Treatment of elderly rheumatoid arthritis

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This review summarizes the current approach to treating rheumatoid arthritis in the elderly and outlines the side effects encountered with the use of antirheumatic agents, including antitumor necrosis factor agents, in this population. With the aging of the western population, the prevalence and incidence of rheumatoid arthritis is increasing among elderly persons. The management of rheumatoid arthritis in the elderly requires special consideration with regards to comorbidities and the potential for an increased frequency of adverse events. There is a substantial need for optimizing various aspects of the diagnosis and therapy of arthritis in an effort to reduce the impact of inflammatory arthritis in the growing elderly population.

Rheumatoid arthritis (RA) is the most common inflammatory arthritis in older adults. It is now known to increase in incidence and prevalence up to 85 years of age. The prevalence of RA in persons of 60 years of age and older is reported to be approximately 2% [1]. There is potential heterogeneity among elderly persons with RA. For example, since there is presently no cure for RA, an older person with RA may have been diagnosed with the disease at a much younger age, and yet may still be suffering the effects of the disease into their later years. Alternatively, an older person may develop RA de novo later in life. In the literature, there is controversy about whether those with younger-onset RA (YORA) differ from those with elderly-onset RA (EORA) with regards to characteristics such as signs and symptoms or outcomes of disease. Importantly, if one compares older persons with YORA, with those with EORA, the most important confounder is probably disease duration. Those older persons with YORA commonly have an advanced stage of the disease, having had the condition for many years. They have often received therapy with multiple agents and may be refractory to treatment. Not uncommonly, they have undergone elective joint surgery. The physical examination of these patients may reveal varying degrees of polyarticular synovitis and deformities in both the upper and lower extremities. Systemic manifestations, such as rheumatoid lung, vasculitic ulcers, peripheral neuropathy and secondary amyloid, all reflect longstanding inflammatory disease and may complicate the care of this population of RA patients. Within the EORA population an acute onset of disease and prominent elevations in the erythrocyte sedimentation rate (ESR) have been reported as being more common than for YORA [2,3]. Clinically, EORA is said to be characterized by disabling morning stiffness and marked pain, predominantly affecting the upper extremities. The physical examination may be notable for pronounced synovitis of the shoulders and the wrists, as well as the metacarpophalangeal joints and proximal interphalangeal joints, with marked limitation of motion and severe soft-tissue swelling. The reviews on this arthritis type have stressed that involvement of large joints, in particular shoulder joints, is a striking feature of arthritis in the elderly [4,5].

The diagnosis of RA in the elderly may be particularly complicated since the accuracy of rheumatologic laboratory tests may differ in older versus younger patients. For example, increases in autoantibodies, including rheumatoid factor (RF), are not uncommon in older persons, and therefore have less specificity for the diagnosis of RA than among younger persons. While it is not strictly a criterion for diagnosis, the ESR also increases nonspecifically in older persons, particularly women. Since the ESR can be a marker of systemic inflammation, it may lead to an erroneous suspicion of an inflammatory process in a healthy older person. If such an older person had osteoarthritis, a high ESR and/or RF could lead to an erroneous diagnosis of RA. Indeed, there are a number of different clinical conditions with similar signs and symptoms to RA, such as polymyalgia rheumatica, calcium pyrophosphate deposition disease, gouty arthritis and osteoarthritis, which are more prevalent among the elderly. This can make the diagnosis of RA more difficult in an older population.

The management of RA in elderly patients is complicated not only by diagnostic uncertainty, but also by the increasing presence of comorbid conditions that can affect treatment and changes in
pharmacokinetics that occur with normal aging. All of these may lead to an increased frequency of adverse drug events [6,7]. While the primary objectives of therapy for RA – to control pain, to stop disease progression and to improve functional status – are similar regardless of age, the efficacy and toxicity of drugs commonly used in RA may differ among the young and aged population.

New agents for the treatment of RA are being investigated in clinical trials. In general, treatment is becoming more aggressive for RA and early intervention is becoming more common. Current strategies include early aggressive treatment with one or more disease-modifying antirheumatic drugs (DMARDs), along with symptomatic therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) and low-dose prednisone.

Nonsteroidal anti-inflammatory agents
In elderly patients, a major consideration with the use of NSAIDs is the increased risk of toxicities, including gastrointestinal (GI) bleeding, renal dysfunction and others. Established risk factors for upper GI bleeding in patients treated with NSAIDs include being aged over 65 years, a history of peptic ulcer disease or other GI bleeding, concomitant use of oral glucocorticoids or anti-coagulants and the presence of certain comorbid conditions, such as significant heart disease and emphysema. The risk of upper GI bleeding can be minimized by the use of cyclooxygenase (COX)-2 specific NSAIDs or with the concomitant use of proton-pump inhibitors. Risk factors for renal dysfunction include being aged over 65 years, a history of hypertension or congestive heart failure, and concomitant use of diuretics and angiotensin-converting enzyme inhibitors. Side effects including upper GI toxicity, renal insufficiency and CNS dysfunction are more serious in the elderly than in younger patients [8]. Routine monitoring for toxicity from NSAIDs remains controversial and the side effects can be unpredictable.

In 1998, COX-2 specific inhibitors were introduced to the clinic, with efficacy comparable to that of traditional NSAIDs [9]. Careful monitoring of blood pressure is warranted after initiation of these agents [10,11]. COX-2 inhibitors may be the preferred agents in situations where bleeding is a concern, for example in patients who are on anticoagulant therapy or during the perioperative period, as they do not interfere with platelet function. However, recent data suggest that certain COX-2 inhibitors increase the rate of thrombotic and cardiovascular events [12]. All NSAIDs should be initiated in older persons with the lowest recommended dose, especially in low-weight subjects, since higher plasma concentrations may be detected in elderly patients [13].

Steroids
Some patients may require low-dose oral steroids (often defined as ≤5–10 mg prednisone equivalent per day) when there is a period of flare of their RA or when initiating another drug therapy. The use of low-dose prednisone has been advocated as the second-line therapy in elderly patients with RA, based on the rapid mode of action of steroids and the predisposition of older patients to functionally deteriorate faster than younger populations [14,15]. In one study, a moderate-to-excellent improvement with prednisone therapy was reported in 80 of 91 patients with EORA [15]. However, this therapy can be hazardous, especially in elderly patients, since it poses an increased risk for osteoporosis, infection, glucose intolerance, GI erosive disease, and hypertension. There are data to suggest that with the long-term use of low-dose prednisone, the risk of osteoporosis may outweigh the clinical benefit [16]. Therefore, bone-protective agents and close monitoring of bone density are warranted with chronic usage of steroids.

Intra-articular steroid injections may provide significant relief as sole or adjunctive therapy in some conditions. They can be safely administered to patients if only one or a few joints are inflamed or have caused severe disability. The rationale is to relieve pain, control inflammation rapidly and sometimes avoid administering systemic steroids.

Disease-modifying antirheumatic drugs
DMARD therapy can change the course of RA, resulting in sustained improvement in physical function, decreased inflammatory synovitis and potentially slowing or preventing structural joint damage. Most DMARDs take several months to achieve significant response. Methotrexate (MTX) had been the most effective antirheumatic therapy until the biologics were introduced. Better response rates have been reported with higher doses of MTX, but when used alone it seldom leads to complete remission [17]. Hydroxychloroquine (HCQ) and sulfasalazine (SSZ) are generally preferred in slowly-progressing disease. In addition, since they carry a less toxic profile and need less frequent monitoring, they are the preferred agents...
in elderly patients with significant underlying medical problems. Leflunomide is a newer DMARD with a comparable efficacy to MTX. Leflunomide can be used in combination with MTX or in patients who cannot tolerate or have incomplete response to MTX [18]. Cyclosporine A and azathioprine are reserved for refractory patients who have failed other agents. Combination DMARD regimens, for example, MTX plus H C Q plus SSZ or MTX plus cyclosporine, have demonstrated significant clinical improvement when compared with single therapy or placebo [18,19]. Close follow-up and repeated evaluations are required for patients on DMARDs (Table 1). Some studies including patients older than 65 years of age have found no significant effect of age on termination of DMARD treatment [20,21]. However, it has been reported that DMARDs have a tendency to be less effective in older compared with younger patients [20,21]. It should be noted that in these studies prolonged disease duration might have been the key reason for early discontinuation of therapy rather than age, since it is well documented that patients fail to remain on any given DMARD long term.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side effects</th>
<th>Precautions &amp; monitoring</th>
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<tbody>
<tr>
<td>Methotrexate</td>
<td>GI irritation</td>
<td>Addition of oral folate supplement</td>
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<tr>
<td></td>
<td>Oral Ulcers</td>
<td>Monitor laboratory tests (LFT, CBC and routine chemistries)</td>
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<td></td>
<td>LFT elevation</td>
<td>Contraindicated in alcoholism, pregnancy (US FDA category X)</td>
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<tr>
<td></td>
<td>BM suppression</td>
<td>Caution in impaired renal function</td>
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<tr>
<td></td>
<td>Pneumonitis (uncommon)</td>
<td>Avoid using in Hepatitis B and C</td>
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<td></td>
<td>Nodulosis (uncommon)</td>
<td>Well-tolerated in the elderly</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>GI irritation</td>
<td>Retinal toxicity increases with &gt;70 years of age, 800 g of cumulative dose and &gt;6.7 mg/kg daily dose</td>
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<td></td>
<td>Rash</td>
<td>Ophthalmological test every 6-12 months</td>
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<td></td>
<td>Headache</td>
<td>Caution in hepatic disease, porphyria and psoriasis</td>
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<td></td>
<td>Skin discoloration</td>
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<tr>
<td></td>
<td>Retinal toxicity (uncommon)</td>
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<tr>
<td>Sulfasalazine</td>
<td>GI irritation</td>
<td>Caution in impaired renal function</td>
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<tr>
<td></td>
<td>Rash</td>
<td>Monitor CBC and LFT every 3-6 months</td>
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<tr>
<td></td>
<td>Itching</td>
<td>Enteric coated tablets are better tolerated</td>
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<td></td>
<td>Dizziness</td>
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<td></td>
<td>Headache</td>
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<td></td>
<td>BM suppression</td>
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<tr>
<td>Leflunomide</td>
<td>GI irritation</td>
<td>Monitor LFT, routine chemistry and CBC</td>
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<tr>
<td></td>
<td>Rash</td>
<td>Avoid using in hepatic impairment</td>
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<td></td>
<td>BM suppression</td>
<td>Contraindicated in pregnancy</td>
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<tr>
<td></td>
<td>LFT elevation</td>
<td>Cholestyramine can be used to reduce plasma levels</td>
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<tr>
<td>Cyclosporine A</td>
<td>Hypertension</td>
<td>Contraindicated in renal failure</td>
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<tr>
<td></td>
<td>Increased creatinine</td>
<td>Avoid in malignancy</td>
</tr>
<tr>
<td></td>
<td>Hirsutism</td>
<td>Monitor BP and creatinine closely</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>Monitor chemistries and uric acid</td>
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<tr>
<td></td>
<td>Tremor</td>
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<td>Gingival hypertrophy</td>
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<tr>
<td>Azathioprine</td>
<td>Fever, chills</td>
<td>Caution in hepatic and renal impairment</td>
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<tr>
<td></td>
<td>GI intolerance</td>
<td>Monitor CBC and differential</td>
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<tr>
<td></td>
<td>BM suppression</td>
<td>Consider checking TMT enzyme deficiency before initiating therapy</td>
</tr>
<tr>
<td></td>
<td>LFT elevation</td>
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BM: Bone marrow; BP: Blood pressure; CBC: Complete blood count; GI: Gastrointestinal; LFT: Liver function test; TMT: Thiopurine methyltransferase.
Biologics

**Antitumor necrosis factor agents**

With better understanding of the pathogenesis of autoimmune diseases and advancing developments in biopharmaceutical technology, biologic therapeutic agents have been introduced. These agents target specific components of the immune response, which is considered central to the etiology of RA. Currently there are three antitumor necrosis factor (TNF)-α agents available for clinical use: infliximab, a chimeric anti-TNF-α monoclonal antibody (mAb); etanercept, a soluble TNF-receptor construct and adalimumab, a human anti-TNF-α mAb (Table 2). Different studies including patients with chronic refractory RA, patients with active disease with or without concurrent MTX therapy and patients with early RA demonstrated rapid and sustained improvement with all three agents [9,22,23]. Joint damage, as measured by x-ray progression, appeared to be slowed by these drugs [24–26]. In general, therapy with TNF inhibitors has been well tolerated. These agents represent a major advance in the treatment of severe inflammatory arthritis. However, the greater frequency of concomitant medical conditions (e.g., latent tuberculosis, malignancy, chronic or active infections or a history of congestive heart failure) that may be found in older as compared with younger persons may somewhat limit their usage in this population [27]. Of note, although early clinical trials with anti-TNF agents resulted in an increased incidence of reactivation of latent tuberculosis, patients with latent tuberculosis are allowed to be started on anti-TNF agents if antipulmonary tuberculosis treatment is concomitantly administered. A history of malignancy is not a contraindication for anti-TNF agents, but since there is evidence that there is a dose-dependent increased risk of malignancies in patients treated with anti-TNF agents, clinicians are recommended to be very cautious in initiating these agents.

Although elderly patients were included in most of the clinical trials with anti-TNF agents, evaluations were based on the total enrolled population in the trials. Recently, retrospective subgroup analyses of the response and toxicity rates of the elderly RA patients were determined for some of the clinical trials. Etanercept was found to be safe and effective in elderly patients with RA. In one analysis, 197 of 1128 patients enrolled in four double-blind, randomized trials and five open-label trials with etanercept were 65 years of age and older. It was reported that 55% of patients showed improvement in ACR 20 criteria, a result comparable to that among young patients. In addition, treatment was generally as well tolerated in older persons. In fact, this age group demonstrated a lower rate of injection-site reactions, headache and rash compared with younger patients. Death and cancer diagnoses in patients over 65 years treated with etanercept were similar to the estimated prevalences for these events for this age group within the general population [27]. In another subset analysis of one double-blind trial and two open-label extension trials, the safety and efficacy of etanercept in elderly (age >65 years) and younger adults (age <65 years) treated for early or late-stage RA were compared. Rates of serious adverse events tended to be higher in elderly than in younger subjects; however, rates of safety events observed in elderly etanercept-treated subjects did not exceed rates in elderly placebo or MTX-treated subjects. Elderly subjects tended to have somewhat less robust responses to treatment than younger subjects. However, for both age groups, treatment with etanercept resulted in improved efficacy and function compared with control treatment; and combination treatment with etanercept plus MTX resulted in greater efficacy than either etanercept or MTX used alone. The progression of joint damage as assessed by analysis of serial radiographs of hands and feet was lower after 1 year in subjects treated with etanercept plus

<table>
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<th>Table 2. Comparison of anti-TNF agents.</th>
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<tr>
<td><strong>Etanercept</strong></td>
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<tr>
<td>Half-life</td>
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<tr>
<td>Binding target</td>
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<tr>
<td>Administration</td>
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<td>Side effects</td>
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iv.: Intravenous; LT: Lymphotoxin; sc.: Subcutaneous; SLE: Systemic lupus erythematous; TNF: Tumor necrosis factor.
MTX compared with subjects treated with either agent alone [28]. Patient-reported outcomes from multiple controlled and open-label extension studies with etanercept were analyzed in elderly and younger adult patients. Improvements in health assessment questionnaire-disability index (HAQ-DI) and proportions of patients achieving an improvement and worsening in HAQ-DI were assessed in elderly versus young patients using data from multiple controlled and open-label extension studies. Elderly patients had significantly worse baseline mean HAQ-DI scores than younger patients, indicating greater disability. Patients with early and late-onset RA, regardless of age group, exhibited similar and rapid improvements in functional status and maintained their improvement in HAQ-DI throughout the open-label extension trials for up to a total of 6 years of etanercept therapy [29].

The effects of various immunosuppressive medications on the risk of cardiovascular events among a group of older patients with RA were investigated in Medicare beneficiaries (n = 3501). When compared with RA patients receiving only DMARD therapy, those receiving biologic immunosuppressive agents had neither an increased nor decreased risk of experiencing a cardiovascular event, whereas use of oral glucocorticoids and cytotoxic immunosuppressive agents other than MTX (azathioprine, cyclosporine and leflunomide) was associated with significant increases in the risk of cardiovascular events [30].

Other biologic agents
Anakinra
Anakinra is an interleukin-1 receptor antagonist. It is most commonly used in patients who are refractory to other treatments and are not good responders to TNF blockers. The overall magnitude of reductions in clinical symptoms and signs (20–30%) were relatively modest when compared with those reported in TNF-α-blocking agents (60–70%). Anakinra is not recommended to be used concomitantly with TNF blockers owing to an increased frequency of toxicity with such combinations. Injection-site reactions are the most frequently reported adverse event with anakinra [31].

Abatacept
Abatacept (CTLA4-Ig) is a fusion protein designed to modulate the T-cell costimulatory signal mediated through the CD28–CD80/86 pathway. It inhibits full activation of T cells. Clinical trials have provided evidence for the efficacy of abatacept in patients with active RA, despite prior treatment with MTX or anti-TNF therapies [32,33].

Rituximab
Rituximab is a chimeric monoclonal antibody to anti-CD20 that has been approved for the treatment of B-cell lymphoma since 1997. Rituximab causes selective and rapid depletion of the CD 20+ B-cell population. The first evidence of efficacy of rituximab in RA came from an open-label trial in a small number of patients who were treated with rituximab in conjunction with cyclophosphamide and high-dose steroids [34,35]. Consequent double-blind, placebo-controlled trials demonstrated that addition of rituximab to MTX appears to significantly reduce the signs and symptoms of RA and is relatively safe [36]. Rituximab has recently been approved for use in patients with RA who fail to respond to anti-TNF agents.

Despite the fact that patients under the age of 75 years were generally accepted in most of the clinical trials of these three biologic agents, initial evaluations did not include separate analyses of the effects of biologic agents on the elderly population. In clinical practice, there has been a trend to treat earlier and more aggressively with DMARDs, combinations of DMARDs and biologic agents. As part of the overall increase in aggressiveness in therapy, along with growing safety experience with biologics and combination therapy, this should result in such approaches being utilized more commonly among the elderly population. In order to assess whether rheumatologists' treatment decisions were influenced by patients' age, 204 rheumatologists were questioned by a mail survey on two hypothetical scenarios that were identical except for the age of the patient. Rheumatologists were more likely to prefer aggressive DMARD treatment for the younger versus the older RA patient [37]. Treatment preferences of patients with RA for DMARDs were evaluated in a different study. Older patients with RA (mean 70 years of age) were initially given information about side effects, effectiveness and cost of MTX, gold, leflunomide and etanercept, and later they were asked to make preferences between these agents. Patients preferred etanercept over other treatment options [38]. In a study where EORA patients were matched with YORA patients based on their disease duration and...
compared in order to assess the types of treatment measures used in the two groups, it was shown that EORA patients received biologic therapy and combination DMARD therapy less frequently than YORA patients, despite identical disease duration, and comparable disease severity and activity [39]. This suggests that there may be an underutilization of aggressive therapeutic regimens in the geriatric population. Although additional investigations are always welcome to help establish the potential hazards and benefits of the newer treatments in the elderly population, current experience suggests that efficacy and toxicity of rheumatologic drugs in the elderly population are comparable to younger adults.

**Executive summary**

**Rheumatoid arthritis in the elderly: therapeutic interventions**

- **Adjunctive**
  - Nonsteroidal anti-inflammatory drugs/cyclo-oxygenase-2 analgesics
  - Glucocorticosteroids
- **Disease-modifying antirheumatic drugs**
  - Methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, azathioprine, cyclosporine, etc
- **Biologics**
  - Tumor necrosis factor inhibitors: etanercept, infliximab and adalimumab
  - Interleukin-1 inhibitor: anakinra
  - Anti-CD20 antibody: rituximab
- **Tumor necrosis factor inhibitors**

**Bibliography**


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