How Do We Evaluate an Inadequate Response in a Patient With Rheumatoid Arthritis in the Clinical Praxis?

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Rheumatoid arthritis (RA) is a chronic disease that particularly affects the joints, causing their destruction, changes in its functional capacity and considerably compromising the quality of life. It is known that early treatment can reduce structural damage and improve the disability in the long term, but the optimal therapeutic strategies are still not universally accepted. As with diabetes and hypertension, strict control of the disease is required, with the objective of achieving no disease activity, which may be seen as a remission, or if this is not possible, to keep the inflammatory activity as low as possible so that the unfavourable consequences, such as the articular damage process and the risks that the patients assume deriving from treatment, do not occur. The improvement criteria of the American College of Rheumatology (ACR) are useful for comparing the efficacy of treatment in clinical trials, but they must not be used as a therapeutic objective, since they do not evaluate the final activity, which can be as important as having an improvement. To evaluate the response, the most logical and convenient for the doctor is to use the same tools that are used to evaluate the activity of the disease in clinical practice, such as the DAS and SDAI activity scores. Some limits which separate the different levels of activity have been proposed to improve their interpretation and establish therapeutic objectives. The categorisation into classes according to activity is important for starting or changing treatment (when it is moderate or high) and to define stages of conceptually different activity (activity or remission). The cut-off points that separate these categories were proposed years ago when the therapeutic possibilities of RA were limited and their long term consequences were not known. The therapeutic objective of remission or lower activity is much easier to achieve these days, therefore the therapeutic categories need to be reconsidered and the definition of lower activity levels as a potential objective. Nowadays, to assume moderate or high activity as a result of treatment is unacceptable, particularly when our therapeutic arsenal is already considerable and strategies and therapeutic combinations have been proposed which have demonstrated higher efficacy with tolerable risks. Although changes happen gradually in all aspects of life, there is no reason not to accept remission of RA as not only a desirable objective, but also an achievable one.

Key words: Rheumatoid arthritis. Activity indexes. Improvement indexes. DAS. SDAJ. ACR.

¿Cómo se evalúa una respuesta inadecuada en un paciente con artritis reumatoide en la práctica clínica?

La artritis reumatoide (AR) es una enfermedad crónica que afecta sobre todo a las articulaciones y produce destrucción articular, alteración de la capacidad funcional y compromete la calidad de vida de manera considerable. Se sabe que el tratamiento precoz es capaz de reducir el daño estructural y mejorar a largo plazo la discapacidad, pero las estrategias terapéuticas óptimas todavía no están unánimemente aceptadas. Igual que en la diabetes o la hipertensión, en la AR es necesario un control estrecho de la enfermedad con el objetivo de lograr la ausencia de actividad, que se puede entender como remisión o, si no es posible, el mantenimiento de una actividad inflamatoria lo más baja posible, de modo que no origine consecuencias desfavorables, como la progresión del daño articular, y que los riesgos derivados del tratamiento sean asumibles por el paciente. Los criterios de mejoría de la ACR (American College of Rheumatology) son útiles para comparar la eficacia de tratamientos en ensayos clínicos, pero no se deben utilizar como objetivo terapéutico ya que no valoran la actividad final, que puede ser importante a pesar de haber tenido mejoría. Para valorar la respuesta, lo lógico y más cómodo para el médico, es utilizar las mismas herramientas que se

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utilizan para valorar la actividad de la enfermedad en la práctica clínica, como son los índices de actividad DAS y SDAI. Para mejorar su interpretación y establecer los objetivos terapéuticos se han propuesto unos límites que separan niveles de actividad diferentes. La categorización en clases según la actividad es importante para iniciar o cambiar un tratamiento (en caso de ser alta o moderada) y para definir estados de actividad conceptualmente diferentes (actividad o remisión). Los puntos de corte que separan estas categorías se propusieron hace años cuando las posibilidades terapéuticas de la AR eran limitadas y no se conocían sus consecuencias a largo plazo. En la actualidad el objetivo terapéutico de la remisión o la baja actividad es mucho más fácil de conseguir, por lo que es necesario una reconsideración de las categorías terapéuticas y definir niveles de actividad más bajos como objetivo potencial. Hoy en día asumir una actividad moderada o alta como resultado de un tratamiento es inaceptable, sobre todo cuando nuestro arsenal terapéutico es ya considerable y se han propuesto estrategias y combinaciones de tratamiento que han demostrado mayor eficacia con unos riesgos tolerables. Aunque en todos los aspectos de la vida los cambios se introducen de manera paulatina, ya no hay ninguna razón para no aceptar la remisión en la AR como un objetivo no solo deseable sino alcanzable.

Palabras clave: Artritis reumatoide. Índices de actividad. Índices de mejoría. DAS. SDAI. ACR.

Rheumatoid arthritis (RA) is a chronic illness that affects joints and leads to their destruction and an alteration in the functional capacity, with a great impact on the quality of life of the patient and has considerable economic and social consequences. The illness characteristically progresses in episodes, alternating phases of different activity that force the chabge in therapeutic attitudes. With time, in the majority of patients there exists a psychological process of adaptation to illness and tolerance to pain that must no be interpreted as improvement[1] and that obliges the physician to continuously evaluate in an objective fashion the situation of the patient to lessen the possibility that the illness is insufficiently treated.

It has been proven that early treatment permits the reduction in structural damage and an improvement of incapacity in the long-term, but the way in which this is achieved is still not unanimously accepted.[2] Whatever the line of treatment chosen, one must take into account that RA is a very heterogeneous disease and the response to treatment is unpredictable.

As is the case with diabetes or hypertension, a strict control of illness is necessary in RA to avoid the catastrophic long-term consequences.[3] This means that every treatment has to be directed to obtain predetermined objectives: absence of activity, that can be understood as remission or, if this is not possible, to maintain inflammatory activity as low as possible without it causing unfavorable consequences. The discussion as to what constitutes an insufficient response is, in reality, a discussion on the measure of inflammatory activity of RA and the limits of activity that we have previously set as acceptable. All that is not within this set must be interpreted as an insufficient response and merits further interventions for them to be attainable.

In all chronic diseases it is necessary to evaluate response to treatment and the logical and easiest way for the physician to do this is to use the same tool that are employed in clinical practice. Diabetes and hypertension have an objective variable that allows their easy measurement, something that does not happen in RA. In RA, both in clinical trials and in everyday practice, there has been a multitude of measurements employed that make comprehension and homogenization of results very difficult.[4] For consistency and uniformity, during the 1990´s, several regulatory agencies such as the American College of Rheumatology (ACR) or the European League against Rheumatism (EULAR), accepted the core set of measurements that must always be evaluated[5-7] and that include the quantification of tender and swollen joints, the evaluation of pain and disease activity by the patient and by the physician, the measurement of functional capacity and an acute phase reactant. The identification of these variables was the result of a scientific process in which the data derived from patients was analyzed according to the filtering criteria of OMERACT.[8,9]

Each of these variables reflect different aspects, even though they are related, of the disease process, but there is no one variable that identifies, in a trustworthy manner, the inflammatory activity nor is useful for measuring the response to treatment, making it necessary to measure several variables simultaneously. Simultaneous evaluation leads to statistical and methodological errors that make interpretation difficult and that are partly solved with the use of indexes.[10] The indexes integrate several measures in one value that represents them, avoiding the multiplicity of variables, eliminating redundancy and the less representative values, improving the validity and the sensibility by combining clinically important variables, increasing the consistency of evaluation between different situations and increasing the power of discrimination therefore allowing a reduction in sample size. In contrast, their comprehension is difficult or, put in another way, its difficult to understand why some variables are included and others are not, and what the method employed to determine their specific weight is, because not all variables in the indexes have the same weight in the final result.[11]

Although some of these indexes have been used in the clinical practice for some years to evaluate the evolution

of the patients, their use was developed as a substantial way in which to define improvement in clinical trials where the proportion of patients responding to treatment, compared to the control group, is a measure of efficacy.

The Paulus criteria were proposed in 1990[12] and required an improvement of at least 20% in 4 of 6 variables, that included erythrocyte sedimentation rate (ESR), tender and swollen joints, morning stiffness, and the global health evaluation by the patient and the physician. This index adequately discriminated between the patients treated with placebo and antirheumatic disease modifying therapy (DMARD) and were used for many years as a measurement of efficacy. The ACR improvement criteria, as is the case with the Paulus criteria, evaluate therapeutic response but do not measure absolute activity values, only their percentage changes. An ACR20 requires an improvement of, at least, 20% in the number of tender and swollen joints and, at least, a reduction of 20% in 3 of the 5 remaining variables that compose the *core set* of measurements. ACR20, 70, or 90 require, at least, a reduction in 50, 70, or 90%, respectively. Nonetheless, a patient with an improvement in the ACR criteria may not have a clinically satisfactory response. For example, if a patient has 20 tender and swollen joints beforte treatment and a clinically significant reduction of 50% is achieved, she will have 10 tender and swollen joints, which is clearly clinically insufficient. If to this we add the complexity in its calculation, we can begin to understand why they are not useful in the daily clinical practice.[13] One modification of these criteria is the ACR-N,[14] that tries to estimate a quantitative improvement over a categorical one, but its use is very limited and has a very relative value because of its development problems as well as the calculations needed and its interpretation.[15]

At the beginning of the 1990´s the Disease Activity Score (DAS) was proposed,[16] developed in a cohort of RA patients who had a relatively short time since onset of disease and a short evolution. It classified patients in 2 groups: high and low activity, using as a pattern the physicians decision to initiate, not modify or reduce the treatment with DMARDs. Using a discriminative analysis, variables were selected that differentiated as best as possible the 2 situations of activity and, by logistical regression, a mathematic formula was obtained, explaining the clinical activity. In its original version, its composed by a measure of joint tenderness (Ritchie index oscillating between 0 and 78), a swollen joint index in 44 joints (0 to 44), the ESR and the patients global activity evaluation in a visual analog scale (0-100 mm); as a consequence of the statistical method employed for its development, it is derived from a complex formula. A few years later the whole process was repeated with the same cohort, but with a mean time since onset of 9 years and gave a result that was practically identical (Table 1).[17]

TABLE 1. Formulas for the Calculation of DAS, DAS28, and DAS-PCR Scores*

$DAS = 0.54 \times \sqrt{\text{I. Ritchie}} + 0.04 \times SCJ\ (44) + 0.72 \times Ln\ (ESR) + 0.013 \times (GEPatient)$
$DAS28 = 0.56 \times \sqrt{TJC\ (28)} + 0.28 \times \sqrt{SCJ\ (28)} + 0.70 \times Ln\ (VSG) + 0.014 \times (GEPatient)$
$DAS28\ CRP = 0.56 \times \sqrt{TJC\ (28)} + 0.28 \times \sqrt{SJC\ (28)} + (0.36 \times Ln\ [CRP\ mg/L] + 1) + 0.014 \times (GEPatient)$

*CRP indicates C reactive protein; SJC, swollen joint count; TJC, tender joint count; ESR, erythrocyte sedimentation rate; GEPatient, global evaluation by the patient.

As the original DAS uses joint indexes that are seldom employed in the clinical practice, the process was repeated using reduced 28 joint indexes, giving as a result the DAS28 (Table 1),[17] being more useful because it uses easier and faster to do joint counts without the loss of precision.[18] As is the case with the original DAS, apart from the tender and swollen joint count, it includes the ESR and the disease activity evaluation by the patient in a complex formula. The values for the DAS and the DAS28 cannot be directly compared but there exists a formula for their transformation.[19] There are modifications to the DAS employing C reactive protein (CRP) instead of ESR (Table 1),[15] developed to be used in clinical trials where CRP is determined by a central laboratory. This index has been developed as a mathematical approximation to the DAS and does not derive from patients nor has it been validated, making its use and interpretation matter of some controversy.

Another index has recently been proposed, the SDAI (Simplified Disease Activity Index),[20] derived from and index that was developed or the evaluation of reactive arthritis.[21] This index has the advantage that it does not need a complex mathematical formula for its determination, depending only on a simple arithmetic sum of the number of swollen and tender joints, using the reduced 28 joint index, the evaluation of activity as determined by the patient and the physician (measured as 0 to 10) and the CRP (mg/L). The inclusion of CRP instead of ESR is based on the fact that CRP is a measure of inflammation that is more precise and than ESR, has been associated with structural damage in a more consistent manner and is less influenced by other variables, such as anemia and rheumatoid factor.[22] As is the case with DAS, there are modifications to the SDAI, in particular one that does not include CRP, the Clinical Disease Activity Index (CDAI)[23] and that was developed for use in cases in which there is no access to the acute phase reactants in an immediate manner. The SDAI was developed and validated in different clinical studies and has been validated by other independent groups posteriorly.[22] In the original study, the correlation with

the baseline DAS28 and after treatment was superior than 0.9, giving it the same value to measure inflammatory activity in RA. All of these variables, DAS and SDAI, are included in the core set of variables recommended by the ACR and EULAR, and both indexes have shown that they are valid and useful to measure the activity and response to treatment.

To improve their interpretation and establish the therapeutic objectives it is necessary that the activity indexes establish some limits to identify the patients with different degrees of activity. The categorization into classes according to disease activity is important to initiate or change a treatment (in the case it is high or moderate) and to fix activity status that are conceptually different (low activity or remission). Recently it has been shown that the outcome of RA improves if activity is measured regularly and is adjusted to treatment to achieve degrees of low activity or remission.[24] The appearance of new drugs and the use of strategies of intensive treatment have considerably improved the potential to achieve very low degrees of activity or even remission,[25] something that was unthinkable a decade ago and makes the therapeutic objective something more than a utopia.

Remission is the ideal objective of treatment, but in RA as is the case of many chronic illnesses, achieving as cure is rarely done. Frequently, the term remission is employed to define a state that is very much approximate to a cure, but in RA this is not clearly defined in a clear manner and can be understood as the absence of inflammatory activity, the absence of clinically detectable activity or a very low clinical activity, probably without consequences, such as joint destruction or a loss in functional capacity.[26]

The definition of remission must be based on a combination of measures and surrogate markers of inflammation and, for it to be useful in the clinical practice it must not be difficult to determine. Apart from this, as it is a state that has become easier to achieve due to new treatments and strategies, this definition must be as precise as possible, so that patients with a low disease activity values, that can be escape the clinical evaluation or not be reflected in the acute phase reactant measurements, are not left out of treatment.

Today, the most utilized criteria to define clinical remission in RA are 3: ACR, DAS, and SDAI. The ACR criteria[27] are the oldest and where proposed by the analysis of 344 patients by 35 rheumatologists (Table 2). To achieve remission, patients must have, at least, 5 of the 6 criteria, which means that remission can be achieved in spite of having swollen and tender joints, but not with both at the same. Remission criteria proposed by the ACR have certain limitations: as is logical, the absence of pain is the one that best discriminates the remission status,[28,29] but its not always real because it can be due to residual alterations or coincidental illness. Apart from this, these criteria include

TABLE 2. ACR Remission Criteria*

Morning stiffness lasting less than 15 min
Absence of fatigue
Absence of joint pain as stated by the patient
Absence of joint pain during exploration
Absence of joint swelling during exploration
ESR<20 in men and <30 in women

*ACR indicates American College of Rheumatology; ESR, erythrocyte sedimentation rate.
Five criteria must be present for at least 2 consecutive months.

2 measurements, morning stiffness and fatigue, that are not included in the core set of variables recommended and are not easy to document. Finally, they require a normal ESR, and can be altered by comorbidities or intercurrent illness. These criteria, still "preliminary," were done at a time when the pharmacologic treatment for RA was very limited and the current concept of serious disease did not exist, so they must be updated.

The usefulness of the ACR remission criteria is very scarce. The logical step is to define remission with the same tools that are employed to measure disease activity, in this case the DAS or the SDAI. The cutpoint for remission in SAS was proposed in 1996 as <1.6,[30] using as a reference pattern a modification of the ACR criteria, making its validity questionable. A few years later, the value for DAS28 was extrapolated, using the formula that relates them; therefore this value is not derived from real patients[31]. This cutpoint (DAS28<2.6), even if it is the most widely used in the clinical practice and in many clinical trials, has been criticized from the theoretical standpoint and the clinical practice. For the development of cutpoints according to DAS, a modification to the ACR criteria, which are considered obsolete, has been employed and the cutpoint for the DAS28 is not derived from real patients, but is instead a mathematical extrapolation of the original DAS. It is possible, according to the DAS, to be in remission with tender and swollen joints, as long as the ESR and the patient evaluation are not to high, and radiographic progression in patients with persistent remission has been described,[32] which means that it does not detect clinically irrelevant degrees of activity. Using different cohorts of patients and always taking into account as a pattern the modified remission criteria of the ACR, discretely superior cutpoints have been described (DAS28<2.81),[28] as well as similar (DAS28<2.6)[33] or inferior (DAS28<2.32).[29] Using the opinion of 35 rheumatologists in ideal patient cases, the cutpoint for DAS28 has been established at 2.4,[34] which reflects the change in perception and attitude toward ACR that has taken place in the last few years. Finally, from a conceptual standpoint, the use of reduced indexes has

been criticized because of their tendency to exclude hips, ankles and feet to evaluate remission, because patients with an affectation of the joints mentioned above could be classified as "in remission." [35,36] Nonetheless, though theoretically true, this index is most useful in the clinic, and therefore, used the most, making it possible to correct errors in part, as has been discussed, by reducing the cutpoint from 2.6.[29]

Originally, the cutpoint for SDAI was established at <5,[20] but in a latter exercise in validation by another group of rheumatologists, in fictional patients and taking into account structural damage and the deterioration in functional capacity that progress in the presence of moderate activity, the limits for remission according to SDAI were lowered to 3.3.[34]

Agreement between the DAS28 and the SDAI is good, making both indexes useful in the clinic with few differences. The behavior of both indexes hen the opinion of the physician is employed as a pattern of reference or the need to change the treatment when the RA activity is moderate or high is excellent; nonetheless, the same does not happen when the activity is low or in remission.[22] In this case, progress in the development of DMARDs and in therapeutic strategies has been ahead of the evaluation methods, because exploratory methods cannot detect small, residual inflammation, sometimes subclinical, that have no repercussion on the acute phase reactants and cannot differentiate joint pain originated by a swollen joint and that which is secondary to a residual alteration or periarticular disease.

Apart from remission, which is important though difficult to achieve, one must differentiate between other categories of activity that have classically been defined as low, moderate or high. To define the cutpoints that separate the previous categories, the original cohort from which DAS derived was employed, separating the patients according to a low or high activity, according to the rheumatologist´s decision to initiate treatment or not. To reduce the superposition of the 2 distributions, an inferior limit of high activity was defined as the 25th percentile and the inferior limit of low activity the 75th percentile, with moderate activity being between both.[37] Cutpoints separating the 3 categories were DAS<2.4 for low activity and DAS>3.7 for high activity (Table 3), and moderate activity in between. As was the case for remission, based on the values of the DAS, the calues for DAS28 were extrapolated, resulting in DAS28<3.2 for low activity and DAS28>5.1 for high (Table 3).[31] With the SDAI, the cutpoints were defined in the original publication, taking as a reference the values for DAS28, and were SDAI<11 for low activity and SDAI>40 for high activity. Recently, a new modification in the DAS28 and SDAI values was proposed, based on the opinion and consensus of experienced rheumatologists, and are exposed on table 3.[34]

DAS and its modification, DAS28, are indexes based on improvement criteria proposed by EULAR and are classified in "absent," "moderate," and "good."[37] For the use of these criteria a substantial improvement is needed in the DAS, defined as 1.2, being double the error measurement, but also the degree of activity that remains after treatment (high, moderate, or low). To this effect a table with two modes of entry is constructed (Figure). Improvement, according to the EULAR criteria ("good" and "moderate"), tends to be discretely higher than ACR20, and improvement is considered "good" if it is higher than

TABLE 3. Cutpoints for the Activity Categories According to DAS, DAS28, and SDAI*

	Category	Original Definition	New Proposed Definition
DAS	Remission	<1.6	
	Low activity	<2,4	
	Moderate activity	2.4<DAS>3.7	
	High activity	>3.7	
DAS28	Remission	<2.6	<2.4
	Low activity	<3.2	<.6
	Moderate activity	3.2<DAS28>5.1	3.6<DAS28>5.5
	High activity	5.1	>5.5
SDAI	Remission	<5	<3.3
	Low activity	<20	<11
	Moderate activity	20<SDAI>40	11<SDAI>26
	High activity	>40	>26

*DAS indicates disease activity score; SDAI, simplified disease activity index.

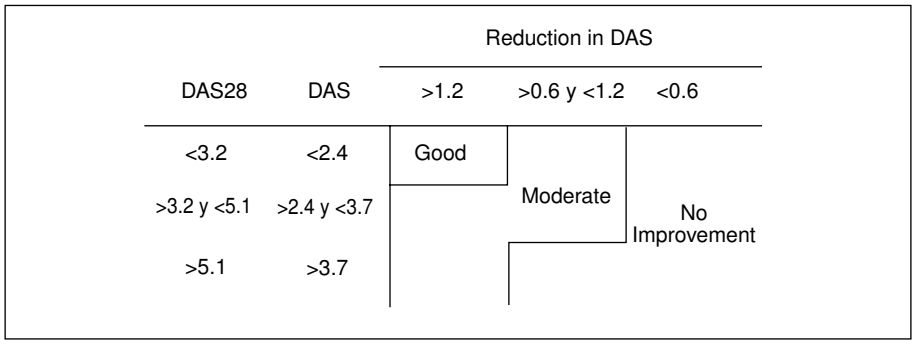

Figura. *Improvement criteria employed by the European League against Rheumatism (EULAR). DAS indicates disease activity score.*

ACR50. Both criteria behave appropriately when used in clinical trials, which does not necessarily mean that they are as useful in the clinical practice, because the objectives tend to be different.[38,39] In the clinical practice, more than the use of of improvement criteria, one must employ measurements of activity in a regular fashion and modify the treatment until a low degree of activity is attained, and of course, if possible, remission.[24]

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