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- What do recent screening guidelines suggest to prevent the possibility of hydroxychloroquine retinopathy?
- Why does methotrexate behave differently in patients with rheumatoid arthritis (RA) compared to those with cancer?
- How do antidrug antibodies predict why some patients fail to respond or lose response to biologic disease-modifying antirheumatic drugs (DMARDs)?
- What new drug pathways are under investigation for the treatment of RA?

Learning Objectives

1. Evaluate the appropriate utilization of traditional DMARDs, such as methotrexate, sulfasalazine, and hydroxychloroquine, in current RA treatment regimens
2. Assess the impact of recently released “treat to target” guidelines on the overall care of patients with RA
3. Describe the potential role of late-stage agents under investigation for the treatment of RA

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With the steady flow of new clinical evidence, updated treatment algorithms, and emerging therapies, standards of care for patients with rheumatoid arthritis (RA) are constantly evolving. Advances have arisen not only in the form of new treatments, but also in the better use of therapies that have been on the shelves in rheumatology clinics for decades. Rheumatology nurses should be aware of new trends in RA treatment, including the optimal use of synthetic and biologic disease-modifying antirheumatic drugs (DMARDs).

MTX DOSING

Many patients with RA do not achieve the full benefits of MTX because of suboptimal dosing, inadequate titration, or both. In a meta-analysis of 38 clinical trials, higher starting doses of MTX (25 mg/week) were more effective than lower starting doses (5-15 mg/week) in controlling the signs and symptoms of RA. Faster dose escalation (5 mg/month) was also more effective than slower dose escalation (5 mg every 3 months). However, higher starting doses and faster dose escalation were also associated with more gastrointestinal (GI) side effects, so the risk/benefit of this approach must be carefully weighed. Thus, the goal of therapy should be to achieve high doses of MTX (25-30 mg/week) as quickly as possible, but in a schedule adapted to individual tolerability. Treatment with leucovorin or other forms of folinic acid supplementation can increase the tolerability of high-dose MTX. In the meta-analysis, the mean tolerable dose of oral MTX was 17-20 mg/week.

SUBCUTANEOUS VS. ORAL MTX

Although current RA guidelines recommend starting most patients on oral MTX, there is renewed interest in the potential benefits of subcutaneous MTX. When administered at the same dose, subcutaneous MTX is associated with better clinical outcomes than oral MTX. Moreover, switching from oral MTX to same-dose subcutaneous MTX provides significant additional reduction in disease activity, particularly among patients with intolerance to oral MTX. Current evidence supports switching to subcutaneous MTX in patients with an insufficient response to the highest tolerable dose of oral MTX (up to 25-30 mg/week).
Hydroxychloroquine

The antiinflammatory agents chloroquine and hydroxychloroquine (HCQ) have immunomodulatory and antiinflammatory properties that are useful in the management of rheumatic diseases. Compared with other DMARDs, antiinflammatory drugs have a less prominent role in current RA treatment guidelines because they do not appear to provide sufficient protection from structural damage, particularly in patients with moderate or severe disease activity and in comparison with sulfasalazine (SSZ). However, given its favorable safety profile, HCQ has a role in the management of patients with very mild disease who have contraindications to other first-line therapies. As an FDA pregnancy category C medication, HCQ is one of the safest DMARDs in pregnancy.

NEW RENALITY SCREENING GUIDELINES

Retinal toxicity is the most feared side effect of antimalarial therapy, but this occurs very rarely with HCQ when appropriate dosing and routine eye exams are employed. In 2011, the American Academy of Ophthalmology (AAO) issued updated recommendations for the management of chloroquine and HCQ retinopathy. The 2011 AAO guidelines recommend baseline screening to rule out maculopathy, which is a contraindication to antimalarial use. Additional recommendations include the following:

- Rather than weight-based dosing, most patients should be given 400 mg HCQ daily. To avoid ovoediasis, patients of short stature should receive lower doses (6.5 mg/kg) based on ideal body weight.
- Annual ophthalmologic screening to detect early retinal changes should begin after 3 years. It should begin earlier if patients have unusual risk factors such as underlying retinal disease.
- Patients should be instructed to report any new visual symptoms, including reduced vision, double vision, or loss of peripheral vision.

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Oncologists began using MTX in 1948, first to treat childhood acute leukemia and later to treat other blood cancers and solid tumors. The average dose used to treat cancer is 1 g/m² (range, 500-600 mg/m²) in approximately 1.5 g/m² per cycle for a body mass index of 18.4 to 34.0 kg/m². At this dose, MTX acts as an antifolate drug and inhibits dihydrofolate reductase (DHFR), an enzyme critical to folate metabolism. With depletive folate levels, cells cannot produce enough thymidine and purine to maintain DNA, RNA, and protein synthesis. Thus, high-dose MTX kills not only rapidly proliferating cancer cells, but also cells in the bone marrow, muscle, and hair follicles. This antiproliferative activity extends to the use of low-dose MTX in cancer treatment, including myelosuppression, infection risk, nausea, vomiting due to gastrointestinal mucositis, and alopecia.1

Treatment goals are different in rheumatology, where clinicians exploit the antiinflammatory effects of low-dose MTX. In rheumatology, the typical dose range for MTX is 7.5-30 mg once weekly – several times lower than the doses used in oncology. At this dose, MTX is thought to inhibit pathways of low-dose MTX. In rheumatology, the typical dose range for MTX is 7.5-30 mg once weekly – several times lower than the doses used in oncology. At this dose, MTX is thought to inhibit pathways...
In current practice, diagnosis and treatment of RA are often delayed, with damaging results. In one recent study, 69% of patients with RA waited 12 weeks or longer after symptom onset to be assessed by a rheumatologist. Compared to patients who had received a timely referral (<12 weeks from symptom onset), delayed assessment by a rheumatologist increased the risk of not achieving DAS28-free remission by 87%. Delayed referral also increased the risk of joint destruction over 6 years by 30%. Certain patients were at especially high risk of delayed referral, including those with very early symptom onset, patients who had received a timely referral (<12 weeks from symptom onset), and those whose symptoms involved small joints. Delays in referral to a rheumatologist can result in patients being seen past the ideal window of opportunity for treatment, which is now considered to be within a few months of symptom onset. The new RA classification criteria, which are meant to capture patients at the earliest stages of disease, may shorten the delay to timely care.

The benefits of an early treatment strategy are clear — identifying patients with the earliest stages of RA expedites treatment and gives patients the best chance for remission. The IMPROVED (Induction Therapy With Methotrexate and Prednisone in Rheumatoid or Very Early Arthritic Disease) study enrolled 261 patients with the earliest signs of RA. Upon entering the study, patients had RA symptoms for a median duration of 4 months and mean disease activity score (DAS) of 3.4. All patients began treatment with MTX 25 mg/week plus prednisone 60 mg/week, tapered over 7 weeks to 7.5 mg/day. After 4 months, 35.8% of RA patients achieved remission, defined as DAS ≤1.6. Patients with lower disease activity at baseline were able to achieve remission earlier. According to the IMPROVED study authors, the strategy of very early intervention dramatically improves remission rates in RA. In previously published reports, comparable remission rates for patients with more active disease are less than 30%.

Treat-to-Target Strategy

With a new treat-to-target strategy, RA joins the ranks of other major chronic diseases with clearly defined treatment goals, including hyper tension (blood pressure ≤140/80 mm Hg) and diabetes (glycosylated hemoglobin ≤7%). Patients with RA should now be treated with the primary goal of achieving clinical remission, defined as the absence of signs and symptoms of significant disease activity (Figure 1). In 2010, the international treat-to-target (T2T) task force described four overarching principles that should guide RA management:

1. RA treatment must be based on shared decisions by patients and rheumatologists
2. The primary goal of RA treatment is to maximize long-term health-related quality of life through symptom control, prevention of structural damage, and normalization of physical and social functioning
3. Eliminating inflammation is the most important method for achieving these treatment goals
4. The treat-to-target strategy requires measuring disease activity and adjusting therapy accordingly to optimize outcomes

Recognizing that complete remission may not be possible for all patients, the T2T task force set “low disease activity” as an acceptable alternative goal for individuals with longstanding disease, considerable joint damage, and several prior treatment failures. Regardless of specific treatment target, drug therapy should be adjusted every 3 months until the desired goal is reached. This may include modifying the dose of existing therapy, switching medications, or adding another agent to the current regimen. Once the RA treatment goal is achieved – clinical remission for most patients, low disease activity for others – this state should be maintained continuously with ongoing drug therapy. Only sustained remission can prevent further joint damage, whereas any increase in disease activity can restart the process of joint destruction.

To guide treatment decisions, disease activity should be routinely measured and documented on a schedule that increases with more intense disease activity. For instance, patients with moderate-to-high disease activity may require monthly evaluation, whereas those with sustained low disease activity or remission may require evaluation as infrequently as every 3 to 6 months. The T2T task force recommended using validated composite measures that include joint assessments, such as the DAS, the DAS with the 28-joint count (DAS28), or the clinical (CDAI) or simplified (SDAI) disease activity index. The choice of composite measure and target value for each patient is up to the rheumatology practice and may be influenced by patient comorbidities, drug-related risks, and other factors. Structural and functional changes should also be considered when assessing response to therapy.

The T2T task force emphasized the importance of patient education in achieving treatment goals. According to the T2T report, patients should be appropriately informed about the reasons for aiming at a specific therapeutic target, as well as the planned strategy for reaching treatment goals. Patients should also understand the need for adjusting therapy and ongoing disease monitoring. Rheumatology nurses can take the lead on addressing these issues with their RA patients. The recently published patient version of the T2T guidelines may be a useful tool for patient education.

Updated ACR/EULAR Remission Criteria

In 2011, the ACR and EULAR jointly issued new definitions for disease remission in RA that can be used in the research and clinical practice settings. The goal of the new criteria was to improve the ability to identify patients with minimal risk of significant disease progression. Prior definitions of remission, including the traditional DAS28 <2.6 and the more stringent DAS28 <2.0, failed to exclude patients with substantial residual clinical disease activity. Moreover, while the DAS instrument is useful in the research setting, it can be cumbersome to apply in the rheumatology clinic.

The new ACR/EULAR research and clinical definitions differ in their incorporation of C-reactive protein (CRP), a laboratory measure that may not be practical to collect in routine practice. All definitions use the 28-joint count for tenderness (TJC28) and swelling (SJC28), as well as global assessments on a scale of 0 to 10.

Are I at risk of cardiovascular disease because of the drugs I’m taking?

In general, RA patients have a greater than twofold risk of myocardial infarction and are twice as likely to experience sudden cardiac death compared to the average population. While the precise molecular mechanism that accelerates risk of cardiovascular disease (CVD) remains unclear, inflammation appears to be the key factor.

Several possible reasons have been offered as to the cause of increased risk of CVD in patients with RA:

1. Chronic inflammatory conditions such as RA accelerate atherosclerosis, an inflammatory disease of the arterial wall
2. Chronic pain and anxiety lead to vascular remodeling and hypertension
3. Elevated CRP levels and cytokines increase lipid levels, alter glucose metabolism, and create a hypercoagulability state that can precipitate thrombosis, resulting in myoccardial infarction

Now for the good news: In 2004, Krishnan et al demonstrated that patients with RA treated between 1980 and 1997 had no increase in rates of mortality compared to the general population. One of their explanations for this was the reduced time between diagnosis and implementation of treatment such as TNF inhibitors and MTX. Although cardiovascular disease must be considered when implementing a TNF inhibitor in patients with a history of heart failure, observational studies suggest that the biologic and glucocorticoids used to decrease the incidence of future CVD events in patients with RA.

Many patients with RA commonly present with one or more risk factors of CVD (obesity, immunity, hypertension, or smoking). It’s important to remind our patients that RA is an inflammatory disease of the whole body and not just their joints. Reducing saturated fats in their diet, quitting smoking, losing weight, and initiating exercise are key to their overall wellness.

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Understanding Antidrug Antibodies

Immunogenicity describes the potential for a drug to elicit an immune response, leading to the development of antidrug antibodies. Adverse drug reactions (ADRs) commonly involve patients with therapeutic antibodies to block the production of antidrug antibodies. Patients who develop antibodies to biologic therapies are more likely to develop infusion-related reactions, allergic reactions, and loss of treatment response. Therefore, monitoring for the development of antibodies against therapeutic therapies may identify patients with an increased risk of antibody-related adverse events, as well as those whose response to therapy may diminish.2 This strategy may be incorporated into routine clinical practice once assays for anti-drug antibodies become commercially available.

The first long-term study of antidrug antibodies in RA was recently published, allowing clinicians to understand how this phenomenon might influence treatment response.2 In a 3-year study by Bartels et al, the development of antibodies against adalimumab decreased the efficacy of treatment and resulted in low remission rates in patients with RA.24 Greater than 30% of patients developed antibodies to adalimumab, and most of these patients (67%) developed antibodies within the first 28 weeks of treatment. Only 4% of patients who developed anti-adalimumab antibodies achieved sustained remission, compared with 34% of patients who did not develop antibodies. Patients who developed antidrug antibodies were 3 times more likely than those without antibodies to stop taking adalimumab due to treatment failure. According to study investigators, these findings are potentially applicable to other biologic therapies, and may explain why some patients fail to respond or lose response to biologic DMARDs. Guidelines are currently under development to guide clinicians in the assessment and management of immunogenicity in patients undergoing treatment with biologic therapy.25

New Formulations of Existing Agents

With advances in drug technology, several existing classes of agents are being studied in new formulations.26 An investigational form of subcutaneous abatacept, for example, provides greater convenience and a more flexible treatment schedule than intravenous therapy, with similar efficacy and low immunogenicity in patients with RA.27 In a phase II study, a new formulation of subcutaneous tocilizumab showed a favorable safety and efficacy profile when given weekly or twice weekly in patients with RA.28

A PEEK AT THE FUTURE OF RA THERAPY

IL-Targeted Therapy

The interleukins play leading roles in joint destruction in patients with RA. Tocilizumab, the first IL-6 receptor inhibitor approved for the treatment of RA, is associated with rapid improvements in the signs and symptoms of RA in patients with active disease.24 Among investigational IL-6 inhibitors, ALD518 is a glycosylated monoclonal antibody that directly binds to free IL-6 rather than the IL-6 receptor.25 Cat6001 and MED15117 are novel anti-IL-6 monoclonal antibodies with promising preclinical and early-phase findings in RA.26-29 IL-17 acts synergistically with TNF to induce joint inflammation and joint and cartilage destruction in RA, and is therefore emerging as another important therapeutic target.30 Investigational IL-17 inhibitors with preliminary evidence in RA include secukinumab (AIN457) and MEDE-571.31,32

JAK Inhibitors

The Janus kinase (JAK) family of tyrosine kinases, including JAK1, JAK2, and JAK3, are leading mediators in the cytokine signaling pathways that promote inflammation. By disrupting this broad signaling network, JAK inhibitors can arrest the inflammatory activity of many cell types, including T cells, B cells, and osteoclasts. Two investigational, orally available JAK inhibitors are currently under evaluation for further study. Tofacitinib (CP-690,550), previously known as tasaocitinib, suppresses inflammatory activity by inhibiting JAK1 and JAK3. In a phase IIIB study, treatment with tofacitinib maintained therapeutic efficacy alone and in combination with MTX for up to 24 months in patients with RA.33-35 Based on these promising results, the ongoing phase III ORAL clinical trials program is evaluating different options for oral JAK inhibitor therapy in the management of RA.

In the ORAL Solo study, tofacitinib—monotherapy significantly improved physical functioning compared with placebo and showed a trend toward greater disease remission in patients with moderate-to-severe RA and an inadequate response to traditional or biologic DMARDs.22 According to a recent preliminary analysis of the ORAL Scan study, tofacitinib added to MTX was superior to placebo in patients with moderate-to-severe RA who had an inadequate response to MTX alone. Compared with placebo, tofacitinib significantly improved the signs and symptoms of RA, slowed the progression of structural damage, and improved physical function at 6 months.36 The ORAL Sync study is a 12-month study of tofacitinib added to background traditional DMARDs in patients with a prior inadequate response to traditional DMARDs. Compared with patients in the placebo group, those in the tofacitinib group were more likely to achieve an ACR20, were more likely to achieve disease remission, and had a greater reduction in disease-related disability. There were 4 deaths and 4 opportunistic infections reported in the tofacitinib arm. However, given that only one-fifth of the study cohort was initially randomized to placebo, and that patients in

Why are you performing certain labs? What information are you looking for?

Diagnosing RA relies on more than an articular history and joint examination. Values from several laboratory tests, including the following, can help to definitively determine whether or not an individual has RA.

- Rheumatoid factor (RF): RF is an autoantibody (usually immunoglobulin M) that binds to the Fc portion of immunoglobulin G. It is present in 75%-85% of patients with established RA. Conventional, in nearly 20% of patients, RF may be absent in the first few months of active disease. Because RF can be positive in the presence of other conditions (e.g., Sjögren’s syndrome, systemic lupus erythematosus, endocarditis, etc.), it is not by itself a definitive indicator of RA. Additionally, because RF does not correlate well with disease activity, serial measurements are rarely performed.

- Anti-cyclic citrullinated (anti-CCP) antibody: Anti-CCP antibodies are very specific for RA (95%). Anti-CCP correlates strongly with aggressive RA, radiographic damage, and the presence of RF. Conversely, low levels of anti-CCP may demonstrate a less aggressive disease process.

In addition to RF and anti-CCP antibodies, tests of acute-phase markers, such as erythrocyte sedimentation rate and C-reactive protein, are often performed along with lipid tests. These tests measure response to therapy. However, results may be affected by disease duration and other comorbidities.

Finally, a complete metabolic panel and complete blood count are often used to monitor the effects of therapy, renal and hepatic function, infection, anemia, and thrombocytosis, among other considerations.

REFERENCES
Three additional phase III ORAL trials are currently underway38:

- ORAL Start: 24-month study of first-line tofacitinib vs. MTX in patients with active RA
- ORAL Step: 6-month study of tofacitinib vs. placebo in RA patients taking MTX with a prior inadequate response to anti-TNF therapy
- ORAL Standard: 12-month study of tofacitinib/MTX vs. adalimumab/MTX in RA patients who had an inadequate response to anti-TNF therapy

A second JAK inhibitor, INCB028050, selectively targets JAK1 and JAK2 and is being tested in once-daily oral dosing. In a recent phase II study, INCB028050 produced clinically meaningful joint counts, in RA patients with inadequate responses to TNF therapy, leading to a reduction in bone degradation in preclinical models of RA.40 It is orally bioavailable and administered twice daily.

Fostamatinib has shown promising activity against RA in phase II clinical trials as add-on therapy for patients with an inadequate response to treatment with DMARDs such as MTX.41,42 In a recent phase II study, there was no difference between fostamatinib and placebo in the primary endpoint of ACR20 response at 3 months in RA patients who did not respond to biologic therapies.43 However, fostamatinib was superior to placebo for the secondary endpoints of reduced CRP level and synovitis score on MRI, suggesting a beneficial effect on underlying disease activity in RA.44 Building on these results, the ongoing Oral Syk Inhibitor in Rheumatoid Arthritis (OSKIRA) clinical trials program will evaluate the safety and efficacy of fostamatinib in patients with RA (see next page).45-49

Syk Inhibitors

Spleen tyrosine kinase (Syk) is a mediator of inflammatory cell signaling that is involved in bone and cartilage destruction.46 Fostamatinib (R788) is an investigational Syk inhibitor that reduces major inflammatory cytokines, including TNF, IL-1, IL-6, and IL-18, leading to a reduction in bone degradation in preclinical models of RA.47-50 It is orally bioavailable and administered twice daily.

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Why does this medication cost so much?

With price tags in the tens of thousands of dollars, the cost of biologic therapies is a common issue. For many of our patients living on a fixed income, cost compounds their decision-making process as they must not only understand the clinical benefits and risks of available medications, but the financial cost as well. This is overwhelming for many patients, especially those who don’t fully understand their insurance policy’s out-of-pocket structure.

When discussing the cost of biologics to my patients, I explain that biologics aim to target the causes of diseases rather than just the symptoms, targeting specific parts of the inflammatory process involved in RA while sparing others. Because of the complexities involved in the manufacturing of these products, costs naturally increase. The route of administration—typically injection or infusion—is another cost driver. So is the lack of generics alternatives—or, more accurately, biosimilar alternatives—that would bring more competition into the marketplace.

One recent article closely examined the cost issue with biologics, and the author highlighted two factors that he saw as the primary reasons for the high price tags:41

- The most expensive drugs are those that have no competitors. When a truly novel drug hits the market, there is very little to guide manufacturers and insurers in their negotiations over price.
- The average cancer medicine, for example, costs approximately $1.75 billion to develop (factoring in research and development costs, failed drugs, etc.). Most chemists that a company experiments with never make it to market. Of those that do, only 20% are ultimately profitable. Drug companies cover these losses by squeezing as much profit out of their few successful agents as possible.

As rheumatology nurses, we can do our best to explain the high cost of medications to our patients, but we must also be prepared to assist them with weighing risk and benefit of specific agents, along with providing directions to patient assistance plans. There are pharmaceutical company programs and pharmacy discount programs that some of our patients will be eligible for that may help defray out-of-pocket expenses. —Joyce M. Murtian, RN

REFERENCE


Anti-BlyS Antibody

Belimumab is a monoclonal antibody that targets the pathogenesis of autoimmune diseases by inhibiting the activity of B-lymphocyte stimulator (BlyS). In 2011, the FDA approved intravenous belimumab to treat patients with active lupus who are already receiving standard therapy. Belimumab has also shown activity in RA.49 Atrasentan, another B-cell-targeted therapy that inhibits both BlyS and a proliferation-inducing ligand (APril), is also under evaluation for the treatment of RA.50,51

SUMMARY

For patients with RA, the goals of treatment are to achieve early suppression of disease activity, prevent long-term joint damage, and maintain physical and social functioning and quality of life. The new treat-to-target approach encourages early treatment with DMARDs to achieve rapid and sustained clinical remission. New remission criteria allow clinicians to more accurately gauge whether disease activity has been suppressed enough to minimize the risk of future joint damage. Armed with new information about the optimal use of MTX and other synthetic and biologic DMARDs, rheumatology nurses are now in a better position to help patients with RA achieve their treatment goals.

How long is this drug going to work?

Patients often ask difficult questions like this one, which we cannot answer with any real confidence. But before you fire off a rapid response—such as “as long as it does”—it’s important to think about several issues, including the following:

- How should you even define response?
- If remission is not attainable, what level of disease activity is acceptable?
- What prognostic indicators may help you answer this type of question?

In the absence of reliable biomarkers or everyday clinical tools that would help predict a patient’s response to treatment, we must rely on data from randomized clinical trials. Studies suggest that many patients derive some benefit from one of the three first-generation TNF inhibitors (etanercept, infliximab, and adalimumab); however, 40%-50% fail to achieve an ACR50 response, and more than 70% fail to achieve clinical remission (defined as DAS28 <2.6) after six months of therapy.41,42

Many patients can expect to see some improvement after the initiation of therapy, but it’s hard to predict whether this improvement will be enough to improve physical functioning and prevent erosion disease and disability. Clinical trials often differ in the number and type of previous medications allowed by enrolled patients, duration of therapy, concomitant medications, and other factors. Therefore, while generalizations can be made, predicting an individual’s response to any specific therapy over time is impossible. Certainly, with the improvements in drug design, we can offer an optimistic outlook to our patients, but making concrete promises remains difficult.

Rather than answering your patient with a definitive response, it may be better to educate them on data from various randomized controlled trials and encourage them to report any physical changes or worsening of disease, side effects, or other indicators that their RA is not controlled so that you may quickly escalate or change therapy as needed. —Nicole M. Furiano, MSN, ARNP

REFERENCE

## References


## Activity Post-Test Questions

(These questions will indicate the correct response for each question to which they refer.)

1. According to EULAR guideline, how long after the initiation of MTX therapy should a synthetic or biologic DMARD be added in patients with residual disease activity?  
   a. Within 45 days  
   b. Within 1-3 months  
   c. Within 9-12 months  
   d. As soon as their DAS28 score is 2.6 or less

2. Is a new patient who reports to you with 3 joint involvements, elevated acute-phase response, and symptom duration of 2 years. Based on the 2010 ACR/EULAR diagnostic criteria, would you consider that she has:  
   a. Yes  
   b. No  
   c. Not enough information is provided to reach a definitive answer

3. Based upon recent research, which of the following patients would be considered as at higher risk of a delayed referral to a rheumatologist?  
   a. A 35-year-old female with sudden onset of synovitis and pain confirmed primarily to large joints  
   b. A 65-year-old female with gradual onset of synovitis and pain primarily found on small joints  
   c. A 70-year-old male with sudden onset of synovitis and pain primarily found on small joints  
   d. A 28-year-old male with gradual onset of synovitis and pain primarily found on small joints

4. Which of the following overarching principles were included in recommendations from the 2010 international T2T taskforce?  
   a. MTX treatment should be determined primarily by the rheumatologist, with minimal patient input  
   b. The primary goal of RA treatment is to improve short-term quality of life through a patient’s return to the workforce  
   c. The target-to-treat strategy requires measuring inflammatory activity reduced by JAK inhibitors?  
   d. Avoiding adverse effects is the most important mechanism to achieve treatment goals

5. Has he been patient for 18 months. After 6 months of combination adalimumab + MTX therapy, she reports to your office today with newly developed symptoms and pain primarily focused on small joints. According to data from a 2004 study, how much hydroxychloroquine should a 5-foot-9, 130-pound patient take daily?  
   a. 200 mg twice daily  
   b. 612.5 mg daily  
   c. 10,000 times more potent

6. According to a data from 2004 study, much of a mortality increase was seen in RA patients treated between 1991 and 1997 compared to the general population?  
   a. No increase  
   b. Twofold increase  
   c. Fourfold increase  
   d. Eightfold increase

7. Which of the following factors play a role in the high cost of biologics agents commonly used for the treatment of RA?  
   a. Costs of failed drugs in past development pipeline  
   b. Relative economic prosperity of the average RA patient  
   c. The recent economic recession  
   d. Preliminary of generic/biosimilar alternatives

8. According to 2011 ACR/ARDA guidelines, what does efficacy of treatment mean if a 5-9, 130 pound woman be given?  
   a. 200 mg twice daily  
   b. 612.5 mg daily  
   c. 400 mg daily  
   d. 845 mg daily

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Safe Travels in the Summertime – Vicky Ruffing, RN

Vacation season is upon us, and as our patients make their way far and near, it’s important to prepare them to travel safely. Recent updates have been made to the package inserts for many of the biologics, and fungal infections are common themes within black box warnings. While most of our patients likely do not live in endemic areas, a vacation or family visit could put them at risk for contracting a fungal infection.

The Fungus Among Us

Coccidiodomyces is a fungal infection most commonly seen in the desert regions of the southwestern United States, parts of Mexico, and South America. The Centers for Disease Control and Prevention (CDC) estimates that 10%-15% of individuals living in endemic regions have evidence of exposure to Coccioidiodes species. Coccidioidomyces, which starts in the lungs, arises as a result of breathing in fungal spores present in the soil. These spores can become airborne after a disturbance of the soil by natural or artificial means (earthquakes, heavy rainstorms, construction work). Symptoms include flu-like illness with fever and cough, headache, rash (especially on lower extremities), night sweats, and body aches. These symptoms typically appear approximately 1.5 weeks after exposure. In a small percentage of individuals, infection may spread from the lungs to other parts of the body, including the skin, brain, bones, and heart.

Blastosporiosis is a very rare fungal infection found in most soil, particularly in the presence of rotting vegetation. The fungus Blastomyces dermatitidis is found in parts of the southern, southeastern, and midwestern United States. Forestry workers, hunters, campers, and other individuals who spend significant time in wooded areas are at particular risk. Symptoms of infection are similar to those of coccidioidomycosis. Disseminated blastomycosis may result in chronic pulmonary disease, genitourinary involvement, and meningitis.

Histoplasmosis is a more common fungal infection found in the Ohio and Mississippi river valleys. The fungus Histoplasma capsulatum is found in soil where there may be an accumulation of bat or bird droppings. Also referred to as “caver’s disease” or “spookers lung,” as many as 80% of individuals living in endemic areas exhibit a positive histoplasma skin test. Signs of infection include chest pain, cough, and fever. Disseminated histoplasmosis may lead to pneumonia, pericarditis, meningitis, adrenal insufficiency, splenomegaly, and hepatomegaly.

Treatment for all of the aforementioned infections involves anti-fungal medications such as amphotericin B, voriconazole, posaconazole, fluconazole, and ketoconazole.

In light of recent natural disasters – tornadoes in Alabama and Missouri, flooding along the Mississippi River – it is also important to remind our patients either living in or visiting these areas of the most common microbes that arise after these events. Contaminated water, food, and even the lightest quakes of evacuation facilities are rife with infectious diseases and parasites such as Shigella, Cryptosporidium, Giardia, and Listeriosis. Patients who will be near these areas should seek medical attention at the first sign of possible exposure. Prescribers may want to consider a prescription antibiotic for diarrhea to be used by patients as needed.

REFERENCES

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