Dr. Fleischmann replies

To the Editor:

I am honored that Dr. Calabrese read my editorial, "Value of the multibiomarker disease activity score to predict remission in RA: what does the evidence show?" with interest[1]. As always, I have great respect for his contributions to rheumatology, particularly in his area of specific expertise; I have also found that he is generally a critical and logical thinker who has advanced our knowledge greatly over the years.

I fully agree with his statement, "this biomarker, along with ALL biomarkers, will fail to answer these questions [the ones I posed in the editorial] in a binary fashion[2]." That is the point of the editorial — there is no "biomarker" that answers these questions in a binary fashion or close to it. In particular, the MBDA has not been shown in a well-designed, prospective, properly controlled clinical study, in relevant disease populations, to answer the question of how well it does define, in a specific patient, the disease activity, clinical state, function, or radiographic progression, and how well the MBDA predicts response to the patient's therapy clinically, functionally, or radiographically. The manufacturer (and its supporters, both academic and practitioners) has relied on posthoc analyses of registries and studies in which these questions were neither prospectively designed nor asked, and using unusual statistical methods at times to make their arguments[3]. Occasionally the "evidence" is anecdotal, such as the examples that Dr. Calabrese uses of the effectiveness of the MBDA[2]. Despite these very significant shortcomings, the manufacturer and its supporters strongly suggest (if not proclaim) that the MBDA is an effective tool to help diagnose and manage rheumatoid arthritis (RA) and that it has great value as a prospective biomarker for radiographic progression, such as in the article referenced by Dr. Calabrese[4]. Many of these articles have alluded to the statistically significant correlation of the results of the MBDA with whatever metric is being discussed; frequently what is not mentioned is that the statistically significant correlations are poor.

Yet, in the only prospective, well-designed, properly controlled trial in which these questions could be answered, the MBDA was found to be significantly lacking clinically, functionally, and radiographically[5]. In a prespecified analysis from the AMPLE study, there was no statistically significant highly correlated association between the MBDA score and disease activity defined by the Clinical Disease Activity Index, the Simplified Clinical Disease Activity Index, the 28-joint Disease Activity Score using C-reactive protein, or Routine Assessment of Patient Index Data 3 in either the abatacept or adalimumab treatment arms, nor was there a positive correlation between disease activity assessed by the MBDA and radiographic progression[5]. It was also pointed out in the editorial questioned by Dr. Calabrese that posthoc analyses from the DRESS and RETRO studies were consistent with the inability of the MBDA to predict flares with medication tapering[1].

Dr. Calabrese is quite correct, of course, that frequently we as rheumatologists cannot be sure what to do in a specific clinical situation in which complaints and physical findings are discordant[2]. Laboratory tests evaluating inflammation and imaging such as ultrasound may be beneficial, but not always. The question is whether it is best to rely on "expert opinion" and anecdotal evidence to decide, as Dr. Calabrese suggests, or on evidence from well-designed prospective, peer-reviewed published studies that have critically evaluated the situation. Dr. Calabrese's opinion, based on his experience and anecdotal evidence, is that the MBDA is very useful in the treatment of RA[2]. My opinion, based on the most current peer-reviewed evidence in multiple studies, is that it is not, and it is certainly not worth the expense to the patient or the insurer.

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