

A predictive model for Simplified Disease Activity Index (SDAI) remission in rheumatoid arthritis

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ABSTRACT

Objectives. To identify predictors for Simplified Disease Activity Index (SDAI) remission in patients with established rheumatoid arthritis (RA) under 12 months of anti-TNF therapy combined with synthetic disease modifying antirheumatic drugs (sDMARD).

Methods. We performed a prospective observational study in 90 RA patients with a high active disease refractory to sDMARDs, starting anti-TNFs. Patients were assessed every 3 months based on a well-defined protocol, including individual parameters (clinical, inflammatory) and composite tools (simplified disease activity index SDAI, functional index HAQ-DI); total and IgA-isotype rheumatoid factor (RF) as well as anti-citrullinated peptide antibodies (ACPAs) were measured at baseline, 6 and 12 months. Therapeutic response was evaluated according to EULAR criteria. The primary endpoint was SDAI remission (≤ 3.3) at 12 months of treatment.

Univariate and multivariate logistic regression analysis (Forward LR method) were used to assess the manner and intensity in which several parameters (demographics, disease-related, labs and medication) power SDAI remission.

Results. SDAI remission was reported in 39.7% cases. We identified nine relevant predictors for SDAI remission at 12 months of therapy by univariate analysis, including: age ≤ 50 years, disease onset ≤ 5 years, RA stages I and II, functional capacity stages I and II, HAQ-DI ≤ 2 , concomitant sDMARD, baseline CRP ≤ 20 mg/l, IgA-RF ≤ 20 IU/ml and ACPAs ≤ 40 IU/ml. A mathematical model was further generated, based only on six out of nine parameters: age, disease stage, functional capacity, concomitant sDMARDs, CRP and ACPA. This model expresses a solid approximation for the analysed cases (the Hosmer-Lemeshow test $\lambda^2 = 0.931$, $p = 0.920 \geq 0.05$, Cox and Snell $R^2 = 0.399$). Finally, three significant factors were recognized (age under 50, disease stages I and II, ACPA levels ≤ 40 IU/ml), predicting SDAI remission with an overall constant precision of 83.3%. However, no significant impact on SDAI remission prediction was reported when adding other parameters to the above mentioned model.

Conclusion. SDAI remission can be predicted in established RA patients using three major predictors, including age ≤ 50 years, disease stages I and II and baseline ACPA levels ≤ 40 IU/ml.

Keywords: anti-TNF agents, established rheumatoid arthritis, predictors, remission, SDAI

INTRODUCTION

Rheumatoid arthritis (RA) is a complex, multifactorial and heterogeneous disease with significant interpatient variation in symptoms, disease course and therapeutic response (1).

Recent advances in understanding the pathologic pathways of RA as well as the availability of emerging newer biological drugs and “treat-to-target” paradigm have redefined the clinical, functional and radiological outcomes of the disease, remission becoming an increasingly attainable goal (2). As the ultimate target of RA management is to achieve re-

mission and to prevent the progression of joint damage, rheumatologists focus also on the durability of sustained remission and the identification of predictors, indication of monitoring and potential cessation of treatment in different RA settings (3).

Various definitions of RA remission have been developed and used over the last years, at least three of them being still employed: Disease Activity Score (DAS)-28 ≤ 2.6 , Simplified Disease Activity Index (SDAI) ≤ 3.3 and Clinical Disease Activity Index (CDAI) ≤ 2.8 score (4,5). Recently, the *American College of Rheumatology* (ACR) and the *European*

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League Against Rheumatism (EULAR), together with the *Outcome Measures in Rheumatology Initiative* (OMERACT) jointly created a new definition of RA remission (6) – the ACR/EULAR provisional definition of RA remission – intended to be used in clinical trials.

SDAI adds the scores from five outcome measures including tender and swollen joint count, patient and physician global assessment of disease and C-reactive protein (CRP). Three cut-off values are currently recognized for SDAI, 3.3 for remission, 11 for low disease activity (LDA), 26 for moderate disease activity (MDA), and more than 26 for high disease activity (7,8).

It is widely accepted that SDAI correlates well with DAS28 and ACR response criteria, as well as with Health Assessment Questionnaire Disability Index (HAQ-DI) (9). Moreover, recently published data defined minor, moderate and major response on SDAI as 50%, 70%, and 85% improvement, based on best agreement with ACR20, ACR50, and ACR70 responses, respectively (8). These definitions allow for various degrees of residual disease activity (2). Furthermore, reported remission rates vary depending on the definition used, from approximately 9% to 17% with the ACR criteria, 14% with CDAI or RAPID3, and 20% to 33% with DAS (10,11).

The accuracy of different composite scores in classifying remission in RA may further be analyzed from the perspective of residual inflammatory activity detected by Doppler and power Doppler ultrasound: SDAI classification of remission is closer than DAS28 to the concept of an absence of inflammatory activity (12).

The therapeutic response varies considerably among patients with RA. Part of this fluctuation is dependent on patient characteristics, such as: age, sex, concomitant medication, body mass index or smoking status. In addition, the clinic response depends on disease activity and severity, the presence of autoantibodies, genetic background as well as cytokine levels and immune cells phenotype (B or T, Th1 or Th17) (13).

Anti-TNF agents induce an early therapeutic response, with a major impact on disease evolution and prognostic (14). However, not all patients respond to TNF inhibitors, and moreover a large number do not achieve remission. A recent study showed that approximately 30% of the patients with RA do not respond or do not tolerate the first anti-TNF agent, while around 50% of them suspend the therapy within the first 2 years (15).

Consequently, a domain of interest for both researchers and practitioners, promoted in nowadays medicine, is identifying the patients that will respond to a particular therapeutic agent and predictors of the response or of the non-response. Therefore, knowing the factors that can influence the therapeutic response to a certain biological agent allows for individualized management, disease evolution optimization, minimizing the risks and maximizing cost-efficiency.

With this background, we aimed to identify predictors for SDAI remission in active established RA forms treated with TNF inhibitors.

PATIENTS AND METHODS

We performed a 12-months prospective observational study in ninety consecutive RA patients (fulfilling the 1987 modified ACR diagnostic criteria for RA) with severe active disease (DAS28 > 5.1) despite sDMARD, requiring biologic therapy for optimal control of the disease.

Inclusion and exclusion criteria in the current study were derived from those endorsed by the Romanian National Board for Biologic Therapy in RA meaning treatment with anti-TNF agents as first line bDMARD in RA with high disease activity developing failure to previous therapy with at least two sDMARD (16).

Patients were further stratified according to their TNF inhibitor, 33 RA receiving adalimumab (ADA), 30 RA etanercept (ETA) and 27 RA infliximab (INF).

Classic doses and administration pathways were used as recommended by manufacturers for each biological agent; concomitant sDMARD including methotrexate (MTX), leflunomide (LEF), sulfasalazine (SSZ) and hydroxychloroquine (HCQ) were given in all the patients, while low doses of corticosteroids (CS) were permitted only if present at the baseline evaluation.

Standard assessments consisted of 28 tender and swollen joint count, patient reported outcomes (general health, pain, HAQ-DI), inflammation (C reactive protein, CRP, erythrocyte sedimentation rate, ESR), immunology (total rheumatoid factor and IgA isotype, anti-cyclic citrullinated peptide antibodies, ACPA), as well as disease activity scores (DA28-ESR and SDAI). All parameters were performed regularly (every three months) except immunological tests which were evaluated every six months. Total RF was measured by latex immune-turbidimetric

method (Cobas 800; Roche; cut-off value of 14 IU/ml) and IgA-RF by ELISA (cut-off 20 IU/ml), while IgG-ACPA by Fluoro-Immuno-Enzymatic Assay (PHADIA250, PHADIA; cut-off 10 IU/ml).

The main outcome of our study was SDAI remission (SDAI ≤ 3.3) at follow-up were considered in remission, those with a SDAI ranging between 3.3 and 11 with low disease activity and between 11 and 26 as having moderate activity. Treatment response measured by EULAR-DAS28 criteria (14).

Local ethical committee approval and informed consent were obtained prior to enrollment.

STATISTICAL ANALYSIS

Univariate and multivariate logistic regression analysis (Forward LR) (odds-ratio with 95% CI and 2-tailed p) were used to estimate the association between potential predictors and SDAI remission at 12 months; statistical analysis was carried out with SPSS16.

RESULTS

Patients and remission rates

Ninety long-standing RA, mainly female (81.1%), with an average age of 55.56 ± 10.75 years, and an average disease duration of 10.9 ± 6.2 years were considered eligible and enrolled in our study. At inclusion, 74.4% patients were classified as RA stages III and IV, 72.2% had RF positivity and 60% ACPA positivity; average SDAI was 51.38 ± 5.42 and HAQ-DI was 2.02 ± 0.33 (Table 1).

During the first 12 months of treatment, 50 patients (56.8%) achieved low disease activity, while 35 patients (39.7%) were in remission according to SDAI criteria. Subgroup analysis showed: 42.4% remission for ADA, 36.6% for ETA and 40% for the INF group.

Univariate regression analysis – predictors

Although all clinical and lab variables as well as demographic and therapeutic data were independently analyzed by univariate logistic regression, only nine parameters were statistically significant ($p < 0.05$) and further used as predictors for SDAI remission: onset before 50 years (OR:5.25, 95% CI 2.27-12.14; $p = 0.000$), a history of disease of at least 5 years (OR:5.53, 95% CI 2.40-12.75; $p = 0.000$), RA stages I and II (OR:4.22, 95% CI 1.99-8.94; $p = 0.000$), baseline functional status as reflected by

TABLE 1. Demographics, clinical and biological characteristics of RA patients at baseline

| RA characteristics | |
|-----------------------------|-------------------|
| Age (years)* | 55.56 \pm 10.75 |
| Women** | 73 (81.1%) |
| RA stagesIII/IV** | 67 (74.4%) |
| Concomitant CS** | 50 (50.6%) |
| Concomitant DMARDs** | |
| MTX | 23 (25.6%) |
| LEF | 28 (31.1%) |
| Others | 39 (43.3%) |
| TJC (28)* | 18.53 \pm 2.82 |
| SJC (28)* | 11.81 \pm 2.42 |
| DAS28-ESR* | 7.50 \pm 0.40 |
| SDAI | 51.38 \pm 5.42 |
| HAQ-DI (0-3)* | 2.02 \pm 0.33 |
| ESR (mm/1h)*** | 66.61 |
| CRP (mg/liter)*** | 36.43 |
| RF (IU/ml)*** | 228.73 |
| RF isotype A (IU/ml)*** | 41.05 |
| ACPA (IU/ml)*** | 99.3 |

ACPA, anti-cyclic citrullinated peptide antibody; CRP, C-reactive protein; DAS28, Disease Activity Score; DMARDs, Disease Modifying Antirheumatic Drugs; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; LEF, leflunomide; MTX, methotrexate; CS, corticosteroids; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC, swollen joint count; SDAI, Simplified Disease Activity Index; TJC, tender joint count; *, mean \pm SD; **, n (%); ***, mean

functional classes I and II and a HAQ-DI ≤ 2 (OR:2.67, 95% CI 1.07-6.68; $p = 0.022$; OR:2.39, 95% CI 1.02-5.60; $p = 0.034$, respectively), baseline CRP ≤ 20 mg/l (OR:1.75, 95% CI 0.81-3.73; $p = 0.041$), IgA-RF ≤ 20 IU/ml (OR:5.76, 95% CI 1.43-23.23; $p = 0.002$), ACPA ≤ 40 IU/ml (OR:1.99, 95% CI 0.95-4.17; $p = 0.047$) and concomitant sDMARDs (OR:5.50, 95% CI 1.36-22.13; $p = 0.003$) (Table 2). Gender, clinical individual parameters and ESR were not predictors for treatment response our study ($p > 0.05$).

Multivariate regression analysis (Forward LR)

A mathematical model was generated subsequently, based on several parameters, as follows: age ≤ 50 years, RA disease stages I and II, functional capacity I and II, concomitant sDMARD, baseline CRP ≤ 20 mg/l and ACPA ≤ 40 IU/ml (Table 3). Therefore, our model represents a solid approximation for the analysed case (the Hosmer-Lemeshow test $\lambda^2 = 0.931$, $p=0.920 \geq 0.05$, Cox and Snell $R^2 0.399$).

Finally, only three significant predictors were selected: age ≤ 50 years, RA stages I and II and the ACPA levels ≤ 40 IU/ml at baseline. These factors support a correct prediction of SDAI remission, with an overall precision of 83.3%. All other analysed

TABLE 2. Significant predictors for SDAI remission

| Parameter | Spearman coefficient | p | OR, IC 95% |
|--------------------------|----------------------|-------|---------------------|
| Age ≤ 50 years | 0.463 | 0.000 | 5.259, 2.277-12.147 |
| Disease onset ≤ 5 years | 0.492 | 0.000 | 5.536, 2.402-12.758 |
| Disease stages I/II | 0.420 | 0.000 | 4.225, 1.995-8.947 |
| Functional capacity I/II | 0.241 | 0.022 | 2.678, 1.073-6.682 |
| HAQ-DI ≤ 2 | 0.224 | 0.034 | 2.391, 1.020-5.605 |
| Concomitants DMARD | 0.311 | 0.003 | 5.500, 1.366-22.137 |
| CRP levels ≤ 20 mg/l | 0.147 | 0.041 | 1.750, 0.819-3.739 |
| RF IgA levels ≤ 20 UI/ml | 0.321 | 0.002 | 5.768, 1.432-23.234 |
| ACPA levels ≤ 40 UI/ml | 0.194 | 0.047 | 1.994, 0.952-4.177 |

ACPA, anti-cyclic citrullinated peptide antibody; CRP, C-reactive protein; sDMARD, synthetic Disease Modifying Antirheumatic Drugs; HAQ-DI, Health Assessment Questionnaire Disability Index; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index.

TABLE 3. Variables included in the predictive model for SDAI remission

| Initially | Variables | Score | df | Sig. |
|-----------|--------------------------|--------|----|------|
| | Age ≤ 50 years | 19.221 | 1 | .000 |
| | Disease stages I/II | 23.061 | 1 | .000 |
| | Functional capacity I/II | 12.449 | 1 | .000 |
| | MTX addition | 2.529 | 2 | .282 |
| | LEF addition | 2.005 | 1 | .157 |
| | Other sDMARD | .485 | 1 | .486 |
| | CRP levels ≤ 20 mg/l | .769 | 1 | .381 |
| | ACPA levels ≤ 40 IU/ml | 17.931 | 1 | .000 |

ACPA, anti-cyclic citrullinated peptide antibody; CRP, C-reactive protein; sDMARD synthetic Disease Modifying Antirheumatic Drugs; HAQ-DI, Health Assessment Questionnaire Disability Index; LEF, leflunomide; MTX, methotrexate; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index.

predictors had no positive impact on the proposed mathematical model (Table 4).

DISCUSSION

Given the destructive and disabling nature of RA, the risk of secondary effects, considerable costs and variable therapeutic response, it is mandatory to identify predictive factors among demographic, clinic, biologic (inflammatory and immunologic), imagistic and genetic parameters in order to define the steps required to obtain remission or low disease activity status.

The topic of therapeutic response to different therapies, either sDMARDs or bDMARDs, was largely addressed in the last decade; moreover, a significant number of studies were directed towards identifying biomarkers of response to TNF inhibitors and B-cell depleting agent rituximab (17-22).

TABLE 4. Significant factors in our predictive model for SDAI remission

| | | B | S.E. | Wald | df | Sig. | Exp(B) |
|--------|------------------------|--------|------|--------|----|------|--------|
| Step 1 | Disease stages I/II | -2.445 | .557 | 19.270 | 1 | .000 | .087 |
| | Constant | 1.293 | .302 | 18.358 | 1 | .000 | 3.643 |
| Step 2 | Age ≤ 50 years | -2.013 | .577 | 12.176 | 1 | .000 | .134 |
| | Disease stages I/II | -2.358 | .613 | 14.817 | 1 | .000 | .095 |
| | Constant | 1.988 | .415 | 23.007 | 1 | .000 | 7.303 |
| Step 3 | Age ≤ 50 years | -2.121 | .636 | 11.112 | 1 | .001 | .120 |
| | Disease stages I/II | -2.142 | .665 | 10.387 | 1 | .001 | .117 |
| | ACPA levels ≤ 40 IU/ml | -1.834 | .618 | 8.789 | 1 | .003 | .160 |
| | Constant | 2.666 | .537 | 24.653 | 1 | .000 | 14.380 |

We developed a prediction model for SDAI remission in patients with established RA, based on three main parameters (age at onset, disease stage and ACPA status), that successfully classified over 83.3% of patients in our cohort; thus, patients with a disease onset before 50, a RA stage I or II, and low ACPA at baseline (under 40 IU/ml) were most likely to achieve SDAI remission after a 12-months of follow-up under anti-TNFs.

The proposed mathematical model for predicting SDAI remission after 12 months of TNF inhibitors therapy, based on independent factors, is appropriate for a particular disease pattern, with an associated factor of 0.399 (Cox and Snell).

In clinical practice, this model is relevant for a well-defined RA subtype: age ≤ 50 years, disease stage I/II, functional capacity I/II, low CRP levels (≤ 20 mg/l) and mild immunologically syndrome (ACPA levels ≤ 40 IU/ml), concomitant sDMARD.

Making the personalized choice of RA treatment in the era of targeted therapy is commonly based on optimal patient outcomes. Therefore, matching patients to a specific drug is powered not only by correct assessment of remission but also by identifying and validating predictors for response. Rheumatologists currently focus on different ways to control disease and assess remission, several standardized measurement tools (DAS28, CDAI, SDAI, RAPID3, ACR/EULAR) and wide ranging remission rates being recognized (4,6,10,11).

To our knowledge no previous study has addressed the issue of SDAI remission in the particular settings of established RA. Although we used SDAI remission at a single time point (12 months) as the

individual criterion to evaluate treatment response, three independent predictors were finally available: age, RA stage and ACPA levels. However, a wider panel of biomarkers, laboratory as well as imaging should be examined.

We accept that it still premature to change the landscape of risk stratification in established RA based on our predictive model, but at this moment is best at predicting those patients who are likely to achieve SDAI remission at 12 months. Future work is required to optimize this approach.

Availability of newer therapies is doubled by a change in rheumatologists thinking changed the tre-

atment paradigm in RA. The clinical rationale for the treat to target approach as well as the concept of predicting remission in established RA are useful to tailor personalized treatment levels.

CONCLUSION

SDAI remission can be predicted in patients with established RA using three relevant predictors: age \leq 50 years, disease stages I or II, and baseline ACPA levels \leq 40 IU/ml.

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