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

To the Editor: I read with interest the article by Bettuzzi et al[1] on the use of sirolimus as a rescue therapy in combination with tumor necrosis factor alpha inhibitors (infliximab, adalimumab, certolizumab) in 9 patients with severe, refractory hidradenitis suppurativa (HS), based on the evidence for the upregulated mammalian target of rapamycin complex 1 (mTORC1) pathway in HS.[1] I have a few comments in relation to this study.

In their study, Bettuzzi et al[1] did not report any adverse effect due to sirolimus except erysipelas in 1 patient.[1] Sirolimus is known to cause serious adverse effects, like bone marrow suppression leading to thrombocytopenia and leukopenia, infections, and metabolic derangements like hyperlipidemia and hyperglycemia. Hyperlipidemia and hyperglycemia are important concerns in patients with HS because they are usually obese and have concomitant metabolic syndrome, and treatment with sirolimus will further compound this risk. The metabolic adverse effects of sirolimus are intriguing because overactivated mTORC1 is also considered responsible for insulin resistance and type 2 diabetes mellitus. To add to these, among cutaneous adverse effects, paradoxical occurrence of HS has been documented in 12% (10/80) of renal transplant recipients on sirolimus-based therapy for a mean duration of 18 months.[2]

Second, Bettuzzi et al[1] used the HS—Physician's Global Assessment (HS-PGA) score to evaluate treatment response and even acknowledged it as one of the limitations of their study.[1] I highlight here that the Hidradenitis Suppurativa Clinical Response (HiSCR) is a novel objective tool that is more responsive to change as a treatment outcome measure and may therefore be used in place of the HS—Physician's Global Assessment in clinical practice and research studies.[3]

Finally, enhanced expression of T helper type (Th) 17 cells and interleukin (IL) 17 in lesional skin and increased serum levels of IL-17 have been reported in patients with HS, and this may explain the reported effectiveness of secukinumab as a targeted treatment option in cases of HS refractory to tumor necrosis factor alpha inhibitors. Interestingly, current evidence points to a link between the mTORC1 and Th17 pathways, which may suggest that sirolimus acts upstream in the pathway, attenuating IL-17 signaling.[4] Enhanced mTORC1 activation in HS leads to increased expression of hypoxia inducible factor, which promotes transcriptional activation of RORγt signaling and, thus, differentiation of Th17 cells and expression of IL-17.[4] Furthermore, increased toll-like receptor (TLR) expression on macrophages in the lesional skin of HS stimulates IL-23 production, which is of pivotal importance for differentiation of naive T cells into Th17 cells.[4] There is increasing evidence to suggest that Notch signaling negatively regulates the TLR-activated innate immune response. However, in HS, the key pathomechanism is impaired Notch signaling that results in inadequate feedback suppression, leading to Th17-driven autoinflammation.[4] Sirolimus has been shown to inhibit the TLR-4 pathway and IL-17 expression in early diabetic nephropathy in rats.[5] This cross-regulation of immune pathways underscores that the efficacy and adverse effects of sirolimus in HS need to be evaluated in blinded randomized controlled trials in a large cohort of patients.

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