The Adjusted Multi-biomarker Disease Activity Score as a Prognostic Test for Radiographic Progression in Rheumatoid Arthritis

ABSTRACT #466

W. Huizinga[1]; Michael E. Weinblatt[2]; Nancy A Shadick[2]; Cecille H. Brahe[3]; Mikkel Ostergaard[3]; Merete Lund Hetland[3]; Karen Hambardzumyan[4]; Saedis Saevarsdottir[4,5]; Megan Horton[6]; Brent Mabey[6]; Dari D. Flake II[6]; Rotem Ben-Shachar[6]; Eric H. Sasso[7]; Jeffrey R. Curtis[8]

[1]Leiden University Medical Center, Leiden, Netherlands, [2]Department of Rheumatology, Brigham and Women's Hospital, Boston, MA, USA; [3]Copenhagen Center Artthritis Research and DANBIO, Center for Rheumatology and Spine Diseases, Rigshospitalet, Glostrup, and Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark, [4]Rheumatology Unit, Department of Medicine, Solna, Karolinsa Institute, Stockholm, Sweden, [5]Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden, [6]Myriad Genetics, Inc, Salt Lake City, UT, [7]Crescendo Bioscience, Inc, South San Francisco, CA, USA, [8]University of Alabama at Birmingham, Birmingham, AL

BACKGROUND

- The multi-biomarker disease activity (MBDA) blood test has been shown to bea predictor of risk for radiographic progression in patients with rheumatoid arthritis (RA).
- The MBDA score has disease activity categories of low (<30), moderate (30-44) and high (>44).
- Since December 2017, the MBDA score has been adjusted to account for the effects of age, sex and adiposity using leptin as a surrogate. In a study of two cohorts (OPERA, BRASS) it was shown to be better than conventional disease activity measures and than the original MBDA score for predicting risk for radiographic progression (Curtis JR, et al. Rheumatology 2018).
- We have now combined 4 cohorts to validate the adjusted MBDA score as a prognostic for radiographic progression over one year in the largest such analysis to date.
- We have also: 1) compared the prognostic ability of the adjusted MBDA score to conventional measures, and 2) developed a curve for predicting risk for radiographic progression over one year with the adjusted MBDA score as a continuous variable.

METHODS

- Four cohorts with requisite data were identified and combined (N=953):

- Leiden registry (N=163) (not previously evaluated)
- OPERA study (N=154) (previously evaluated)
- SWEFOT study (N=235) (not previously evaluated)
- BRASS registry (N=401) (previously evaluated)

- The associations of the adjusted MBDA score, seropositivity (RF and/or ACPA positive), CRP, baseline total TSS, DAS28-CRP, swollen jaunt count, sex, age, and CDAI with radiographic . progression over one year as a continuous variable {LITSS) were evaluated using linear regression.
- Logistic regression was used to estimate risk of radiographic progression (LI. TSS >5), as a function of the continuous adjusted MBDA score.

RESULTS

Table 1. Cohort designs

Study/ Registry	Leiden	OPERA	SWEFOT	BRASS
Patients, N	163	154	235	401
Type of study	Registry	RT	RT	Registry
Inclusion criteria and treatment				
Previous treatment	Non-biologic DMARDs (biologic-naive)	DMARD-naive	Treatment - naive	DMARDs (non-biologic & biologic)
Symptom duration	Variable[b]	Early RA (<6 months)	Early RA (<1 year)	Variable
Treatment during year of radiographic evaluation	Ongoing non-bi-ologic DMARDs (alone or in combination)	MTX monother-apy, MTX+ADA; each with IA CS for swollen joints	MTX monother-apy, MTX+SSZ+ HCQ, MTX + infliximab	DMARDs any non-biologic 89.3%, MTX 50.6%; any biologic 38.7%, anti-TNF 38.4%

Abbreviations: ADA, adalimumab; CS, corticosteroids; DMARD, Disease-modifying anti-rheumatic drug; HCQ hydroxychloroquine; IA, intra-articu-lar; MTX, methotrexate; n/a, not available; RA rheumatoid arthritis; RT randomized trial; SSZ, sulfasalazine.
[a]Parent study or registry that provided the cohorts analyzed for the relationship between MBDA score and radiographic progression.
[b]Upon enrollment in the Leiden Early Arthritis Clinic (EAC), all patients had recent onset RA (<2 years); time between EAC enrollment and inclusion in the cohort used here was variable.

- Patients in the OPERA and SWEFOT cohorts had early onset RA (mean durations 87 days and 6.1 months, respectively). Patients in the BRASS and Leiden cohorts tended to have established RA (mean duration 13.8 years, median duration 4.6 years, respectively).
- The four cohorts combined (N=953) included patients receiving biologic and non-biologic DMARDS (Table 1), with mean values of DAS28-CRP 4.5, SJC 8, and CRP 20 mg/L The mean adjusted MBDA score, 51.2, was high (>44) (Table 2).
- In continuous and binary analyses, the MBDA score was the most significant predictor of radiographic progression over one year compared to eight other variables (Table 3).
- The frequency of radiographic progression agreed more with the adjusted MBDA score than with DAS28- CRP, CRP, SJC or CDAI, both overall and when they were discordant (Figure 1).

Figure 1. Radiographic progression (RP; TSS >5) by category of adjusted MBDA score cross-classified with conventional disease activity measures

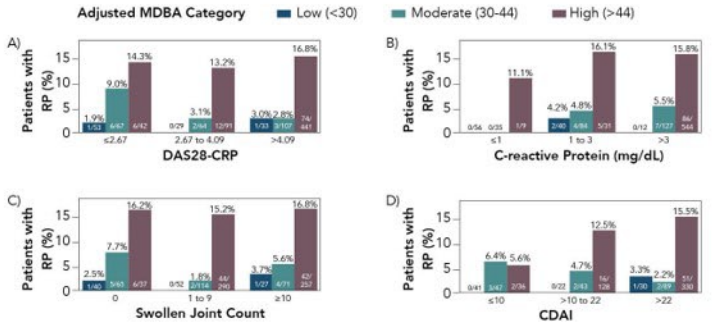


Table 2. Demographics & disease measures

4 cohorts combined (N=953)	
Patient characteristics, mean or %	
Age, years (SD)	55.4 (13.4)
Female, %	74.5%
Seropositive, %	75.5%
Symptom duration[a]	6.8 years
Baseline disease activity or radiographic progression, mean (SD)	
DAS28-CRP	4.5 (1.6)
Swollen Joing Count[b]	8.0 (6.6)
CRP, mgL	20.0 (31.1)
Adjusted MBDA score	51.2 (18.2)
TSS	29.1 (58.9)

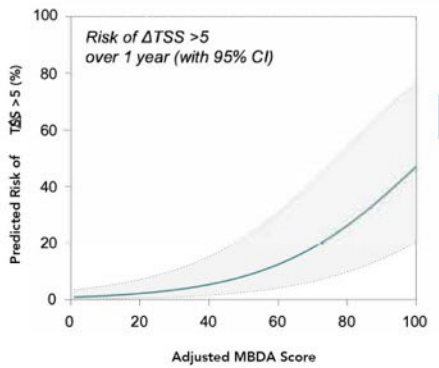
Abbreviations: SD, standard deviation;
[a]Medianvalue used from Leiden
[b]Swollen Joint Count is based on 28-joint counts.

Table 3. Univariate analyses of association of baseline measures with radiographic progression

Variable	4 Cohorts Combined				
	N[a]	Δ TSS (continuous)		Δ TSS >5	
		Coefficient[b] (95% CI)	p-value	Odds Ratio	p-value
Adjusted MBDA score	953	0.061 (0.044, 0.076)	$2.5x10^{-13}$	1.05 (1.03, 1.06)	$2.5x10^{-11}$
Seropositivity[c]	719/952	1.47 (0.89, 2.06)	$9.9x10^{-7}$	6.20 (2.90, 16.1)	$7.0x10^{-8}$
log (CRP +1)	946	0.58 (0.33, 0.83)	$4.7x10^{-6}$	1.57 (1.29, 1.91)	$6.8x10^{-6}$
Baseline Tss	953	0.0074 (0.0028, 0.012)	0.0018	1.01 (1.00, 1.01)	0.0072
DAS28-CRP	927	0.31 (0.11, 0.50)	0.0026	1.24 (1.05, 1.46)	0.0096
Swollen Joint Count	953	0.062 (0.020, 0.100)	0.004	1.04 (1.00, 1.07)	0.05
Male Sex	243/953	-0.45 (-1.04, 0.14)	0.14	0.78 (0.47, 1.26)	0.32
Age	953	-0.0043 (-0.024, 0.015)	0.66	1.00 (0.98, 1.01)	0.67
CDAI	766	0.014 (-0.0053, 0.034)	0.15	1.01 (0.99, 1.02)	0.47

Abbreviations: aCRP, C-reactive protein; DAS28-CRP, Disease Activity Score using 28-joing count and CRP; MBDA, multi-biomarker disease activity; TSS, total Sharp score.
[a]Patients within total group that had suitable radiographic data and for whom baselin data were available for indicated variable. Ratios indicate number of patients in indicated category and total number with data available for that variable.
[b]Coefficients for continuous variables (all except seropositivity, male & smoking status) represent slope of linear regression line, expresses as units of Δ mTSS per one-unit change in indicated variable.
[c]Seropositivity defined as having tested positive for rheumatoid factor and/or anti-CCP antibodies.

Figure 2. Risk curve for radiographic progression



- Risk for radiographic progression over one year increased continuously with the MBDA score, ranging from 1 % to 3% in the low (1-30) adjusted MBDA category to 7% to 47% in the high (45-100) adjusted MBDA category (Figure 2).

CONCLUSIONS

- The adjusted MBDA score was validated in four cohorts combined as a superior prognostic of radiographic progression, compared with conventional measures.
- Progression risk increased continuously with the adjusted MBDA score, exceeding 40% for the highest scores.

DISCLOSURES: