Outcomes and costs of incorporating a multibiomarker disease activity test in the management of patients with rheumatoid arthritis

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Abstract

Objective. The multibiomarker disease activity (MBDA) blood test has been clinically validated as a measure of disease activity in patients with RA. We aimed to estimate the effect of the MBDA test on physical function for patients with RA (based on HAQ), quality-adjusted life years and costs over 10 years.

Methods. A decision analysis was conducted to quantify the effect of using the MBDA test on RA-related outcomes and costs to private payers and employers. Results of a clinical management study reporting changes to anti-rheumatic drug recommendations after use of the MBDA test informed clinical utility. The effect of treatment changes on HAQ was derived from 5 tight-control and 13 treatment-switch trials. Baseline HAQ scores and the HAQ score relationship with medical costs and quality of life were derived from published National Data Bank for Rheumatic Diseases data.

Results. Use of the MBDA test is projected to improve HAQ scores by 0.09 units in year 1, declining to 0.02 units after 10 years. Over the 10 year time horizon, quality-adjusted life years increased by 0.08 years and costs decreased by US$457 (cost savings in disability-related medical costs, US$659; in productivity costs, US$2137). The most influential variable in the analysis was the effect of the MBDA test on clinician treatment recommendations and subsequent HAQ changes.

Conclusion. The MBDA test aids in the assessment of disease activity in patients with RA by changing treatment decisions, improving the functional status of patients and cost savings. Further validation is ongoing and future longitudinal studies are warranted.

Key words: rheumatoid arthritis, biomarkers, outcome assessment, quality of life, health economics.

Rheumatology key messages

- MBDA test is projected to improve functional status and reduce costs for patients with RA.
- MBDA test remained below willingness-to-pay levels found among therapies reported in other cost-effectiveness analyses.

Introduction

RA is a chronic, debilitating disease affecting 1.1% of the entire US population and between 0.2% and 0.9% of populations elsewhere [1]. RA can result in joint erosion, loss of physical function and premature death [2–4]. Early detection and appropriate treatment of RA increases the probability of achieving remission, delays or halts radiographic progression and preserves physical function [5, 6]. For patients with active disease, treatment guidelines recommend regular assessments (i.e. every 1–3 months) and treatment to achieve remission and
sustained low disease activity [7–9]. Frequent evaluations of patient disease activity, with appropriate adjustments in treatment regimens (tight-control), have been shown to improve clinical outcomes and health-related quality of life (QoL) [9, 10].

The ACR recommends using at least one of the five clinical measures to assess disease activity [9]. However, current measures have limitations, including interreader variability [11], inability to detect subclinical synovitis and structural damage [12] and inability to account for the potential influence of co-morbidities (e.g. FM, joint infections, obesity) [13–15]. Because joint destruction occurs rapidly in the first 2 years of disease, guidelines have stressed the importance of accurate measurement of disease activity to guide the use of treatments that can limit joint damage [16]. Despite the benefits of this strategy, the assessment of disease activity and risk of radiographic progression are performed inconsistently, which has been attributed to ambivalence about the predictive qualities of current measurements and time constraints [17].

Researchers have been seeking serum biomarkers that can complement clinical disease measures to improve the evaluation of disease activity in patients with RA [15, 18]. A multibiomarker disease activity (MBDA) blood test for RA (Vectra DA; Crescendo Bioscience, South San Francisco, CA, USA) measures serum concentrations of 12 proteins and combines them in a validated algorithm to produce a score of 1–100 that indicates the level of disease activity in patients with RA. MBDA test results are significantly associated with RA disease activity and treatment response [19–21]. In clinical studies, patients with RA who were in remission (according to the 28-joint DAS using CRP) and had high MBDA scores had increased radiographic progression compared with those with lower MBDA scores [22]. The MBDA test was subsequently shown to provide information that altered therapeutic recommendations for patients seen in routine clinical practice [23]. The primary aim of this study was to evaluate the outcomes and costs of the MBDA test when used as an adjunct to current clinical practice for the management of treatment in RA patients.

Methods

Analytical framework

A decision analysis was conducted to quantify the outcomes and costs of the MBDA test when used by physicians to help guide patient-specific RA treatment decisions compared with current clinical practice. The analysis was conducted from a US perspective, including third-party payers and employers, using a 10 year time horizon. The analytical framework was constructed to be consistent with independently validated analyses that reported long-term outcomes in RA [24–26].

Direct costs that were evaluated in this analysis included those associated with use of the MBDA test, RA drugs (including administration costs for intravenously administered drugs), treatment of drug-related adverse events and other direct costs (e.g. outpatient, hospitalization, disease monitoring). Indirect costs were those related to labour force participation and the percentage of work activity while at work, referred to as presenteeism. Benefits were assessed using quality-adjusted life years (QALYs). All costs were inflated to 2014 US dollars (USD) using the medical component of the US Bureau of Labor Statistics Consumer Price Index [27]. See supplementary Fig. S1, available at Rheumatology Online, for a summary of the structural framework.

Patient characteristics, treatment effects and disease progression were derived from published clinical trial and registry data (Table 1 and supplementary Table S1, available at Rheumatology Online, for data sources and sensitivity analysis ranges). A fixed annual discount rate of 3% was applied to all costs and benefits.

Target patient population

The analysis quantified the effect of the MBDA test on outcomes for representative patients with RA (see supplementary data, section on patient population, available at Rheumatology Online). A post hoc analysis of data from the clinical management study of RA treatment recommendations was performed to describe the distribution of patients with early (i.e. ≤1 year disease duration, 28%) or established (i.e. >1 year, 72%) RA at baseline (data on file, Crescendo Bioscience, South San Francisco, CA, USA).

Treatment changes and resulting changes in outcome

Treatment changes following use of the MBDA test were based on results of a clinical management study in which 38.0% of treatment decisions (regarding the use of MTX, synthetic DMARDs and biologics) were adjusted following knowledge of the MBDA test results [23]. Results of a subanalysis of these data found almost 30% of treatment strategies were increased in intensity, which was defined as increasing the drug dosage, changing the formulation of the drug (e.g. oral to injectable) or recommending a drug in a more intensive drug class (e.g. MTX monotherapy to one comprising a biologic). Nine per cent of treatment strategies decreased in intensity.

Physicians ordered 1.91 tests per patient (range 1–3; data on file, Crescendo Bioscience), and most were ordered in the first year. This amount and timing of test ordering is consistent with an incentive to identify as early as possible the regimen that will achieve guideline-recommended targets for response and remission. Tests ordered after the first year were presumably related to patients who had not yet achieved a response after 1 year or the physician wanted to assess disease status in patients whose signs and symptoms suggested a relapse. We assumed that only those tests ordered within the first 5 years had an effect on disease progression. The cumulative effect of changes in disease progression on HAQ, QoL and costs were analysed over 10 years.
**Table 1** Patient characteristics and treatment effect cost estimates for decision analysis model input

| Variable | Estimate |
|----------|----------|
| Direct costs | |
| Contract price of MBDA (per test) | $789 |
| Drug costs* | |
| Annual drug costs with MBDA (reflects impact on drug costs) | $17,978 |
| Commercial markup, % | 18 |
| Reduction for patient adherenceb, % | 21 |
| Moderate-to-severe adverse event | $24,149 |
| Other direct medical costs | |
| Annual cost per unit increase in HAQ score | $1637 |
| Percentage of patients receiving MBDA with early RAc | 28 |
| Current clinical practice | |
| Baseline HAQ score, early RA | 1.53 |
| Baseline HAQ score, established RA | 1.03 |
| HAQ score standard deviation | 0.71 |
| Annual change in HAQ score | 0.005 |
| With MBDA | |
| MBDA’s average effect on HAQ score in early RA, year 1d | 0.29 |
| MBDA’s average effect on HAQ score in established RA, year 1d | 0.02 |
| Years until half of HAQ score difference remains | 4 |
| Indirect costs | |
| Absenteeism | |
| HAQ <0.25 | $7719 |
| HAQ 0.25–0.75 | $8393 |
| HAQ 0.75–1.25 | $12,369 |
| HAQ >1.25 | $16,636 |
| Presenteeism | |
| HAQ <0.25 | $2297 |
| HAQ 0.25–0.75 | $5429 |
| HAQ 0.75–1.25 | $8542 |
| HAQ >1.25 | $7650 |
| Average annual income | $25,734 |
| Utilities | |
| Baseline utility | 0.91 |
| Utility decrement | |
| Per unit increase in HAQ score | 0.17 |
| Mild adverse event | 0.10 |
| Moderate-to-severe adverse event | 0.45 |
| Rates and risks | |
| Rate of mild adverse events, % | |
| MTX | 25 |
| sDMARDs | 45 |
| Biologic | 30 |
| Rate of moderate to severe adverse events, % | |
| MTX | 2 |
| sDMARDs | 3 |
| Biologic | 1 |
| Change in mortality risk | |
| Due to RA for each unit change in HAQ score | 1.33 |
| Other parameters | |
| Average age at baseline, years | |
| Prevalent RA | 60 |
| Early RA | 50 |
| Average duration of treatment effect, years | 10 |
| Average number of eligible visits per RA patient | 4 |
| Average number of tests per patient | 1.91 |
| Time horizon, years | 10 |
| Discount rate, % | 3 |

*Current drug costs reflect CMS reference prices with a commercial markup and an adjustment for patient adherence. The reduction for patient adherence accounts for imperfect adherence to prescribed therapies and is based on the medical possession ratio for a cross section of patients on a mixture of biologic and synthetic DMARDs. Early RA is defined as ≤1 year duration. For early RA, this number is adjusted for baseline HAQ score. For established RA, this number is adjusted by the proportion of patients with established RA who experience an escalation in therapy. See supplementary Table S1, available at Rheumatology Online, for input data sources and sensitivity analysis ranges. All costs reported in 2014 US dollars. sDMARDs: synthetic DMARDs.
Progression of RA

For this decision analysis, functional status was assessed with the HAQ score. The mean baseline HAQ score for patients with early RA was 1.53 based on a similar patient population enrolled in the GO-BEFORE study; for the established RA population we used findings from the National Data Bank (see supplementary Fig. S2A, available at Rheumatology Online) [28, 29]. Changes in HAQ score of patients with early and established RA following the MBDA test were estimated by combining the results of 5 tight-control and 13 treatment-switch trials (see supplementary data, section on changes in outcome and supplementary Fig. S2, available at Rheumatology Online). Half of the difference in HAQ score between current clinical practice and adjunctive use of MBDA was expected to be maintained up to 4 years after the initial treatment change [16, 30]. This waning, on average, in the treatment effect accounts for incomplete control of the disease through worsening of symptoms. Radiographic damage was expected to be correlated with HAQ score as reported in longitudinal clinical studies [16, 30, 31].

QoL adjustments and costs

QoL adjustments and costs are presented in Table 1. Lower QoL scores were associated with increased HAQ scores (i.e. declining disability) and the occurrence of treatment-related adverse events.

Costs were assigned to treatment strategies (drug dosing and frequency) reported in the MBDA test clinical management study before and after physicians reviewed the MBDA test results (data on file, Crescendo Bioscience). Annual drug prices were obtained from the Centers for Medicare & Medicaid Services (CMS) National Average Drug Acquisition Costs database [32, 33]. An 18% markup was applied to account for differences in reimbursement between payers (i.e. private and public). We included a 21% reduction in costs to account for treatment non-adherence among patients with RA [34].

The analysis incorporated changes in disability-related costs associated with changes in health status. Each unit increase in HAQ score has been reported to increase direct medical costs by $1637 [35]. As mentioned previously, the difference in costs diminished over time; half of the benefit remained after 4 years [16, 30].

Changes in functional status were directly related to labour force participation and work productivity (supplementary Table S2, available at Rheumatology Online). Hourly wages and the number of hours worked per week were estimated using the February 2014 US Bureau of Labor Statistics data for private workers [27, 36].

Sensitivity analyses

Sensitivity analyses were run to assess the effect of uncertainty in costs and outcomes with use of the MBDA test. The lower and upper bounds of parameter values were established using the maximum and minimum values reported in the literature. We used the study estimate’s 95% CI for the range, if available; when no range was reported in the literature, we relied on expert opinion or varied the estimate by ±15% (supplementary Table S1, available at Rheumatology Online). The univariate analyses provided the best- and worst-case results when altering individual parameters. We conducted probabilistic analyses, which simultaneously varied parameters using randomly selected estimates that fell within the upper and lower bound of each parameter.

Results

Use of the MBDA test was projected to increase the number of patients with a lower HAQ score, as observed in Fig. 1 (the curve shifts to the left based on benefits received with treatment changes following use of the MBDA test). Overall, patients’ HAQ scores decreased by a mean of 0.09 units in year 1 compared with current clinical practice (Table 2); a 0.02 difference remained at 10 years (Fig. 2). This improvement in patient health status resulted in cumulative 0.08 QALYs gained per patient tested over 10 years. Use of the MBDA test was projected to have a modest effect on the rate of adverse events, and thus on QALYs (Table 2).

Over a 10-year period, use of MBDA was projected to save $457 per patient in direct and indirect costs. Annual drug costs totalled $17 284 in current clinical practice and $17 455 with MBDA testing (year 1). Changes in treatment recommendations thus led to an increase in RA drug costs of $171 per patient in year 1 and $881 over the 10-year time horizon. Adoption of the MBDA test accounted for an increase of $146 per year in costs (Table 2).

Improvements in patient health status resulted in mean per-patient savings in other direct costs of $150 in the first year and $661 over the 10-year time horizon. Moreover, treatment changes following the MBDA test contributed to increased labour force participation and
work productivity, resulting in savings of $514 in the first year and $2137 over the time horizon (Table 2).

The MBDA test costs $22,088 per QALY gained from the perspective of the third-party payer. When including both third-party payer costs and costs related to work productivity, use of the MBDA test was cost saving ($6011) (Table 2). From the payer’s perspective, for patients with early RA, the MBDA test is cost saving ($3073) and improves QALYs by 0.23 per patient; in established RA there is an improvement in QALYs of 0.02, while adding $275 in overall costs.

The MBDA test improved patient health across all variations of input parameters of the one-way sensitivity analysis. Factors that most influenced overall costs were the effect of the MBDA test on clinician treatment recommendations and changes in HAQ score over time (Fig. 3). The probabilistic sensitivity analysis showed the MBDA test was projected to increase QALYs in all scenarios; it was cost saving in 55% of scenarios. Ninety-three per cent of analyses resulted in a cost per QALY gained of <$50,000 (Fig. 4).

**Discussion**

This decision analysis assessed the outcomes and costs of using the MBDA test in the management of patients with RA. Improved control of disease activity derived from treatment changes with use of the MBDA test resulted in an improvement in HAQ scores of 0.09 units in year 1, declining to 0.02 after 10 years. Cumulatively, QALYs increased by 0.08 years. Overall, costs decreased

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**Table 2** Results of cost-effectiveness analysis of the MBDA test from a US health care perspective

| Outcomes over budget horizon | Current clinical practice | MBDA | Difference |
|------------------------------|--------------------------|------|------------|
| **HAQ score**                |                          |      |            |
| Year 1                       | 1.17                     | 1.08 | −0.09      |
| Year horizon                 | 1.22                     | 1.20 | −0.02      |
| **Quality-adjusted life years** |                        |      |            |
| Disability-related           | 5.57                     | 5.65 | 0.08       |
| Adverse-event related        | −0.04                    | −0.04| −0.00002   |
| Total                        | 5.54                     | 5.61 | 0.08       |

**Costs**

| Direct medical costs         |                          |      |            |
| MBDA test                    | $0                       | $1460| $1460      |
| RA drug costs                | $140,577                 | $141,458| $881     |
| Other direct costs for RA    | $15,426                  | $14,765| $661     |
| Adverse-event related        | $370                     | $371 | $0.24      |
| Total                        | $156,373                 | $158,053| $1680    |

| Indirect costs               |                          |      |            |
| Labour force participation   | $67,344                  | $65,866| −$1478    |
| Work productivity            | $37,632                  | $36,973| −$659     |
| Total                        | $104,976                 | $102,839| −$2137    |

| Total direct and indirect costs | $261,349 | $260,092 | −$457 |

| Incremental cost per QALY gained |                          |      |            |
| Payer perspective              | $22,088                  |      |            |
| Payer and employer perspective | Cost-saving              |      |            |

*Current clinical practice refers to outcome measures currently used in the practice setting to ascertain disease activity among patients diagnosed with RA. Guidelines recommend using outcome measures that combine information from the patient, provider and/or laboratory results to measure disease progression in RA (e.g. DAS28, CDAI, RAPID-3) [9]. All costs reported in 2014 US dollars. CDAI: Clinical Disease Activity Index; DAS28: 28-joint DAS; MBDA: multibiomarker disease activity; QALY: quality-adjusted life year; RAPID: Routine Assessment of Patient Index Data.

Fig. 2 Mean HAQ progression over a 10-year time horizon with and without MBDA test adjunct

Dark grey: current clinical practice; light grey: with Vectra DA. MBDA: multibiomarker disease activity.
by $457, with a $1680 cost increase to third-party payers offset by savings in labour force participation and work productivity (−$2137). Adoption of the MBDA test to inform disease activity was cost saving in >50% of all scenarios of the probabilistic sensitivity analysis; QALYs increased in all scenarios.

Guidelines panels recommend patients be treated early in the disease because long-term disability is a potential consequence of underrecognized, cumulative joint damage [7–10]. They also recommend patients have frequent assessments of disease activity so that treatment regimens may be adjusted to increase the proportion of patients in disease remission [5, 7–10]. Current disease activity measures have several limitations that seem to contribute to slow or variable uptake in their use [15, 17, 37, 38].

The MBDA test may be a useful adjunct to clinical assessment to evaluate the effectiveness of a treatment regimen when trying to reach targeted treatment goals, given its ability to identify progression-free remission and assess subclinical disease [22, 23]. Based on the results of the test, physicians may recommend appropriate treatments to limit joint damage when the risk of progression is high or avoid intensification of treatment when the risk is low, as it provides an objective measure that may help improve the likelihood of achieving guideline-recommended goals. Other technologies such as CT scanning, ultrasonography, computerized image analysis and MRI have been proposed as potential methods for measuring disease activity. The role and affordability of these approaches in clinical practice is unresolved [39–41]. Costs and outcomes of MRI use in early RA were analysed by Suter et al. [24], reporting the cost per unit increase in health benefit over a 10-year time horizon as $167,783. The reason for this high cost was directly related to the high false-positive rate, which led to more treatment-intensive strategies. In contrast, use of the MBDA test was projected to lead to only modest increases of biologic therapies (by 2%) in patients with established RA, and no increase among patients with...
early RA [23]. Furthermore, our analyses showed that the cost of using the MBDA test to monitor disease activity remains below the willingness-to-pay threshold ($50 000), which is used to assess the value of biologic therapies (vs standard treatment) [42].

The MBDA test was projected to increase QALYs by 0.08, or 1 month, over the 10-year time horizon. The implications of adoption of this test in the management of treatment strategies for patients with RA may seem trivial at first glance. However, it is important to note the magnitude of the effect, with and without use of the test, in the context of different RA patient populations and its effectiveness compared with other medical interventions. Progression of the disease worsens with increasing age, thus early use of the MBDA test (i.e. at a younger age) would likely be of greater benefit, allowing patients to experience the maximized effect of prescribed pharmacotherapy regimens to achieve the treatment goal. These changes may prevent and delay the occurrence of preliminary radiographic damage and lead to the retention of functionality, which hampers QoL, for a longer period of time. When extrapolating the QALY benefit in RA in the context of other medical interventions, the benefit of the MBDA test in the management of RA is greater than that derived from the use of ticlopidine (vs aspirin) for prevention of stroke among high-risk patients and testing of the blood supply for HIV prior to use in surgical patients ≥ 70 years of age [43].

Use of the MBDA test is expected to improve the quality of care for patients with RA, as quantified by changes in HAQ score and QALYs, through more informed therapy selection. This analysis indicated it can do so while also

**Fig. 4** Probabilistic sensitivity analysis

(A) Incremental costs vs incremental QALYs. (B) Probability that cost per QALY gained is less than or equal to the willingness-to-pay threshold per QALY gained. MBDA: multibiomarker disease activity; QALY: quality-adjusted life years.
being affordable. Affordability is part of the Triple Aim initiative, along with outcomes and patient experiences, required for certification by CMS for status as an Accountable Care Organizations (ACOs) under the Affordable Care Act of 2010 [44]. The MBDA test appears to meet the three criteria and align with ACOs goals.

This analysis relied on an analytical framework and parameters used in earlier studies [24–26]. We sought to assess how outcomes reported herein align with costs and outcomes reported from other sources, referred to as external validity [45]. Specifically, compared with a recent US registry study, the treatment patterns observed in pre-MBDA treatment recommendations are consistent with the trend towards increasing utilization of biologics [59% in the decision impact study vs 40% in the Consortium of Rheumatology Researchers of North America (CORRONA) for patients with established RA] [46]; utilization of biologics increased from 3% to 26% between 1999 and 2006 [47].

A number of limitations should be considered when interpreting the results of this analysis. First, the influence of the MBDA test on clinicians’ treatment decisions contributed the greatest variation in outcomes and costs. Further research is needed to validate this estimate and its effect on treatment cost changes. Prospective studies of MBDA test use in other settings are warranted to increase the precision and generalizability on medical resource utilization (e.g. lab tests, imaging procedures, patient treatment adherence). By further stratifying clinical utility, based on patient features, it will extend the breadth of future analyses of health care utilization. Furthermore, long-term studies will be useful to monitor whether the predicted effects on outcomes and cost persist under different conditions than those analysed herein.

The MBDA test provides an objective assessment of disease activity in RA that addresses well-reported limitations of existing clinical measures constraining their widespread adoption [12, 13, 15]. The information provided by the MBDA test has been shown to aid monitoring of disease activity, thus allowing for more informed selection of treatments in RA, potentially helping to slow disease progression and/or preserve joint integrity. This measure is projected to influence RA-related disability and reduce overall combined costs to third-party payers and in labour force participation and work productivity.

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Supplementary data

Supplementary data are available at Rheumatology Online.

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