Reply to: Comment on "Sirolimus as combination rescue therapy with tumor necrosis alpha inhibitors for severe, refractory hidradenitis suppurativa"

To the Editor: We read with interest the correspondence by Khullar[1] about our article reporting the major efficacy of sirolimus in combination with tumor necrosis factor (TNF) inhibitors in a real-life series of patients with severe refractory hidradenitis suppurativa (HS).[2]

In this comment, the author criticized the use of the HS—Physician's Global Assessment (HS-PGA) as an efficacy outcome, claiming that Hidradenitis Suppurativa Clinical Response (HiSCR) should be used instead, a limitation we already acknowledged in our original article. However, despite validation studies of the HiSCR, we still doubt that it can be relevant at a large scale in real-life studies. That is why response according to the demanding criteria of the HS-PGA 0/1 outcome was privileged in our study. Also, it is worth noting that despite its limitations, the HS-PGA has been and is used in numerous randomized clinical trials in HS and that the HiSCR has been shown to strongly correlate with the HS-PGA, with a Spearman rho of -0.61 ($P < .001$).[3]

Regarding safety considerations, Khullar[1] is absolutely right to emphasize various sirolimus-associated adverse events, including dyslipidemia and diabetes. This is why, in our study, sirolimus was considered only in patients with severe HS after failure of a median number of 8 previous therapeutic lines, including TNF-α inhibitors, at high doses for all of them. Moreover, although no dyslipidemia nor hyperglycemia was observed in our study, the body mass index of enrolled patients was 26.3 kg/m^2 (interquartile range, 25.3-28.0) and, therefore, was lower than that commonly reported in studies of moderate to severe HS.[3] Indeed, the safety profile of sirolimus across different metabolic profiles is one of the endpoints to prioritize in future prospective studies. Also, because TNF-α inhibitors, mainly infliximab, have been reported to improve insulin resistance in patients with ankylosing spondylitis and rheumatoid arthritis, the incidence rate of sirolimus-related metabolic adverse events may eventually be lower in the setting of combined regimens, another issue that remains to be properly assessed.[4] We also acknowledge Dr Khullar's comment that, to date, only 1 study reported HS interpreted as a paradoxical reaction to sirolimus treatment, although acne seems to be more common. However, we would like to stress that paradoxical HS has also been reported with both TNF-α inhibitors[5] and secukinumab, which, in the case of the former, does not challenge the relevance of adalimumab and infliximab in the therapeutic armamentarium of moderate to severe HS.

Finally, regarding the mode of action of sirolimus, we prefer not to be biased or to be driven by 1 hypothesis, because mTORC1 is influencing several physiologic and pathogenic pathways, including autophagy, regulatory T-cell expansion, and T helper 17 differentiation, to name a few. For us, the interleukin 17 pathway cannot be considered at this stage to be proven to be causally and canonically engaged in the pathogenesis of HS inflammation, an issue that is the major rationale for ongoing phase 3 randomized controlled studies, which will clarify this major aspect. In any case, there is high probability that adjuvant therapies combined with biologics will be needed in patients with severe HS refractory to biologicals as a single-agent therapy. Whether sirolimus might be part of those requires prospective controlled trials.

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