



Review

Does early treatment of Rheumatoid Arthritis lead to a better long-term prognosis?

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ABSTRACT

Time is a crucial dimension in most chronic diseases, especially in inflammatory rheumatic disease, which it affects in many ways. Early treatment in rheumatoid arthritis (RA) is an essential issue, as joint damage occurs within the first weeks or months of the disease process and inflammatory activity maintained over time is responsible for all of the consequences of the disease. The introduction of new drugs with faster and more effective action, such as tumor necrosis factor (TNF) inhibitors, has represented a major shift in the strategy of RA treatment, allowing the clinician to aim for remission and prevention of structural damage as realizable goals.

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¿El control precoz de la artritis reumatoide augura un mejor pronóstico a largo plazo?

RESUMEN

El tiempo es una dimensión de importancia capital en la mayoría de las enfermedades crónicas y, especialmente, en las enfermedades reumáticas inflamatorias, donde influye en muchos aspectos. El tratamiento precoz de la artritis reumatoide es esencial, debido a que el proceso destructivo articular comienza muy pronto, en las primeras semanas o meses, y la actividad inflamatoria mantenida en el tiempo es responsable de todas las consecuencias de la enfermedad. La introducción de fármacos nuevos con una acción más rápida y eficaz, como los fármacos biológicos anti-TNF, ha supuesto un cambio radical en la estrategia de tratamiento de la artritis reumatoide, permitiendo, incluso, que la inducción de la remisión y la detención del proceso destructivo articular sean unos objetivos posibles.

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Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that affects 0.5% of the Spanish population.¹ Although in the '60s it was considered a relatively benign disease, in recent decades it has been shown that its natural evolution leads to not only major radiological and functional deterioration, but also a decline in the quality of life and increased morbidity and mortality,² which does not correspond to the old concept of 'benign'.

Although radiological and functional deterioration progresses slowly over the course of the disease, it has been found that the maximum speed of development of structural damage occurs during the first years,^{3,4} so it is important to approach the disease early, and

the outcome has improved considerably due both to the availability of new drugs and the development of more effective therapeutic strategies, such as early and aggressive treatment, the combination of drugs, steroids or close monitoring of disease.⁵ One of the most important therapeutic principles is intense and early treatment, which has been particularly highlighted in the recent EULAR guidelines for management of arthritis of recent onset^{6,7} (Table 1).

The meaning of time in the treatment of RA has at least three dimensions, and although conceptually different, have similar prognostic significance. The first aspect is the time it takes to start treatment with disease modifying drugs (DMARDs) as the joint destructive process begins very early, in the first weeks or months of disease. In mouse models, activation of osteoclasts, which precedes erosion is detected even before clinical symptoms are evident⁸ and in early RA of less than 6 months, radiological erosions can be detected

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Table 1

EULAR recommendations for management of recent onset arthritis.⁶ DMARD indicates disease modifying drugs; RA, rheumatoid arthritis

<p>Patients with arthritis of more than one joint should be referred and assisted by the rheumatologist in the first 6 weeks after onset of symptoms</p> <p>Physical examination is the method of choice to detect synovitis. In doubtful cases, ultrasound, power Doppler and magnetic resonance imaging may be useful</p> <p>To exclude other rheumatic diseases, a careful history and physical examination must be performed. The following tests must be performed: complete blood count, transaminases, urinalysis, and antinuclear antibody titers</p> <p>In all patients with recent arthritis onset, the rheumatologist must measure the number of tender and swollen joints, ESR or CRP, rheumatoid factor, anti-CCP antibodies and search for radiological erosions</p> <p>Patients at high risk of persistent disease and/or erosive arthritis, but that do not meet the classification criteria for established RA, should receive DMARD therapy as soon as possible</p> <p>It is very important to inform the patient about the course of the disease and its treatment. Educational programs can be used to improve disability and help support work activity</p> <p>The prescription of NSAIDs should be considered in symptomatic patients after assessing the gastrointestinal, renal and cardiac risk</p> <p>Systemic corticosteroids reduce pain and inflammation and should be considered (temporarily) as part of combination therapy with DMARDs. Corticosteroid injections should be considered to improve local pain and inflammation</p> <p>Among the DMARDs, methotrexate is the first choice to be used in patients at risk of developing persistent disease</p> <p>The main goal of DMARD therapy is to achieve remission. Regular monitoring of disease activity and adverse effects of medication (DMARD, including biologics), will help in making decisions and in changing the therapeutic strategy</p> <p>Non-pharmacological interventions such as dynamic exercises, occupational therapy and hydrotherapy may be recommended</p> <p>Disease monitoring should include: tender and swollen joint count, global assessment of disease by the physician and patient, ESR and CRP. One must assess arthritis activity every 1-3 months, until remission has been achieved. Joint damage should be evaluated by radiographs of the hands and feet every 6-12 months during the early years. The HAQ can be used to assess disease activity and monitor structural damage</p>

in 8%-40% of patients, and in up to 45%-72% with more sensitive imaging techniques such as MRI.⁹ Therefore, the sooner an effective treatment is started, the sooner progression of the disease will stop or slow and existing damage may stop or progress more slowly. The benefits of early treatment compared with later therapy have been demonstrated with all anti-rheumatic drugs such as gold salts,¹⁰ sulphasalazine,^{11,12} hydroxychloroquine, methotrexate¹³ or drug combinations.¹⁴ However, an important aspect, albeit controversial, is the duration of a period that is closely linked to the existence of a so-called “window of opportunity”.⁶ This hypothesis suggests that there exists a short period of time at the start of the inflammatory process in which effective treatment could substantially alter the course of the disease and even lead to healing. An appropriate therapeutic intervention at this time will have a far greater impact on outcome, such as structural damage progression or the appearance of remission, than the same intervention initiated later on.¹⁵

In RA there are several features that have been associated with a worse prognosis^{3,16} (Table 2). Some are directly dependent on the disease and, therefore, slightly modified, such as the initial number of swollen joints, presence of rheumatoid factor and antibodies to citrullinated peptide, elevated acute phase reactants, the initial existence of early radiographic erosions, a high degree of initial disability and the presence of HLA shared epitope,¹⁷ while another, as or more important than the above, is the time since the onset of disease until treatment begins.^{8,18,19} It has been shown in two meta-analysis that the duration of the disease at the time of the introduction of the first DMARD is the main factor predicting treatment response²⁰ and that the early use of DMARDs in recent onset RA is capable of achieving a significant decrease of the progression of structural damage in the medium and long term.²¹ As the prognosis depends largely on early treatment (ideally before the onset of radiological consequences), early referral to a specialist from primary care and

Table 2

Predictors of progression of disease in recent onset rheumatoid arthritis

<p>Acute phase reactants (ESR, CRP)</p> <p>Rheumatoid factor</p> <p>Anti-CCP antibodies</p> <p>Radiological erosions</p> <p>Duration of symptoms</p> <p>High number of tender and swollen joints</p> <p>Smoking</p> <p>HLA DRB1*04 genes</p>
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early diagnosis are key,^{7,22} and this reason alone justifies the existence of clinics aimed at addressing recent onset arthritis.²³⁻²⁵ According to the latest recommendations by EULAR, a patient with arthritis of more than one joint should be treated by a specialist within the first 6 weeks after onset of symptoms (Table 1).⁶

The second aspect is related to the time the inflammatory process has been present. Sustained activity is the cause of all articular and extraarticular consequences of RA²⁶ and it has been shown, unequivocally, that there is a very close relationship between the duration and amount of inflammatory activity, as measured by classic indices such as DAS or SDAI, and the extent of structural damage.²⁷ This relationship is both for the joint cartilage damage, assessed by the reduction of joint space, as for bony destruction, which is reflected in the number and size of erosions. These two processes, although closely related, are pathogenetically distinct and can be distinguished by detailed radiological indices and may be affected differently by the treatments.²⁸ Although conventional radiography remains the standard for the assessment of joint damage, new imaging techniques such as MRI and ultrasound can not only define better the structural lesions (more sensitive in detecting bone erosions), but also allow direct visualization of synovial inflammation of the tendons and detect varying degrees of synovial inflammation even in asymptomatic joints.²⁹⁻³¹

Disability is one of the most important complications of RA and one of the more difficult to assess, since it has various components. Part of disability is not directly related to joint involvement in RA and is due to factors that may or may not be related, such as age, gender, social and psychological factors, muscle strength and comorbidities.³² Another part of disability, specific joint involvement, has at least two components, one related to inflammatory activity and, therefore, reversible, while the other is related to joint damage and, therefore, irreversible.^{7,33,34} In recent onset arthritis, disability is fundamentally related to inflammatory activity, while in established RA, the permanent structural damage is a major component, so the only way to prevent permanent disability is to effectively treat and control inflammatory activity. The duration of the disease has a similar relationship with disability, as it is a reflection of activity during time,³⁴ so that in disease over 10 years since onset, the ability to detect significant changes in the HAQ disability questionnaire³⁵ is very limited. Disability has major implications for patients, since it is the factor that most consistently predicts serious outcomes such as costs or mortality.³⁶

Another lesser-known consequence of sustained inflammatory activity in RA is increased mortality due mainly to comorbidities and especially to cardiovascular diseases. In RA, the systemic inflammatory process is key to the accelerated development of atherosclerosis.^{37,38} These patients have more prevalent cardiovascular disease than the general population, manifested in a less evident manner and associated with increased mortality after a first cardiovascular event (Table 3). This excess cardiovascular mortality has been observed in patients with early RA in primary care.³⁹ The measurement of the size of the intima in the carotid area is an index that has been accepted as evidence of subclinical atherosclerosis⁴⁰ and allows for measuring

Table 3
RA and cardiovascular disease (CV). RA indicates rheumatoid arthritis

1. Increased prevalence of CV disease
<ul style="list-style-type: none"> • The presence of CV risk factors associated with RA and independent of traditional risk factors Dependent on the inflammatory process Dependent of RA in particular • Accelerated atherosclerosis A condition involving multiple vascular territories Influence of disease severity Affection at different stages of RA: preclinical, early and evolved • CV mortality correlates with RA activity Influence of effective treatment in CV mortality
2. Increased cardiovascular mortality
<ul style="list-style-type: none"> • Reduction of screening and treatment of traditional CV risk factors in patients with RA • Underdiagnosed CV disease • Larger extension of CV disease • Increased mortality after the appearance of the first CV event

cardiovascular risk in patients with RA, correlated with increased C-reactive protein, cytokines, adhesion molecules, smoking and age at onset. The early and effective treatment of the inflammatory process determines a regression of intimal thickness in the area of the carotid artery induced by RA and improves prognosis.^{41,42} Finally, the prevalence of lymphoproliferative disorders is also more common in RA and is associated with the degree of joint swelling over time.⁴³ Besides the direct impact on patient health, RA has important economic consequences in both direct and indirect costs, which are the result of sustained activity and relate directly to disability measured by HAQ.⁴⁴

The last but not least aspect related to time, is the speed of therapeutic response. Until recently, the main objective in the management of RA was to reduce the impact the disease had on patients, including reducing pain and inflammation. With the emergence of new strategies and therapeutic targets, the goal of treatment has changed substantially^{5,7} and now should be the early suppression of inflammation and, ideally, the induction of remission to prevent structural damage, disability and comorbidities of long-term illness. In both clinical trials and observational studies, the therapeutic response, assessed by the possibility of reaching minimal inflammatory activity⁴⁵ (Table 4) depends, as discussed above, on the duration of arthritis²⁰ and also, very importantly, on the baseline inflammatory activity.^{46–48} Both in clinical trials and observational studies,⁴⁹ the therapeutic response of recent onset RA is clearly superior to that of established RA and the probability of achieving remission and/or minimal inflammatory activity a year after starting treatment directly depends on the level of baseline activity,⁵⁰ which justifies the early use of all drugs and strategies to prevent inflammatory activity in RA from reaching very high levels that would be difficult to monitor. Admittedly, there is a lag between the disappearance of clinical symptoms and improvement in inflammatory activity, which can be detected by highly sensitive imaging tests such as ultrasound,³¹ and that clinically translates to the appearance of erosions in patients in remission. This finding is surprising and is often a result of inflammatory activity that preceded remission,⁵¹ so the faster and more effectively we reduce clinical activity, the lesser the permanent consequences. It has been shown that no radiological progression occurs with methotrexate if remission was achieved in the first 3 months of treatment, while concomitant treatment with an anti-TNF drug was enough to reach low activity at 3 months.⁵² The speed and quality of the initial response predicts outcome more satisfactorily, since the duration of disability is lower and therefore associated to fewer job loss^{53,54} and improvement is more likely to be maintained in the long-term.⁵⁵

Table 4
Parameters of the WHO/ILAR to define minimal inflammatory activity in RA. Must meet at least five of the seven criteria

Pain visual analogue scale (0–10)	≤ 2
Number of painful joints (0–28)	≤ 1
Number of swollen joints (0–28)	≤ 1
HAQ (0–3)	≤ 0.5
Disease activity defined by the physician (0–10)	≤ 1.5
Disease activity defined by the patient (0–10)	≤ 1.5
ESR	≤ 20 mm

If the speed of the clinical effect is important, we must know how to achieve a clinically significant effect as soon as possible. The classic DMARDs, such as methotrexate (in a pattern of rapid dose escalation) and leflunomide, are still the initial treatment in most patients,^{56,57} being able to show a clinically relevant effect between 4 and 6 weeks,⁵⁸ but other DMARD such as sulphasalazine or antimalarials have a slower effect and a higher frequency of treatment failure. That is why before the onset of sustained inflammatory activity, biological therapy, usually in combination with traditional DMARDs, is the most convenient, because it also has a faster and more intense onset than classic DMARD.⁵⁹ One of the characteristics of anti-TNF biologics in combination with methotrexate is the speed of clinical response, which is higher than that of methotrexate alone and can already be seen in the first 2 weeks of treatment, as has been demonstrated with adalimumab in the PREMIER study,⁴⁷ with infliximab in the ASPIRE study,⁶⁰ with etanercept in the ERA study⁶¹ and with certolizumab pegol in a paper published by Keystone.⁶² The results of these studies support the early and intense treatment of RA, as well as the superiority of the combination of methotrexate and anti-TNF versus methotrexate alone in terms of controlling symptoms and preventing structural damage and disabilities.^{63,64} Inhibition of the progression of structural damage can be observed even at 16 weeks of starting anti-TNF therapy, as demonstrated⁶⁵ with the anti-TNF certolizumab pegol (PEGylated). The speed of response of anti-TNF can also be seen in the results of the BeSt study⁶³ which compared four treatment strategies in patients with recent onset arthritis, in sequential monotherapy, additive treatment (*step-up regimen*), *step down* combination therapy or COBRA type treatment (methotrexate, sulphasalazine and high doses of prednisone 60 mg/day at the beginning, lowered in 6 weeks to 7.5 mg until suspension at 28 weeks) and finally initial treatment with infliximab plus methotrexate. The improvement in the variables related to clinical activity, quality of life, HAQ and radiological progression were higher in the groups that had a more rapid initial improvement (groups 3 and 4) compared with initial monotherapy treatment groups (Groups 1 and 2) who had a slower response. The utility of high doses of prednisone, included in a combination treatment for inducing remission in RA patients, was demonstrated in the COBRA study. Despite the recognized effectiveness of treatment, several reports demonstrate its limited use in clinical practice, due to the complexity of administration and the reluctance of patients.^{64,66} In general, it is recognized that long term high-dose steroid therapy should be avoided, but low doses (5 mg of prednisone) in addition to treatment with DMARDs can be very effective when osteoporosis prevention is also performed. However, the duration of low-dose steroid therapy in the long term remains a matter of controversy.^{6,7}

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