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A phase 2, double-blinded, placebo-controlled trial of toll-like receptor 7/8/9 antagonist, IMO-8400, in dermatomyositis

To the Editor: Dermatomyositis (DM) is a rare inflammatory disease of muscle and skin. DM severity is thought to be driven, in part, by type I interferon signaling.[1] Because interferon is primarily induced by toll-like receptors (TLRs) 7/9, we hypothesized that antagonizing TLR7/9 could improve DM disease activity.[2,3]

Table I. Baseline characteristics of the intent-to-treat population

Characteristics	Placebo	IMO-8400 0.60 mg/kg	IMO-8400 1.8 mg/kg
n	11	9	10
Age, y, mean (SD)	51.3 (10.6)	48.3 (14.2)	54.6 (14.1)
Sex, n (%)			
Female	7 (63.6)	7 (77.8)	9 (90.0)
Male	4	2	1
Race, n (%)			
White	11 (100)	8 (88.9)	9 (90.0)
Black or African American	0	1 (11.1)	1 (10.0)
CDASI, n (%)			
15-20	1 (9.1)	0	2 (20.0)
≥21	10 (90.9)	9 (100)	8 (80.0)
CDASI activity score, mean (SD)	30.2 (9.8)	33.0 (8.4)	33.5 (14.7)
Treatment-concomitant drugs, n (%)			
Systemic corticosteroids* (%)	8 (72.7)	5 (55.6)	5 (50.0)
DMARDs† (%)	5 (45.5)	6 (66.7)	6 (60.0)
Immunoglobulins (%)	1 (9.1)	0	1 (10.0)

CDASI, Cutaneous Dermatomyositis Disease Area and Severity Index; *DMARD*, disease-modifying antirheumatic drugs; *SD*, standard deviation.
*Methylprednisolone, prednisolone, and prednisone.
†Azathioprine, leflunomide, methotrexate, mycophenolate mofetil, and mycophenolic acid.

We conducted a phase 2, multicenter, double-blind, randomized, placebo-controlled trial of IMO-8400, an oligonucleotide antagonist of TLR7/8/9, in DM.[4,5] Thirty patients with Cutaneous Dermatomyositis Disease Area and Severity Index version 2 (CDASIv2) scores of 15 or greater were enrolled between November 2015 and June 2018. Patients were allowed to remain on stable prednisone (≤20 mg/d) and up to 1 immunomodulatory therapy from a prespecified list (Table I and Supplemental Table 1, *A* and *B*; available via Mendeley at https://doi.org/10.17632/f9vx46p3fc.1).

Participants were stratified into 2 groups by CDASIv2 activity score (15-20 vs ≥21) and randomized 1:1:1 to receive weekly subcutaneous injections of IMO-8400 0.6 mg/kg, IMO-8400 1.8 mg/kg, or placebo for 24 weeks. Because IMO-8400 is associated with injection site reactions, the primary outcome used a modified CDASIv2 activity score (CDASI-a) excluding the injection site.

Secondary assessments included the Manual Muscle Test 8 (MMT8).

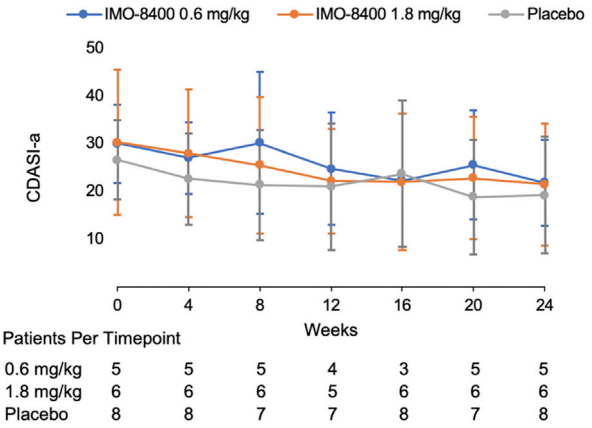

Fig 1. CDASI-a throughout the 24-week study between IMO-8400 treatment arms as compared to placebo in the per-protocol population. The graph depicts the mean CDASI-a score of the per-protocol population for each treatment arm over the course of the trial. The error bars represent the standard deviation. The table below lists the corresponding number of available patient measurements every time point in each treatment arm. *CDASI-a*, Cutaneous Dermatomyositis Disease Area and Severity Index version 2 activity score.

Participants were predominantly white (93.3%) and female (76.7%), with a median age of 54.5 years (Table I). The mean baseline CDASI-a was 32.1 and was generally equal across treatment arms (30.2 for placebo, 33.0 for 0.6 mg/kg, and 33.5 for 1.8 mg/kg). The most common injection site reactions were erythema, pain, and induration (Supplemental Tables II and III; available via Mendeley at https://doi.org/10.17632/f9vx46p3fc.1). Out of 30 patients, 11 discontinued the study—5 (16.7%) because of adverse events, 4 (13.3%) for lack of efficacy, and 2 (6.7%) because of withdrawal by the participant.

CDASI-a improved for all groups over 24 weeks (−9.3 for 0.6 mg/kg, −8.8 for 1.8 mg/kg, and −7.3 for placebo) (Fig 1). There was no significant difference between placebo and treatment groups; the repeated-measures mixed model analysis of CDASI-a across visits of the combined IMO-8400 group compared to that of placebo showed a least squares mean difference of −1.9 ($P = .238$).

The average changes in MMT8 between the end of trial and baseline were as follows: +3.8 for placebo, +1.8 for 0.6 mg/kg, and +2.8 for 1.8 mg/kg. Across visits, in comparison to the placebo, the least squares mean difference of MMT8 in the 0.6 mg/kg group and 1.8 mg/kg group was +0.4 ($P = .846$) and +2.3 ($P = .250$), respectively.

IMO-8400 did not show clinical efficacy over placebo in treating DM skin or muscle disease. IMO-8400 may not have achieved high enough doses for the pharmacologic blockade of TLR7/9, or there may be roles for pathways outside of TLR7/9 in DM. Limitations of the study include the small sample size and patient use of concomitant medications.

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Efficacy of sonidegib in histologic subtypes of advanced basal cell carcinoma: Results from the final analysis of the randomized phase 2 Basal Cell Carcinoma Outcomes With LDE225 Treatment (BOLT) trial at 42 months

To the Editor: Basal cell carcinoma (BCC) is the most common cancer worldwide.[1] Major histologic subtypes of BCC include nonaggressive (nodular and superficial) and aggressive forms (morpheaform, infiltrative, micronodular, and basosquamous).[1] Locally advanced BCC and metastatic BCC can cause extensive tissue destruction, limiting effective treatment options.[1]

Sonidegib, a Hedgehog pathway inhibitor selectively targeting Smoothened, is approved in the United States for the treatment of adult patients with recurrent locally advanced BCC after surgery or radiation therapy or those who are not candidates for surgery or radiation therapy.[2] Here we examine the long-term efficacy of sonidegib 200 and 800 mg once daily across histologic subtypes of BCC at 42 months.

Basal Cell Carcinoma Outcomes With LDE225 Treatment (BOLT; NCT01327053) is an international, randomized, double-blind, phase 2 study with patients randomized 1:2 to sonidegib 200 or 800 mg once daily. The primary endpoint was objective response rate (ORR) by central review. Key secondary endpoints included duration of response, time to tumor response, progression-free survival, and overall survival. Tumor evaluations and ORR were assessed per BCC-modified Response Criteria In Solid Tumors (mRECIST) for locally advanced BCC and RECIST version 1.1 for metastatic BCC.[3] Tumor evaluations were conducted at baseline, weeks 5 and 9, every 8 weeks during the first year, and every 12 weeks thereafter.

Overall, 230 patients enrolled; 36 (15.7%) with metastatic BCC and 194 (84.3%) with locally advanced BCC (aggressive, 112 of 194 [57.7%]; nonaggressive, 82 of 194 [42.3%]). The ORRs at 42 months for patients with aggressive and nonaggressive locally advanced BCC were 59.5% (22 of 37) and 51.7% (15 of 29) for 200 mg and 45.3% (34 of 75) and 47.2% (25 of 53) for 800 mg, respectively. Among patients with metastatic BCC, ORRs were 7.7% (200 mg) and 17.4% (800 mg).

Highest ORRs were in infiltrative (200 mg, 51.6% [16 of 31]; 800 mg, 36.8% [21 of 57]) and morpheaform (200 mg, 50.0% [3 of 6]; 800 mg, 75.0% [6 of 8]) for aggressive subtypes. Approximately 50% of patients with nonaggressive subtypes in each group achieved objective response (Table I). Median duration of response for patients with nodular subtype was not estimable and was 15.7 months (95% confidence interval, 7.4-26.4 months) for 200 mg and 800 mg, respectively (Table II).

Patients with infiltrative locally advanced BCC receiving 800 mg had a longer median progression-free survival but lower ORR vs patients receiving 200 mg, highlighting that this analysis was underpowered to determine differences between treatment groups within a histologic subtype.

Subtypes with more enrolled patients generally demonstrated ORRs similar to those observed in the entire population, suggesting a consistent response to sonidegib across histologic subtypes. Comparably, BCC histopathologic subtype did not appear to influence overall tumor response to vismodegib over 12 to 24 weeks.[4]

Limitations of this study include the small patient sample size and the exclusion of patients with

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