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Drs. Bessette and Kinch reply

To the Editor:

We thank Dr. Tchetina for their interest in our article,[1] and we appreciate the opportunity to respond to their Letter to the Editor.[2] In the letter and their recent publication, Tchetina et al describe the utility of gene expression analyses using peripheral blood mononuclear cells (PBMCs) from patients with rheumatoid arthritis (RA) to predict clinical response to tofacitinib (TOF).[2,3] Specifically, the authors propose that sensitivity and resistance to treatment with TOF may be associated with changes in energy metabolism in RA T cells.[3] T cells in patients with RA appear to be prematurely aged compared with those in aged-matched healthy individuals,[4] and this premature aging is coupled with alterations in cellular metabolism.[2-4] Therefore, they hypothesized that differential expression of the genes pyruvate kinase M2 and succinate dehydrogenase subunit B, which are involved in the energy-generating metabolic pathways, glycolysis and oxidative phosphorylation, respectively, may provide insight into which patients with RA are more likely to achieve treatment targets following TOF treatment.[2,3]

In our study,[1] we report results from a post hoc analysis that evaluated the effect of treatments in phase III and phase IIIb/IV TOF RA randomized controlled trials (ClinicalTrials.gov: NCT00847613, NCT00856544, NCT00853385, NCT02187055) on the proportions of patients achieving ≥ 20/50/70% improvement from baseline in the components of the American College of Rheumatology (ACR) response criteria, as well as mean percent improvement from baseline in the ACR components, the Simplified Disease Activity Index (SDAI) score, and the Clinical Disease Activity Index (CDAI) score in patients achieving an ACR20/50/70 response (ACR20/50/70 responders), and the proportions of ACR20/50/70 responders achieving SDAI or CDAI low disease activity and remission.[1] The purpose of these analyses was to assist clinicians in interpreting clinical study results and to define expected responses to advanced therapies, thereby facilitating tangible treatment target settings using measures routinely collected in the clinic.[1] We agree with the suggestion from Dr. Tchetina that it would be beneficial to "add some mechanistic characteristics for standard composite disease activity status measures to monitor treatment response involving gene expression analyses in the PBMCs of patients with RA prior to TOF treatment."[2] Indeed, teams of researchers worldwide have been searching for unbiased markers of gene expression at baseline that could serve as predictors of response to TOF treatment for many years. Unfortunately, most of these efforts have been unsuccessful on account of failure to identify biomarkers that could be implemented for clinical use. Previous studies in the literature have reported on the use of genetics and genomics to predict response to tumor necrosis factor inhibitors[5-8] or methotrexate[9,10] in patients with RA. Although some of these individual studies have identified predictive markers, very few have been successfully replicated in other studies.[11,12] Although it makes sense, conceptually, to add the additional molecular characterization of patients participating in clinical trials at baseline, this is challenging due to the absence of validated biomarkers. Further, exploratory biomarkers, such as those described by Dr. Tchetina, are generally assessed ad hoc and after primary outcomes from the trial have been reported, or they are evaluated prospectively in small cohorts.

Notwithstanding, we concur that there are limitations to the use of individual and composite measures in clinical and research settings to assess disease activity and response to treatment in RA. There remains an unmet need for immunological and genetic markers predictive of a clinical response that would enable a personalized therapeutic approach in rheumatic diseases. Once identified, predictive genetic markers (and other omics approaches), together with clinical evaluation and patient-reported outcomes, all of which we consider important and necessary, will converge to support both ideal clinical evaluation and overall patient management. We commend Dr. Tchetina and colleagues for their provocative exploratory work within this space,[3] and we look forward to the future integration of validated biomarkers of response into clinical practice.

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