

Association between red cell distribution width and response to methotrexate in rheumatoid arthritis

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SUMMARY

Red cell distribution width (RDW) is an unconventional biomarker of inflammation. We aimed to explore its role as a predictor of treatment response in rheumatoid arthritis (RA).

Eighty-two RA patients (55 females), median age [interquartile range] 63 years [52-69], were selected by scanning the medical records of a rheumatology clinic, to analyze the associations between baseline RDW, disease activity scores and inflammatory markers, as well as the relationship between RDW changes following methotrexate (MTX) and treatment response.

The lower the median baseline RDW, the greater were the chances of a positive EULAR response at three months, 13.5% [13.0-14.4] being among those with good response, vs 14.0% [13.2-14.7] and 14.2% [13.5-16.0] ($p=0.009$) among those with moderate and poor response, respectively. MTX treatment was followed by a significant RDW increase ($p<0.0001$). The increase of RDW was greater among patients with good EULAR response, becoming progressively smaller in cases with moderate and poor response (1.0% [0.4-1.4] vs. 0.7 [0.1-2.0] vs. 0.3 [-0.1-0.8]; $p=0.03$).

RDW is a strong predictor of early response to MTX in RA. RDW significantly increases after MTX initiation in parallel to treatment response, suggesting a role as a marker of MTX effectiveness.

Key words: Red cell distribution width, rheumatoid arthritis, methotrexate, biomarker.

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■ INTRODUCTION

Red cell distribution width (RDW) is a measure of the variability in size of circulating erythrocytes (1). Recently, it has gained popularity as a novel prognostic biomarker: in a prospective cohort of middle-aged and older adults, for every 1% increment in RDW, all-cause mortality risk increased by 22% (2), in line with other reports that confirmed the predictive role of RDW for cardiovascular (3) and cancer-related mortality (4).

Among systemic lupus erythematosus (SLE) patients, RDW is directly associated with disease activity and inflammatory markers; a normal RDW predicts a better response to treatment (5). A higher RDW has been reported in patients with systemic

sclerosis than in healthy controls, marking cardiopulmonary involvement (6, 7). Patients affected by rheumatoid arthritis (RA) have a higher RDW than healthy subjects (8); a greater RDW is associated with more severe disease (9) and predicts cardiovascular events in RA (10). Nevertheless, the potential role of RDW in the prediction of response to treatment in RA is unexplored. In this study, we aimed to evaluate whether baseline RDW in RA patients is associated with early response to methotrexate (MTX) treatment.

■ MATERIALS AND METHODS

We performed a retrospective analysis of clinical records of patients affected by RA evaluated at the Immunorheumatology

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Unit of the Maggiore della Carità Hospital in Novara between 1st January 2010 and 31st December 2018.

We included patients who:

- 1) fulfilled 2010 ACR/Eular classification Criteria (11);
- 2) were not on MTX and were starting MTX;
- 3) had a chemistry panel performed at the central laboratory of the Maggiore della Carità Hospital in Novara, at the beginning of MTX treatment and after 3 months.

Concomitant treatments with hydroxychloroquine or low dose prednisone were admitted.

The study has been conducted in accordance with the local ethical guidelines.

Out of 233 records, 45 were discarded because they presented overlapping characteristics with other rheumatologic diseases and 106 because of the unavailability of laboratory data at baseline and/or after 3 months of MTX treatment. Thus, the final study population included 82 RA patients.

We recorded demographic, clinical and laboratory data at baseline and after treat-

ment. RDW was measured by XN2000 Hematology Analyzer, Sysmex.

Treatment response was evaluated at the follow-up visit at 3-months and graded according to EULAR response criteria (12).

Statistical analysis

Data were analyzed by the statistical software package MedCalc v.18.10.2 (MedCalc Software, Broekstraat 52, 9030, Mariakerke, Belgium). For continuous variables, the measures of centrality and dispersion of data chosen were medians and interquartile ranges [IQR].

The correlation between continuous variables was tested by Spearman's rank correlation coefficient; the trend for the baseline RDW and for the RDW variations after treatment according to different categories of EULAR response were assessed by the Jonkheere-Terpstra trend test. We built an ROC curve to evaluate the predictive value of RDW for a good EULAR response.

Predictors of good EULAR response were identified by multivariate logistic regression analysis; we built two different models. In the first one, we included RDW and

Table 1 - Main demographic and clinical features of the study population. Continuous variables are presented as median [Interquartile range]; categorical variables are shown as N. %.

Variable	General population (N. 82)	Good responders (N. 32)	Moderate and poor responders (N. 50)	p
Age, years	62.5 [52.0-69.0]	62.5 [51.0-67.5]	63.0 [53.7-69.3]	0.65
Gender, F/M	55 (67.1)/27 (32.9)	21 (65.6)/11 (34.4)	34 (68.0)/16 (32.0)	0.80
Seropositive arthritis (RF and/or ACPA), y/n	58 (70.7)/24 (29.3)	25 (78.1)/7 (21.9)	33 (66.0)/17 (34.0)	0.32
RDW, %	13.9 [13.1-14.8]	13.5 [13.0-14.4]	14.1 [13.3-15.7]	0.01
Hb, gr/dL	13.4 [12.4-14.3]	13.5 [13.0-14.4]	13.0 [12.0-13.9]	0.14
MCV, fl	87.6 [84.5-91.2]	86.3 [83.9-91.3]	88.2 [85.4-91.3]	0.28
CRP, mg/dL	0.82 [0.31-1.73]	0.91 [0.36-1.69]	0.66 [0.25-1.82]	0.48
ESR, mm/h	18 [9-30]	19 [12-32]	16 [8-27]	0.33
DAS28-ESR	4.20 [3.27-5.03]	4.85 [4.19-5.55]	3.51 [2.85-4.69]	0.0002
Methotrexate dose, mg/week	10.0 [10.0-15.0]	10.0 [10.0-15.0]	10.0 [10.0-11.3]	0.44
Steroid, y/n	73 (89.0)/9 (11.0)	28 (87.5)/4 (12.5)	44 (88.0)/6 (12.0)	0.73
Prednisone dose, mg/day	5.0 [5.0-10.0]	5.6 [5.0-10.0]	5.0 [2.5-8.1]	0.20
Hydroxychloroquine, y/n	16 (19.5)/66 (80.5)	7/25	9/40	0.78
Disease duration, months	6 [2-26]	6 [2-19]	8 [2-28]	0.38

F, females; M, males; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibodies; RDW, red cell distribution width; Hb, haemoglobin; MCV, mean corpuscular volume; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; DAS28-ESR; disease activity score ESR; y, yes; n, no.

the inflammatory markers ESR and CRP; in the second one, we included known predictors of treatment response (RDW, age, gender, haemoglobin and prednisone daily dose).

The RDW post-treatment was compared with the baseline RDW by the Wilcoxon test for paired samples.

The level of significance chosen for all statistical tests was 0.05 (two-tailed).

■ RESULTS

We selected 82 patients; in Table I we report the main features of the general population. At baseline, RDW had no association with erythrocyte sedimentation rate (ESR) ($\rho=0.141$, $p=0.21$), while was in direct correlation with C-reactive protein (CRP) ($\rho=0.258$, $p=0.02$).

After three months of MTX treatment, EULAR response was good in 32 (39.0%) patients, moderate in 20 (24.4%) and poor in 30 (36.5%). RDW was significantly lower in patients with a good EULAR response (Table I). Moreover, we observed a significant trend towards poorer EULAR responses at 3 months in patients with larger RDW at baseline (Figure 1; RDW 13.5[13.0-14.4] % in patients with good EULAR response, 14.0[13.2-14.7] % with moderate response and 14.2[13.5-16.0] % with poor response, respectively; $p=0.009$).

In Figure 2, we report the ROC curve for RDW; a value $>13.7\%$ predicts a poor/moderate response, being 69.4% sensitive and 62.5% specific.

At multivariate logistic regression, RDW ($p=0.02$), but not CRP or ESR ($p=0.61$ and $p=0.38$ respectively), was a predictor of a good EULAR response. In a further logistic regression model including known predictors of EULAR response, RDW was the only independent predictor of the 3-months response to MTX (1.53[1.01-2.31]; $p=0.04$); conversely, age (1.00[0.97-1.05]; $p=0.68$), gender (1.12[0.37-3.43]; $p=0.84$), haemoglobin (0.88[0.58-1.33]; $p=0.54$) and prednisone daily dose (0.99 [0.95-1.05]; $p=0.80$) did not affect response to treatment.

MTX treatment was followed by an increase of RDW, from 13.9[13.1-14.8] % to 14.7[14.0-15.8] % ($p<0.0001$), while haemoglobin levels remained unchanged (13.4[13.0-13.6] gr/dL vs. 13.2[12.9-13.6] gr/dL). The greater the increase in RDW, the better was the EULAR response (1.0[0.4-1.4] % in good responders vs. 0.7[0.1-2.0] % in moderate responders vs. 0.3[-0.1-0.8] % in poor responders; $p=0.03$).

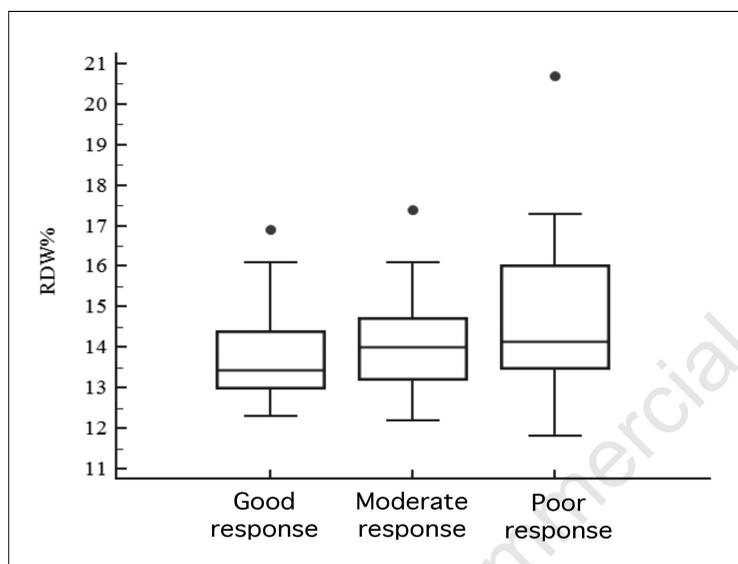


Figure 1 - Baseline RDW according to EULAR response at three months. This box & whiskers plot demonstrates the presence of a significant trend for baseline RDW according to the EULAR response ($p=0.008$).

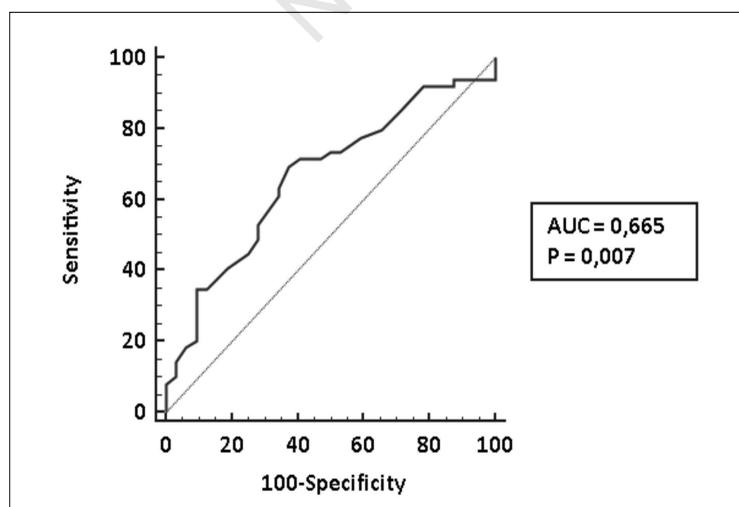


Figure 2 - ROC Analysis for RDW.

■ DISCUSSION AND CONCLUSIONS

In the present study, the two major findings are:

- 1) a larger baseline RDW is associated with poorer treatment response at three months;
- 2) MTX is followed by an increase in RDW from baseline: the larger the increase, the better the patient responds to MTX.

RDW has been reported to increase in patients affected by RA and to correlate with inflammatory markers (8, 13) and disease activity (9). In our cohort, we confirmed the association with CRP, but not with ESR, in line with a previous study (14). This supports the idea that RDW might not be merely considered a surrogate biomarker of inflammation in patients affected by RA; conversely, RDW could be a valuable prognostic marker in RA. Indeed, a higher RDW at baseline is predictive of a poorer response to MTX. This is the first paper reporting this finding in RA; similarly a larger RDW predicts poor treatment response in SLE (5). The reason why this happens might relate to the interference that inflammation has on erythropoiesis, mediated by inflammatory cytokines (15). Indeed, RDW is positively associated with TNF α and IL-6, witnessing that, the higher the plasmatic concentration of inflammatory cytokines, the larger the impact on erythropoiesis. In this context, RDW seems far more useful than the other inflammatory markers, as demonstrated by our logistic regression, which confirms that RDW, but not CRP and ESR, predicts a good EULAR response.

MTX induces a significant increase in RDW, as recently reported by Held et al. (16), probably related to the interference of the drug with bone marrow activity. Strikingly, the higher the increase of RDW, the better the response to treatment. This is an apparent paradox; in fact, a more significant dampening of inflammatory response is paralleled by the development of anisocytosis. A possible explanation of this finding might be that the variation of

RDW marks the responsiveness to MTX treatment. The impact on erythropoiesis could therefore represent a biomarker of effectiveness of MTX. Therefore, a smaller RDW increase may help to intercept patients deserving an earlier switch to a more aggressive treatment strategy.

Our study is limited by the small sample size and by its retrospective design. With this caution, RDW is a promising, simple, inexpensive and easy to use a novel tool for prognostic stratification of RA patients, capable of identifying patients with a more severe disease at baseline and less likely to respond to MTX.

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