

## Letter

### Baseline Gene Expression Analysis in the Peripheral Blood of Patients With Rheumatoid Arthritis as an Important Supplement to Standard Composite Measure

To the Editor:

I read with great interest an article “Impact of Tofacitinib on Components of the ACR Response Criteria: Post Hoc Analysis of Phase III and Phase IIIb/IV Trials” by Bessette et al.<sup>1</sup> The authors carried out an extensive study on clinical response to tofacitinib (TOF) in patients with rheumatoid arthritis (RA) and concluded that a divergence between physician- and patient-reported measures highlights the importance of identifying appropriate patient-reported outcomes to manage RA symptoms in a clinical setting. However, although physicians aim to achieve remission or low disease activity and to use composite disease activity assessments to monitor treatment response, there is no standard composite measure so far.

In view of this, I, along with my co-authors, would like to add some mechanistic characteristics for standard composite disease activity status measures to monitor treatment response involving gene expression analyses in the peripheral blood mononuclear cells (PBMCs) of patients with RA prior to TOF treatment. Indeed, in our recent publication,<sup>2</sup> we proved the importance of baseline expression of genes involved in energy generation, as prognostic biomarkers for remission attainment after treatment of 28 patients with RA with TOF for 3 months. Clinical response was evaluated based on the Disease Activity Score in 28 joints using erythrocyte sedimentation rate (DAS28-ESR), and serum levels of anticitrullinated peptide antibodies, rheumatoid factor, C-reactive protein, and ESR. Clinical remission was assessed based on DAS28 < 2.6. Before and after TOF therapy, a significantly higher expression of succinate dehydrogenase and pyruvate kinase genes was observed in all the examined patients compared to healthy subjects. However, the pre-therapy expression of these genes measured by quantitative reverse transcription PCR and corresponding proteins analyzed by ELISA was significantly lower in patients who showed remission than in other examined patients with RA. The rationale behind these findings might support previous observations that RA T cells differ from those in healthy age-matched subjects, primarily by the abnormal expression of metabolic regulators<sup>3</sup> and premature aging associated with functional decline.<sup>4</sup> This is also related to changes in cellular metabolism resulting in reduced adenosine triphosphate synthesis by mitochondria and the delivery of citric acid cycle intermediates.<sup>4</sup> Mechanistically, the putative association of TOF effect and cellular energy metabolic conversions could be caused by the “super-effector cell” functions of RA T cells, with a low threshold for effector cytokine production,<sup>3</sup> which is mediated by the activation of Janus kinase proteins.<sup>5</sup>

Moreover, cytokine protein synthesis is a high-energy-consuming process.<sup>6</sup> In view of this, another approach for the prediction of the patient response in RA might involve the assessment of TOF effects on expression of proteolytic and proinflammatory genes in PBMCs cultured in vitro prior to treatment.<sup>7</sup> It is well established that degradation of articular cartilage and bone in RA was associated with the excessive production of matrix metalloproteinases (MMPs) and osteolytic enzymes, such as MMP-9 and cathepsin K; all of these were detected in serum and synovial fluid of these patients.<sup>8</sup> In addition, serum concentrations of cathepsin K were associated with radiological joint destruction, whereas MMP-9 expression can be upregulated by proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin 1 $\beta$  that are subjected to change in response to RA therapy.<sup>9,10</sup> Out of 12 TOF-naïve patients with RA examined in our study, 6 patients reached clinical remission criteria whereas others preserved high and moderate disease activity after 3 months of TOF therapy.<sup>7</sup> Expression of all the examined genes was significantly upregulated in PBMCs cultured with TOF compared with untreated counterparts from patients who maintained high or moderate disease activity. In contrast, TNF gene expression was significantly downregulated compared with untreated counterparts in PBMCs cultured with TOF of patients who achieved remission.

In conclusion, mechanistic approaches involving baseline gene expression examination in the peripheral blood of patients with RA prior to therapy might serve as an important supplement to clinical assessments in predicting TOF treatment efficacy.

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The study was supported by the Russian Ministry of Science and Higher Education (project no. 1021062512064-0).

The author declares no conflict of interest relevant to this article.

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