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What Clinicians Need to Know About Glucagon-like Peptide 1 Agonists

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ABSTRACT. The interplay between metabolic health and autoimmune diseases such as psoriasis (PsO) and psoriatic arthritis (PsA) has garnered increasing attention. Obesity, a key feature of metabolic syndrome, exacerbates disease severity in these conditions, prompting the exploration of treatments addressing both the immune system and metabolism. Glucagon-like peptide 1 receptor agonists (GLP-1RAs), primarily used for type 2 diabetes mellitus, have demonstrated benefits beyond glycemic control, including promoting weight loss, improving metabolic health, and potentially modulating immune responses. There is also a dual GLP-1 and glucose-dependent insulinotropic polypeptide receptor agonist with similar and potentially superior capabilities; throughout this manuscript these will be collectively known as GLP-1RA. Recent studies also suggest that GLP-1RAs may help manage PsO and PsA in patients with obesity. These medications may offer dual benefits by reducing inflammation and addressing metabolic abnormalities like insulin resistance and hyperlipidemia. This article reports on a presentation given at the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2024 annual meeting underscoring the potential of GLP-1RAs as a therapeutic option, particularly for obese patients with PsO and PsA. Although promising, the evidence supporting GLP-1RAs for treating PsO and PsA remains limited, necessitating further clinical research to evaluate their safety and efficacy.

Key Indexing Terms: glucagon-like peptide 1 receptor agonists, GRAPPA, psoriasis, psoriatic arthritis

Introduction

Interest in the relationship between metabolic health and autoimmune diseases like psoriasis (PsO) and psoriatic arthritis (PsA) has been growing. Obesity, a key component of metabolic syndrome, is increasingly recognized as a significant comorbidity in these conditions, affecting around 27% of patients, often exacerbating disease severity. Weight gain can lead to onset of PsA.[1] Conversely, weight loss can improve disease outcomes—including achieving minimal disease activity—and treatment response in patients with PsA.[1-3] These findings have led to a search for therapeutic strategies that address both metabolic and autoimmune aspects of these diseases.

Glucagon-like peptide 1 receptor agonists (GLP-1RAs) represent a promising class of medications for the management of type 2 diabetes mellitus (T2DM). These agents are designed to mimic the effects of GLP-1, an incretin hormone naturally produced in the intestines in response to food consumption. GLP-1 plays a central role in regulating glucose homeostasis and promoting satiety, which is why its agonists are effective for managing both blood sugar levels and body weight. Specifically, GLP-1RAs stimulate insulin secretion in a glucose-dependent manner, reduce glucagon secretion, slow gastric emptying, and enhance feelings of fullness, all of which contribute to improved glycemic control and weight loss.[4]

Beyond their well-established effects on blood sugar regulation and weight management, recent studies have highlighted additional potential benefits of GLP-1RAs. Notably, there is emerging evidence suggesting that these medications may possess immunomodulatory properties, which could expand their therapeutic potential beyond diabetes care. Some studies have pointed to the potential of GLP-1RAs in modulating immune responses, indicating their possible use in autoimmune diseases like PsO and PsA. The ability of GLP-1RAs to exert such effects is thought to be related to their ability to influence inflammatory pathways and immune cell functions. These findings are leading to ongoing investigations into the broader applications of GLP-1RAs, particularly in managing conditions characterized by autoimmune inflammation.[5]

Moreover, GLP-1RAs are being studied for their potential cardiovascular benefits. The medications have shown promise in improving cardiovascular outcomes, a key concern for patients with T2DM, who are at higher risk for heart disease. This makes GLP-1RAs an increasingly important tool not only for glycemic control but also for addressing the broader health issues faced by individuals with T2DM. As ongoing research continues to explore these various benefits, GLP-1RAs are becoming a cornerstone in the management of T2DM and may hold promise for future treatments of other complex, chronic conditions.[6,7]

The lecture presented at the Group for Research and

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Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2024 annual meeting emphasized the need for further investigation evaluating the effectiveness of GLP-1RAs alone or combined with immunomodulatory therapies approved for management of PsO and PsA, particularly in patients with obesity.

GLP-1RAs and PsO/PsA

There is increasing interest in the potential of GLP-1RAs to improve outcomes in patients with PsO and PsA, particularly given their ability to induce significant weight loss. Obesity is a well-established risk factor for both conditions, contributing to disease severity and progression. Weight reduction has been associated with improvements in disease activity, supporting the rationale for interventions that target both metabolic and inflammatory pathways.

Beyond weight loss, some studies have explored the direct effects of GLP-1RAs on PsO. A metaanalysis by Chang et al suggested that liraglutide therapy may reduce PsO severity independently of changes in weight and glycemic control.[7] However, these findings remain controversial, warranting further investigation to clarify the mechanisms underlying this potential benefit.[6,7]

Similarly, Gisondi et al found that obese patients with moderate-to-severe chronic plaque PsO who lost weight showed an enhanced response to cyclosporine therapy, a common immunosuppressive treatment for PsO.[8] These findings suggest that interventions targeting weight loss may offer significant therapeutic benefits for patients with obesity-related PsO and PsA.[8]

Given the potent weight-loss effects of GLP-1RAs, these medications could potentially serve as a complementary treatment to standard immunomodulatory therapies for PsO and PsA. GLP-1RAs have been shown to promote weight loss through multiple mechanisms, including appetite suppression, slowing gastric emptying, and improving insulin sensitivity. This makes them an attractive option for individuals whose disease severity is exacerbated by obesity. Notably, current studies are exploring the combination of the GLP-1/glucose-dependent insulinotropic polypeptide agonist tirzepatide with ixekizumab, an interleukin 17 inhibitor, to assess whether the dual therapy approach could offer superior benefits compared to ixekizumab alone. These studies are a testament to the growing recognition of the importance of metabolic factors in managing immune-mediated diseases like PsO and PsA.[6,8]

In addition to their weight-loss benefits, there is emerging evidence that GLP-1RAs may have direct immunomodulatory effects. These medications have been found to reduce systemic inflammation and modulate immune responses, which could directly influence the underlying pathophysiology of PsO and PsA, both of which are characterized by chronic inflammation and immune system dysregulation. Studies have shown that GLP-1RAs can lower circulating inflammatory markers, such as C-reactive protein and tumor necrosis factor, independent of glycemic control, suggesting a potential role in immune modulation.[9,10]

The antiinflammatory effects of GLP-1RAs may help to alleviate the inflammatory burden associated with these conditions, potentially improving patient outcomes. Although more research is needed to fully elucidate the immunomodulatory properties of GLP-1RAs, their potential to improve both metabolic health and immune function makes them a promising addition to the treatment landscape for PsO and PsA.[10]

Potential benefits and considerations

The potential benefits of GLP-1RAs in PsO and PsA include the following:

- *Weight loss.* GLP-1RAs are effective in promoting weight loss, with patients typically losing 5-10% of their body weight over several months. This weight loss can significantly improve disease severity in conditions like PsA and PsO, including reducing inflammation and improving disease control. Klingberg et al demonstrated that even modest weight loss can reduce disease activity in obese patients with PsA.[6] Additionally, weight loss may play a preventive role in psoriatic disease progression. Evidence suggests that reducing excess body weight lowers the incidence of PsA in patients with PsO, highlighting another potential benefit of GLP-1RA therapy in this population. Therefore, GLP-1RAs may not only improve disease severity and treatment outcomes but also help mitigate the risk of PsA development in patients with PsO.[11]
- *Improved metabolic health.* These medications can potentially help address metabolic abnormalities associated with PsO and PsA, such as insulin resistance and hyperlipidemia.
- *Immunomodulation.* GLP-1RAs, such as liraglutide, may offer direct immunomodulatory effects that could help reduce inflammation and improve disease symptoms in conditions like PsA and PsO. Studies have shown that GLP-1RAs can modulate the immune system by influencing the balance of proinflammatory and antiinflammatory cytokines. This mechanism is thought to contribute to the reduction in disease activity observed in inflammatory conditions. For instance, Sullivan et al found that treatment with liraglutide in patients with inflammatory arthritis was associated with an improvement in disease activity, suggesting a direct immunomodulatory effect.[12]
- *Side effects.* Although GLP-1RAs are generally well tolerated, side effects can include nausea, vomiting, diarrhea, and hypoglycemia. These risks should be carefully weighed against the potential benefits when considering their use in PsO and PsA.[12-15]

Conclusion

GLP-1RAs should be further explored in PsO and PsA management as there is little evidence directly linking GLP-1RAs to improved PsA symptoms to date.[5] Weight-loss properties of GLP-1RAs coupled with potential immunomodulatory effects hold promise for a new therapeutic approach, particularly for obese patients with PsO and PsA.[9,10] The lecture at the GRAPPA 2024 annual meeting called for further investigations into GLP-1RAs as a new therapeutic approach to treating PsO and PsA.

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