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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Early treatment (ideally before the onset of radiological erosions) is crucial, as it can stop or slow structural damage and prevent high disability. Non-pharmacological interventions such as dynamic exercises, occupational therapy, and hydrotherapy can be beneficial.

### Table 1

**EULAR recommendations for management of recent onset arthritis**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indications</th>
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<tr>
<td>Disease modifying drugs</td>
<td>RA, rheumatoid arthritis</td>
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**Physical examination** should be performed by the rheumatologist in the first 6 weeks after onset of symptoms. The examination should include assessment of the gastrointestinal, renal, and cardiovascular systems. Systemic corticosteroids can be used to control pain and inflammation, and methotrexate is the first-choice treatment for patients at risk of developing persistent disease.

**Disease monitoring** should include tender and swollen joint count, global assessment of disease, and measurement of ESR and CRP. The number of tender and swollen joints, HAQ, and CRP are important for assessing the disease activity and monitoring structural damage.

### Table 2

**Predictors of progression of disease in recent onset rheumatoid arthritis**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Acute phase reactants (ESR, CRP)</td>
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<tr>
<td>Rheumatoid factor</td>
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<tr>
<td>Anti-CCP antibodies</td>
<td></td>
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<tr>
<td>Radiological erosions</td>
<td></td>
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<tr>
<td>Duration of symptoms</td>
<td></td>
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<tr>
<td>High number of tender and swollen joints</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
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<tr>
<td>HLA DRB1*04 genes</td>
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</table>

Early diagnosis is key, and this reason alone justifies the existence of clinics aimed at addressing recent onset arthritis. According to the latest recommendations by EULAR, a patient with arthritis more than one joint should be treated by a specialist within the first 6 weeks after onset of symptoms (Table 1).

The second aspect is related to the time the inflammatory process has been present. Sustained activity is the cause of many articular and extraarticular consequences of RA, 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.

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. Although conventional radiography remains the standard for the assessment of joint damage, new imaging techniques such as MRI and ultrasound cannot 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.

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.

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. 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, so that in disease over 10 years since onset, the ability to detect significant changes in the HAQ disability questionnaire 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.

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. These patients have more prevalent cardiovascular disease than the general population, manifested in a less evident manner and allowing for measuring the measurement of the size of the intima in the carotid artery is an index that has been accepted as evidence of subclinical atherosclerosis and allows for measuring
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. \(^6\) Finally, the prevalence of lymphoproliferative disorders is also more common in RA and is associated with the degree of joint swelling over time. \(^4\) 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. \(^5\)

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 \(^3\) 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 activity \(^6\) (Table 4), depends, as discussed above, on the duration of arthritis \(^2\) and also, very importantly, on the baseline inflammatory activity. \(^6\) Both in clinical trials and observational studies, 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, \(^5\) 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, \(^3\) 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, \(^5\) 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. \(^5\)

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 \(^5\) and improvement is more likely to be maintained in the long-term. \(^5\)

### Table 3

<table>
<thead>
<tr>
<th>RA and cardiovascular disease (CV)</th>
<th>RA indicates rheumatoid arthritis</th>
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| 1. Increased prevalence of CV disease | ● 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 | ● 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 |

### Table 4

<table>
<thead>
<tr>
<th>Parameters of the WHO/ILAR to define minimal inflammatory activity in RA. Must meet at least five of the seven criteria</th>
</tr>
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<tbody>
<tr>
<td>Pain visual analogue scale (0-10)</td>
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<tr>
<td>Number of painful joints (0-28)</td>
</tr>
<tr>
<td>Number of swollen joints (0-28)</td>
</tr>
<tr>
<td>HAQ (0-3)</td>
</tr>
<tr>
<td>Disease activity defined by the physician (0-10)</td>
</tr>
<tr>
<td>Disease activity defined by the patient (0-10)</td>
</tr>
<tr>
<td>ESR</td>
</tr>
</tbody>
</table>

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 \(^3\), \(^6\) being able to show a clinically relevant effect between 4 and 6 weeks, \(^3\) 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. \(^5\) 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, \(^6\) with infliximab in the ASPIRE study, \(^6\) with etanercept in the ERA study \(^6\) and with certolizumab pegol in a paper published by Keystone. \(^5\) 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. \(^6\) Inhibition of the progression of structural damage can be observed even at 16 weeks of starting anti-TNF therapy, as demonstrated \(^2\) with the anti-TNF certolizumab pegol (PEGylated). The speed of response of anti-TNF can also be seen in the results of the BeSt study \(^5\) 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. \(^3\)

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. \(^5\)

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References


