Toward Cannabinoid Use for Refractory Cutaneous Dermatomyositis

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Dermatomyositis (DM) is a rare but potentially devastating autoimmune disease typically characterized by myositis, interstitial lung disease, and a characteristic rash. DM, systemic lupus erythematosus, and scleroderma share some immunopathogenic pathways, and these diseases show clinical overlaps. Dysregulation of nucleic acid metabolism and disordered type I IFN production contributing to autoantibody production may be a common denominator across these disorders.

DM therapy is anchored in initial corticosteroid therapy and immunosuppression or immunomodulation with agents, including intravenous Ig, cyclophosphamide, mycophenolate, methotrexate, rituximab, and the ongoing assessment of experimental therapies. The rarity of DM and the sometimes suboptimal therapy responses, especially in subjects with specific autoantibodies, including Anti-Jo-1 (antisynthetase syndrome) and anti-MDA5, attest to the need for further experimental therapies. The randomized, double-blind, placebo-controlled phase II trial presented by Werth et al. (2022) highlights the beneficial effects of lenabasum as a therapy for difficult-to-treat DM skin manifestations in patients without significant myositis, most of whom received concomitant immunosuppression therapy. All patients included had failed or not-tolerated hydroxychloroquine treatment. Patients were treated with oral lenabasum (up to 20 mg twice daily), which is not considered to be an immunosuppressive drug.

The study met its primary outcome at week 16 (day 113) regarding overall reduction in skin disease activity (Cutaneous Dermatomyositis Disease Area and Severity Index [CDASI]) as a primary endpoint. Interestingly, hair loss was one of the secondary outcomes, which was also favorably influenced by lenabasum. In keeping with proof-of-concept studies in DM, where cases are rare, the total study population included 11 patients in the active group and 11 in the placebo group. In skin biopsies, mRNA for IFNγ and IFNβ but not for other mediators (including TNFa, IL1β, and type 2 cytokines) were significantly reduced in the lenabasum-treated group on day 85. The fall in type I and type II IFN levels is consistent with the importance of the recognized role of IFN across the previously mentioned connective tissue diseases.

Although not well-recognized outside dermatology, DM is one of the few connective tissue diseases with skin manifestations, for which patients report intense itch, often reported as affecting the scalp most acutely. This itch response seems largely refractory to immunosuppressant or hydroxychloroquine therapy. IL-31, produced mainly by T helper (Th) 2 cells, is now widely accepted as the itch cytokine, and a therapeutic all-31Ra antibody (nemolizumab) is in advanced phase III clinical trials for atopic dermatitis and prurigo (Kabashima and Irie, 2021; Silverberg et al., 2020). IL-31 is
known to affect the skin barrier (Hänel et al., 2016) and to suppress keratinocyte differentiation. Analyzing the responders to lenabasum (defined as >5-point change in the CDASI activity score) versus nonresponder patients, there was a marked difference in IL-31 expression in skin lesions in immunohistochemistry. Also of interest, in those patients who reported significant improvement of itch, IL-31 was found to be significantly decreased. Although this may point to a causal link, cannabinoid receptor agonists may also influence itch by means of other mediators. It will be interesting to see the effect of an IL-31 blocker on pruritus in patients with DM.

Lenabasum increases the production of PGD2, and the resulting mediator production of 15-deoxy-D12,14-prostaglandin J2 promotes the resolution of inflammation affecting different signaling pathways. Lenabasum is also believed to increase the resolution of inflammation by its action on so-called specialized proresolving mediators, which include lipoxins, resolvins, protectins, and maresins. These inflammation-resolving properties suggest that lenabasum could be a promising addition to the limited armamentarium available to effectively treat DM, other chronic inflammatory conditions, as well as advanced stages of established disease.

On the other hand, PGD2 metabolites activate type 2 innate lymphoid cells as well as eosinophils, including through CRTH2, which is preferentially expressed on Th2 cells (He et al., 2010). A regulatory impact of Th2 cytokine IL-4 on Th1 cell polarization is possible, resulting in reduced IFNγ production, which is indeed detectable in the study discussed in this paper.

So far, lenabasum has not been used as monotherapy in DM trials but as a combination with existing systemic immunomodulators. The best combination therapy with lenabasum will have to be determined.

This study suggests that despite previously disappointing phase III trial results, lenabasum may play a role in skin DM therapy. A key task for future research is to identify the patient subpopulation that benefits most from lenabasum therapy. High baseline itch scores, high IL-31 levels, and hair loss symptoms may be parameters to support patient stratification.

In line with previous studies performed, major adverse events with lenabasum have not been reported in this trial, which makes this drug discovery even more exciting. Finally, feedbacks from patients indicate that they are very interested in therapy alternatives to classical systemic immunosuppressants.