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Joint Bone Spine

Letters to the editor

Calprotectin alone is not sufficient to predict response to methotrexate in early ACR/EULAR 2010 rheumatoid arthritis: Analysis of the ESPOIR cohort

suppl.
Informations

ARTICLE INFO

Methotrexate (MTX) remains the cornerstone of RA (Rheumatoid arthritis) treatment according to EULAR (European League Against Rheumatism) recommendations [1]. However, theragnostic tools, which help to better identify responders to MTX, are scarce [2,3]. Calprotectin is a neutrophil-related protein which is locally released in inflammatory joints in contrast with CRP (C reactive protein). Calprotectin has been suggested as a biomarker for structural damage prediction in RA [4].

We conducted a post-hoc analysis of prospective ESPOIR cohort [5], NCT03666091, of early arthritis on patients from 18 to 70 years old, with 2 or more inflammatory arthritis for a period lasting between 6 weeks and 6 months, in order to assess whether baseline serum calprotectin levels would be predictive of a good EULAR response to MTX. We included patients (i) who fulfilled the 2010 EULAR criteria for RA at baseline, (ii) with a baseline DAS28 > 3.2, (iii) were naïve from any DMARD or corticosteroids and (iv) who were treated with monotherapy MTX, oral route, with a dose superior to 0.15 mg/kg/week for at least 6 months. Primary outcome measure was EULAR good response. A total of 98 patients fulfilling the inclusion criteria were analyzed Fig. S1. A total of 48 patients (49%) were classified as responders upon 6 months of MTX treatment. Responders were significantly younger (Table 1). A Younden approach determined a threshold of 446 mg/l, calprotectin was a predictive marker for good EULAR response to MTX, Odds Ratio (OR) 2.8, 95% confidence interval (CI) [1.2, 6.8], $P = 0.024$, (area under the curve of 0.61). Likewise, age under 47 was predictive of a good response to MTX, OR 2.5, 95%CI [1.1, 5.9], $P = 0.005$. The multivariable model including potential predictive factors presenting a P-value < 0.2 in the univariate analysis showed that calprotectin and age displayed a sensitivity of 0.54, 95%CI [0.39, 0.69] and specificity of 0.76, 95%CI [0.62, 0.87] (Fig. 1). The multivariable model including CRP did not add any predictive value.

Despite the fact that MTX is the first line treatment of RA, few studies have investigated predictive markers of clinical response to MTX. Age has been reported as a predictive factor in a study [2] but not in another [3]. Even MTX polyglutamate metabolites failed to predict disease activity in patients with RA who were receiving long-term MTX therapy [6]. We included a broad spectrum of early RA patients in order to study real-life settings. Another strength of our study is the large number of covariates collected in the ESPOIR cohort, which minimized the risk of bias. A few limits should be emphasized. First, we excluded from our analysis patients who withdrew MTX because of side effects in order to focus on MTX efficacy. Second, we aimed at characterizing predictive factors of response to MTX when first prescribed according to international recommendations. Therefore, we did not include patients starting MTX with low dose, which explains why a large number of patients of the ESPOIR cohort were discarded from our analysis. Nevertheless, calprotectin was not predictive amongst those patients. The results of our study suggest the potential interest of a multivariable score including calprotectin and age as a tool for personalized medicine in early RA management.

Table 1
Baseline characteristics.

Total ($n = 98$)	Responders ($n = 48$)	Non-responders ($n = 50$)	P-value*
Women, n (%)	80 (82)	36 (75)	0.2
Age, years	50.6 (39.4–56.4)	46.4 (37.4–55.3)	0.03
BMI, kg/m^2	23.1 (20.4–25.3)	22.2 (20.5–24.7)	0.4
DAS28-ESR	5.4 (4.7–6)	5.4 (4.7–5.9)	0.9
ESR, mm/h	24.0 (14.0–39.5)	27.5 (14–36.5)	0.5
CRP, mg/l	9.0 (0.75–24.8)	11.0 (4–26.5)	0.2
MTX dose, mg/kg/week	0.20 (0.18–0.24)	0.20 (0.18–0.25)	0.6
MTX dose, mg/week	12.5 (10–15)	12.5 (10–15)	1
RF positive, n (%)	57 (58)	28 (58)	1.0
RF IgM positive, n (%)	61 (62)	29 (60)	0.9
RF IgA positive, n (%)	55 (56)	24 (50)	0.3
ACPA positive, n (%)	61 (62)	28 (58)	0.6

* P values corresponding to Chi^2 or Wilcoxon tests when appropriate. Patients were considered as ACPA or RF positive when ACPA or RF titer > to the upper limit of normal [ULN] for the laboratory and assay; RF: rheumatoid factor; BMI: Body Mass Index; DAS: Disease Activity score; CRP: Creative Protein; MTX: Methotrexate; RF: Rheumatoid Factor; ACPA: Anti-Citrullinated Protein Antibodies; ESR: Erythrocyte Sedimentation Rate. Data are expressed as medians and interquartile range or otherwise stated.
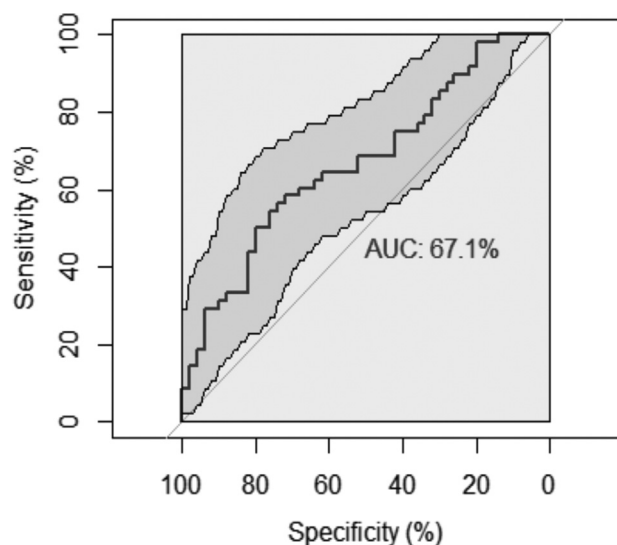
Fig. 1. Age and calprotectin are associated with a good EULAR response in RA (Rheumatoid arthritis) patient treated by methotrexate ($n = 98$). AUC: Area Under the Curve; EULAR: European League Against Rheumatism. Thin grey lines indicate 95% confidence interval.

Contribution

S.L. critically reviewed the study proposal; C.B. critically reviewed the study proposal, A.C. generated statistical analysis and critically reviewed the study proposal; D.W. served as scientific advisor and critically reviewed the study proposal; F.B. served as scientific advisor and critically reviewed the study proposal; B.T. served as scientific advisor and critically reviewed the study proposal; M.V.C.N. served as scientific advisor, collected data, provided and cared for study patients and critically reviewed the study proposal; P.G. served as scientific advisor and critically reviewed the study proposal; M.H.P. served as scientific advisor and critically reviewed the study proposal; A.B. served as scientific advisor, collected data, provided and cared for study patients.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jbspin.2019.07.001.

References

[1] Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biologicaldisease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960–77.
[2] Saevarsdottir S, Wallin H, Seddighzadeh M, et al. Predictors of response to methotrexate in early DMARD naive rheumatoid arthritis: results from the initial open-label phase of the SWEFOT trial. Ann Rheum Dis 2011;70:469–75.
[3] Wevers-de Boer K, Visser K, Heimans L, et al. Remission induction therapy with methotrexate and prednisone in patients with early rheumatoid and undifferentiated arthritis (the IMPROVED study). Ann Rheum Dis 2012;71:1472–7.
[4] Chevreau M, Paclet M-H, Romand X, et al. Calprotectin is not independent from baseline erosion in predicting radiological progression in early rheumatoid arthritis. Comment on « Calprotectin as a marker of inflammation in patients with early rheumatoid arthritis » by Jonsson et al. Ann Rheum Dis 2018;77:e84.
[5] Combe B, Rincheval N. Early lessons from the recent-onset rheumatoid arthritis cohort ESPOIR. Jt Bone Spine Rev Rhum 2015;82:13–7.
[6] Stamp LK, O'Donnell JL, Chapman PT, et al. Methotrexate polyglutamate concentrations are not associated with disease control in rheumatoid arthritis patients receiving long-term methotrexate therapy. Arthritis Rheum 2010;62:359–68.

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