Anti-Proteinuric Effect of GLP1-RA as Add-On to SGLT2-i and ACE-i in a Diabetic Patient with IgA Nephropathy

Nefrologo in corsia

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ABSTRACT

Immunoglobulin A (IgA) nephropathy is a common glomerulonephritis, but its treatment remains matter of debate. Recommendation for corticosteroids has been supported, but renin-angiotensin inhibitors, RAAS, and sodium-glucose co-transporter 2 inhibitors (SGLT2i) are increasingly used because of a better benefit/safety balance in comparison with systemic steroids and immunosuppressive treatments. In this case report, a patient with type 2 diabetes (T2DM) and biopsy-proven nephrotic IgA-related nephropathy documented a rapid meaningful reduction of proteinuria and the effect was persistent for 2 years, after receiving the treatment with a GLP1-RA on top of the previous treatment with ACE-inhibitors and SGLT2-i. Considering the beneficial effects of GLP1-RA in diabetes related chronic kidney disease, the present case report supports the notion that these drugs could also represent a beneficial treatment option in IgA nephropathy.

KEYWORDS: IgA nephropathy, Dulaglutide, Empagliflozin, DAPA-CKD, Empa-Kidney

Introduction

IgA nephropathy is the most frequent glomerular disease worldwide. Its clinical course is variable, but in most cases there is a decline in renal function and, despite advances in our understanding of its pathogenesis, treatment strategies haven't changed much over the last 2 or 3 decades. Patients at greatest risk of progressive renal impairment are those with hypertension, proteinuria >1 g/24 h and reduced glomerular filtration rate at diagnosis [1].

There are no disease-specific therapies for IgA nephropathy and the established treatment approach for most patients is to apply supportive measures that include the use of renin-angiotensin-aldosterone system blockade (RAAS) [1, 2] and more recently SGLT2i (as evidenced by the DAPA-CKD study [3] and by the subanalysis of EMPAKIDNEY study, in which 25% of patients were affected by glomerular diseases) [4].

At present, there is insufficient evidence for the additional use of immunosuppressive agents, antiplatelet agents or anticoagulants. The role of immunosuppressive therapy remains controversial and is usually reserved for patients who don't respond to supportive measures [2].

There's another class of drugs with a proven nephroprotective effect utilized in the treatment of type 2 diabetes mellitus, GLP1-RA. They significantly reduced the risk for a composite kidney disease outcome (macroalbuminuria, eGFR decline, progression to kidney failure, death from kidney disease) largely driven by reduction in albuminuria [5]. The GLP1-RAs that have shown cardiovascular and CKD benefits (liraglutide, semaglutide, albiglutide, dulaglutide) are preferred agents as reported by the KDIGO guidelines [6].

In addition to the glucose-lowering action of GLP-1RAs, several other mechanisms appear to underpin the effects of these agents on renal function. GLP-1RAs lower blood pressure both due to weight loss and due to direct effects on the kidney. Indeed, it has been reported that GLP-1RAs promote natriuresis and diuresis due to the inhibition of the sodium-hydrogen exchanger 3, which is located in the renal proximal tubular cells, and preclinical models suggest that GLP-1RAs exert anti-inflammatory effects and decrease oxidative stress in the kidneys [5].

Case report

Man, born in 1948, with a history of diabetes since 2005 and ischemic cardiomyopathy for which he underwent triple coronary artery revascularization in 2017. Since then, treated with insulin degludec, empagliflozin and metformin. UAC and eGFR levels are within limits.

In January 2020, the patient reported the appearance of purpura on the lower limbs and the abdomen and a dermatologic evaluation was obtained. He underwent a skin biopsy which showed leukocytoclastic vasculitis. ASA gets substituted by clopidogrel with an immediate spontaneous resolution of the purpura (UACR 20 mg/g crea, GFR 90 ml/min/1.73m^2).

In September 2020, the patient's tests showed UACR 1817 mg/g and GFR 80 ml/min/1.73m^2. A nephrological consultation was performed. Both abdomen ultrasound and renal artery doppler ultrasonography results were negative, but proteinuria increased to 3.7 g/24 hours (Table I). Ramipril 2.5 mg/day was prescribed confirming the diagnosis of proteinuria in diabetes.

In the following months, the patient developed progressively invalidating arthromyalgia. Proteinuria was 3.15 g/24 hours (Table I) and a new nephrology consultance advised to perform a renal biopsy. Histological analysis confirmed a glomerulonephritis with mesangial IgA deposits and previous purpura points to ongoing glomerulonephritis of Henoch-Shoenlein vasculitis (Figure 1).

DATE	01/2020	09/2020	03/2021	10/2021	04/2022	11/2022	11/2023
THERAPY	EMPA 25 mg	EMPA 25 mg RAM 2.5 mg	EMPA 25 mg RAM 5 mg	EMPA 25 mg RAM 5 mg DULA 0,75 mg	EMPA 25 mg RAM 5 mg DULA 1.5 mg	EMPA 25 mg RAM 5 mg DULA 1.5 mg	EMPA 25 mg RAM 5 mg DULA 1.5 mg
PROTEINURIA g/24 hours		3.7	3.15	1.2	0.42	0.4	0.187
CREATININE mg/l	0,98	1.02	0.91	0.91	0.88	1.18	0.89
MA mg/g crea	22	1817	518	259	159	47	28
HbA1c mmol/mol	55	53	54	53	49	47	46
BMI kg/mq	32	31.08	30.74	30.74	29.05	28.88	27.7

Table I. Modification of therapy, laboratory tests and anthropometric parameters. EMPA: empagliflozin; RAM: ramipril; DULA: dulaglutide; MA: microalbuminuria; HbA1c: glycated hemoglobin; BMI: body mass index.

An increase in ramipril to 5 mg/day was recommended together with tight blood pressure control. Proteinuria decreased to 1.2 g/24 hours (Table I. In order to maximize renal protective treatment, especially in terms of albuminuria reduction, dulaglutide was added to existing therapy).

Proteinuria further decreased during a follow-up visit in May 2022 (0.42 g/24 hours) and UACR decreased too (150 mg/g crea). The effect on proteinuria was persistent in November 2022 (proteinuria 0.4 g/24 hours) and UACR decreased more (47 mg/g crea) (Table I). In November 2023 UACR was in a normal range (MA 28 mg/g crea) and proteinuria was just above the limits (0.187 g/24h, normal value <0.150 g/24h).

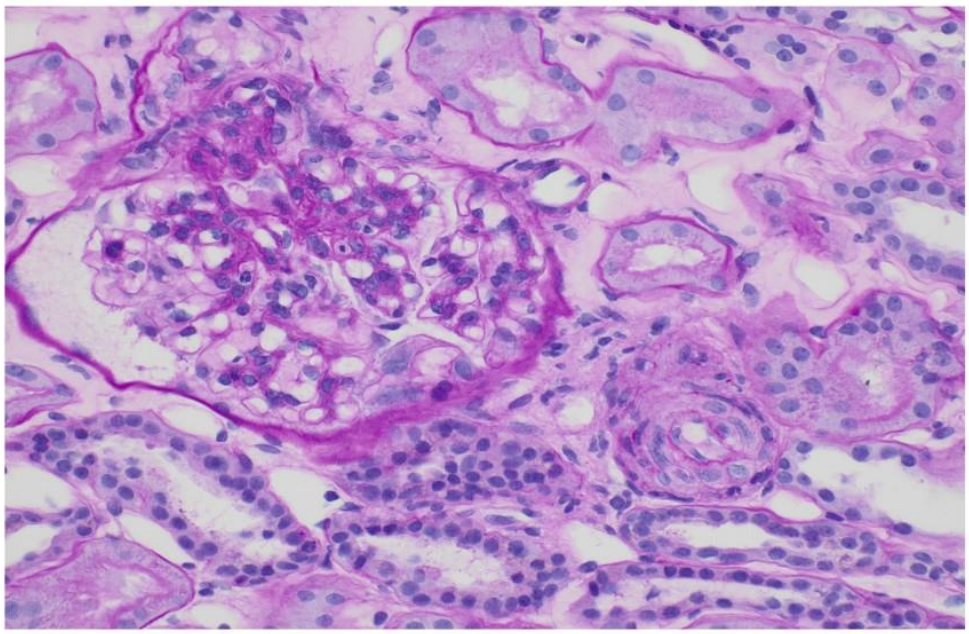

Figure 1. MO: frustule of cortical and renal medullary in which 7 glomeruli are observed, of which 2 are hyaline globally (29%). Some glomeruli have an increase in the mesangial matrix and exudation of capillary loops (+). In 2 Glomeruli Small fibroepithelial half-moons with adhesion to the capillary floccule are observed. The interstitium has a small area of fibrosis with tubular atrophy (+) and modest inflammatory infiltrate focal. Many arterioles and some medium-sized vessels have a marked concentric myointimal proliferation with reduction of the vascular lumen (++). IF: IgA = ++ granular, mesangial and parietal; IgG, IgM, C3, C1q, fibrinogen = NEGATIVE.

Discussion

The case reported here highlights how IgA nephropathy's diagnosis may sometimes be overlooked and delayed in patients affected by type 2 diabetes mellitus, as diabetes itself is often considered the sole cause behind kidney disorders. However, the patient presented specific associated symptoms (purpura and arthromyalgia), whose persistence led the diabetologist to seek further nephrology consultation. Nonetheless, the first nephrologist underestimated the signs and symptoms associated with the rapid onset of proteinuria, concluding for diabetic nephropathy in a patient already being treated with SGLT2i. The diabetologist insisted that the patient be visited by another nephrologist and this finally led to a renal biopsy that confirmed the clinical suspicion of IgA nephropathy. Therefore, it's essential to suspect different diagnoses in diabetic patients with renal damage, especially if it arises suddenly and is associated with other signs or symptoms.

The combination of supportive antiproteinuric agents, ACE inhibitors, SGLT2i and finally Dulaglutide was preferred to steroid treatment because of a more favorable risk/benefit balance when confronted with immunosuppressive therapy and to double blockade of RAAS system. Despite the patient had good renal function (GFR 90 ml/min), the association of ACE inhibitors and angiotensin receptor blockers (ARB) was not taken into consideration. As shown in the literature, combination therapy with ACE inhibitors and ARB reduces albuminuria and proteinuria, but the safety and effects on the progression of renal disease in terms of benefit on GFR are uncertain, with an increased risk of hyperkalemia [7, 10]. Furthermore, the Agenzia Italiana del Farmaco (AIFA) and the European Society of Hypertension (ESH) formally advised against the association [11, 12].

The rationale of association of SGLT2-i and GLP1-RAs is to achieve direct renoprotective effects through the suppression of inflammatory responses, inhibition of oxidative injury, and prevention of apoptosis as a result of the combined impact of glucose-lowering treatment and extra-glycemic effects. More intensive glycemic control, achieved by addition of GLP1-RAs and SGLT2i, justifies a potential benefit on renal function in diabetic patients; however, it is obvious that other renoprotective mechanisms exist such as hemodynamic effects, blood pressure control, and body weight loss. Even if there is no data on greater effectiveness compared to the individual drugs on the progression of renal disease in diabetic patients and even less in other types of nephropathy, this association could be a potential therapy for other forms of nephropathy.

The clinical studies published to date highlight the nephroprotective role of the SGLT2i class. SGLT2is decrease tubuloglomerular feedback, vasoconstriction of afferent arteriole, intraglomerular hypertension, hyperfiltration, blood pressure and afterload. These are responsible for reduction of the albuminuria and eGFR slope improvement. Various national and international diabetological [13, 14], nephrological [5] and cardiovascular guidelines [15] recommend the use of the SGLT2i class for patients with chronic kidney disease regardless of the presence or absence of type 2 diabetes. The first study that included analyses of prespecified renal outcomes was the EMPA-REG-OUTCOME study in which empagliflozin showed a 39% reduction in the risk of chronic kidney disease (CKD) incidence and progression, with a lower risk of progression to macroalbuminuria, of doubling of serum creatinine and of initiation of renal replacement therapy compared to the placebo group [16, 17] in diabetic patients. Further evidence in studies of renal outcomes as primary endpoint (CREDENCE, DAPA-CKD, EMPA-KIDNEY) confirmed the nephroprotective effect of SGLT2i not only in a population with type 2 diabetes, but also in non-diabetic subjects with CKD [3, 4, 18]. In particular, two studies, DAPA-CKD and EMPA-KIDNEY (in which 25% of patients were affected by glomerular diseases), randomized subjects with chronic kidney disease with different etiopathogenesis (Diabetic Kidney Disease, Glomerular Disease, Hypertensive/renovascular Disease) and various levels of eGFR and albuminuria. When glomerular diseases were further divided into disease subcategories, we found no evidence of heterogeneity between patients with IgA nephropathy,

focal segmental glomerulosclerosis, or other glomerulonephritis [19]. In a post-hoc analysis of EMPA-KIDNEY, empagliflozin reduced the risk of kidney progression in non-diabetic patients with chronic kidney disease at risk of progression. Relative effect sizes were broadly similar irrespective of the cause of primary kidney disease, suggesting that SGLT2 inhibitors should be part of a standard of care to minimize the risk of kidney failure in chronic kidney disease [20].

In addition, GLP-1RAs offer the potential for adequate glycemic control in multiple stages of diabetic kidney disease (DKD) without an increased risk of hypoglycemia and with additional benefits in weight reduction, cardiovascular outcomes and exploratory kidney outcomes [21].

In the AWARD 7 study, in patients with type 2 diabetes and moderate-to-severe chronic kidney disease, Dulaglutide produced glycaemic control similar to that achieved with insulin glargine, with reduced decline in eGFR. The authors observed a reduction in the renal composite endpoint (appearance of macroalbuminuria, reduction in eGFR < 30%, renal replacement therapy with hemodialysis) [22]. In the post-hoc analysis of AWARD 7, a reduction in the composite endpoint (reduction in eGFR < 40% and progression to ESRD) and in the individual components is observed in patients treated with dulaglutide 1,5 mg [23]. In the post-hoc analysis of REWIND, the estimated 25% reduction hazard of a kidney function-related outcome among participants assigned to Dulaglutide highlights its potential for delaying or slowing the development of diabetic kidney disease in people with type 2 diabetes [24].

Although there aren't data about the nephroprotective effects of GLP1-RAs in patients without diabetes, it's known that the association of SGLT2i and GLP1-RAs is of interest because of mostly complementary mechanisms of action. They have been shown to reduce cardiovascular risk, improve various glycaemic measures and cardiovascular risk factors in patients with type 2 diabetes, with acceptable tolerability and safety profile [25, 27]. SGLT2i and GLP1-RAs can modify the natural history of patients with type 2 diabetes by reducing the risk of cardiovascular disease and progression of renal disease. In recent years, all guidelines suggest the use of SGLT2i and GLP1-RAs in patients with a previous event or patients in primary prevention at high or very high risk with or without metformin regardless of the glycated hemoglobin value. The aim is not only to achieve a therapeutic objective (treat-to-target), but to directly induce a benefit (treat-to-benefit) by reducing organ damage. The association constitutes a valid option both to obtain strictly metabolic therapeutic objectives and for containing the risk of T2DM complications, even if the data are not yet definitive [28, 30].

The presence of diabetes, which allowed for the prescription of a combination of three drugs with proved renal protection effectiveness (i.e., ACE-I, SGLT2i and GLP1-RA), may have delayed the correct diagnosis at first and later turned out to be an opportunity to maximize antiproteinuric treatment and possibly better long-term outcome.

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