

Elderly onset RA: a diagnostic and therapeutic challenge

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Dr Chathurika Dandeniya
MBBS MD MRCP (UK) MRCP (Lond)
Higher Clinical Fellow in Rheumatology,
Department of Rheumatology,
Addenbrooke's Hospital, Cambridge, UK,
Lecturer in Medicine,
Faculty of Medicine,
University of Peradeniya,
Sri Lanka

Dr Andra Negoescu
MD
Consultant Rheumatologist,
Department of Rheumatology,
Addenbrooke's Hospital,
Cambridge, UK



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AUTHORS

Dr Chathurika Dandeniya

MBBS MD MRCP (UK)
MRCP (Lond)
Higher Clinical Fellow in Rheumatology,
Department of Rheumatology,
Addenbrooke's Hospital,
Cambridge, UK,
Lecturer in Medicine,
Faculty of Medicine,
University of Peradeniya, Sri Lanka

Dr Andra Negoescu

MD
Consultant Rheumatologist,
Department of Rheumatology,
Addenbrooke's Hospital,
Cambridge, UK

FIGURE 1

X-rays of the hands of an 84-year-old woman with late onset seropositive rheumatoid arthritis (diagnosed at the age of 83). There is severe joint space narrowing of the right metacarpal joints, and a marginal erosion of the right index finger metacarpal head



What are the key features of RA in older patients?

How should diagnosis be confirmed?

What are the treatment options?



RHEUMATOID ARTHRITIS (RA) IS CLASSICALLY KNOWN AS A DISEASE OF THE YOUNG AND MIDDLE

aged with a peak age at onset of 30 to 50 years and a female: male ratio of 3:1.¹ However, the case history, see box 1, right, does not fit the classic picture. The patient belongs to a distinctly different subset of patients with certain characteristics that set it apart from the usual cohort of patients with RA. This entity is known as elderly onset rheumatoid arthritis (EORA).

RHEUMATOID ARTHRITIS IN THE ELDERLY

EORA is defined as RA with age of first onset ≥ 65 years.³ Drawing from the case history (right) the clinical picture is that of an acute onset proximal or large joint arthritis with a prominent systemic

syndrome represented by constitutional symptoms and a higher ESR than in the younger patient, see table 1, p12.

The differences between the commonly seen young onset rheumatoid arthritis (YORA) and EORA »

Box 1

Case history

A 70-year-old man was admitted with a one week history of low-grade fever. He had lost his appetite and reported feeling unwell over the two weeks preceding hospital admission. He had also developed bilateral knee joint pain and swelling which worsened rapidly over two days. There was no other joint involvement and no symptoms or signs of enthesitis. He had no personal or family history of psoriasis and no family history of inflammatory arthritis. An exhaustive screen failed to reveal any focus of infection and the aspirate of the right knee joint was negative for crystals or microorganisms. X-rays of the knees were unremarkable. Later he was found to have a rheumatoid factor level of 125 and an anti-CCP antibody level > 340 .

He was diagnosed with rheumatoid arthritis and started on a short course of prednisolone and methotrexate. He responded well to this treatment and one year later was still in remission.

SYMPOSIUM CARE OF THE ELDERLY

ELDERLY ONSET RHEUMATOID ARTHRITIS

are not yet completely understood. The genetic basis of EORA with regard to the association with HLA genes is less well established and it is speculated that the cytokine profiles of the two groups may be significantly different.^{3,4} The currently available evidence indicates that EORA is a distinct subgroup of RA rather than a different disease.

DIFFERENTIAL DIAGNOSIS

Diagnosis remains a challenge in EORA. One reason is the higher prevalence of seronegative disease. There are also a range of commonly occurring conditions in this age group that have a similar presentation. These include crystal arthritis (both gout and pseudogout - polyarticular forms), inflammatory osteoarthritis, polymyalgia rheumatica and less commonly, paraneoplastic arthritis, see table 2, below, right.

These conditions are more common and may present with constitutional symptoms, large joint mono- or oligo-arthritis and predominant involvement of the proximal large joints.

Practical tip 1: Poor response to corticosteroids in a patient with typical inflammatory joint symptoms/signs raises the index of suspicion for paraneoplastic arthritis, particularly if the inflammatory arthritis is accompanied by a systemic inflammatory response.

DIAGNOSTIC WORK UP

Investigations in primary care should focus on trying to establish the cause of the symptoms and ruling out differential diagnoses. They should include inflammatory markers, serum uric acid, full blood count, rheumatoid factor/anti-CCP antibodies, and X-rays of the affected joint as well as hands (see figure 1, p11) and feet.

The possibility of malignancy should always be borne in mind and screening investigations guided by the history and examination.

Practical tip 2: Consider testing for rheumatoid factor and anti-CCP antibodies in older patients presenting with shoulder or hip girdle pain and inflammatory stiffness.

Practical tip 3: Consider PSA screening in older men with new onset inflammatory arthritis. Prostate cancer can sometimes cause an atypical inflammatory arthritis.

REFERRAL

Referral to a rheumatologist should be considered if no alternative explanation can be found for the symptoms. This recommendation is based on the existing outcome data for patients with EORA. Although it was earlier thought that EORA had a better prognosis with a milder clinical course compared with

YORA, evidence now suggests that this is not the case.^{5,6}

The outcomes and disability from untreated disease are similar in EORA and YORA. Therefore, early treatment is imperative. Urgent referral of all suspected cases of RA has been endorsed by NICE guidance on the management of RA in adults.^{7,8}

MANAGEMENT

Management is challenging for a variety of reasons, see table 3, below. In general, the pharmacokinetics of drugs differ in the elderly partly as a result of declining renal function and changes in body composition with aging.⁹

In addition, older patients may have multiple comorbidities and may be taking a wide range of medications. All this translates to a higher risk of adverse reactions, drug interactions and complications caused by polypharmacy.

Further research into the management of this group of patients is ongoing and no specific treatment recommendations are currently available. In theory, if the disease

Table 1

Comparison of clinical features of elderly onset rheumatoid arthritis (EORA) and young onset rheumatoid arthritis (YORA)

Feature	YORA	EORA
Age at onset	< 65 years with the peak at 30-50 years	≥ 65 years
Female: male ratio	3:1	2:1 or 1:1
Onset	Insidious/subacute	Acute
Number of joints involved	More likely to be polyarticular	More likely than YORA to be mono- or oligo-articular
Pattern of joint involvement	Onset more commonly in small joints especially of the hands	Large joint onset is more common than in YORA, for example with shoulder and hip joint involvement at onset
Symmetry	Largely symmetrical	Largely asymmetrical
Constitutional symptoms including fever	Less likely	More likely
Serology	Majority seropositive (> 80%)	Less likely to be seropositive

Table 2

Differential diagnosis of elderly onset rheumatoid arthritis^{1,3,5}

- Crystal arthritis: gout and pseudogout
- Polymyalgia rheumatica
- Peripheral spondyloarthritis including psoriatic arthritis and reactive arthritis
- Osteoarthritis
- Infections: viral arthritis, septic arthritis
- Sarcoidosis
- Paraneoplastic manifestations (including hypertrophic pulmonary osteoarthropathy)

Table 3

Challenges in the management of elderly onset rheumatoid arthritis

- Comorbidities frequently found in the affected population: heart disease, malignancy, chronic obstructive pulmonary disease, chronic kidney disease, diabetes mellitus, osteoporosis
- Polypharmacy leading to:
 - Poor treatment adherence
 - Higher risk of drug interactions and toxicity
- Frailty
- Alteration of pharmacokinetics of medications with aging

key points

SELECTED BY

Dr Peter Saul

GP Wrexham and Associate GP Dean for North Wales, UK

Elderly onset rheumatoid arthritis (EORA) is defined as rheumatoid arthritis (RA) with age of first onset ≥ 65 years. It comprises an acute onset proximal or large joint arthritis with a prominent systemic syndrome represented by constitutional symptoms and a higher ESR than in the younger patient with RA. Currently available evidence indicates that EORA is a distinct subgroup of RA which may have a significantly different cytokine profile.

Diagnosis is difficult because of the higher prevalence of seronegative disease and a range of other conditions have a similar presentation. These include crystal arthritis, inflammatory osteoarthritis, polymyalgia rheumatica and less commonly, paraneoplastic arthritis. Investigations should focus on trying to establish the cause and ruling out differential diagnoses. They should include inflammatory markers, serum uric acid, full blood count, rheumatoid factor/anti-CCP antibodies, and X-rays of the affected joint as well as the hands and feet. The possibility of malignancy should always be borne in mind. PSA screening should be considered in older men with new onset inflammatory arthritis.

Referral to a rheumatologist should be considered if no alternative explanation can be found for the symptoms. Outcomes and disability from untreated disease are similar in EORA and young onset RA so early treatment is imperative. NICE recommends urgent referral of all suspected cases. In EORA the treatment guidelines for RA should be followed but with more careful tailoring to the individual patient taking account of any comorbidities.

The backbone of treatment remains methotrexate which is a conventional synthetic disease modifying drug (DMARD). Other options in this category include leflunomide, sulphasalazine and hydroxychloroquine. Since the onset of action of these medications can take up to 12 weeks, glucocorticoids can be used as bridging therapy. In cases of failure to achieve remission or low disease activity with conventional DMARDs, addition of biologic DMARDs is recommended, although generally not as monotherapy.

All adults with RA should be followed up regularly in secondary care with frequent monitoring in the initial stages which can be extended to 12 monthly once the disease and treatment regimen have become stable. Regular blood monitoring is necessary for patients on DMARD therapy (excluding hydroxychloroquine). An annual review is recommended for all patients to assess disease activity, functional ability, development of comorbidities (hypertension, ischaemic heart disease, osteoporosis, depression) or complications (vasculitis, disease of the cervical spine, lung or eyes) and the impact the disease is having on the patient's life.

outcome of EORA is similar to YORA, the treatment protocols should not be any different and this concept is supported by evidence.^{5,10} However, in a practical setting this will be challenging and older patients may be offered less aggressive treatment. It has been shown that as a consequence, patients with EORA run the risk of being undertreated resulting in poor disease control, see figure 2, p14.⁶

The current recommendation would be to follow the treatment guidelines for RA but with more careful tailoring to the individual patient taking account of any comorbidities. Tailoring treatment should not mean withholding treatment purely based on age. The current NICE treatment recommendations for adult RA are summarised in table 4, below.^{7,8}

Common misconceptions about the management of inflammatory arthritis are listed in table 5, below.

The backbone of treatment remains methotrexate which is a conventional synthetic disease modifying drug (DMARD). Other options in this category include leflunomide, sulphasalazine and

hydroxychloroquine. Since the onset of action of these medications can take up to 12 weeks, glucocorticoids can be used as bridging therapy. However, the potential limitations of glucocorticoids in this age group, for example comorbidities such as diabetes and neuropsychiatric side effects such as agitation, confusion or psychosis need to be considered.

In cases of failure to achieve remission or low disease activity with conventional DMARDs, addition of biologic DMARDs is recommended, although generally not as monotherapy. Biologic medication classes approved for the treatment of RA include IL-6 inhibitors (tocilizumab, sarilumab), TNF inhibitors (etanercept, infliximab, adalimumab etc), anti-CD20 antibodies (rituximab) and T cell inhibitors (abatacept). Janus kinase (JAK) inhibitors (tofacitinib and baricitinib) have also been approved.

MONITORING

All adults with RA should be followed up regularly in secondary care. In the initial stages, monitoring should be more ➤

Table 4

Summary of the NICE recommendations on the management of adult rheumatoid arthritis, relevant to primary care^{7,8}

- Refer to secondary care all patients with clinical synovitis of undetermined cause. Refer urgently (within three days of presentation) if the small joints of hands and feet are affected, more than one joint is affected, or there is a delay of three months or longer in seeking medical advice
- Investigation with rheumatoid factor, anti-CCP antibody and X-rays of the hands and feet is recommended in primary care, although negative results should not preclude the referral of a suspected case
- Short-term glucocorticoids as a bridging therapy is recommended on initiation of a synthetic DMARD

Table 5

Common misconceptions concerning the management of inflammatory arthritis

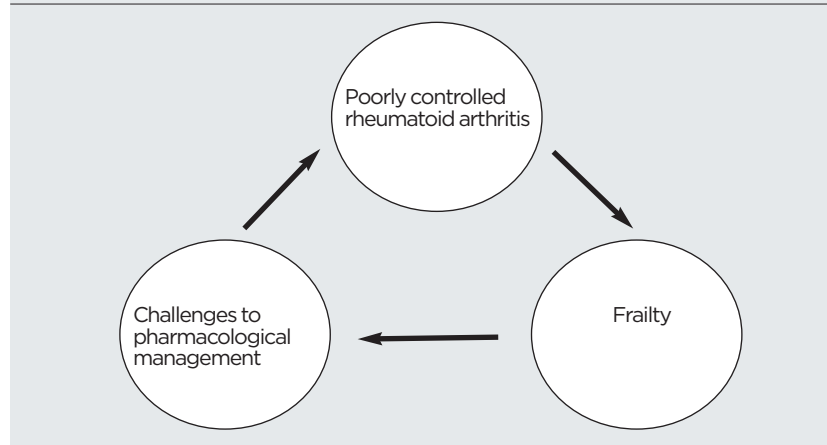
Steroid response reliably differentiates inflammatory arthritis from other differentials: Many articular syndromes other than autoimmune inflammatory arthritis can respond symptomatically to moderate doses of steroids including osteoarthritis, mechanical back pain, gout and pseudogout

Steroids are safer than DMARDs such as methotrexate: In the medium to long term, the side effect profile, including the infection risk, of steroids is far worse

Methotrexate causes interstitial lung disease (ILD) and is contraindicated in the presence of lung disease: The current consensus in the rheumatology community is that most cases of ILD in patients with RA are probably caused by their disease rather than the treatment. Pre-existing lung disease alone does not contraindicate the use of methotrexate

Figure 2

Vicious cycle of difficult pharmacological management leading to frailty which ultimately results in poor functional outcome in elderly onset rheumatoid arthritis



frequent to ensure the treatment target is achieved (remission or low disease activity). It can be extended to 12 monthly once the disease and treatment regimen have become stable.

Regular blood monitoring is necessary for patients on DMARD therapy (excluding hydroxychloroquine), this can be done in primary or secondary care according to local or national guidelines, or shared care arrangements.

An annual review is recommended for all patients to assess the following aspects: disease activity, functional ability, development of comorbidities (hypertension, ischaemic heart disease, osteoporosis, depression) or complications (vasculitis, disease of the cervical spine, lung or eyes) and the impact the disease is having on the patient's life.

CONCLUSION

RA is a systemic disease which can present at any age. Although it primarily affects the small joints of the hands and feet, it can present with large joint synovitis. Constitutional symptoms and a systemic inflammatory response can be present, and these are more common in the EORA group.

Early diagnosis and treatment can improve long-term outcomes and reduce the development of comorbidities and complications.

While methotrexate remains first-line therapy, the development of numerous biologic and other new therapies over the past 15 years has contributed to better control of articular and extra-articular disease, and reduced disability.

Competing interests: None

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Useful information

National Rheumatoid Arthritis Society
www.nras.org.uk

The British Society for Rheumatology
www.rheumatology.org.uk

Versus Arthritis
www.versusarthritis.org

Arthritis and Musculoskeletal Alliance
www.arma.uk.net

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editor@thepractitioner.co.uk