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Severe Alopecia, Dermatitis and Acute Interstitial Nephritis Following Oral Semaglutide (Rybelsus) That Is Amenable to Drug-Discontinuation and 6-Weeks of Prednisone

—Rybelsus Interstitial Nephritis

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Abstract

Background: Oral Semaglutide with the brand name Rybelsus (R) is the first long-acting oral glucagon-like peptide 1 receptor agonist approved by the U.S. Food and Drug Administration for treatment of obesity and hence type 2 diabetes in 2019. It is associated with short-term side effects (SEs) viz. gastrointestinal upsets, anaphylaxis, angioedema and drug-interaction as well as long-term ones viz. gastroparesis, retinal disease, gall stones and suicidal ideation. The reported spectrum of its renal SEs was thought to be limited to volume depletion following gastrointestinal upsets. In this case report; we add an intrinsic etiology to its renal SEs. **The Case:** A 56-year-old man developed malaise, diffuse myalgia, skin rash and alopecia for 1 month following intake of R for weight reduction. He did not have a previous medical illness or chronic intake of other medications. Moreover; he had acute and progressive renal failure. His kidney biopsy showed acute interstitial nephritis. Serum complements, ANA, ANCA, protein electrophoresis, IgG4 level, and hepatitis B and C serology were within normal levels. R was discontinued and the patient was treated with Prednisone 60 mg/day. By 2 weeks later; his clinical picture and renal function returned to normal. Hence; the Prednisone dose was tapered down gradually and discontinued by the end of 6 weeks. Over the past year, no disease recurrence was observed. **Conclusion**: Acute allergic reactions associated with interstitial nephritis can develop, in genetically predisposed pa-

tients, following R-use yet they are amenable to drug-discontinuation and 6-week therapy with Prednisone.

Keywords

Genetic-Predisposition, Interstitial Nephritis, Prednisone, Rybelsus, Semaglutide, Side-Effects, Triggers

1. Introduction

After metformin and life-style intervention; glucagon-like peptide 1 receptor agonists (GLP-1RAs) are recommended as an add-on therapy in patients with type 2 diabetes and established atherosclerotic cardiovascular disease [1]. Subsequently; the impact of their injectable forms in control of morbid obesity was evident [2]. By 2022, 1 of their members, Semaglutide (S), was the 48th most commonly prescribed medication in the United States, with more than 13 million prescriptions [3]. It was the top selling medication in the US in 2023, with expenditures of US$38.6 billion [4]. To avoid injectable forms; Rybelsus (R) was introduced as the first long-acting oral form of S and was approved by the U.S. Food and Drug Administration (FDA) for the treatment of obesity and hence type 2 diabetes in 2019 [2]. Despite its oral advantage; R remains a costly drug with an average wholesale price at $30.89 per tablet (all doses), equating to a monthly cost of $926.92 [1]. R and all other GLP-1RA are contraindicated in subjects with a personal or family history of medullary thyroid carcinoma or in people with multiple endocrine neoplasia type 2 [5]. Moreover; and despite its wide-spread use and success; it is associated with short-term side effects (SEs) viz. gastrointestinal upsets, anaphylaxis, angioedema and drug-interaction as well as long-term; gastroparesis, retinal disease, gall stones and suicidal ideation [6]-[9]. The reported spectrum of its renal SEs was limited to volume depletion following gastrointestinal upsets [9]. In this case report; we expand such spectrum with an intrinsic one.

2. The Case

A 56-year-old man presented with malaise, diffuse myalgia, skin rash and alopecia for 1 month following intake of R for weight reduction. He did not have a previous medical illness or chronic intake of other medications. On his initial physical examination; he had evident scalp alopecia and generalized skin rash (**Figure 1**). His body weight was 102 kg, blood pressure was normal and he was afebrile. Systemic examination did not show abnormality. He had normal peripheral leucocytic and platelets counts. Hemoglobin was normal. Serum sugar, electrolytes and liver functions were normal. Serum urea and creatinine were elevated at 21 mmol/L and 240 umol/L, respectively. Urine routine and microscopy was negative for proteinuria, hematuria and pyuria. Ultrasound examination of the abdomen and pelvis did not show abnormality. Since; he had increase in serum urea and creatinine

as compared to his tests prior to starting R, indicating acute renal injury, kidney biopsy was done. It showed normal glomeruli, tubules and vasculature yet severe and diffuse interstitial infiltrate with lymphocytes, eosinophils and plasma cells indicating acute interstitial nephritis (Figure 2). Moreover; serological tests viz. serum complements (C3&C4), ANA, ANCA, protein electrophoresis, IgA level, anti-CCP, HIV, hepatitis B surface antigen and anti-HCV antibodies were within normal levels. R was discontinued and the patient was treated with Prednisone 60 mg/day. By 2 weeks later; his clinical picture and renal function returned to normal. Hence; the Prednisone dose was tapered down gradually and discontinued by the end of 6 weeks. Over the past year, no disease recurrence was observed.

Figure 1. Showing scalp alopecia (A) and leg skin rash (B) in a patient following Rybelsus therapy.

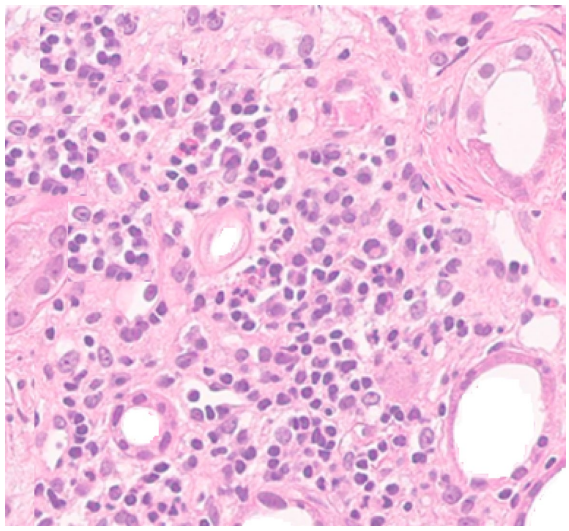

Figure 2. Photomicrograph of a kidney biopsy showing interstitial infiltration with lymphocytes, eosinophils and plasma cells (H&E X400).

3. Discussion

Injectable forms of GLP-1RAs are potent oral antidiabetic and anti-obesity agent with multiple modes of action. They work via activation of the GLP-1 receptor leading to enhanced glucose-dependent insulin secretion from beta-cells after meals and reduces glucagon release [9]. Moreover; its long-term use increases pancreatic β-cell proliferation. Their antiobesity effect is mediated via; (a) slowing gastric emptying, and (b) decreasing hunger by stimulation of hypothalamic GLP-1 receptor [10]. As with injectable forms, R is efficacious and after oral administration R is rapidly absorbed reaching peak serum concentration in 1 - 2 h with half-life time below 12 h [11]. It is available in 3-, 7-, and 14-mg tablets and to avoid its gastrointestinal SEs; the manufacturer recommends initiating R at the 3-mg dose once daily and then increasing the dose, as tolerated, to 7 mg once daily after 30 days. For patients requiring additional glycemic lowering, the dose can be further increased to 14 mg once daily after at least 30 days at the 7-mg dose [8]. To avoid decreasing its efficacy; it is recommended that R be administered, on an empty stomach at least 30 min before the first food, beverage, or other oral medications of the day and with no more than 4 oz plain water only. These instructions may prove difficult for some patients, particularly if they are taking other oral medications that are recommended to be taken first thing in the morning on an empty stomach, such as levothyroxine or bisphosphonates. Furthermore, the prescribing information notes that, when coadministered with thyroxine, the total exposure (area under the curve) of thyroxine was increased by 33% [8]. Though oral administration of R is an advantage; its gastrointestinal SEs remain a major limiting factor that can result in dehydration and subsequent pre-renal kidney injury. Discontinuation or dose-reduction of R is recommended rather than relying solely on symptomatic treatment of volume depletion [9]. Unfortunately; renal SEs may not be limited to plain dehydration as in our patient. He developed AIN that needed different approach with drug-discontinuation rather than dose-decrement and short-course of Corticosteroids rather than plain volume expansion. The latter SE is different from the reported severe type 1 hypersensitivity reactions, such as anaphylaxis and angioedema, with R which was associated with cross reactivity to other GLP-1Ras [7]. Such drug-induced interstitial nephritis is a delayed T-cell-mediated hypersensitivity reaction that takes days to manifest as in our patient. The host immunogenic response is elicited by: 1) a drug or its metabolite (hapten) with a carrier protein (haptenization) or 2) a direct interaction of the drug with a specific host protein (p-i concept). Moreover, if the offending drug is not identified and discontinued in a timely manner, irreversible fibrosis and chronic kidney disease have been described [12].

4. Conclusion

R has a major role in the management of diabetes mellitus and obesity. However; healthcare providers should be aware of its short-term and long-term SEs to achieve patent's safety and drug-efficacy.

Author's Contributions

Prof/Kamel El-Reshaid conceived the study, participated in its design, and drafted the manuscript. Dr. Abdulmohsen Al-Bader participated in the study design, follow-up of patients, data collection and tabulation of data.

Data Availability Statement

The data provided in the current review are available from the references.

Conflicts of Interest References

All authors have read and approved the final version of the manuscript. The authors declare no conflicts of interest regarding the publication of this paper.

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