REVIEW ARTICLE

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Elderly Onset Rheumatoid Arthritis

Differential Diagnosis and Choice of First-Line and Subsequent Therapy

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Abstract

Elderly onset rheumatoid arthritis (EORA) has been considered a benign form of rheumatoid arthritis (RA). However, it most probably encompasses different subsets of patients with distinct outcomes. According to data reported in the most recent studies directly comparing older and younger RA patients, it seems that, overall, the prognosis of EORA patients is not very different from that of other patients with this disease. However, some cases with negative rheumatoid factor and polymyalgia-like symptoms appear to be a distinct subset with a different genetic basis and a more benign course.

The differential diagnosis of EORA from other rheumatological disorders that are prevalent in this stratum of the population, such as polymyalgia rheumatica, crystal-induced arthritis or osteoarthritis, may be complicated because these disorders can present with signs and symptoms similar to those of RA in some circumstances. A prompt diagnosis of true RA is important because early treatment should be implemented.

It is recommended that therapy of EORA be tailored according to disease activity, with the aim of achieving clinical remission or the lowest possible level of disease activity in order to minimize potential functional sequelae. Co-morbidities and drug toxicity profiles are major considerations when choosing the most suitable therapy for EORA patients. Prudent use and

careful follow-up of all treatments are also required because of the increased risk of adverse events in elderly patients. However, no special contraindications to the use of disease-modifying antirheumatic drugs in this age group apply, and use of biological therapies currently used in younger RA patients has also been described in these patients. Therefore, a therapeutic strategy for first-line and subsequent treatment that is in accordance with the disease activity of patients with EORA is suggested.

Rheumatoid arthritis (RA) is a multisystem, chronic, inflammatory disorder characterized by destructive synovitis with a prevalence of approximately 2% among people aged >60 years.[1] Disease onset may vary between childhood and latter decades of life but peaks in the sixth decade of life.[2] Usually, patients who develop RA between the age of 60 and 65 years are defined as having elderly onset RA (EORA). EORA patients represent a clinical subset of individuals who differ in presentation, severity, prognosis and treatment from patients with younger onset RA (YORA).

The purpose of this review is to characterize the EORA subset of patients and describe the potential differences from their younger counterparts with regard to demographic and clinical features, therapeutic options and outcomes, and to outline the differential diagnosis of EORA from other elderly rheumatological conditions.

1. Epidemiology and Genetic Predisposition

The most reliable estimates of incidence, prevalence and mortality in RA are those derived from population-based studies. Several such studies have been conducted in populations with diverse geographic and ethnic backgrounds, and with important methodological differences.[3] In the US, these studies indicate a prevalence of RA of between 0.5% and 1% with a prevalence among persons aged ≥60 years of ~2%.[1] In Finland, a recent study showed that the prevalence of RA in people aged ≥65 years was 1.2% in men and 2.2% in women.[4] Annual incidence rates around the world are highly variable (from 9 to 900 per 100 000), depending on sex and ethnicity.[5] In the UK, the Norfolk Arthritis Register (NOAR) has shown that the incidence of RA in men rises steeply with age, whereas in women the incidence increases up to age 45 years and plateaus until age 75 years, after which it declines.[6] Gabriel et al.,[7] who investigated the epidemiology of RA in Rochester, Minnesota, USA, have reported similar conclusions.

Genetic influences in RA have been supported by numerous studies. The best-known genetic association for RA is with the HLA class II region containing the *DRB1* locus.[8] The RA-associated *DRB1* alleles share a conserved linear sequence of amino acids between positions 70 and 74 in the HLA-DRβ1 chain of the HLA-DRα/β heterodimer, which has led to the ''shared epitope'' (SE) hypothesis.[9] The presence and the dose effect of these *DRB1* alleles have been associated with early disease onset,[10] radiological erosions[11] and extra-articular manifestations.[12] There are ethnic variations in the allele frequency of the *DRB1* alleles associated with RA, and some variations have been described between elderly and young patients at disease onset. For example, in Spain, Gonzalez-Gay et al.[13] reported that YORA was strongly associated with *DRB1*∗04, whereas EORA was associated with *DRB1*∗01 and not associated with *DRB1*∗04. In addition, seronegative EORA patients exhibited increased frequency of *DRB1*∗13/∗14 similar to patients with polymyalgia rheumatica (PMR). Wu et al.[14] also reported that fewer than half of patients who develop RA in their sixth or later decades had *DRB1*∗04 alleles, in contrast to 92% of patients with disease onset before the age of 30 years who carried at least one of the *DRB1*∗04 alleles.

2. Clinical Features and Subsets

Several reports have studied patients with EORA and their differences in presentation and outcome compared with YORA patients. Cecil and Krammerer[15] first argued that RA in aged patients did not differ essentially from that seen in younger patients. Subsequent studies, however, have tended to support the notion that differences exist between elderly onset and earlier onset disease.[16,17] Deal et al.[18] compared presenting features and disease outcome in EORA patients with those in YORA patients with disease duration of ≤10 years. They found that abrupt disease onset and large joint involvement, particularly of the shoulder girdle and hip mimicking a PMR-like presentation, occurred more commonly in the EORA group. In contrast, younger patients, in general, had a 'classic' clinical picture of RA with small joint involvement. Furthermore, physicians and patients reported better outcomes in the elderly, despite the fact that the two groups were treated with similar therapies.

One year later, Healey[19] suggested that RA in older patients differed from that in other adults and described different subsets among EORA patients. The first subset corresponds to patients with classic RA whose clinical onset is similar to that in patients who develop seropositive RA at an earlier age. They present with high levels of disease activity, and most require aggressive management. The second subset includes patients with symmetrical arthritis associated with Sjögren's syndrome. The synovitis is less severe and more readily controlled than in the first subset. In the third subset the clinical picture mimics that of PMR. These patients have high levels of acute-phase reactants, but rheumatoid factor (RF) is negative in the vast majority of cases. The arthritis in these patients is usually well controlled with low-dose corticosteroid treatment, and joint damage or radiological changes are less severe than in the other forms.

Bajocchi et al.[20] also studied and compared EORA and YORA patients. They described the following aspects that should distinguish EORA from YORA: a balanced sex distribution with a female to male ratio of about 1.5–2 : 1 versus 4–4.5 : 1 in YORA patients; greater incidence of large joint involvement and constitutional symptoms (fever, weight loss and fatigue); and more acute disease onset, lower presence of RF and higher erythrocyte sedimentation rate (ESR). These authors also distinguished seropositive from seronegative EORA patients. The former were very similar to YORA seropositive patients, whereas the latter (seronegative EORA) constituted a more heterogeneous group with a clinical picture overlapping with other syndromes such as PMR and remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) syndrome.

3. Outcomes

Outcomes in EORA patients have been reported to be more benign than those in YORA patients. However, a large majority of studies have been observational with no direct comparison between YORA and EORA patients. More recent studies that have included cohorts of EORA and YORA patients have reported that the outcome of EORA may be comparable with or even worse than that of YORA.[21,22]

In 1999, Pease et al.[23] published a prospective study comparing clinical, radiological and functional outcomes in patients presenting with RA above and below the age of 65 years and attempting to identify predictors of poor clinical and radiological outcome after a follow-up of at least 1 year. Statistical analysis in the EORA group showed that a high Health Assessment Questionnaire (HAQ) score (odds ratio [OR] = 7.42) and RF seropositivity (OR = 8.17) predicted poor functional outcome, but none of the other co-variates (presence of HLA DR1 or DR4, increased inflammatory markers at presentation) achieved statistical significance as predictors of poor functional outcome. The analysis also showed that, overall, EORA patients were more likely to go into clinical remission (OR = 2.99), with the remission rate being much higher in the seronegative EORA group than in other groups of patients, including seronegative YORA patients. Finally, it was also observed that

continuous corticosteroid use for >3 months in EORA patients was associated with joint erosion (OR = 4.09) and had no effect on the frequency of remission (OR = 0.91).

The results of this study[23] underscore the fact that EORA requires early and appropriate disease-modifying antirheumatic drug (DMARD) treatment similar to that given to patients with YORA. However, the higher remission rate in seronegative EORA patients suggests that treatment in this subset of patients might be given for a shorter period compared with seropositive patients.

Similar conclusions about the outcome of EORA patients have been reported in another study from Spain.[24] This study compared disease outcomes in patients aged ≤45 years and ≥65 years with a disease duration of between 2 and 7 years. The results showed that, overall, elderly patients did not have a benign disease course; rather, they had worse functional and anatomical outcomes than their younger counterparts.

Recently, studies from the UK[25-27] using the NOAR showed that higher age at symptom onset appears to be an independent factor for the initial development of erosions, although the exact mechanism involved is unclear. In addition, these investigators found that older age at onset was a predictor of mortality from cardiovascular disease and suggested that primary cardiovascular disease prevention and aggressive therapy from the time of presentation are crucial to avoiding premature death.

4. Differential Diagnosis

RA in elderly patients must be differentiated from a number of other common subacute or chronic rheumatic conditions, such as osteoarthritis (OA), spondyloarthritides, crystal-related arthritis, infectious arthritis, PMR, RS3PE syndrome, connective tissue diseases and others (table I). The diagnostic process includes a careful clinical history, a meticulous physical examination, and laboratory and imaging studies.

By far the most important of these diagnostic procedures is the clinical history. Crucial in this regard is a clear assessment of the distribution of joint involvement, whether pain is articular or extra-articular, whether pain follows trauma or infection, the duration of the process and the presence of extra-articular findings.[28]

Table I. Differential diagnosis of rheumatoid arthritis

Crystalline arthropathy (gout, pseudogout or chronic pyrophosphate arthropathy)
Spondyloarthropathy
Polymyalgia rheumatica
Osteoarthritis
Remitting seronegative symmetrical synovitis with pitting oedema syndrome
Arthritis related to connective tissue disease or systemic vasculitis
Malignancy-related arthritis
Hypertrophic osteoarthropathy
Sarcoidosis
Infectious arthritis (hepatitis B and C, HIV and others)

4.1 Crystal-Related Arthritis

Gout and pseudogout typically behave as acute intermittent monoarticular attacks of limited duration. However, sometimes they can closely resemble persistent polyarticular rheumatoid disease.

Acute gouty arthritis is usually easily diagnosed. However, sometimes patients with tophaceous gout may present to the physician with a chronic, symmetrical inflammatory polyarthritis, and tophi may resemble subcutaneous nodules. Tophi tend to occur in locations similar to those of rheumatoid nodules. Although patients with RA rarely develop gout, the correct diagnosis of the polyarthritis can usually be resolved by fluid aspiration from affected joints and examination of the sample under polarized light microscopy for monosodium urate crystals. Radiological changes of gout can also mimic RA, but in gout, periarticular osteoporosis is typically lacking and the erosions are located close to but outside the joint instead of being intra-articular as occurs in RA and typically have sclerotic margins.[5,28-30]

In 2–6% of patients with clinically manifest calcium pyrophosphate dehydrate (CPPD) crystal deposition disease, the arthritis simulates RA (sometimes called pseudorheumatoid arthritis),[31] but more commonly inflammatory

arthritis as a result of CPPD deposition is mono- or oligoarticular. The presence of chondrocalcinosis on joint radiographs can be helpful, but it is not always present. Aspiration of an affected joint and identification of intracellular positively birefringent rhomboid-shaped crystals under polarized microscopy helps with the diagnosis in a large majority of these cases. The presence of RF may suggest the diagnosis of RA in doubtful cases, but it should be kept in mind that RF can also be found in a significant percentage of elderly people, including patients with microcrystalline arthritis.

4.2 Spondyloarthropathies

The spondyloarthritides include ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, inflammatory bowel disease-associated arthritis and undifferentiated forms of spondyloarthropathies. By and large, these pathologies present at early ages, but in some cases they may produce diagnostic dilemmas in elderly patients.[32]

Peripheral arthritis develops in almost 50% of patients with AS. However, the asymmetrical pattern of joint involvement with preference for lower limbs and the axial involvement allow differentiation of this entity from RA.

The articular manifestations of psoriasis may clinically resemble RA, but the distribution is usually different, being less symmetrical and frequently involving distal interphalangeal joints and interphalangeal joints of the toes, producing small 'sausage appendages'. In addition, peripheral enthesitis and dactylitis are present in PsA, but are not typical in RA. A subset of psoriatic patients develop a polyarthritis indistinguishable from RA. In these cases, cutaneous lesions plus the absence of RF and subcutaneous nodules help to establish the diagnosis. Anti-cyclic citrullinated peptide (CCP) antibodies have been found in 7–16% of cases of PsA and do not help to differentiate PsA from RA.[33,34]

Inflammatory bowel disease-associated arthritis can be differentiated from RA only if it precedes the overt bowel involvement. Peripheral arthritis tends to be more asymmetrical than in RA and more frequently involves the large joints of the lower extremities. Reactive arthritis, which typically follows a gastrointestinal or genitourinary infection, may also resemble RA, but it is usually self-limited (i.e. continues for <6 months) and may be associated with specific extra-articular manifestations such as urethritis, conjunctivitis and iritis. As in other spondyloarthropathies, the pattern of joint involvement is asymmetrical rather than symmetrical, and the lower limbs are usually affected.[5]

Finally, Dubost and Sauvezie[35] and, more recently, Olivieri et al.[36] have described a form of elderly-onset undifferentiated spondyloarthritis with a broad clinical spectrum mainly characterized by oligoarthritis occurring with extensive pitting oedema of the lower limbs, minimal involvement of the axial skeleton, constitutional symptoms and elevated ESR.

4.3 Polymyalgia Rheumatica

The difficulty in distinguishing PMR from RA has been recognized since 1963 when Bagratuni[37] described a group of such patients as having anarthritic rheumatoid syndrome. PMR may be an overlapping syndrome with seronegative EORA. Not infrequently, a follow-up period is necessary to establish a definitive diagnosis. Thus, some patients initially presenting with a polymyalgic clinical picture may later develop features more consistent with seronegative RA and thus meet the American College of Rheumatology (ACR) criteria for RA. In this regard, a population-based study confirmed that late-onset seronegative RA may initially mimic PMR and that some patients initially considered as having PMR were finally diagnosed as having RA after an extended follow-up period because they fulfilled ACR criteria for the diagnosis of RA.[38] As a result, some investigators have emphasized the importance of considering late-onset RA in the differential diagnosis of elderly patients presenting with PMR features.[39] Peripheral synovitis may be present in up to 25% of patients with PMR. In these cases, the synovitis is frequently asymmetrical and non-erosive, small joints are spared and rheumatoid nodules are not observed.[34,40-42] López-Hoyos et al.[43] studied

the prevalence of anti-CCP antibodies in EORA and PMR patients and showed that the presence of anti-CCP antibodies in a patient with clinical symptoms of PMR must be interpreted as being highly suggestive of EORA. In addition, these investigators found a significant correlation between anti-CCP antibodies and RF in EORA but not in YORA. Ultrasonographic and magnetic resonance imaging may be useful in differentiating these patients in specific cases showing the presence of synovitis in locations characteristic of RA.[44,45]

4.4 Osteoarthritis

OA is the most common form of arthritis among the elderly.[30] OA typically affects the distal interphalangeal joints, proximal interphalangeal joints, knees and first carpo-metacarpal joints. It can cause stiffness, pain, loss of motion and even deformities secondary to the formation of Heberden's and Bouchard's nodes, but inflammatory arthritis is lacking and the radiological findings (asymmetrical joint narrowing, subchondral sclerosis and osteophytes) are different from those found in RA.[28] Infrequently, an erosive form of OA involving small finger joints can develop, but this occurs mainly in middle-aged women and does not present with synovial proliferation.[46]

4.5 Remitting Seronegative Symmetrical Synovitis with Pitting Oedema

RS3PE is a syndrome characteristic of elderly patients that develops abruptly with oedematous symmetrical arthritis involving the hands and wrist and/or feet and ankles. Extensor tenosynovitis is the lesion responsible for swelling on the dorsum of the hands and feet. Patients with RS3PE do not develop bony erosions and lack RF. They generally respond well to low doses of corticosteroids, and the prognosis is excellent. RS3PE-like findings can be seen in PMR, other inflammatory rheumatic disorders (including RA and spondyloarthritis), and in patients with haematological and solid malignancies; in such cases, the oedema is often distributed asymmetrically. Whether this syndrome is a different entity or enters into the spectrum of RA is still open to debate.[47-49]

4.6 Connective Tissue Diseases

Systemic lupus erythematosus (SLE) frequently causes symmetrical peripheral joint arthritis and commonly affects young women. However, late onset SLE and even drug-induced SLE may produced a clinical picture similar to RA. This is especially the case in patients who develop Jaccoud's arthropathy, which can occur in lupus and is characterized by deformation of the hands with ulnar deviation, reducible swan-neck deformities, paucity of synovitis and absence of erosions. Frequently, these patients can be positive for RF, but the presence of high titres of antinuclear antibodies in addition to systemic manifestations characteristic of SLE allows the diagnosis to be established. Mixed connective tissue disease can cause oedema and synovitis of the hands, but is distinguished from RA by the presence of U1-ribonucleoprotein (RNP) antibodies, Raynaud's phenomenon and acrosclerosis. Systemic vasculitides such as Wegener's granulomatosis and polyarteritis nodosa can cause arthritis, but other findings, such as skin lesions, renal disease, neuropathy and the lack of erosive disease, distinguish these entities from RA. Proximal and symmetrical muscle weakness is the most common presenting feature of dermatomyositis and polymyositis. Non-erosive inflammatory polyarthritis may be present in patients with severe disease, but the presence of elevated serum muscle enzymes, myopathic changes on electromyography and skin lesions in the case of dermatomyositis can help to distinguish these conditions from RA.[5,28,29]

4.7 Other Diseases

Occult malignancies, including solid tumours and haematological cancers, can cause RA-like arthritis, but these cases are usually RF negative and non-erosive.[50,51] Effective therapy of the malignancy can result in remission of arthritis. Acute hypertrophic osteoarthropathy (HOA) may be associated with pulmonary malignancy and may resemble RA.[5] HOA is usually not

persistent, is associated with other features such as digital clubbing or pain along the bones and does not display RF, nodules or erosive changes. Chronic articular sarcoidosis can rarely produce a clinical picture that resembles RA and may be associated with a positive RF, but is typically oligoarticular, asymmetrical and often associated with cutaneous lesions that display typical findings on histopathological study.[28]

Viral arthritis may mimic early RA and should be considered as part of the differential diagnosis in older age groups. Erosions and rheumatoid nodules are absent and the clinical course is usually milder and self-limited.[52,53]

5. Pharmacological Therapy

Elderly patients have an increased number of co-morbidities and increased incidences of polypharmacy, non-compliance, risk of dosage errors, changes in the pharmacokinetics and pharmacodynamics of the drugs, and adverse drug events. All these factors may profoundly alter the therapy response in EORA patients. Corticosteroids, NSAIDs, analgesics, DMARDs and biological agents are currently used for the treatment of EORA.[54-56]

Objectives in the treatment of EORA patients are: (i) prompt recognition of these patients in order to initiate early treatment; (ii) reduction in the signs and symptoms of inflammation; (iii) prevention of radiological damage, tissue destruction and disease progression; (iv) retardation of disability; and (v) achievement of remission or the lowest possible level of disease activity.[57,58]

Erosions may be seen within a few years of disease onset, and even patients with <3 months' duration of symptoms may already have evidence of destruction.[59] Therefore, referral to a specialist should not be delayed. Early diagnosis and therapy have been proven to improve long-term outcomes.[60-65] However, not all EORA patients require the same type of management. Thus, EORA patients with RF or anti-CCP antibodies, particularly those with *HLA-DRB1**0401 and *DRB1**0404 alleles, early erosions, functional impairment or persistently active synovitis with high levels of disease activity, should be considered candidates for aggressive therapy, including biological agents.[66,67] In contrast, seronegative EORA patients with low disease activity at onset usually require a less aggressive approach, and some cases can be managed with only low doses of corticosteroids.

The European League Against Rheumatism recommendations[68] in 2006 indicated that among the DMARDs, methotrexate is the first option for those patients with persistent disease, and leflunomide seems to be the best alternative. Studies of the pharmacokinetics of methotrexate in elderly RA patients showed that methotrexate clearance decreases along with the decline in creatinine clearance, and that dose regimen adjustments should be performed in elderly patients with renal insufficiency.[69,70] In addition, some other drugs, such as NSAIDs, ciclosporin and salicylates, may reduce creatinine and methotrexate clearance or displace methotrexate from albumin; in these cases, renal function should be monitored closely. Meta-analysis[71] of the available trials has demonstrated that age does not affect methotrexate efficacy, which is equivalent in elderly and younger RA patients. Bone marrow toxicity and CNS disturbances are adverse events particularly associated with methotrexate treatment in elderly patients,[72,73] and special attention should be paid to these possible considerations. In conclusion, low-dose methotrexate treatment appears safe and effective in EORA patients and close monitoring of liver and renal function can prevent the major risks associated with this treatment.[69,71-78]

Although specific pharmacodynamic, pharmacokinetic and toxicity studies of leflunomide have not been carried out in the elderly, administration of leflunomide in elderly patients does not seem to require special precautions. Even so, we recommend starting with lower doses of leflunomide in this population, such as 10 mg/day or 20 mg every other day, to prevent adverse events. Blood pressure and liver function should be monitored in EORA patients because of the risk of hypertension and hepatic toxicity associated with leflunomide.[79-81]

Controlled trials of hydroxychloroquine have confirmed the efficacy of this drug in RA, and

there has been no suggestion that its efficacy declines with increasing age; however, its efficacy is low compared with that of methotrexate.[82] Hydroxychloroquine is usually safe, and treatment with this agent does not require monthly blood tests as is the case with other DMARDs. Special attention must be paid to elderly people with reduced renal function and eye fundus disorders, because the kidneys are the main route of elimination of hydroxychloroquine and retinal toxicity is the principal adverse effect associated with its use. Eye examinations must be performed prior to initiating therapy and regular follow-up examinations every 6–12 months for patients with risk factors and every 18 months for patients without any risk factors are required.[83-85] We suggest use of hydroxychloroquine in EORA patients with mild, seronegative and non-aggressive forms of RA in association with low-dose corticosteroid therapy. Combination therapy with low-dose methotrexate has been shown to increase methotrexate bioavailability and may generate synergistic and anti-inflammatory effects, so this combination could be an alternative in refractory patients.[86-88]

Svartz created sulfasalazine in 1938 for the treatment of rheumatic polyarthritis.[89] Sulfasalazine has a longer elimination half-life in elderly RA patients[90] and interaction studies have shown that sulfasalazine may decrease digoxin serum concentrations by 25%.[91] The main adverse effects of sulfasalazine in elderly patients are nausea and vomiting, which can be decreased by starting with a lower dose and gradually increasing up to the dosage of 2–3 g/day. Clinical efficacy has been proven in various controlled studies, but the action of sulfasalzine on radiological progression seems modest.[92,93]

After first-line therapy has been administered, it is mandatory to assess disease activity using the appropriate validated instruments to define response to therapy. Several studies[76,94] have shown that frequent evaluations of disease activity using validated tools combined with therapy adjustments to achieve the lowest possible level of disease activity result in better disease outcome than routine care. Regarding the assessment of clinical activity, it has been shown that newer indices, such as the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI), correlate highly with other indices more widely used, such as the Disease Activity Score (DAS), physical function and progression of radiographic damage.[95]

The Working Group for Therapeutic Strategies for Rheumatoid Arthritis (STPR)[96,97] has suggested that the best options for the treatment of refractory patients may be addition of a corticosteroid or switching to another DMARD when there is no new structural damage and disease activity is low or moderate, and addition of a biological agent when radiographic joint damage occurs, particularly in patients with positive anti-CCP antibodies and RF.[96-100]

The latest consensus statement on biological agents for the treatment of rheumatic disease[101] reported that there is category A evidence indicating that tumour necrosis factor (TNF) receptor antagonists are effective for the treatment of RA in conjunction with methotrexate and in methotrexate-naive patients. There is no evidence that any of the current TNF receptor antagonists are better than any others in its class, but if the first agent fails another one can be tried. Severe adverse events include infections, potential worsening of heart failure and demyelinating disease.[101] TNF receptor antagonists should not be prescribed to patients with active infection and should be used with caution in elderly patients with co-morbidities or underlying conditions that predispose them to infection.[101] Recently, Genevay et al.[102] evaluated the tolerance to and effectiveness of anti-TNF agents in EORA in comparison with younger patients. These investigators concluded that, as in previous reports,[103,104] anti-TNF agents could be administrated to elderly patients with RA with similar levels of effectiveness and tolerability as in younger patients. Therefore, age in itself should not interfere with therapeutic decisions concerning the introduction of anti-TNF agents, although in a subset of patients aged >75 years, no functional improvement according to HAQ should be expected, despite improvements in disease activity.[102] It is probable that the frequent presence of other co-morbidities (e.g. co-existent

OA) may limit the expected benefit from these drugs, and this possibility should be carefully evaluated when making the decision to use these drugs. In the case of absence of response to a TNF receptor antagonist or toxicity, another agent can be used, although primary non-responding patients are less likely to respond to a second anti-TNF agent. Patients who have not tolerated one TNF receptor antagonist may respond to a second agent, but they are more likely to be intolerant of the second agent.

For those patients who do not achieve or maintain a good response to TNF receptor antagonists, novel biological agents with different modes of action, such as rituximab and abatacept, are now available. Overall, the newer biologicals are generally well tolerated and have proven their effectiveness in patients with established RA that does not respond to TNF receptor antagonists.[105]

Discontinuation of biological therapy once remission is achieved while continuing therapy with DMARDs could be an alternative that prevents unnecessary continuation of biologicals.[106] Recent results from the CORRONA (Consortium of Rheumatology Researchers of North America) database[107] confirm that maintenance of clinical response is possible after discontinuation of anti-TNF treatment, especially in patients with early RA, although definitive guidelines in this regard have not been established yet.

6. Conclusions

EORA disease encompasses different subsets of patients, although, overall, its prognosis is not very different from that of other RA patients. Some cases with negative RF and polymyalgia-like symptoms seem to be a distinct subset with a different genetic basis and a more benign course. Differential diagnosis of the other condition from other entities that are prevalent in this population (PMR, crystal-induced arthritis and OA) may be complicated because they can present with similar signs and symptoms. Early treatment according to disease activity with the aim of achieving clinical remission must be initiated as soon as possible, although co-morbidities and differences in drug pharmacodynamics and pharmacokinetics are major factors that must be taken into consideration when choosing the most suitable therapy for EORA patients. We propose a therapeutic strategy for first-line and subsequent treatment based on disease activity in these patients. However, careful follow-up and prudent use of these therapies are required because of the increased risks of adverse events in elderly patients.

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