

viSNE (visualization of t-distributed stochastic neighbor embedding, a tool for mapping high-dimensional cytometric results in a two-dimensional format), in which we compared our patient with four healthy controls with a mean (\pm SD) age of 27.8 ± 7.3 months. The algorithm clearly identified a single cluster of CD3+CD4+CCR4+CCR6+CXCR3⁻ cells in our patient that was absent in the controls. This cluster matched the phenotype of T-helper 17 (Th17) cells³ (Fig. 1C) and consisted of 53.4% effector-memory cells and 45.4% central-memory cells (Fig. S1A in the Supplementary Appendix). In our patient, the frequency of Th17 cells was 30 times that in the controls, and the frequency of interleukin-17-producing T cells was 67 times that in the controls (Fig. 1D and 1E and Fig. S1B). The plasma level of interleukin-17A was 38 times that in the controls (83.4 pg per milliliter and 2.2 pg per milliliter, respectively). A Th17 dysregulation was confirmed in a second patient with genetic confirmation of SAM syndrome (see the Results section in the Supplementary Appendix).

Available treatments targeting Th17 cells include biologic drugs that are currently licensed for psoriasis therapy, such as ustekinumab and secukinumab.⁴ Ustekinumab was recently evaluated, with encouraging results, in two patients with DSP mutations,⁵ but we had obtained little cutaneous improvement in another patient with SAM syndrome who had *DSG1* mutations. Because 99% of the Th17 cells in our patient had a memory phenotype, we hypothesized that long-survival memory Th17 cells would not be vulnerable to the neutralization of interleukin-23 (as with ustekinumab), whereas secukinumab could neutralize the effect of the preformed Th17 pool by blocking the action of interleukin-17A on the skin.

We initiated therapy with 75 mg of secukinumab subcutaneously at weeks 0, 1, 2, 3, and 4 and then monthly on a compassionate-use basis when our patient was 18 months of age. The improvement was evident 3 weeks after treatment initiation (Fig. S3). At week 35, the patient showed a

marked cutaneous improvement (Fig. 1B), the pruritus had almost disappeared, her weight and length charts had improved dramatically (Fig. 1F and 1G), and the weight-for-height z score had increased from -2.3 SD to $+1.9$ SD (Table S3).

The major effect of secukinumab on our patient's quality of life supports interleukin-17A as a new target to treat patients with serious skin disorders, such as SAM syndrome. Furthermore, our study proposes an innovative strategy to identify individualized immune biomarkers to exploit with precision the biologic therapeutic arsenal.

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Trial of SAGE-217 in Patients with Major Depressive Disorder

TO THE EDITOR: Gunduz-Bruce et al. (Sept. 5 issue)¹ report promising results for acute anti-

depressant effects of SAGE-217. The drug is a positive allosteric modulator of γ -aminobutyric

acid type A (GABA_A) receptors.² This mechanism is similar to that of benzodiazepines, which also increase GABA_A signaling. Benzodiazepines have been shown to also rapidly decrease the severity of depressive symptoms when started with an antidepressant.³ In a meta-analysis of randomized, controlled trials, combined therapy (e.g., antidepressant plus benzodiazepine) had greater acute antidepressant effects at weeks 1 and 4 than antidepressants alone; however, no significant difference was observed after 6 to 12 weeks or in the maintenance phase.³ Some pharmaco-epidemiologic data have also suggested that simultaneous antidepressant and benzodiazepine use for depression provides no benefits as compared with antidepressants alone after 6 months.⁴ Combined treatment was associated with an increased risk of long-term benzodiazepine use.⁴

Taken together, acute antidepressant effects of treatments that increase GABA_A signaling, such as SAGE-217, may be expected given the previously observed effects of benzodiazepines. However, the medium-to-long-term benefits, and risks, remain unknown and merit caution in extrapolating from a day 15 primary end point.

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THE AUTHORS REPLY: Benzodiazepines are often used in combination with antidepressants to manage anxiety and insomnia in patients with major depressive disorder. However, there is little evidence that benzodiazepines have clinically meaningful effects on the core symptoms of depression when used as monotherapy. Thus, benzodiazepines are almost never used alone to treat major depressive disorder.^{1,2} In contrast, in our trial SAGE-217 was largely administered as monotherapy. Moreover, the mechanism of action of SAGE-217 is distinct from that of benzodiazepines. Benzodiazepines bind only GABA_A receptors expressing γ subunits in combination with α 1, α 2, α 3, or α 5 subunits that largely mediate phasic inhibition, and these drugs have no activity on α 4- or δ -subunit-containing extrasynaptic receptors that mediate tonic inhibition, which neurosteroids such as SAGE-217 potentially modulate.³ Consistent with these pharmacologic characteristics, the reduction in depression scores by SAGE-217 occurred across several scales and was not driven by improvements in anxiety and insomnia,⁴ which would have been expected if efficacy were a consequence of selective modulation of phasic inhibition alone.

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