

Is the DAS28 Score the Most Adequate Method to Estimate Activity in Rheumatoid Arthritis? Clinimetric Considerations and Simulations Scenarios

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Introduction: The DAS28 score has now consolidated as a fundamental variable for the assessment of rheumatoid arthritis activity and is the main parameter used to establish therapeutic decisions in this disease, including the start and change of biologic therapies.

Objectives: We have studied the clinimetric properties of DAS28, including ceiling and floor effects and its behavior in several clinical scenarios.

Material and method: Individualized study of the variables included in the DAS28 formula along its possible range. Sensitivity analysis of the results of the DAS28 of 4 variables in four theoretical scenarios corresponding to low (DAS28=2.43), fair (DAS28=4.05), high (DAS28=6.32), or very high (DAS28=8.40) clinical activity.

Results: Tender joint count (NAD) and erythrocyte sedimentation rate (ESR) have a weight of 35%-40% each on the total DAS28 score, while swollen joint count (SJC) and global health assessed by the patient (GH) only contribute with 15% each. As tender joints weights double than swollen joints, in the simulation models having one swollen joint needed just 3 tender joints to get the DAS28 above the non remission level (DAS28>2.6), while having one tender joint needed 5 swollen joints to be above remission. Given its logarithmic calculation in the DAS28 formula, ESR contribution is much higher in its lower range, and thus small variations of ESR in the normal range can influence decisively in the final DAS28 score.

Conclusions: The asymmetric weight of each component in the complex DAS28 formula must be taken into account when interpreting changes in the DAS28 lower range as they influence the estimation of clinical remission and thus can be relevant when taking therapeutic decisions.

Key words: DAS28. Clinimetrics. Sensitivity analysis. Clinical scenarios. Simulation. Rheumatoid arthritis. Therapeutic decision. Activity assessment. Severity of illness index.

¿Es la puntuación DAS28 el método más adecuado para estimar la actividad de la artritis reumatoide? Consideraciones clinimétricas y escenarios de simulación

Introducción: El índice DAS28 se ha consolidado como variable fundamental para valorar la actividad de la artritis reumatoide y es el principal parámetro utilizado para establecer decisiones terapéuticas en esta enfermedad, incluidos el inicio y el cambio de tratamientos biológicos.

Objetivos: Estudiar las propiedades clinimétricas del DAS28, incluidos los efectos techo y suelo teóricos. Analizar el comportamiento de este índice compuesto al variar sus parámetros en una modelización teórica correspondiente a diversos escenarios hipotéticos de actividad clínica.

Material y método: Estudio individualizado de las variables que componen el DAS28 a lo largo de su recorrido. Análisis de sensibilidad del comportamiento del DAS28 de cuatro variables en cuatro escenarios teóricos correspondientes a actividad baja (DAS28 = 2,43), media (DAS28 = 4,05), alta (DAS28 = 6,32) o muy alta (DAS28 = 8,40).

Resultados: El recuento de articulaciones dolorosas y la velocidad de sedimentación globular (VSG) aportan, cada una de ellas, un 35-40% del valor del DAS28, en tanto que el recuento de articulaciones tumefactas y la valoración global del paciente aportan sólo un 15%, respectivamente. Dado que los recuentos de articulaciones dolorosas cuentan el doble que los de tumefactas, en los modelos de simulación con una articulación tumefacta son necesarias tan sólo 3 dolorosas para estar por encima del umbral de remisión (DAS28 > 2,6), mientras que con una dolorosa son necesarias 5 articulaciones tumefactas para estar encima de dicho umbral. Dado su carácter

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logarítmico en la fórmula DAS28, la contribución de VSG es mucho mayor en el rango más bajo de su recorrido, por lo que pequeñas variaciones de una VSG dentro del rango de normalidad influyen decisivamente en la puntuación final del DAS28.

Conclusiones: El carácter asimétrico de los elementos incluidos en la compleja fórmula del DAS28 debe tenerse en cuenta al valorar sus cambios, especialmente en el rango inferior de puntuación, ya que pueden influir en la estimación de remisión y, por lo tanto, ser relevantes en la toma de decisiones terapéuticas.

Palabras clave: DAS28. Clinimetría. Análisis de sensibilidad. Escenarios clínicos. Simulación. Artritis reumatoide. Valoración de actividad. Decisión terapéutica. Índice de severidad de enfermedad.

Introduction

The evaluation of activity in rheumatic disease has fundamental importance for therapeutic decisions and for the establishment of prognosis in patients with these diseases. Although traditionally this evaluation has been performed in a purely orientation form from the physicians and the patients impressions, during the past decades diverse instruments have been extensively developed and validated to this end; among them, the Health Assessment Questionnaire-Disability Index (HAQ-DI) of Stanford, the ACR20-50-70 scores and the combined disease activity score (DAS) stand out. This last has been converted into the activity score preferred by most of the researchers and clinicians in Europe because, in contrast with the ACR scores, it is a continuous range measurement, of a linear type which does not require a previous reference point, and which allows a continuous measurement of the clinical state of activity both in individual patients as well as clinical trials. The popularity and importance of the DAS are evident not only because it is currently the most employed score in most of the clinical trials that involve drugs in rheumatoid arthritis (RA), but also because it has been included in several clinical practice guidelines (CPG) for treatment related decision making in patients with RA, especially to evaluate the need to start biologic therapy and for the evaluation of efficacy.^{1,2}

Determination of the DAS in low or moderate ranges has critical importance because it determines the continuation or change in treatments, as well as the determination of whether the patient is in remission or is clinically active. In different informal forums the question has risen on whether small variations in the parameters which form this score in patients with low activity of RA could lead to important effects in the total score, in which case unexpected leaps from remission to activity or from efficacy to inefficacy of the treatments could be seen. Therefore,

we have performed a study of simulations to evaluate the mathematical and clinimetric properties of the DAS28 score, with special emphasis in the lower part of its application range. This study has been performed on the DAS28 of four variables and any further mention in the text regarding DAS28 will be synonymous to DAS28-4.

Material and Method

DAS28 is a compound score which evaluates, in an asymmetric form, 4 components that constitute it. The mathematical formula from which this score is derived is:

$$\text{DAS28} = 0.56 \times \sqrt{\text{TJC}} + 0.28 \times \sqrt{\text{SJC}} + 0.7 \times \ln(\text{ESR}) + 0.014 \times \text{GH}$$

where TJC is the recount of pain in 28 joints, SJC is the recount of swelling in the same 28 joints, and $\ln(\text{ESR})$ is the natural logarithm of the erythrocyte sedimentation rate, and GH (global health) is the evaluation of the health status and activity of the disease as estimated by the patient in a visual scale of 100 mm, in which higher numbers mean more activity or a worse state of health.

Development of Clinical Models and Scenarios

We have designed models of the value reached by DAS28 throughout the range of each individual variable that forms it, with the rest of the variables set to zero, with the objective of observing their isolated behavior and the degree to which each contributes (relative weight) to the final DAS28 score.

In order to prove the solidity of the DAS28 score we performed an analysis of its behavior in different scenarios and practical cases, using values in the low, moderate, high and very high ranges of the score. With that end in mind we divided Table 1 with progressive values of the 4 parameters, taking as clinical models of different severity rows 3, 6, 13, and 23 of this Table, supposing values of 2, 5, 12, and 22 swollen and painful joints and final DAS28 values of 2.43, 4.05, 6.32, and 8.40, respectively. Values of ESR and GH also increased progressively in the Table, making the global effect a combination of the effect of the 4 parameters. Although this model is only one of the almost infinite types of possible combinations to form the DAS28 score, we have chosen it because it combines a very realistic situation in the daily practice. In fact, usually higher values of the SJC and TJC are associated to larger values of ESR and GH, and the four components present a significant correlation among them. We have proven this point based on the data of EMECAR, in which the correlation between the four parameters is positive and the range of Pearson's R is 0.13 to 0.47 ($P < .01$).

TABLE 1. Table With Progressive Increments of Each One of the DAS28 Components and Their Absolute Contribution to the Global DAS28-4 Compound Index^a

	TJC	SJC	ESR	GH	DAS28-4	DAS-TJC	DAS-SJC	DAS-ESR	DAS-GH
1	0	0	1	0	0	0	0	0	0
2	1	1	3	4	1.67	0.56	0.28	0.77	0.06
3	2	2	5	8	2.43 ^b	0.79	0.40	1.13	0.11
4	3	3	7	12	2.99	0.97	0.48	1.36	0.17
5	4	4	10	16	3.52	1.12	0.56	1.61	0.22
6	5	5	15	20	4.05 ^b	1.25	0.63	1.90	0.28
7	6	6	20	24	4.49	1.37	0.69	2.10	0.34
8	7	7	25	28	4.87	1.48	0.74	2.25	0.39
9	8	8	30	32	5.20	1.58	0.79	2.38	0.45
10	9	9	35	36	5.51	1.68	0.84	2.49	0.50
11	10	10	40	40	5.80	1.77	0.89	2.58	0.56
12	11	11	45	44	6.07	1.86	0.93	2.66	0.62
13	12	12	50	48	6.32 ^b	1.94	0.97	2.74	0.67
14	13	13	55	52	6.56	2.02	1.01	2.81	0.73
15	14	14	60	56	6.79	2.10	1.05	2.87	0.78
16	15	15	65	60	7.02	2.17	1.08	2.92	0.84
17	16	16	70	64	7.23	2.24	1.12	2.97	0.90
18	17	17	75	68	7.44	2.31	1.15	3.02	0.95
19	18	18	80	72	7.64	2.38	1.19	3.07	1.01
20	19	19	85	76	7.84	2.44	1.22	3.11	1.06
21	20	20	90	80	8.03	2.50	1.25	3.15	1.12
22	21	21	95	84	8.21	2.57	1.28	3.19	1.18
23	22	22	100	88	8.40 ^b	2.63	1.31	3.22	1.23
24	23	23	105	92	8.57	2.69	1.34	3.26	1.29
25	24	24	110	96	8.75	2.74	1.37	3.29	1.34
26	25	25	115	100	8.92	2.80	1.40	3.32	1.40
27	26	26	120	100	9.03	2.86	1.43	3.35	1.40
28	27	27	125	100	9.14	2.91	1.45	3.38	1.40
29	28	28	130	100	9.25	2.96	1.48	3.41	1.40
30	29	28	200	100	9.55	2.96	1.48	3.71	1.40

^aESR indicates erythrocyte sedimentation rate; GH, global health; SJC, swollen joint count; TJC, tender joint count.

^bRows selected for the 4 simulation models.

Sensitivity Analysis

Finally, we performed a sensitivity or strength analysis of DAS28 in the lower part of the table, in cases of low or moderate activity, with the goal of observing how the final score varies in relation to small variations of its components.

Therefore we have used 2 theoretical models: in one of them we fixed the number of swollen or tender joints to 1 and in the other, the recount varied from 1 to 5, and a second model that fixed the number of tender or swollen joints to 5, with another which did so similarly, from 1 to 5. In this way it was possible to objectify the individual

behavior of these variables with respect to the others in cases of low or very low activity. For this model the values of ESR were constant at 5 mm, first hour and GH 20 mm in order to prove the exclusive influence of the joint counts in low activity subjects.

Results

Clinimetric Study of the DAS28 Components

We established the real contribution of each parameter to the final DAS28 score with a mathematical model which simply establishes as 0 the rest of the parameters in the global index calculated formula. In this way we were able to obtain a very informative graphic of the behavior of each parameter in all of its range of application. In Figures 1 and 2 we present the contributions of the TJC, SJC, ESR, and GH to the final DAS28 score. We see that the joint recounts give a hemiparabolic graph, with an important increase in the first 5 values and then almost linear increments. ESR follows an obviously logarithmic curve in which very important increases in the first part can be seen, up until 20 mm, first hour of the ESR, following then a softer curve. The global health evaluation of the patient is performed in a completely linear form. If we look for in these graphs for the maximum value which may be reached by each one of the parameters, we see that the tender joint count and the ESR can contribute with up to 3 points to the final DAS28, while the tender joints and the patient global health evaluation have a ceiling of approximately 1.5 points. This proves, therefore, that both the TJC and ESR are evaluated in a far superior

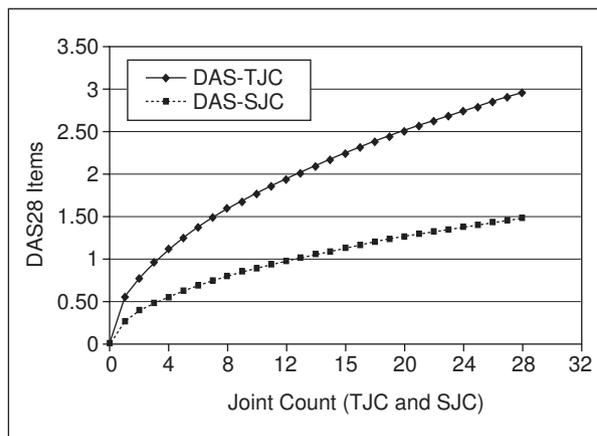


Figure 1. Absolute contribution of the tender (TJC) and swollen (SJC) joint counts to the DAS28 score. DAS-TJC: items contributed by TJC to DAS28. DAS-SJC: items contributed by SJC to DAS28. Simulation of each individual variable with the rest of the DAS28 variables to zero.

manner than the SJC and GH, something especially relevant in the inferior ranks of these parameters. As a whole, the maximum participation of each one of the components in the total DAS28 score is shown as a graph in Figure 3.

Sensitivity Analysis of the Theoretical Scenarios

The results of the scenario model proposed is summarized on Table 2 and is visualized in Figure 4. We proved that the contribution of the TJC and the SJC are very constant

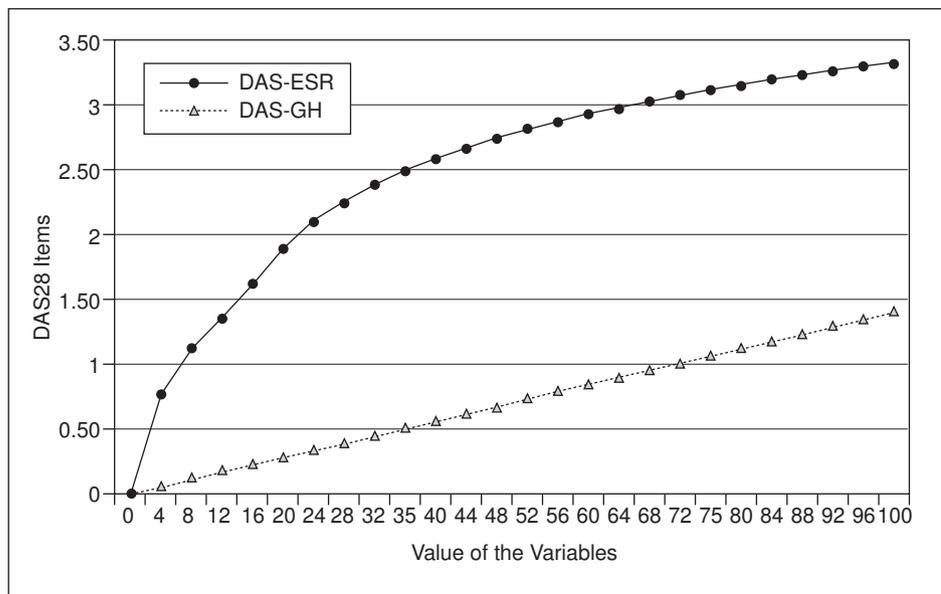


Figure 2. Absolute contribution of erythrocyte sedimentation rate (ESR) and global health (GH) to the DAS28 compound index. DAS-ESR: items contributed by the ESR variable to DAS28. DAS-GH: items contributed by the patient's global evaluation to the DAS28. Simulation of each individual variable with the rest of the DAS28 variables to zero.

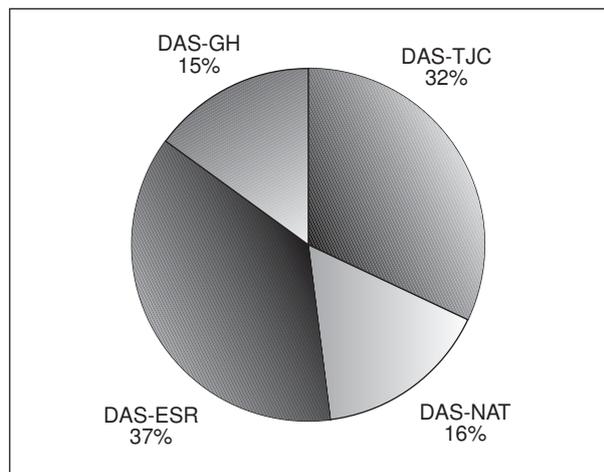


Figure 3. Maximum contribution of each one of the compound value components of DAS28. ESR indicates erythrocyte sedimentation rate; GH, global health evaluation of the patient; SJC, swollen joint count; TJC, tender joint count.

throughout the score, which is 31%–33% for the TJC and 15%–16% for the SJC. The contribution of GH is also stable because the observed increase is mainly due to the linear increase of this parameters values in the four scenarios. The most interesting point is that the relative contribution of ESR to DAS28 is larger in the scenario of low activity than in the high activity one, in spite of the fact that the absolute value of ESR is larger in the latter. This is owed to the logarithmic character of this parameter, as is shown in Figure 2 and has important

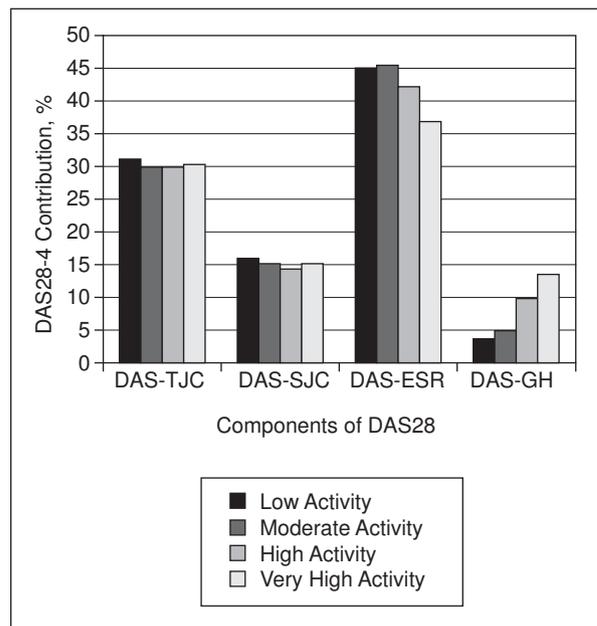


Figure 4. Relative contribution of each component to DAS28 in 4 simulated cases. Low activity: DAS28=2.43; moderate activity: DAS28=4.05; high activity: DAS28=6.32; very high activity: DAS28=8.40. Note that the contribution of erythrocyte sedimentation rate (ESR) is larger in the low activity situation in spite of the fact that the value of the variable increases if activity is elevated. GH indicates global health evaluation of the patient; SJC, swollen joint count; TJC, tender joint count.

implications for the adequate evaluation of patients with low activity.

TABLE 2. Table of Simulations of the 4 Scenarios or Practical Cases; the Relative Contribution of Each Component of the DAS28-4 Index Is Indicated^a

Component	TJC	SJC	ESR	GH	DAS Total	Clinical Estimate
Value of the item	2	2	5	8		
Contribution DAS28	0.79	0.40	1.13	0.11	2.43	Low activity
Contribution	33%	16%	46%	5%	100%	
Item value	5	5	15	20		
Contribution DAS28	1.25	0.63	1.90	0.28	4.05	Moderate activity
Contribution	31%	15%	47%	7%	100%	
Item value	12	12	50	48		
Contribution DAS28	1.94	0.97	2.74	0.67	6.32	High activity
Contribution	31%	15%	43%	11%	100%	
Item value	22	22	100	88		
Contribution DAS28	2.63	1.31	3.22	1.23	8.40	Very high activity
Contribution	31%	16%	38%	15%	100%	

^aESR indicates erythrocyte sedimentation rate; GH, global health; TJC, tender joint counts; SJC, swollen joint count.

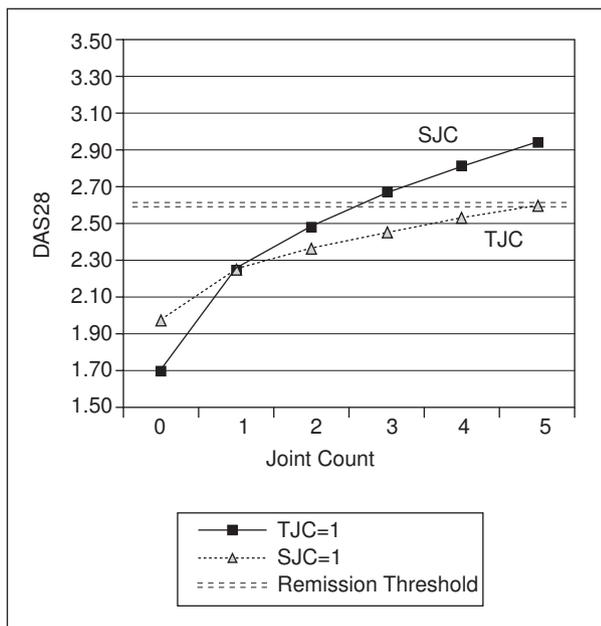


Figure 5. DAS28 variation with different values in joint count, with one of the recounts prefixed to $n=1$. Remission threshold according to DAS28 criteria. Only one swollen joint and 3 tender ones reach an activity threshold ($DAS28 > 2.6$), while 1 tender needs 5 swollen in order to reach it. Constant values in erythrocyte sedimentation rate of 5 mm and global patient evaluation of 20 mm. SJC indicates swollen joint count; TJC, tender joint count.

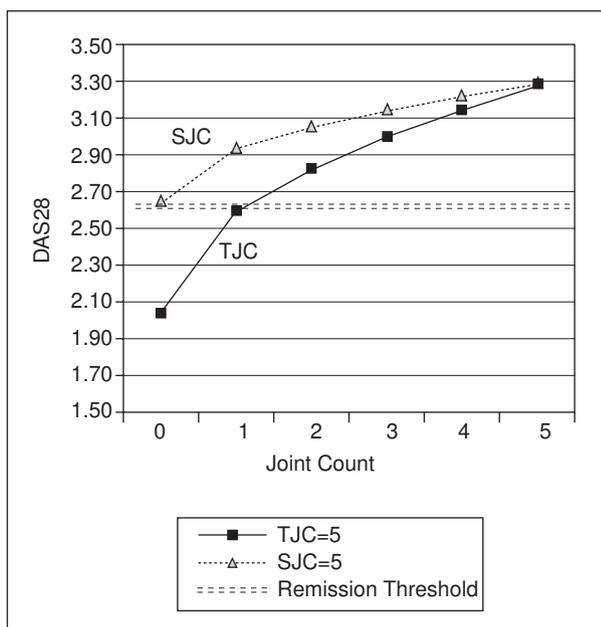


Figure 6. Variation in DAS28 with different joint count values with a prefixed recount of $n=5$. Remission threshold according to DAS28 criteria. Both lines coincide when $n=5$ for the 2 of them. Constant erythrocyte sedimentation rate of 5 mm and global patient evaluation in 20 mm. SJC indicates swollen joint count; TJC, tender joint count.

It is evident, parting from the DAS28 formula, that the estimation of the tender joint count counts as double the swollen joints in the calculation of this score. We know that the determination of these parameters has an important subjective component and that several studies have shown a low agreement between examiners. In order to prove the effects that small variations in the values of the joint counts may have, we have performed a simulation in the inferior zone of the score and varied its values from 0 to 5, maintaining the values of ESR and GH constant in 5 and 20 mm, respectively. The graphic results are shown in Figures 5 and 6. In the first we see that a TJC value fixed at 1, in other words, only one swollen joint, the changes from 0 to 5 for the value of TJC strongly and rapidly modify the estimation of DAS28, overcoming the remission threshold ($DAS28=2.6$) with only 3 painful joints. In the inverse case, fixing the TJC at 1 painful joint, it is not possible to reach such a threshold even when 5 joints are swollen. Figure 6 is similar to the previous one, but represents the results obtained when the recounts in 5 tender or swollen joints are fixed. Here we can see that with 5 painful joints the activity threshold is reached even when no swollen joints are seen. Inversely, with 5 swollen joints no threshold is reached until there is at least a painful one.

These curves logically are modified when the other 2 parameters are prefixed: ESR and GH, which in these models are 5 and 20 mm, as has been indicated previously. If we increase the ESR to 20 mm, we obtain the same type of curves, but with a n increased DAS28 in one point in all of the levels. In this case the level of 2.6 would be reached in the global index with only one swollen or tender joint.

The importance of these simulations must be emphasized by their high clinical prevalence, because when one reviews the EMECAR cohort, we find that up to 60% of patients had 5 or less painful joints and 4 or less swollen joints, while 50% of the subjects had an ESR of 21 mm or lower (data obtained by this author from the analysis of the EMECAR database, unpublished).

Discussion

DAS is a compound index³ designed in the Netherlands in 1993 which is based on a multiple regression formula whose original dependent variable was the level of global disease activity of as determined by the physician in a 10 cm visual analog scale (VAS). The original DAS index is composed of 4 parameters: the Ritchie type joint count with a graduation of pain upon pressure in 44 joints, the ESR and the global health evaluation on the part of the patient on a VAS.⁴ There are also versions which substitute the ESR 4 CRP, as well as a simplified version by Smolen (SDAI) based on the simple sum of the parameters forming the score. A short time after validating the the original

method, a more practical model based on the standard evaluation of the joint count of 28 painful and swollen joints was developed, according to the proposal by Fuchs et al,⁵ which is validated in the clinical environment⁶ and called DAS28. This model, the one most currently employed because of its simplicity, has two variants depending on whether the four original variables or only the joint counts and the ESR are employed (DAS28-4 and DAS28-3, respectively).⁷ It is important to note that the same patient can give different readings according to whether we employ DAS, DAS28-3, and DAS28-4, although formulas exist that approximate the results obtained from one method to another.⁸ In this sense, Prevoo et al⁹ established in 1996 a $DAS \leq 1.6$ value as a cutpoint in patients who were in clinical remission according to the ACR criteria. Using a formula to convert DAS values into DAS28 values, this cutpoint for remission was extrapolated to 2.6 for DAS28. In a study by Balsa et al¹⁰ on the EMECAR cohort, the most predictive cutpoints for clinical remission according to ACR criteria, excluding fatigue, were determined to be 2.81 for DAS28-4 and 2.95 for DAS28-3. On the other hand there is a certain consensus in admitting that the value of 3.2 for DAS28-4 is a cutpoint between low and moderate activity, and >5.1 points defines intense activity in RA.^{7,11} These points have relevance for the institution or change in disease modifying treatment (DMARD) in these patients, so the DAS28 score as a decision element has been contemplated in the SER consensus document for biologic therapy in RA published in 2005¹² similar to those published by the Portuguese Society of Rheumatology.¹³ A simple look at the formula of DAS28 shows some interesting data: painful joints are evaluated as double the swollen ones; joint counts and ESR are evaluated in a non linear form while GH is evaluated linearly. This form of weighing the parameters that compose the DAS28 formula have important implications, especially when we move in the lower range of the score. This impression was recently confirmed by Makinen et al¹⁴ who have shown that in the FIN-RACo RA cohort, ESR and SJC have a far superior effect than the other 2 variables on the DAS28 score, with ample overlapping of the individual components of the index in the low, moderate, and high groups. From this theoretical modeling study, several conclusions are reached:

1. The DAS28 has a theoretical floor and ceiling effect which must be known. Although in its original design the total range of the score continuously oscillates between 0 and 10 points, in clinical practice it is difficult to find lower than 1 or higher than 9 values. In fact, with an ESR of 5 mm the DAS28 is 1.13, although no painful or swollen joint is present and the patient evaluation shows zero activity. DAS28 scores over 9 are only reached with joint counts of 26 TJC + 26 SJC, ESR >120 and GH of 100 mm.

2. When developing the DAS tender joints received double importance over swollen joints. This point is counterintuitive with respect to the common clinical experience, because in general the rheumatologists give more importance to swelling than pain upon pressure due to its relatively larger objectivity. It must be remembered when evaluating the recounts, especially when low values are found.

3. The contribution of the TJC and SJC and the patient evaluation (this being intrinsically linear), to the global DAS28 score is very stable and constant throughout the range of the combined score (Figure 4), giving it, in general, good clinimetric properties.

4. ESR gives the DAS approximately a 40% of its final value. It is, therefore, the main individual parameter within the score. Due to its logarithmic nature, the contribution of ESR is much larger when its values are less. In the daily clinical practice little importance is given to ESR in the 3-10 mm range, but the value provided by these numbers to the DAS makes it increase from 0.77 to 1.61 points, almost a complete unit of the global score. This could represent the difference between remission and activity or a good progression and a poor one, leading to unjustified changes in the therapeutic plan. Biologic variability must be considered in ESR as well as laboratory techniques, and although clinically we do not evaluate small changes, we must consider the great effect they may have on the DAS score.

It must finally be pointed out that the DAS score is an artifice with which we intend to weigh, with a single number, a complex clinical construct such as disease activity of RA. All simplifications has their limits and DAS is no exception. This type of combined score allows comparisons of different patients between them, sometimes with very distinct clinical characteristics, to be done with relative ease. It can be useful when comparing patient populations, such as the case of clinical trials, but becomes more problematic when used as the main parameter for the evaluation of individual patients, such as has recently been proven by Wolfe et al.¹⁵ Even so, DAS28 represents an important leap in quality if we take into account that in the past the physician carried out the evaluation of the inflammatory activity of the disease in a purely subjective way.

Conclusions

DAS28 allows us to objectify, albeit imperfectly, patient progression. In this sense it turns into, along with the HAQ, in one of the most useful instruments for follow-up for the rheumatologist in charge of patients with RA. This motivates their systemic application in the daily practice, and its determination is recommended at least every 6 months. It must be remembered, however, the

DAS28 is very sensitive to small variations in the ESR levels located in the lower range (less than 20 mm, first hour) and its larger sensitivity for the tender joint count over the swollen ones, which must be taken into account when interpreting the results obtained in patients with low inflammatory activity. In these cases, probably the clinical evaluation of the joint recounts must be taken into account and not only the strict DAS28 value, because this factor, in its entirety, is very useful but, as we have seen, has its weakest points in the lowest range of its parameters.

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