AB016. A double-blind, placebo-controlled, phase 2 trial of a novel toll-like receptor 7/8/9 antagonist (IMO-8400) in dermatomyositis

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Background: Dermatomyositis (DM) is an inflammatory disease of skin and muscle. Increased interferon (IFN) signaling is a prominent feature of DM, but the mechanisms leading to IFN production in DM are not understood. As toll-like receptor (TLR) 7/8/9 activation can lead to type I IFN production, TLR7/8/9 antagonism may provide therapeutic benefit in DM.

Methods: A double-blind, randomized, placebo-controlled, 24-week trial of IMO-8400 [a novel oligonucleotide TLR7/8/9 antagonist (Idera Pharmaceuticals, Inc.)] was conducted with 30 participants meeting definite or probable criteria of Bohan and Peter for DM. Participants were randomized to treatment with IMO-8400 0.6 mg/kg, IMO-8400 1.8 mg/kg, or placebo. The primary endpoint was the change in the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity score. Exploratory analysis included type I IFN signaling and the 5-D Itch Scale. Blood and skin samples were obtained at baseline and end of treatment to measure changes in type I IFN signaling.

Results: CDASI activity scores decreased in all arms by the end of the trial, per repeated measures mixed model analysis: –9.3 in 0.6 mg/kg, –8.8 in 1.8 mg/kg, and –7.3 in placebo. We observed no change in skin and blood type I IFN signature scores or CDASI activity scores across treatment arms. We found an association between CDASI and skin IFN signature scores (β=12.9, P=0.0002), an association between 5-D Itch Scale and skin IFN signature scores (Rho =0.65, P<0.0001), a lack of association between 5-D Itch Scale and blood IFN signature scores (Rho =0.22, P=0.24), and a positive trend that did not reach significance between CDASI and 5-D Itch Scale scores. Five patients experienced treatment-emergent adverse effects prompting discontinuation: 3 in low-dose (abdominal discomfort/flu, anxiety, urticaria), 1 in high-dose (thrombocytopenia), and 1 in placebo (muscle weakness).

Conclusions: IMO-8400 did not significantly reduce DM disease activity or type I IFN expression. Our study demonstrates that cutaneous DM disease activity may be better studied through skin biopsies, rather than peripheral blood draws, and that type I IFN signaling could be a potential target in improving pruritus in DM patients.

Keywords: Clinical research; dermatomyositis (DM); toll-like receptors (TLRs)

doi: 10.21037/atm.2021.AB016

Cite this abstract as: Kim YJ, Schiopu E, Dankó K, Mozaffar T, Chunduru S, Lees K, Goyal N, Sarazin J, Fiorentino DF, Sarin KY. A double-blind, placebo-controlled, phase 2 trial of a novel toll-like receptor 7/8/9 antagonist (IMO-8400) in dermatomyositis. Ann Transl Med 2021;9(5):AB016. doi: 10.21037/atm.2021.AB016

