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LEADING ARTICLE

Difficult-to-Treat Rheumatoid Arthritis in Older Adults: Implications of Ageing for Managing Patients

Marta Novella-Navarro[1] · **Alejandro Balsa**[1]

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Abstract

Difficult-to-treat rheumatoid arthritis is a heterogeneous term in which patients may present with difficulties in their management for different reasons. This can ultimately lead to patients being exposed to multiple treatments because of inefficacy (resulting from mechanisms intrinsic to rheumatoid arthritis or from non-inflammatory causes such as chronic pain syndrome or structural damage, among others), toxicity or adverse effects that may be linked to comorbidities. One particular group in which such characteristics may be more patent is older patients. Increasing life expectancy, an ageing population and the late onset of rheumatoid arthritis have led to an increased interest in the particularities of treating older patients. This may pose a challenge for physicians, as ageing has implications for optimal patient treatment owing to the potential presence of comorbidities, the risk of adverse events and perceptions of disease status by both physicians and patients. All of these factors may have implications for classifying and managing patients aged > 65 years as difficult-to-treat rheumatoid arthritis, as these patients could be misclassified. This can occur when a significant proportion may still exhibit signs of active disease but not necessarily be difficult to treat because the treatment criterion has not been fulfilled. Alternatively, patients may be exposed to multiple biologic/targeted disease-modifying antirheumatic drugs because of contraindications and/or comorbid conditions. Treatment-to-target strategies and an adequate assessment of inflammatory rheumatoid arthritis activity in older patients should be undertaken, taking special care with associated comorbidities, polypharmacy and risk profiles. Such an approach can help to ensure appropriate treatment for older adults and avoid the misclassification of difficult-to-treat patients.

Key Points

Treatment of rheumatoid arthritis in older patients should be carried out in the same manner as in younger patients in accordance with the treat-to-target strategy.

The management of an older rheumatoid arthritis population requires special care in drug selection and dose adjustments to ensure adequate treatment.

Age-related conditions can lead to patients classified as difficult to treat, owing to the need for frequent treatment changes in response to comorbidities or adverse effects.

✉ Marta Novella-Navarro
mnovellanavarro@gmail.com

[1] Rheumatology Department, Hospital Universitario La Paz, Madrid, Spain

1 Introduction: Defining "difficult-to-treat rheumatoid arthritis"

In recent years, outcomes in rheumatoid arthritis (RA) have been transformed, thanks to a better understanding of the immunological mechanisms involved in the pathophysiology of RA, treatment algorithms that measure disease activity with composite indices, treatment-to-target strategies and therapeutic options based on disease-modifying anti-rheumatic drugs (DMARDs) [conventional, biologic and targeted]. Long-term damage and functional decline have significantly reduced and systemic features diminished [1–4].

While currently prospects are good for most patients, there remains a percentage who do not achieve the desired therapeutic goals despite receiving multiple DMARDs over the course of their disease. At first, these patients were considered to have refractory RA, and some attempts were made to establish clinical factors that could determine this resistance to disease-modifying drugs [5–9]. Given the variability of the criteria used to classify these patients, and recognising this refractory condition as an emerging issue in the

treatment of RA [10], in 2020, the European League Against Rheumatism (EULAR) established a definition of difficult-to-treat RA (D2TRA) [11]. Its goal was to advance a valid definition that could be used in clinical practice and clinical trials and be applicable to future research in order to obtain a better overall understanding of this disease.

This definition consists of three criteria encompassing treatment failures, uncontrolled disease activity and clinical perception of the management of RA signs/symptoms. All three criteria must be present in D2TRA including: (1) treatment according to EULAR recommendations and the failure of two or more biologic and targeted synthetic (b/ts) DMARDs (with different mechanisms of action) after no response to conventional synthetic DMARD therapy (unless contraindicated); (2) signs suggestive of active/progressive disease defined as presenting with one or more of the following: moderate disease activity according to validation composite indexes, signs and/or symptoms suggestive of active disease, inability to taper glucocorticoid treatment below 7.5 mg/day of prednisone or equivalent, rapid radiographic progression or well-controlled disease according to standards but still presenting with RA symptoms; and (3) the management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient [11].

Difficult-to-treat RA ultimately involves the exposure of patients to multiple treatments because of inefficacy (resulting from mechanisms intrinsic to RA or because of non-inflammatory causes such as chronic pain syndrome or structural damage, among others), toxicity or adverse effects that may be linked to comorbidities [12]. A special group of patients in which these characteristics may be more patent is older patients. Mechanisms attributable to immunosenescence may lead to increased chronic inflammation and comorbidities [13], limiting treatment options or necessitating therapeutic changes. In addition, some studies suggest that the prognosis of elderly-onset RA is more severe because these patients may also have higher scores on composite activity indices, which may suggest that the disease is not well controlled [14], leading to changes in disease management. The differences between elderly-onset RA and young-onset RA may be owing to changes in pro-inflammatory cytokine profiles that occur in old age [15] that lead to typical features of elderly-onset RA (including a more balanced sex distribution, a common abrupt onset with involvement of large proximal joints and increased systemic symptoms) [16]. In addition, these clinical features become more evident as ageing continues [17].

Difficult-to-treat RA in older adults is particularly important because the older RA population is expanding, as a result of an increased life expectancy and an increasing incidence of elderly-onset RA [18]. In the following sections, we break down the implications of ageing on managing older patients with D2TRA.

2 Treatment with b/tDMARDs in Older Population

Treatment of older patients should have exactly the same goals as with younger patients: to control disease activity, prevent structural damage, preserve functionality and decrease the excess mortality conferred by RA. Therefore, the treatment-to-target approach used with older patients with RA should be the same as with younger patients. In addition, patients should be treated early in order to achieve low disease activity/remission [2–4, 19]. However, in older patients, this treatment-to-target approach may be limited by the greater prevalence of comorbidities as well as the higher risk of potential adverse effects, which can result in those patients not receiving optimal treatment [2, 4, 20].

Assessments of efficacy in older patients in randomised clinical trials are hampered by the scarcity of data as these patients typically do not meet the established inclusion criteria, or drop out of the studies early, generally because of comorbidities and/or adverse effects. However, there are studies of real-world data showing that the efficacy of RA-specific treatments is similar in older and younger patients [19, 21]. Thus, real-world data suggest that the efficacy of tumour necrosis factor inhibitors (TNFi) in older patients is similar to that in younger patients, especially in terms of clinical response, although functional indexes may not be similar because of associated comorbidities and the presence of osteoarthritis [22–24]. Abatacept has a favourable disease control profile in both younger and older patients [25, 26]. Data about the effectiveness of rituximab in older patients are scarce but suggest that this treatment is less effective in comparison with younger patients [27]. In the case of tocilizumab, a recent study carried out in a Japanese population revealed that the retention rates of this drug are higher than those of TNFi in older patients. In addition, the study showed that discontinuation because of inefficacy was lower in the tocilizumab group than in the TNFi group [28]. This could be explained because apparently in older patients there is an overexpression of interleukin-6 [15]. As for JAK inhibitors (JAKi), according to the published data, efficacy in older populations is quite similar to that in younger populations. In addition, these DMARDs seem to offer a valid alternative for those patients who already meet the criteria for D2TRA because of multiple treatment failures, as these drugs possess mechanisms of action against a greater number of cytokines [29].

3 Limitations on the Use of b/tsDMARDs in the Older Population

3.1 Comorbidities and Extra-Articular Manifestations

The exposure of older patients to multiple b/tsDMARDs may have no correlation with a lack of efficacy because as mentioned above, these treatments do not necessarily have to be less effective, per se, in controlling disease activity. However, multiple failures/changes of b/tsDMARDs may be linked to suboptimal treatment because of patient comorbidities or the potential risks of these treatments. Such problems hamper optimal RA management in this group of patients and constitute a contributing factor to the occurrence of D2TRA [30].

When referring to comorbidities in persons aged 65 years and older we must consider both those typically associated with ageing and those that are closely linked to RA, as they share the same pathogenic mechanisms that lead to a chronic inflammatory status and increased risk factors. The most frequent comorbidities associated with RA are cardiovascular, pulmonary, infections, osteoporosis, depression and malignancies [31]. The presence of age-associated or RA-associated comorbidities is difficult to distinguish, but in either case they pose a limitation to the usual application of optimal treatment strategies because of contra-indications in drug prescription strategies [32].

In addition to dramatic increases in the incidence and prevalence of age-related diseases, there has also been a rise in certain extra-articular features of the disease. Rheumatoid arthritis populations have an increased risk of pulmonary disease with respect to the general population, with RA-associated interstitial lung disease being a particular example. Indeed, it has a higher prevalence in older versus younger individuals, which implies a steady worsening in the overall RA management strategies employed in the older population [33–35].

In addition to the increased comorbidities that can lead not only to polypharmacy, but also to increases in adverse effects and drug interactions, pharmacokinetics in older patients can vary (e.g. absorption, distribution, metabolism and elimination) in direct relation to age [32, 36]. Renal function may also be impaired, which may necessitate dose adjustments in accordance with creatinine clearance [37]. This is frequent in treatment with methotrexate, in which doses in older adults may be lower than those in younger patients. What this means is that full doses of conventional synthetic DMARDs, or even combinations of DMARDs, cannot be used, thus hampering optimal control of RA [38]. Such problems may lead to the need for a change in treatment, for example, switching from a TNFi to a different b/tsDMARD with another mechanism of action more suitable for use in monotherapy [39, 40]. Not only do conventional DMARDs require such adjustments, but so do other recently introduced agents such as JAKi, filgotinib and baricitinib, which can be administered with a lower daily dose in those aged >75 years compared with younger patients. Baricitinib can be administered at dosages of 2 mg/day and filgotinib at 100 mg/day versus 4 mg/day and 200 mg/day, respectively [41, 42].

Because of the importance of this issue, several studies have taken into account validated comorbidity indices for RA in order to determine the most appropriate drug choice for achieving good clinical control and/or good drug retention rates [43–46]. Therefore, the impact of comorbidities on the choice of treatment in the older population can lead to the scenario in which such comorbidities may necessitate multiple changes in the prescription of b/tsDMARDs, thereby affecting the D2TRA status [47, 48]. Moreover, these same comorbidities could limit therapeutic options, leaving clinicians unable to optimally control RA. For all these reasons, the risk/benefit factor of switching b/tsDMARDs in older patients must be carefully weighed now more than ever [49–52].

3.2 Safety of Using b/tsDMARDs in the Older Population

There is increasing evidence concerning the safety of specific RA therapies in the older population. In fact, safety data concerning biologics in older individuals are often similar to those in younger patients, and evidence on TNFi and abatacept has steadily increased. Tumour necrosis factor inhibitors have shown similar safety profiles in both older and younger patients [23, 24]. However, rates of serious adverse events (AEs), severe infections and cancer were slightly higher in the former, although this risk does not appear to increase with age and/or in relation to comorbidities [22, 53]. Abatacept is the biologic with the lowest AE discontinuation rates in the Japanese RA population [25, 26]. Rituximab, however, has been associated with numerically higher infection rates in older patients [27].

One of the AEs of greatest concern in patients receiving biologic therapies is the risk of infection, as infections are among the primary causes of premature mortality in this population. This risk may be higher in the older population because of the worsening of the immune system with age. In fact, a data analysis of the German Biologics Register (RABBIT) revealed an increased risk of infection in those aged older than 60 years with active disease, receiving high doses of corticosteroids and presenting with comorbidities such as pulmonary or renal disease. Thus, not only has age been shown to be an independent risk factor for the

development of infections in RA [54, 55], but the presence of comorbidities also then poses a risk factor for the onset of AEs [32, 56].

The case of JAKi seems to be more closely associated with varicella zoster virus risk in older versus younger patients [41, 57]. One concern regarding JAKi is data from a recently published study on the safety of tofacitinib [58]. This study concludes that the use of tofacitinib in patients >50 years of age and/or smokers and with at least one cardiovascular risk factor resulted in an increase of AEs such as major adverse cardiovascular events and malignancies with respect to TNFi. Thus, use of this drug in the older population should be restricted. Ultimately, these findings have also been extended to other JAKi and potentially limit treatment options in older patients.

Malignancies are also important in RA populations, as it has long been recognised that RA is associated with an increased risk of malignancy in general. Indeed, the immunological processes that occur during ageing and RA may contribute to an increased risk of cancer owing to the presence of chronic inflammation and defective DNA repair. Therefore, care must be exercised in treating RA in older patients as the risk of many types of cancer increases with age [59]. Indeed, it would be advisable to perform screening procedures in line with the well-known risk factors and with the health recommendations for cancer prevention for the general population. Examples of such screening in current medical practice include the following: fecal occult blood screening and colonoscopy for colorectal cancer (although incidence of the latter in RA is lower than in the general population); β2-microglobulin for haematological malignancies; determination of prostate-specific antigen for prostate carcinoma; mammography and screening for estrogen-dependent malignancies in postmenopausal women; and chest X-rays especially in patients with a long history of smoking [60]. Therefore, following the clinical context, this would be useful for tailoring treatment but currently there are no screening recommendations to apply more comprehensive cancer screening procedures in patients requiring b/tsDMARDs [61].

Nevertheless, the overall risks associated with biologic DMARDs, primarily TNFi, appear to be low after accounting for confounders. Moreover, as for non-TNF biologic DMARDs, no safety signals of concern have emerged in meta-analyses of clinical trial data, albeit within their limitations. There is a clear need for further investigation of the safety of all biologic DMARD treatments in regard to malignancies [62, 63]. This is also true of new targeted synthetic DMARDs, which require special vigilance owing to recently published data on the incidence of malignancies and cardiovascular events [58].

4 Assessment of Signs of Active/Progressive Disease in the Older Population

In addition to the potential limitations of using different b/tsDMARDs, another issue related to the definition of D2TRA concerns the persistent signs of disease activity and/or progression. In persons aged 65 years and older, patient assessments can prove more challenging and complex versus those conducted on younger patients. Therefore, following the recent publication of the EULAR Task Force on D2TRA, different points must be considered in order to provide holistic management for therapeutic decisions [64].

4.1 Disease Activity

As the erythrocyte sedimentation rate increases with age, it may interfere with interpretations of disease activity indices such as the Disease Activity Score-28, although the former (erythrocyte sedimentation rate) remains adequate for assessing disease activity in moderate-to-severe RA regardless of age or sex. However, remission rates could be underestimated in the older population because of this problem [14]. Baseline disease activity in late-onset RA seems to be higher than in young-onset RA, perhaps owing to the aforementioned elevation of the erythrocyte sedimentation rate; in fact, once corrected for age, there is little difference [65, 66]. However, the duration of disease in terms of therapeutic goal achievement is somewhat controversial, as it appears that a longer disease duration may influence the response to subsequent treatments [40, 67]. In addition, older patients generally score a higher visual analogue scale assessment as they age, which may render assessments of activity indices problematic, as the Disease Activity Score-28 parameter could be overestimated in terms of activity and therapeutic target achievement [68].

4.2 Functional Status

With regard to functional indexes, the health assessment questionnaire may vary with disease duration, presumably because the longer the duration, the worse the functional status, thus leading to a higher disability index. This may correlate with a higher number of painful joints, which ultimately translates into higher scores in the activity indexes as well. This is true not only for long-standing RA, but also for late-onset RA, in which the health assessment questionnaire both at baseline and at follow-up had a higher score [52, 69–71].

4.3 Radiographic Progression

Regarding radiographic progression, we found different data in the studies. Mueller et al. noted that late-onset RA may be more erosive at baseline, although there were no significant

differences in the variation of radiographic progression between young-onset and late-onset RA during the patient follow-up [65]. However, Krams et al. did find that age at RA onset was associated with greater radiological damage and the occurrence of at least one or more erosions during the 1–2 years of follow-up with respect to younger patients [70].

4.4 Tapering Corticosteroids

Late-onset RA is usually more prevalent in male individuals, with acute systemic onset and large joint involvement, which may mimic polymyalgia rheumatica [72]. In this case, older patients may initially require treatment with higher doses of corticosteroids in order to alleviate symptoms more quickly. Although, as we have seen, DMARDs are generally well tolerated in the older population, these patients may be exposed to a more frequent use of corticosteroids in monotherapy compared with younger individuals. This may lead to a misclassification of such patients as D2TRA because of the inability to taper corticosteroids below 7.5 mg/day of prednisone (or equivalent) [39, 73, 74].

5 Management of Signs or Symptoms is Perceived as Problematic by the Rheumatologist and/or the Patient

Clinical guidelines have played an essential role in improving healthcare for people with RA; however, the application of these guidelines may not take into account the biological and psychosocial changes associated with ageing. Older patients and physicians often have different priorities regarding treatment and health outcomes. Patients may be more focused on current symptom control and, especially older patients, complain of symptoms that might not even been related to the rheumatic disease itself. Therefore, this change in patients' priorities, in addition to comorbidities, treatment idiosyncrasies and the potential difficulties assessing disease activity assessment in older patients is important in the management of the disease. We now focus on these factors such as psychosocial issues, outcome values, self-efficacy expectancies, patient education and adherence to treatment [75].

While these factors can play various roles in both younger and older patients, in the former (late-onset RA and established RA diagnosed in youth), treatment management can be complicated by the frailty related to ageing and the onset of geriatric syndromes, leading to an overall sense of a lack of control of the disease [76]. The presence of sarcopenia, a syndrome involving a progressive decrease in skeletal muscle mass and strength, which is associated with poor physical condition, fatigue, functional impairment and disability, leads to high morbidity and mortality in these patients [77]. This syndrome is associated with both advanced age and systemic inflammation, while RA per se is a major contributing factor to physical disabilities in patients and is associated with age. Therefore, sarcopenia and inflammation can be regarded as the biological underpinnings of physical frailty. Frailty is associated with older adults who appear more fragile than their age-matched counterparts, despite sharing similar comorbidities, demographics, sex and age [78, 79]. Therefore, it is necessary to take into account not only ageing (understood as age >65 years), but also frailty as an indicator of a state of greater vulnerability.

As we have seen, long-standing RA and the persistence of high disease activity linked to ageing can lead to greater degrees of disability. Approximately 10% of older patients have difficulty performing the basic activities of daily living and experience functional impairment [76]. Patients with RA are associated with a seven-fold greater risk of disability than patients of the same age and sex [80]. This, together with age and the onset of geriatric syndromes such as depression, frailty, cognitive impairment, falls and/or nutritional deficits, contributes to a lower success rate in the treatment of RA and a tendency to depression in these patients [76, 81–83].

Depression is a frequent comorbidity in patients with RA, particularly in older patients in which it is coupled with geriatric syndromes. Indeed, cognitive impairment can affect compliance and subsequently the response of older patients to treatment [84, 85]. In fact, some studies have proposed interventions focused on the outpatient management of older patients and multi-morbidities given that frailty and cognitive impairment may be present. These studies have mainly involved comprehensive multidisciplinary reviews by a nurse, pharmacist and physician every 6 months [86, 87] or by primary care teams [88, 89]. In addition, a recent pilot study tried to improve the efficiency of care provided based on patient goals and medication reviews [90]. However, the results of these studies were not entirely promising because of the complexity of implementing these systems.

However, there are data in the literature regarding rheumatology nursing consultations and the resulting quality from a patient standpoint [91, 92]. Thus, in older patients it would be very interesting to attempt this type of intervention in which support is provided to both the patient and his or her close environment (family and/or social) in the management of anti-rheumatic therapies (at least at the beginning of treatment). Education about the disease and the administration route of DMARDs, always tailored to the individual patient and taking into account the burden of disease and concomitant treatments, can be essential to optimising treatment and ensuring compliance to the greatest degree possible.

Therefore, physicians must take into account all of these psychosocial factors. Shared decisions, explaining treatment expectations and providing information on practical aspects

can improve adherence. Although the lack of adherence is not directly related to age, a physician's manner and explanations to older patients, as well as other non-pharmacologic interventions, may improve treatment success in this population [93–95].

6 Conclusions

Treatment of RA in the older population should be carried out in the same manner as in younger patients in accordance with the treatment-to-target strategy. However, the associated comorbidities, polypharmacy-related issues and risk profiles of older patients should be carefully assessed in order to treat RA. Care should be taken in drug selection and dose adjustments to ensure adequate treatment. In addition, an inflammatory RA activity assessment is essential prior to any DMARD adjustments. With regard to osteoarthritis, other physiological conditions and geriatric syndromes that may impact the patient's quality of life, in the older population, it is crucial to better incorporate non-pharmacological actions in order to improve and optimise the treatment of functional disability, pain and fatigue, including physical, physiological, educational exercise and self-management interventions. Older patients present a group of particular concern in D2TRA, as their age-related condition can lead to a misclassification into the D2TRA group, owing to the need for frequent treatment changes in response to comorbidities or adverse effects. In addition, the use of b/tsDMARDs in the older population is constrained by the many issues discussed above and must be undertaken with great caution.

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