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GRAPPA Point-Counterpoint: Should Biologics Be Used for Mild Psoriasis?

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ABSTRACT. Psoriasis (PsO) is commonly classified as mild, moderate, or severe, usually based on body surface area (BSA) or other validated measures. Although most dermatologists agree that mild PsO should be treated with topical therapies, there are circumstances where mild or limited PsO should be treated with biologics, even as first line. A debate about use of topical vs biologic therapy was presented at the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2023 annual meeting. Arguments in favor of using biologics when patients have mild disease on limited BSA included presence of psoriatic arthritis (PsA) and symptoms on special sites (ie, scalp, face, body folds, genitals, nails, palms, soles). New data suggest that treating limited or early PsO may decrease the risk of developing PsA. Arguments against using biologics for mild PsO focused on the definition of mild PsO, citing that limited BSA with PsA and significant quality of life impact should not be defined as mild. Truly mild PsO should be treated with topical agents, given their safety and relative low cost. The availability of newer agents like roflumilast and tapinarof have expanded therapeutic choice and have data supporting their use for treatment of special sites.

Key Indexing Terms: biological therapy, GRAPPA, psoriasis, psoriatic arthritis

Introduction

Body surface area (BSA) or other validated measures of psoriatic symptoms allow disease severity to be classified as mild, moderate, or severe. Categorization of psoriasis (PsO) severity is necessary to evaluate eligibility for systemic treatments or clinical trials, but there is no consensus on what defines mild, moderate, or severe disease.[1] There are many existing definitions of mild PsO, including BSA < 3%, BSA < 5%, and Psoriasis Area and Severity Score (PASI) < 3.[2,3] Most providers would concur that mild PsO should be treated first line with topical agents prior to systemic or biologic therapies. However, there are many circumstances where patients with limited BSA require systemic biologic therapies, which challenges traditional definitions of mild PsO. In a point-counterpoint discussion, moderated by Dr. Kristina Callis Duffin at the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2023 annual meeting, Dr. Alice Gottlieb presented arguments in favor of using biologics for mild PsO, and Dr. Brian Kirby presented counterarguments opposing the use of biologics for mild PsO.

In favor of biologics for mild PsO

Arguments in favor of using biologics were presented in the context of using a narrow definition of mild PsO as limited BSA of skin involvement. The first argument for the use of biologics in the setting of mild cutaneous PsO is the presence of psoriatic arthritis (PsA). PsA is underrecognized and undertreated, and is associated with mild PsO and areas of special site involvement, including the scalp, nails, palms, soles, and body folds.[4] Treating

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mild skin disease with topical therapies and failing to diagnose and treat PsA can lead to significant disability and joint destruction.[5] Biologic therapies, including inhibitors of tumor necrosis factor (TNF), interleukin 17 (IL-17), IL-12/23, IL-23, Janus kinase inhibitors, and tyrosine kinase 2 inhibitors, control signs and symptoms of both skin and joints and improve quality of life (QOL). Many also inhibit radiographic progression of disease.[6]

Additionally, data suggest that treating cutaneous PsO with biologics may affect the incidence of PsA. A 2022 retrospective cohort study of 1326 patients with PsO aimed to determine if the risk of PsA was affected by the use of biologics.[7] These patients did not have PsA at baseline; 663 patients received biologics (intervention group), whereas the remaining 663 (control group) did not. Controls were matched by age at diagnosis, time until treatment initiation, maximum BMI (calculated as weight in kilograms divided by height in meters squared), and smoking. The control group had a statistically significantly higher risk of developing PsA than the biologic-treated group, with an adjusted hazard ratio (HR) of 1.39 (95% CI 1.03-1.87), suggesting a role for biologics in the prevention of PsA. Another 2022 retrospective cohort study of 1719 patients with PsO found that those treated with biologic disease-modifying antirheumatic drugs had a significantly lower risk of developing PsA compared to those treated with topicals, with an incidence rate ratio of 0.26 (95% CI 0.03-0.94, $P = 0.01$).[8] This provides further evidence that biologic treatments in patients with PsO may reduce the risk of developing PsA.

The second argument for using biologics is that patients with mild PsO often experience significant negative impact on their QOL. Additionally, patients with limited BSA often have special site involvement, including the scalp, face, nails, body folds, genitals, palms, and soles, where topical agents are often insufficient, contraindicated, or poorly tolerated. Palmoplantar PsO, by definition, affects < 5% BSA and yet many patients experience significant disability and discomfort.[9] Patients with palmoplantar PsO exhibit burning, soreness, and greater functional disability compared to other forms of psoriatic disease (PsD). Palmoplantar PsO is often resistant to traditional topical and oral treatment. One systematic review evaluating the efficacy of biologics in palmoplantar PsO found that several biologics (adalimumab, guselkumab, ixekizumab, secukinumab, and ustekinumab) were highly efficacious for the treatment of hyperkeratotic palmoplantar PsO.[10] Likewise, patients with mild PsO with < 5% BSA and sensitive area involvement (eg, groin, axilla, face, neck) experience greater QOL burden, as highlighted by the International Psoriasis Council (IPC), and should be considered for biologic therapy.[11]

Finally, it is important to note that the availability of biosimilar drugs for PsO has made biologic therapy more accessible for patients. Biologic medications, despite their high efficacy in treating PsO, are expensive and thus underused in certain patient populations. Currently, biosimilar drugs of adalimumab, etanercept, and ustekinumab are available on the market, offering cost-effective treatment alternatives without compromising efficacy and safety.[12] This broader access to biologic medications can lead to better overall management of PsO for a wider range of patients, including those with limited BSA.

Arguments against using biologics for mild PsO

The arguments against using biologics for mild PsO were made in the context of a more holistic definition of mild, moderate, and severe PsD. As noted above, the definition of mild PsO is a topic of controversy. A reasonable definition would be an involved BSA of < 5% with a small impact on QOL (eg, Dermatology Life Quality Index score < 5) and the absence of PsA. With that in mind, both the IPC and GRAPPA guidelines suggest that topical therapies be recommended as the initial therapy.[6,11]

Traditional topical therapies such as topical steroids and vitamin D analogs are effective in the majority of patients with mild disease. Newer topical therapies have been approved in both the United States and Europe. Roflumilast 0.3% cream, a phosphodiesterase-4 (PDE4) inhibitor, has been shown to be effective in 2 phase III randomized placebo-controlled trials with over 800 patients with moderate PsO. Patients treated with roflumilast 0.3% cream were more likely to achieve investigator global assessment (IGA) success (IGA clear/almost clear) compared to placebo (37.5-42.4% vs 6.1-6.9% across both trials, respectively).[13] Tapinarof is a topical therapy that acts via the aryl hydrocarbon receptor. In 2 phase III, placebo-controlled trials, 35.4% and 40.2% of patients achieved the primary endpoint (IGA clear/almost clear) compared to 6% and 6.3% of placebo patients, respectively.[14] Roflumilast and tapinarof are both very well tolerated.[13,14]

If topical therapies are insufficient, phototherapy and oral systemic therapy with apremilast both offer favorable risk-benefit ratios for limited PsO. Narrowband ultraviolet B phototherapy is a well-established safe and effective treatment for mild PsO.[15] Apremilast, a PDE4 inhibitor, is approved for the treatment of mild to moderate PsO by the US Food and Drug Administration. Relative to biologics, apremilast has a low rate of serious infection, offering a favorable risk/benefit ratio for patients with limited BSA.[16,17]

Although there is no argument to refute the need for biologics for PsA in patients with otherwise mild PsO, the concept of using biologics to prevent development of PsA remains controversial. The simplest arguments against using biologics for mild PsO are the cost and risk relative to the incidence of PsA. Although PsA is the most common comorbidity associated with PsO,[18] the incidence of new-onset PsA is between 2 to 3 cases per 100 patient-years.[19] Therefore, even if biologics were proven to prevent PsA, the number of patients who would benefit from such an intervention would be limited and the number needed to treat would be too high to justify the cost and risk of serious infections.

Although the above-mentioned Rosenthal et al study[7] suggests there may be a role for biologics preventing or slowing development of PsA, this study and others have significant methodologic issues and conflicting conclusions. In a single-center retrospective of 464 patients, there was a reduced incidence of PsA in those treated with biologics compared to phototherapy. The annual incidence of PsA was 1.20 cases (95% CI 0.77-1.89)

vs 2.17 cases (95% CI 1.53-3.06) per 100 patients/year in the biologic-treated patients compared to the phototherapy group, respectively (HR 0.29, 95% CI 0.12-0.70, $P = 0.01$).[20] Singla et al also performed a retrospective study using claims data, reporting an incidence of PsA of 2.58/100 patient-years and suggested that the incidence of new-onset PsA may be lower in patients receiving IL-23 inhibitors compared to those on TNF or IL-17 inhibitors.[21] In contrast, Meer et al suggested that the incidence of PsA may be higher in patients with PsO treated with biologics.[22] Using the OptumInsights Electronic Health Record Database, the incidence of PsA was 9.75/1000 patient-years. The incidence of PsA was highest in biologic-treated patients compared to those treated with systemic therapies, phototherapy, and topical therapies.[22] These studies illustrate the potential for biases such as channeling and protopathic biases to influence results in single-center and retrospective studies. A prospective, randomized controlled trial has launched to assess whether guselkumab treatment reduces the incidence of PsA, but results will not be available for some time.[23] Registries are ideally positioned to contribute to the body of literature. Hopefully, a clearer picture will emerge in time, but to date there is insufficient evidence that biologics mitigate the development of PsA to justify their use for this purpose.

Summary

This point-counterpoint discussion was held to explore the controversies around selecting appropriate therapy when cutaneous involvement of PsO is considered mild. The definition of mild PsO is central to both arguments. Both speakers agree that PsO should not be classified as mild when the impact on QOL is significant or symptoms are not mild. Special site involvement, specifically the face, scalp, body folds, genitals, hands, feet, and nails, are associated with more symptom and QOL burden. Additionally, a more holistic view of PsD should be taken to appropriately select therapy; when PsA is present, PsD should not be considered mild and biologics are often indicated. When considering the quality of data, risk-benefit ratio, and the burden of cost, the use of biologics to prevent PsA in patients with otherwise mild PsO is not advised. Although there are new topical agents to treat mild PsO, there remain many gaps in therapeutic options for special site involvement and prevention of PsA.

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