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NEWS, VIEWS, & REVIEWS

Spotlighting Emerging Therapies for Benign Familial Pemphigus

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INTRODUCTION

Benign familial pemphigus (BFP) is a rare blistering genodermatosis characterized by recurrent vesicular and erosive lesions involving intertriginous areas. BFP affects approximately 1/50,000 people in the general population,[1] and is inherited through an autosomal dominant mutation of the gene *ATP2C1* causing disrupted intracellular calcium sequestration that impairs keratinocyte adhesion, leading to acantholysis.[2] Intertriginous sites are most often affected by BFP, and exacerbating factors include friction, sweating, stress, and heat.[3] Treatment and management focus on avoiding triggering factors and a variety of medications to decrease the severity of disease and burden of complications. Herein, an update on emerging treatment modalities will be reviewed.

TREATMENT

Traditional treatments for BFP include oral and topical antibiotics and corticosteroids, cyclosporine, dapsone, and methotrexate for patients with recalcitrant disease. However, achieving disease remission is challenging as these agents infrequently provide sustained disease clearance. With limited treatment options, BFP poses a major burden on patients, with a significant impact on quality of life (QoL). A recent national qualitative study in Germany found that 39.77% of surveyed patients had a dermatology life quality index (DLQI) score indicating severe impact on their QoL and 56.92% rated systemic treatments as ineffective (n=90).[5] Within the past decade, several approaches have been investigated for widespread recalcitrant BFP, notably anticholinergic agents, apremilast, low-dose naltrexone (LDN), magnesium chloride ($MgCl_2$), and oral vitamin D.

Anticholinergics

Anticholinergic therapies, including glycopyrrolate and oxybutynin, have demonstrated clinical efficacy in preventing precipitating factors of BFP exacerbations. Glycopyrrolate 1 mg daily used in combination with standard therapies then as a monotherapy thereafter, achieved disease clearance with 6 months of remission in one patient.[6] The effects of glycopyrrolate may be amplified in conjunction with localized onabotulinumtoxinA injections in disease-prone areas as combining treatments potentiates sweat blockage.[7] More recently, a double-blind, placebo-controlled single-center study found that all patients except 1 who received an initial or reinjection of onabotulinumtoxinA at 4 weeks decreased 2 levels on a 4-point clinical scale for BFP severity after 8 or 12 weeks.[8] OnabotulinumtoxinA was found to be safe and effective for most cases of BFP as a monotherapy, though severe cases likely require polytherapy.

Apremilast

The use of apremilast for BFP was first reported by Kieffer et al in a case series involving 4 patients with severe, treatment-resistant disease.[9] All patients improved after 1 month of treatment, with 3 patients achieving a physician global assessment score of 1 by 6 months. To date, 9 cases have documented successful treatment response to apremilast,[9-12] with one case incorporating onabotulinumtoxinA as an adjunctive treatment,[13] and 5 cases have demonstrated poor therapeutic response despite combined treatment with dermabrasion.[14] Interestingly, an early improvement of BFP lesions was associated with improved disease outcomes in all cases demonstrating response to therapy.[12] Apremilast is generally well tolerated, with some patients experiencing minor gastrointestinal symptoms, myalgia, and headache.

Naltrexone

Naltrexone has been historically used to treat pruritus associated with inflammatory skin diseases, including psoriasis and atopic dermatitis. More recently, compelling evidence supports using LDN in patients with BFP for postulated benefits on keratinocyte differentiation and wound healing.[15] In initial documentation of its use in BFP, improvement in lesions was observed with a nightly dosage of 3 mg, titrated to 4.5 mg nightly in one patient (n=3).[16] These improvements were seen within 1 to 2 weeks, with clearance achieved within 2 months. Since then, numerous case reports have shown clinical efficacy, with most patients achieving 80% to 95% disease clearance within months,[17,18] whether used as a monotherapy or an adjunct to other systemic therapies. One case even reported a reduction in a patient's DLQI Score from 29 to 4 within 7 months.[19] Notably, incorporating LDN in medication regimens is practical, as it is a relatively inexpensive and well-tolerated drug.

Magnesium Chloride

$MgCl_2$ may inhibit calcium-extrusion processes in keratinocytes, increasing intracellular calcium levels and thus facilitating a calcium-dependent pathway for desmosome assembly.[20] Its use was first described in a patient with a long-standing disease who

achieved clearance with a daily intake of $MgCl_2$ solution intended for arthritis.[21] In a subsequent report, a daily intake of 70 mL of oral $MgCl_2$ solution containing 300 mg of elemental magnesium resulted in significant improvement after 2 weeks and complete remission after 4 weeks without electrolyte disturbances (n=2).[22] In recurrent cases, increasing the dose to a 140 mL dilution per day relieves flares.[23]

Oral Vitamin D

Oral vitamin D regulates keratinocyte differentiation and proliferation, thus preventing acantholysis by increasing calcium levels. Only two cases supporting its efficacy have been described. The first described successful disease management with 800 IU of vitamin D and 300 mg of magnesium citrate in a patient who failed topical antimicrobials, botulinum toxin, and CO_2 laser therapy.[24] The second described a patient treated with topical calcitriol and vitamin D 800 IU for 10 days followed by vitamin D monotherapy, achieving 7 months of remission.[25] Given these promising outcomes, further studies evaluating vitamin D are warranted.

CONCLUSION

The evidence-based therapeutic armamentarium for BFP has expanded in recent years, namely anticholinergics, apremilast, LDN, $MgCl_2$, and oral vitamin D. Randomized clinical trials are still needed to establish evidence-based recommendations and evaluate safety profiles for these emerging therapies.

DISCLOSURE

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