharmacologic and pharmacologic therapies in OA of the hand, hip and knee.[60] Unlike previous versions of the guidelines, the 2012 OA recommendations do not recommend the sequence of subsequent interventions for those failing to have an adequate response to initial therapies, citing lack of high-quality studies. In order to develop recommendations that are as evidenced based as possible the Grading of Recommendations Assessment, Development and Evaluation, or GRADE, methodology was implemented. The OA ACR authors cite the adoption of this approach by the World Health Organization, or WHO; the Cochrane Collaboration; the agency of Health Care Research and Quality, or AHRQ; and numerous other professional organizations, including the ACR.[60] The intended purpose of the guidelines is to provide an update to management of hip and knee OA and create new recommendations for the management of hand OA. The OA ACR authors caution healthcare providers not to use the guidelines in a "cookbook" fashion, but instead to guide practitioners. Goals of therapy are to:

1. Educate the patient, family members and caregivers;
2. Relieve pain and stiffness;
3. Maintain or improve joint mobility;
4. Limit functional impairment; and
5. Maintain or improve quality of life.[60-62]

Treatment of OA generally consists of four intervention categories:

1. Nonpharmacologic;
2. Pharmacologic;
3. Complementary and alternative; and
4. Surgical.

Patients with OA should receive some form of intervention from the nonpharmacologic and pharmacologic categories.[52] Surgical interventions should be reserved as a last line for patients who fail pharmacologic therapy, suffer from intractable pain and experience a loss of function.[52]

Nonpharmacologic interventions- OA

All patients with OA should receive patient education about the disease process, treatment and prognosis. Patient education is a crucial component of the treatment process in that patients often see OA as a normal part of the aging process where little or nothing can be done to alleviate symptoms

or progression of the disease. The 2012 ACR and British guidelines encourage an exercise regimen that can consist of aquatic, aerobic and/or resistance land-based activities.[60,63] The ACR guidelines do not recommend one form of exercise over another; instead, the patient's preference and physical ability should be used to guide the decision process. Weight loss also should be recommended when possible, particularly if the patient is overweight or obese.[7,52] Recent randomized control trials have shown that weight loss as small as 4% can reduce pain, improve physical function, and even have positive effects on cartilage structure.[7,64-66] Referral to an occupational or physical therapist also may be considered to help tailor exercise regimens, assess muscle strength and stability and recommend such joint protection modalities as canes, walkers and braces. Other alternative treatment modalities with scant evidence and small effect size include insoles, lasers, transcutaneous electrical nerve stimulation, ultrasound, electrotherapy and acupuncture.[7,67-71] Heat and ice are additional options that have been shown to be effective, and appropriate counseling should take place to ensure patients avoid burns from heat or frostbite from cold therapies.[7,72]

Pharmacologic therapy-OA

Acetaminophen

Traditionally the mainstay of mild osteoarthritis treatment has been the use of acetaminophen. It is an inexpensive agent, generally considered safe, and is effective.[52] A 2006 Cochrane review determined that acetaminophen was more effective than placebo, equal to nonsteroidal anti-inflammatory drugs, or Intra s, and had fewer gastrointestinal side effects.[52,73] In contrast, a 2016 network meta-analysis concluded that there was no role for single-agent paracetamol (acetaminophen) for the treatment of patients with osteoarthritis regardless of dose.[74] The authors stated that even though paracetamol has been on the market for more than 50 years, the efficacy of the drug has never been properly established or quantified in chronic disease and thus, most likely not as useful as once believed.[74] Since this meta-analysis was published in May 2016 and the most recent 2012 ACR OA guidelines still support the use of acetaminophen as a first-line agent, it is very likely that practitioners may still recommend its use due to the safety profile, long-term experience with the drug and low cost. The risk versus benefit should be taken into account when recommending acetaminophen compared with other oral pain relievers with respect to this new evidence and efficacy.

Oral NSAIDs

In knee and hip OA, the 2012 ACR OA guidelines include NSAIDs as an alternative first-line therapy to acetaminophen in patients who do not respond to, or who have contraindications to, the use of acetaminophen. Additionally, patients who have had an upper GI bleed in the past (>1 year) are strongly recommended to receive a selective cyclooxygenase 2 (COX-2) inhibitor or a nonselective NSAID in combination with a proton-pump inhibitor (PPI). Patients who have had an upper bleed within the last year should be initiated on a selective COX-2 inhibitor with a PPI. In chronic management of patients with knee and hip OA, a PPI should be considered for all patients to reduce the risk of developing GI events. Patients who are using low-dose aspirin (<325 mg) in whom an oral NSAID is recommended, a nonselective NSAID (besides ibuprofen) should be initiated. This recommendation came partly as a result of a FDA warning for concomitant ibuprofen and aspirin leading to lower efficacy of aspirin in cardioprotection and stroke protection due to a known pharmacodynamic interaction.[60] NSAIDs should not be used in patients with stage IV and V chronic kidney disease, and conservatively based on an individual patient basis in stage III.

NSAIDs also_should not be used in patients with contraindications to these agents and appropriate caution should be exercised with respect to gastrointestinal adverse effects and cardiovascular risk, especially in patients ages 75 years and older. In July 2015, the FDA strengthened its warning of heart attack and stroke risk for NSAIDs.[75] Previously in 2005, a boxed warning was added to NSAID prescription drug labels for heart attack and stroke risk. Recent data reviewed by the FDA now suggests that previous cardiovascular history is not necessary for patients to be at risk of an event that could lead to death.[76-78] Previous thought also included that patients would be at increased risk with long-term NSAID use. However, the new FDA warning now states that risk of heart attack or stroke can occur early in the first few weeks with risk increasing with longer use and higher doses.[76] In addition, it also was understood that the risk among NSAIDs as a total class was similar or no different; however, recent data the FDA reviewed suggests that some NSAIDs may have greater risk than others requiring future research to determine relative risk.[76] Patients should be instructed to seek medical attention immediately if they experience chest pain, shortness of breath or trouble breathing, weakness in one part or side of their body or experience slurred speech.[76]

Topical NSAIDs

Topical NSAIDs are preferred in patients who are ages 75 years and older due to their limited absorption and low GI risk for knee OA as an alternative to or if a patient has failed acetaminophen.[60]

Intra-articular corticosteroid injections

Intra-articular corticosteroid injections are recommended in knee and hip OA as an alternative first-line agent when patients have failed acetaminophen and NSAIDs.[60] Intra-articular corticosteroids are considered safe and well-tolerated, and frequency should be limited to no more than every three months due to the risk of systemic side effects.[52,79] Patients should be counseled that they may experience a flare-up in the first 24 hours after injection, with expected improvement from baseline at 48 hours.[52] Patients can expect the effects of the corticosteroid injection to provide short-term relief lasting approximately four to eight weeks.[52]

Tramadol

Tramadol is recommended as an alternative first-line agent in patients for hand, hip and knee OA who have failed treatment or contraindications are present for acetaminophen, NSAIDs and intra-articular injections.[60] Additionally, tramadol can be combined for improved pain control with acetaminophen or NSAIDs. Patients should be counseled on the risk of such common adverse events as drowsiness, dizziness and constipation. Patients also should be instructed to avoid operating heavy machinery or driving while using tramadol.

Topical capsaicin

Topical capsaicin may be considered as a first-line alternative agent in hand OA by the 2012 ACR OA guidelines.[60] The guidelines do not recommend in the use of hip or knee OA. Clinical evidence is limited to small studies that showed a small improvement in pain but is an acceptable alternative for patients who cannot use oral NSAIDs due to the low risk of side effects (i.e., skin irritation, burning, etc.).[79-80]

Opioid analgesics

The 2012 ACR OA guidelines reserve opioid analgesics as a last line of therapy in patients who have not responded adequately to first-line agents or in those with intractable pain who are unwilling to undergo — or are not candidates for — total joint arthroplasty.[60] The authors further suggest that practitioners should follow the recommendations of the American Pain Society/American Academy of Pain Medicine for chronic management of noncancer pain.[81]

Duloxetine

Duloxetine is recommended as adjunc-

tive therapy in patients with OA who have had a partial response to acetaminophen or NSAIDs.[60,79, 82-83] Patients who suffer from neuropathic pain and/or depression may make duloxetine a preferred second-line agent. Common side effects associated with duloxetine are nausea, vomiting, constipation and nominal blood-pressure increases.

Complementary and alternative medicine-OA

Effectiveness of acupuncture for OA was reviewed in a meta-analysis where a short-term benefit was observed but considered clinically irrelevant by the authors.[52,84] Glucosamine and chondroitin are conditionally not recommended by the authors of the 2012 ACR OA guidelines.[60] The authors cite heterogeneity in effect size, lack of efficacy and lack of prescription quality preparations in their decision. Their decision also was based on multiple studies and meta-analyses that affirm the lack of efficacy for glucosamine and chondroitin.[85-89] In spite of this evidence, both nonprescription agents still are widely used by the public within the United States as nutritional supplements. In contrast, a 2015 Cochrane review of chondroitin in osteoarthritis concluded that chondroitin, alone or in combination with glucosamine, was better than placebo in improving pain in patients with OA in short-term studies.[90] The authors recommended further studies to explore the role of chondroitin in the treatment of osteoarthritis.

TREATMENT AND MANAGEMENT -RA

In the past, RA treatment primarily consisted of symptom and pain control utilizing NSAIDs.[91] However, NSAIDs have lost their first-line treatment due to concerns of limited efficacy, inability to prevent long-term bone/cartilage damage and gastrointestinal and cardiovascular side effects.[43,95,97] Instead, management with NSAIDs for pain and inflammation should utilize short-acting agents for the shortest period of time combined with proton-pump inhibitors to minimize risk.[43,54] Additionally, a 2011 Cochrane review found that, when used at inflammatory arthritis doses — excluding inflammatory doses of aspirin — NSAIDs can be safely combined with methotrexate, or MTX.[98] Furthermore, in the last decade, there have been significant developments in the treatment of RA, increasing options for pharmacologic intervention and making disease remission a realistic goal.[99] Remission is defined by the 2015 ACR RA panel as "a tender joint count, swollen joint count, C-reactive protein level (mg/dL) and patient global assessment of ≤1 each or a simplified disease activity score, or DAS, of ≤3.3".[9] The 2015 ACR RA guidelines stratify treatment into early RA, which is disease duration shorter than six months; established RA, which is disease duration longer than six months; or meet 1987 ACR RA criteria .[9] Further, the ACR panel identifying early RA as its own separate treatment category is directly related to evidence that suggests a delay in treatment is a prognostic factor for poor treatment response.[95,99-101] DMARDs are the mainstay of treatment; current traditional DMARDs and biologics available for RA treatments in the United States are reviewed in Table 5. In January 2016, the ACR published updated guidelines for the treatment of rheumatoid arthritis, citing the rapid availability of new evidence, new treatment modalities, advancement of guideline methodologies and the need to broaden its 2012 recommendations.[9,91] The new ACR RA guidelines focused on six key areas:

1. Use of traditional disease-modifying anti-rheumatic drugs, or DMARDs, biologic DMARDs ("biologics") and tofacitinib;
2. Use of glucocorticoids;
3. Use of biologics and DMARDs in high-risk populations;
4. Use of vaccines in patients starting or receiving DMARDs or biologics;
5. Screening for tuberculosis, or TB, with respect to biologics or tofacitinib; and
6. Laboratory monitoring for traditional DMARDs.

The new ACR RA guidelines are further distinguished by their methodology using GRADE and a group consensus process citing its internationally accepted systematic approach to guideline development. [9,92-94] The intended purpose of the new ACR RA guidelines is to provide direction for clinicians and patients in a rapidly advancing environment in the context of treatment of RA.

In the previous 2012 update to the 2008 ACR RA guidelines, it was important to identify features associated with poor prognosis to facilitate escalation of treatment when necessary.[91] Poor prognosis is associated with functional limitation on standardized health questionnaires, extra-articular disease, positive RF, positive ACPA or bony erosion documented by radiograph.[91,95] This stratification measure of poor prognosis in the context of disease activity has been removed in the new 2015 ACR RA guidelines with an exclusive treat-to target strategy regardless of disease activity level, with the ideal target being remission or LDA as determined by the clinician and patient.[9] The 2015 ACR RA Guideline Panels justified the removal of "prognosis," believing it is already largely addressed in disease activity with little gained in the clinically relevant decision-making process.[9] Rheumatoid arthritis disease activity measures are recommended to be implemented into practice, and for RA to be characterized based upon level of disease activity:

- Low-disease activity, or LDA;
- Moderate-disease activity, or MDA;
- High-disease activity, or HDA; or
- Remission.[9,96]

For the purpose of this lesson, these disease activity measures will not be discussed in detail but have been reviewed elsewhere.[9,95-96] These validated measures support the treat-to-target strategy and allow practitioners to utilize the ACR RA recommendations to treat RA. [9,91,96]

Pharmacologic treatment- RA

Current goals of therapy include attaining remission or LDA to prevent joint damage, deformity, maintaining quality of life and controlling long-term complications (e.g., extra-articular disease).[54,91,95] It is crucial that practitioners take special precautions in women of child-bearing age, as treatment modalities have harmful effects on conception and pregnancy.[43,54]

Table 4
Drug category and treatment options per the 2015 ACR RA guidelines

RA DRUG CATEGORY	DRUG TREATMENT OPTIONS
DMARD monotherapy*	Typically MTX, but also may be SSZ, HCQ or LEF
Double DMARD therapy	MTX + SSZ, MTX + HCQ, SSZ + HCQ or combinations with LEF
Triple DMARD therapy	MTX + SSZ + HCQ
TNF biologics	Adalimumab, certolizumab pegol, etanercept, golimumab or infliximab
Non-TNF biologics**	Abatacept, rituximab or tocilizumab (excluding anakinra)
Low-dose glucocorticoid	≤10 mg/day of prednisone (or equivalent)
High-dose glucocorticoid	>10 mg/day of prednisone (or equivalent)
Short-term glucocorticoid	<3 months of treatment

*Azathioprine, cyclosporine, minocycline, and gold, were considered but not included in 2015 ACR RA guidelines due to their infrequent use in RA and/or lack of new data since 2012
**Anakinra was considered but not included in the 2015 ACR RA guidelines due to its infrequent use in RA and/or lack of new data since 2012
MTX: methotrexate, SSZ: sulfasalazine, HCQ: hydroxychloroquine, LEF: leflunonide, TNF: tumor necrosis factor
Adapted from resource 9: Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2016 Jan;68(1):1-25

Table 5
Comparison of available disease modifying anti-rheumatic drugs for the treatment of rheumatoid arthritis

MEDICATION CLASS	MEDICATION	PHARMACOLOGY	DOSE AND ROUTE	DOSE	ADVERSE EFFECTS
Traditional DMARDs	Auranofin*	Gold salt; unknown mechanism	Oral	3 mg to 6 mg daily or 3 mg twice daily	Diarrhea Hypersensitivity reactions
	Azathioprine*	Antiproliferative to T- and B-cells	Oral	50 mg to 200 mg daily	Hepatotoxicity Myelotoxicity GI toxicity
	Cyclosporine*	Calcineurin inhibitor decreases IL-2	Oral	2.5 mg/kg to 5 mg/kg per day	Nephrotoxicity Hypertension Hirsutism
	Hydroxychloroquine	Interferes with antigen processing an immune function	Oral	200 mg to 400 mg daily	Rare ocular toxicity (retinopathy)
	Leflunomide	Antimetabolite	Oral	10 mg to 20 mg daily	Hepatoxicity Myelotoxicity Hypertension Teratogenesis
	Methotrexate	Antimetabolite	Oral or Sub-Q	7.5 mg to 25 mg weekly	Hepatotoxicity Myelotoxicity Hair loss Teratogenesis
	Sodium aurothiomalate	Gold salt with unknown mechanism	IM	50 mg weekly	Hypersensitivity reactions Nephritis Fibrosing alveolitis
	Sulfasalazine	Anti-inflammatory/ antimicrobial	Oral	1000 mg to 1500 mg twice daily	Hepatotoxicity Myelotoxicity Hypersensitivity reactions Anemia in G6DP deficiency
Biologic TNF inhibitors	Adalimumab	Human mab	Sub-Q	40 mg every two weeks	Injection-site reactions Opportunistic infections TB
	Certolizumab pegol	Pegylated Fab fragment from humanized mab	Sub-Q	200 mg every two weeks or 400 mg monthly	Injection site reactions opportunistic infections TB
	Etanercept	Recombinant TNF receptor (p75) dimerized on IG frame	Sub-Q	50 mg weekly or 25 mg twice weekly	Injection-site reactions Opportunistic infections TB
	Golimumab	Human mab	Sub-Q	50 mg or 100 mg every four weeks	Injection-site reactions Opportunistic infections TB
	Infliximab	Chimeric mab	IV	3 mg/kg (weeks zero, two and six) then 3 mg/kg to 10 mg/kg every four to eight weeks	Infusion reactions Opportunistic infections TB
Non-TNF biologics	Abatacept	Recombinant CTLA4 molecule dimerized on IG frame; Blocks T-cell costimulation and Th17 cell response/IL-6	IV then Sub-Q (can give Sub-Q without loading dose)	8 mg/kg to10 mg/kg at weeks zero, two and four then monthly or 500 mg to1000 mg IV loading dose then 125 mg Sub-Q within a day, then once weekly	Infusion reactions Opportunistic infections
	Anakinra**	Recombinant IL-1 receptor antagonist	Sub-Q	100 mg daily	Injection-site reactions Opportunistic infections Neutropenia
	Rituximab	Chimeric mab to CD20 for B-cell depletion	IV	1000 mg in two infusions, two weeks apart, repeating every four to eight months	Infusion reactions Opportunistic infections
	Tocilizumab	Humanized mab, IL-6 receptor blockade	IV	8 mg/kg every four weeks	Infusion reactions Opportunistic infections Elevated cholesterol
	Tofacitinib	Cytokine inhibitor	Oral	5 mg twice daily	Serious infections Malignancy Elevated cholesterol Neutropenia

*Not included in the 2015 ACR RA Guidelines due to infrequent use in RA and/or lack of data since 2012
**Not included in the 2015 ACR RA guidelines due to infrequent use in RA and/or lack of data since 2012
Mab = GI= gastrointestinal, Sub-Q = subcutaneous, IV= intravenous, mab= monoclonal antibody
Information from resources 12 and 54

Traditional DMARDs

There are four traditional DMARDs that are recommended by the 2015 ACR RA guidelines for the treatment of RA:

1. Methotrexate;
2. Leflunomide, or LEF;
3. Sulfasalazine, or SSZ; and
4. Hydroxychloroquine, or HCQ.[9]

MTX remains the preferred first-line agent

and should be initiated as soon as disease is first diagnosed.[9] If MTX is contraindicated or not tolerated, LEF, SSZ or HCQ also can be considered as alternative therapy. If disease activity as measured by one of the six validated indices recommended by the ACR RA panel is moderate or high after DMARD monotherapy combination, double or triple DMARD therapy may be considered (see Table 4). Additionally, a TNF inhibitor plus or minus MTX or a non-TNF inhibitor plus or minus MTX may be considered. If a patient has failed either DMARD monotherapy or biologic therapy (plus or minus MTX) with moderate to high disease activity, the patient should then be treated based upon the established RA guidelines. It is important to note that throughout the early and established RA guidelines, short-term glucocorticoids (≤10 mg/day of prednisone or equivalent) may be added for disease flares or in patients with DMARD failure. Glucocorticoids have been shown to reduce synovitis in the short-term and decrease joint damage long-term.[43,102] However, the risk versus benefit does not support routine use due to such adverse effects as infection and osteoporosis. Thus, they are typically used short-term (less than three months) for disease flare-ups and to allow other slow-acting therapies, such as DMARDs, to take effect. Intra-articular glucocorticoids have also been shown to be effective for local treatment of specific active joints.[43,103] Patients should be monitored every two to four weeks for the first three months, every eight to 12 weeks for the following three to six months and every 12 weeks thereafter for 6 months or longer. The 2015 ACR RA panel recommends patients with comorbidities, abnormal laboratory values and/or multiple therapies may require more frequent monitoring.[9] Adverse effects of traditional DMARDs include, but are not limited to, nausea, hepatotoxicity, blood dyscrasias, teratogenesis, nephrotoxicity, hypertension, cancer and infertility. Monitoring should include pretreatment screening (i.e. pregnancy test in women) and such routine follow-up tests as complete blood cell counts and renal and hepatic function tests.

DMARD biologics

Biologic agents include monoclonal antibodies and recombinant receptors to block cytokines that promote the inflammatory cascade (see Table 4).[54] Such TNF inhibitors as adalimumab, certolizumab pegol, etanercept, golumumab and infliximab are first-line among biologic therapy, followed by non-TNF inhibitors abatacept, rituximab and tocilizumab.[43] The biologic agents have been well-studied, and their efficacy has been established.[43,104-110] Biological agents are recommended in patients who have moderate or high disease activity who are already on DMARD monotherapy. Combination with MTX is preferred due to superior combination efficacy over biologic monotherapy.[9] Adverse effects include reactions and infections at infusion and injection sites.[43] TNF inhibitors pose serious risks for the development of tuberculosis, and pretreatment screening should be conducted (e.g., chest radiography or skin test). Hepatitis B and C also should be ruled out prior to treatment with biologics. Infection is the main risk due to the immune suppressive effects of the biologic agents. Risk includes bacterial infections (i.e., sepsis, abscesses) fungal infections (i.e., candidiasis) and viral infections (i.e., herpes zoster).[43] Additionally, cancer risk, especially lymphoma, has been researched and observed risk is increased in severe RA.[111] However, there is not sufficient evidence that the biologic agents increase risk of lymphoma beyond RA alone.[43, 112] The 2015 ACR RA guidelines recommend patients should be monitored every three months for traditional TNF inhibitors and every six months for non-TNF inhibitors due to their longer time for peak onset of action.

Tofacitinib

Tofacitinib is a targeted synthetic DMARD that was approved for the treatment of RA by the FDA in November 2012. It is a novel drug that inhibits janus kinase, or JAK, an intracellular enzyme that regulates cytokine-receptor mediated functions on the cellular membrane.[99] The 2015 ACR RA panel has a conditional recommendation in early RA to use TNF inhibitor monotherapy over tofacitinib monotherapy and TNF inhibitor plus or minus MTX over tofacitinib plus or minus MTX due to low quality of evidence, long-term safety concerns needing further study and shorter experience using tofacitinib.[9] In established RA, tofacitinib is again conditionally recommended as a last-line agent for the same reasons cited in early RA.[9] A 2016 Cochrane review concluded that in patients with incomplete response to methotrexate or other traditional DMARDs TNF-inhibitors were superior to anakinra and tofacitinib.[113] The authors cite that there are very few head-to-head randomized control trials of biologic agents in patients with RA and that further research is needed to evaluate the role of tofacitinib and its long-term safety. The safety of tolfacitinib also is a FDA concern, as a Risk Evaluation and Mitigation Strategy, or REMS, document was issued in 2015 that highlighted concerns for serious infections, malignancies, decreases in peripheral lymphocyte counts, neutrophil counts, hemoglobin and increases in lipid panel parameters associated with tofacitinib.[113] As such, the use of tofacitibib should be considered

PRACTICE POINTS: OSTEOARTHRITIS

- Osteoarthritis is the most prevalent joint disease in the United States affecting approximately 27 million Americans.[4-7]
- Osteoarthritis is commonly referred to as a "wear and tear" disorder of the joints focusing on the loss of cartilage; however, it now is widely accepted that the disease process involves the entire joint.[19]
- Obesity is one of the most important preventable risk factors for the development of OA.[5-6]
- It is important to note that while OA occurs from a combination of factors, including excessive mechanical stress, it is not a guaranteed outcome of aging.[26]
- Pain generally is characterized by patients as deep and aching, and the stiffness or pain usually resolves in less than 30 minutes.
- Future advances in OA phenotypes and evaluation mechanisms — beyond pain and disability — will help increase the specificity of treatment selection, according to the OARSI-FDA collaboration group.[59]

PRACTICE POINTS: RHEUMATOID ARTHRITIS

- Rheumatoid arthritis is the most common systemic inflammatory autoimmune disease in the United States.[8-9]
- More recently, RA has been regarded as a clinical syndrome with several disease subsets that involve multiple inflammatory cascades that converge into a final pathway leading to characteristic RA damage.[43]
- Genetic factors account for 50% of risk associated with RA development.[17,43]
- Gene and environment interactions result in the loss of self-tolerance driving the influx of inflammatory mediators and the characteristic destructive processes seen in rheumatoid arthritis
- Morning stiffness that lasts longer than one hour is a defining characteristic of RA.
- NSAIDs have lost their first-line treatment due to concerns of limited efficacy, inability to prevent long-term bone/cartilage damage, and gastrointestinal and cardiovascular side effects.[43,95,97]

on a case-by-case basis in which the practitioner and patient have weighed the risk versus benefit of treatment.

CONCLUSION

In conclusion, there are millions of adult patients within the United States who suffer from arthritis. Two of the most common forms of arthritis — osteoarthritis and rheumatoid arthritis — can present with similar risk factors and clinical presentation. In order for patients to receive the proper treatment, patients should be thoroughly evaluated, and additional tests conducted as necessary to aid in diagnosis. Early diagnosis has been shown to improve outcomes in both disease states, and treatment guidelines have updated accordingly with aggressive new strategies aiming to reduce erosive joint damage and advanced disease. Research in both disease states must be continued to further the development of novel drug treatment options to meet goals of therapy and improve patient's quality of life.

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Learning Assessment

Successful completion of "Management of osteoarthritis and rheumatoid arthritis in adults" (0401-0000-16-011-H01-P) is worth two contact hours of credit. To submit answers, visit our website at www.DrugStoreNewsCE.com. Please note: Assessment questions submitted online will appear in random order.

1. Risk of arthritis increases with age, but two-thirds of people with arthritis are actually younger than what age?
a. 45 years of age
b. 55 years of age
c. 65 years of age
d. 75 years of age

2. Men are more likely to be affected by osteoarthritis than women after the age of 50.
a. True
b. False

3. What percentage of patients are work-disabled within two and five years once diagnosed with RA?
a. 30% (two years); 50% (five years)
b. 40% (two years); 60% (five years)
c. 50% (two years); 70% (five years)
d. 60% (two years); 80% (five years)

4. Obesity is the most important preventable risk factor for the development of osteoarthritis.
a. True
b. False

5. Which risk factor for the development of OA accounts for approximately 50% of risk?
a. Age
b. Genetics
c. Environment
d. Gender

6. What are the two cytokines that are the primary focus in the pathogenesis of rheumatoid arthritis?
a. TNF-α and IL-1
b. TNF-α and IL-6
c. TNF-α and IL-17a
d. TNF-α and IL-23

7. Although pain in advanced disease can occur during rest, the deep, aching stiffness that is associated with osteoarthritis usually resolves in 30 minutes or less.
a. True
b. False

Learning Assessment

8. RJ is a 56-year-old female patient who presented to her primary care physician with a chief complaint of left hip pain with walking. The patient denies any recent trauma or fever, and states the pain is intermittent and usually resolves in 30 minutes. Are laboratory tests and radiographic examinations indicated for the diagnosis of OA in this patient based upon her clinical presentation?
a. Yes, the patient presented with atypical symptoms of OA.
b. Yes, the patient's duration of pain suggests an inflammatory etiology.
c. No, the patient's duration of pain suggests an inflammatory etiology.
d. No, the patient presented with typical symptoms of OA.

9. Which of the following is not a hallmark characteristic of rheumatoid arthritis?
a. Bony erosions
b. Cartilage damage
c. Crepitus
d. Synovial hyperplasia

10. Patients who are identified earlier in the disease process of rheumatoid arthritis have not been found to have improved outcomes with respect to erosive joint damage and extra-articular disease.
a. True
b. False

11. Which of the following inflammatory markers have been added to the 2010 classification criteria for rheumatoid arthritis since they are commonly elevated?
a. ACPA and RF
b. CRP and RF
c. ESR and ACPA
d. ESR and CRP

12. According to the OARSI-FDA collaboration group, future advances in OA phenotypes and evaluation mechanisms, beyond pain and disability, will help increase the specificity of treatment.
a. True
b. False

13. In which two treatment categories should patients with osteoarthritis receive some form of intervention?
a. Complementary / alternative and nonpharmacologic
b. Nonpharmacologic and surgical
c. Pharmacologic and surgical
d. Nonpharmacologic and pharmacologic
e. Complementary / alternative and pharmacologic

14. In 2015, the Food and Drug Administration strengthened the warning for NSAIDs on OTC and prescription labels due to the risk of which of the following?
a. Heart attack and stroke
b. Heart attack and GI risk
c. Stroke and GI risk
d. None of the above

15. KP is a 70-year-old female who failed full dose (4000 mg/day) acetaminophen for the treatment of her hip osteoarthritis. She presented to her primary care physician who wants to step up to an oral NSAID. What is the preferred oral NSAID treatment in this patient?
a. Nonselective NSAID
b. Selective COX-2 inhibitor
c. Nonselective NSAID and PPI
d. Selective COX-2 inhibitor and PPI

16. Glucosamine and chondroitin are effective options for the reduction of pain in patients with osteoarthritis.
a. True
b. False

17. Poor prognosis as a stratification measure was removed from the updated 2015 rheumatoid arthritis guidelines for an exclusive treat-to-target strategy regardless of disease activity level.
a. True
b. False

18. Which therapeutic agent lost its first-line treatment status due to limited efficacy, inability to prevent long-term bone/cartilage damage and adverse effects?
a. Acetaminophen
b. Hydroxychloroquine
c. Ibuprofen
d. Methotrexate

19. Which of the following traditional DMARDs is the preferred first-line agent in patients, regardless of disease activity level, and should be initiated as soon as the patient is diagnosed?
a. Hydroxychloroquine
b. Leflunomide
c. Methotrexate
d. Sulfasalazine

20. What is the maximum length of time glucocorticoids are recommended for the treatment of disease flare-ups in patients with rheumatoid arthritis due to their adverse effect profile?
a. 30 days
b. 60 days
c. 90 days
d. 120 days

21. Pre-treatment screening is required in all patients in whom a TNF inhibitor is initiated to rule out which of the following?
a. Candadiasis
b. Herpes zoster
c. Sarcoidosis
d. Tuberculosis

22. Which of the following is the novel biologic agent approved by the FDA in 2012 for the oral treatment of rheumatoid arthritis?
a. Anakinra
b. Etanercept
c. Rituximab
d. Tofacitinib