UNITED RHEUMATOLOGY

A Specialty Networks Company

CLINICAL PRACTICE GUIDELINE

Rheumatoid Arthritis (RA)—Adult

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Abbreviations

ACPA	Anti-citrullinated protein antibody. Also: anti CCP
ACR	American College of Rheumatology

bDMARD(s)	Biologic originator and biosimilar disease-modifying antirheumatic drug(s)
boDMARD(s)	Biologic originator disease-modifying antirheumatic drug(s)
bsDMARD(s)	Biosimilar disease-modifying antirheumatic drug(s)
CBC	Complete blood count
CDAI	Clinical Disease Activity Index
CDC	Centers for Disease Control and Prevention
CRP	C-reactive protein
csDMARD(s)	Conventional synthetic disease-modifying antirheumatic drug(s)
DAS28	Disease activity score, based on 28 joints
DMARD(s)	Disease-modifying antirheumatic drug(s)
EHR	Electronic health record
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDA	High disease activity
HIV	Human immunodeficiency virus
HLA-DRB1	Human leukocyte antigen D related beta 1
HPV	Human papillomavirus
Ig	Immunoglobulin
IL-6	Interleukin 6
IU	International units
JAK	Janus kinase
LDA	Low disease activity
MDA	Moderate disease activity
MDHAQ	Multidimensional Health Assessment Questionnaire
MMR	Measles, mumps, and rubella
MRI	Magnetic resonance imaging
MTX	Methotrexate
OMERACT	Outcome Measures in Rheumatology
PCV13	13-valent pneumococcal conjugate vaccine
PG	Polyglutamate
PGA	Physician Global Assessment
PPSV23	23-valent pneumococcal polysaccharide vaccine
PRO(s)	Patient-reported outcome(s)
PtGA	Patient Global Assessment
PTPN22	Protein tyrosine phosphatase non-receptor type 22
QoL	Quality of life
RA	Rheumatoid arthritis
RAPID3	Routine Assessment of Patient Index Data 3

RCZ	Recombinant zoster
RF	Rheumatoid factor
SQ	Subcutaneous
TB	Tuberculosis
Tdap	Tetanus, diphtheria, and pertussis
TNF	Tumor necrosis factor
TNFi	Tumor necrosis factor inhibitor
tsDMARD(s)	Targeted synthetic disease-modifying antirheumatic drug(s)
ULN	Upper limit of normal
US	United States
VAS	Visual acuity scale

Introduction

Rheumatoid arthritis (RA) is a multisystem autoimmune disease affecting primarily diarthrodial joints of the hands and feet; however, it can also affect larger joints (shoulder, elbow, hip, ankle, and knee). The disease causes joint inflammation, synovial hyperplasia, and synovitis with increased synovial vascularity. Inflammatory cells within the joint lead to synovial proliferation and pannus formation, which ultimately results in the destruction of articular cartilage and bone.[1,2] RA is three times more common in women than in men,[3] and can begin at any age. However, it is usually diagnosed between the ages of 18 and 60 years in women and over the age of 45 years in men.[4] Although the odds of developing RA are increased in first-degree relatives of people who have the disease, most people with RA do not have a family history of it.[5]

The destructive process in RA is thought to be related to an overproduction of a number of inflammatory cytokines, including tumor necrosis factor (TNF) and interleukin-6 (IL-6).[6,7]

Some important factors possibly associated with an increased risk of RA include:[8-15]

- Smoking (current, former)
- Bacteria in the lungs
- Chronic periodontitis
- Silica exposure
- Air pollution
- Changes in gut flora

Studies of families with twins suggest that genetics contribute at least 50% to the etiology of RA.[16] The presence of human leukocyte antigen D related Beta 1 (*HLA-DRB1*) or protein tyrosine phosphatase non-receptor type 22 (*PTPN22*) alleles are associated with an increased risk for RA. However, different genetic risks may be seen in different ethnic groups.[17,18]

RA is frequently but not always associated with the production of auto-antibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA or anti-CCP).

A more recently described serum marker for RA is 14-3-3η. According to Maksymowych et al.,[19] the use of this marker in addition to ACPA and RF may improve the identification of patients with early RA and, when elevated, 14-3-3η can be used as a prognostic indicator of more severe disease.

In addition to joint destruction, RA is characterized by serious extra-articular manifestations (Table 1), which tend to occur more frequently in patients with severe, active disease; in those who test positive for RF and ACPA; in men; and in patients with a history of smoking at the time of diagnosis. Extra-articular manifestations of RA include rheumatoid nodules, inflammatory eye disease, hematologic abnormalities, Felty's syndrome, rheumatoid lung, and vasculitis. Extra-articular manifestations are associated with increased mortality.[20,21] Another common complaint of patients with RA is fatigue or tiredness. This can be found in 40 to 80% of RA patients.[22]

 Table 1. Extra-articular manifestations of RA

Organ System/Disease	Extra-articular Manifestation
Pulmonary	• Pulmonary fibrosis • Lung nodules • Pleural effusion • Bronchiolitis obliterans organizing pneumonia
Cardiac	• Pericardial effusion • Myocarditis • Endocarditis • Pericarditis
Skin	• Subcutaneous nodules • Ulceration
Kidneys	• Glomerulonephritis • Amyloidosis
Eyes	• Keratoconjunctivitis sicca • Scleritis • Episcleritis
Felty's syndrome	• Splenomegaly • Neutropenia
Vascular	• Vasculitis (small and large vessel)
Other	• Splenomegaly • Lymphadenopathy • Anemia • Thrombocytosis • Secondary Sjögren's syndrome • Muscle wasting • Peripheral neuropathy • Fatigue

RA is incurable. The estimated incidence of RA in the United States (US) adult population is about 0.44 per 1000.[15] Prevalence of RA in the US population has increased from 2004 to 2014. In 2014 the prevalence of RA in adult males was estimated at 0.53 to 0.55% and for adult females at 0.73 to 0.78%. In 2014, it was estimated that about 1.3 million adults were affected by RA.[23]

The disease is characterized by intermittent exacerbations (also known as flares) and is often more active during the first years after diagnosis. However, with proper management, patients can achieve periods of complete or near complete remission or stabilization of symptoms. Flares can occur, even in patients with previously good control. Flares or acute worsening of inflammation is manifested by increased joint pain and swelling, and systemic complaints such as fatigue and difficulty with activities of daily living. Patients

should be evaluated as soon as possible during an acute flare, because additions or changes in medication are often needed to regain control.

Historically, RA (especially nontreated or inadequately treated disease) was associated with a decrease in life expectancy by, on average, 5 to 10 years. However, with the availability of better treatment, this is no longer the case. A study published in 2016 compared the death rates of patients diagnosed with RA from 1996 to 2000 with those diagnosed from 2001 to 2006 and found that the death rate in the first 5 years after diagnosis had decreased for those more recently diagnosed.[24] The authors speculate that this may be due to improved management and better control of inflammation.

Patients with RA also have an increased risk for coronary heart disease, even before they are diagnosed with RA, and are more likely than patients without RA to have an unrecognized myocardial infarction or experience sudden death. They also have an increased risk of stroke, lung cancer, nonmelanoma skin cancer, and lymphoma when compared to the general population.[25-27] Patients with RA have an increased risk for serious infections, including tuberculosis (TB), which may be related to the immunologic abnormalities associated with RA as well as the immunosuppressive effects of the drugs used to treat the disease.[28]

Patients with RA report a diminished quality of life (QoL) compared with those without arthritis. According to Gabriel et al.,[29] 15% of patients with RA reported that they were unable to find employment due to their disease, as opposed to only 3% of those with osteoarthritis and 1% of those without arthritis. Patients with RA are more likely to retire early or lose their jobs than the general population. Some patients decrease their work hours voluntarily due to limitations from their illness. In another study, 40% of patients with RA were more likely to report fair or poor general health when compared to nonarthritic controls. They also were 30% more likely to need help with activities of daily living and twice as likely to have some limitation of activity due to RA.[30]

RA care is very costly. In 2012, Kawatkar et al.[31] compared the annual direct medical costs associated with caring for these patients with a control group of patients without RA, based on the 2008 Medical Expenditure Panel Survey. Overall, the annual cost of caring for patients with RA was $22.3 billion in 2008. Importantly, the cost of drugs was the greatest contributor to the overall cost of care, whereas prior to 2008, most studies reported that inpatient hospital stays were the greatest contributor to overall costs. Interestingly, Kawatkar et al.[31] found that 26.6% of the patients with RA had one comorbidity and 24.0% had two or more comorbidities whereas, in the non-RA group, 71.5% had no comorbidities, 22.1% had one, and only 6.5% had two or more comorbidities. Drug costs were nearly 40% of the total cost of care in the RA group but only 29% of the total in the non-RA group. In 2008, the total direct medical costs of caring for an RA patient averaged $13 012; those for a patient in the control group were $4950. The pharmacy expense was $5825 for a patient with RA and $1264 for a patient in the control group.[31]

However, when discussing financial burden, it is also important to consider the overall costs to employers, which include not only the cost of health insurance premiums but also the cost of disability insurance, absenteeism, reduced productivity, and early retirement. A systematic review of 38 papers concerning work disability, limitations, and absenteeism secondary to RA revealed that approximately two-thirds of employed individuals with RA were absent from their jobs for a median duration of 39 days per year.[32] A

2005 study of 6396 patients with RA in the US reported that patients had income losses between $2319 and $3407 per year.[33] In addition, almost one third of those under the age of 65 years considered themselves disabled 15 years after diagnosis.

The continued increases in the cost of drugs escalate the cost of care. However, new medications introduced over the past two decades, have dramatically improved the lives of patients with RA. Although a cure has not yet been realized, these medications have been shown to slow or prevent the progression of the disease.

In 2012, Hallert et al.[34] published a paper demonstrating a significant decrease in disability in patients with RA who took biologics. The dramatic impact of these drugs can be life changing for many patients. Improvement in QoL associated with the use of biologic agents has led to a decrease in cost of disability, early retirement, work hours lost, and reduced productivity. In addition, recent studies have found that both joint replacement and soft-tissue surgical procedures have decreased, probably as a result of more effective treatments.[35-37] One study evaluated patients with RA in California, who were over 40 years of age, for trends in total knee replacement, total hip replacement, total ankle replacement or fusion, and total wrist replacement or fusion between 1983 and 2007.[36] The rate of joint surgery was highest in the 1990s. The authors reported that, for patients between 40 and 59 years of age, the rate of knee surgery decreased by 19% between 2003 and 2007 when compared with knee surgery between 1983 and 1987; hip surgery decreased by 40% during the same time interval. However, for patients over 60 years of age, there was no significant change.

The *United Rheumatology Clinical Practice Guideline—Rheumatoid Arthritis (RA)* is designed to assist healthcare professionals to diagnose, treat, and monitor patients with RA with the goal of preserving function, optimizing the number of patients who achieve remission or near remission, improving QoL, and monitoring outcomes in the safest and most cost-effective fashion possible.

Diagnosis

The workup of patients with suspected RA should be done by a rheumatologist and is based on clinical findings. Early in the course of the disease, symptoms may be subtle. There is no definitive laboratory test for the disorder, and X-rays may be normal. Patients usually present with complaints of joint pain, tenderness, swelling, and stiffness. Prolonged morning stiffness lasting ≥30 minutes is common. Symptoms are typically bilateral and symmetric but may be asymmetric, particularly at the onset of the disease. Small joints of the wrists, hands, and feet are commonly affected. In addition, systemic symptoms such as fatigue, low-grade fever, and weight loss may be reported.

Irreversible destructive joint changes may occur early in the course of the disease. Because current pharmacologic treatments can minimize joint destruction, it is important to establish the diagnosis of RA and begin appropriate treatment as early as possible, preferably before joint destruction occurs. The use of disease-modifying antirheumatic drugs (DMARDs), including biologic agents, has dramatically changed the long-term course of this disease.

Determining the Diagnosis

In 2010, the American College of Rheumatology (ACR), in collaboration with the European League Against Rheumatism (EULAR), published criteria for the classification of RA that were aimed at new patients.[38] They were designed to classify patients for clinical trials. According to these classification criteria, any patient presenting **with clinical evidence of synovitis in ≥1 joint for which there is no alternative diagnosis to explain the finding should be evaluated for RA.** Classification criteria are based on four domains:

1. Number and site of joints involved (score range, 0 to 5)
2. Serological abnormalities (score range, 0 to 3)
3. Elevated acute-phase reactants (score range, 0 to 1)
    a. C-reactive protein (CRP) or
    b. Erythrocyte sedimentation rate (ESR)
4. Duration of symptoms (score range, 0 to 1)

Each of these domains is assigned a score. A total score of ≥6 is required to classify a patient as having definite RA. A patient with a score of <6 is not definitively classified as having RA but may reach a score of ≥6 at a future visit and therefore may be at risk for the disorder. The point allocation is shown in

Table 2.

Using the ACR/EULAR classification system, a patient may score 6 points and be classified as having RA without any positive laboratory tests (e.g., ≥10 joints involved [5 points] and duration of symptoms for ≥6 weeks [1 point]).

Table 2. Point allocation for the classification of RA according to ACR/EULAR criteria

Symptoms and Joint Count (any swollen or tender joint; excluding any distal interphalangeal joints, 1st metacarpophalangeal joints, and 1st metatarsophalangeal joints)	**Points**
1 large joint (Shoulder, elbow, hip, knee, or ankle)	0
2 to 10 large joints (Shoulder, elbow, hip, knee, or ankle)	1
1 to 3 small joints (may also have large joints) (Wrist; metacarpophalangeal, proximal interphalangeal, or 2nd – 5th metatarsophalangeal joints; or interphalangeal joint of the thumb)	2
4 to 10 small joints (may also have large joints) (Wrist; metacarpophalangeal, proximal interphalangeal, or 2nd – 5th metatarsophalangeal joints; or interphalangeal joint of the thumb)	3
>10 joints with at least ≥1 small joint (Sternoclavicular, temporomandibular, or acromioclavicular joints)	5
Serologic Markers	**Points**

Negative RF and negative ACPA (Results in IU are <ULN for the parameter)	0
Low positive RF or ACPA (Results in IU are >ULN but <3 times ULN for the parameter)	2
High positive RF or ACPA (Results in IU are >3 times ULN for the parameter)	3
Acute-phase Reactants	**Points**
Normal CRP and normal ESR	0
Abnormal CRP and/or abnormal ESR (above ULN for the laboratory parameter)	1
Duration of Symptoms*	**Points**
6 weeks	0
>6 weeks	1

*Duration is reported by patients.

ACPA, anti-citrullinated protein antibody or anti-CCP; ACR, American College of Rheumatology; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; IU, international units; RA, rheumatoid arthritis; RF, rheumatoid factor; ULN, upper limit of normal

Laboratory Tests

The following tests should be done, if a patient is suspected of having RA:

- Acute-phase reactant(s) – ESR and CRP
- Complete blood count (CBC)
- Serologic markers ○ RF (consider RF isotypes) ○ Antinuclear antibodies ○ ACPA
  - High specificity for RA
  - Often associated with more aggressive disease
  - In combination with a positive RF, the diagnosis of RA is virtually certain

A positive RF test is not unique to RA. It is positive in 5% to 8% of the population, and its incidence increases with normal aging. It can also be seen in other autoimmune disorders (such as lupus or Sjögren's syndrome), in chronic infections (such as endocarditis, TB, or viral hepatitis), and in granulomatous diseases. Rheumatoid factor is positive in approximately 60% to 80% of patients with RA.[39]

There are three known isotypes of RF—Immunoglobulins (Ig)M, IgG, and IgA—that may be present prior to the onset of RA symptoms.[40] The IgA isotype is found in 25%, the IgG isotype in 18%, and the IgM isotype in 26% of asymptomatic patients who eventually develop RA. At the time of diagnosis; IgA, IgG, and IgM isotypes were found in 64%, 57%, and 79% of patients, respectively.[41]

Houssien et al.[42] reported that patients who tested positive for IgA and IgM isotypes had higher disease activity scores and greater joint damage than those who tested negative for these immunoglobulins. The

authors also reported that patients with RA who were positive for the IgA isotype alone (without the IgM isotype) had more severe disease than those who were positive for only the IgM isotype or for both IgA and IgM. Gioud-Paquet et al.[43] also found an association of elevated IgA and IgM with high disease activity (HDA).

ACPA is highly specific for RA.[44] It is associated with more aggressive disease and, when seen in combination with a positive RF, the diagnosis of RA is virtually certain. Both RF and ACPA may be positive before RA symptoms develop.[44,45] Patients with active RA can sometimes have normal acute-phase reactants (ESR and CRP).

Antinuclear antibodies are present in about 40% of patients with RA. This test, however, is not specific for RA.

Patient Assessment

At the initial visit, the patient should be asked to complete a Patient Global Assessment (PtGA) form, a Routine Assessment of Patient Index Data 3 (RAPID3) or a Multidimensional Health Assessment Questionnaire (MDHAQ; see Glossary). Irrespective of the form used, it should also be completed at subsequent visits, because serial measurements can assist rheumatologists with defining progress and adjusting treatment.

Due to dysregulated immune function and exposure to immunomodulating medications, patients with RA have an increased risk of infection. Prior to starting pharmacologic therapy, it is important to obtain a detailed vaccination history. Providers should asses the need for a variety of vaccinations according to the Centers for Disease Control and Prevention (CDC) schedule, which includes the following:[46]

- Annual flu vaccine
- 13-valent pneumococcal conjugate vaccine (PCV13)—one dose, if not previously administered, followed by one dose of 23-valent pneumococcal polysaccharide vaccine (PPSV23) at least 8 weeks later, then another dose of PPSV23 at least 5 years after the prior PPSV23. In patients aged 65 years or older, only one additional dose of PPSV23 should be given least 5 years after the most recent dose of PPSV23.
- Recombinant zoster (RCZ) vaccine for adults 50 years of age and older—two doses (for markedly immunocompromised patients, the use of RCZ is currently under review, with no recommendation provided by the CDC for these patients.
- Human papillomavirus (HPV) vaccine—two or three doses for patients up to the age of 26 years
- Hepatitis A vaccine—two to three doses, if the patient tests antibody negative
- Hepatitis B vaccine—three doses, if the patient tests antibody negative
- Tetanus, diphtheria, and pertussis (Tdap) vaccine—if the patient has had a prior primary vaccination for tetanus, diphtheria, and pertussis, one dose followed by a booster every 10 years.
- Messenger ribonucleic acid (mRNA) vaccine for COVID-19.[47]

Vaccination of patients for measles, mumps, and rubella (MMR) is contraindicated in severely immunocompromised patients.

Biologics should not be delayed if killed virus vaccines are used. However, if live attenuated vaccines are used, then biologics should be delayed.

ACR in its recent guidance for COVID-19 vaccination of patients with rheumatoid diseases recommends vaccination regardless of disease activity or severity.[47] When possible, DMARD-naïve patients should be given their first dose of a COVID-19 vaccine before the start of immunomodulatory therapy. In addition, the guidance indicates that for patients taking rituximab the vaccination series should be timed so that it is given about 4 weeks prior to the next cycle of the drug.

However, MTX should be withheld for 1 week after each injection of an mRNA vaccine for patients with well-controlled disease. For single-dose vaccines, MTX should be withheld for 2 weeks. Janus kinase (JAK) inhibitors should be withheld for 1 week after vaccination. When SQ abatacept is being used, it should not be given for 1 week prior to and 1 week after the first dose of an mRNA vaccine is given. It should not be withheld for the second dose of the vaccine. However, if this drug is used intravenously, the first vaccine dose should be given 4 weeks after abatacept is administered and the next dose of abatacept should be delayed for 1 week. No modifications are suggested for the next dose of the vaccine. More detailed information regarding the timing of vaccination can be found in the guidance document cited above.[47]

All decisions regarding vaccines in RA patients should be based on a shared decision-making process between the patient and their provider. United Rheumatology recommends that all providers become familiar with the latest ACR guidance regarding COVID-19 vaccinations in patients with rheumatic and musculoskeletal diseases.[47]

Imaging

Imaging is an important part of the overall workup of patients with RA. Radiographs are inexpensive and widely available. Currently, X-ray is the initial imaging test of choice. It can be helpful in establishing the diagnosis of RA, particularly in difficult or unclear cases, and it can demonstrate progression of the disease.

Plain radiographs are not used in the classification of RA according to the ACR/EULAR classification system described above, because they are frequently normal in patients with very early disease. However, radiographs can and should be used to establish the diagnosis of RA. For instance, if available, recent X-rays of the hands and feet may be helpful in establishing a diagnosis for a patient who does not score ≥6 points in the ACR/EULAR classification system, because some of the available radiographs may demonstrate typical RA erosions; the patient can then be diagnosed with RA.

When using radiographs to diagnose RA, it is important to be precise. In 2013, EULAR published a definition of typical RA erosions to assist physicians in diagnosing patients who do not fulfill the classification criteria but in whom a diagnosis of RA is suspected.[37] To establish the diagnosis of RA based on radiographs of the hands and feet, there must be an erosion (defined as a break in the cortex of bone) of any size in ≥3 different joints from the following list:

- Proximal interphalangeal joints
- Metacarpophalangeal joints
- Metatarsophalangeal joints
- Wrist (counts as one joint)

If a patient meets the classification criteria for RA, baseline radiographs of the hands and feet should be obtained, if not recently performed. The presence of X-ray evidence of erosions at the time of diagnosis is associated with a poor prognosis.

Baseline X-rays (posteroanterior, lateral, and ball-park or Norgaard views) of the hands and three views of the feet should be obtained in all patients with a definite or possible diagnosis of RA. Bone changes may lag behind symptoms by as much as 6 to 12 months; baseline imaging is important to properly follow these patients.

Ultrasound of the hands and feet can be considered for patients with normal X-rays, because bone erosions may be detected on ultrasound before they are seen on plain films.

If there is suspicion of cervical spine involvement based on history or clinical evaluation, lateral radiographs of the cervical spine in neutral, flexion, and extension views should be obtained. Magnetic resonance imaging (MRI) of the cervical spine should be obtained in any patient with RA who has radiographic evidence of instability or clinical signs or symptoms of neurological involvement.[48]

ACR recommends against the routine use of MRI for the evaluation of inflammatory arthritis.[49] United Rheumatology supports this recommendation.

Treatment

It is important that the patient has a clear understanding of the goals of therapy, as well as the risks and benefits of the proposed treatment plan. The goal of treatment of RA is to maximize long-term health-related QoL by controlling symptoms, preventing structural progression, preserving normal function, and improving patient-reported outcomes (PROs).

United Rheumatology believes these goals are best accomplished by using a treat-to-target paradigm, with remission as the primary and ultimate clinical goal. Early and aggressive treatment is important, because even a brief delay of therapy can adversely affect long-term outcomes. If a clinical remission cannot be achieved due to long-standing disease or comorbidities, low disease activity (LDA) is an acceptable alternative.[50]

Treatment should be based on accepted, objective, and consistently utilized metrics of disease activity. Drugs should be adjusted, if the established targets are not achieved within the expected timeframe and should always be directed by a rheumatologist or managed under the supervision of a rheumatologist.

With the currently available drugs, it is possible to achieve remission in many patients. If treatment is started early, some patients may have no or minimal joint damage or disability. Without adequate treatment, approximately 60% of patients develop significant and irreversible joint damage within the first

2 years of diagnosis.[51] Progressive joint damage is often faster early in the course of the disease,[52] so that early and aggressive treatment is essential to minimize joint damage. Studies have demonstrated that this treatment approach is associated with better therapeutic outcomes; including a decrease in disease activity score, more favorable radiographic outcomes, and improvement in physical function and QoL.[53]

A poor outcome increases with the number of risk factors such as:[54,55]

- HDA
- Elevated acute-phase reactants such as ESR and CRP
- High swollen joint count
- High levels of auto-antibodies at (RF and ACPA)
- Extra-articular disease
- Early erosions
- Moderate disease activity (MDA) to HDA after treatment with methotrexate (MTX) for at least 3 months, with therapeutic blood levels of the drug
- Multiple comorbidities

When treating patients with RA, objective measures of disease activity should be used. The most common measures for RA are based on clinical, laboratory, and imaging results. Currently, several validated tools are available. These include the Disease Activity Score 28 (DAS28), the Clinical Disease Activity Index (CDAI), and the RAPID3.

Although all of these tools are commonly used, United Rheumatology favors a composite score (that includes swollen and tender joints) such as the CDAI rather than evaluator-only or patient-only derived measures. The DAS28 has been reported to be insufficiently stringent for consistent identification of remission.[56] In a study involving 864 patients with RA receiving MTX monotherapy, DAS28 remission was comparable to remission based on the CDAI scores, *only if* the patient did not have any residual swollen joints. The CDAI allows for a maximum of two swollen joints in remission but, according to the authors, DAS28 allowed for more than twelve swollen joints when the patient was said to be in remission.[57] Therefore, United Rheumatology supports the use of the CDAI as the best-validated method for determining disease activity in RA.

The CDAI scoring system is built around five core disease-activity parameters, which include the following:

- Tender joint count (based on evaluation of 28 joints)
- Swollen joint count (based on evaluation of 28 joints)
- PtGA
- Patient Health Assessment
- Physician Global Assessment (PGA)

Scores range from 0 to 76 (Table 3). A calculator for the CDAI can be found in the Appendix.

Table 3. Disease activity categories according to the CDAI scoring system

Disease Activity	Scores
Remission	≤2.8
LDA	≤10
MDA	>10.0 to 22.0
HDA	>22.0

CDAI, Clinical Disease Activity Index; HDA, high disease activity; LDA, low disease activity; MDA, moderate disease activity

There is no single gold standard disease-activity laboratory marker for RA. Currently, ESR and CRP are used as markers of inflammation, although they are not specific for RA. In addition, as discussed above, isotypes of RF may be helpful. A study by Keenan et al.[58] that included 188 patients with RA found no strong relationship between ESR and CRP values and other measures of disease activity and suggested that these acute-phase reactants had limited usefulness for making treatment decisions. More recently, the Vectra® DA test has become a validated serologic marker of disease activity.[59] High Vectra DA scores have been predictive of radiographic disease progression.[59] A baseline Vectra DA can be considered in patients with RA, especially if this test will be used in conjunction with other data to monitor response to therapy or to support tapering of medications in a patient who has been in remission for at least 6 months.[60] According to EULAR, patients who achieved LDA rather than remission should not be considered for drug tapering[61] because they are more likely to develop flares than those in remission.

In remission, patients should have no evidence of radiographic progression and might even show healing of erosions.

When a validated scoring system is used and treatment adjusted based on the results of an objective measure of disease activity, clinical outcomes improve.[50] For patients with HDA or MDA, scores should be calculated at 1- to 3-month intervals; in those with sustained remission or LDA, scores should be calculated at 6- to 12-month intervals.[56] To obtain an objective assessment of changes in disease activity, the same measures should be used at each visit. If desired, more than one measure can be calculated at each visit.

The consistent use of RA disease measurements is essential for quantitative comparisons of disease activity over time and for gauging response to treatment.

Pharmacologic Therapy Overview

Aggressive drug therapy should begin early. Disease-modifying antirheumatic drugs are a staple in the treatment of patients with RA (

Table 4).

Until the desired treatment target is achieved, drug therapy should be assessed and adjusted as often as required. Disease activity should be calculated at each visit, and medications adjusted appropriately.

Unfortunately, noncompliance with prescribed drugs is a significant problem in the management of patients with RA. A recent study by Kan et al.[62] retrospectively reviewed electronic health records (EHRs) from more than 50 provider organizations in the US and looked at pharmacy claims, provider claims, and facility claims. The authors identified patients who were newly prescribed either oral or injectable MTX, a biologic, or tofacitinib. Primary nonadherence was defined as a new prescription of MTX or a new prescription or infusion of biologics or tofacitinib written by a physician (as recorded in the EHR) but not filled or administered within 2 months for MTX or within 3 months for biologics/tofacitinib (based on claims). Approximately 36.8% of patients in the MTX group and 40.6% of those in the biologic/tofacitinib group were nonadherent.

Irrespective of the pharmacologic therapy prescribed, patients must be counselled regarding the importance of adherence with the medical program, especially because noncompliance may result in poor outcomes that could have been avoided. The importance of compliance should be re-enforced at every visit. As part of this discussion, a behavioral agreement between the patient and the physician may be considered for new patients as a way to encourage adherence with medications.

Before pharmacologic therapy is initiated, laboratory tests, including but not limited to the following, should be considered if not already recently done:

- CBC with differential count
- Liver function test
- Electrolytes
- Blood urea nitrogen and creatinine
- Glomerular filtration rate
- TB testing for patients starting biologic originator and biosimilar disease-modifying antirheumatic drugs (bDMARDs), or targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs)

When selecting pharmacologic therapy, existing comorbidities must be considered.[63] Treatment modifications may be required in patients with a history of (but not limited to) any the following:

- Congestive heart failure Class 3 or 4 (TNF inhibitors should not be used until adequate restoration and stabilization of cardiac function is achieved.)
- Active hepatitis B virus (HBV) infection
- Prior exposure to hepatitis C virus (HCV) or HCV infection
- Previous serious infections
- Previously treated or untreated malignancy
- Skin cancer of any type
- Previously treated lymphoproliferative disorder
- Renal disease

- Anemia of chronic disease
- Thrombocytopenia
- Leukopenia
- Human immunodeficiency virus (HIV)

All patients who will be treated with hydroxychloroquine should have a complete baseline ophthalmologic evaluation within the first year of starting therapy. Annual ophthalmologic examinations should be obtained while the patient remains on this drug. One of the major complications associated with hydroxychloroquine therapy is the development of issues of the cornea and/or macula of the eye. The cornea can develop cornea verticillate, which is usually reversible after stopping the drug. A more serious potential problem is the development of pigment deposits in the macula resulting in irreversible vision loss.

Physicians must also be aware of possible drug interactions with other medications taken by the patient.

Table 4. Drugs used in the management of RA

Drug	Route of Administration	Warnings
csDMARDs		
MTX (Rheumatrex®)	Oral	
MTX (Rasuvo®, Otrexup™)	SQ	
Leflunomide (Arava®)	Oral	
Sulfasalazine (Azulfidine®)	Oral	
Hydroxychloroquine (Plaquenil®)	Oral	
Azathioprine (Imuran®)	Oral	
bDMARDs		
boDMARDs		
Non-TNFi		
Abatacept (Orencia®) – T-cell costimulation inhibitor	IV or SQ	
Rituximab (Rituxan®) – B cell directed monoclonal antibody	IV	
TNFi		
Adalimumab (Humira®)	SQ	
Certolizumab pegol (Cimzia®)	SQ	
Etanercept (Enbrel®)	SQ	
Golimumab (Simponi® and Simponi® Aria)	SQ and IV	
Infliximab (Remicade®)	IV	
IL-6 inhibitors		
Tocilizumab (Actemra®)	IV or SQ	
Sarilumab (Kevzara®)	SQ	
bsDMARDs		
Erelzi® (etanercept-szzs; originator drug: Enbrel)	SQ	
Amjevita™ (adalimumab-atto; originator drug: Humira)	SQ	
Cyltezo® (adalimumab-adbm; originator drug: Humira)*	SQ	
Inflectra® (infliximab-dyyb; originator drug: Remicade)	IV	
Renflexis® (infliximab-abda; originator drug: Remicade)	IV	

tsDMARDs (JAK inhibitors) Tofacitinib (Xeljanz®) Baricitinib (Olumiant®) Upadacitinib (Rinvoq®)	 Oral Oral Oral	On September 1, 2021 the FDA[64] issued significant warnings for the 3 JAK inhibitors currently approved: Xeljanz, Olumiant and Rinvoq. The warnings state that there is an increased risk of cardiac events such as myocardial infarction or stroke; blood clots, cancer and death compared to TNF drugs when used to treat RA. It advised that these drugs only be used when patients have failed to respond or are intolerant to TNFi or non-TNFi biologic drugs or their biosimilars.
Corticosteroids** Short term	Oral, IM, or IV	

*On October 15, 2021, the FDA announced that Cyltezo (adalimumab-adbm) had been approved as interchangeable (may be substituted for) its originator drug Humira and may be used for any of the approved indications. (FDA news release 3, FDA approves cyltezo, the first interchangeable biosimilar to Humira, accessed at https://www.fda.gov/news-events/pressannouncements/fda-approves-cyltezo-first-interchangeable-biosimilar-humira , October 19, 2021.

**Short-term corticosteroids are taken for <3 months.

bDMARD, biologic originator and biosimilar disease-modifying antirheumatic drug; boDMARD, biologic originator diseasemodifying antirheumatic drug; bsDMARD, biosimilar disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; IL-6, interleukin 6; IM, intramuscular; IV, intravenous; JAK, Janus kinase; MTX, methotrexate; SQ, subcutaneous; tsDMARD, targeted synthetic disease-modifying antirheumatic drug such as JAK inhibitors; TNF, tumor necrosis factor; TNFi, TNF inhibitor

Initial Treatment of DMARD-naïve Patients

For DMARD-naïve patients with RA, conventional synthetic disease-modifying antirheumatic drug (csDMARD) monotherapy should be started as soon as possible. Unless contraindicated, MTX, taken orally or subcutaneously, is the initial drug of choice (Figure 1).[60,61]

A 2013 Cochrane review[65] reported that the use of folic or folinic acid by patients taking MTX for RA can reduce some of the adverse effects of the drug; including but not limited to nausea, abdominal pain, abnormal liver function tests and oral ulcers. By decreasing side effects, folic or folinic acid helped patients to continue taking MTX rather than moving to a bDMARD. Using either of these supplements does not decrease the efficacy of MTX. Every patient taking MTX, orally or subcutaneously, should also take folic or folinic acid.[66]

In the 2019 EULAR recommendations for the treatment of RA, folic acid supplementation is strongly encouraged to decrease the side effects of MTX.[61] In the 2021 ACR guideline, the use of folic acid to decrease side effects of MTX in patients who are either taking a split dose of MTX or subcutaneous (SQ)

injections of the drug is conditionally recommended. The starting dose of folic acid is usually 1 mg daily. This appears to be an adequate dose even with MTX doses up to 25 mg per week.[66] If symptoms of MTX toxicity occur or increase, folic acid should be slowly increased up to 5 mg/week. Sometimes folic acid does not adequately control symptoms of drug toxicity in which case folinic acid can be tried.

United Rheumatology strongly recommends the use of folic or folinic acid with any method of administration or dose of MTX to decrease side effects.

Methotrexate

Both EULAR and ACR support the use of MTX, orally or subcutaneously, as the initial drug of choice for the management of early RA.[60,61]

MTX is usually started at a dose of 10 to 15 mg/week (along with folic or folinic acid). If the lower dose is used the drug should be rapidly titrated up to 15 mg/week over the first 4 to 6 weeks. If remission or LDA is not achieved by 6 weeks MTX should be titrated to a maximum dose of 25 mg per week or until the highest tolerable dose has been reached.[54,63] If the patient is on ≥15 mg/week, split doses taken about 8 hours apart is strongly encouraged.[67] This may increase absorption of MTX by 15% and is associated with

less toxicity, especially GI issues. In addition, at this dose, SQ administration of MTX should also be considered if the patient does not achieve remission or LDA in the expected time frame on oral MTX.

According to a report by Herman et al.,[68] the bioavailability of oral MTX is about 70%. The efficacy of MTX can be limited by several factors; however, the most important one is inadequate absorption, especially at doses over 15 mg per week.[68,69] It has been well documented that the **bioavailability of oral MTX is not as reliable as that of SQ MTX**[70] especially when the oral dose is ≥15 mg/week taken all at once. Increasing the oral dose to increase the amount of drug available in a patient's system does not necessarily improve the bioavailability of the drug but it may lead to more adverse events and higher toxicity, which can be a limiting factor for the use of oral MTX.[70] However, it has been found that taking oral MTX (≥15 mg/week) in split doses about 8 hours apart improves the bioavailability of the drug.[67] Before changing to or adding a biologic to oral MTX, SQ administration should be considered if oral MTX has not achieved the goals of treatment.

Although MTX is approved in the US for both oral and SQ use, the latter route, which has been shown to be very effective and less costly than biologics or tsDMARDs, is under-utilized.[71] In one study, only approximately 38% of commercially insured and Medicare patients received doses of oral MTX exceeding 20 mg per week[71] and patients who advanced to a biologic rarely had a trial of SQ MTX.

In a study by Hazlewood et al.,[72] SQ MTX was associated with a lower failure rate (49%) than with oral administration (77%). There was no difference in treatment failure due to toxicity between the two routes of administration, but there was a significant difference in failure secondary to lack of efficacy, which was higher in patients treated orally. These findings were consistent with those of an earlier study in which SQ MTX had been shown to be more effective than the oral administration at the same dose.[73]

The results of a retrospective review of 196 patients with RA who had been changed from oral to SQ MTX was reported in 2014.[74] Half of the patients in this study were changed to SQ MTX, because they had an inadequate response to oral MTX. Of those who were changed to SQ MTX, approximately 44% did not tolerate the drug orally. Of this group, 83% continued with SQ MTX for 1 year, 75% for 2 years, and 47% were still using SQ MTX at 5 years. Less than 10% of this group required a biologic in addition to MTX during the first 2 years of the study because of an inadequate response.

Rohr et al.[75] looked at a large population of DMARD-naive RA patients diagnosed in 2009 and 2012. The patients were followed for 3 (2012 group) to 5 years (2009 group). The authors looked at initial treatment in these patients and for any evidence of change in prescribing habits of their providers.

In the 2009 group, 25% received a biologic before a trial of MTX; 7% were initially started on SQ MTX, and 68% were initially started on oral MTX. Of those started on oral MTX, 44% remained on it for the 5 years of the study. The average dose of MTX was 15.3 mg/week (a low dose) before either a biologic was introduced or a change to SQ MTX was initiated. In 41% of the patients who had a change in medication, the change occurred within the first 3 months after starting MTX. Interestingly, 72% of the patients who switched from oral MTX to SQ MTX remained on it for the duration of the study. The 2012 group had a modest increase in oral MTX dose (15.9 mg/week) before changing treatment and a small but significant increase in their use of SQ MTX (from 13% to 16%).[75]

The authors concluded that, in patients with RA, treatment with oral MTX may be suboptimal, both in dose and duration, before a change to a biologic or SQ MTX is initiated. They also reported that a significant number of patients who started on or changed to SQ MTX did **not** require biologic therapy.[75]

In 2011, the Canadian Rheumatology Association published recommendations for pharmacologic management of RA.[76] Recommendation 11 (Page 6) states the following:

> Dosing of methotrexate (MTX) should be individualized to the patient (IV). MTX should be started oral or parenteral and titrated to a usual maximum dose of 25 mg per week by rapid dose escalation. In patients with an inadequate response or intolerance to oral MTX, parenteral administration should be considered (I). (Level I, IV, Strength A).

Renal and liver function tests and a CBC should be closely followed in all patients taking MTX, regardless of dose or route of administration. In some cases, it may be necessary to change medications based on the results of these tests. Patients should be monitored for uncommon but potentially serious adverse events, including pulmonary toxicity. Monitoring also requires thorough patient education relating to side effects and adverse events. MTX must be given for at least 3 months before maximum efficacy can be determined.

When csDMARDs are initiated or the dose is increased, short-term steroids (<7.5 mg per day) may be considered. If steroids are used, an attempt to taper them after 3 months should be tried, if clinically possible according to the 2019 update of the EULAR recommendations for the management of RA.[61,77] ACR, on the other hand, conditionally recommends that csDMARDS be started without the use of short-term steroids for patients with MDA or HDA. However, ACR acknowledges that low-dose steroids (<10 mg per day) may be needed to reduce pain and inflammation. If needed, steroids should be tapered over no more than 3 months. In some patients, it may not be possible to completely stop oral steroids or taper over 3 months or less; however, the dose should be as low as possible and used for the shortest time possible.[60]

For patients with any disease activity level, MTX is preferred over other csDMARD therapy or dual or triple csDMARD therapy. For patients with LDA, some providers may consider starting treatment with hydroxychloroquine or sulfasalazine instead of MTX in order to decrease side effects and/or immune suppression.[60]

If MTX is contraindicated or not tolerated, then leflunomide at 20 mg daily and/or sulfasalazine at up to 3 g daily and/or hydroxychloroquine can be considered (Figure 2).[54]

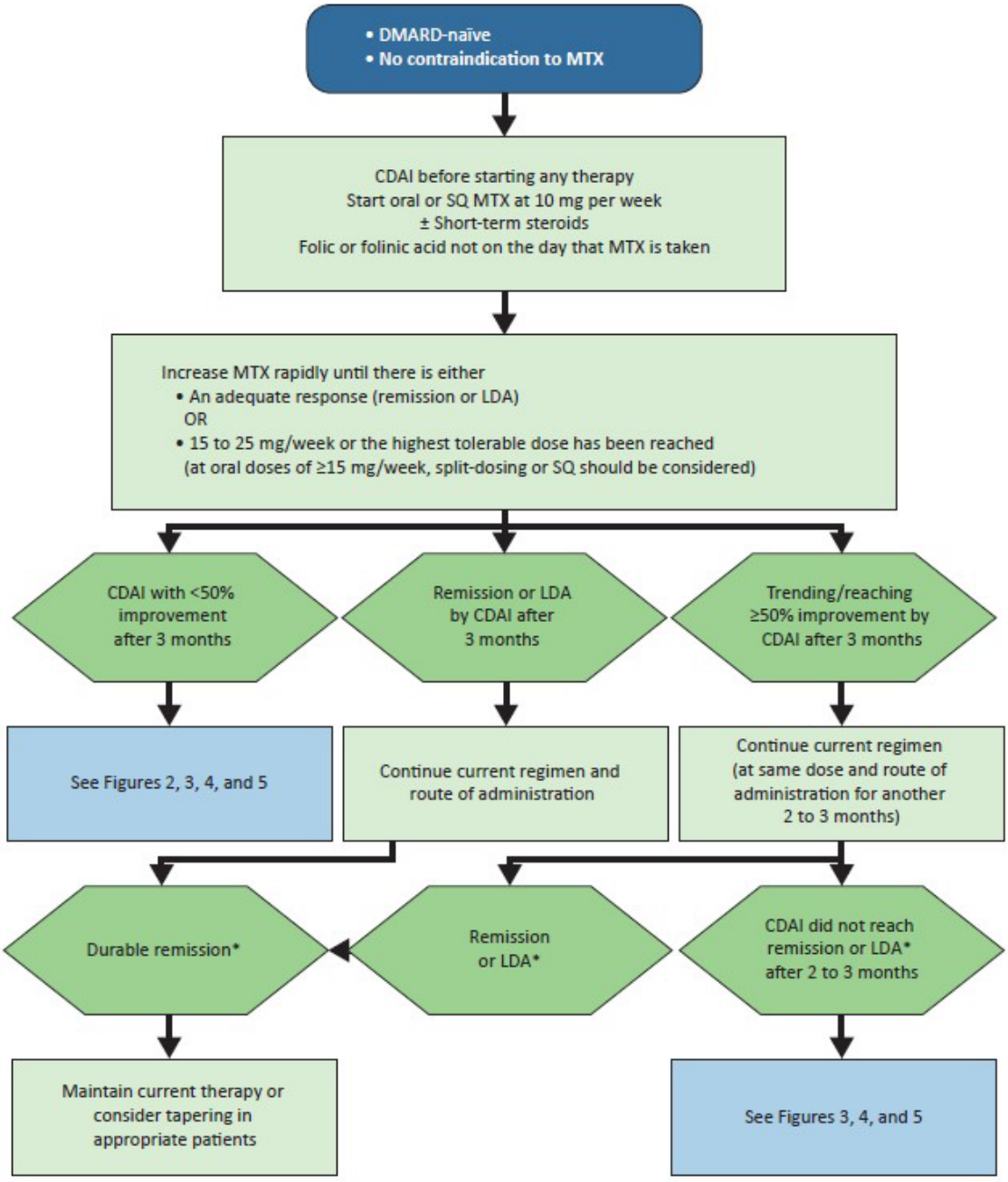


Figure 1. Initial pharmacologic management of DMARD-naïve patients with RA and no contraindication to MTX

*In some patients with comorbidities, LDA may be the treatment target; when LDA is reached, continue the same regimen and do not consider tapering of drugs. In other patients with very significant or multiple comorbidities, it may not be possible to escalate treatment to reach LDA.

CDAI, Clinical Disease Activity Index; DMARD, disease-modifying antirheumatic drug; LDA, low disease activity; MTX, methotrexate; RA, rheumatoid arthritis; SQ, subcutaneous

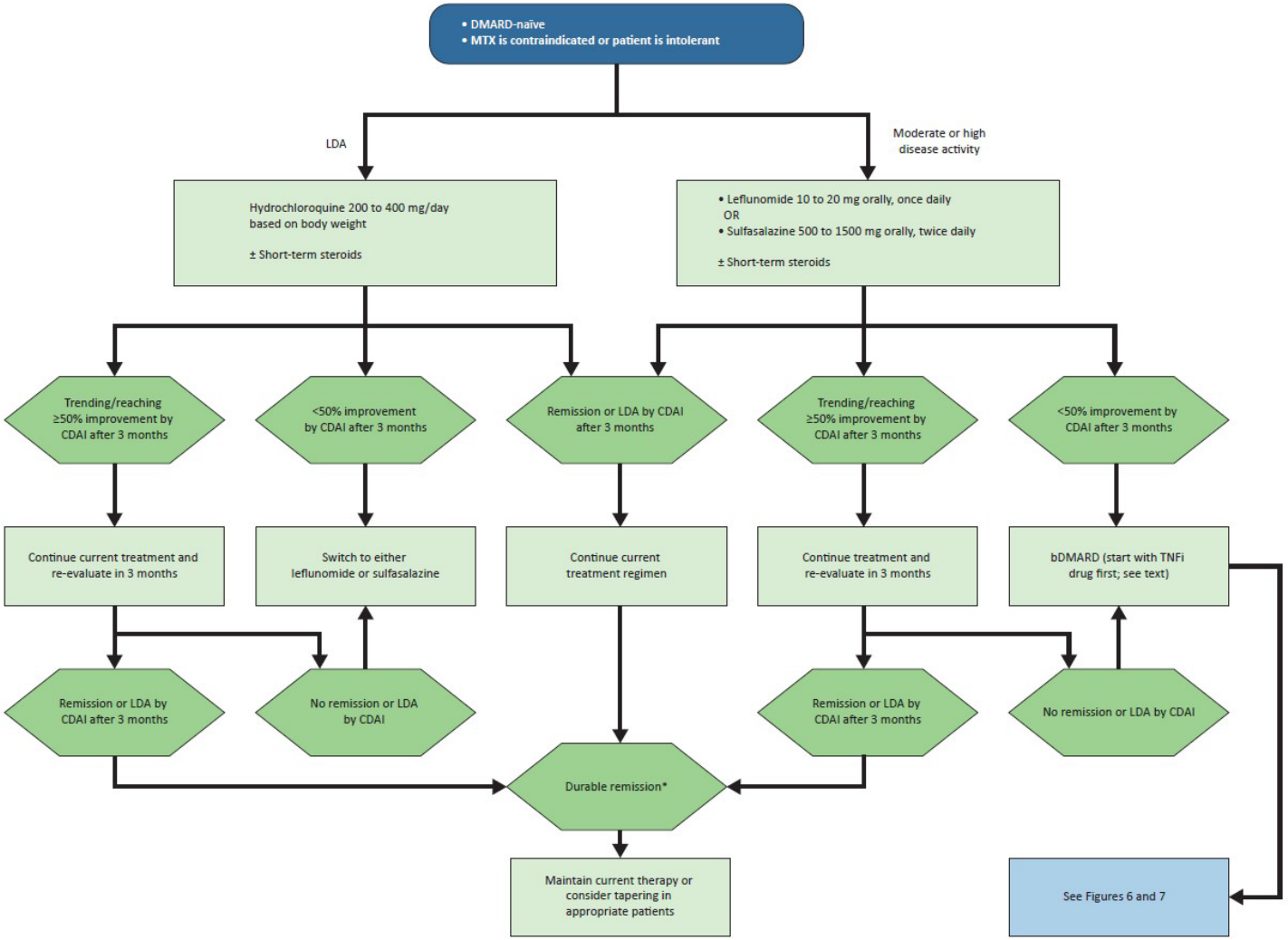


Figure 2. Initial pharmacologic management of DMARD-naïve patients with RA and a contraindication to MTX

*In some patients, LDA is the treatment target; when LDA is reached, continue the same regimen and do not consider tapering bDMARD, biologic originator and biosimilar disease modifying antirheumatic drugs; CDAI, Clinical Disease Activity Index; DMARD, disease-modifying antirheumatic drug; LDA, low disease activity; MTX, methotrexate; RA, rheumatoid arthritis; TNFi, tumor necrosis factor inhibitor

In DMARD-naïve patients with early RA, the response to treatment should be carefully re-evaluated at 3 months using an objective measure (CDAI). Based on their pooled analysis of clinical trial data, Aletaha et al.[78] considered 3 months after initiating treatment to be a critical decision point. They reported that patients demonstrating an improvement of at least 50% in disease activity had a very good likelihood of reaching remission in another 3 months on the current dose. Patients who demonstrated a less-than-50% improvement in their disease activity scores were not likely to achieve remission after an additional 3 months on the same medication regimen.

After the initiation of csDMARD therapy, the patient should be seen as often as necessary for re-evaluation and dose adjustment until a stable drug regimen and an adequate disease level is established. The initial trial of oral MTX should last at least 3 months to see the maximum effect of the drug. During that time, the dose should be escalated rapidly until remission or LDA by CDAI, or the maximum tolerated dose is reached, or an oral dose of 25 mg a week is reached.

Patients with an Adequate Response to Methotrexate at 3 Months

For patients who have reached either remission or LDA at the end of 3 months, the dose and route of administration of MTX should not be adjusted. These patients should be monitored for any change in disease activity, flares, or signs of drug toxicity that may require modification of drug therapy.

In general, once a patient is stable on MTX, re-evaluation is usually needed on a quarterly basis. For those with no comorbidities, less frequent evaluation may be appropriate. Repeat disease activity scoring should be performed at each visit, and drug doses should be adjusted, based on a combination of disease activity score and clinical evaluation.

The importance of reaching a durable state of remission or LDA and the need for continued follow-up should be stressed to all patients at every visit. Unfortunately, **30% to 40% of patients may not have an adequate response to MTX,**[79] even after a trial of SQ MTX or split dosing.

Patients with an Inadequate Response to Methotrexate at 3 Months

Patients who have achieved an improvement of at least 50% in disease activity but are not yet in remission or at LDA after 3 months of MTX have a very good chance of achieving their target at the end of another 2 to 3 months with the same dose and route of administration, or a change to SQ MTX at the same dose to improve bioavailability of the drug may be indicated.

United Rheumatology recognizes that there are patients who have not completely reached the 50% improvement target but are close to it at the end of 3 months. Additional consideration may be given to the trajectory of improvement for these individuals. For example, if a patient is close to the 50% threshold of improvement in CDAI, and there is more improvement toward the end of the 3-month trial than at the beginning, the physician may decide to maintain the current medication dose for another 2 months, because the patient may not yet have reached a steady state; alternatively, the physician may decide to switch the patient to SQ MTX at the same dose. If this patient does not reach remission or LDA

 at the end of the additional 2 to 3 months, a change to a bDMARD (start with TNFi) is indicated (Figure 3). MTX should be continued, if appropriate.

A patient on oral MTX who has reached slightly more than a 50% improvement in disease level at the 3-month mark but with a considerably slowed rate of improvement in the last few weeks may be less likely to reach the target of remission or LDA in another 2 months at the same dose. The physician may consider keeping the patient on the same dose of MTX for another 2 to 3 months or changing to SQ MTX at the same dose for 2 to 3 months and then re-evaluating disease activity. If there is remission or LDA, the patient may be kept on the same dose and route of administration of the drug. If remission or LDA has not been reached, an MTX polyglutamate (PG) level should be considered (Figure 3).

For patients who have achieved a less than 50% improvement in disease activity at the end of 3 months of oral MTX, measuring the MTX PG level should also be considered (Figure 3) (see discussion below). A MTX PG level of <20 may indicate that the patient is either not compliant with the drug regimen or not adequately absorbing or metabolizing the drug. A trial of SQ MTX is indicated and if the patient does not achieve LDA or remission the patient should be changed to a bDMARD (initial drug choice should be a TNFi).

Methotrexate Polyglutamate Levels

MTX is a folate antagonist, and the doses required to obtain an adequate response (remission or LDA) vary from patient to patient and are unpredictable. MTX may also be associated with numerous adverse events such as – but not limited to – nausea, vomiting, fatigue, hair loss, elevated liver function tests, rising creatinine, infection, and cytopenia.

After MTX is ingested or parenterally administered, the serum concentration falls rapidly. The biochemical reactions that occur when MTX enters a cell are very complex. If the reader is interested in more information on this subject, he/she is referred to the following:

- Danila MI, Hughes LB, Brown EE, Morgan SL, Baggott JE, et al. Measurement of erythrocyte methotrexate polyglutamate levels: ready for clinical use.[80]
- Kremer JM. Toward a better understanding of methotrexate.[81]
- Goodman S. Measuring methotrexate polyglutamates.[79]

When MTX enters a cell, it forms PG. Many different forms of MTX PG are synthesized over time. The MTX PG test measures the level of MTX PG in circulating erythrocytes. The results are reported as one of three categories: therapeutic (>60 nmol/L), intermediate (20 to 60 nmol/L), or subtherapeutic (<20 nmol/L).[80,82] According to Exagen Diagnostics, one of the providers of this test, patients falling into the subtherapeutic group were three times more likely to have a poor response to MTX than those with a level >20 nmol/L; patients with a MTX PG level >60 nmol/L were five times more likely to have a good response to MTX than those with a level of ≤60 nmol/L.[82]

Patients with Therapeutic Methotrexate Polyglutamate Levels

Patients who have a therapeutic level of MTX PG at 3, 5, or 6 months but failed to reach remission or LDA should not continue with it as monotherapy. Changing to a bDMARD (preferably a TNFi) is the preferred treatment and these patients may reach remission or LDA quickly. MTX should be continued, if appropriate.

In some situations, adding sulfasalazine and hydroxychloroquine to MTX (triple therapy) rather than changing to a bDMARD is conditionally recommended by ACR because it is less expensive and has fewer adverse events compared to MTX monotherapy.[60]

Patients with less than 50% improvement in disease activity level at the end of the first 3 months despite a therapeutic MTX PG level should also be started on a bDMARD (preferably a TNFi) (Figure 3). MTX should be continued, if appropriate.

Patients with Subtherapeutic Methotrexate Polyglutamate Levels

If, at the 3-month decision point, response to MTX is inadequate by CDAI and the MTX PG level is subtherapeutic, a change to SQ MTX should be strongly considered (see discussion on SQ MTX below) (

Figure 4). If there is concern that the patient is noncompliant, this issue should also be addressed; a second trial of oral MTX can be considered or the patient can be switched to SQ MTX.

The patient should be re-evaluated 2 to 3 months after switching to SQ MTX. If there is less than 50% improvement in the disease activity score and the patient has been taking the medication and has a subtherapeutic level of MTX PG, a bDMARD (preferably a TNFi) should be started. MTX should be continued, if appropriate.

If the patient has reached remission or LDA at the end of the additional 2 to 3 months of MTX, the current medication regimen should be maintained. These patients should be monitored for any change in disease activity, flares, or signs of drug toxicity that may require modification of drug therapy.

Patients achieving remission or LDA with a subtherapeutic MTX PG level should be maintained on the dose and route of administration that has achieved the treatment target. They should be followed for evidence of increasing disease activity, flares, and signs of MTX toxicity.

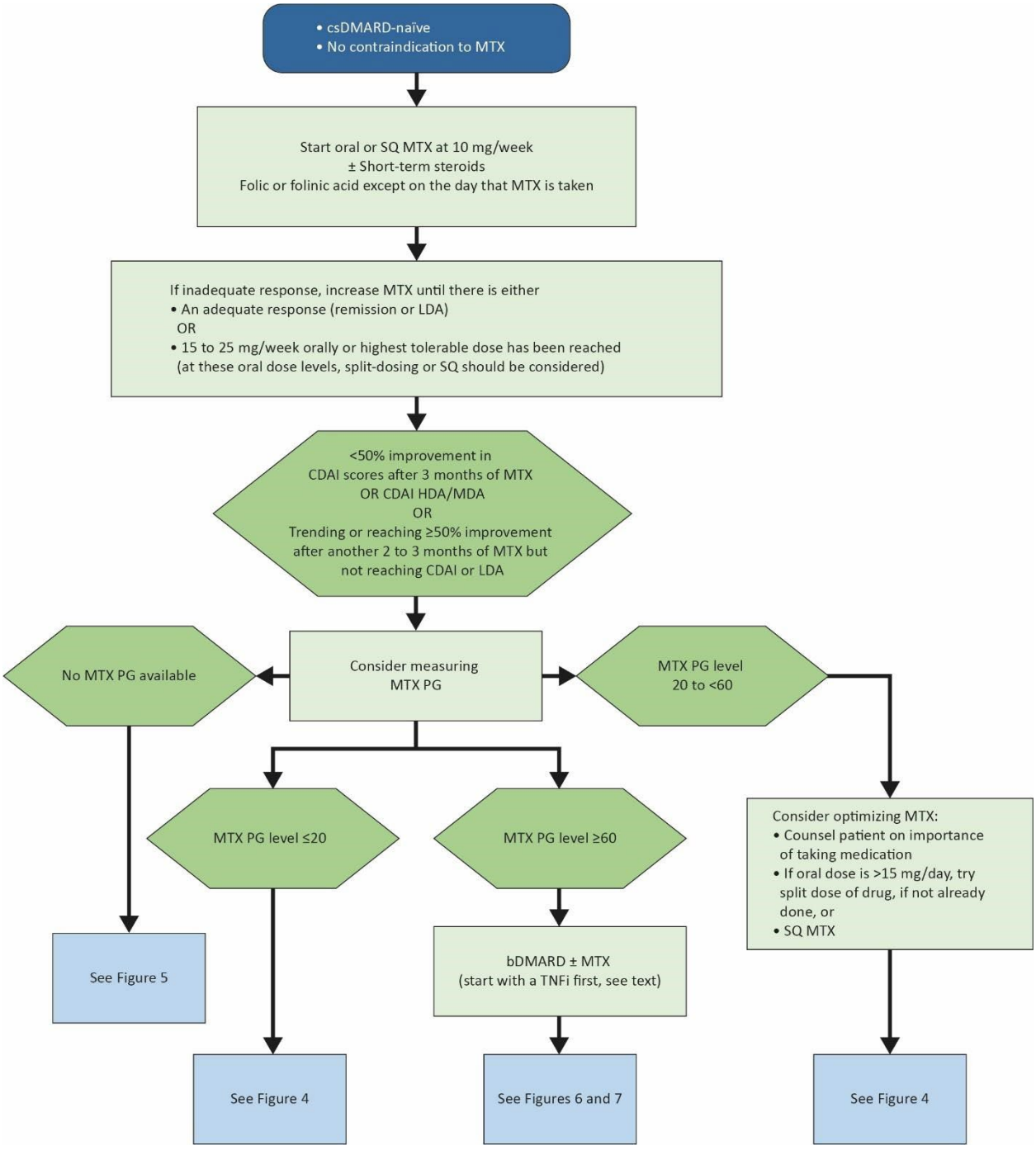


Figure 3. Pharmacologic management of patients with RA and therapeutic levels of MTX PG and either <50% improvement in CDAI after 3 months of treatment with MTX or failure to attain remission after 6 months of MTX

bDMARD, biologic originator and biosimilar disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HDA, high disease activity; MDA, moderate disease activity; MTX, methotrexate; PG, polyglutamate; RA, rheumatoid arthritis; SQ, subcutaneous; TNFi, tumor necrosis factor inhibitor

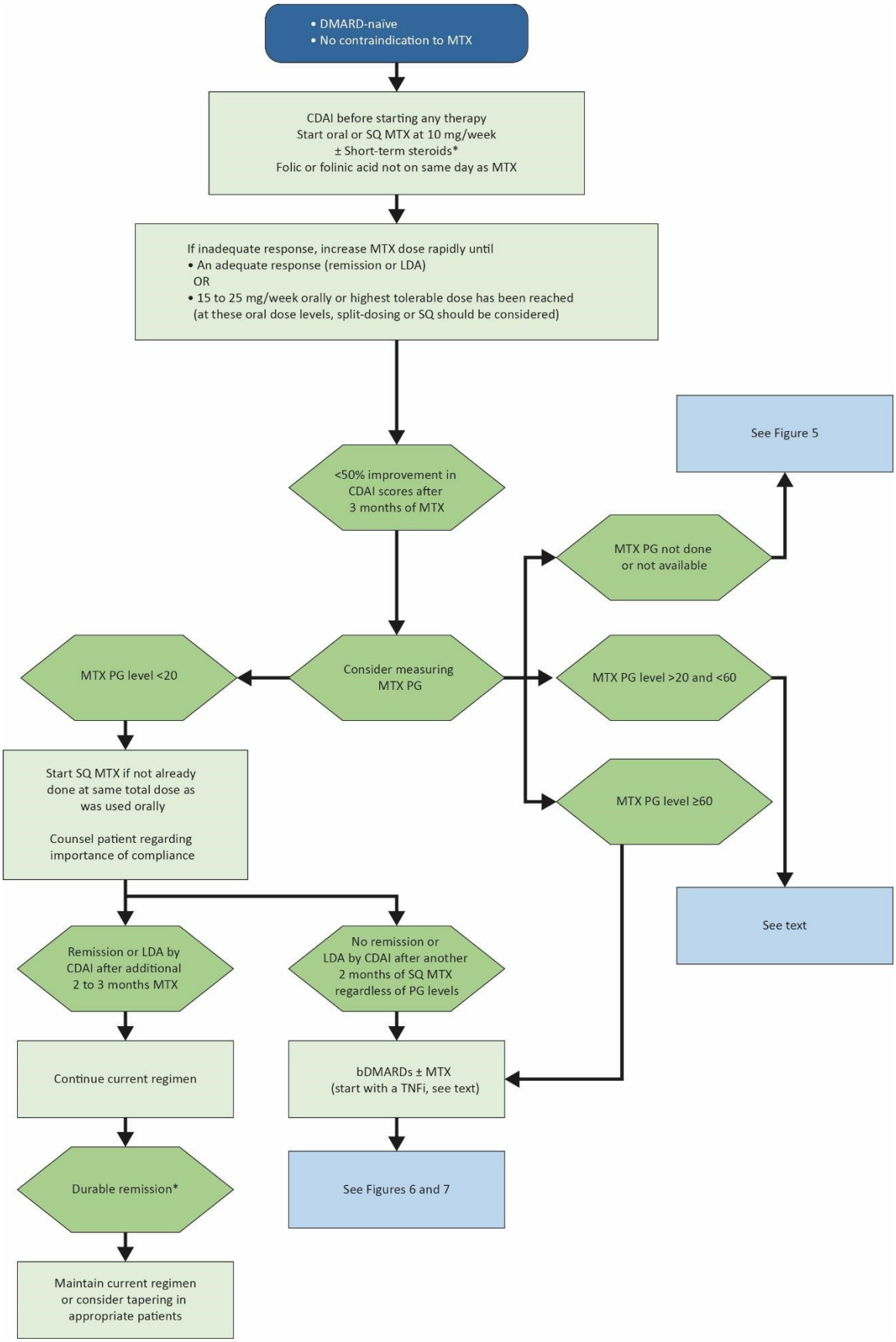

• DMARD-naïve
• No contraindication to MTX
CDAI before starting any therapy
Start oral or SQ MTX at 10 mg/week
± Short-term steroids*
Folic or folinic acid not on same day as MTX
If inadequate response, increase MTX dose rapidly until
• An adequate response (remission or LDA)
OR
• 15 to 25 mg/week orally or highest tolerable dose has been reached
(at these oral dose levels, split-dosing or SQ should be considered)
<50% improvement in CDAI scores after 3 months of MTX
See Figure 5
MTX PG not done or not available
Consider measuring MTX PG
MTX PG level <20
MTX PG level >20 and <60
MTX PG level ≥60
Start SQ MTX if not already done at same total dose as was used orally
Counsel patient regarding importance of compliance
See text
Remission or LDA by CDAI after additional 2 to 3 months MTX
No remission or LDA by CDAI after another 2 months of SQ MTX regardless of PG levels
Continue current regimen
bDMARDs ± MTX
(start with a TNFi, see text)
Durable remission*
See Figures 6 and 7
Maintain current regimen or consider tapering in appropriate patients

Figure 4. Pharmacologic management of patient with RA and subtherapeutic levels MTX PG who have had either <50% improvement in CDAI after 3 months of treatment with MTX or failure to attain remission after 5 months of MTX

Note: for patients treated initially with SQ MTX with subtherapeutic levels of MTX PG, please see Figure 6

In some patients, LDA is the treatment target; when LDA is reached, continue the same regimen and do not consider tapering.
bDMARD, biologic originator and biosimilar disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; DMARD, disease-modifying antirheumatic drug; LDA, low disease activity; MTX, methotrexate; PG, polyglutamate; RA, rheumatoid arthritis; SQ, subcutaneous; TNFi, tumor necrosis factor inhibitor

Patients with Intermediate Methotrexate Polyglutamate Levels

Management of patients with MTX PG levels in the intermediate-category range after 3 months of oral MTX is not as clear as for those in the subtherapeutic or therapeutic levels who have not reached remission or LDA. Those who fall into the intermediate range of MTX PG and have reached remission or LDA should be kept on the current dose and administration route and be monitored carefully for evidence of flares or an increase in disease activity.

There is no conclusive evidence that higher MTX PG levels correlate with better patient response, particularly in the intermediate range. Approximately one third of patients will never respond to MTX regardless of dose or mode of delivery, and regardless of the MTX PG level.[79] According to Goodman (Page S24):[79]

> There is no absolute correlation of MTX PG levels with beneficial effect, although efficacy is more likely at higher levels. Patients with MTX PG levels above 60 nmol/L are more likely to have a therapeutic benefit than those patients with lower levels. There is considerable overlap between the groups. Moreover, the lag to steady state equilibrium diminishes the timeliness necessary if this were to be used to guide dose escalations.

Dervieux et al.[83] stated that well-designed prospective studies are needed to determine how MTX PG may be used to determine the effectiveness of MTX in a particular patient. In addition, pharmacogenetic factors must be investigated to understand how these might influence an individual's response to MTX.

Several published studies have tried to determine whether higher levels of MTX PG correlate with better response to MTX. The results are inconsistent. The demographics and study designs are highly variable, and these two factors may be partly responsible for the inconsistent results.

In a study published by Murosaki et al.[84] in 2017, the authors state that MTX PG may have the potential to assist physicians in determining the efficacy of MTX and help them to determine doses and mode of administration. However, although this study was promising, even the authors acknowledge that the protocol for the study had not been followed rigorously; instead, it had been conducted under the conditions of routine clinical practice and more rigorous studies were needed before MTX PG could be used to determine dosing. An investigation published in 2013, demonstrated that higher MTX PG levels were associated with LDA, after 3 months and disease activity continued to improve at 6 months and 9 months.[85] No specific correlations of MTX PG levels with disease activity scores were provided. Additional studies were recommended by these authors as well.

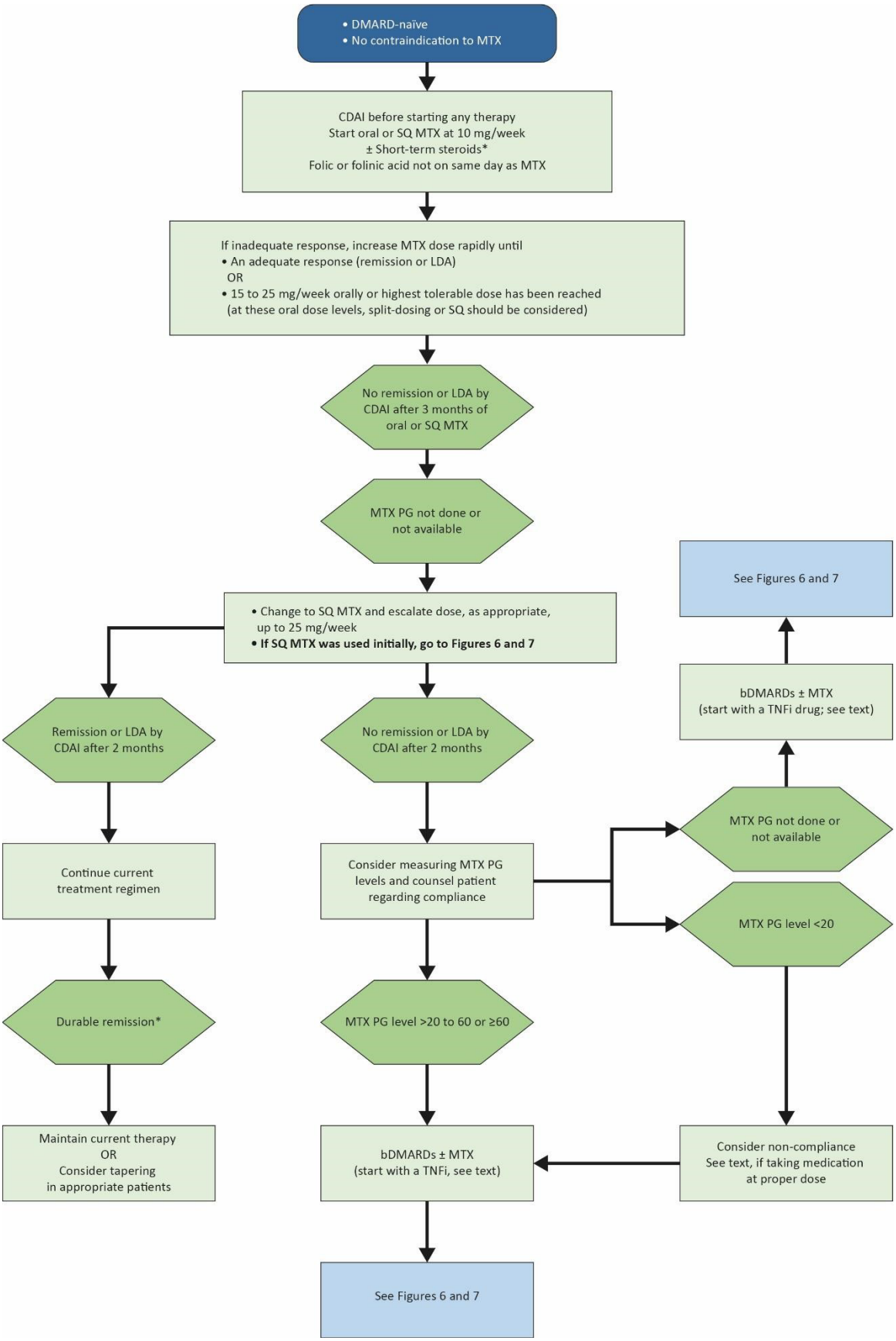
A 76-week study using a more rigorous protocol than that employed by Murosaki et al. found that, in 79 MTX-naïve patients, dose escalation of MTX resulted in higher levels of MTX PG and a decrease in disease activity scores.[86] The MTX PG concentrations were found to be affected by both body mass index and serum albumin level. The researchers found that patients with a good EULAR response at 12 and 24 weeks had higher MTX PG levels than those who had not achieved a good response; however, the investigators were not able to provide guidance as to which numbers were significant. Some of their patients had a poor response despite increased doses of MTX. In addition, some patients experienced adverse events that required either stopping MTX or decreasing the dose. The authors noted that (Page 8), "despite the dosages of MTX used being largely similar, the MTX-PG concentrations in our patients were markedly higher than those observed in other studies from Europe or the USA." This demonstrates that patient characteristics can significantly affect MTX PG levels and the response to MTX, suggesting that studies performed on different patient populations may not be comparable.

Patients in the intermediate group who have not reached remission or LDA may benefit from a change to SQ MTX, because this has the potential of increasing the bioavailability of the drug. If, after 2 to 3 months of SQ MTX, the patient is in remission or has LDA, the same dose and administration route should be continued, regardless of the MTX PG level. For those patients who do not reach an acceptable disease activity level after 2 to 3 months of SQ MTX, a bDMARD should be given.

When Methotrexate Polyglutamate Levels Are Not Feasible or Not Available

If, at the end of 3 months of oral MTX, a serum MTX PG level is not available, and the patient has not reached either a clinical remission or LDA by CDAI, a change to SQ MTX should be strongly considered (Figure 5).

If there is a less than 50% improvement in disease activity after 2 to 3 months of SQ MTX, the patient should be switched to a bDMARD (preferably a TNFi). MTX should be continued, if appropriate. If the patient has an improvement of at least 50% in disease activity level after 2 to 3 months of SQ MTX, the patient should be kept on the same drug regimen and re-evaluated in another 2 to 3 months. If the patient has not achieved remission at the end of the second 2- to 3-month trial, the patient should be switched to a bDMARD (preferably a TNFi). MTX should be continued, if appropriate.


• DMARD-naïve
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CDAI before starting any therapy
Start oral or SQ MTX at 10 mg/week
± Short-term steroids*
Folic or folinic acid not on same day as MTX
If inadequate response, increase MTX dose rapidly until
• An adequate response (remission or LDA)
OR
• 15 to 25 mg/week orally or highest tolerable dose has been reached
(at these oral dose levels, split-dosing or SQ should be considered)
No remission or LDA by CDAI after 3 months of oral or SQ MTX
MTX PG not done or not available
• Change to SQ MTX and escalate dose, as appropriate, up to 25 mg/week
• If SQ MTX was used initially, go to Figures 6 and 7
Remission or LDA by CDAI after 2 months
No remission or LDA by CDAI after 2 months
Continue current treatment regimen
Consider measuring MTX PG levels and counsel patient regarding compliance
Durable remission*
MTX PG level >20 to 60 or ≥60
Maintain current therapy
OR
Consider tapering in appropriate patients
bDMARDs ± MTX
(start with a TNFi, see text)
See Figures 6 and 7
MTX PG not done or not available
MTX PG level <20
Consider non-compliance
See text, if taking medication at proper dose
bDMARDs ± MTX
(start with a TNFi drug; see text)
See Figures 6 and 7

Figure 5. Pharmacologic management of patients with RA and no MTX PG levels with either <50% improvement in CDAI after 3 months of treatment with oral MTX or failure to attain remission after 5 to 6 months' treatment with oral MTX

For patients treated initially with SQ MTX with subtherapeutic levels of MTX PG, go to Figure 6

In some patients, LDA is the treatment target; when LDA is reached, continue the same regimen and do not consider tapering bDMARD, biologic originator and biosimilar disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; DMARD, disease-modifying antirheumatic drug; LDA, low disease activity; MTX, methotrexate; PG, polyglutamate; RA, rheumatoid arthritis; SQ, subcutaneous; TNFi, tumor necrosis factor inhibitor

Patients Receiving Subcutaneous Methotrexate Initially

If, at the 3-month decision point, SQ MTX has resulted in an improvement of at least 50% in disease activity score (based on CDAI), the dose may be maintained for an additional 3 months. At the end of a total of 6 months, many patients will have reached the treatment target of remission or LDA. If remission is not achieved at the end of a total of 6 months, then a bDMARD (preferably a TNFi) should be started and MTX continued as appropriate. The considerations of the improvement trajectory described above can also be applied to this patient group.

In patients who have shown a less-than-50% improvement in disease activity score (based on CDAI) at the end of 3 months, a bDMARD (preferably a TNFi) should be started and MTX continued as appropriate.

Patients with a Contraindication to Methotrexate

For patients with LDA or a contraindication to MTX, and who received leflunomide, hydroxychloroquine, or sulfasalazine but did not achieve remission at the 3-month decision point, the use of a bDMARD (preferably a TNFi) should be considered (Figure 2).

Treatment with bDMARDs, or tsDMARDs

If disease activity remains unacceptably high despite optimizing oral and/or SQ MTX (possibly in combination with short-term steroids) for an adequate time interval, then a bDMARD (preferably a TNFi), should be started. In general, the combination of MTX with a biologic is more effective than a biologic alone. However, in some cases, monotherapy with a biologic is appropriate. The patient should be re-evaluated in 3 months and, if the target is achieved, the treatment should be continued (Figure 6).

Recently the FDA has put out a warning about the use of tsDMARDs (JAK inhibitors tofacitinib, baricitinib, and upadacitinib). According to the data that the FDA has regarding a study comparing serious adverse events in patients taking tofacitinib (to treat arthritis and ulcerative colitis) to those taking TNFi medications (to treat arthritis), there is an increased risk of cardiac events such as myocardial infarction and stroke, malignancy, blood clots, and death with tofacitinib than with TNFi medications.[64]

If, after 3 months of a biologic the patient still fails to achieve the treatment target (remission or LDA by CDAI) then a change in medication is indicated. The choice of the second drug could be a different TNFi or a non-TNFi. If the patient still fails to achieve remission or LDA, a different biologic can be tried (either a different TNFi or a non-TNFi) until all clinically appropriate bDMARDs have been tried. At times one drug may fail to improve the patient's disease activity and another with the same mode of action will have a

positive impact on disease activity. **This does not include changing to the biosimilar of the originator drug**.[61] (Figure 7).

The drugs used for the treatment of RA have been associated with a number of potentially serious adverse events. Physicians should be familiar with the FDA-approved prescribing information for the medications listed in

Table 4,[87-90] and with the management of potential complications. Providers should also be familiar with the recent FDA warnings regarding the three JAK inhibitor drugs currently available for the treatment of RA. Patient adherence to medication is critical in order to achieve the targeted outcome of remission or LDA. Some of the biologics can be self-administered by patients at home. Drugs that are administered intravenously should be given at an in-office infusion center under the direct supervision of a rheumatologist. Intravenous infusions prevent missed doses and assure compliance. When infusions are given, the supervising physician must be familiar with known adverse events and their management, and with contraindications such as allergies, current infections, or congestive heart failure. Because there are many potentially serious infusion reactions, United Rheumatology considers home infusions to be unsafe and not in the best interest of the patient.

When a patient requires a bDMARD, United Rheumatology recommends that the decision of which drug is the most appropriate choice should be the result of a joint decision with the patient. In general, United Rheumatology supports the use of a TNFi drug as the initial bDMARD. If this fails, a different TNFi drug can be used or the patient may be changed to a biologic with a different mode of action. If the second biologic fails to achieve remission or LDA, the patient may be changed to a different TNFi drug or a biologic with a different mode of action. This should be continued until all bDMARDs have been tried and none have had an adequate response. JAK inhibitors should only be used after a shared decision-making discussion between the provider and the patient and should be presented as a last option when all safer drugs have failed to achieve remission or LDA.

United Rheumatology does not support changing a patient who has attained remission or LDA on a biologic originator disease-modifying antirheumatic drug (boDMARD), to treatment with a biosimilar disease-modifying antirheumatic drug (bsDMARD; of the originator drug).

United Rheumatology does not support the requirement to change medications in a stable patient (durable remission or LDA) because of health insurance formulary changes. This can put a stable patient at risk for flares and the possibility of failure to achieve or regain remission or LDA.

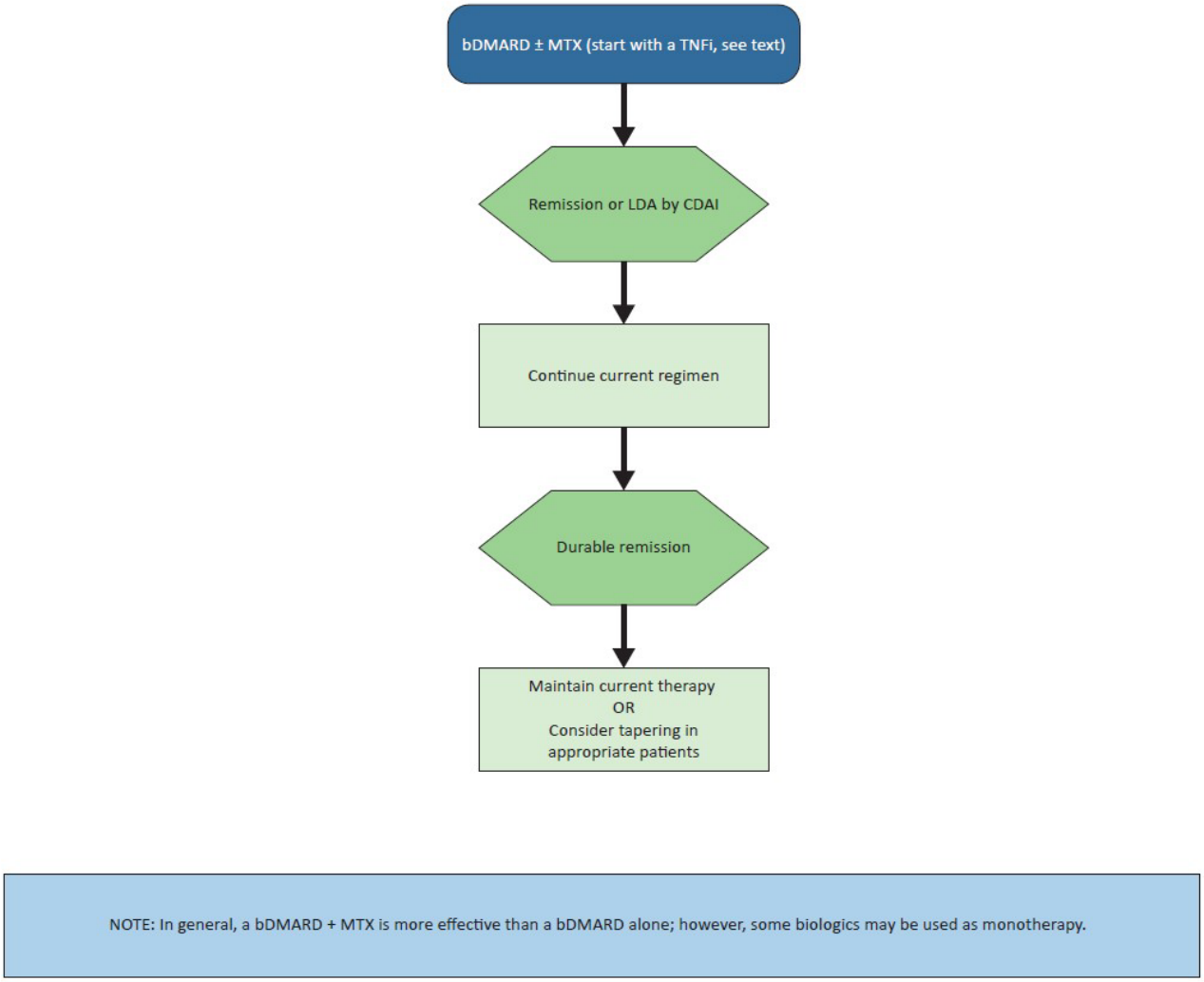

Figure 6. Pharmacologic management of patients with RA who failed oral or SQ MTX, leflunomide or hydroxychloroquine, or sulfasalazine but had an adequate response to a biologic, or a tsDMARD

*In some patients, LDA is the treatment target; when LDA is reached, continue the same regimen and do not consider tapering
bDMARD, biologic originator and biosimilar disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; JAK, Janus kinase; LDA, low disease activity; MTX, methotrexate; RA, rheumatoid arthritis; SQ, subcutaneous; TNFi, tumor necrosis factor inhibitor; tsDMARD, target-specific disease-modifying antirheumatic drug (such as a JAK inhibitor)

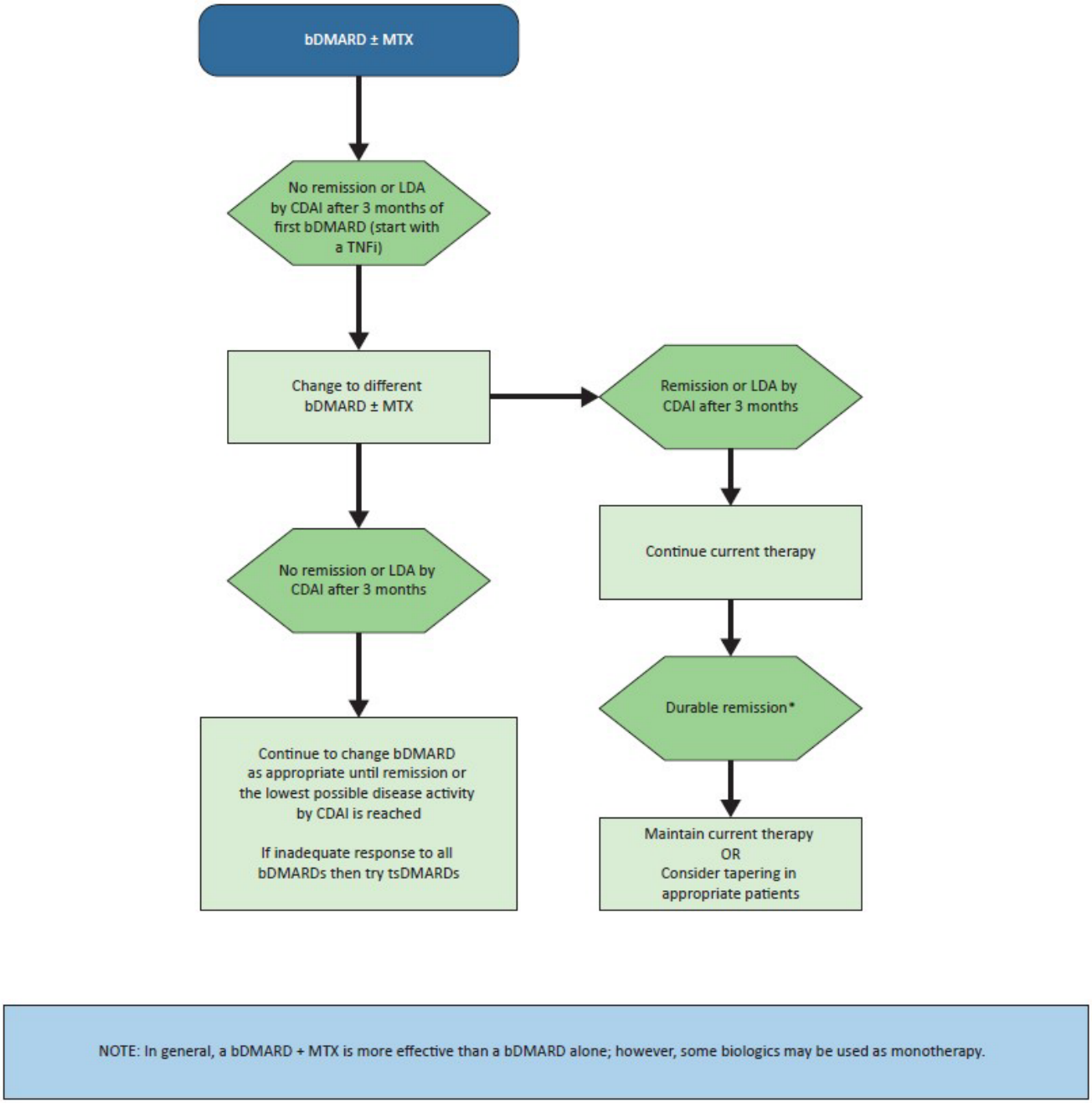

Figure 7. Pharmacologic management of patients with RA who failed conventional DMARDs and did not have an adequate response to bDMARDs or tsDMARDs

bDMARD, biologic originator and biosimilar antirheumatic drug; CDAI, Clinical Disease Activity Index; DMARD, disease-modifying antirheumatic drug; JAK, Janus kinase; LDA, low dose activity; MTX, methotrexate; RA, rheumatoid arthritis; TNFi, tumor necrosis factor inhibitor; tsDMARD, target-specific disease-modifying antirheumatic drug (such as a JAK inhibitor)

Monitoring

Until the desired treatment target is achieved, drug therapy should be continually assessed, initially at fairly frequent intervals. Drug doses or combinations should be appropriately adjusted until remission or the lowest disease activity possible is reached. A CDAI score, MDHAQ or RAPID3, PtGA (only if MDHAQ or RAPID3 are not done), and PGA should be completed at each visit. Some patients with HDA scores and/or comorbidities may require more frequent monitoring, calculation of disease activity scores, and adjustment of medications. Once remission or LDA is reached, patients are usually seen every 3 to 6 months. However, if patients experience any change in symptoms or develop flares, they should be seen as soon as possible.

Blood tests should be performed as needed, based on a patient's overall medical status and the medications used.

Annual radiographic evaluation is not necessary for patients with normal initial X-rays and remission or LDA. In these patients, X-rays can be performed every 2 to 4 years. If erosions are seen on initial X-rays, an annual radiographic examination of the hands and feet can be used to determine disease progression. If baseline X-rays are normal, regardless of disease activity, ultrasound may be helpful in detecting erosions or clinically undetected synovitis.

Ultrasound is increasingly used in the diagnosis and management of RA. However, there are currently no firm guidelines that address either the frequency of ultrasound or its use in scoring of disease activity. According to EULAR, ultrasound may be helpful in establishing a diagnosis of RA in a patient who does not meet RA classification criteria, by demonstrating active synovial inflammation on power Doppler examination.[48] In addition, the presence of synovitis on power Doppler studies can be helpful in predicting which patients with undifferentiated inflammatory arthritis may progress to RA. The EULAR imaging recommendations[48] also suggest that ultrasound may be helpful in demonstrating inflammation and/or early joint damage in patients with normal X-rays at initial diagnosis. However, the recommendations do not support the use of ultrasound as a substitute for plain films at this time. Together, EULAR and Outcome Measures in Rheumatology (OMERACT) have recently published the results of a joint ultrasound task force developing a "consensus-based scoring system" for the use of ultrasound for RA. However, the system has not yet been validated, and additional clinical studies are needed to see how it may assist physicians in caring for patients with RA.[91]

United Rheumatology supports the use of ultrasound as an adjunctive test for the diagnosis of RA, when the diagnosis is confusing.

RA is a chronic inflammatory disease. With proper management, patients can achieve periods of complete or near-complete remission, and stabilization of symptoms and function. However, episodes of flare do occur despite previously good control. Flares or acute worsening of inflammation are manifested by increased joint pain and systemic complaints such as fatigue and difficulty with activities of daily living. When flares occur, changes in medication are often indicated, and affected patients should be seen and re-evaluated quickly.

If a patient achieves a stable, durable remission (at least 6 months); the current drug(s) should not be abruptly discontinued; instead, slow tapering (one drug at a time) may be considered, but only after a discussion with the patient that should address the risk of flares and the possibility of disease progression.

Serious adverse events can occur with the use of bDMARDs. Therefore, it is important to carefully monitor patients taking these medications. All patients on bDMARDs, or tsDMARDs should have an annual TB evaluation and a flu vaccination. If patients on these drugs have an exposure to TB, a screening should be performed, regardless of most recent tests. An annual skin examination is also recommended.

Depression

Patients with RA have a higher incidence of depression than the general population.[92]

The prevalence of depression in patients with RA reported in the literature is inconsistent, but it is more common in women than in men. One study reported depression in 36.5% of women and 23.7% of men within 5 years of an RA diagnosis.[93] Others reported depression in 16.8% of RA patients.[94]

A recent study followed 469 patients (73% women) with early RA over 8 years.[95] The mean CDAI score of the entire group was consistent with HDA at the time of enrollment. Twenty-six percent of the patients reported depression at baseline; these patients had more comorbidities than the group not reporting depression. As expected, more women than men reported depression. The authors postulated that quickly controlling disease activity to the lowest possible level may limit depression in patients with RA.

Patient-reported Outcomes (PROs)

United Rheumatology suggests the use of two PRO questionnaires at baseline and at each follow-up visit—the MDHAQ or RAPID3, and the PtGA. These patient questionnaires are only three of many PRO tools available. In a busy office, it is important to use patient questionnaires that are simple to understand, straightforward to answer, and not too time consuming. Both the MDHAQ and the RAPID3 include the PtGA and can be answered quickly by most patients.

The PtGA is answered using a visual acuity scale (VAS) on a 10-cm line, with each centimeter corresponding to a number from 1 to 10. The PtGA can be used in the calculation of the CDAI.

A sample of the single question asked in the PtGA taken from a 2017 article is (Page 203), “Considering all of the ways your disease affects you, how well are you doing in the past week?”[96] The wording of the question for the PtGA is not standardized resulting in some differences in patient interpretation and response. However, a score of □2 (on a scale ranging from 1 to 10) is considered to be consistent with a global assessment of LDA.[97]

Neither the MDHAQ nor the RAPID3 is used to calculate the CDAI disease activity scale, which is recommended in this guideline. However, it is possible to use the MDHAQ or RAPID3 to obtain the PtGA required to calculate the CDAI score. These PRO tools can be completed by the patient in the waiting room or online prior to the visit. Occasionally, it may be necessary to have the questions asked by staff in the office or over the phone. These forms evaluate:[98]

- Multiple activities of daily living, including advanced activities
- Sleep
- Mental and emotional health
- Pain
- Limits on physical activity
- Ability to walk 2 miles
- Physical function
- PtGA

The use of PRO questionnaires is important, because it provides the physician with a more complete evaluation of the patient's perception of his/her disease. The patient's perspective on overall well-being is sometimes discordant with that of the physician, particularly if the patient has not achieved the target of remission or LDA. According to Grossec,[99] a patient's perspective of overall well-being relates more to his/her perception of the burden of disease (which includes subjective aspects such as social support, function, mood, sleep, ability to perform activities of daily living, and disability) than to an improved disease activity score based on physical findings and laboratory data. Physicians, on the other hand, tend to evaluate how a patient is doing based on treatment targets such as disease activity scores that include clinical information such as swollen and/or tender joints, erosions, joint deformities, acute-phase reactants, PtGA, and a PGA.

The patient's response to the questions in either the MDHAQ or RAPID3 and the physician's response to the PGA and disease activity score should be considered to be complementary. If patient and physician responses are discordant, it is important to discuss the differences with the patient and suggest additional treatment such as physical therapy or anti-depressants to improve the patient's perception of the burden of his/her disease.

Tapering Medications

The decision to taper medications should be a joint decision of the patient and provider after a thorough discussion of the benefits and risks. Patients should be aware that tapering of drugs may result in flares. Tapering includes either gradually decreasing the dose of a drug or slowly increasing the dosing interval.[61] Tapering of medications can be considered if the patient has been in remission or LDA for at least 6 months, according to ACR.[60] On the other hand, EULAR does not recommend tapering of patients with LDA because they have an increased incidence of flares when drug dose is decreased as compared to those in remission. These flares, if not controlled quickly, can result in irreversible joint damage. However, if a patient at LDA wants to try to decrease their use of DMARDs they must be very closely monitored and if a flare occurs the prior doses of medication(s) should be started as quickly as possible.[61]

According to EULAR, if a patient would like to try tapering of medications the following schedule should be followed: 1. if the patient is still taking low-dose glucocorticoids these should be the first drug tapered and then stopped; 2. if the treatment target is maintained after glucocorticoids are stopped then bDMARDs or tsDMARDs can be tapered next. If the patient tolerates tapering of bDMARDs and/or tsDMARDs, then tapering of csDMARDs can be considered. If the patient is only on a csDMARD drug then decreasing the dose can be considered but it should not be completely stopped.

ACR, in its 2021 guideline, also encourages tapering of medications but strongly indicates that all patients for whom tapering is being considered remain on "a therapeutic dose of at least 1 DMARD" (Page 8).[60] Medications should not be stopped abruptly but the dose slowly decreased or the interval between doses slowly increased over time.

ACR differs from EULAR in the order of tapering medications. ACR conditionally recommends gradually reducing the dose of csDMARDs (usually MTX) first rather than reducing the dose of either bDMARDs or tsDMARDs, which is different from the EULAR recommendations above. For patients on triple therapy ACR recommends reducing the dose of sulfasalazine first. Usually, a bDMARD or tsDMARD is added to MTX when a patient fails to reach the targeted level of disease activity on MTX alone. This guideline indicates that csDMARDs, such as MTX, should be tapered first. Continuing the bDMARD or tsDMARD is more likely to maintain remission or LDA than the continued use of MTX. However, it is understood that there may be special circumstances that may indicate that gradually reducing the dose of a bDMARD or tsDMARD initially may be preferred. Comorbidities, cost, and risk of infection may influence which drug is tapered. It should be remembered that a patient treated with a monoclonal antibody may require MTX in order to prevent anti-drug antibodies. In this case MTX should not be tapered first.[60]

Patients should be closely monitored for flares when any drug is tapered. If a flare occurs the patient should be quickly started on full doses of the drugs that resulted in either remission or LDA in an attempt to restore remission or LDA as quickly as possible.

Glossary

Biologics	Include TNF inhibitors or non-TNF inhibitors (excluding anakinra).
csDMARD monotherapy	The use of a single csDMARD, usually MTX; however, any csDMARD such as leflunomide, sulfasalazine, or hydroxychloroquine can be used as monotherapy.
Disease-modifying antirheumatic drugs (DMARDs)	A number of different types of DMARDs have become available in recent years. To enable precise reference to these medications, Smolen et al.[91] have proposed the following nomenclature: • ***Conventional synthetic DMARDs (csDMARDs)*** include MTX, leflunomide, sulfasalazine, hydroxychloroquine, and azathioprine. • ***Biologic originator DMARDs (boDMARDs)*** include TNF biologics such as adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab; non-TNF biologics such as abatacept and rituximab; and IL-6 inhibitors such as tocilizumab and sarilumab. • ***Biosimilar DMARDs (bsDMARDs)*** include the biosimilars Erelzi (etanercept-szzs), Amjevita (adalimumab-atto), Cyltezo (adalimumab-adbm), Inflectra infliximab-dyyb), and Renflexis (infliximab-abda). • ***Targeted synthetic DMARD (tsDMARD)*** include the JAK inhibitors tofacitinib, baricitinib, and upadacitinib.
Interleukin-6 (IL-6) inhibitors	Tocilizumab and sarilumab.
Multidimensional Health Assessment Questionnaire (MDHAQ)	The MDHAQ is a practical patient self-report tool assessing that patients can complete in the waiting room.
Non-TNF inhibitors	Abatacept and rituximab.
TNF inhibitors	Adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab.
Vectra DA	Measure of 12 biomarkers for RA that provides a score indicating disease activity.

Appendix

CDAI Calculator

Clinical Variable	Value
Tender Joint Count (0-28)	0
Swollen Joint Count (0-28)	0
Patient Global Activity (0-10.0 cm)	0
Provider Global Activity (0-10.0 cm)	0

Tool	Result
CDAI	0.0

Disease Activity

Range	Remission	Low	Moderate	High
0-76	≤2.8	>2.8 - 10.0	>10.0 - 22.0	>22.0

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Document Updates

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1.1.2016	Creation of first version	12 Sep 2016
1.1.2017	Updated with current research findings	Jun 2017
1.1.2018	2018 update	Jul 2018
1.1.2019	2019 update	Aug 2019
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