Vectra DA for the objective measurement of disease activity in patients with rheumatoid arthritis

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Received on September 15, 2014; accepted in revised form on September 16, 2014.

Clin Exp Rheumatol 2014; 32 (Suppl. 85): S29-S34.

Key words: rheumatoid arthritis, Vectra DA, multi-biomarker disease activity (MBDA) score, tight control, therapy response monitoring

Competing interests:
O.G. Segurado and E.H. Sasso are employees of Crescendo Bioscience, South San Francisco, USA.

ABSTRACT

Quantitative and regular assessment of disease activity in rheumatoid arthritis (RA) is required to achieve treatment targets such as remission and to optimise clinical outcomes. To assess inflammation accurately, predict joint damage and monitor treatment response, a measure of disease activity in RA should reflect the pathological processes resulting in irreversible joint damage and functional disability.

The Vectra DA blood test is an objective measure of disease activity for patients with RA. Vectra DA provides an accurate, reproducible score on a scale of 1 to 100 based on the concentrations of 12 biomarkers that reflect the pathophysiologic diversity of RA. The analytical validity, clinical validity, and clinical utility of Vectra DA have been evaluated for patients with RA in registries and prospective and retrospective clinical studies.

As a biomarker-based instrument for assessing disease activity in RA, the Vectra DA test can help monitor therapeutic response to methotrexate and biologic agents and assess clinically challenging situations, such as when clinical measures are confounded by non-inflammatory pain from fibromyalgia. Vectra DA scores correlate with imaging of joint inflammation and are predictive for radiographic progression, with high Vectra DA scores being associated with more frequent and severe progression and low scores being predictive for non-progression.

In summary, the Vectra DA score is an objective measure of RA disease activity that quantifies inflammatory status. By predicting risk for joint damage more effectively than conventional clinical and laboratory measures, it has the potential to complement these measures and optimise clinical decision making.

Introduction

The regular assessment of disease activity is the cornerstone of tight control and treat-to-target strategies in rheumatoid arthritis (RA) (1). In routine clinical practice, the assessment of disease activity is primarily based on *gestalt,* with limited examination of joints and, typically, no formal or quantitative evaluation of the articular and systemic manifestations of inflammation (2).

Conventional clinical measures and indices of disease activity include subjective patient-reported and physician-reported assessments, swollen and tender joint counts, and laboratory tests (3). Patient-reported assessments have been proposed to be comparable to joint counts for assessing remission (4). Patient and physician assessments reflect both joint inflammation and subjective functional status of the patient and can be confounded by comorbidities and non-inflammatory pain, as from fibromyalgia (5, 6). Joint counts can be influenced by patient and physician subjectivity (7) and can be confounded by pre-existing joint damage, fibrotic changes, and osteoarthritis (8, 9). The conventional laboratory tests used for assessing RA disease activity, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are often normal despite demonstrable joint inflammation (10, 12). These clinical measures and the composite indices that use them, such as the 28-joint disease activity score (DAS28), require time and expertise, which has limited their adoption in routine practice.

In RA, long-term disability is driven in part by inflammation and joint damage (13), and may be affected by time to remission (14). Advanced imaging of joints by magnetic resonance imaging (MRI) or ultrasound is considered the *gold standard* to assess objectively the degree of synovial inflammation and os-

teitis (15). These pathological processes drive the cumulative and irreversible joint damage that is characteristic of inadequately treated RA (16). Prediction of joint damage in RA has proven difficult because not all patients with apparently active disease demonstrate radiographic progression, and because progression is observed in patients who are in clinical remission (17).

This review will discuss the evidence supporting the utility of the Vectra® DA score as a quantitative and objective blood test for the management of patients with RA. Three key aspects of the Vectra DA score will be addressed:

1. association with synovitis and osteitis and prediction of subsequent joint damage;
2. ability to assist measurement of disease activity in patients with confounding conditions; and
3. ability to monitor response to therapies. In addition, the potential of Vectra DA to optimise drug utilisation is being investigated.

Analytical and clinical validation and decision impact

Vectra DA is a blood test that integrates the concentrations of 12 biomarkers that were selected after an evaluation of nearly 400 potential candidates using gene expression profiling and other serological and molecular techniques (18). The Vectra DA biomarkers reflect the complexity of systemic inflammation and the biological processes occurring in RA joints, such as increased trafficking and adhesion of immune cells, vascular proliferation, and the production of destructive enzymes, tissue metabolites, and acute phase reactants. The biomarkers that were most informative in preliminary testing and met laboratory requirements of reproducibility, stability and technical feasibility were selected for the Vectra DA algorithm (19).

The following biomarkers are measured for Vectra DA in the Crescendo Bioscience CLIA- and CAP-certified clinical laboratory using an automated, multiplexed sandwich immunoassay: vascular cell adhesion molecule-1 (VCAM-1), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF-A), interleukin 6 (IL-6), tumour necrosis factor receptor type I (TNF-R1), matrix metalloproteinase 1 (MMP-1), matrix metalloproteinase 3 (MMP-3), human cartilage glycoprotein-39 (YKL-40), leptin, resistin, serum amyloid A (SAA), and CRP. Applied bioinformatics and modeling using serum samples of well-characterised patients with RA led to development and validation of the Vectra DA algorithm (18). The Vectra DA score, on a scale of 1 to 100, and disease activity categories of low (<30), moderate (30–44), and high (>44), is precise and reproducible (19).

The clinical validity of the Vectra DA score as an objective measure of disease activity was evaluated in a study of 371 patients from 3 cohorts from North America and Europe. Vectra DA was statistically significantly associated with DAS28 based on CRP (DAS28-CRP), the Simplified Disease Activity Index (SDAI), the Clinical Disease Activity Index (CDAI) and the Routine Assessment of Patient Index Data 3 (RAPID3) in both seropositive and seronegative patients (20).

Two other studies have confirmed the clinical validity of Vectra DA to assess RA disease activity, based on evaluation of patients in early RA: the CAMERA tight-control study (21) and the BeSt study, which demonstrated a statistically significant correlation with DAS28 based on ESR (DAS28-ESR), SDAI, CDAI, and the Health Assessment Questionnaire (HAQ) Disability Index (22).

The impact of Vectra DA on clinical decision-making has been evaluated in a prospective cross-sectional study of 101 RA patients seen in rheumatology office practices. Vectra DA tests were ordered as part of routine care. Based on a questionnaire completed before and after the practitioner had seen the test result, the Vectra DA score led to changes in the treatment plans of 38% of patients with RA, with approximately half of these changes involving disease-modifying anti-rheumatic drugs. Despite this effect, overall drug utilisation was minimally affected. This study suggests that Vectra DA can support the clinical decision-making process (23).

Assessment and prediction of joint damage

The clinical utility of Vectra DA is supported by evidence that the Vectra DA score is associated with measurements of joint pathology based on imaging. This evidence supports validation of the Vectra DA score as a measure of RA inflammation and establishes it as a predictor of joint damage progression. In a post hoc analysis of ASSET, a randomised, placebo-controlled trial of intravenous abatacept for treatment of methotrexate (MTX)-inadequate responders, the amount of joint inflammation seen by MRI, as synovitis or bone marrow edema (osteitis), was significantly correlated with the Vectra DA score but not with DAS28-CRP (24). Similarly, correlations have been observed between the Vectra DA score and joint inflammation detected by power Doppler ultrasound (25, 26).

Joint damage on radiographs of patients with RA is a record of the cumulative destruction to bone and cartilage caused by inflammation. Analyses of 3 prospective and 1 retrospective cohorts have shown that Vectra DA scores are predictive for radiographic progression. In a study of patients receiving ongoing DMARD therapy for established RA from Leiden, the Netherlands, Vectra DA score was associated more significantly with radiographic progression than was DAS28-CRP (Fig. 1) (27). Patients who were in remission defined by Vectra DA score <25 had a statistically significantly reduced likelihood of progression, whereas those in remission by DAS28-CRP or the stringent American College of Rheumatology (ACR)-European League Against Rheumatism (EULAR) Boolean criteria did not. This result illustrates that Vectra DA can detect potentially destructive disease activity when conventional clinical measures do not. Exploratory analyses demonstrated that the Vectra DA score supplemented CRP and serological status for predicting radiographic progression (27).

An association between Vectra DA scores and risk for radiographic progression was also found in the Swedish Pharmacotherapy (SWEFOT) randomised trial of tight control strategies

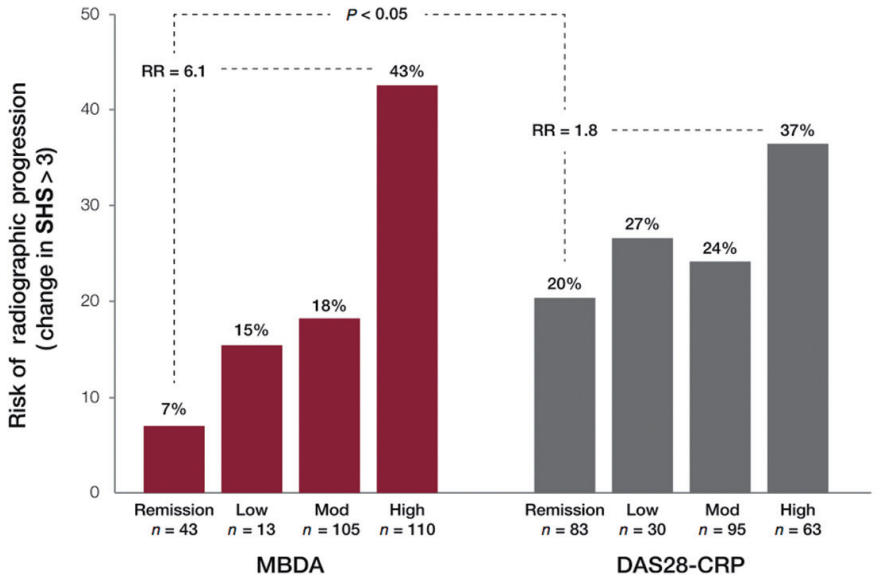

Fig. 1. Risk of radiographic progression *vs*. level of disease activity (27).
DAS28-CRP: 28-joint disease activity score based on C-reactive protein; MBDA: multi-biomarker disease activity (Vectra DA); Mod: moderate; RR: relative risk; SHS: Sharp-van der Heijde score.
Adapted from VAN DER HELM-VAN MIL A, KNEVEL R, CAVET G *et al*.: An evaluation of molecular and clinical remission in rheumatoid arthritis by assessing radiographic progression. *Rheumatology* (Oxford) 2013; 52(5):839-46, by permission of the British Society for Rheumatology.

for MTX-naïve patients with early RA. The Vectra DA score at baseline was a significant predictor of clinically meaningful rapid radiographic progression (change of Sharp-van der Heijde score [SHS] >5) over the first year (28), with rapid progression observed for 21%, 3%, and 0% of patients with high, moderate, or low Vectra DA scores, respectively. In addition, Vectra DA score at baseline differentiated rapid progressors from non-progressors more effectively than baseline CRP or DAS28-ESR (Fig. 2) (29). Among the 30% of patients with low CRP (<10 mg/L) at baseline, rapid progression occurred only among those with a high baseline Vectra DA score. This discordance between Vectra DA and CRP indicates that Vectra DA detected destructive disease activity when CRP did not. Multivariate analysis established that Vectra DA score was an independent predictor of rapid progression. Additional SWEFOT analyses suggested that lowering disease activity with therapy, as measured by the Vectra DA score, may lower risk for subsequent progression (30).

BeSt, a prospective study of tight-control strategies for patients with early RA, confirmed the association between Vectra DA and risk for progression. A multivariate analysis showed that Vectra DA was an independent predictor of progression (31). In a retrospective study from Japan, patients with long-standing RA and inadequate response to MTX were treated with TNF inhibitors. Radiographic progression was greatest in patients who had consecutive high Vectra DA scores despite TNF inhibition (32).

Viewed together, these 4 studies demonstrate that: 1) a low Vectra DA score is associated with infrequent progression; 2) a high Vectra DA score is associated with more frequent and more severe progression; and 3) Vectra DA is a better predictor of progression and non-progression than measures that are used to assess disease activity in routine clinical care. The results also suggest that Vectra DA may help clarify risk for progression among patients who are in clinical remission or have low clinical disease activity. Based on this evidence, Vectra DA appears to be a more sensitive measure of disease activity and a more effective discriminator of risk for joint damage than conventional clinical or laboratory measures.

Resolution of clinical uncertainty

Clinical uncertainty is a common problem for the management of patients with RA. For example, patients who appear to have little or no clinically active disease may have destructive synovitis when examined by MRI or ultrasound (17). As discussed above, the Vectra DA score can be elevated in patients with low DAS28-CRP or CRP, indicating an increased risk for joint damage. Another type of uncertainty occurs when clinical assessment is confounded by non-inflammatory pain, as from fibromyalgia, osteoarthritis, or depression. Fibromyalgia occurs in up to 20% of patients with RA, and by confounding the predominantly subjective signs and symptoms used to assess RA disease activity, may lead to costly over-treatment of RA and under-treatment of the non-inflammatory complaints (33). An accurate, objective measure is needed in such cases. CRP and ESR are objective measures, but they are in the normal range in a large portion of patients with active RA and are not well suited to the assessment of RA patients with fibromyalgia (10, 11, 13).

In a study conducted in collaboration with the Brigham Rheumatoid Arthritis Sequential Study (BRASS) registry, mean values for DAS28-CRP, CDAI, SDAI, RAPID3, patient global assessment, physician global assessment, and pain score were all approximately twice as high for patients with RA and fibromyalgia compared with RA alone. By contrast, Vectra DA and CRP did not appear to be affected by secondary fibromyalgia, as they were similar between groups. However, despite this similarity, CRP and Vectra DA detected disease activity differently because when CRP was in a range generally considered normal, which was observed in the majority of patients, Vectra DA was frequently elevated (34). This result is consistent with the Leiden and SWEFOT radiographic studies by suggesting that Vectra DA is able to detect RA disease activity when CRP does not.

Monitoring of therapy response

Monitoring disease activity over time is needed to assess response to conventional and biologic therapies in RA. In clinical trials, registries, and observational studies, Vectra DA has demonstrated the ability to track response in patients receiving methotrexate (MTX)

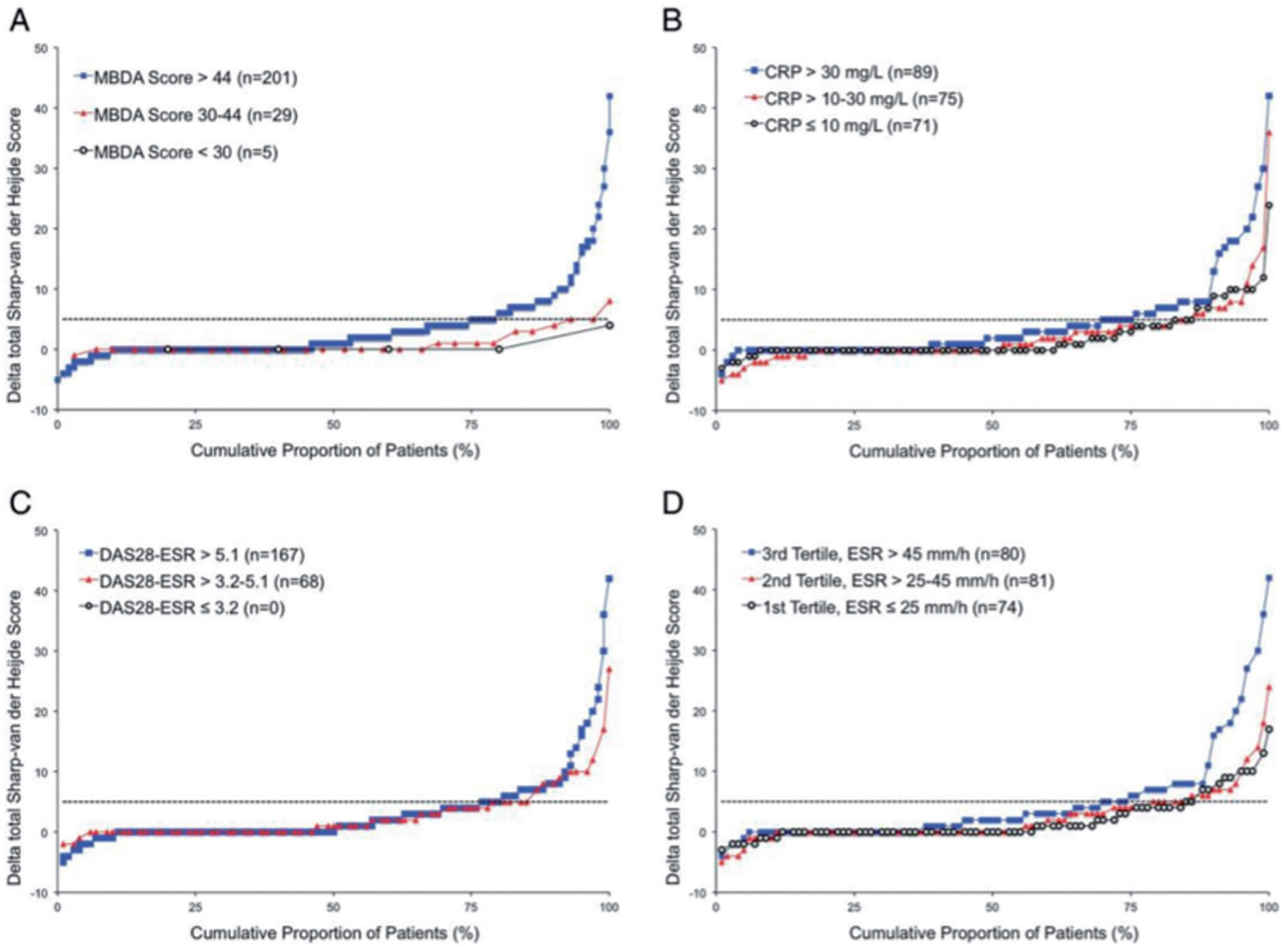

Fig. 2. Probability plots of radiographic progression at Year 1 for high, moderate and low disease activity patients (n=235) grouped according to baseline MBDA/Vectra DA score (**A**), CRP (**B**), DAS28 (**C**) and ESR (**D**). Each black circle represents a patient with low disease activity, red triangle-moderate disease activity and blue square-high disease activity. Horizontal dashed lines represent ΔSHS=5 from baseline to 1 year, above which the change is considered as rapid radiographic progression (ΔSAH>5). DAS28, disease activity score; ESR, erythrocyte sedimentation rate; MBDA, multi-biomarker disease acitivity (Vectra DA); SHA, Sharp-van Heijde score.
Reproduced from: HAMBARDZUMYAN K, BOLCE R, SAEVARSDOTTIR S *et al*.: Pretreatment multi-biomarker disease activity score and radiographic progression in early RA: results from the SWEFOT trial. *Ann Rheum Dis* doi:10.1136/annrheumdis-2013-204986, published online before print 8 May 2014, with permission from BMJ Publishing Group Ltd.

with or without prednisone (21, 35); biologic agents that inhibit TNF (20, 36, 30), cytotoxic T-lymphocyte antigen-4 (24), and the granulocyte macrophage-colony-stimulating factor receptor (37); and the Janus kinase inhibitor tofacitinib (38).

As a representative example, in Nested-1, a prospective observational study of MTX and anti-TNF treatment conducted within the BRASS cohort, Vectra DA tracked changes in disease activity over 12 weeks (Table I) (20). The change in Vectra DA score at Week 2 was associated with DAS28-CRP change at final visit, and the area under the receiver operator characteristic (AUROC) for the ability of the change in Vectra DA score at the final study visit to differentiate ACR 50% improvement responders was significantly greater than for the change in CRP (p=0.04) (Table I) (20).

Conclusion and future directions

Vectra DA offers rheumatologists an objective tool for assessing disease activity in patients with RA. By being associated with joint inflammation and subsequent radiographic progression, it offers prognostic support that can supplement the information available from conventional clinical measures of disease activity, ESR or CRP. Vectra DA appears to be unaffected by non-inflammatory pain and, as such, may be useful when clinical assessment is confounded by fibromyalgia and potentially other comorbidities. When Vectra DA is measured both at baseline and following the initiation of a treatment, it can track disease activity and discriminate responders from non-responders more effectively than CRP.

In the future, Vectra DA may prove helpful in the selection, maintenance, or switching of therapies. Vectra DA is being studied as a potential tool to select patients most likely to respond to TNF inhibition (39). Vectra DA has been compared to clinical measures of RA disease activity (21) and is being investigated as a potential criterion for tapering or withdrawing therapy and predicting flares for patients in remis-

Table I. Association of changes (Δ) in Vectra DA algorithm score and CRP with treatment-induced changes in clinical disease activity in the Nested-1 study (20)*.

Clinical outcome at final visit†	Δ Vectra DA score	Δ CRP‡
Correlation to change in clinical disease activity, Spearman's p		
Baseline to final visit†		
Δ DAS28-CRP	0.51 (p<0.001)	0.43 (p=0.004)
ACR-N	0.45 (p=0.002)	0.33 (p=0.027)
Discrimination of clinically-defined response, AUROC		
Baseline to final visit†		
DAS28-CRP response	0.77 (p=0.002)	0.68 (p=0.03)
ACR50 response	0.69 (p=0.03)	0.59 (p=0.30)
Baseline to week 2		
DAS28-CRP response	0.72 (p=0.02)	0.69 (p=0.03)
ACR50 response	0.65 (p=0.11)	0.51 (p=0.91)

*ACR50: ACR criteria for 50% improvement; ACR-N: American College of Rheumatology N; AUROC: area under the receiver operating characteristic; DAS28-CRP: 28-joint disease activity score based on C-reactive protein.
†The final visit for each patient corresponds to week 6 or 12 (last available).
‡Percent change in CRP was used for AUROC; change in log (CRP) was used for correlation analyses.
Adapted from: CURTIS JR, VAN DER HELM-VAN MIL AH, KNEVEL R *et al*.: Validation of a novel multibiomarker test to assess rheumatoid arthritis disease activity. *Arthritis Care Res* 2012; 64: 1794-803. Copyright © 2012 by the American College of Rheumatology.

sion. In drug development, Vectra DA may serve as an objective measure of disease activity reflecting distinct biological processes targeted by therapeutic agents. It may also have potential as a supplementary criterion to identify patients with active RA despite a low CRP, and thereby increase the number of patients who are eligible for enrolment in clinical trials.

Acknowledgements

We thank Sara Arzeno for editorial assistance.

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