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Original Article

DAS28-ESR and DAS28-CRP - are they Interchangeable in Measuring the Activity of Rheumatoid Arthritis in Response to Treatment with Biological Agents?

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Abstract

Introduction: The European League Against Rheumatism updates the recommendations for managing rheumatoid arthritis. Again, it is not specified which DAS28 is there in view (with erythrocyte sedimentation rate or C-reactive protein).

Aim: The aim of the study is to check whether Disease Activity Score-28 (erythrocyte sedimentation rate) and Disease Activity Score-28 (C-reactive protein) represent equally the activity of rheumatoid arthritis in the course of treatment with biological agents.

Materials and methods: In a retrospective study we analyzed the database of real clinical practice over a 12-month period of biological treatment of rheumatoid arthritis. Disease Activity Score-28 (erythrocyte sedimentation rate) and (C-reactive protein) are compared at the start and at the end of the study.

Results: The mean difference between the two variants of disease activity scores at baseline and at the end of the study is significant ($p < 0.001$). The Disease Activity Score-28 (erythrocyte sedimentation rate) represents a remarkably small proportion of patients with remission and low activity (<3.2) at baseline (18.46%) and at the end of the study (40.51%). Disease Activity Score-28 (C-reactive protein) represents a significantly high proportion of patients in remission and low activity (<3.2) at the end of the study (69.74%). Estimates of activity according to the two variants show significant discrepancy between each other and low level of agreement (kappa = 0.235-0.464). Discrepancies are not related to the type of biological drug (anti-TNF or not).

Conclusion: The two DAS28 variants are not interchangeable with the same threshold for low activity in measuring the response to biological therapy.

Keywords

DAS28-ESR, DAS28-CRP, rheumatoid arthritis

INTRODUCTION

There has been enormous advance in the management of patients with rheumatoid arthritis (RA) in recent years.[1] There are clear recommendations for therapeutic behavior and clear goals to achieve. The European League Against Rheumatism (EULAR) recommendations for managing RA refer to remission and low disease activity (LDA) cal-

culated using DAS28 but do not specify which version of DAS 28 is considered - ESR or CRP. Consequently, clinicians may assume that values of DAS28-CRP and DAS28-ESR are interchangeable.[2]

It seems that the tools for assessing the effect of treatment are lagging behind in this process. In the everyday clinical practice, the evaluation of Disease Activity Score 28 (DAS28) has become the main measure. Prevoo ML et al. in 1995 introduced DAS28 as a composite measure of RA activity using ESR.[3] A few years later, Fransen et al. offered a new version in which the ESR was replaced by the CRP.[4] The latter (DAS28-CRP) variant is used with the same thresholds validated for the DAS28-ESR.

AIM

The aim of the study was to check whether DAS28-ESR and DAS28-CRP represent equally the activity of RA in the course of treatment with biological agents in the RA.

MATERIALS AND METHODS

Study design and patient population

A retrospective study conducted in real-life practice in adult patients with RA. An administrative database of daily clinical practice is analyzed. The medical records of 195 consecutive patients were analyzed. All patients were treated with biological disease modifying anti-rheumatic drugs (bDMARDs). A condition for inclusion was that treatment with bDMARDs had started at least 6 months before data analysis. Concomitant non-biological anti-rheumatic drugs modifying the disease (DMARDs) – Methotrexate (MTX) were been analyzed.

Assessments

Patient's data were analyzed for a 12-month period of long-term treatment with biological agents. Assessments included demographic and clinical variables at the start of the study. Effectiveness was assessed using DAS28 calculated with erythrocyte sedimentation rate (DAS28-ESR), a validated disease activity measure[3] at baseline and at the end of trial (0 and 12 months). Other variables assessed included ESR (capillary photometry) (reference range 2-37 mm/h), C-reactive protein (latex-enhanced immunoturbimetric analysis) (CRP) (reference range 0-5.0 mg/L), DAS28-CRP, swollen and tender joint counts (SJC-28, TJC-28), patient's visual analogue scale.

Both versions of the DAS28 were calculated simultaneously by online calculators: http://www.das-score.nl. The RA activity was classified as low and remission (< 3.2) and moderate and high (>3.2).

DAS28-ESR values and DAS28-CRP values were analyzed and compared: a) at baseline and at the end of study using a paired-samples T test; b) DAS28-ESR values were compared with DAS28-CRP values with paired simple t test; c) The relative share of patients with remission and low activity (<3.2) of RA versus those with moderate and high activity (> 3.2) according to the two DAS 28 variants were compared with the Pearson Chi-Square test at baseline and at the end of trial; d) the proportion of discordance is calculated using table 2×2. The sum of the estimates according to the two DAS28 non-matching variants (YES / NO + NO / YES) is presented as a relative share of all estimates.

Statistical analysis

The data were analysed using descriptive statistics of category data, comparison of means of quantitative data (independent-samples T test, paired samples T test, and ANOVA), correlation analysis and Kappa statistics. The obtained kappa coefficients were interpreted according to McHugh ML.[5] For categorical variables we used nonparametric tests – Chi-square, Kruskal Wallis, and Mann-Whitney U test. A threshold of significance <0.05 is used to determine the significance of the results. Results are presented in tables. SPSS version 23 for Windows is used.

RESULTS

Patient demographics and disease characteristics

The patients in the study group were predominantly female (85.13%), mean age 58.84 years. Patients over 55 years were 68.21%, overweight patients were 38.46%, patients older than 40 years of age - 76.92%, and non-smokers - 69.23%. The mean age at diagnosis of RA was 46.88 years, the duration of RA was 11.95 years. The mean time from onset of RA to initiation of treatment with biological agents was 8.28 years, the duration of bDMARDs therapy was 3.71 years (at baseline). Methotrexate was used by 62.56% of patients and 53.8% of patients were treated with anti-TNFα inhibitors **(Table 1)**. Of the anti-TNFα inhibitors, adalimumab (ADA) was the most widely used for the investigated patients (37.95%). Of those who were treated with non-TNFα inhibitors, 43.6% were treated with tocilizumab (TCZ), and 2.56% - rituximab (RTX). The mean duration of treatment

Table 1. Patient demographics and clinical characteristics at baseline

Characteristics	RA patients (N=195)
Female, n (%)	166 (85.13%)
Age, yrs, mean (SD)	58.84 (11.19)
Age ≥ 55 years, n (%)	133 (68.21%)
BMI, kg/m^2 mean (SD)	26.94 (5.34)
Underweight [<18.5 kg/m^2], n (%)	5 (2.56%)
Normal weight [18.5-24.9 kg/m^2], n (%)	60 (30.77%)
Overweight [25-29.9 kg/m^2], n (%)	75 (38.46%)
Obesity [>30 kg/m^2], n (%)	55 (28.21%)
Smokers, n (%)	60 (30.77%)
RA duration (years), mean (SD)	11.95 (9.14)
Time to the beginning of bDMARDs, yrs, mean (SD)	8.28 (8.62)
Duration of bDMARDs therapy, yrs, mean (SD)	3.71 (2.09)
Anti-TNFα blockers, n (%)	105 (53.85%)
Receiving methotrexate, n (%)	122 (62.56%)
DAS28-CRP mean (SD)	3.32 (0.66)
DAS28-ESR mean (SD)	3.80 (0.80)

RA: rheumatoid arthritis; BMI: body mass index; bDMARDs: biological disease-modifying antirheumatic drug; TNF: tumor necrosis factor; DAS28-ESR: disease activity score 28 with erythrocyte sedimentation rate, DAS28-CRP: disease activity score 28 with C-reactive protein. Level of significance $p<0.05$.

Table 2. Mean difference in clinical characteristics from baseline to 12 months

Signs	Mean Difference (±SD) *	*p* value‡
TJC (28 joints)	1.24(±2.41)	<0.001
SJC (28 joints)	0.55(±1.72)	<0.001
VAS, mm	3.94(±8.14)	<0.001
ESR, mm/h	1.73(±13.71)	0.079
CRP, mg/L	0.85(±8.58)	0.167
DAS28-CRP	0.41(±0.57)	<0.001
DAS28-ESR	0.37(±0.70)	<0.001
DAS28-ESR vs. DAS28-CRP 0 m ⁑	0.48(±0.52)	<0.001
DAS28-ESR vs. DAS28-CRP 12 m ⁑	0.51(±0.46)	<0.001

* Data are expressed as mean difference ± SD; ‡ Paired samples t-test. TJC: tender joint count; SJC: swollen joint count; VAS: visual analogue scale; CRP: C reactive protein; ESR: erythrocyte sedimentation rate; DAS28-ESR: disease activity score 28 with ESR; DAS28-CRP: disease activity score 28 with CRP; ⁑ DAS28-ESR and DAS28-CRP are compared with each other at the beginning and end of the study by the paired sample t-test, level of significance $p<0.05$

with etanercept (ETA) (MD = 6.92 years) was significantly greater than that with other biological drugs ($p<0.05$).

A comparison of the values of assessments at the end of the survey with those at baseline

The clinical criteria for investigating the activity of RA included in the DAS28 core set show significant dynamics as a result of the 12-month period of biological treatment. The number of tender and swollen joints, as well as the VAS value, decreased significantly over the period under study. In contrast, the two laboratory parameters (included in DAS 28 variants) did not change significantly during the study period (**Table 2**).

There was no significant difference in the values of DAS28-CRP depending on the type of biological medicinal product. Patients treated with TCZ had significantly lower values of DAS28-ESR than those treated with ETA at the start of the period (MD = 3.64 vs. 4.20) ($p=0.006$) and at the end (MD = 3.25 vs. 3.88) ($p<0.001$). DAS28-CRP at the end of the observational period had significantly lower values in patients receiving MTX (MD = 0.19) ($p=0.033$).

The values of DAS28-ESR were significantly higher than those of DAS28-CRP at baseline (MD = 0.48 (SD±0.52), $p<0.001$) and at the end of the study period (MD = 0.51 (SD±0.46), $p<0.001$) **(Table 2)**.

Patients in remission and low RA activity (≤3.2), according to DAS28-ESR, represented a relatively small relative share, compared to the rest, at the beginning (18.45%) and at the end (40.51%) of the study period. According to DAS28-CRP, the relative proportion of patients in remission and low RA activity (≤3.2) did not differ significantly from those with activity> 3.2 at the beginning of the study period (45.64%). At the end of the study period, the relative proportion of patients with DAS28-CRP values ≤3.2 was significantly higher (69.74%) than the rest. There was a significant proportion of discrepancy between the estimates of the two versions of DAS28 using cut off point 3 (14.3-35.4%) and low to weak level of agreement between them (Cohen's kappa = 0.296-0.462). This discrepancy and low level of agreement are not related to the type of biological medicament **(Table 3)**.

According to DAS28-CRP, patients treated with TCZ and those with ADA with a lower value of 3.2 are significantly higher than the DAS28-ESR at baseline and at the end of the study. A significant proportion of discordance was found between the two versions of DAS 28 when treated with these drugs. There was no such difference in patients treated with INF and GOL ($p>0.05$). For RIT and ETA could not be calculated **(Table 4)**.

Table 3. Proportion of discordance between two variants of DAS28 and level of agreement

All patients N=195	Proportion of <3.2 disease activity n (%)		PD n (%)	Spearman Correlation*	K coefficient▼	p value‡
	DAS28-ESR	DAS28-CRP		DAS28-ESR vs. DAS28-CRP		
At the start of study	36 (18.4)	89 (45.6)	65 (33.3)	0.361	0.296	<0.001
At the end of study	79 (40.51)	136 (69.7)	63 (32.3)	0.481	0.405	<0.001
Non anti-TNFα blockers (n=90) n (%)						
At the start of study	24 (26.6)	42 (46.6)	28 (14.3)	0.393	0.358	0.001
At the end of study	41 (45.5)	62 (68.8)	69 (35.4)	0.517	0.462	<0.001
Anti-TNFα blockers (n=105) n (%)						
At the start of study	12 (11.4)	47 (44.8)	37 (18.9)	0.34	0.235	<0.001
At the end of study	38 (36.2)	74 (70.4)	39 (20.2)	0.453	0.361	<0.001

‡ Pearson chi-squared; ▼Kappa statistic (k coefficient); PD: proportion of discordance; DAS28-ESR: disease activity score 28 with erythrocyte sedimentation rate; DAS28-CRP: disease activity score 28 with C reactive protein; TNFα: tumor necrosis factor α; Level of significance $p<0.05$.

Table 4. Proportion of <3.2 DAS28-ESR and DAS28-CRP and proportion of discordance between them according to the administered biological therapy

Biological drug		n (%)		*p* value*	PD n (%)	n (%)		*p* value*	PD n (%)
		At the beginning of the study				At the end of the study			
	n	DAS28-ESR	DAS28-CRP	DAS28-ESR vs. DAS28-CRP		DAS28-ESR	DAS28-CRP	DAS28-ESR vs. DAS28-CRP	
TCZ	85	24 (28.2)	40 (47.05)	<0.001	69 (81.2)	40 (47.1)	59 (69.4)	<0.001	66 (77.6)
ADA	74	9 (12.2)	37 (50.0)	0.011	47 (63.5)	32 (43.2)	58 (78.4)	<0.001	50 (67.5)
INF	13	2 (15.4)	5 (38.46)	0.052	10 (76.9)	4 (30.7)	7 (53.8)	0.559	10 (76.9)
ETA	13	0	2 (15.4)	g	2 (15.4)	0	6 (46.2)	g	6 (46.2)
GOL‡	5	1 (20.0)	3 (60.0)	0.361	3 (60.0)	2 (40.0)	3 (60.0)	0.136	4 (80.0)
RIT‡	5	0	2 (40.0)	g	2 (40.0)	1 (20.0)	3 (60.0)	1.000	3 (60.0)

PD: proportion of discordance; DAS28-ESR: disease activity score 28 with erythrocyte sedimentation rate; DAS28-CRP: disease activity score 28 with C-reactive protein; TCZ: tocilizumab; ADA: adalimumab; INF: infliximab; ETA: etanercept; GOL: golimumab; RIT: rituximab; *- Pearson Chi-Square or Fisher's exact test; ‡ the GOL and RIT groups include only 5 subjects which is quite a small sample to make statistical inferences; g: no statistics are computed because DAS28-ESR is a constant; Level of significance $p<0.05$.

DISCUSSION

Our results show that, on average, 3.7 years after initiation of biological therapy, the activity of RA continues to decrease. This reduction is demonstrated by both variants of DAS28. The analysis of each of the main indicators of DAS28 shows that this continuous improvement is the result of the continuous reduction of subjective indicators (TJC and VAS) and objective - SJC. Significant discrepancies were found between the two variants of DAS28 when categorizing activity with generally accepted threshold 3.2 as low or moderate. The DAS28-CRP categorizes the majority of patients with low activity and remission, while the DAS28-ESR categorizes the majority of patients in moderate and high activity. The level of agreement we found between the two DAS28 versions (ESR or CRP) in categorizing of patients in remission and low activity or moderate and high activity is between 14.3-35.4%. Already in 2007, T. Matsui et al. reported that DAS28-CRP underestimates disease activity and overestimates EULAR response criteria compared with DAS28 using erythrocyte sedimentation rate.[4]

Roy M Fleischmann et al. (2015), based on a data ana-lysis of a total of 2534 RA patients, reported that the percentage of patients achieving remission and LDA with a threshold ≤ 3.2 is higher for DAS28-CRP compared to DAS28-ESR and SDAI.[6] In the same year Nielung L et al. reported a good agreement (61/75; 81%) between DAS28-CRP and DAS28-ESR in determining the response to biological treatment according to EULAR criteria, but only in 109 patients.[7]

There is no agreement on this issue in the rheumatologycommunity. Updated EULAR recommendations (2016 update) again do not specify which version of DAS28 is considered when discussing DAS28.[2] It is considered to be DAS28-ESR, as the EULAR response criteria are established prior to the introduction of DAS28-CRP.[8]

Our results support the thesis that DAS28-CRP has lower values than DAS28-ESR. When used with threshold ≤3.2, DAS28-CRP determines a larger proportion of patients with low activity compared to DAS28-ESR. This is important when assessing the effectiveness of biological treatment.

CONCLUSION

The two DAS28 variants are not interchangeable with the same threshold for low RA activity in measuring the response to biological therapy.

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Являются ли DAS28-ESR и DAS28-CRP взаимозаменяемыми при измерении активности ревматоидного артрита в ответ на лечение биологическими агентами?

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Абстракт

Введение: Европейская лига против ревматизма обновляет свои рекомендации по борьбе с ревматоидным артритом. Тем не менее, не уточняется, какой DAS28 имеется ввиду (со скоростью оседания эритроцитов или с С -реактивным белком).

Цель: Цель этого исследования - проверить, одинаково ли отражают активность ревматоидного артрита при лечении биологическими агентами шкала оценки активности болезни 28 (Disease Activity Score-28) (скорость оседания эритроцитов) и шкала оценка активности болезни 28 (Disease Activity Score-28) (С-реактивный белок).

Материалы и методы: В ретроспективном исследовании мы проанализировали базу данных фактической клинической практики за 12-месячный период биологического лечения ревматоидного артрита. Шкала активности заболевания 28 (скорость оседания эритроцитов) и (С-реактивный белок) сравнивались в начале и в конце исследования.

Результаты: Среднее различие между двумя вариантами шкалы активности заболевания в начале и в конце исследования было значительным (p <0,001). Шкала активности болезни-28 (скорость оседания эритроцитов) является репрезентативной для очень небольшой доли пациентов с ремиссией и низкой активностью (<3,2) в начале исследования (18,46%) и в конце исследования (40,51%). Шкала активности болезни-28 (С-реактивный белок) была репрезентативной для большинства пациентов с ремиссией и низкой активностью (<3,2) в конце исследования (69,74%). Оценка активности по двум вариантам показала значительное расхождение друг с другом и низкий уровень соответствия (kappa = 0,235-0,464). Расхождения не связаны с типом биологического препарата (анти- TNF или нет).

Вывод: Два варианта DAS28 не являются взаимозаменяемыми с одним и тем же порогом для низкой активности при измерении ответа на биологическую терапию.

Ключевые слова

Ревматоидный артрит, DAS28-ESR, DAS28-CRP