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Treatment of Rheumatoid Arthritis in the Elderly

Geoffrey J McColl

ABSTRACT

Rheumatoid arthritis is the commonest form of inflammatory arthritis and may have its onset in the elderly or continue into older age with an earlier onset. Patients with elderly-onset rheumatoid arthritis are more likely to have systemic features (weight loss, fever, fatigue) and large joint involvement and these features may result in diagnostic uncertainty. The principles of treatment for rheumatoid arthritis in the elderly or elderly-onset rheumatoid arthritis are to maintain quality of life by eradicating joint inflammation (thus reducing joint damage) while minimising treatment-related adverse effects. Therapies include disease-modifying anti-rheumatic drugs, non-steroidal anti-inflammatory drugs and corticosteroids, and non-pharmacological strategies such as education, diet and exercise. In the elderly, therapy needs to be adjusted to account for the physiology of ageing and the presence of comorbidity.

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INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory condition mainly of synovial joints with a prevalence of approximately 1%. The peak age of onset is the third and fourth decade and women are more commonly affected than men. RA is associated with profound joint damage and a poor functional outcome. Significant changes in therapeutics have occurred over the past 10 years with the widespread use of methotrexate, combination therapies and biological agents. These advances have substantially altered the goals of therapy from those of palliation and pain relief to remission induction and joint damage prevention. A greater focus on RA-associated comorbidities of osteoporosis and atherosclerosis will further improve clinical outcomes. RA occurs in the elderly in two forms:

- elderly-onset RA (EORA)—the arthritis has its onset after 60 years of age; and
- RA in the elderly—the onset of arthritis occurred earlier in life but has continued after 60 years of age.

This review will focus on EORA but the principles of therapy are identical for RA in the elderly.

ELDERLY-ONSET RHEUMATOID ARTHRITIS

The clinical presentation of EORA is different to that of younger-onset RA.¹ Firstly, the sex distribution is more equal and approaches a ratio of 1:1. Secondly, the presentation of EORA is more often acute with prominent systemic features (fatigue, weight loss, significantly raised erythrocyte sedimentation rate) and thus may be confused with infection or malignancy. Thirdly, the pattern of joint involvement may be different with large

joints, particularly shoulders, more commonly affected in EORA. Finally, rheumatoid factor is less frequently detected in EORA and clinical outcomes are worse than younger-onset RA.

The differential diagnosis of inflammatory arthritis in the elderly is also somewhat different with a higher likelihood of conditions such as polymyalgia rheumatica, remitting seronegative symmetrical synovitis with pitting oedema and crystal-induced arthropathies (gout, pseudogout). Once a diagnosis of EORA has been made the therapeutic goals are the same as in younger-onset RA, but specific treatments may have to be modified in the context of the patient's age and comorbidities.

To plan appropriate therapy for EORA the likely prognosis of the arthritis needs to be established. The prognostic algorithm in RA is imperfect and it is important to consider treatment outcomes longitudinally as well as at the onset of disease. Patients in which rheumatoid factor is detected have a worse prognosis and a much lower likelihood of spontaneous remission. Alternatively, those patients in whom rheumatoid factor is not detected and who have other features such as pitting oedema have much better outcomes. Other factors that portend a poor prognosis include severity of joint involvement, degree of disability and response to treatment.

The overall aim of therapy is to maintain quality of life in the long term by:

- controlling joint inflammation, principally with disease-modifying anti-rheumatic drugs (DMARDs) and thus preventing joint damage;
- preventing or treating RA-associated comorbidities;
- minimising therapy-associated adverse events by the quality use of medicines; and
- educating patients and involving them in disease management.

RA therapy in the elderly is guided by the principles outlined above and includes non-pharmacological and pharmacological options.

Non-Pharmacological Therapies

Exercise

Joint pathology can reduce physical activity due to pain or joint dysfunction. A recent review has identified that an increase in aerobic exercise (moderate to high intensity, 3 times/week for 30 to 60 minutes) and strengthening exercise (moderate to hard resistance training 2 to 3 times/week) will result in better outcomes for patients with RA.² This review also demonstrated that disease activity was not substantially altered by exercise.² A recommendation for regular aerobic and strengthening exercise in all patients is therefore appropriate but in the elderly some modification of the exercise regimen may need to be made to allow for comorbidity. Exercise may also reduce the risk of osteoporosis and atherosclerosis, but this has not been formally demonstrated.

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Diet

The role of diet remains controversial but recent evidence suggests that some dietary modifications may modestly reduce disease activity. Of interest is a small study demonstrating that the Mediterranean diet (high consumption of fruit, vegetables, cereals, legumes, little red meat, more fish, olive oil, and moderate intake of wine) reduced disease activity in patients with RA.³ The Mediterranean diet has also been demonstrated to reduce cardiovascular risk in those not affected by RA and therefore would be a useful adjunct in RA patients.⁴ The control of weight in RA reduces risk of cardiovascular disease and osteoarthritis.

Education

There is evidence to suggest that patients with RA who have high levels of helplessness in relation to their disease have worse outcomes when compared to those with less helplessness.⁵ This information was the basis for the development of a variety of educational programs designed to decrease helplessness by increasing self-efficacy. The best evaluated of these programs is the arthritis self-management course developed by Lorig et al.⁶ This six-week course improved pain and fatigue scores in patients with various forms of arthritis while decreasing health distress and increasing self-efficacy. This course is currently delivered by Arthritis Foundations in every state and territory.

Pharmacological Therapies

The aim of pharmacological therapy is to eradicate joint and other inflammation and thus prevent tissue damage and maximise quality of life. In the elderly, this principle remains true but the application of pharmacological therapies has to be modified to take account of age and comorbidities. There is some variation of practice for early RA in Australia, particularly in regard to the use of DMARDs. A growing view, which is supported by recent literature,⁷ is that RA should be treated aggressively from its onset with multiple DMARDs in combination. An alternative view is that rapid dose escalation with methotrexate followed by other DMARDs in combination will have a similar outcome. The principle underlying both approaches is that the activity of the disease should be objectively recorded and acted upon with dose and drug escalation if remission is not attained. The parameters used to assess RA disease activity would include (but not be limited to) the swollen joint count, tender joint count, patient's global assessment of their disease activity and a measure of inflammation such as erythrocyte sedimentation rate or C-reactive protein. Applying this aggressive approach in the elderly remains appropriate but should be modified in light of age and comorbidities.

Non-Steroidal Anti-Inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective for inflammatory joint disease including EORA but they are symptom modifying not disease modifying.¹ The safety profile of NSAIDs progressively worsens with age, therefore, prior to starting an NSAID for EORA, a gastrointestinal and renal risk analysis needs to be performed (Table 1).⁸⁻¹¹ If risk factors are present then alternative therapies need to be considered or careful monitoring undertaken to minimise risk. The cyclo-oxygenase-2 inhibitors (celecoxib, meloxicam) may have marginal advantages with regard to gastrointestinal risk but renal and other risk is not reduced.¹²⁻¹⁴ Alternative

Table 1. Risk factors for gastrointestinal^{8,10,11} and renal⁹ complications with non-steroidal anti-inflammatory drug use

Gastrointestinal	Renal
Age > 65 years	Raised serum creatinine
Comorbid medical problems	Age > 65 years
Use of oral glucocorticoids	Hypertension
Use of anticoagulants	Congestive heart failure
Past history of peptic ulcer disease	Use of angiotensin-converting enzyme inhibitors
Past history of upper gastrointestinal bleeding	Use of diuretics

treatment strategies for patients with risk factors could include regular paracetamol or low-dose glucocorticoids.

Glucocorticoids

Glucocorticoids (prednisolone, prednisone) are often used for the management of inflammatory joint disease in the elderly—in particular polymyalgia rheumatica and remitting seronegative symmetrical synovitis with pitting oedema, where low-dose glucocorticoids may be the treatment of choice.¹ In EORA, however, glucocorticoids should be started only if other strategies have failed or if the risks of other drugs are too great. Glucocorticoids have significant side effects and therefore should be used at the lowest dose for the shortest period possible.

Of special relevance in the elderly is the risk of glucocorticoid-induced osteoporosis.¹⁵ Bone density reduces with age and the loss of bone accelerates after menopause increasing the risk of fracture.¹⁶ The elderly may also have reduced dietary calcium intake and low levels of vitamin D (particularly those in institutional care) further increasing the risk of osteoporosis.¹⁷ Prior to commencing glucocorticoids, it would be reasonable to look for other risk factors for osteoporosis on history and examination, and perform a measure of bone density and 25-hydroxy vitamin D level. To minimise the effects of glucocorticoids the lowest possible dose for the shortest period is recommended and any strategy to achieve this is to be encouraged, particularly the use of DMARDs. If glucocorticoids are prescribed a calcium and vitamin D supplement is recommended.¹⁵ The use of prophylactic bisphosphonates (alendronate, risedronate) should be considered in patients requiring high doses of glucocorticoid for a prolonged period or with low measured bone density prior to commencing therapy.¹⁵

Glucocorticoids have many other adverse effects and the risks and benefits of using them must be weighed against their potential toxicity. Some issues to be considered would include thinning of the skin and poor wound healing, worsening or induction of hypertension or diabetes, cataracts, myopathy (leading to falls, weight gain) and confusion or mania.

Disease-Modifying Anti-Rheumatic Drugs

The choice of DMARDs will be informed by the severity of arthritis and the characteristics of the patient. Regularly monitoring outcomes and increasing therapy if they are not attained is central to a modern approach to RA or EORA. Important aspects of the pharmacokinetics of DMARDs in the elderly have been recently reviewed.¹⁸

Hydroxychloroquine

Hydroxychloroquine is an effective and safe DMARD and is used in mild disease or in combination with other therapies.^{19,20} Its most common complication is rash

(approximately 1:200) and generally requires cessation. Hydroxychloroquine retinopathy is a rare complication but yearly retinal monitoring is recommended.²¹ No specific studies have addressed the safety and efficacy of its use in EORA but it plays a role, particularly in combination therapy.

Sulfasalazine

Sulfasalazine is effective in the management of RA, alone in mild disease and in combination with methotrexate and hydroxychloroquine in severe disease.^{20,22} Sulfasalazine may cause nausea, particularly on initiation, and therefore the dose is often escalated from 500 mg to 2 g daily over a few weeks. Other potential complications include rash, neutropenia and abnormal liver function tests. It is recommended that a patient taking sulfasalazine have a full blood examination and liver function tests monthly for three months and then three monthly thereafter. No formal trials have evaluated its safety and efficacy in EORA but it is an effective choice particularly in combination with methotrexate and hydroxychloroquine.

Methotrexate

Methotrexate is highly effective for RA, alone and in combination with DMARDs.^{20,23-25} It is usually given as a single weekly dose (5–25 mg) with folic acid (approximately 10 mg weekly), which reduces the risk of nausea and mouth ulcers. Occasionally methotrexate is administered as an intramuscular or subcutaneous injection if oral administration is ineffective or not tolerated. Nausea and mouth ulcers are the commonest adverse events. Low white cell and platelet count and elevated liver function tests are also occasionally seen. Monitoring would include fortnightly full blood examination and liver function tests for 6 weeks then 6 to 8 weekly thereafter. Although safe and effective in EORA, methotrexate must be used carefully in the elderly.²⁶ Methotrexate is predominantly excreted via the kidney and therefore any reduction in renal function potentially results in its accumulation. This may result in neutropenia if not detected. To minimise this risk, it is contraindicated in patients with a serum creatinine above 0.2 mmol/L and dose reduction should be considered if the creatinine is raised above the normal range or in those over 80 years of age. It is also reasonable to conduct full blood examinations more frequently in the elderly. If methotrexate-induced neutropenia occurs it is treated with folic acid.

Leflunomide

Leflunomide inhibits lymphocytes and is effective for RA, alone and in combination with methotrexate.^{27,28} Leflunomide has a long half-life, therefore three daily loading doses of 100 mg are recommended to precede the standard daily dose of 20 mg to reduce the time to clinical response. This regimen is often complicated by gastrointestinal complications (particularly diarrhoea) and therefore often omitted. Rash, increased hair loss and abnormal liver function tests may also result from leflunomide therapy. A full blood examination and liver function tests every month for three months and then three-monthly is recommended for routine monitoring. No studies have examined efficacy and toxicity of leflunomide in EORA but it is probably a fairly safe option.

Other Disease-Modifying Anti-Rheumatic Drugs

A variety of other DMARDs have been used previously including cyclosporin, intramuscular or oral gold,

penicillamine, azathioprine and cyclophosphamide. All of these have relatively high rates of toxicity and would not be recommended routinely in patients with EORA unless other DMARDs had failed.

Biological Disease-Modifying Anti-Rheumatic Drugs

With improved understanding of the inflammatory process in RA, particularly the role of pro-inflammatory cytokines, new biological treatment strategies have been developed. Collectively termed the biological DMARDs they are a growing group of therapies targeting specific pro-inflammatory molecules including tumour necrosis factor (TNF) and interleukin-1 (Table 2).

Table 2. Biological disease-modifying anti-rheumatic drugs

Name	Target	Structure	Dosing
Infliximab (Remicade)	TNF	Monoclonal antibody	3 mg/kg IV every 8 weeks
Adalimumab (Humira)	TNF	Monoclonal antibody	40 mg SC every 2 weeks
Etanercept (Enbrel)	TNF and lymphotoxin	Soluble TNF receptor	25 mg SC twice weekly
Anakinra (Kineret)	IL-1	IL-1 receptor antagonist	100 mg SC daily

TNF = tumour necrosis factor; IL-1 = Interleukin-1

Infliximab is given as an infusion every 8 weeks after an induction regimen with more frequent infusions. It is recommended that infliximab be used in conjunction with methotrexate to reduce the frequency of infusion reactions and tachyphylaxis. Infliximab is effective in RA at the recommended dose of 3 mg/kg every 8 weeks.²⁹ Infusion reactions are the most frequent adverse event. For mild reactions the infusion rate can be reduced and an antihistamine administered. For more serious reactions the infusion should be stopped, hydrocortisone and antihistamines administered and consideration made about the safety of subsequent infusions. The risk of infections is increased in patients receiving TNF inhibitors, including infliximab.³⁰ Of special concern is the possibility of reactivating tuberculosis.³¹ As a result, tuberculosis screening in the form of a Mantoux test and chest X-ray is recommended prior to starting TNF inhibitors. Other rare complications of infliximab include the induction of a demyelinating illness and lymphoma.³⁰ Adalimumab is given as a subcutaneous injection every two weeks. It has been evaluated in randomised studies and is an effective therapy in RA, alone and in combination with methotrexate.^{32,33} Its safety profile is similar to infliximab except for the occurrence of injection site reactions.

Etanercept is given subcutaneously twice weekly and is effective for RA, alone and in combination with methotrexate.^{34,35} Its safety profile is similar to the other TNF inhibitors. A recent study evaluated the effectiveness of etanercept in 197 RA patients over 65 years of age and found efficacy and safety was comparable with the group under 65 years of age.³⁶ Despite this result it would seem prudent to monitor EORA patients receiving TNF inhibitors carefully, particularly with regard to infectious risk.

Anakinra inhibits interleukin-1, is given subcutaneously daily, is modestly effective and has a relatively good safety profile (Table 2).^{37,38} No studies have evaluated its effectiveness in EORA.

In Australia, the biological DMARDs are prescribed in RA after routine DMARD therapy and combination therapy has failed or not been tolerated.

Combination Therapy

Combination therapy with DMARDs has an increasing role in RA with an increasing range of clinical trials demonstrating greater efficacy without increased toxicity when certain DMARDs are combined. The combination of methotrexate, hydroxychloroquine and sulfasalazine (triple therapy) is particularly effective and is recommended for severe or resistant disease.^{24,39} Methotrexate combined with leflunomide or any of the TNF inhibitors is also highly effective.^{29,34,40,41} Although effective in RA, combination therapy in EORA must be weighed against the patient's risk profile and the severity of the disease, as toxicity may be more frequent in this group.

CONCLUSION

The management of patients with EORA represents a significant challenge with an increased necessity to acknowledge the physiological changes of age and comorbidities. The underlying principles of management, however, remain the same as the management of younger-onset RA. The application of biological DMARDs and DMARD combinations will further complicate these considerations but an emphasis on maintaining the quality of life by the control of inflammation remains crucial.

Competing interests: None declared.

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