Response to: 'Regulatory T cell frequencies in patients with rheumatoid arthritis are increased by conventional and biological DMARDs but not by JAK inhibitors' by Meyer *et al*

Commenting on Meyer *et al*¹ our recent publication² 'Immunological and clinical effects of low-dose interleukin-2 (IL-2) across 11 autoimmune diseases in a single, open clinical trial', Dr Meyer and colleagues point to the issue of concomitant background therapies that could affect the effects of low-dose IL-2. They reported a significant increase of Treg cell frequencies in peripheral blood of patients with rheumatoid arthritis treated with methotrexate, adalimumab, etanercept, golimumab and tocilizumab, which they discuss could affect the increase expected after an IL-2 treatment.

Only four rheumatoid arthritis patients were included in our study, all being treated with low-dose corticosteroids and/or low doses of immunosuppressants. Their baseline Treg evaluation was similar to that of patients with other diseases treated with similar background therapies (figure 1A). In addition, in the whole cohort of patients, we did not observe significant differences in baseline Treg values for patients receiving (1) 'non-specific immunological therapy' (including medications like nonsteroidal anti-inflammatory drugs for joint pain, or ursodeoxycholic acid for sclerosing cholangitis); (2) low-dose corticosteroids and/or low doses of immunosuppressants; compared with patients receiving (3) anti-tumour necrosis factor- α (TNF α) or (4) 'combination of biological disease modifying antirheumatic drug and low doses of immunosuppressants' (figure 1B). Furthermore, as reported in our study, there were no significant differences in the Treg response to low-dose IL-2 according to the background treatment.²

We believe that baseline levels of Tregs in peripheral blood cannot be a criteria for low-dose IL-2 treatment decision nor a robust enough biomarker of the clinical response. First, IL-2 treatment should not be limited to patients (or diseases) with qualitative or quantitative Treg deficiency as the mere presence of an autoimmune disease signals a Treg insufficiency, that is, that Tregs are unable to control the effector immune response

as they should³; second, Treg peripheral blood levels may not accurately reflect Treg counts at sites where they are needed for therapeutic efficacy, that is, tissues or draining lymph nodes; third, IL-2 treatment not only expands Tregs, but also improves their fitness^{2,4} and reshapes their T cell receptor repertoire, both parameters likely playing a role in IL-2 therapeutic activity.

IL-2 has pleiotropic³ dose-dependent⁴ biological activities and patients show some heterogeneity in response to it. Future studies will have to look for biomarkers of IL-2 activity through multiple omics studies, so as to optimise precision medicine-driven modalities.

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Figure 1 Percentage of Tregs at baseline in patients included in the TRANSREG study.² (A) Treg percentages in rheumatoid arthritis patients compared with all other patients receiving low-dose corticosteroids and/or low doses of immunosuppressants. (B) Comparison of baseline Treg percentages in patients according to their background treatment: group 1: non-specific immunological therapy; group 2: low-dose corticosteroids and/or low doses of immunosuppressants; group 3: anti-TNF α ; group 4: combination of biological disease-modifying antirheumatic drug and low doses of immunosuppressants. RA, rheumatoid arthritis.