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BRIEF REPORT

Enhancement of Patient Recruitment in Rheumatoid Arthritis Clinical Trials Using a Multi-Biomarker Disease Activity Score as an Inclusion Criterion

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Objective. Rheumatoid arthritis (RA) clinical trials often exclude patients who have low C-reactive protein (CRP) levels, which slows enrollment into the trial. The purpose of this study was to determine whether high Multi-Biomarker Disease Activity (MBDA) scores (>44) in RA patients with low CRP levels (≤10 mg/liter) could be used as a complement to CRP levels >10 mg/liter to enhance patient recruitment without affecting clinical trial outcomes.

Methods. We evaluated patients from the Swedish Pharmacotherapy (SWEFOT) trial, which did not include any selection criteria for CRP levels. Clinical outcomes were assessed after 3 months of methotrexate (MTX) monotherapy in MTX-naive RA patients (n = 220) and after 3–10 months of add-on therapy in patients who were incomplete responders to MTX alone (MTX-IR) (n = 127). Radiographic outcomes were assessed at 1 year in all patients. Within each cohort, the outcomes were compared between patients with a CRP level of ≤10 mg/liter and an MBDA score of >44 at the start of the respective treatment interval versus those with a CRP level of >10 mg/liter.

Results. Patients with both a CRP level of ≤10 mg/liter and an MBDA score of >44 at baseline had clinical and radiographic outcomes that were comparable to those in patients with a CRP level of >10 mg/liter at baseline. This broadened definition of the inclusion criteria identified an additional 24% of patients in the MTX-naive cohort and 47% in the MTX-IR cohort.

Conclusion. Patient recruitment into RA clinical trials may be substantially enhanced, without any decrease in clinical and radiographic outcomes, by using as an inclusion criterion “a CRP level of >10 mg/liter and/or an MBDA score of >44.”

Clinical trials of new pharmaceutical agents for rheumatoid arthritis (RA) have often used elevated C-reactive protein (CRP) levels as an inclusion criterion in order to reduce the placebo response and increase the likelihood of radiographic progression (1–3). However, the CRP level is often discordant with the level of disease activity, indicating that use of the CRP as an inclusion criterion may exclude patients who have active RA (4–6).

In a study by the Consortium of Rheumatology Researchers of North America (CORRONA), the CRP level was <8 mg/liter in 71% of 9,135 patients with active RA, as defined by the Clinical Disease Activity Index (CDAI) >2.8 (5). Because clinical trial enrollment can be challenging, some RA trials have required little or no ele-
vation of the CRP level at baseline (7,8). The results of these trials were often mixed or negative, suggesting that it is important to ensure the inclusion of appropriate study patients by requiring an objective measure of inflammation. Thus, patient recruitment for RA clinical trials may be enhanced, without undermining the clinical and radiographic outcomes achievable by requiring an elevated CRP level, if a new inclusion criterion could identify patients who have active disease despite having a low CRP level.

The Multi-Biomarker Disease Activity (MBDA) test has been validated for the assessment of disease activity in patients with RA (9). It provides an objective disease activity measure that complements clinically based RA assessment tools (6,10,11). The MBDA instrument is scored on a scale of 1–100, with disease activity categories of high (score >44), moderate (score 30–44), and low (score <30). Our previous study of patients from the Swedish Pharmacotherapy (SWEFOT) trial found that the MBDA score frequently detected high levels of disease activity when the CRP level did not: 30% of patients had a low CRP level (≤10 mg/liter) at baseline, yet 58% of them had high MBDA scores (>44), and 24% of those patients showed rapid radiographic progression at year 1 (6). The SWEFOT study did not include a CRP enrollment criterion, and all patients were treated according to the protocol, irrespective of their CRP values (12).

In the present study, we analyzed data from SWEFOT to explore the possibility that the MBDA score may be useful as an inclusion criterion for RA clinical trials. We hypothesized that patients with a high MBDA score and a low CRP level may have active disease and would have similar clinical outcomes and degrees of radiographic progression as patients with an elevated CRP level. If so, inclusion of patients with a high MBDA score may enhance recruitment to RA clinical trials.

PATIENTS AND METHODS

Two patient populations commonly targeted for new drug therapies were analyzed: methotrexate (MTX)-naive patients and MTX–incomplete responder (MTX-IR) patients. The MTX-naive cohort (n = 220) included those patients from our previous study (6) who had complete clinical and serologic data available at both baseline and 3 months. Patients in the MTX-IR cohort (n = 127) had a Disease Activity Score in 28 joints using the erythrocyte sedimentation rate (DAS28-ESR) that was >3.2 after 3 months of MTX treatment and were randomized to begin intensified treatment (MTX with sulfasalazine and hydroxychloroquine or MTX with infliximab). These MTX-IR patients had complete clinical and serologic data available at both 3 months and 1 year. Radiographs were available at baseline and 1 year for both cohorts (data available upon request from the corresponding author).

Clinical assessments included the DAS28-ESR (13), CDAI (14), Simplified Disease Activity Index (SDAI) (15), tender joint count (TJC), and swollen joint count (SJC). The response according to the European League Against Rheumatism (EULAR) criteria (16) was also determined. Radiographic progression was assessed by the change in the modified Sharp/van der Heijde score (ASHS) (17). Descriptive statistics were used to evaluate disease activity and radiographic damage at baseline, as well as changes over time.

MBDA testing was performed on deidentified frozen serum samples obtained at the baseline visit for the trial (i.e., prior to treatment) and at the 3-month visit (i.e., prior to randomization) in the MTX-IR group. MBDA analyses were performed at Crescendo Bioscience in their Clinical Laboratory Improvement Amendments (CLIA)–approved laboratory. A validated algorithm was used to generate the MBDA score for each sample (scale of 1–100) (9,18). P values were calculated using Wilcoxon’s rank sum test for continuous variables and chi-square test for categorical variables.

Patients were cross-classified by CRP level (≤10 mg/liter versus >10 mg/liter) and by MBDA score (>44 versus ≤44) into 1 of 4 groups (groups a–d) (Figures 1A and B). To understand how the conventional approach (Figure 1A) to clinical trial recruitment, which requires an elevated CRP level (defined in this study as >10 mg/liter; groups c and d), compares to the combined approach (Figure 1B), which also includes patients with a high MBDA score and a low CRP level (group b), we performed 2 types of comparisons. First, patients in group b were compared with patients in groups c and d. Second, patients in group a were compared with patients in groups b, c, and d. Comparisons were made for baseline data and for the change in data over the intervals relevant to each cohort. For MTX-naive patients, baseline corresponds to the baseline SWEFOT visit. For MTX-IR patients, baseline corresponds to the SWEFOT month 3 visit.

RESULTS

Patient groups based on MBDA score and CRP level. The MTX-naive cohort (n = 220) contained 154 patients with elevated CRP levels (>10 mg/liter; groups c and d) and 66 patients with low CRP levels (≤10 mg/liter; groups a and b), of whom 37 had high MBDA scores (>44; group b). The MTX-IR cohort (n = 127) contained 49 patients who at month 3 of the trial (making this the baseline point for the next step in the treatment) had elevated CRP levels (groups c and d) and 78 who had low CRP levels (groups a and b), of whom 23 had high MBDA scores (group b). Thus, when compared with patients who had elevated CRP levels, the presence of a high MBDA score with a low CRP level identified 24% additional patients in the MTX-naive cohort and 47% additional patients in the MTX-IR cohort (Figures 1A and B).

Characteristics of, and outcomes in, the MTX-naive patients with high MBDA scores (>44) and low CRP levels (≤10 mg/liter) as compared with the other patients. To understand how a hypothetical study of MTX-naive patients would be affected if, instead of enrolling only those with elevated CRP levels (>10 mg/liter), it also
included patients with high MBDA scores (>44) and low CRP levels (≤10 mg/liter), we analyzed baseline data and changes from baseline and compared these data in the 4 patient groups based on the MBDA score and the CRP level (Table 1 and data available upon request from the corresponding author).

Figure 1. Study approaches and inclusion/exclusion of patients. A, With the conventional approach, patients were classified according to their baseline C-reactive protein (CRP) level alone (top). B, With the combined approach, patients were cross-classified according to both their CRP level and their Multi-Biomarker Disease Activity (MBDA) score (top). The numbers of patients from the Swedish Pharmacotherapy (SWEFOT) trial who were included/excluded according to each approach are shown for the methotrexate (MTX)-naïve cohort (middle) and for the MTX–incomplete responder (MTX-IR) cohort (bottom).
In the MTX-naive cohort, patients with elevated CRP levels at baseline (groups c and d) had significantly higher levels of disease activity, as determined by scores on the MBDA, the DAS28, and the SDAI, than did those with low CRP levels and high MBDA scores at baseline (group b), due predominantly to the values in Table 1.

**Table 1.** Disease activity and radiographic outcomes among MTX-naive and MTX-IR patients according to baseline CRP level and MBDA score*

| Response measure | CRP ≤10 mg/liter | CRP >10 mg/liter | Intergroup comparison, difference (95% CI), P |
|------------------|------------------|------------------|-------------------------------------------|
|                  | Total cohort     | Group a, MBDA ≤44 | Group b, MBDA >44 | Group c, MBDA ≤44 | Group d, MBDA >44 | Group b versus groups c and d | Group a versus groups b, c, and d |
| MTX-naive cohort |                  |                  |                  |                  |                  |                                |                                |
| No. of patients  | 220              | 29               | 37               | 5                | 149              | –                               | –                               |
| Baseline score† |                  |                  |                  |                  |                  |                                |                                |
| MBDA             | 59.1             | 35.2             | 51.8             | 39.6             | 66.3             | 13.6 (9.8, 17.5) <0.0001        | 27.5 (23.1, 32.0) <0.0001       |
| DAS28            | 5.7              | 5.0              | 5.2              | 5.2              | 6.0              | 0.8 (0.4, 1.1) <0.0001          | 0.8 (0.4, 1.2) <0.0001          |
| SHS              | 4.5              | 1.4              | 5.6              | 3.4              | 4.8              | -0.8 (−3.8, 2.2) <0.920         | 3.5 (0.5, 6.6) <0.004           |
| Disease activity change at 3 months |                  |                  |                  |                  |                  |                                |                                |
| ∆MBDA            | -14.2            | -5.5             | -11.9            | -8.2             | -16.7            | -4.5 (−9.5, 0.4) 0.106          | -10.1 (−15.3, −4.8) 0.0001      |
| ∆DAS28           | -1.7             | -1.5             | -1.6             | -1.2             | -1.8             | -0.1 (−0.6, 0.4) 0.525          | -0.3 (−0.8, 0.2) 0.211          |
| EULAR responders, % | 74               | 76               | 78               | 60               | 73               | -6 (−20, 9) 0.483              | -2 (−19, 15) 0.815              |
| Radiographic change at 1 year |                  |                  |                  |                  |                  |                                |                                |
| ∆SHS at 1 year   | 3.0              | 0.8              | 3.1              | 2.4              | 3.5              | 0.3 (−2.0, 2.6) 0.668          | 2.6 (0.2, 4.9) 0.018           |
| ∆SHS >3 at 1 year, % | 30               | 10               | 35               | 40               | 33               | -2 (−19, 15) 0.815            | 23 (10, 36) 0.012             |
| ∆SHS >5 at 1 year, % | 18               | 0                | 24               | 20               | 19               | -5 (−20, 10) 0.512            | 20 (15, 26) 0.007             |
| MTX-IR cohort    |                  |                  |                  |                  |                  |                                |                                |
| No. of patients  | 127              | 55               | 23               | 3                | 46               | –                               | –                               |
| Baseline score† |                  |                  |                  |                  |                  |                                |                                |
| MBDA             | 48.5             | 33               | 49.8             | 40.3             | 66.9             | 15.4 (10.4, 20.5) <0.0001       | 27.3 (23.5, 31.1) <0.0001       |
| DAS28            | 4.9              | 4.3              | 4.9              | 4.7              | 5.5              | 0.6 (0.1, 1.1) 0.021           | 0.9 (0.6, 1.3) <0.0001         |
| SHS              | 5.0              | 4.6              | 5.5              | 3.3              | 5.5              | -0.1 (−4.6, 4.3) 0.310         | 0.8 (−2.0, 3.5) 0.774          |
| Disease activity change at 1 year |                  |                  |                  |                  |                  |                                |                                |
| ∆MBDA            | -13.5            | -4.2             | -15.4            | -5.3             | -24.3            | -7.7 (−16.6, 1.2) 0.184         | -16.5 (−22.2, −10.8) <0.0001   |
| ∆DAS28           | -1.5             | -1.1             | -1.4             | -0.9             | -2               | -0.5 (−1.2, 0.1) 0.102         | -0.7 (−1.1, 0.3) 0.0002        |
| EULAR responders, % | 77               | 73               | 70               | 67               | 87               | 16 (−5, 37) 0.106             | 8 (−7, 23) 0.298              |
| Radiographic change at 1 year |                  |                  |                  |                  |                  |                                |                                |
| ∆SHS at 1 year   | 3.8              | 1.6              | 4.0              | 1.7              | 6.3              | 2.0 (−2.3, 6.4) 0.274          | 3.7 (1.3, 6.2) 0.005           |
| ∆SHS >3 at 1 year, % | 38               | 24               | 39               | 33               | 54               | 14 (−10, 38) 0.270          | 25 (9, 41) 0.004              |
| ∆SHS >5 at 1 year, % | 21               | 11               | 26               | 0                | 33               | 4 (−18, 27) 0.694            | 18 (5, 32) 0.013              |

*Except where indicated otherwise, values are the mean. CRP = C-reactive protein; MBDA = Multi-Biomarker Disease Activity; 95% CI = 95% confidence interval; DAS28 = Disease Activity Score in 28 joints; SHS = modified Sharp/van der Heijde score; EULAR = European League Against Rheumatism.

† In the methotrexate (MTX)-naive patients, the baseline value for these analyses was also the baseline visit (randomization visit) in the Swedish Pharmacotherapy (SWEFOT) trial, whereas in the MTX incomplete responder (MTX-IR) patients, the baseline visit for these analyses was the month 3 visit in the SWEFOT trial because that was when the next treatment step was initiated.
group d. However, the MBDA score and clinical measures outcome at month 3 and the radiographic outcomes at 1 year were not significantly different. Patients in group a, who had the least evidence of inflammation based on low CRP levels and low-to-moderate MBDA scores (CRP <10 mg/liter and MBDA <44), had significantly less joint damage at baseline, significantly less radiographic progression at 1 year, and a significantly lower percentage of patients with radiographic progression at 1 year as compared with groups b, c, and d combined (Table 1).

Characteristics of, and outcomes in, the MTX-IR patients with high MBDA scores (>44) and low CRP levels (<10 mg/liter) as compared with the other patients. Analyses similar to those above were performed in the MTX-IR cohort (n = 127), using month 3 as the clinical baseline relative to the start of intensified therapy and month 12 as the clinical and radiographic end points for assessing change (Table 1 and data available upon request from the corresponding author). Results for each set of comparisons (group b versus groups c and d, as well as group a versus groups b, c, and d) were similar to those described above, except that the extent to which clinical improvements were larger in groups b, c, and d as compared with group a was greater than that observed in the MTX-naive cohort. Group a in the MTX-IR cohort also had significantly less radiographic progression and a significantly lower percentage of patients with radiographic progression at 1 year as compared with groups b, c, and d combined (Table 1).

Effect of including patients with high MBDA scores (>44) and low CRP levels (<10 mg/liter) in the group of patients with elevated CRP levels (>10 mg/liter). In both the MTX-naive and the MTX-IR cohorts, clinical and radiographic outcomes were similar in patients with either a high MBDA score and a low CRP level or an elevated CRP level (groups b, c, and d) as compared with only those with an elevated CRP level (groups c and d) (Table 2). Thus, in this model, combined enrollment of group b together with groups c and d would have increased the size of the MTX-naive and the MTX-IR populations by 24% and 47%, respectively, without compromising the clinical or radiographic outcomes.

**DISCUSSION**

Inclusion criteria for RA clinical trials often require an elevated level of an acute-phase reactant, such as a CRP level >10 mg/liter, to objectively confirm active inflammation. However, this CRP criterion may limit patient eligibility and slow recruitment because the CRP value can be low in many patients with active disease. This study demonstrated that using the criterion of a high MBDA score and/or an elevated CRP level as a study inclusion criterion could increase the number of patients who are eligible for RA clinical trials.

A limitation of this study is the relatively high level of disease activity at baseline in the patient cohort. This will necessitate further studies to determine the generalizability of our findings.
In this analysis of the SWEFOT study, which we used as a model, 30% of MTX-naïve and 70% of MTX-IR patients would have been excluded by an inclusion criterion of a CRP level of >10 mg/liter. In contrast, the additional inclusion of patients with a CRP level of ≤10 mg/liter and a high MBDA score (>44) would have increased the eligible populations by 24% and 47%, respectively, without meaningfully altering the clinical outcomes or the degree of radiographic progression. Thus, incorporating a high MBDA score as an inclusion criterion may allow for more effective clinical trial recruitment by including patients with active RA who would otherwise be excluded due to a low CRP level.

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AUTHOR CONTRIBUTIONS
All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. van Vollenhoven had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data. Van Vollenhoven, Bolce, Forslind, Petersson.

Analysis and interpretation of data. Van Vollenhoven, Bolce, Hambardzumyan, Saevarsdottir, Forslind, Sasso, Hwang, Segurado, Geborek.

ADDITIONAL DISCLOSURES
Crescendo Bioscience, Inc. provided funding for editorial, graphic, and statistical support and performed the serum analyses for the MBDA score at no cost to the investigators. The employees Crescendo Bioscience, Inc. had a role in the study design, the analysis and interpretation of the data, and the writing of the manuscript. They had no role in collection of the data. Publication of this article was not contingent upon approval by Crescendo Bioscience, Inc. Schering-Plough Sweden provided an unrestricted grant for the original SWEFOT trial (2003–2010).

REFERENCES
1. Maini R, St Clair EW, Breedveld F, Burbridge D, Kalden J, Weisman M, et al, for the ATTRACT Study Group. Infliximab (chimeric anti-tumour necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. Lancet 1999;354:1932–9.
2. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al, for the PREMIER Investigators. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54:26–37.
3. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med 2006;144:865–70.
4. Sokka T, Pincus T. Erythrocyte sedimentation rate, C-reactive protein, or rheumatoid factor are normal at presentation in 35%-45% of patients with rheumatoid arthritis seen between 1980 and 2004: analyses from Finland and the United States. Arthritis Rheum 2009;60:3057–63.
5. Kay J, Morigaeva O, Messing SP, Kremer JM, Greenberg JD, Reed GW, et al. Clinical disease activity and acute phase reactant levels are discordant among patients with active rheumatoid arthritis: acute phase reactant levels contribute separately to predicting outcome at one year. Arthritis Res Ther 2014;16:R40.
6. Hambardzumyan K, Bolce R, Saevarsdottir S, Cruickshank SE, Sasso EH, Chernoff D, et al. Pretreatment multi-biomarker disease activity score and radiographic progression in early RA: results from the SWEFOT trial. Ann Rheum Dis 2015;74:1102–9.
7. Genovese MC, Kavanaugh A, Weinblatt ME, Peterfy C, DiCarlo J, White ML, et al. An oral SYK kinase inhibitor in the treatment of rheumatoid arthritis: a three-month randomized, placebo-controlled, phase II study in patients with active rheumatoid arthritis that did not respond to biologic agents. Arthritis Rheum 2011;63:337–45.
8. Genovese MC, Greenwald MW, Alloway JA, Baldassare AR, Chase W, Newman C, et al. Efficacy and safety of baminercept in the treatment of rheumatoid arthritis (RA) results of the phase 2B study in the TNF-IR population [abstract]. Arthritis Rheum 2009;60 Suppl:S154.
9. Curtis JR, van der Helm-van Mil AH, Knevel R, Huizinga TW, Haney DJ, Shen Y, et al. Validation of a novel multibiomarker disease activity score to assess rheumatoid arthritis disease activity. Arthritis Care Res (Hoboken) 2012;54:809–13.
10. Van der Helm-van Mil AH, Knevel R, Cavet G, Huizinga TW, Haney DJ. An evaluation of molecular and clinical remission in rheumatoid arthritis by assessing radiographic progression. Rheumatology (Oxford) 2013;52:839–46.
11. Goldman JA. Erosions are like cockroaches, when you see one there are many others you do not see. It’s just one erosion! No, it is not! [letter]. Clin Exp Rheumatol 2014;32 Suppl 87:S5–6.
12. Van Vollenhoven RF, Ernestam S, Geborek P, Petersson IF, Coster L, Woltbrand E, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (SWEFOT trial): 1-year results of a randomised trial. Lancet 2009;374:459–66.
13. Prevoo ML, van’t Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight–joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.
14. Aletaha D, Nell VP, Stamm T, Uffmann M, Pfleger B, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Rheumatology (Oxford) 2005;44:694–9.
15. Goldman JA. Erosions are like cockroaches, when you see one there are many others you do not see. It’s just one erosion! No, it is not! [letter]. Clin Exp Rheumatol 2014;32 Suppl 87:S5–6.
16. Van Vollenhoven RF, Ernestam S, Geborek P, Petersson IF, Coster L, Woltbrand E, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (SWEFOT trial): 1-year results of a randomised trial. Lancet 2009;374:459–66.
17. Van der Helm-van Mil AH, Knevel R, Cavet G, Huizinga TW, Haney DJ. An evaluation of molecular and clinical remission in rheumatoid arthritis by assessing radiographic progression. Rheumatology (Oxford) 2013;52:839–46.
18. Goldman JA. Erosions are like cockroaches, when you see one there are many others you do not see. It’s just one erosion! No, it is not! [letter]. Clin Exp Rheumatol 2014;32 Suppl 87:S5–6.
19. Haney DJ, Shen Y, et al. Validation of a novel multibiomarker disease activity score to assess rheumatoid arthritis disease activity. Arthritis Care Res (Hoboken) 2012;54:809–13.
20. Van der Helm-van Mil AH, Knevel R, Cavet G, Huizinga TW, Haney DJ. An evaluation of molecular and clinical remission in rheumatoid arthritis by assessing radiographic progression. Rheumatology (Oxford) 2013;52:839–46.
21. Goldman JA. Erosions are like cockroaches, when you see one there are many others you do not see. It’s just one erosion! No, it is not! [letter]. Clin Exp Rheumatol 2014;32 Suppl 87:S5–6.