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CASE REPORT

Upadacitinib in end stage renal disease: A case of acute severe ulcerative colitis

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Abstract

Recent data, indicating that inflammatory bowel disease (IBD) may be a risk factor for future chronic kidney disease, highlight the need to study the safety and clinical effectiveness of advanced IBD therapies in patients with end stage renal disease (ESRD), defined as an eGFR <15 mL/min/1.73m^2. Upadacitinib, a selective oral Janus kinase (JAK) 1 inhibitor, has demonstrated efficacy in the management of moderate to severe ulcerative colitis. There is also emerging data indicating that JAK inhibition may be clinically effective in the setting of steroid-refractory acute severe ulcerative colitis (ASUC). There is, however, a lack of "real-world" data documenting the use of JAK inhibitors in patients with ESRD. Here, we report the use of upadacitinib in a patient with ESRD for the management of steroid-refractory ASUC, demonstrating, for the first time, the safe and clinically effective use of upadacitinib in this population.

Introduction

A meta-analysis of observational studies approximated that 13.4% of the global population has chronic kidney disease (CKD), a significant proportion of whom have late stage (3–5) disease.[1] This reflects that CKD is common and indicates that the likelihood of needing to administer advanced medical therapies for the treatment of inflammatory bowel disease (IBD) in patients with end stage renal disease (ESRD) is foreseeable. This is further exemplified by a retrospective study of more than 80 000 persons, which found that IBD was associated with an increased risk of CKD, with the hazard ratio noted to be highest among younger patients.[2]

Several therapeutic advances in IBD have been observed over the past two decades, including the recent emergence of janus kinase (JAK) inhibitors. These small molecule agents offer the advantages of oral administration, rapid onset of action, short half-life, and unlike their biologic counterparts, are not vulnerable to immunogenicity. Tofacitinib, a pan-JAK inhibitor with a higher affinity to inhibit both JAK1 and JAK3, has been approved for the management of chronically active moderate to severe ulcerative colitis, as has upadacitinib, a selective JAK1 inhibitor.[3,4] There are also emerging data indicating that JAK inhibition may be safe and clinically effective in the setting of steroid-refractory acute severe ulcerative colitis (ASUC).[5,6]

Studies have demonstrated that inflammation signaled by the JAK–STAT pathway promotes inflammation that may lead to progression of diabetic kidney disease.[7] This led to the study of baricitinib, an oral, reversible, selective JAK1 and JAK2 inhibitor, in patients with diabetic nephropathy, finding that baricitinib decreased albuminuria in this population.[8] However this study did not include patients with an eGFR below 25 mL/min/1.73m^2, highlighting that the use of JAK inhibitors in patients with end stage renal disease (ESRD), defined as an eGFR below 15 mL/

min/1.73m^2, remains yet to be described. Here, we report the safe and clinically effective use of upadacitinib in a patient with ESRD for the management of steroid-refractory ASUC.

Case report

A 75-year-old female with long-standing ulcerative colitis was admitted for management of ASUC. She presented to hospital with >10 bloody bowel motions daily associated with tachycardia, meeting Truelove and Witt's criteria for ASUC. At the time of admission, the patient was on ustekinumab 90 mg 4-weekly monotherapy, having previously failed both infliximab and vedolizumab, with limited remaining medical options for her colitis. Her medical history was also significant for ESRD secondary to renovascular disease with a baseline eGFR of 11 mL/min/1.73m^2 and preserved urine output. The patient did have cardiovascular risk factors including dyslipidemia for which she was on rosuvastatin 10 mg daily with a fasting cholesterol of 4.6 mmol/L; however, the patient did not have any history of venous thromboembolism.

On admission, the patient's partial Mayo score was 8, with an elevated fecal calprotectin (301ug/g), CRP (21.6 mg/L), and moderate (Mayo 2, UCEIS 5, Fig. 1) proctosigmoiditis to the point of insertion on sigmoidoscopy (Table 1). Stool culture excluded infections, including clostridium difficile. The patient was commenced on intravenous hydrocortisone 100 mg q.i.d and renally adjusted enoxaparin for venous thromboembolic prophylaxis. In the setting of insufficient clinical response to 72 h of intravenous hydrocortisone therapy and failure of multiple previous biologic therapies, the prospect of colectomy was discussed with the patient. Owing to a strong reluctance from the patient and their family to undergo surgery, the off-label use of JAK inhibition was considered, on the basis of emerging data in ASUC.

Multidisciplinary discussion between the gastroenterology, pharmacology, and renal medical teams was supportive of a limited trial of upadacitinib. The decision to use upadacitinib rather than tofacitinib was made based on the patient's age and cardiometabolic risk factors. The off-label use of upadacitinib was discussed with the patient, including potential implications on her underlying renal disease. On the basis of the patient's disease

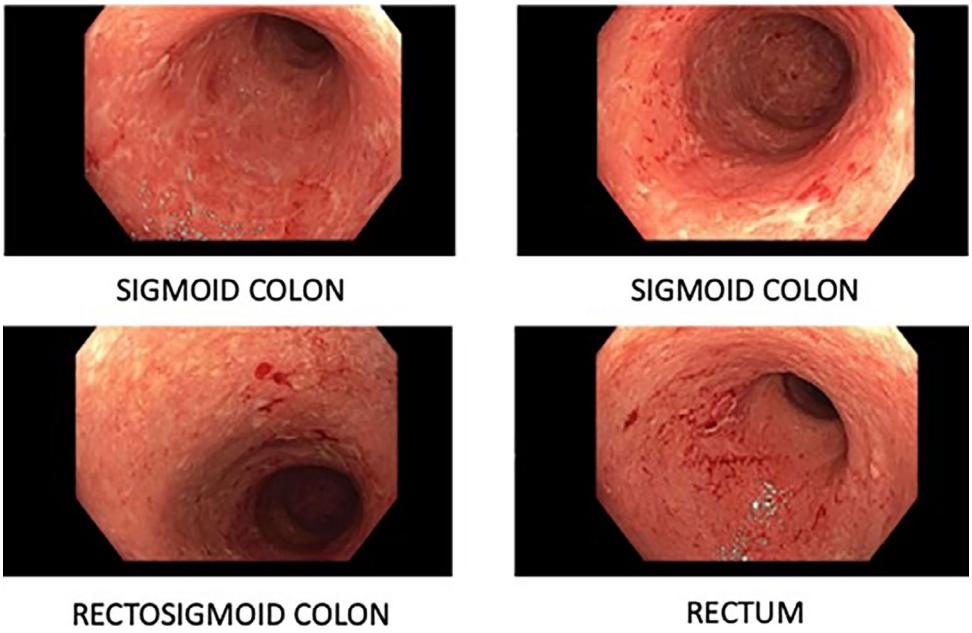

Figure 1 Endoscopic images prior to starting upadacitinib therapy.

Table 1 Investigations on patient admission and follow-up.

	On admission	Upadacitinib initiated	Upadacitinib +3 days	Upadacitinib +28 days	Upadacitinib +84 days
Partial Mayo score	8	8	1	1	1
C –reactive protein (mg/L)	21.6	21.6	4.4	0.3	12.7
Fecal Calprotectin (ug/g)	301	n/a	n/a	281	39
Serum creatinine (micromol/L)	342	342	332	329	338
eGFR (mL/min/1.73m^2)	11	11	11	11	11

severity, the decision was made to initiate upadacitinib 45 mg daily which was dose reduced to 30 mg daily after 3 days in the setting of rapid clinical (partial Mayo Score 8 to 1) and biochemical (CRP 21.6 to 4.4 mg/L) response. The patient was transitioned to oral prednisolone 40 mg and discharged on upadacitinib 30 mg once daily with a weaning course of corticosteroids and sulfamethoxazole/trimethoprim (160/800 mg, thrice weekly) for pneumocystis jirovecii prophylaxis. The patient completed 8 weeks of upadacitinib 30-mg daily induction dosing and successfully weaned off corticosteroid therapy prior to transitioning to upadacitinib 15-mg daily dosing. In view of high risk of herpes zoster infection, two doses of the adjuvanted recombinant herpes zoster subunit vaccine (Shingrix) were also administered 2 months apart. After completing a total of 4 months of upadacitinib therapy, the patient remained in steroid-free clinical and biochemical remission, with normalization of both her CRP and fecal calprotectin. During this time, the patient did not experience any adverse events or infections and was able to continue upadacitinib without interruption. The patient's renal function was closely monitored and observed to remain stable with no change in her eGFR over 4 months of follow-up, including the period of induction dosing during which upadacitinib was dosed above 15 mg daily.

Discussion

Despite the obvious appeal of JAK inhibitors, as an oral fast-acting and highly effective medical therapy for several chronic inflammatory conditions, concerns regarding herpes zoster infections, venous thromboembolism, malignancy, and cardiovascular risks remain to be considered.[9–11] These risks are particularly relevant to older and comorbid patient populations, highlighting the need to adopt risk mitigation strategies such as vaccination against herpes zoster infection. Moreover, several of these risks may be dose related, highlighting the need to dose reduce JAK inhibitors as soon as practicable. These principles were applied in the case described, with administration of the Shingrix vaccine to protect against herpes zoster infection and dose reduction of upadacitinib to the lowest maintenance dose for ulcerative colitis.

The increasing prevalence of both CKD and IBD, including recent data indicating that IBD itself may be a risk factor for future CKD, highlights the need to study the safety and clinical effectiveness of advanced IBD therapies in patients with ESRD. To-date, data pertaining to the use of advanced IBD therapies in patients with ESRD with(out) dialysis is scare; with case reports dominating the published literature. These have described the safe and effective use, across varying inflammatory diseases, of monoclonal antibodies such as infliximab, adalimumab, ixekizumab, secukinumab, and ustekinumab in patients with ESRD, including patients requiring dialysis.[12] However, patients with coexisting IBD and CKD, particularly those with ESRD, have traditionally been excluded from clinical trials, accentuating the need for publish data to assist clinicians and inform clinical practice.

Upadacitinib achieves a maximum serum concentration 2–4 h following ingestion, with drug metabolism occurring mainly via CYP3A4 and elimination via glomerular (24%) and biliary (38%) pathways.[6] A single-dose open-label study that evaluated the pharmacokinetics and safety of upadacitinib in subjects with mild to severe renal impairment demonstrated that renal impairment had no clinically meaningful impact on the systemic exposure or maximal concentrations (C_{max}) of upadacitinib relative to subjects with normal renal function.[13] Hence, upadacitinib does not warrant dose reduction in the setting of renal impairment associated with an eGFR of 15 mL/min/1.73m^2 or above.

Here, we described, for the first time, the safe and clinically effective use of upadacitinib for ASUC in a patient with ESRD in the context of limited licensed medical alternatives. The risks associated with the use of upadacitinib in this case were juxtaposed with risks associated with emergent colectomy in a highly comorbid patient, with the use of upadacitinib justified on the basis of the patient refusing the medical and surgical recommendation for colectomy. The lack of any significant adverse outcomes, including a lack of any deterioration in eGFR during the period of higher upadacitinib dosing, is reassuring. Nevertheless, the optimal dose of upadacitinib in patients with ESRD requires clarification, although we surmise that doses above 15 mg daily may be safe if only used for a limited duration.

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Patient consent

The patient has consented for the de-identified publication of this case report and a signed copy of the consent form can be provided upon request.

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