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Therapeutic Options

FOCUS ON RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disease that affects approximately 0.5% to 1% of the population.[1,2] Peak incidence occurs between the ages of 50 and 60 years and, like many autoimmune disorders, RA is more common in females.[1,3] A hallmark of the disease is polyarticular synovial inflammation, which causes joint swelling, stiffness, and pain.[2] Over time, inflammation can lead to cartilage damage, bone erosions, and joint destruction, resulting in decreased physical function and quality of life.[1,2,4] RA is also associated with many comorbidities and complications, including cardiovascular disease, which is responsible for higher mortality rates among RA patients compared with the general population.[2]

Fortunately, the outlook for patients with RA has improved substantially over the past two decades, at least in part as a result of earlier diagnosis and proactive treatment.[1] Nonetheless, outcomes remain suboptimal for many patients,[4] underscoring the importance of aggressive management strategies that involve close and frequent monitoring.

This article provides a brief overview of RA, with a focus on the pharmacological management of core symptoms and complications.

ETIOLOGY & PATHOGENESIS

The etiology and pathogenesis of RA are complex and incompletely understood.[3,5] It is believed that an antigen-mediated triggering event, possibly autoimmune or infectious in nature, leads to immune cell activation in a genetically susceptible individual.[3,5] Activation of T cells results in proliferation of synoviocytes, endothelial cells, and other proinflammatory cells, as well as induction of autoantibodies and secretion of proinflammatory cytokines (e.g., tumour necrosis factor [TNF]-α, interleukin 1) and proteases.[1,3] Ultimately, interactions among multiple immune cell types and their cytokines, proteases, and growth factors mediate joint destruction and systemic complications.[3,5]

SIGNS & SYMPTOMS

Swelling, pain, and stiffness in affected joints—most commonly the hands, wrists, feet, and knees—are typical of RA.[1,4] Pain is usually polyarticular and symmetrical, but may afflict only a few joints at onset.[1] Distal interphalangeal joints are normally spared.[1,3] Stiffness is generally present in the morning, lasts more than 30 minutes, and improves throughout the day.[1] Patients often complain of fatigue and general malaise.[1]

In those with long-standing, inadequately controlled RA, joint damage and its associated deformities (e.g., ulnar deviation, swan neck, and boutonniere deformities of the hands; images available at http://images.rheumatology.org/albums.php?albumId=75692) are common.[1] Loss of joint motion and function are routinely present.[1,4]

Classic radiographic findings in patients

Drug Information and Research Centre
375 University Avenue, Suite 800, Toronto, Ontario M5G 2J5
Phone: 1-800-268-8058 Fax: (416) 385-2442 www.dirc-canada.org

with RA include juxta-articular osteopenia, joint-space narrowing, and erosions.[1]

Many extra-articular (e.g., dermatologic, ophthalmologic, pulmonary, cardiac, gastrointestinal, renal, hepatic, neurologic, hematologic) manifestations are also possible.[1] However, a thorough discussion of such manifestations is beyond the scope of this review.

DIAGNOSIS

The diagnosis of RA is clinical in nature and is based on patient symptom history, physical examination, and laboratory tests.[1,2] In 2010, updated RA classification criteria were put forth by the American College of Rheumatology (ACR) and the European League Against Rheumatism[6] (Table 1). According to these criteria, a classification of "definite RA" is based on the presence of confirmed synovitis (swelling, not just tenderness) in at least one joint (that cannot be better explained by an alternative diagnosis) and a total score ≥6 (out of a possible 10).[6] As these are classification criteria and not diagnostic criteria, it remains to be seen whether they can be used to accurately diagnose RA.[2]

PHARMACOTHERAPY

The primary goal for the treatment of RA is to achieve disease remission according to a validated disease activity measure.[1,4,7] Various disease activity measures, and their corresponding definitions of remission (as well as low, moderate, and high disease activity), are summarized in guidelines for the pharmacological management of RA from the Canadian Rheumatology Association (CRA)[7] (see References, below, for URL). Achieving remission as quickly as possible is recommended since early sustained remission has been shown to prevent the progression of joint damage.[4] In patients for whom remission may not be realistic (e.g., those with late-stage disease), targeting the lowest degree of disease activity feasible should be the goal, bearing in mind that functional impairment exists, and progressive joint damage can occur, during low disease activity.[4]

Early intensive therapy with disease-modifying antirheumatic drugs (DMARDs) should be employed to achieve goals and improve clinical outcomes.[3,4] CRA recommendations for the use of traditional and biologic DMARDs and other selected therapies are summarized under the subheadings below. Generally speaking, therapy should be adjusted every three to six months if treatment goals have not been achieved.[7] Combination therapy is required in many patients.[3] In instances of sustained remission* after ancillary treatments (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], glucocorticoids) have been discontinued, a reduction in biologic and/or traditional DMARD therapy can be attempted with caution, recognizing the potential for disease flares.[7]

Dosing guidelines and other pertinent information about some DMARDs used to treat RA are provided in Table 2.

Vaccine recommendations for patients undergoing treatment with traditional and biologic DMARDs have been made by the CRA (see full online guidelines[8] for details).

Traditional DMARDs

Traditional DMARDs are the mainstay of RA treatment; they improve symptoms, reduce joint damage, and allow a subset of patients to achieve remission.[4] Commonly prescribed agents include methotrexate (MTX), leflunomide, sulfasalazine, and hydroxychloroquine.[7] The CRA guidelines recommend that DMARD therapy be instituted as soon as possible in patients with persistent synovitis,

Table 1 – ACR/EULAR classification criteria for RA*[6]

Criteria	Score†
Joint involvement‡	
1 large joint	0
2–10 large joints	1
1–3 small joints (with/without large joint involvement)	2
4–10 small joints (with/without large joint involvement)	3
>10 joints (at least 1 small joint§)	5
Serology	
Negative RF *and* negative ACPA	0
Low-positive‖ RF *or* low-positive‖ ACPA	2
High-positive‖ RF *or* high-positive‖ ACPA	3
Acute-phase reactants	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
Symptom duration	
<6 weeks	0
≥6 weeks	1

ACPA = anti-citrullinated protein antibody; **ACR** = American College of Rheumatology; **CRP** = C-reactive protein; **ESR** = erythrocyte sedimentation rate; **EULAR** = European League Against Rheumatism; **RA** = rheumatoid arthritis; **RF** = rheumatoid factor

* The criteria are aimed at classification of newly presenting patients. Patients with long-standing disease that has become inactive or less active who previously fulfilled the criteria, or have erosions on radiographs, will still be classified as having RA.[2]

† The total score is derived from the sum of the individual scores of the four criteria domains.

‡ Joint involvement refers to any swollen or tender joint on examination. Large joints include the shoulders, elbows, hips, knees, and ankles. Small joints include the metacarpophalangeal joints, proximal interphalangeal joints, 2nd through 5th metatarsophalangeal joints, thumb interphalangeal joints, and wrists.[6]

§ Other joints can include any combination of large and additional small joints, as well as joints not specifically listed above (e.g., temporomandibular, sternoclavicular, etc.).[6]

‖ Low-positive refers to values that are higher than the upper limit of normal (ULN) but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay.[6]

* No validated definition for sustained remission in RA currently exists; however, a duration of at least one year has been used in some trials.[7]

Table 2 – Some DMARDs for rheumatoid arthritis[1,7,9,10]

Drug	Usual Adult Dose	Comments*
Traditional DMARDs†		
Methotrexate	5–25 mg/week PO, SC or IM, single dose	• The cornerstone of most RA treatment regimens based on a more beneficial efficacy/tolerability profile and lower discontinuation rates compared with other DMARDs • Consider parenteral administration in patients with an inadequate response or intolerance to oral dosing • The combination of methotrexate and leflunomide is associated with higher toxicity (GI and liver) and has no added benefit relative to other traditional DMARD combinations; use with caution (see comment under leflunomide) • Increases efficacy of biologic agents when used in combination regimens • Folic acid (1 mg daily) should be given concurrently • Caution in liver disease; may be continued in the presence of increased (up to 2- to 3-fold above normal) liver transaminases with frequent monitoring and dose reductions
Hydroxychloroquine	200–400 mg PO daily	• Rarely leads to adequate symptom control as monotherapy; often used in combination with methotrexate • Minimal need for blood test monitoring • Caution in G6PD deficiency
Leflunomide	20 mg PO daily‡	• Long half-life; may take 4–12 weeks for benefit • If used with methotrexate, liver enzymes should be monitored monthly; consider dose reduction of leflunomide (to 10 mg daily) or methotrexate (see comment under methotrexate)
Sulfasalazine	2–3 g/day PO, divided doses	• Has shown efficacy equivalent to methotrexate 10–15 mg/week over 1 year, but far less effective over 5 years, especially compared with methotrexate 20–25 mg/week • May be used in combination with methotrexate and hydroxychloroquine
Biologic DMARDs§		
Anti-TNF agents‖		
Adalimumab	40 mg SC q2wks	• Efficacy increased when used in combination with methotrexate • All anti-TNF agents increase the risk for opportunistic infections and nonopportunistic infections (e.g., upper respiratory tract infections, urinary tract infections)
Certolizumab pegol	200 mg SC q2wks *or* 400 mg SC q4wks¶	
Etanercept	50 mg SC q1wk *or* 25 mg SC twice/week	
Golimumab	50 mg SC monthly	
Infliximab	3–10 mg/kg IV q4–8wks	
T cell costimulation inhibitor		
Abatacept	8–10 mg/kg IV q4wks**	• Efficacy similar to anti-TNF agents; increased when used in combination with methotrexate • Increased risk of infection similar to anti-TNF agents
B lymphocyte-depleting agent		
Rituximab	1000 mg IV on days 1 & 15††	• Efficacy similar to anti-TNF agents; increased when used in combination with methotrexate • Used mainly in RF-positive patients according to CRA guidelines • Increased risk of infection similar to anti-TNF agents
Interleukin 6 antagonist		
Tocilizumab	4–8 mg/kg‡‡ IV q4wks	• Efficacy similar to anti-TNF agents; increased when used in combination with methotrexate • Increased risk of infection similar to anti-TNF agents
Interleukin 1 antagonist		
Anakinra	100 mg SC daily	• Used infrequently in RA due to the need for daily SC injections and potentially lower efficacy in some scenarios compared with other biologics

CRA = Canadian Rheumatology Association; **DMARDs** = disease-modifying antirheumatic drugs; **G6PD** = glucose-6-phosphate dehydrogenase; **GI** = gastrointestinal; **RA** = rheumatoid arthritis; **RF** = rheumatoid factor; **TNF** = tumour necrosis factor

* It is notable that the comments do not focus on safety aspects of the treatment options; however, guidelines from the Canadian Rheumatology Association[8] provide a more detailed discussion of this subject matter (see References, below, for URL).

† About 30% to 50% of patients have an inadequate response to traditional DMARDs.[1]

‡ Following a loading dose of 100 mg once daily for 3 days.[1]

§ Broadly, the biologics appear to have similar efficacy,[11-13] although individual responses vary widely.[1]

‖ Approximately 50% of patients do not achieve a substantial clinical response (i.e., ACR50 or ACR70) with anti-TNF agents; only a minority achieve disease remission.[4]

¶ Following an initial regimen of 400 mg SC at weeks 0, 2, and 4.[1]

** Following an initial regimen of 8–10 mg/kg IV (<60 kg = 500 mg; 60–100 kg = 750 mg; >100 kg = 1 g) at weeks 0, 2, and 4.[1,10]

†† Further courses may be necessary.[1] The Canadian Rheumatology Association guidelines state that retreatment can occur as early as 6 months if the patient had an initial response but has persistent synovitis.[7]

‡‡ Maximum dose = 800 mg.[1]

and that MTX is the first-line DMARD based on efficacy and safety.[7] Initial combination DMARD therapy (with MTX as the anchor drug[†]) should be considered, particularly for patients with:

- poor prognostic features;[‡]
- moderate to high disease activity; or
- recent-onset disease.[7]

Combination therapy should also be considered for patients who have an inadequate response to monotherapy (i.e., not reaching target by three to six months[§]), although switching to an alternative DMARD is an option in such a scenario.[7]

In addition to the situations outlined above, traditional DMARDs may also be used concurrently with, or after failure of, biologic agents (see below for details).

Box 1 – Biologic agents approved in Canada[7]

Tumour necrosis factor inhibitors
- Adalimumab
- Certolizumab pegol
- Etanercept
- Golimumab
- Infliximab

T cell costimulation inhibitor
- Abatacept

B lymphocyte-depleting agent
- Rituximab

Interleukin 6 antagonist
- Tocilizumab

Interleukin 1 antagonist
- Anakinra

Biologic DMARDs

Biologic agents currently approved in Canada for use in patients with RA are listed in Box 1. The CRA guidelines recommend that biologics[**] generally be reserved for patients with an inadequate response to traditional DMARDs,[††] but note that anti-TNF therapy may be an option after failure of DMARD monotherapy, or in DMARD-naïve patients, in exceptional situations (e.g., contraindications to traditional DMARDs, high disease activity plus poor prognostic factors).[7] Routine coprescription of MTX with the biologics is recommended to improve efficacy.[7]

In patients who have failed treatment with one anti-TNF therapy (either due to lack of efficacy or toxicity), options include:

- switching to another anti-TNF agent;
- switching to a biologic with a different mechanism of action; or
- adding MTX (or another traditional DMARD) if the initial anti-TNF agent was used as monotherapy.[7]

After failure of two anti-TNF agents, switching to abatacept, rituximab, or tocilizumab is recommended.[7] Robust data to guide therapeutic decisions after failure of abatacept, rituximab, and tocilizumab are unavailable.[7] Nonetheless, strategies for consideration include: (1) switching to any biologic not previously tried and failed; (2) adding or switching to a traditional DMARD not previously tried and failed; or (3) enrolling the patient in a clinical trial.[7]

Other Agents

According to the CRA guidelines, oral, intramuscular, or intra-articular glucocorticoids can be used as part of the initial DMARD treatment strategy, and are also an option for managing disease flares.[7] In addition, they can be used as bridge therapy while waiting for DMARDs to take effect, or for symptom control when no other options exist.[7] Glucocorticoids should be used in the lowest doses possible and tapered as soon as clinically feasible.[7]

NSAIDs are used primarily for controlling pain in patients with RA and are not considered a necessary part of treatment.[1]

MONITORING

In patients with active RA, disease activity should be assessed as frequently as every one to three months.[7] In those with well controlled disease, or those in remission, monitoring can take place at longer intervals.[7] Radiographs of the hands and feet are recommended at baseline, and as often as every six to 12 months in patients with recent-onset disease.[7] Radiographs can be done less frequently in those with established disease.[7]

Detailed safety monitoring recommendations are beyond the scope of this review, but are available in online guidelines[7,8,15] (see References, below, for URLs). In brief, all patients receiving DMARDs should have a baseline complete blood count, liver transaminase profile, and serum creatinine measurement.[7,15] Follow-up testing for these parameters is recommended at various intervals, depending on the specific drug(s) and duration of therapy.[15] Screening for hepatitis B and C, human immunodeficiency virus, and latent tuberculosis is also recommended for patients commencing certain DMARDs.[7,15]

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[†] CRA guidelines recommend non-MTX-based combinations be considered on a case-by-case basis.[7]

[‡] Defined by the CRA guidelines as: positivity for rheumatoid factor or anti-cyclic citrullinated peptide antibody, functional limitation, high number of swollen and tender joints, early erosions, extra-articular features, or high erythrocyte sedimentation rate or C-reactive protein levels.[7]

[§] Guidelines from the ACR recommend changes to therapy at 3-month intervals if moderate–high disease activity persists in patients with disease duration ≥6 months.[14]

[**] The CRA guidelines exclude anakinra from their recommendations; otherwise, they do not note preference for particular biologic agents in patients who respond inadequately to traditional DMARDs.

[††] Defined by the CRA guidelines as moderate to high disease activity despite treatment with at least two DMARDs (including MTX unless contraindicated), used individually or as combination therapy, for three months at target doses.[7]