Editorial

# Quantitative Clinical Rheumatology: Why Is a Test for Anti-CCP Antibodies Included in Most Routine Care for Rheumatoid Arthritis While a HAQ/MDHAQ Remains Largely a Research Tool?

Quantitative assessment of rheumatoid arthritis (RA) has been greatly advanced over the last few decades by important new measures. In 1980, the Health Assessment Questionnaire (HAQ) was reported by Fries and colleagues[1]. Eighteen years later, anti-cyclic citrullinated peptides (anti-CCP) in RA were reported by Schellekens and colleagues[2].

Since 1980, the HAQ has been incorporated to provide 3 of the 7 Core Data Set measures for RA[3], physical function, pain, and patient global estimate. The HAQ has been adapted for usual care as a modified HAQ (MHAQ), HAQ II, and multidimensional HAQ (MDHAQ)[4]. A HAQ/MDHAQ physical function score predicts severe longterm RA outcomes of work disability and premature mortality over 5–20 years at far higher levels of significance than radiographic scores or laboratory tests[5]. RAPID3 (Routine Assessment of Patient Index Data) scores of 3 HAQ/MDHAQ self-report measures distinguish active from control treatments in clinical trials as sensitively as joint counts, laboratory tests, and Disease Activity Score (DAS)28[6]. RAPID3 is correlated significantly with DAS28 and the Clinical Disease Activity Index (CDAI) in clinical trials[6] and clinical care[7], and is informative in patients with all rheumatic diseases[8].

Since 1999, anti-CCP has offered important insights into the pathogenesis, prognosis, and course of RA[9] and has been adapted for usual care with a variety of kits[10,11]. Anti-CCP provides a significantly higher hazard ratio than rheumatoid factor (RF) to identify people with early arthritis who will develop progressive disease[9,11]. These ratios are based on greater specificity of 95% in a metaanalysis of 37 studies, compared to 85% in 50 studies of RF for RA[11]. The pooled sensitivity for RA of anti-CCP for progressive inflammatory arthritis in 37 studies was 67%, compared to 69% for RF[11]. Therefore, 67% of RA patients have anti-CCP[11]. By contrast, 86% have an abnormal MDHAQ-RAPID3 score[7].

A "false-negative" rate of 33% for anti-CCP is of considerable concern. Current practice suggests that all patients who have possible RA should be treated with "tight" control of inflammation, guided by clinical measures, without regard to anti-CCP or any other antibody status[12]. Evidence-based information to guide management of RA is not yet available based on anti-CCP.

Nonetheless, anti-CCP tests are included in routine care based on suggestions that: (1) anti-CCP positivity identifies a distinct subset of patients who should be "monitored more carefully"; (2) anti-CCP-positive patients respond better to methotrexate (MTX) than anti-CCP-negative patients; (3) anti-CCP status may be useful when making treatment decisions in poor responders to MTX; (4) anti-CCP-positive patients are less likely to be able to withdraw therapy[9-11].

While all of these statements appear valid, we ask: (1) Should anti-CCP-negative patients be monitored less carefully than anti-CCP-positive patients? (2) Should a CCP-negative patient not be treated with MTX? (3) How does anti-CCP status change decisions in poor responders to MTX? (4) How does a lower likelihood to withdraw from therapy affect clinical decisions?

At this time, the "gold standard" to interpret a positive anti-CCP test remains a history and joint examination by a rheumatologist or other experienced physician. Anti-CCP provides considerable information concerning pathogenesis and outcomes in patient *groups*, but may have limited utility in the clinical care of *individual* patients. While anti-CCP ultimately may provide evidence-based guidance for management of individual patients, such knowledge will emerge from research settings, rather than from routine clinical testing.

The above information may suggest that a HAQ/MDHAQ might be used in usual patient care by all rheumatologists, while anti-CCP might be used primarily in research settings to better understand the pathogenesis and course of RA. Paradoxically, anti-CCP has been incorporated by most rheumatologists into standard clinical care, while HAQ/MDHAQ remains used primarily in research settings[13].

This situation may be explained in part by the apparent importance of anti-CCP to the pathogenesis and prognosis of RA. A biomedical model, the guiding paradigm of 20th century medicine[14], regards "objective" laboratory data, such as anti-CCP test, as having considerably greater value in the clinic than "subjective" data from patients, such as a HAQ/MDHAQ. The biomedical model has been spectacularly successful in acute medical situations and in development of new therapies for chronic diseases, including RA. Nonetheless, as noted, severe outcomes of work disability, costs, and death are predicted far more significantly by a HAQ/MDHAQ than by radiographs or laboratory tests identified to date[5], suggesting a need for a supplementary biopsychosocial model for RA[15].

Some observers (including 2 of the authors) have suggested that any patient who is considered to be a candidate for an anti-CCP test might be given an "n of 1" trial of weekly low-dose MTX and/or low-dose prednisone ($\leq$ 5 mg/day)[16]. This empirical approach is analogous to treatment of possible infections with antibiotics. Ironically, weekly low-dose MTX and low-dose prednisone ($\leq$ 5 mg/day) have fewer adverse events than most, if not all, antibiotics (or antihypertensive, antidepressant agents, etc.)[17]. A response provides presumptive evidence of inflammatory arthritis or spontaneous remission. No response would lead to discontinuation in 1–3 months, and further diagnostic and therapeutic measures.

Both anti-CCP and HAQ/MDHAQ are important advances in quantitative measurement of RA. Further research concerning CCP will likely lead to advances regarding the pathogenesis, course, and treatment of RA that cannot be provided by a HAQ/MDHAQ. However, such advances also cannot be provided by anti-CCP tests in routine care. We suggest that rigorous statistical scientific analysis indicates that any rheumatologist who orders an anti-CCP test at this time should also include a HAQ/MDHAQ in clinical care.

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