BMJ Best Practice

Rheumatoid arthritis

Straight to the point of care

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Summary

Rheumatoid arthritis (RA) is a chronic, erosive arthritis that requires early and aggressive treatment.

Diagnosed clinically. Laboratory and radiographic testing provide prognostic information more often than diagnostic information.

Early and aggressive treatment with disease-modifying anti-rheumatic drugs (DMARDs), potentially combined with a biological agent or a targeted synthetic DMARD, is recommended.

Disease activity scores (e.g., 28-joint count version of disease activity score [DAS28], clinical disease activity index [CDAI], simplified disease activity index [SDAI], routine assessment patient index data [RAPID3]) are used routinely to provide optimum care for RA patients.

Definition

RA is a chronic inflammatory condition affecting around 1% of the population, making it the most common inflammatory arthritis seen by physicians.[1] [2][3] [4] It primarily affects the small joints of the hands and feet and, if not treated aggressively, can be a major cause of work loss, decreased quality of life, need for joint replacement surgery, and mortality.[5] RA is a clinical diagnosis; laboratory and radiographic tests help to confirm the diagnosis and provide useful prognostic information.

[BMJ talk medicine: Rheumatoid arthritis] (https://soundcloud.com/bmjpodcasts/rheumatoid-arthritis?in=bmjpodcasts/sets/bmj-best-practice-clinical)

THEORY

Epidemiology

The global prevalence of rheumatoid arthritis (RA) is estimated to be between 0.24% and 0.56%.[2] [3] [4]

In North America, studies report age-adjusted prevalence ranging from 0.44% to 0.55%.[2] [9] Among an insured population in the US, RA prevalence in females exceeded that of males (0.73% to 0.78% vs. 0.29% to 0.31%, respectively).[9] Global prevalence data suggest a similar trend regarding the sex-specific burden of disease (0.35% vs. 0.13% for females and males, respectively).[2]

Globally, an age-standardised annual incidence rate of 14.9 per 100,000 has been reported.[3] In the US and western Europe, age-standardised incidence rates for RA were 22.5 per 100,000 and 20.4 per 100,000, respectively.

A higher incidence and prevalence of RA has been demonstrated in people who smoke, and people with overweight or obesity.[10] The increased risk of RA for people who smoke is dependent on the amount smoked per day combined with number of years they smoked.[10] [11] [12] [13]

Some reports have suggested a declining incidence of RA.[14] [15] However, data from the Global Burden of Diseases, Injuries, and Risk Factors study indicate that incidence is increasing.[3] Greater reported incidence and prevalence in industrialised regions may reflect geographical risk differences. Some evidence indicates that socioeconomic inequality may have an effect on reported incidence and prevalence of RA.[16] Poor case reporting in resource-limited healthcare settings and changing methodology in RA classification may contribute to discrepancies between epidemiological data sets.[15]

Aetiology

The aetiology of rheumatoid arthritis (RA) is unknown. Some studies have, however, pointed to possible causative factors.

Genetic factors

Family history confers a two- to fourfold increased risk for RA in first-degree relatives.[17] The presence of a major histocompatibility complex class II allele human leukocyte antigen (HLA), DRw4, is more common in patients with RA. These HLA alleles code for a shared amino acid sequence that has been named the shared epitope, which may be involved in the pathogenesis of RA.[18]

A role for polymorphisms of genes in both the innate and adaptive immune system have been demonstrated to increase the risk of RA, some of these include:[19] [20] [21] [22] [23] [24] [25]

- PTPN22
- T-cell subsets, for example, Tph cells
- macrophage subsets, including MERTK-, MerTK+, CX3CR1+ tissue-resident macrophages
- IL-6 promoter polymorphism (-174 G>C, -572 G>C, and -597 G>A) in Asian populations

In susceptible people, the interaction of genes and environment may result in a loss of tolerance of self-proteins that contain a citrulline residue.[26]

Environmental factors

Smoking and overweight/obesity have been associated with an increased risk of RA.[10]

Smoking is associated with the production of rheumatoid factor and anti-CCP antibodies, which are both specific and sensitive antibodies that increase the risk of developing RA.[27] The increased risk of RA for people who smoke is dependent on the amount smoked per day combined with number of years they smoked.[10] [11] [12] [13] A gene-environment interaction between heavy smoking and HLA-DRB1 has been demonstrated in patients with HLA-SE seropositive RA risk.[28] [29]

Excess body mass index is associated with an increase in inflammatory markers and chronic low grade inflammation, and may be associated with an increased risk of autoimmune diseases including RA.[30] [31]

Infection

An infection as a triggering factor for RA in genetically susceptible individuals has been proposed, but no specific infectious agent has been identified.[32]

Pathophysiology

The synovitis, swelling, and joint damage which characterise active RA are the result of complex autoimmune and inflammatory processes that involve components of both the innate and adaptive immune systems.[26] Inflamed synovium is central to the pathogenesis of RA. The synovium shows increased angiogenesis, cellular hyperplasia, influx of inflammatory cells, changes in the expression of cell surface adhesion molecules, and many cytokines.[1] The synovial lining becomes hyperplastic, with infiltration of the sublining with mononuclear cells including T cells, B cells, macrophages, and plasma cells. This formation of locally invasive synovial tissue is characteristic and it is involved in causing the erosions seen in RA.[26]

Cytokines affect all phases of the inflammatory process, and tumour necrosis factor (TNF), interleukin 1, and interleukin 6 seem to be the most abundant in the joint. Both TNF and interleukins promote proliferation, metalloproteinase expression, adhesion molecule expression, and further secretion of other cytokines.[33] High levels of metalloproteinase activity are thought to contribute to joint destruction. The proliferation of new blood vessels provides for the hypertrophic synovium. This very inflammatory setting, when not treated, leads to the eventual destruction of the involved joint.

Sclerostin, a regulator of bone metabolism and vascular calcification involved in regulating the Wnt/β-catenin signaling pathway, has been shown to be involved in the pathogenesis of RA.[34] [35] Evidence from one systematic review suggests that people with RA have a higher level of circulating sclerostin compared with people without RA.[35]

Pentraxin-3 (PTX-3) has been demonstrated to be involved in acute and chronic inflammation and in innate immunity.[36] [37] Compared with healthy controls, circulating PTX-3 levels are significantly higher in people with RA.[38]

Case history

Case history #1

A 52-year-old woman presents with a 2-month history of bilateral hand and wrist pain, and swelling in her fingers. She has also recently noted similar pain in the balls of her feet. She finds it hard to get going in the morning and feels stiff for hours after waking up. She also complains of increasing fatigue and is

unable to turn taps on and off or use a keyboard at work without a significant amount of pain in her hands. She denies any infections before or since her symptoms started.

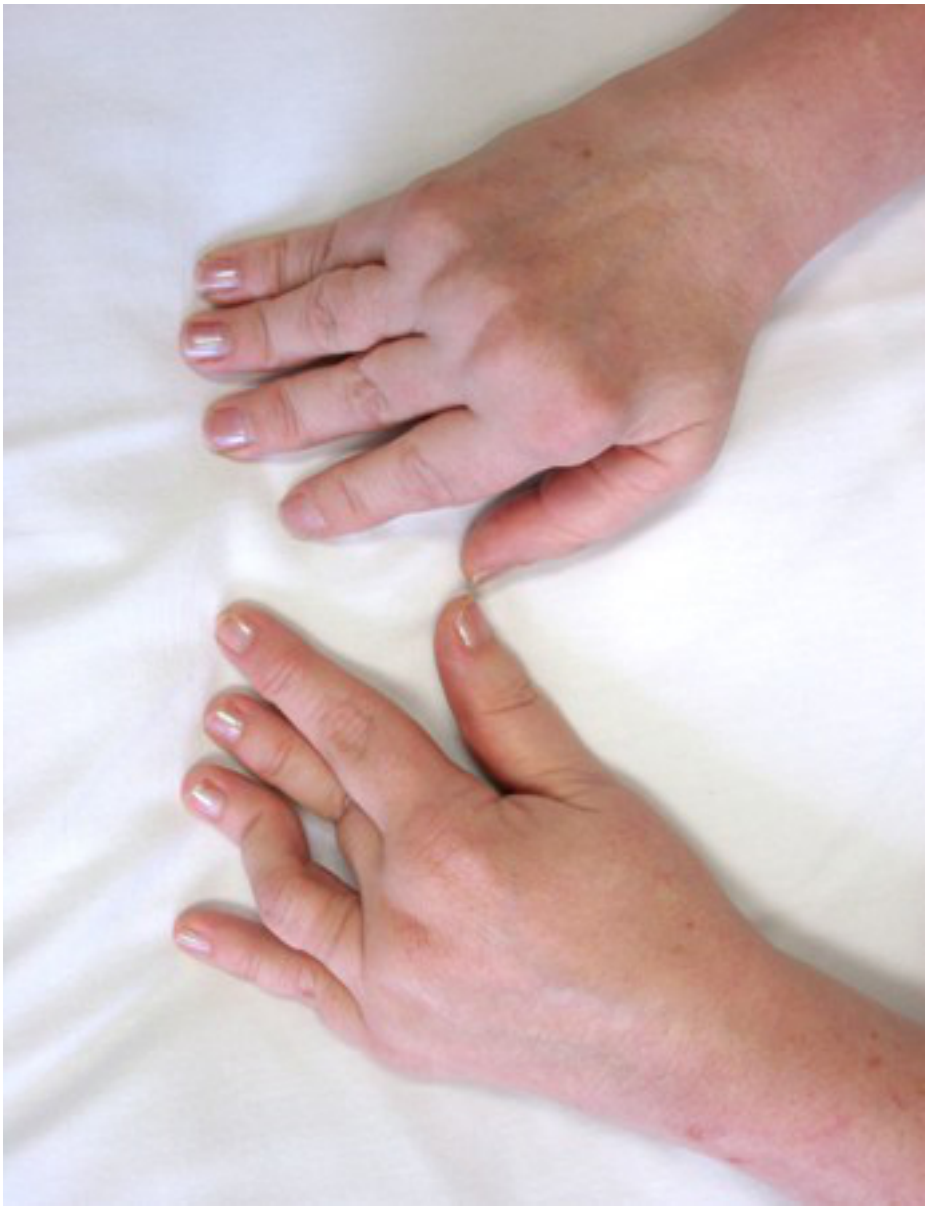
Other presentations

Rheumatoid arthritis (RA) can sometimes present in large joints like the knees and shoulders but this is less common. There is some evidence that elderly-onset RA may present this way more often.[6] Elderly-onset RA has also been grouped with polymyalgia rheumatica (PMR) and may represent a continuum of clinical features of both RA and PMR.[7] Rheumatoid nodules can be seen at presentation in some patients who have very active disease with large numbers of joints involved; these patients also have a higher incidence of other extra-articular manifestations.[8]

Approach

The diagnosis of rheumatoid arthritis (RA) is made on the basis of the clinical manifestations of the disease. Laboratory tests or radiographic examinations can be useful in determining prognostic information, but are not essential for making a diagnosis. Patients are referred to a rheumatologist for confirmation of diagnosis.

Classification criteria have been published in an attempt to diagnose RA earlier in the disease course.[48]



Rheumatoid arthritis (chronic hand deformities)

From the collection of Dr Soumya Chatterjee

Early diagnosis and treatment is associated with improved outcomes, and is an important principle of management.[49]

Work-up and treatment should not be delayed while waiting for all RA criteria to be fulfilled; however, there is still a good chance that undifferentiated polyarthritis of <6 weeks' duration will subside spontaneously.

Clinical presentation

Most patients present between the ages of 40 and 60.[50] Patients who meet diagnostic criteria for RA usually present with a history of bilateral, symmetrical pain and swelling of the small joints of the hands and feet that has lasted for >6 weeks. Morning stiffness lasting over 1 hour is commonly reported but can also be seen in other inflammatory conditions. Extra-articular features (e.g., rheumatoid nodules over the extensor surfaces of tendons or vasculitic skin involvement) may be seen but are less common.

Swan neck deformity is seen in advanced RA with damage to the ligaments and joints. Classically, there is distal interphalangeal (DIP) hyperflexion with proximal interphalangeal (PIP) hyperextension. Boutonniere's deformity is similar, where there is PIP flexion with DIP hyperextension. These deformities are no longer common, as most patients are treated with disease-modifying anti-rheumatic drugs (DMARDs) at an early stage.

Ulnar deviation, due to inflammation of the metacarpophalangeal (MCP) joints, causes the fingers to become dislocated. As the tendons pull on the dislocated joints, the fingers tend to drift towards the ulnar side.

Extra-articular manifestations seen in more severe disease include pleuritis, interstitial lung disease, pericarditis, and inflammatory eye disease.

Laboratory tests

Once a clinical diagnosis is made, several laboratory tests help to determine prognosis. Rheumatoid factor (RF) is positive in about 60% to 70% of patients with RA.[51] It is not required for diagnosis but is helpful if present. It should be tested at presentation and does not need to be repeated if positive. The higher the values, the worse the prognosis and the greater the need for aggressive treatment.

Anti-cyclic citrullinated peptide antibody (anti-CCP), a prognostic marker, is reported in about 70% of patients with RA.[52] Anti-CCP can be positive when RF is negative, and it seems to play more of a pathogenic role in the development of RA.[53] Anti-CCP does not need to be serially measured, even though it tends to decrease with better disease control.

Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels are also usually obtained because they reflect the level of inflammation. However, up to 40% of patients with RA may have normal levels.[54] [55]

Imaging

Baseline radiographs of the hands and feet are obtained to help with diagnosis and in determining disease severity.[56] Patients with erosions at baseline who fulfil one of the classification criteria for RA are at risk for severe disease.

Ultrasound may complement x-ray in the evaluation of suspected RA; it may detect synovitis of the wrist and fingers at the initial presentation.[57] [58] Ultrasound may add value in the diagnosis of early seronegative RA.[59] The presence of erosions, synovial hypertrophy, and hyperaemia on ultrasound increases the post-test probability of inflammatory arthritis in seronegative patients.[60] It is not clear whether the addition of ultrasound to disease activity score strategies is of benefit.[61] UK guidelines do not currently recommend ultrasound for routine monitoring of disease activity in adults with RA.[62]

Disease activity scores

Determining disease activity and presence of poor prognostic factors at diagnosis (functional limitation, extra-articular disease, positive RF, positive anti-CCP, bony erosions on radiograph) should be used to support physician acumen to inform initial treatment decisions.

Composite disease measures are derived from the American College of Rheumatology (ACR) core data set, which includes:

- Tender joint count
- Swollen joint count
- Functional status measured by a health assessment questionnaire (HAQ)
- Multidimensional HAQ (MDHAQ) or its derivatives
- Pain
- Patient and physician global assessment of disease activity, and
- Either an ESR or CRP as a marker of inflammation

Any three or more of these combined into a composite index can be used for disease activity monitoring. The most commonly used measures are the disease activity score (DAS), the 28-joint count version of DAS (DAS28), the simplified disease activity index (SDAI), the clinical disease activity index (CDAI), and routine assessment patient index data (RAPID3), all of which are recommended by the ACR.[63] [64] [65] [66]

Each disease activity measure has its own thresholds of disease activity. For consistency, the same disease activity measure should be used throughout the patient's management. Studies have shown that with close monitoring of disease activity and treating to a target value, it is possible to achieve good responses with any DMARD or combination with biological agents.[67] [68] [69]

History and exam

Key diagnostic factors

active symmetrical arthritis lasting >6 weeks (common)

- There may be clues that this will develop into rheumatoid arthritis, such as positive blood tests or lack of precipitating infections. There is still a good chance that undifferentiated polyarthritis of <6 weeks' duration will subside spontaneously.

age 50 to 55 years (common)

- Most patients present between the ages of 40 and 60.[50] There are cases seen in teenagers and very old people, but alternate diagnosis should be sought before rheumatoid arthritis is definitively diagnosed.

female sex (common)

- Usually females outnumber males 2:1, the lifetime risk of rheumatoid arthritis developing in the US has been reported as 3.6% for women and 1.7% for men.[70]

joint pain (common)

- Most commonly bilateral metacarpophalangeal (MCP), proximal interphalangeal (PIP), and metatarsophalangeal (MTP) joints are involved. They are painful to touch and when range of motion (ROM) exercises are performed. Wrists, elbows, and ankles are also affected.

joint swelling (common)

- Most commonly bilateral metacarpophalangeal (MCP), proximal interphalangeal (PIP), and metatarsophalangeal (MTP) joints are involved. They are painful to touch and when range of motion (ROM) exercises are performed. Wrists, elbows, and ankles are also affected.
- Tender and swollen joint count is one of the important outcome measures used in routine care and in randomised controlled clinical trials.

Other diagnostic factors

morning stiffness (common)

- Even though morning stiffness is not specific to rheumatoid arthritis, >1 hour of morning stiffness is considered a sign of inflammatory disease.[71]

swan neck deformity (uncommon)

- Seen in advanced rheumatoid arthritis with damage to the ligaments and joints. Classically, there is distal interphalangeal (DIP) hyperflexion with proximal interphalangeal (PIP) hyperextension. No longer common, as most patients are treated with DMARDs at an early stage.

Boutonniere's deformity (uncommon)

- Typically, there is proximal interphalangeal (PIP) flexion with distal interphalangeal (DIP) hyperextension. No longer common, as most patients are treated with DMARDs at an early stage.

ulnar deviation (uncommon)

- Ulnar deviation, due to inflammation of the metacarpophalangeal (MCP) joints, causes the fingers to become dislocated. As the tendons pull on the dislocated joints, the fingers tend to drift towards the ulnar side.

rheumatoid nodules (uncommon)

- Extra-articular features, such as rheumatoid nodules over the extensor surfaces of tendons, can be seen at presentation in some patients who have very active disease with large numbers of joints involved. Now seen less frequently.

vasculitic lesions (uncommon)

- Most common vasculitic lesions seen in rheumatoid arthritis are skin rashes. They are rarely seen and are associated with severe disease.

pleuritic chest pain (uncommon)

- Pleuritis or pericarditis may occur in severe rheumatoid arthritis.

scleritis and/or uveitis (uncommon)

- Inflammatory eye disease may be seen in severe rheumatoid arthritis, although it is an uncommon manifestation. Scleritis and uveitis are the more common presentations.

Risk factors

Strong

genetic predisposition

- Family history confers a two- to fourfold increased risk for rheumatoid arthritis (RA) in first-degree relatives.[17]
- Heritability of RA appears to be approximately 40%, and is higher for seropositive RA than for seronegative RA.[17] [39]
- The presence of a major histocompatibility complex class II allele human leukocyte antigen (HLA), DRw4, is more common in patients with RA. These HLA alleles code for a shared amino acid sequence that has been named the shared epitope, which may be involved in the pathogenesis of RA.[18]
- A role for polymorphisms of genes in both the innate and adaptive immune system have been demonstrated to increase the risk of RA.[19] [20][21][22] [23][24] [25] [40][41] [42]

Weak

smoking

- Smoking is associated with the production of rheumatoid factor and anti-CCP antibodies, which are both specific and sensitive antibodies that increase the risk of developing rheumatoid arthritis (RA).[27] The increased risk of RA for people who smoke is dependent on the amount smoked per day combined with number of years they smoked.[10] [11] [12] [13] A gene-environment interaction between heaving smoking and HLA-DRB1 has been demonstrated in patients with HLA-SE seropositive RA risk.[28] [29]
- Some evidence suggests that childhood exposure to passive smoking increases the risk of developing RA in later life, compared with children not exposed to passive smoking.[43]

overweight or obesity

- Excess body mass index is associated with an increase in inflammatory markers and chronic low grade inflammation, and may be associated with an increased risk of autoimmune diseases including rheumatoid arthritis.[30] [31]

infection

- An infection as a triggering factor for rheumatoid arthritis in genetically susceptible individuals has been proposed, but no specific infectious agent has been identified.[32]

Investigations

1st test to order

Test	Result
rheumatoid factor (RF) • One of the autoantibodies frequently seen in patients with rheumatoid arthritis (RA) but can also be seen in hepatitis C, chronic infections, and other rheumatological conditions. Approximately 30% of RA patients are RF negative.[51] Very high values (i.e., >100 IU) are more specific for RA. However, values >1000 IU are not common and should prompt consideration of other conditions, such as hepatitis C and cryoglobulinaemia, as the cause.	**positive (60% to 70% of patients)**
anti-cyclic citrullinated peptide (anti-CCP) antibody • Positive in about 70% of rheumatoid arthritis (RA) patients.[52] Anti-CCP can be positive when RF is negative, and it seems to play more of a pathogenic role in the development of RA.[53]	**positive (70% of patients)**
radiographs • Erosions start at the margins of the joint, affecting the subchondral bone first, and progress to cause joint space narrowing. Radiographs are done at baseline and then repeated as needed if clinically indicated. Erosions are seldom useful for treatment decisions because they are seen in late disease; most of the benefit of treatment of rheumatoid arthritis is seen when treatment is started before erosions develop. Erosions signify a worse prognosis.	**erosions**
ultrasonography • May complement x-ray in the evaluation of suspected rheumatoid arthritis (RA); it may detect synovitis of the wrist and fingers at the initial presentation.[57] [58] • The presence of erosions, synovial hypertrophy, and hyperaemia on ultrasound increases the post-test probability of inflammatory arthritis in seronegative patients.[60] • Ultrasound provides prognostic information linked to progression (e.g., detecting synovitis).[56] It may be a useful monitoring tool when clinical examination is inconclusive or is inconsistent with other signs of disease activity.[72] • UK guidelines do not currently recommend ultrasound for routine monitoring of disease activity in adults with RA.[62]	**synovitis of the wrist and fingers**

Other tests to consider

Test	Result
disease activity score(s) • Determining disease activity and presence of poor prognostic factors at diagnosis (functional limitation, extra-articular disease, positive rheumatoid factor [RF], positive anti-cyclic citrullinated peptide [anti-CCP], bony erosions on radiograph) helps to inform initial treatment decisions. • Composite disease measures are derived from the American College of Rheumatology (ACR) core data set, which includes: tender joint count; swollen joint count; functional status measured by a health assessment questionnaire (HAQ); multidimensional HAQ (MDHAQ) or its derivatives; pain; patient and physician global assessment of disease activity; and either an erythrocyte sedimentation rate (ESR) or CRP as a marker of inflammation. • Any three or more of these combined into a composite index can be used for disease activity monitoring. The most commonly used measures are the disease activity score (DAS), the 28-joint count version of DAS (DAS28), the simplified disease activity index (SDAI), the clinical disease activity index (CDAI), and routine assessment patient index data (RAPID3), all of which are recommended by the ACR.[63] [64] [65] [66] • Each disease activity measure has its own thresholds of disease activity. For consistency the same disease activity measure should be used throughout the patient's management. Studies have shown that with close monitoring of disease activity and treating to a target value, it is possible to achieve good responses with any DMARD or combination with biological agents.[67] [68] [69]	**affirmative**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Psoriatic arthritis (PsA)	• Commonly involves small joints of the hands and feet but is less often symmetrical. Fewer than 5 joints are commonly affected (oligoarthritis). Distal interphalangeal (DIP) joint involvement is more common in psoriatic arthritis than rheumatoid arthritis (RA). • Psoriasis is present in >90% of PsA patients, but is unusual in RA patients.	• PsA is for the most part seronegative, even though there are patients with low levels of rheumatoid factor (RF) diagnosed with PsA because of presence of psoriasis. • Skin biopsy of suspicious lesions can show psoriasis, supporting the diagnosis.
Infectious arthritis	• Direct infection of a joint is rare, and urgent specialist advice should be obtained if suspected. Reactive arthritis, where there is no direct infection in the joint, can cause symmetric hand and feet arthritis and can be seen after viral/bacterial infections.	• Most resolve within 6 weeks and leave no long-term effects.
Gout	• A small percentage of gout patients present with polyarticular gout, which can mimic rheumatoid arthritis (RA). Tophi and high levels of uric acid are specific for gout, but are very rare in RA. In addition, erosions seen in gout where the tophi have eroded into the bone differ from the erosions seen in RA.	• Serum uric acid >416 micromols/L (>7 mg/dL), urate crystals from the joint aspirate or tophus. Tophus eroding into the joint in gout is more destructive and much larger; RA erosions are more limited to cartilage-bone interface and tend to be smaller.
Systemic lupus erythematosus	• Systemic lupus erythematosus (SLE) can present with polyarthritis in the small joints of the hands and feet. • SLE arthritis is usually non-deforming.	• A wide range of autoantibodies seen in SLE help differentiate the two conditions. High antinuclear antibody (ANA) titre, anti-extractable nuclear antigen (ENA) autoantibodies are seen rarely in rheumatoid arthritis. • On radiographs, erosions are not typically seen in the joints of SLE patients.

Condition	Differentiating signs / symptoms	Differentiating tests
Osteoarthritis	• Prevalence increases with age. The most commonly affected joints are the knee, hip, hands, and lumbar and cervical spine. Patients present with joint pain and stiffness that is typically worse with activity.	• Radiographs show loss of joint space, subchondral sclerosis, and osteophytes.
Adult-onset Still's Disease	• Intermittent high-spiking fever, occurring at least daily over a period of at least one week.[73] • Arthralgia/arthritis, most commonly affecting the proximal interphalangeal joints, wrists, elbows, knees, and ankles.[74] [75] [76] [77] [78] [79] • Salmon-pink, maculopapular skin rash, occurring transiently during fevers. • Other common symptoms include pharyngitis, myalgia, and pleuritis.	• Largely a diagnosis of exclusion after ruling out infections, malignancy, and other rheumatological conditions. • Hyperferritinaemia is a sensitive but poorly specific marker. The combination of markedly elevated serum ferritin (≥5 x ULN) together with glycosylated ferritin <20% (if test is available) can act as a sensitive and specific marker.[80] [81] [82]
Calcium pyrophosphate deposition	• Acute CPPD causes erythema, warmth, and swelling of the affected joint. • Fever and constitutional symptoms may also be present. • The knee is the most commonly affected joint, followed by the wrist.	• Synovial fluid analysis shows the presence of positively birefringent rhomboid-shaped crystals.[83] X-rays show calcification in small joints.[84]

Criteria

American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) collaborative initiative 2010 rheumatoid arthritis classification criteria[48]

Any patient with six or more points after the criteria have been applied is considered to have rheumatoid arthritis (RA). Before the criteria can be applied, patients need to have at least one joint with synovitis, and other reasons for it need to be ruled out.

Joint distribution

- 1 large joint - 0 points
- 2-10 large joints - 1 point
- 1-3 small joints (large joints excluded) - 2 points

- 4-10 small joints (large joints excluded) - 3 points
- >10 joints (at least 1 small joint) - 5 points

Serology

- Negative rheumatoid factor (RF) and negative anti-cyclic citrullinated peptide (anti-CCP) antibodies - 0 points
- Low positive RF or anti-CCP antibodies (≤3 x upper normal limit) - 2 points
- High positive RF or anti-CCP antibodies (>3 x upper normal limit) - 3 points

Symptom duration

- <6 weeks - 0 points
- ≥6 weeks - 1 point

Acute-phase reactants

- Normal CRP and erythrocyte sedimentation rate (ESR) - 0 points
- Abnormal CRP or ESR - 1 point

American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis[71]

For classification purposes, patients are said to have RA if they satisfy at least 4 of these 7 criteria (criteria 1-4 must have been present for ≥6 weeks):

- Morning stiffness: lasting ≥1 hour before maximal improvement
- Arthritis of three or more joint areas: simultaneously have had soft tissue swelling or fluid, observed by a physician. The 14 possible areas are right or left proximal interphalangeal (PIP), metacarpophalangeal (MCP), wrist, elbow, knee, ankle, and metatarsophalangeal (MTP) joints
- Arthritis of hands: at least one swollen area in a wrist, MCP, or PIP
- Symmetrical arthritis
- Rheumatoid nodules: subcutaneous nodules over bony prominences or extensor surfaces or in juxta-articular regions observed by a physician
- Serum rheumatoid factor
- Radiographic changes: typical changes in posteroanterior hand and wrist radiographs; must include erosions or unequivocal bony decalcification localised in or most marked adjacent to the involved joints

EULAR definition of difficult-to-treat rheumatoid arthritis[85]

Developed for use in clinical practice and research, the definition of difficult-to-treat rheumatoid arthritis are based on the following three criteria:

- A patient being treated according to the EULAR recommendations who experiences treatment failure of two or more biological or targeted synthetic disease-modifying anti-rheumatic drugs (DMARDs) (with different mechanisms of action)* after failing conventional synthetic DMARD therapy (unless contraindicated)**.
- The patient will have signs suggestive of active/progressive disease, defined as one or more of the following:
    - At least moderate disease activity (according to validated composite measures including joint counts, for example, DAS28-ESR Score*** >3.2 or clinical disease activity index (CDAI) >10)

- Signs (including acute phase reactants and imaging) and/or symptoms suggestive of active disease (joint related or other)
- Inability to taper glucocorticoid treatment (below 7.5 mg/day prednisone or equivalent
- Rapid radiographical progression (with or without signs of active disease)****
- Well-controlled disease according to above standards, but still having RA symptoms that are causing a reduction in quality of life

- The management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or patient.

All three criteria must be present in difficult-to-treat Rheumatoid Arthritis.

*Unless restricted by access to treatment due to socioeconomic factors.

**If conventional synthetic DMARD treatment is contraindicated, failure of ≥2 biological or targeted synthetic DMARDs with different mechanisms of action is sufficient.

***DAS28-ESR, disease activity score assessing 28 joints and erythrocyte sedimentation rate.

****Rapid radiographical progression: change in van der Heijde-modified Sharp score ≥5 points at 1 year.

ACR/EULAR remission criteria for Rheumatoid Arthritis 2022 revision[86] [87]

To provide a definition of remission that is stringent but attainable for clinical trials, and for patient assessment in clinical practice.

Definition of remission in rheumatoid arthritis clinical trials:

At any time point, patient must satisfy all of the following:

Tender joint count ≤1*

Swollen joint count ≤1*

C-reactive protein ≤1 mg/dL

Patient Global Assessment ≤1 (on a 0-10 scale)**

OR

At any time point, the patient must have simplified disease activity (SDAI) ≤3.3***

Definition for rheumatoid arthritis in clinical practice:

Tender Joint Count 28 ≤1

Swollen Joint Count 28≤1

Patient Global Assessment ≤2

OR

CDAI ≤2.8****

*For swollen joint counts, a 28 joint count may miss active joints especially in the feet and ankles and it is preferable to include feet and ankles when evaluating remission.

**The following working and response categories should be used for global assessment: considering all of the ways your arthritis has affected you, how do you feel your arthritis is today? Verbal anchors for the response can range from 'asymptomatic' to severe 'symptoms'.

***SDAI, simplified Disease Activity Index is defined as the simple sum of the tender joint count (28), swollen joint count (28), patient global assessment score (on a scale of 0-10), physician global assessment (on a scale of 0-10), and C-reactive protein (mg/dL).

****CDAI, Clinical Disease Activity Index, same as SDAI but without C-reactive protein.

Approach

Early and aggressive treatment with conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs), potentially combined with a biological agent or a targeted synthetic DMARD, is recommended.[88] Rheumatoid arthritis (RA) is a cause of morbidity and mortality, and any delay in treatment contributes greatly to both.[88] [89]

Early diagnosis and treatment is associated with improved outcomes and is an important principle of management.[49] Presence of poor prognostic factors should alert the clinician that more aggressive therapy may be needed.

Hepatitis B and C status, purified protein derivative (PPD), full blood count (FBC), and liver function tests (LFTs) need to be checked before starting treatment.

FBC and LFTs should be monitored regularly during treatment.

Treat-to-target

Treat-to-target - involving frequent monitoring of disease activity using validated instruments, and the modification of treatment to minimise disease activity with the goal of reaching a predefined target - is recommended.[49]

An initial treatment target of low disease activity is recommended rather than a goal of remission, as established remission criteria may not be achievable for many patients.[49] [62][88] See Diagnostic criteria for ACR/EULAR remission criteria.

Patients should be at target (low disease activity or remission) for at least 6 months prior to tapering of treatment.[49]

Tapering/discontinuing DMARDs

For patients at target for at least 6 months, the preferred option is to continue all DMARDs, rather than reducing the dose or gradual discontinuation of DMARD treatment.[49]

For patients taking combination therapy who wish to discontinue a DMARD, gradual discontinuation of methotrexate is recommended rather than gradual discontinuation of the biological agent or targeted synthetic DMARD.[49] [90] One open-label randomised trial comparing half-dose conventional synthetic DMARD with stable-dose conventional synthetic DMARDs found that patients receiving half-dose conventional synthetic DMARD had significantly more disease flares than those on the stable dose.[91] However, subsequent systematic reviews demonstrated that tapering methotrexate from combination treatment with DMARDs treated at target may increase the risk of disease activity, compared with no tapering, but had limited effect on patients in established remission.[92] [93]

Two systematic reviews concluded that reducing the dose or increasing time between DMARD treatments did not impact disease activity, the risk of serious adverse effects, malignancies, cardiovascular adverse effects, or death in patients with RA who have achieved remission.[94] [95]

Conversely, an additional systematic review reported tapering tumour necrosis factor (TNF)-alpha inhibitors increased the risk of flare in people with RA in remission for more than one year.[96]

One systematic review and meta-analysis suggests that for patients with low disease activity RA, tapering corticosteroids reduce time to flare compared with patients who did not taper corticosteroids.[97]

Sulfasalazine is the preferred option for gradual discontinuation among patients taking triple therapy (hydroxychloroquine, sulfasalazine, and either methotrexate or leflunomide).[49]

Low disease activity at initial presentation

In practice, patients with low disease activity are usually started on a single conventional synthetic DMARD (i.e., hydroxychloroquine, sulfasalazine, methotrexate, or leflunomide).[49] [62] [88]

The American College of Rheumatology and the National Institute of Health and Care Excellence (NICE) in the UK recommend first-line hydroxychloroquine treatment for patients with low disease activity, over other DMARDs.[49] [62] It is better tolerated and has a more favourable risk profile in patients with RA. Sulfasalazine is recommended over methotrexate as patients with low disease activity may wish to avoid the adverse effects associated with methotrexate therapy. Methotrexate is recommended over leflunomide due to its greater dosing flexibility.[49] Treatment with methotrexate has been demonstrated to significantly reduce overall mortality for patients with RA, including cardiovascular and interstitial lung disease mortality.[98]

Short-term corticosteroid treatment may be used for symptom control in patients with early disease, those with acute flare of disease activity, or those starting or changing DMARD treatment, but should be tapered and discontinued as quickly as clinically possible.[62] [88] [99] There is some evidence to suggest that there is an association between methotrexate dose and bacterial infections during treatment with biological agents in combination with corticosteroids in people with RA.[100]

For patients taking a corticosteroid to remain at target, addition of, or switching to, a DMARD is preferred (as a corticosteroid-sparing measure) to continuation of the corticosteroid.[49]

Non-steroidal anti-inflammatory drugs (NSAIDs) can be used in patients with early disease or those with acute flares of disease activity.[62] [99] The lowest effective dose for the shortest effective duration should be used with appropriate preventative therapy (e.g., a proton-pump inhibitor).[62]

Moderate-to-severe disease activity at initial presentation

A more aggressive approach may be needed if the patient has:

- Moderate-to-severe disease activity with or without extra-articular manifestations (e.g., pleuritis, interstitial lung disease, pericarditis, inflammatory eye disease) with poor prognostic factors, such as rheumatoid factor (RF) positivity and/or anti-cyclic citrullinated peptide (anti-CCP) antibodies, and
- Radiographic evidence of bony erosions at presentation.

Conventional synthetic DMARDs

Methotrexate monotherapy is the initial treatment of choice for patients with moderate-to-severe disease activity.[49] [88]

Evidence suggests that methotrexate administered subcutaneously is more effective than oral methotrexate. Oral administration is, however, preferred for patients initiating methotrexate, due to the ease of administration and similar bioavailability at typical starting doses.[49] [101]

For patients who are not able to tolerate oral weekly methotrexate, a split dose of oral methotrexate over 24 hours or weekly subcutaneous injections, and/or an increased dose of folic acid, is recommended before switching to an alternative DMARD.[49]

If methotrexate cannot be used, then leflunomide, hydroxychloroquine, or sulfasalazine are alternatives. [49] [88]

No or inadequate response to conventional synthetic DMARD

If the patient does not respond or has an inadequate response to methotrexate monotherapy, a biological agent (e.g., TNF-alpha inhibitor, an interleukin 6 [IL-6] inhibitor, abatacept, or rituximab), or a targeted synthetic DMARD such as an oral Janus kinase (JAK) inhibitor, can be added to methotrexate, taking into account pertinent risk factors.[49] [88][102] [103] [104] [105] [106] [Evidence C]

One systematic review concluded that the combination of methotrexate with a biological agent does increase efficacy of treatment for people with RA compared with methotrexate treatment alone.[107] In absolute terms, 7 to 16 more people out of 100 may have increased overall likelihood of responding to treatment with combination therapy.[107]

Combination therapy with methotrexate in addition to certolizumab pegol, abatacept, or tocilizumab is generally well tolerated in people with early RA at 24 weeks.[108] Adverse effects tend to increase at the target dose, and these were more frequent in combination with tocilizumab compared with active conventional treatment, which included either methotrexate plus an oral corticosteroid, or methotrexate plus sulfasalazine plus hydroxychloroquine plus intra-articular corticosteroids at 24 weeks.[108]

Rarely, a biological agent or a targeted synthetic DMARD may be started as monotherapy, but the benefits and risks should be carefully considered for each individual patient before initiating treatment.

One systematic review suggests that patients with RA who smoke have an increased risk of having an inadequate response to methotrexate, especially DMARD naive patients with early RA.[109]

TNF-alpha inhibitors

TNF-alpha inhibitors (e.g., etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol) have proven efficacy in placebo-controlled trials.[110] [111] One network meta-analysis reported that biological agents in combination with methotrexate (with the exception of golimumab) were associated with significantly lower rates of radiographic progression at 1 year compared with methotrexate alone.[112]

In the UK, adalimumab, etanercept, or infliximab, added to methotrexate, is recommended for adult patients with moderate RA (a disease activity score [DAS28] of 3.2 to 5.1) who have an inadequate response with two or more conventional synthetic DMARDs.[113] Adalimumab and etanercept can be used as monotherapy for patients when methotrexate is contraindicated, or not tolerated, provided that the above criteria are met.[113]

TNF-alpha inhibitors have been associated with increased risk for serious infection (tuberculosis and other opportunistic infections) compared with synthetic DMARDs, and increased risk for treatment discontinuation.[114] [115] [116]

Lymphoma and other malignancies have been reported in patients treated with TNF-alpha inhibitors. However, systematic reviews and meta-analyses have not reported an increased risk of malignancy

among patients with RA receiving TNF-alpha inhibitor therapy.[116] [117] [118] [119] [120] [121] When evaluating relevant systematic reviews and meta-analyses, consider that:[117] [118]

- Studies subject to meta-analysis have typically been of short duration and increased long-term risk of malignancy cannot, therefore, be excluded
- Patients with a prior history of cancer may have been excluded from studies, making it difficult to extrapolate results to patients with a previous cancer.

Ongoing research seeks to establish the effect of specific DMARDs on risk of malignancy, particularly risk for non-melanoma skin cancer and melanoma.[122]

Potential adverse effects associated with TNF-alpha inhibitors can be minimised by using an individualised dose reduction/withdrawal strategy once disease control has been established. The results of two systematic reviews suggest that:[123] [124]

- Disease activity-guided dose tapering of TNF-alpha inhibitors is comparable to continuation of treatment with respect to the proportion of patients with persistent remission and may be comparable regarding disease activity
- Discontinuation of TNF-alpha inhibitors is inferior to continuation of treatment with respect to disease activity, the proportion of participants with persistent remission, function, and minimal radiographic damage.

IL-6 inhibitors

Tocilizumab and sarilumab are approved for the treatment of adults with moderately to severely active RA who have had an inadequate response to one or more DMARDs.

They may be used as monotherapy, or in combination with methotrexate or other conventional synthetic DMARDs.[125] [126] [127]

Evidence from systematic reviews using indirect comparisons suggest that tocilizumab may be more effective than sarilumab for treating people with RA who inadequately respond to either methotrexate or TNF-alpha inhibitors.[128] [129] An additional systematic review concluded that for people with RA with an inadequate response to conventional synthetic DMARDs, sarilumab monotherapy is more effective than adalimumab, biological agents, and targeted synthetic DMARDs.[130]

One open-label randomised trial evaluated the efficacy and safety of increasing the dose interval of subcutaneous tocilizumab in patients with RA who are in remission.[131] The study reported that although most patients sustained remission with a half-dose of tocilizumab, increasing the dose interval to 2 weeks was associated with a lower likelihood of maintaining remission, with no improvement in tolerability.[131]

There is evidence to suggest that treatment with interleukin (IL) inhibitors, including IL-6 inhibitors, may increase the risk of serious infection, opportunistic infections, and cancer in patients with RA compared with placebo.[132] Tocilizumab has been associated with a drug-induced sarcoidosis-like reaction, occurring in temporal relationship with the initiation of tocilizumab, and a significant risk of the reactivation of hepatitis B virus (HBV) in people with RA and chronic HBV.[132] [133] [134] [135]

The European Medicines Agency (EMA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA) identified serious hepatotoxicity (including acute liver failure, hepatitis, and jaundice) in eight patients treated with tocilizumab worldwide.[136] [137] Two cases required liver transplantation. Serious liver injury has been reported from 2 weeks to >5 years after starting treatment. While liver toxicity occurs rarely, and the risk-benefit profile still supports the use of tocilizumab, the MHRA

recommends monitoring alanine aminotransferase (ALT) or aspartate aminotransferase (AST) at initiation of treatment, every 4-8 weeks for the first 6 months of treatment, and then every 12 weeks thereafter. Be cautious when considering starting tocilizumab treatment in patients with ALT or AST levels higher than 1.5 times the upper limit of normal (ULN). Tocilizumab is not recommended if ALT or AST levels are higher than 5 times the ULN. If liver enzyme abnormalities are identified, dose modification should be considered (reduction, interruption, or discontinuation) according to the manufacturer's recommendations. Advise patients to seek medical help immediately if they experience signs and symptoms of hepatic injury.[137]

Abatacept

Abatacept is approved for the treatment of moderately to severely active RA. It has similar safety and efficacy to the TNF-alpha inhibitors, and is indicated in patients who have an inadequate response to methotrexate.[138] [139] Abatacept or adalimumab given subcutaneously with background methotrexate (as would usually be the case in clinical practice) have been shown to have similar efficacy, safety, and time to response in patients with active RA who were naive to biological agents and who had an inadequate response to methotrexate.[139]

Evidence suggests that abatacept, as monotherapy or in combination with methotrexate, provides more effective disease control compared with conventional treatment (methotrexate with corticosteroids), methotrexate alone, or biological agents or targeted synthetic DMARDs in patients with RA.[140] [141] [142] There is evidence demonstrating sustained remission with abatacept following dose reduction.[143] Few patients sustain a major response 1 year after withdrawal of abatacept therapy; re-treatment with abatacept plus methotrexate may be effective in this setting.[144]

Abatacept is recommended over other biological agents and targeted synthetic DMARDs for patients with non-tuberculous mycobacterial lung disease who have moderate-to-high disease activity despite conventional synthetic DMARDs.[49]

Rituximab

Rituximab is a B-cell modulator approved for use in combination with methotrexate for the treatment of adults with moderate to severely active RA who have had an inadequate response to one or more TNF-alpha inhibitors.[49]

Rituximab is recommended over other DMARDs, regardless of previous DMARD experience, for patients who have a previous lymphoproliferative disorder (for which rituximab is an approved treatment), and who have moderate-to-high disease activity, because it would not be expected to increase the risk of recurrence or worsening of lymphoproliferative disorders.[49]

In the setting of persistent hypogammaglobulinaemia without infection, continuation of rituximab therapy for patients at target is conditionally recommended over switching to a different biological agent or targeted synthetic DMARD.[49] Continuing rituximab in patients who are at target is preferred due to the uncertain clinical significance of hypogammaglobulinaemia in patients without infection. Although an increased risk of infection has been described in RA patients with hypogammaglobulinaemia, it is not known if a switch in DMARDs in patients who are at target is more effective in lowering infection risk while maintaining disease control than continuation of rituximab.

Targeted synthetic DMARDs

Targeted synthetic DMARDs include the oral Janus kinase (JAK) inhibitors tofacitinib, baricitinib, and upadacitinib, which are all approved to treat moderate to severely active RA.[49] Filgotinib, another selective inhibitor of JAK1, is approved in Europe and the UK for the treatment of moderate to severely active rheumatoid arthritis in adults who have responded inadequately to, or who are intolerant to, one or more DMARDs.

The US Food and Drug Administration (FDA) has issued a warning about an increased risk of serious cardiovascular events, malignancy, thrombosis, and death with tofacitinib, baricitinib, and upadacitinib.[145] This follows final results from a large randomised safety clinical trial comparing tofacitinib with tumour necrosis factor (TNF)-alpha inhibitors in patients with RA. The study found an increased risk of blood clots and death with the lower dose of tofacitinib (5 mg twice daily); this serious event had previously been reported only with the higher dose (10 mg twice daily) in the preliminary analysis.[146]

The FDA advises clinicians to:[145]

- Reserve tofacitinib, baricitinib, and upadacitinib for patients who have had an inadequate response or are intolerant to one or more TNF-alpha inhibitors
- Consider the patient's individual benefit-risk profile when deciding to prescribe or continue treatment with these medications, particularly in patients who are current or past smokers, patients with other cardiovascular risk factors, those who develop a malignancy, and those with a known malignancy (other than a successfully treated non-melanoma skin cancer).

The European Medicines Agency (EMA) has also recommended measures to minimise the risk of serious adverse effects with JAK inhibitors. The EMA advice relates to patients aged >65 years, those who are current or past smokers, patients with other cardiovascular risk factors (such as heart attack or stroke), and patients with other malignancy risk factors. In these patient groups, JAK inhibitors should only be used to treat moderate or severely active RA, if no suitable treatment alternative is available.[147]

The EMA recommends that JAK inhibitors should be used with caution in patients with risk factors for blood clots in the lungs and in deep veins (venous thromboembolism, VTE); and that doses should be reduced in patient groups who are at risk of VTE, cancer, or major cardiovascular problems, if possible. This recommendation is based on one observational study comparing the safety of baricitinib with TNF-alpha inhibitors.[147] [148]

In the UK, the National Institute for Health and Care Excellence (NICE) has recommended filgotinib (a JAK1 inhibitor) in combination with methotrexate as an option for adult patients with moderate to severe RA (i.e., a disease activity score [DAS28] of 3.2 or more) who have an inadequate response to intensive therapy with two or more conventional synthetic DMARDs.[149]

For severe disease (DAS28 of more than 5.1) NICE recommend filgotinib with methotrexate as an option if the patient:[149]

- Cannot tolerate rituximab, and has responded inadequately to or cannot have other DMARDs, including at least one biological DMARD
- Has an inadequate response to rituximab and at least one biological DMARD.

Filgotinib can be used as monotherapy in a patient with a contraindication to or intolerance of methotrexate when the above criteria are met.[149] [150]

Corticosteroids

Although DMARD therapy is the preferred initial treatment for patients with moderate to severely active RA, corticosteroids are commonly used in combination with a first-line DMARD, particularly for patients with early RA starting or changing DMARD treatment, and for patients with disease flare.[49] [88][99] In addition to working faster than most DMARDs, corticosteroids also have some disease-modifying effect, which contributes to overall disease control.[67] [151] [152] [153] [154] [155] [156]

Corticosteroid treatment usually involves low-dose daily oral prednisolone; doses >10 mg/day are rarely required. However, there is evidence to suggest that high- or moderate-dose prednisolone tapered to a low dose is effective for remission induction when combined with methotrexate in patients with early RA and poor prognostic markers.[157] Corticosteroid doses as low as 2.5 mg/day have been associated with BMD loss in people with inflammatory rheumatic disease, but is preventable with the use of medicines for osteoporosis prophylaxis.[158] See Osteoporosis . Low dose corticosteroids have been demonstrated to increase weight by approximately 1 kg after two years of treatment.[159]

In one double-blind trial, adults with RA receiving tocilizumab and corticosteroids for 24 weeks were randomised either to continue masked prednisolone for 24 weeks or to taper masked prednisolone by week 16.[160] In all patients assigned to the continued prednisolone regimen, disease activity control was superior compared with patients assigned to the tapered prednisolone regimen.

A delayed-release formulation of low-dose oral prednisolone may have a role in RA when used as an adjunct to DMARDs.[161]

Patients can be treated with intramuscular corticosteroids as needed in addition to DMARD therapy, especially early in disease when rapid symptom relief may be desired while patients are waiting for DMARDs to start working.

Intra-articular corticosteroid injections are used to control individually inflamed joints in acute flares of disease activity.

If corticosteroids are given daily, calcium and vitamin D supplementation and yearly to biannual bone density assessment are recommended. However, some evidence suggests that suppression of inflammation by corticosteroids may counterbalance their adverse effects on bone remodelling up to 24 months in patients with early RA.[162]

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs can be used for symptom control in patients with early disease or those with acute flare of disease activity.[62] [99] The lowest effective dose for the shortest effective duration should be used.[62]

Failure to reach low disease activity after 3 months

Patients are usually re-assessed at 3 months or less using the same disease activity measure employed during diagnosis/initial treatment visit. This will objectively document improvement (or lack of) and determine the next step in the treatment plan.

A small percentage (2.7%) of people with RA may present with poly-refractory RA defined as failure of all biological agents and targeted synthetic DMARDs.[163]

First-line options

Combination therapy with methotrexate and either a biological agent or a targeted synthetic DMARD is recommended first line for these patients.[49] [88]

For patients taking weekly oral methotrexate who are not at target, switching to subcutaneous methotrexate is recommended over addition of/switching to alternative DMARD(s).[49]

A combination of methotrexate plus a TNF-alpha inhibitor has been shown to be more effective in patients with high disease activity than either methotrexate or a TNF-alpha inhibitor alone.[102] [164] [165] [166] One systematic review and network meta-analysis reported only minor differences in efficacy between biological treatments, in combination with methotrexate, among RA patients after methotrexate failure.[167] All have proven efficacy in placebo-controlled trials.[111] [167]

For patients on combination therapy not at target, switching to a biological agent or targeted synthetic DMARD of a different class is recommended, although evidence for this approach is unclear.[49] [88][168] [169]

There are data to suggest that switching to tocilizumab or JAK inhibitor monotherapy may be as effective as combination tocilizumab plus methotrexate in some RA patients with an inadequate response to methotrexate.[170] [171] However, more long-term data and studies in methotrexate-naive patients are needed to confirm these findings.

One prospective cohort study reported that among adults with refractory RA (inadequate response to a TNF-alpha inhibitor), rituximab and tocilizumab are associated with greater improvements in outcomes at 24 months (survival without drug failure, good or moderate EULAR response) compared with abatacept.[172]

A corticosteroid and/or NSAID may be used for symptom control in patients with early disease or those with acute flare of disease activity.[99]

Second-line options

Triple therapy with synthetic DMARDs (e.g., methotrexate plus hydroxychloroquine plus sulfasalazine) may be a second-line option in select patients who fail to reach low disease activity after 3 months.[62] However, this regimen is rarely used now that biological agents/targeted synthetic DMARDs are available, and it is not recommended by US guidelines.[49]

In a prospective study of RA patients registered on the nationwide Swedish Rheumatology Quality Register, the likelihood of reaching sustained remission was higher with biological therapy (a biological agent plus methotrexate) than with triple therapy.[173] For specific RA patients, however, triple therapy was believed to be an alternative to biological therapy without prejudicing future likelihood of sustained remission.

Evidence from one systematic review suggests that treatment with biological agents seems to be more effective compared with triple DMARD therapy in terms of radiological progression in RA with inadequate response to methotrexate.[174]

A corticosteroid and/or NSAID may be used for symptom control in patients with early disease or those with acute flare of disease activity.[99]

Pregnant patients

Most medicines used to treat RA cannot be used while a patient is pregnant or planning a pregnancy; however, symptoms of RA usually diminish during pregnancy.[175]

Corticosteroids are considered the safest option for patients who are planning pregnancy or who are pregnant, although sulfasalazine or hydroxychloroquine can also be used. There is a lack of human data for use of sulfasalazine and hydroxychloroquine in pregnancy, so these agents are only recommended if corticosteroids are not an option, and only under a specialist with experience of treating pregnant women.

Biological agents and JAK inhibitors are generally not recommended in pregnancy due to a lack of safety data; some agents may be considered if the benefits outweigh the risks to the mother and fetus. There are data to suggest that certolizumab may be an option in pregnancy due to a lack of placental transfer.[176] A specialist should be consulted for guidance on using these drugs in pregnant women.

FBC and LFTs need to be checked before starting sulfasalazine or hydroxychloroquine and should be monitored every 4-8 weeks at the start of treatment. When the patient is on a stable dose, monitoring can be done every 3-4 months.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)		
mild disease activity at initial presentation: not pregnant or planning pregnancy		
	1st	**conventional synthetic disease-modifying anti-rheumatic drug (DMARD)**
	adjunct	**corticosteroid**
	adjunct	**non-steroidal anti-inflammatory drug (NSAID)**
moderate-to-severe disease activity at initial presentation: not pregnant or planning pregnancy		
	1st	**conventional synthetic disease-modifying anti-rheumatic drug (DMARD)**
	adjunct	**biological agent or targeted synthetic DMARD**
	adjunct	**corticosteroid**
	adjunct	**non-steroidal anti-inflammatory drug (NSAID)**
pregnant or planning pregnancy		
	1st	**corticosteroid, sulfasalazine, or hydroxychloroquine**

Ongoing		(summary)
failure to reach low disease activity after 3 months of therapy: not pregnant or planning pregnancy		
	1st	**methotrexate**
	plus	**biological agent or disease-modifying anti-rheumatic drug (DMARD)**
	adjunct	**corticosteroid**
	adjunct	**non-steroidal anti-inflammatory drug (NSAID)**
	2nd	**triple DMARD therapy**
	adjunct	**corticosteroid**
	adjunct	**non-steroidal anti-inflammatory drug (NSAID)**

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

mild disease activity at initial presentation: not pregnant or planning pregnancy

1st **conventional synthetic disease-modifying anti-rheumatic drug (DMARD)**

Primary options

» hydroxychloroquine: 400-600 mg/day orally given in 1-2 divided doses initially, reduce dose to 200-400 mg/day after clinical response is obtained
Dose refers to hydroxychloroquine sulfate.

Secondary options

» sulfasalazine: 0.5 to 1 g/day orally (enteric-coated) for 7 days initially, increase by 500 mg/day increments every week according to response, maximum 2 g/day given in 2-3 divided doses

OR

» methotrexate: 7.5 mg orally once weekly (on the same day each week) initially, increase gradually according to response, maximum 20 mg/week

OR

» leflunomide: low risk for hepatotoxicity or myelosuppression: 100 mg orally once daily for 3 days, followed by 20 mg once daily; high risk for hepatotoxicity or myelosuppression: 20 mg orally once daily without loading dose
Reduce dose to 10 mg orally once daily in patients who cannot tolerate 20 mg/day.

» Patients with mild disease at presentation are usually started on a single conventional synthetic DMARD.[49] [62] [88]

» The American College of Rheumatology and the National Institute of Health and Care Excellence (NICE) in the UK recommend first-line hydroxychloroquine treatment for patients with low disease activity over other DMARDs; it is better tolerated and has a more favourable

Acute

risk profile in patients with rheumatoid arthritis (RA).[49] [62]

» Sulfasalazine is recommended over methotrexate as patients with low disease activity may wish to avoid adverse effects associated with methotrexate therapy. Methotrexate is recommended over leflunomide due to its greater dosing flexibility.[49] Treatment with methotrexate has been demonstrated to significantly reduce overall mortality for patients with RA, including cardiovascular and interstitial lung disease mortality.[98]

» Folic acid supplementation can also be started at the same time as starting methotrexate, as a prophylactic measure to reduce the risk of some adverse effects.

» Hepatitis B and C status, purified protein derivative (PPD), FBC, and LFTs need to be checked before starting DMARDs.

adjunct **corticosteroid**

Treatment recommended for SOME patients in selected patient group

Primary options

» prednisolone: 1-10 mg orally once daily
Doses >10 mg/day are rarely required; however, higher doses may be required in some patients.

OR

» methylprednisolone acetate: 4-80 mg intra-articularly every 1-5 weeks; 40-120 mg intramuscularly every 1-4 weeks
Intra-articular dose depends on the size and location of the affected joint.

» Commonly used in combination with a disease-modifying anti-rheumatic drug (DMARD), particularly for patients with early rheumatoid arthritis (RA) starting or changing DMARD treatment, and as management for acute flares of disease activity.[49] [88] [99] Corticosteroids also have some disease-modifying effect and hence contribute to overall disease control.[67] [151] [152] [153] [154] [155] [156]

» Treatment usually involves low-dose daily oral prednisolone; doses >10 mg/day are rarely required. However, there is evidence to suggest that high- or moderate-dose prednisolone

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tapered to a low dose is effective for remission induction when combined with methotrexate in patients with early RA and poor prognostic markers.[157] In one double-blind trial, adults with RA receiving tocilizumab and corticosteroids for 24 weeks were randomised to either continue masked prednisolone for 24 weeks or to taper masked prednisolone by week 16.[160] In all patients assigned to the continued prednisolone regimen, disease activity control was superior compared with patients assigned to the tapered prednisolone regimen. Corticosteroid doses as low as 2.5 mg/day have been associated with BMD loss in people with inflammatory rheumatic disease, but is preventable with the use of medicines for osteoporosis prophylaxis.[158] See Osteoporosis . Low dose corticosteroids have been demonstrated to increase weight by approximately 1 kg after two years of treatment.[159]

» High-dose corticosteroids may be required for the treatment of severe extra-articular involvement, such as vasculitis or eye involvement. A delayed-release formulation of low-dose oral prednisolone may have a role in RA when used as an adjunct to DMARDs.[161]

» Patients can also be treated with intramuscular corticosteroids as needed in addition to DMARD therapy, especially early in disease when quicker symptom relief may be desired while patients are waiting for DMARDs to start working.

» Intra-articular corticosteroid injections are used to control individually inflamed joints in acute flares of disease activity.

» If corticosteroids are given daily, calcium and vitamin D supplementation and yearly to biannual bone density assessment are recommended. However, some evidence suggests that suppression of inflammation by corticosteroids may counterbalance their adverse effects on bone remodeling up to 24 months in patients with early RA.[162]

» For patients taking a corticosteroid to remain at target, addition of or switching to a DMARD is preferred (as a corticosteroid-sparing measure) to continuation of the corticosteroid.[49]

adjunct **non-steroidal anti-inflammatory drug (NSAID)**

Treatment recommended for SOME patients in selected patient group

Primary options

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» ibuprofen: 400-800mg orally three to four times daily, maximum 3200 mg/day

OR

» naproxen: 250-500 mg orally twice daily, maximum 1500 mg/day

OR

» diclofenac potassium: 50 mg orally (immediate-release) three to four times daily, maximum 200 mg/day

OR

» diclofenac sodium: 50 mg orally (delayed-release) three to four times daily, or 75 mg twice daily, maximum 200 mg/day; 100 mg orally (extended-release) once daily, may increase to 100 mg twice daily if necessary

» Can be used for symptom control in patients with early disease or those with acute flare of disease activity.[62] [99]

» The lowest effective dose for the shortest effective duration should be used.[62]

» Should be taken with food to minimise the risk of gastrointestinal adverse effects (e.g., gastritis, ulcer, gastrointestinal bleeding). Appropriate preventative therapy (e.g., proton-pump inhibitor) should be given when needed to prevent adverse gastrointestinal effects.[62]

moderate-to-severe disease activity at initial presentation: not pregnant or planning pregnancy

1st

conventional synthetic disease-modifying anti-rheumatic drug (DMARD)

Primary options

» methotrexate: 7.5 mg orally/subcutaneously once weekly (on the same day each week) initially, increase gradually according to response, maximum 20 mg/week

Secondary options

» sulfasalazine: 0.5 to 1 g/day orally (enteric-coated) for 7 days initially, increase by 500 mg/day increments every week according to response, maximum 2 g/day given in 2-3 divided doses

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OR

» hydroxychloroquine: 400-600 mg/day orally given in 1-2 divided doses initially, reduce dose to 200-400 mg/day after clinical response is obtained
Dose refers to hydroxychloroquine sulfate.

OR

» leflunomide: low risk for hepatotoxicity or myelosuppression: 100 mg orally once daily for 3 days, followed by 20 mg once daily; high risk for hepatotoxicity or myelosuppression: 20 mg orally once daily without loading dose
Reduce dose to 10 mg orally once daily in patients who cannot tolerate 20 mg/day.

» If the patient has moderate-to-severe disease with or without extra-articular manifestations (e.g., pleuritis, interstitial lung disease, pericarditis, inflammatory eye disease) with poor prognostic factors such as rheumatoid factor (RF) positivity and/or anti-cyclic citrullinated peptide (anti-CCP) antibodies, and radiographic evidence of bony erosions at presentation, a more aggressive approach to initial therapy may be needed.

» Methotrexate monotherapy is the initial treatment of choice.[49] [88] Evidence suggests that methotrexate administered subcutaneously is more effective than oral methotrexate. Oral administration is, however, preferred for patients initiating methotrexate, due to the ease of administration and similar bioavailability at typical starting doses.[49] [101]

» For patients who are not able to tolerate oral weekly methotrexate, a split dose of oral methotrexate over 24 hours or weekly subcutaneous injections, and/or an increased dose of folic acid, is recommended before switching to an alternative DMARD.[49]

» Folic acid supplementation can also be started at the same time as starting methotrexate, as a prophylactic measure to reduce the risk of some adverse effects.

» If methotrexate cannot be used then leflunomide, hydroxychloroquine, or sulfasalazine are alternatives.[49] [88]

Acute

» Hepatitis B and C status, purified protein derivative (PPD), FBC, and LFTs need to be checked before starting DMARDs.

adjunct **biological agent or targeted synthetic DMARD**

Treatment recommended for SOME patients in selected patient group

Primary options

» etanercept: 50 mg subcutaneously once weekly; or 25 mg subcutaneously twice weekly

OR

» infliximab: 3 mg/kg intravenous infusion at weeks 0, 2, 6, and then every 8 weeks thereafter
Consider increasing dose up to 10 mg/kg or increasing frequency to every 4 weeks in patients with an incomplete response.

OR

» adalimumab: 40 mg subcutaneously every 2 weeks

OR

» certolizumab pegol: 400 mg subcutaneously at weeks 0, 2, and 4, and then 200 mg every 2 weeks or 400 mg every 4 weeks thereafter

OR

» golimumab: 50 mg subcutaneously once monthly; or 2 mg/kg intravenous infusion at weeks 0 and 4, and then every 8 weeks thereafter

OR

» abatacept: body weight <60 kg: 500 mg intravenous infusion at weeks 0, 2, and 4, and then every 4 weeks thereafter; body weight 60-100 kg: 750 mg intravenous infusion at weeks 0, 2, and 4, and then every 4 weeks thereafter; body weight >100 kg: 1000 mg intravenous infusion at weeks 0, 2, and 4, and then every 4 weeks thereafter

Acute

A subcutaneous formulation is available. The same dose is used in patients regardless of body weight (125 mg subcutaneously once weekly). However, an intravenous loading dose may be used in some patients. Consult specialist for guidance on subcutaneous dosing.

OR

» rituximab: 1000 mg intravenous infusion on days 1 and 15, may repeat course every 16-24 weeks if inadequate response

OR

» tocilizumab: 4 mg/kg intravenous infusion every 4 weeks, may increase to 8 mg/kg every 4 weeks if necessary, maximum 800 mg/dose; body weight <100 kg: 162 mg subcutaneously every 2 weeks initially, increase to 162 mg once weekly if necessary; body weight ≥100 kg: 162 mg subcutaneously once weekly

OR

» sarilumab: 200 mg subcutaneously every 2 weeks
A dose reduction (150 mg subcutaneously every 2 weeks) is required in patients who have or develop neutropenia, thrombocytopenia, or elevated liver enzymes.

OR

» tofacitinib: 5 mg orally (immediate-release) twice daily; 11 mg orally (extended-release) once daily

OR

» baricitinib: 2 mg orally once daily

OR

» upadacitinib: 15 mg orally once daily

OR

» filgotinib: 100-200 mg orally once daily

Acute

» If the patient does not respond or has an inadequate response to methotrexate, a biological agent (e.g., a tumour necrosis factor [TNF]-alpha inhibitor, an interleukin 6 [IL-6] inhibitor, abatacept, or rituximab) or a targeted synthetic DMARD such as an oral Janus kinase (JAK) inhibitor (e.g., tofacitinib, baricitinib, upadacitinib) can be added to methotrexate, taking into account pertinent risk factors.[49] [88] [102] [103] [104] [105] [Evidence C]

» One systematic review concluded that the combination of methotrexate with a biological agent does increase efficacy of treatment for people with rheumatoid arthritis (RA) compared with methotrexate treatment alone.[107] In absolute terms, 7 to 16 more people out of 100 may have increased overall likelihood of responding to treatment with combination therapy.[107]

» Combination therapy with methotrexate in addition to certolizumab pegol, abatacept, or tocilizumab is generally well tolerated in people with early RA at 24 weeks.[108] Adverse effects tend to increase at the target dose, and these were more frequent in combination with tocilizumab compared with active conventional treatment, which included either methotrexate plus an oral corticosteroid, or methotrexate plus sulfasalazine plus hydroxychloroquine plus intra-articular corticosteroids at 24 weeks.[108]

» TNF-alpha inhibitors (etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol) have proven efficacy in placebo-controlled trials.[110] [111] One network meta-analysis reported that biological agents in combination with methotrexate (with the exception of golimumab) were associated with significantly lower rates of radiographic progression at 1 year compared with methotrexate alone.[112]

» In the UK, adalimumab, etanercept, or infliximab, added to methotrexate, is recommended for adult patients with moderate RA (a disease activity score [DAS28] of 3.2 to 5.1) who have an inadequate response with two or more conventional synthetic DMARDs.[113] Adalimumab and etanercept can be used as monotherapy for patients when methotrexate is contraindicated, or not tolerated, provided that the above criteria are met.[113]

» TNF-alpha inhibitors are approved for use either with or without methotrexate depending on the specific drug; check local drug formulary for specific licence information.

Acute

» TNF-alpha inhibitors have been associated with increased risk for serious infection (tuberculosis and other opportunistic infections) compared with synthetic DMARDs, and increased risk for treatment discontinuation.[114] [115] [116]

» Lymphoma and other malignancies have been reported in patients treated with TNF-alpha inhibitors. However, systematic reviews and meta-analyses have not reported an increased risk of malignancy among patients with RA receiving TNF-alpha inhibitor therapy.[116] [117] [118] [119] [120] [121] When evaluating relevant systematic reviews and meta-analyses, consider that studies subject to meta-analysis have typically been of short duration and increased long-term risk of malignancy cannot, therefore, be excluded; patients with a prior history of cancer may have been excluded from studies, making it difficult to extrapolate results to patients with a previous cancer. Ongoing research seeks to establish the effect of specific DMARDs on risk of malignancy, particularly risk for non-melanoma skin cancer and melanoma.[122]

» Potential adverse effects associated with TNF-alpha inhibitors could be minimised by using an individualised dose reduction/withdrawal strategy once disease control has been established.

» The results of two systematic reviews suggest that disease activity-guided dose tapering of TNF-alpha inhibitors is comparable to continuation of treatment with respect to the proportion of patients with persistent remission and may be comparable regarding disease activity, while discontinuation of TNF-alpha inhibitors is inferior to continuation of treatment with respect to disease activity, the proportion of participants with persistent remission, function, and minimal radiographic damage.[123] [124]

» Abatacept is a T-cell modulator approved for the treatment of moderately to severely active RA. It has similar safety and efficacy to the TNF-alpha inhibitors, and is indicated in patients who have an inadequate response to methotrexate.[138] [139] Abatacept or adalimumab given subcutaneously with background methotrexate (as would usually be the case in clinical practice) have been shown to have similar efficacy, safety, and time to response in patients with active RA who were naive to biological agents and those who had an inadequate response to methotrexate.[139]

Acute

» Evidence suggests that abatacept, as monotherapy or in combination with methotrexate, provides more effective disease control compared with conventional treatment (methotrexate with corticosteroids), methotrexate alone, biological agents or targeted synthetic DMARDs in patients with RA.[141] [142] There is evidence demonstrating sustained remission with abatacept following dose reduction or complete drug withdrawal.[141] [143] Few patients sustain a major response 1 year after withdrawal of abatacept therapy; re-treatment with abatacept plus methotrexate may be effective in this setting.[144]

» Abatacept is recommended over other biological agents and targeted synthetic DMARDs for patients with non-tuberculous mycobacterial lung disease who have moderate-to-high disease activity despite conventional synthetic DMARDs.[49]

» Rituximab is a B-cell modulator approved for use in combination with methotrexate for the treatment of adults with moderately to severely active RA who have had an inadequate response to one or more TNF-alpha inhibitors.

» Rituximab is recommended over other DMARDs, regardless of previous DMARD experience, for patients who have a previous lymphoproliferative disorder (for which rituximab is an approved treatment), and who have moderate-to-high disease activity, because it would not be expected to increase the risk of recurrence or worsening of lymphoproliferative disorders.[49]

» In the setting of persistent hypogammaglobulinaemia without infection, continuation of rituximab therapy for patients at target is conditionally recommended over switching to a different biological agent or targeted synthetic DMARD.[49] Continuing rituximab in patients who are at target is preferred due to the uncertain clinical significance of hypogammaglobulinaemia in patients without infection. Although an increased risk of infection has been described in RA patients with hypogammaglobulinaemia, it is not known if a switch in DMARDs in patients who are at target is more effective in lowering infection risk while maintaining disease control than continuation of rituximab.

» Interleukin 6 (IL-6) inhibitors (e.g., tocilizumab and sarilumab) are approved for the treatment of adults with moderately to severely active RA

Acute

who have had an inadequate response to one or more DMARDs.

» They may be used as monotherapy, or in combination with methotrexate or other conventional synthetic DMARDs.[125] [126]

» Evidence from systematic reviews using indirect comparisons suggest that tocilizumab may be more effective than sarilumab for treating people with RA who inadequately respond to either methotrexate or TNF-alpha inhibitors.[128] [129] An additional systematic review concluded that for people with RA with an inadequate response to conventional synthetic DMARDs, sarilumab monotherapy is more effective than adalimumab, biological agents and targeted synthetic DMARDs.[130]

» One open-label randomised trial evaluated the efficacy and safety of increasing the dose interval of subcutaneous tocilizumab in patients with RA who are in remission.[131] The study reported that although most patients sustained remission with a half-dose of tocilizumab, increasing the dose interval to 2 weeks was associated with a lower likelihood of maintaining remission, with no improvement in tolerability.[131]

» There is evidence to suggest that treatment with IL-6 inhibitors may increase the risk of serious infection, opportunistic infections, and cancer in patients with RA compared with placebo.[132] Tocilizumab has been associated with a drug-induced sarcoidosis-like reaction, occurring in temporal relationship with the initiation of tocilizumab, and a significant risk of the reactivation of hepatitis B virus (HBV) in people with RA and chronic HBV.[132] [133] [134] [135]

» The European Medicines Agency (EMA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA) identified serious hepatotoxicity (including acute liver failure, hepatitis, and jaundice) in eight patients treated with tocilizumab worldwide.[136] [137]

» Monitor alanine aminotransferase (ALT) or aspartate aminotransferase (AST) at initiation of treatment, every 4-8 weeks for the first 6 months of treatment, and then every 12 weeks thereafter.[136] [137] Advise patients to seek medical help immediately if they experience signs and symptoms of hepatic injury.[137]

Acute

» Targeted synthetic DMARDs include the oral Janus kinase (JAK) inhibitors tofacitinib, baricitinib, and upadacitinib, which are all approved to treat moderate to highly active RA.[49] [150] Filgotinib, another selective inhibitor of JAK1, is approved in Europe and the UK for the treatment of moderate to severely active rheumatoid arthritis in adults who have responded inadequately to, or who are intolerant to, one or more DMARDs.

» The US Food and Drug Administration (FDA) has issued a warning about an increased risk of serious cardiovascular events, malignancy, thrombosis, and death with tofacitinib, baricitinib, and upadacitinib.[145] This follows final results from a large randomised safety clinical trial comparing tofacitinib with tumour necrosis factor (TNF)-alpha inhibitors in patients with RA. The study found an increased risk of blood clots and death with the lower dose of tofacitinib (5 mg twice daily); this serious event had previously been reported only with the higher dose (10 mg twice daily) in the preliminary analysis.[146]

» The FDA advises clinicians to reserve tofacitinib, baricitinib, and upadacitinib for patients who have had an inadequate response or are intolerant to one or more TNF-alpha inhibitors, and consider the patient's individual benefit-risk profile when deciding to prescribe or continue treatment with these medications, particularly in patients who are current or past smokers, patients with other cardiovascular risk factors, those who develop a malignancy, and those with a known malignancy (other than a successfully treated non-melanoma skin cancer).[145]

» The European Medicines Agency (EMA) has also recommended measures to minimise the risk of serious adverse effects with JAK inhibitors. The EMA advice relates to patients aged >65 years, those who are current or past smokers, patients with other cardiovascular risk factors (such as heart attack or stroke), and patients with other malignancy risk factors. In these patient groups, JAK inhibitors should only be used to treat moderate or highly active RA, if no suitable treatment alternative is available.[147]

» The EMA recommends that JAK inhibitors should be used with caution in patients with risk factors for blood clots in the lungs and in deep veins (venous thromboembolism, VTE); and that doses should be reduced in patient groups who are at risk of VTE, cancer, or major

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cardiovascular problems, if possible. This recommendation is based on one observational study comparing the safety of baricitinib with TNF-alpha inhibitors.[147] [148]

» In the UK, the National Institute for Health and Care Excellence (NICE) has recommended filgotinib (a JAK1 inhibitor) in combination with methotrexate as an option for adult patients with moderate to severe RA (i.e., a disease activity score [DAS28] of 3.2 or more), who have an inadequate response to intensive therapy with two or more conventional synthetic DMARDs.[149]

» For patients with severe disease (DAS28 of more than 5.1) NICE recommends filgotinib with methotrexate as an option if the patient cannot tolerate rituximab and has responded inadequately to or cannot have other DMARDs, including at least one biological DMARD, or if the patient has an inadequate response to rituximab and at least one biological DMARD.[149]

» Filgotinib can be used as monotherapy in a patient with a contraindication to or intolerance of methotrexate when the above criteria are met.[149] [150]

adjunct **corticosteroid**

Treatment recommended for SOME patients in selected patient group

Primary options

» prednisolone: 1-10 mg orally once daily
Doses >10 mg/day are rarely required; however, higher doses may be required in some patients.

OR

» methylprednisolone acetate: 4-80 mg intra-articularly every 1-5 weeks; 40-120 mg intramuscularly every 1-4 weeks
Intra-articular dose depends on the size and location of the affected joint.

» Commonly used in combination with a disease-modifying antirheumatic drug (DMARD), particularly for patients with early disease starting or changing DMARD treatment, and as management for acute flares of disease activity.[88] [99] Corticosteroids also have some disease-modifying effect and hence contribute

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to overall disease control.[67] [151] [152] [153] [154] [155] [156]

» Treatment usually involves low-dose daily oral prednisolone; doses >10 mg/day are rarely required. However, there is evidence to suggest that high- or moderate-dose prednisolone tapered to a low dose is effective for remission induction when combined with methotrexate in patients with early rheumatoid arthritis (RA) and poor prognostic markers.[157] In one double-blind trial, adults with RA receiving tocilizumab and corticosteroids for 24 weeks were randomised to either continue masked prednisolone for 24 weeks or to taper masked prednisolone by week 16.[160] In all patients assigned to the continued prednisolone regimen, disease activity control was superior compared with patients assigned to the tapered prednisolone regimen. Corticosteroid doses as low as 2.5 mg/day have been associated with BMD loss in people with inflammatory rheumatic disease, but is preventable with the use of medicines for osteoporosis prophylaxis.[158] See Osteoporosis . Low dose corticosteroids have been demonstrated to increase weight by approximately 1 kg after two years of treatment.[159]

» High-dose corticosteroids may be required for the treatment of severe extra-articular involvement, such as vasculitis or eye involvement. A delayed-release formulation of oral prednisolone may have a role in RA when used as an adjunct to DMARDs.[161]

» Patients can also be treated with intramuscular corticosteroids as needed in addition to DMARD therapy, especially early in disease when quicker symptom relief may be desired while patients are waiting for DMARDs to start working.

» Intra-articular corticosteroid injections are used to control individually inflamed joints in acute flares of disease activity.

» If corticosteroids are given daily, calcium and vitamin D supplementation and yearly to biannual bone density assessment are recommended. However, some evidence suggests that suppression of inflammation by corticosteroids may counterbalance their adverse effects on bone remodelling up to 24 months in patients with early RA.[162]

» For patients taking a corticosteroid to remain at target, addition of or switching to a DMARD is

Acute

preferred (as a corticosteroid-sparing measure) to continuation of the corticosteroid.[49]

adjunct **non-steroidal anti-inflammatory drug (NSAID)**

Treatment recommended for SOME patients in selected patient group

Primary options

» ibuprofen: 400-800 mg orally three to four times daily, maximum 3200 mg/day

OR

» naproxen: 250-500 mg orally twice daily, maximum 1500 mg/day

OR

» diclofenac potassium: 50 mg orally (immediate-release) three to four times daily, maximum 200 mg/day

OR

» diclofenac sodium: 50 mg orally (delayed-release) three to four times daily, or 75 mg twice daily, maximum 200 mg/day; 100 mg orally (extended-release) once daily, may increase to 100 mg twice daily if necessary

» Can be used for symptom control in patients with early disease or those with acute flare of disease activity.[62] [99]

» The lowest effective dose for the shortest effective duration should be used.[62]

» Should be taken with food to minimise the risk of gastrointestinal adverse effects (e.g., gastritis, ulcer, gastrointestinal bleeding). Appropriate preventative therapy (e.g., proton-pump inhibitor) should be given when needed to prevent adverse gastrointestinal effects.[62]

pregnant or planning pregnancy

1st **corticosteroid, sulfasalazine, or hydroxychloroquine**

Primary options

» prednisolone: 1-10 mg orally once daily Doses >10 mg/day are rarely required; however, higher doses may be required in some patients.

Acute

Secondary options

» hydroxychloroquine: 400-600 mg/day orally given in 1-2 divided doses initially, reduce dose to 200-400 mg/day after clinical response is obtained
Dose refers to hydroxychloroquine sulfate.

OR

» sulfasalazine: 0.5 to 1 g/day orally (enteric-coated) for 7 days initially, increase by 500 mg/day increments every week according to response, maximum 2 g/day given in 2-3 divided doses

» Most medications used to treat rheumatoid arthritis (RA) cannot be used while a patient is pregnant or planning a pregnancy; however, symptoms of RA usually diminish during pregnancy.[175]

» Corticosteroids are considered the safest option for patients planning pregnancy or who are pregnant, although sulfasalazine and hydroxychloroquine can also be used. There is a lack of human data for use of sulfasalazine and hydroxychloroquine in pregnancy, so these agents are only recommended if corticosteroids are not an option, and only under a specialist with experience treating pregnant women.

» FBC and LFTs need to be checked before starting sulfasalazine or hydroxychloroquine and should be monitored every 4-8 weeks at the start of treatment. When the patient is on a stable dose, monitoring can be done every 3-4 months.

» Biological agents and Janus kinase inhibitors are generally not recommended in pregnancy due to a lack of safety data; some agents may be considered if the benefits outweigh the risks to the mother and fetus. There are data to suggest that certolizumab may be an option in pregnancy due to a lack of placental transfer.[176]

» A specialist should be consulted for guidance on using these drugs in pregnant women.

Ongoing

failure to reach low disease activity after 3 months of therapy: not pregnant or planning pregnancy

1st **methotrexate**

Primary options

» methotrexate: 7.5 mg orally/subcutaneously once weekly (on the same day each week) initially, increase gradually according to response, maximum 20 mg/week

» Combination therapy with methotrexate and either a biological agent or a targeted synthetic disease-modifying anti-rheumatic drug (DMARD) is recommended first line in these patients.[49] [88]

» For patients taking weekly oral methotrexate who are not at target, switching to subcutaneous methotrexate is recommended over addition of/switching to alternative DMARD(s).[49]

» Folic acid supplementation can also be started at the same time as starting methotrexate, as a prophylactic measure to reduce the risk of some adverse effects.

plus **biological agent or disease-modifying anti-rheumatic drug (DMARD)**

Treatment recommended for ALL patients in selected patient group

Primary options

» etanercept: 50 mg subcutaneously once weekly; or 25 mg subcutaneously twice weekly

OR

» infliximab: 3 mg/kg intravenous infusion at weeks 0, 2, 6, and then every 8 weeks thereafter
Consider increasing dose up to 10 mg/kg or increasing frequency to every 4 weeks in patients with an incomplete response.

OR

» adalimumab: 40 mg subcutaneously every 2 weeks

OR

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» certolizumab pegol: 400 mg subcutaneously at weeks 0, 2, and 4, and then 200 mg every 2 weeks or 400 mg every 4 weeks thereafter

OR

» golimumab: 50 mg subcutaneously once monthly; or 2 mg/kg intravenous infusion at weeks 0 and 4, and then every 8 weeks thereafter

OR

» abatacept: body weight <60 kg: 500 mg intravenous infusion at weeks 0, 2, and 4, and then every 4 weeks thereafter; body weight 60-100 kg: 750 mg intravenous infusion at weeks 0, 2, and 4, and then every 4 weeks thereafter; body weight >100 kg: 1000 mg intravenous infusion at weeks 0, 2, and 4, and then every 4 weeks thereafter
A subcutaneous formulation is available. The same dose is used in patients regardless of body weight (125 mg subcutaneously once weekly). However, an intravenous loading dose may be used in some patients. Consult specialist for guidance on subcutaneous dosing.

OR

» rituximab: 1000 mg intravenous infusion on days 1 and 15, may repeat course every 16-24 weeks if inadequate response

OR

» tocilizumab: 4 mg/kg intravenous infusion every 4 weeks, may increase to 8 mg/kg every 4 weeks if necessary, maximum 800 mg/dose; body weight <100 kg: 162 mg subcutaneously every 2 weeks initially, increase to 162 mg once weekly if necessary; body weight ≥100 kg: 162 mg subcutaneously once weekly

OR

» sarilumab: 200 mg subcutaneously every 2 weeks
A dose reduction (150 mg subcutaneously every 2 weeks) is required in patients

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who have or develop neutropenia, thrombocytopenia, or elevated liver enzymes.

OR

» tofacitinib: 5 mg orally (immediate-release) twice daily; 11 mg orally (extended-release) once daily

OR

» baricitinib: 2 mg orally once daily

OR

» upadacitinib: 15 mg orally once daily

OR

» filgotinib: 100-200 mg orally once daily

» TNF-alpha inhibitors (etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab) all have proven efficacy in placebo-controlled trials.[110] [111]

» One systematic review and network meta-analysis reported only minor differences in efficacy between biological treatments in combination with methotrexate in patients with rheumatoid arthritis (RA) after methotrexate failure.[167]

» One network meta-analysis reported that biological agents in combination with methotrexate (with the exception of golimumab) were associated with significantly lower rates of radiographic progression at 1 year compared with methotrexate alone.[112]

» TNF-alpha inhibitors are approved for use either with or without methotrexate depending on the specific drug; check local drug formulary for specific licence information.

» TNF-alpha inhibitors have been associated with increased risk for serious infection (tuberculosis and other opportunistic infections) compared with synthetic DMARDs, and increased risk for treatment discontinuation.[115] [116] However, systematic reviews and meta-analyses have not reported an increased risk of malignancy among patients with RA receiving TNF-alpha inhibitor therapy.[116] [117] [118] [119] [120] [121] Ongoing research seeks to establish the effect of specific DMARDs on

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risk of malignancy, particularly risk for non-melanoma skin cancer and melanoma.[122]

» Potential adverse effects associated with TNF-alpha inhibitors could be minimised by using an individualised dose reduction/withdrawal strategy once disease control has been established.

» The results of two systematic reviews suggest that disease activity-guided dose tapering of TNF-alpha inhibitors is comparable to continuation of treatment with respect to the proportion of patients with persistent remission and may be comparable regarding disease activity, while discontinuation of TNF-alpha inhibitors is inferior to continuation of treatment with respect to disease activity, the proportion of participants with persistent remission, function, and minimal radiographic damage.[123] [124]

» Abatacept is a T-cell modulator approved for the treatment of moderately to severely active RA. It has similar safety and efficacy to the TNF-alpha inhibitors, and is indicated in patients who have an inadequate response to methotrexate.[138] [139] Abatacept or adalimumab given subcutaneously with background methotrexate (as would usually be the case in clinical practice) were shown to have similar efficacy, safety, and time to response in patients with active RA who were naive to biological agents and who had an inadequate response to methotrexate.[139]

» Evidence suggests that abatacept, as monotherapy or in combination with methotrexate, provides more effective disease control compared with conventional treatment (methotrexate with corticosteroids), methotrexate alone, biological agents or targeted synthetic DMARDs in patients with RA.[140] [141] [142] There is evidence demonstrating sustained remission with abatacept following dose reduction or complete drug withdrawal.[141] [143] Few patients sustain a major response 1 year after withdrawal of abatacept therapy; re-treatment with abatacept plus methotrexate may be effective in this setting.[144]

» Abatacept is recommended over other biological agents and targeted synthetic DMARDs for patients with non-tuberculous mycobacterial lung disease who have moderate-to-high disease activity despite conventional synthetic DMARDs.[49]

» Rituximab is a B-cell modulator approved for use in combination with methotrexate

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for the treatment of adults with moderately to severely active RA who have had an inadequate response to one or more TNF-alpha inhibitors.[49]

» Rituximab is recommended over other DMARDs, regardless of previous DMARD experience, for patients who have a previous lymphoproliferative disorder (for which rituximab is an approved treatment), and who have moderate-to-high disease activity, because it would not be expected to increase the risk of recurrence or worsening of lymphoproliferative disorders.[49]

» In the setting of persistent hypogammaglobulinaemia without infection, continuation of rituximab therapy for patients at target is conditionally recommended over switching to a different biological agent or targeted synthetic DMARD.[49] Continuing rituximab in patients who are at target is preferred due to the uncertain clinical significance of hypogammaglobulinaemia in patients without infection. Although an increased risk of infection has been described in RA patients with hypogammaglobulinaemia, it is not known if a switch in DMARDs in patients who are at target is more effective in lowering infection risk while maintaining disease control than continuation of rituximab.

» Interleukin 6 (IL-6) inhibitors (tocilizumab and sarilumab) are approved for the treatment of adults with moderately to severely active RA who have had an inadequate response to one or more DMARDs. They may be used as monotherapy, or in combination with methotrexate or other conventional synthetic DMARDs.[125] [126] [127]

» Evidence from systematic reviews using indirect comparisons suggest that tocilizumab may be more effective than sarilumab for treating people with RA who inadequately respond to either methotrexate or TNF-alpha inhibitors.[128] [129] An additional systematic review concluded that for people with RA with an inadequate response to conventional synthetic DMARDs, sarilumab monotherapy is more effective than adalimumab, biological agents and targeted synthetic DMARDs.[130]

» One open-label randomised trial evaluated the efficacy and safety of increasing the dose interval of subcutaneous tocilizumab in patients with RA who are in remission.[131] The study reported that although most patients sustained

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remission with a half-dose of tocilizumab, increasing the dose interval to 2 weeks was associated with a lower likelihood of maintaining remission, with no improvement in tolerability.[131]

» There is evidence to suggest that treatment with IL-6 inhibitors may increase risk of serious infection, opportunistic infections, and cancer in patients with RA compared with placebo.[132] Tocilizumab has been associated with a drug-induced sarcoidosis-like reaction, occurring in temporal relationship with the initiation of tocilizumab, and a significant risk of the reactivation of hepatitis B virus (HBV) in people with RA and chronic HBV.[132] [133] [134] [135]

» The European Medicines Agency (EMA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA) identified serious hepatotoxicity (including acute liver failure, hepatitis, and jaundice) in eight patients treated with tocilizumab worldwide.[136] [137] Monitor alanine aminotransferase (ALT) or aspartate aminotransferase (AST) at initiation of treatment, every 4-8 weeks for the first 6 months of treatment, and then every 12 weeks thereafter.[136] [137] Advise patients to seek medical help immediately if they experience signs and symptoms of hepatic injury.[137]

» Targeted synthetic DMARDs include the oral Janus kinase 1-selective (JAK1) inhibitors tofacitinib, baricitinib, and upadacitinib, which are all approved to treat moderate to highly active RA.[49] [150] Filgotinib, another selective inhibitor of JAK1, is approved in Europe and the UK for the treatment of moderate to severely active rheumatoid arthritis in adults who have responded inadequately to, or who are intolerant to, one or more DMARDs.

» The US Food and Drug Administration (FDA) has issued a warning about an increased risk of serious cardiovascular events, malignancy, thrombosis, and death with tofacitinib, baricitinib, and upadacitinib.[145] This follows final results from a large randomised safety clinical trial comparing tofacitinib with tumour necrosis factor (TNF)-alpha inhibitors in patients with RA. The study found an increased risk of blood clots and death with the lower dose of tofacitinib (5 mg twice daily); this serious event had previously been reported only with the higher dose (10 mg twice daily) in the preliminary analysis.[146]

» The FDA advises clinicians to reserve tofacitinib, baricitinib, and upadacitinib for

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patients who have an inadequate response or are intolerant to one or more TNF-alpha inhibitors, and to consider the patient's individual benefit-risk profile when deciding to prescribe or continue treatment with these medications, particularly in patients who are current or past smokers, patients with other cardiovascular risk factors, those who develop a malignancy, and those with a known malignancy (other than a successfully treated non-melanoma skin cancer).[145]

» The European Medicines Agency (EMA) has also recommended measures to minimise the risk of serious adverse effects with JAK inhibitors. The EMA advice relates to patients aged >65 years, those who are current or past smokers, patients with other cardiovascular risk factors (such as heart attack or stroke), and patients with other malignancy risk factors. In these patient groups, JAK inhibitors should only be used to treat moderate or highly active RA, if no suitable treatment alternative is available.[147]

» The EMA recommends that JAK inhibitors should be used with caution in patients with risk factors for blood clots in the lungs and in deep veins (venous thromboembolism, VTE); and that doses should be reduced in patient groups who are at risk of VTE, cancer, or major cardiovascular problems, if possible. This recommendation is based on one observational study comparing the safety of baricitinib with TNF-alpha inhibitors.[147] [148]

» In the UK, the National Institute for Health and Care Excellence (NICE) has recommended filgotinib (a JAK1 inhibitor) in combination with methotrexate as an option for adult patients with moderate to severe RA (i.e., a disease activity score [DAS28] of 3.2 or more), who have an inadequate response to intensive therapy with two or more conventional synthetic DMARDs.[149]

» For patients with severe disease (DAS28 of more than 5.1) NICE recommends filgotinib with methotrexate as an option if the patient cannot tolerate rituximab and has responded inadequately to or cannot have other DMARDs, including at least one biological DMARD, or has had an inadequate response to rituximab and at least one biological DMARD.[149]

» Filgotinib can be used as monotherapy in a patient with a contraindication to or intolerance

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of methotrexate when the above criteria are met.[149] [150]

» For patients at target for at least 6 months, the preferred option is to continue all DMARDs at their current dose, rather than reducing the dose or gradual discontinuation of DMARD treatment.[49]

» For patients taking combination therapy who wish to discontinue a DMARD, gradual discontinuation of methotrexate is recommended rather than gradual discontinuation of the biological agent or targeted synthetic DMARD.[49] [90] One open-label randomised controlled trial comparing half-dose with stable conventional synthetic DMARDs found that patients given the half-dose had significantly more disease flares than those on the stable dose.[91]

adjunct **corticosteroid**

Treatment recommended for SOME patients in selected patient group

Primary options

» prednisolone: 1-10 mg orally once daily
Doses >10 mg/day are rarely required; however, higher doses may be required in some patients.

OR

» methylprednisolone acetate: 4-80 mg intra-articularly every 1-5 weeks; 40-120 mg intramuscularly every 1-4 weeks
Intra-articular dose depends on the size and location of the affected joint.

» Commonly used in combination with a disease-modifying antirheumatic drug (DMARD), particularly for patients with early rheumatoid arthritis (RA) starting or changing DMARD treatment, and as management for acute flares of disease activity.[62] [88][99] Corticosteroids also have some disease-modifying effect and hence contribute to overall disease control.[67] [151] [152] [153] [154] [155] [156]

» Treatment usually involves low-dose daily oral prednisolone; doses >10 mg/day are rarely required. However, there is evidence to suggest that high- or moderate-dose prednisolone tapered to a low dose is effective for remission induction when combined with methotrexate

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in patients with early RA and poor prognostic markers.[157] Corticosteroid doses as low as 2.5 mg/day have been associated with BMD loss in people with inflammatory rheumatic disease, but is preventable with the use of medicines for osteoporosis prophylaxis.[158] See Osteoporosis . Low dose corticosteroids have been demonstrated to increase weight by approximately 1 kg after two years of treatment.[159]

» High-dose corticosteroids may be required for the treatment of severe extra-articular involvement, such as vasculitis or eye involvement. A delayed-release formulation of low-dose oral prednisolone may have a role in RA when used as an adjunct to DMARDs.[161]

» Patients can also be treated with intramuscular corticosteroids as needed in addition to DMARD therapy, especially early in disease when quicker symptom relief may be desired while patients are waiting for DMARDs to start working.

» Intra-articular corticosteroid injections are used to control individually inflamed joints in acute flares of disease activity.

» If corticosteroids are given daily, calcium and vitamin D supplementation and yearly to biannual bone density assessment are recommended.

» For patients taking a corticosteroid to remain at target, addition of or switching to a DMARD is preferred (as a corticosteroid-sparing measure) to continuation of the corticosteroid.[49]

adjunct **non-steroidal anti-inflammatory drug (NSAID)**

Treatment recommended for SOME patients in selected patient group

Primary options

» ibuprofen: 400-800 mg orally three to four times daily, maximum 3200 mg/day

OR

» naproxen: 250-500 mg orally twice daily, maximum 1500 mg/day

OR

» diclofenac potassium: 50 mg orally (immediate-release) three to four times daily, maximum 200 mg/day

Ongoing

OR

» diclofenac sodium: 50 mg orally (delayed-release) three to four times daily, or 75 mg twice daily, maximum 200 mg/day; 100 mg orally (extended-release) once daily, may increase to 100 mg twice daily if necessary

» Can be used for symptom control in patients with early disease or those with acute flare of disease activity.[62] [99]

» The lowest effective dose for the shortest effective duration should be used.[62]

» Should be taken with food to minimise the risk of gastrointestinal adverse effects (e.g., gastritis, ulcer, gastrointestinal bleeding). Appropriate preventative therapy (e.g., proton-pump inhibitor) should be given when needed to prevent adverse gastrointestinal effects.[62]

2nd **triple DMARD therapy**

» Triple therapy with synthetic DMARDs (e.g., methotrexate plus hydroxychloroquine plus sulfasalazine) may be a second-line option in select patients who fail to reach low disease activity after 3 months.[62] However, this regimen is rarely used in the era of biological agents/targeted synthetic DMARDs, and is not recommended by US guidelines.[49]

» In a prospective study of rheumatoid arthritis (RA) patients registered on the nationwide Swedish Rheumatology Quality Register, the likelihood of reaching sustained remission was higher with biological therapy (a biological agent plus methotrexate) than with triple therapy.[173] For specific RA patients, however, triple therapy was believed to be an alternative to biological therapy without prejudicing future likelihood of sustained remission.

» Evidence from a systematic review suggests that treatment with biological agents seems to be more effective compared with triple DMARD therapy in terms of radiological progression in RA with inadequate response to methotrexate.[174]

» A corticosteroid and/or NSAID may be used for symptom control in patients with early disease or those with acute flare of disease activity.[99]

adjunct **corticosteroid**

Treatment recommended for SOME patients in selected patient group

Ongoing

Primary options

» prednisolone: 1-10 mg orally once daily
Doses >10 mg/day are rarely required; however, higher doses may be required in some patients.

OR

» methylprednisolone acetate: 4-80 mg intra-articularly every 1-5 weeks; 40-120 mg intramuscularly every 1-4 weeks
Intra-articular dose depends on the size and location of the affected joint.

» Commonly used in combination with a disease-modifying antirheumatic drug (DMARD), particularly for patients with early rheumatoid arthritis (RA) starting or changing DMARD treatment, and as management for acute flares of disease activity.[62] [88][99] Corticosteroids also have some disease-modifying effect and hence contribute to overall disease control.[67] [151] [152] [153] [154] [155] [156]

» Treatment usually involves low-dose daily oral prednisolone; doses >10 mg/day are rarely required. However, there is evidence to suggest that high- or moderate-dose prednisolone tapered to a low dose is effective for remission induction when combined with methotrexate in patients with early RA and poor prognostic markers.[157] Corticosteroid doses as low as 2.5 mg/day have been associated with BMD loss in people with inflammatory rheumatic disease, but is preventable with the use of medicines for osteoporosis prophylaxis.[158] See Osteoporosis . Low dose corticosteroids have been demonstrated to increase weight by approximately 1 kg after two years of treatment.[159]

» High-dose corticosteroids may be required for the treatment of severe extra-articular involvement, such as vasculitis or eye involvement. A delayed-release formulation of low-dose oral prednisolone may have a role in RA when used as an adjunct to DMARDs.[161]

» Patients can also be treated with intramuscular corticosteroids as needed in addition to DMARD therapy, especially early in disease when quicker symptom relief may be desired while patients are waiting for DMARDs to start working.

Ongoing

» Intra-articular corticosteroid injections are used to control individually inflamed joints in acute flares of disease activity.

» If corticosteroids are given daily, calcium and vitamin D supplementation and yearly to biannual bone density assessment are recommended.

» For patients taking a corticosteroid to remain at target, addition of or switching to a DMARD is preferred (as a corticosteroid-sparing measure) to continuation of the corticosteroid.[49]

adjunct **non-steroidal anti-inflammatory drug (NSAID)**

Treatment recommended for SOME patients in selected patient group

Primary options

» ibuprofen: 400-800 mg orally three to four times daily, maximum 3200 mg/day

OR

» naproxen: 250-500 mg orally twice daily, maximum 1500 mg/day

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» diclofenac potassium: 50 mg orally (immediate-release) three to four times daily, maximum 200 mg/day

OR

» diclofenac sodium: 50 mg orally (delayed-release) three to four times daily, or 75 mg twice daily, maximum 200 mg/day; 100 mg orally (extended-release) once daily, may increase to 100 mg twice daily if necessary

» Can be used for symptom control in patients with early disease or those with acute flare of disease activity.[62] [99]

» The lowest effective dose for the shortest effective duration should be used.[62]

» Should be taken with food to minimise the risk of gastrointestinal adverse effects (e.g., gastritis, ulcer, gastrointestinal bleeding). Appropriate preventative therapy (e.g., proton-pump inhibitor) should be given when needed to prevent adverse gastrointestinal effects.[62]

Emerging

RNA sequencing-based stratification of synovial tissue

Tocilizumab appears to be more effective than rituximab (which targets CD20 B cells) in patients classified as B-cell poor using RNA sequencing, but not in patients histologically classified as B-cell poor.[177] These results suggest that RNA sequencing-based stratification of rheumatoid arthritis (RA) synovial tissue is more strongly associated with clinical response than histopathological classification; further research is required before treatment recommendations can be made.

Olokizumab

Olokizumab, an investigational humanised monoclonal antibody targeting interleukin-6, in combination with methotrexate has been demonstrated to significantly improve the percentage of people with RA achieving ACR20/50/70, DSA28-CRP, CDAI and HAQ-DI response at 12 weeks compared with placebo.[178] [179] [180] Treatment-related adverse effects were significantly higher in the olokizumab group compared with the placebo group, but serious treatment-related adverse effects did not differ significantly between the olokizumab group and the placebo group.[180] Further large randomised controlled trials are needed to establish long term effects.[179]

Peficitinib

Peficitinib, an investigational Janus kinase inhibitor, has been found to significantly increase the ACR20/50/70 response rate for people with RA compared with placebo using direct and indirect comparison meta-analysis.[181] An additional indirect comparison meta-analysis concluded that peficitinib is one of the most effective treatments for people with RA with an inadequate response to disease-modifying anti-rheumatic drugs (DMARDs).[182] Results from one subsequent double blind phase 3 study suggests that peficitinib significantly increases the ACR20 response rate in Asian people with RA who have an inadequate response or intolerance to methotrexate compared with placebo.[183]

Primary prevention

There are no primary prevention measures for rheumatoid arthritis (RA). Even though patients commonly have serological markers (rheumatoid factor, anti-cyclic citrullinated peptide [anti-CCP] antibodies) years before they develop the disease, most patients with these markers do not go on to develop RA.[21] [44] [45]

One phase IIb trial suggests that for people at high risk of developing RA (with serum antibodies to citrullinated protein antigens, rheumatoid factor, and symptoms, such as inflammatory joint pain) treatment with abatacept during the at-risk phase of RA significantly reduces the risk of developing RA at 24 months, compared with placebo. The estimated proportion of people remaining arthritis-free at 12 months was 93% in the abatacept group and 69% in the placebo group.[46] Abatacept has also been demonstrated to decrease MRI inflammation, clinical symptoms and risk of RA development in high risk individuals at 12 months in one randomised, multi-centre, double-blind, placebo-controlled trial.[47]

Patient discussions

Patients must be aware that treatment should not be stopped or reduced without seeking the advice of their doctor, even if their symptoms are much improved or they seem to be in remission. Some patients may find patient support groups helpful.

Advise patients to engage in consistent exercise.[195]

[National Rheumatoid Arthritis Society] (https://www.nras.org.uk)

FOLLOW UP

Monitoring

Monitoring

Careful monitoring of disease activity and adverse effects related to multiple medication use is essential.

Laboratory monitoring

Hepatitis B and C status, purified protein derivative (PPD), full blood count (FBC), and liver function tests (LFTs) need to be checked before starting disease-modifying antirheumatic drugs (DMARDs). Laboratory monitoring for FBC and LFT abnormalities is done every 4-8 weeks at the start of treatment. When the patient is on a stable dose, they should be checked every 3-4 months.[193] [194]

Disease activity and response to therapy

Monitored by any of the composite scores available. These include the disease activity score (DAS) and its derivatives, health assessment questionnaire (HAQ) and its derivatives, routine assessment patient index data (RAPID3), simplified disease activity index (SDAI), and clinical disease activity index (CDAI).[185] [186] [187] However, these scores are not commonly used in routine care and are one of the important aspects of management that needs to improve in routine rheumatology care.

The American College of Rheumatology (ACR) Working Group has recommended the following scores for measuring disease activity in rheumatoid arthritis patients: the 28-joint count version of DAS (DAS28), CDAI, SDAI, patient activity scale (PAS), and RAPID3. These scores appear to perform similarly in RA patients.[66]

Complications

Complications	Timeframe	Likelihood
work disability	**long term**	**high**
Long-term significant outcome of rheumatoid arthritis (RA) if not treated adequately. In a review of biological agents in patients with RA, almost all studies showed positive results with respect to work presenteeism.[190]		
increased joint replacement surgery	**long term**	**high**
Long-term significant outcome of rheumatoid arthritis if not treated adequately.		
increased coronary artery disease	**long term**	**high**
Rheumatoid arthritis is a risk factor by itself, in addition to traditional cardiovascular risk factors. Patients with RA have more prevalent coronary artery disease, higher coronary calcium scores, more high risk plaques and multi-vessel disease compared with controls.[191]		
increased mortality	**long term**	**high**
Untreated rheumatoid arthritis leads to, on average, 8- to 10-year shortening of life span.		
interstitial lung disease (ILD)	**long term**	**high**
ILD is an increasingly recognised complication of rheumatoid arthritis and is associated with significant morbidity and mortality.[192] Patients with RA-related ILD are at high risk of infection and drug toxicity, which, along with comorbidities, complicates further treatment decision-making.		
Felty syndrome	**long term**	**low**
A complication of long-standing rheumatoid arthritis (RA). It is defined by the presence of 3 conditions: RA, splenomegaly, and an abnormally low white blood cell count. It affects <1% of patients with RA.		
carpal tunnel syndrome (CTS)	**variable**	**medium**
Rheumatoid arthritis can be associated with the development of CTS. Rates as high as 29% have been reported (but more typically around 10% to 20%). Presumably the main mechanism is due to a narrowing of the carpal tunnel from thickening of the wrist joint synovium and tendon sheaths.[188] [189]		
methotrexate-related liver toxicity and lung involvement	**variable**	**low**
Dose is adjusted or treatment discontinued.		

FOLLOW UP

Complications	Timeframe	Likelihood
TNF-alpha inhibitor-related infections	**variable**	**low**
Treatment should be stopped while the infection is being treated. If serious, discontinuation of the TNF-alpha inhibitor should be considered. Repeated episodes should also lead to consideration of discontinuation. This complication can occur at any time but is more common in the first 6 months after treatment is started.[185] One study showed that there is no increased risk of serious infection and malignancy among patients with early disease who have not previously been treated with disease-modifying antirheumatic drugs and/or methotrexate.[117]		
TNF-alpha inhibitor-related malignancy	**variable**	**low**
Treatment should be discontinued. This complication can occur at any time but may be more common early in treatment course.[186] [187] One study showed that there is no increased risk of serious infection and malignancy among patients with early disease who have not previously been treated with disease-modifying antirheumatic drugs and/or methotrexate.[117]		

Prognosis

RA patients treated aggressively and early have a good prognosis with most patients achieving good disease control.[69] If there is a delay in treatment initiation or the disease remains untreated, many patients are disabled within 10 years.[184] Untreated, RA is also associated with increased premature mortality, most commonly from coronary artery disease.

Flares of disease are common, even in patients well controlled with disease-modifying antirheumatic drugs (DMARDs). Temporary measures, such as oral corticosteroids, are usually adequate.

For patients in remission or with low disease activity who are taking biological agents, studies suggest that discontinuing the biological agents leads to an increased risk of losing remission or low disease activity and an increased risk of radiographic progression.[124] [131]

The results of two systematic reviews suggest that:[123] [124]

- Disease activity-guided dose tapering of TNF-alpha inhibitors is comparable to continuation of treatment with respect to the proportion of patients with persistent remission and may be comparable regarding disease activity
- Discontinuation of TNF-alpha inhibitors is inferior to continuation of treatment with respect to disease activity, the proportion of participants with persistent remission, function, and minimal radiographic damage.

Diagnostic guidelines

United Kingdom

Rheumatoid arthritis in adults: management (https://www.nice.org.uk/guidance/ng100)

Published by: National Institute for Health and Care Excellence **Last published:** 2020

Europe

EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis (https://www.eular.org/recommendations-management#2013)

Published by: European League Against Rheumatism **Last published:** 2013

North America

ACR appropriateness criteria: chronic extremity joint pain - suspected inflammatory arthritis (https://www.acr.org/Clinical-Resources/ACR-Appropriateness-Criteria)

Published by: American College of Radiology **Last published:** 2022

Treatment guidelines

United Kingdom

Rheumatoid arthritis in adults: management (https://www.nice.org.uk/guidance/ng100)

Published by: National Institute for Health and Care Excellence **Last published:** 2020

Biologic DMARD safety guidelines in inflammatory arthritis (https://www.rheumatology.org.uk/practice-quality/guidelines)

Published by: The British Society for Rheumatology **Last published:** 2019

Therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis (https://www.nice.org.uk/guidance/dg36)

Published by: National Institute for Health and Care Excellence **Last published:** 2019

Prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs (https://www.rheumatology.org.uk/practice-quality/guidelines)

Published by: British Society for Rheumatology; British Health Professionals in Rheumatology Standards **Last published:** 2017

Baricitinib for moderate to severe rheumatoid arthritis (https://www.nice.org.uk/guidance/ta466)

Published by: National Institute for Health and Care Excellence **Last published:** 2017

Tofacitinib for moderate to severe rheumatoid arthritis (https://www.nice.org.uk/guidance/ta480)

Published by: National Institute for Health and Care Excellence **Last published:** 2017

Sarilumab for moderate to severe rheumatoid arthritis (https://www.nice.org.uk/guidance/ta485)

Published by: National Institute for Health and Care Excellence **Last published:** 2017

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (https://www.nice.org.uk/guidance/ta375)

Published by: National Institute for Health and Care Excellence **Last published:** 2016

Tocilizumab for the treatment of rheumatoid arthritis (https://www.nice.org.uk/guidance/TA247)

Published by: National Institute for Health and Care Excellence **Last published:** 2012

United Kingdom

Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (https://www.nice.org.uk/guidance/TA195)

Published by: National Institute for Health and Care Excellence **Last published:** 2010

Total wrist replacement (https://www.nice.org.uk/guidance/IPG271)

Published by: National Institute for Health and Care Excellence **Last published:** 2008

Europe

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs (https://www.eular.org/recommendations-management#2022)

Published by: European League Against Rheumatism **Last published:** 2022

ESMO management of toxicities from immunotherapy (https://www.esmo.org/guidelines/guidelines-by-topic)

Published by: European Society for Medical Oncology **Last published:** 2022

EULAR points to consider for the management of difficult-to-treat rheumatoid arthritis (https://www.eular.org/recommendations-management#2021)

Published by: European League Against Rheumatism **Last published:** 2021

EULAR recommendations for the implementation of self-management strategies in patients with inflammatory arthritis (https://www.eular.org/recommendations-management#2021)

Published by: European League Against Rheumatism **Last published:** 2021

Management of patients with rheumatoid arthritis (https://www.ser.es/profesionales/que-hacemos/investigacion/guias-de-practica-clinica)

Published by: Spanish Society of Rheumatology **Last published:** 2019

Clinical practice guidelines for rheumatoid arthritis: from the Italian Society for Rheumatology (https://www.reumatologia.it/en/leggi-decreti)

Published by: Italian Society for Rheumatology **Last published:** 2019

2016 update of the EULAR recommendations for the management of early arthritis (https://www.eular.org/recommendations-management)

Published by: European League Against Rheumatism **Last published:** 2016

North America

2023 American College of Rheumatology (ACR) guideline for the screening and monitoring of interstitial lung disease in people with systemic autoimmune rheumatic disease (https://rheumatology.org/clinical-practice-guidelines)

Published by: American College of Rheumatology; American College of Chest Physicians **Last published:** 2023

2023 American College of Rheumatology (ACR) guideline for the treatment of interstitial lung disease in people with systemic autoimmune rheumatic disease (https://rheumatology.org/clinical-practice-guidelines)

Published by: American College of Rheumatology; American College of Chest Physicians **Last published:** 2023

Guideline for vaccinations in patients with rheumatic and musculoskeletal diseases (https://rheumatology.org/clinical-practice-guidelines)

Published by: American College of Rheumatology **Last published:** 2023

Guideline for exercise, rehabilitation, diet, and additional integrative interventions for rheumatoid arthritis (https://rheumatology.org/clinical-practice-guidelines)

Published by: American College of Rheumatology **Last published:** 2022

Canadian Rheumatology Association living guidelines for the pharmacological management of rheumatoid arthritis with disease-modifying antirheumatic drugs (https://rheum.ca/resources/publications)

Published by: Canadian Rheumatology Association **Last published:** 2022

American College of Rheumatology guideline for the treatment of rheumatoid arthritis (https://rheumatology.org/clinical-practice-guidelines)

Published by: American College of Rheumatology **Last published:** 2021

Latin America

2017 recommendations of the Brazilian Society of Rheumatology for the pharmacological treatment of rheumatoid arthritis (https://pubmed.ncbi.nlm.nih.gov/34819172)

Published by: Brazilian Society of Rheumatology **Last published:** 2021

Asia

The use of methotrexate in patients with rheumatoid arthritis (https://academic.oup.com/mr/article/34/1/1/7306778)

Published by: Japan College of Rheumatology **Last published:** 2023

Management of rheumatoid arthritis (https://link.springer.com/article/10.1007/s10067-019-04761-5)

Published by: Published by: Hong Kong Society of Rheumatology **Last published:** 2019

APLAR recommendations for treatment of rheumatoid arthritis (https://pubmed.ncbi.nlm.nih.gov/30809944)

Published by: Asia Pacific League of Associations for Rheumatology **Last published:** 2019

Management of rheumatoid arthritis: from the Hong Kong Society of Rheumatology (https://www.rheumatology.org.hk)

Published by: Hong Kong Society of Rheumatology **Last published:** 2019

Oceania

Australian living guideline for the pharmacological management of inflammatory arthritis (https://rheumatology.org.au/For-Healthcare-Professionals/Australian-Living-Guidelines/Adult-Living-Guidelines)

Published by: Australian Rheumatology Association **Last published:** 2024

Online resources

1. BMJ talk medicine: Rheumatoid arthritis (https://soundcloud.com/bmjpodcasts/rheumatoid-arthritis?in=bmjpodcasts/sets/bmj-best-practice-clinical) *(external link)*

2. National Rheumatoid Arthritis Society (https://www.nras.org.uk) *(external link)*

Evidence tables

What are the effects of a tumour necrosis factor (TNF)-alpha inhibitor plus methotrexate compared with combination traditional disease-modifying anti-rheumatic drugs (DMARDs), or a non-TNF biologic or an oral Janus kinase (JAK) inhibitor plus methotrexate in people with early rheumatoid arthritis with moderate or high disease activity who have failed traditional DMARD therapy?[49]

This table is a summary of the analysis reported in a guideline (underpinned by a systematic review) that focuses on the above important clinical question.

View the full source guideline (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Rheumatoid-Arthritis)

Evidence C *	Confidence in the evidence is very low or low where GRADE has been performed and there may be no difference in effectiveness between the intervention and comparison for key outcomes. However, this is uncertain and new evidence could change this in the future.

Population: People with early rheumatoid arthritis (RA) and moderate or high disease activity

Intervention: TNF-alpha inhibitor plus methotrexate

Comparison: Combination traditional DMARDs; or a non-TNF biologic plus methotrexate; or tofacitinib (a JAK inhibitor) plus methotrexate

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
TNF-alpha inhibitor plus methotrexate versus triple DMARD therapy (methotrexate, sulfasalazine, and hydroxychloroquine)		
ACR20 response (RA disease activity)	No statistically significant difference	Low
ACR50 response (RA disease activity)	No statistically significant difference	Low
ACR70 response (RA disease activity)	No statistically significant difference	Low
Sharp radiographical progression score (higher score indicates more severe radiographical progression)	Favours intervention	Low
Serious adverse events (SAEs)	No statistically significant difference	Low

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Infections and infestations	Occurs more commonly with a TNF-alpha inhibitor plus methotrexate compared with triple DMARD therapy (favours comparison)	Low
Hepatotoxicity (Swedish reporting criteria)	No statistically significant difference	Low
Gastrointestinal adverse events	Occurs more commonly with triple DMARD therapy compared with methotrexate plus TNF-alpha inhibitor (favours intervention)	Low
TNF-alpha inhibitor plus methotrexate versus non-TNF biologic plus methotrexate		
DAS-28 (RA disease activity) (higher score indicates more severe disease activity)	No statistically significant difference	Low
ACR50 response (RA disease activity)	No statistically significant difference	Low
Health Assessment Questionnaire -Disability Index (HAQ-DI) (higher score indicates more severe disability)	No statistically significant difference	Low
Sharp radiographical progression score (higher score indicates more severe disease progression)	No statistically significant difference	Low
Serious Adverse Events (SAEs)	No statistically significant difference	Low
Serious infections	No statistically significant difference	Low
Malignancies	No statistically significant difference	Low
Local injection site reactions	Occurs more commonly with a TNF-alpha inhibitor plus methotrexate compared with a non-TNF biologic	Low

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
	plus methotrexate (favours intervention)	
TNF-alpha inhibitor plus methotrexate versus tofacitinib plus methotrexate		
DAS-28 <2.6 (RA disease activity) (percentage of participants achieving DAS-28 remission)	No statistically significant difference	Low
ACR20 response (RA disease activity)	No statistically significant difference	Low
HAQ-DI (higher score indicates more severe physical disability)	Favours comparison	Low
SAEs	No statistically significant difference	Low
Serious infections	No statistically significant difference	Low
Hepatotoxicity (ALT>3x upper limit of normal)	No statistically significant difference	Very Low

Recommendations as stated in the source guideline

The 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis makes the following recommendations:

- If disease activity remains moderate or high despite DMARD monotherapy (with or without a glucocorticoid), use combination traditional DMARDs or a TNF-alpha inhibitor or a non-TNF biologic agent (all choices with or without methotrexate, in no particular order of preference), rather than continuing DMARD monotherapy alone (strong recommendation; low-quality evidence).
- If disease activity remains moderate or high despite combination traditional DMARDs, use a TNF-alpha inhibitor plus methotrexate over tofacitinib plus methotrexate (conditional recommendation; low-quality evidence)

Note

- The guideline committee rated the first recommendation in this table as strong, despite the low quality of evidence, because clinical experience and indirect evidence supports the benefits of adding the listed treatment options as opposed to continuing with monotherapy. The guideline panel also agreed that whenever possible, biologic therapy should be in combination with methotrexate due to superior efficacy compared with biologic monotherapy.
- The second recommendation was rated as conditional due to the low quality of the evidence and potential long-term safety concerns of tofacitinib.

* Evidence levels

The Evidence level is an internal rating applied by BMJ Best Practice. See the EBM Toolkit (https://bestpractice.bmj.com/info/evidence-tables/) for details.

Confidence in evidence

A - High or moderate to high

B - Moderate or low to moderate

C - Very low or low

† Effectiveness (BMJ rating)

Based on statistical significance, which demonstrates that the results are unlikely to be due to chance, but which does not necessarily translate to a clinical significance.

‡ Grade certainty ratings

High	The authors are very confident that the true effect is similar to the estimated effect.
Moderate	The authors are moderately confident that the true effect is likely to be close to the estimated effect.
Low	The authors have limited confidence in the effect estimate and the true effect may be substantially different.
Very Low	The authors have very little confidence in the effect estimate and the true effect is likely to be substantially different.

BMJ Best Practice EBM Toolkit: What is GRADE? (https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/)

Key articles

- Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. 2021 Jul;73(7):1108-23. Full text (https://onlinelibrary.wiley.com/doi/10.1002/art.41752) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34101376?tool=bestpractice.bmj.com)
- National Institute for Health and Care Excellence. Rheumatoid arthritis in adults: management. Oct 2020 [internet publication]. Full text (https://www.nice.org.uk/guidance/ng100)
- Smolen JS, Landewé RBM, Bergstra SA, eta al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis. 2023 Jan;82(1):3-18 Epub 2022 Nov 10. Full text (https://ard.bmj.com/content/82/1/3.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/36357155?tool=bestpractice.bmj.com)

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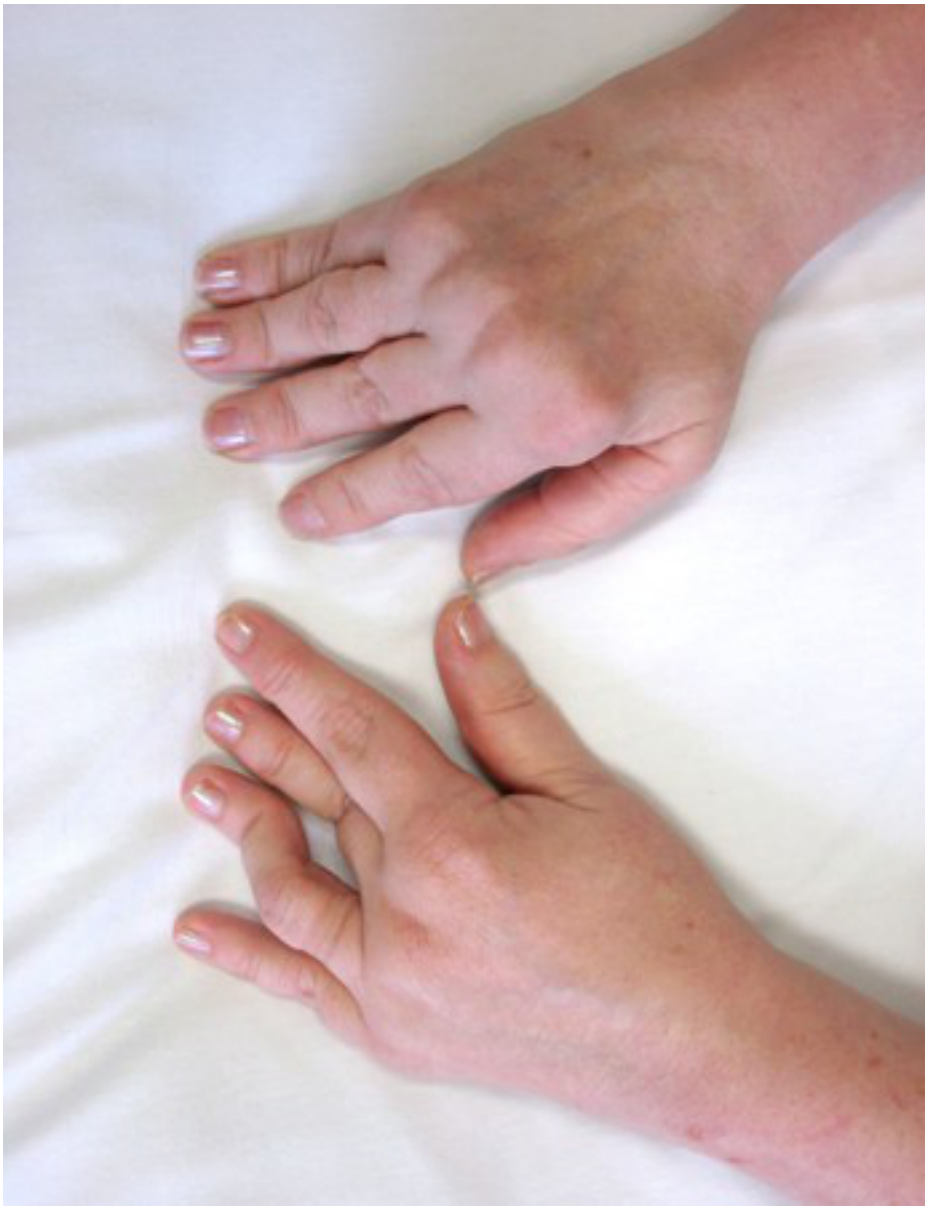

Figure 1: Rheumatoid arthritis (chronic hand deformities)

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Figure 1 – BMJ Best Practice Numeral Style

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