



## A case report describing the failure of upadacitinib as sequential medical rescue therapy in treatment resistant acute severe ulcerative colitis

\*Corresponding Author: *Jonathan P Segal*

Tel: +61-03-93427000 & +61-03-9342 7802; Email: [Jonathan.segal@mh.org.au](mailto:Jonathan.segal@mh.org.au)

### Abstract

This case report summarises the treatment failure with upadacitinib as sequential rescue therapy in the setting of steroid and dose-intensified infliximab refractory acute severe ulcerative colitis. This patient proceeded to have a colectomy and end ileostomy. In addition, CMV reactivation was found on the histopathology from the surgical resection, potentially because of extended immunosuppression with steroids, infliximab and upadacitinib. This case suggests that upadacitinib as a sequential salvage therapy may not be effective and has potential side effects of CMV reactivation.

**Keywords:** Ulcerative colitis; Colorectal surgery; Surgery for IBD.

### Background

Acute Severe Ulcerative Colitis (ASUC) can be a life-threatening presentation for patients with Ulcerative Colitis (UC) with up to 30-40% morbidity if left untreated [1]. The Truelove and Witts criteria defines ASUC as tachycardia >90 bpm, erythrocyte sedimentation rate >30 mm/hr, Hb<105, pyrexia with temperature >37.8°C and bloody stools >6 times per day [2]. Diagnosis of severe UC occurs when the criteria for frequency of bowel movements are met and there are ≥1 systemic features present [2].

Treatment of ASUC requires early recognition and rapid administration of intravenous corticosteroids. The Travis cri-

*Andrea Chan<sup>1</sup>; Ella Cockburn<sup>2</sup>; Joanna Y Huang<sup>3</sup>; Jonathan P Segal<sup>4\*</sup>*

<sup>1</sup>Resident Doctor, Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia.

<sup>2</sup>Medical Registrar, Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia.

<sup>3</sup>Gastroenterology Registrar, Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia.

<sup>4</sup>Consultant Gastroenterologist, Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia.

**Received:** Oct 18, 2024

**Accepted:** Nov 04, 2024

**Published Online:** Nov 11, 2024

**Journal:** Annals of Surgical Case Reports & Images

**Online edition:** <https://annsri.org>

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**Cite this article:** Chan A, Cockburn E, Huang JY, Segal JP. A case report describing the failure of upadacitinib as sequential medical rescue therapy in treatment resistant acute severe ulcerative colitis. *Ann Surg Case Rep Images*. 2024; 1(6): 1056.

teria can be used to determine adequate response to steroid therapy and predict the risk of requiring a colectomy at three days. Those with either a stool frequency >8 per day or >3 times per day with a C-Reactive Protein (CRP) over 45 despite steroid therapy have an 85% likelihood of requiring a colectomy [1]. Colectomy should be pursued early in patients who have perforated or where perforation is impending due to severe dilatation, massive haemorrhage or intractable colitis [1].

In steroid non-responders, primary medical therapies include cyclosporine, tacrolimus and infliximab [1]. Current studies are exploring alternate medical salvage therapy options. There has been emerging evidence for the effective use of Janus Kinase (JAK) 1 inhibitors in the induction and maintenance of

remission in moderate to severe UC [3]. However, their role in ASUC salvage therapy continues to be studied [4,5]. Upadacitinib has recently been suggested as a possible safe and effective option in ASUC [4].

### Case presentation

A male in his 30s presented with six weeks of up to twenty loose bloody stools a day, associated with urgency, tenesmus and left lower quadrant abdominal pain. He described ongoing fevers and had lost over 20 kilograms over weeks. He had no previous medical diagnosis of inflammatory bowel disease. He had a strong family history for UC: his father, paternal grandfather, and two siblings were affected. He was admitted to hospital due to the severity of his symptoms.

### Investigation

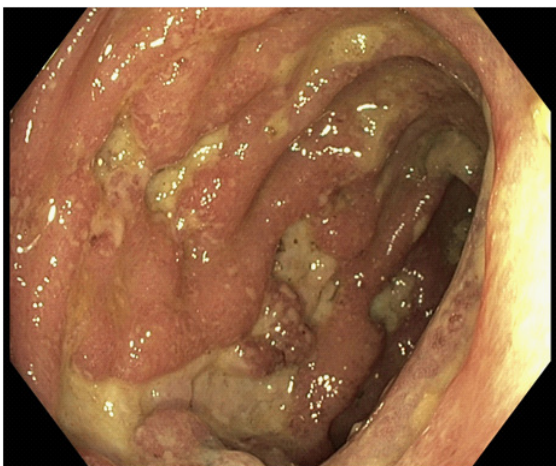
Bloods showed a raised CRP of 233 mg/L, iron deficiency anaemia with a haemoglobin of 105 g/L, haematocrit of 0.32 L/L and transferrin saturation of 7%, and low albumin of 20 g/L. Calprotectin was raised at 1,110 ug/g. An abdominal computed tomography showed pancolitis, but no collection or perforation. He was started on intravenous steroids. Faecal pathogen testing returned negative. He had a Mayo score of 11 points, and UCEIS score of 6 points. Flexible sigmoidoscopy showed severe proximal left sided colitis and moderate sigmoid disease suggestive of a new diagnosis of inflammatory bowel disease (Figure 1). Histopathology of biopsies showed diffuse inflammatory changes and CMV PCR was negative. He was diagnosed with ASUC.

### Treatment

Despite initial rescue therapy with intravenous steroids and dose intensified infliximab (Day 2 and 4), the patient showed only partial clinical response. He was deemed a surgical candidate and colorectal surgery was involved early however their input was limited by the patient's strong wishes against surgical management. This was despite the warning of the life-threatening risk of medical therapy failure. In the context of this, JAK inhibitor therapy with upadacitinib was trialled as sequential salvage therapy on Day 9.

### Outcome and follow-up

Over the following 4 days, the CRP increased from 77 to 134 mg/L, and he continued to have febrile episodes. His serial abdominal films showed evidence of toxic megacolon. He had



**Figure 1:** Deep ulceration in the splenic flexure seen on flexible sigmoidoscopy.

a total colectomy and end ileostomy on Day 12. The surgical findings included ischaemic toxic pancolitis with the left colon densely adherent to the left sidewall. There were inflammatory adhesions along the loop of the sigmoid colon in the pelvis. Histopathology from the total colectomy specimen demonstrated fulminant pancolitis with extensive ulceration and pseudo polyp formation. There was also evidence of superimposed CMV infection, with scattered but conspicuous CMV positive cells on immunohistochemistry. Hospital admission was prolonged with postoperative complications of ileus and intra-abdominal collections requiring drainage. He was discharged after a 43-day admission.

### Discussion

ASUC is a life-threatening medical emergency needing immediate hospitalisation with morbidity of 30 to 40% if untreated [1]. Current standard management in adults is the use of steroids as the first-line therapy, although one-third of patients do not respond [1]. Subsequent medical therapy following steroids includes cyclosporine, tacrolimus and infliximab, with a range of responses and side effects. The choice between agents depends on physician preference and availability given similarities in efficacy, however infliximab use is common due to their favourable side-effect profile and option to continue their use as maintenance therapy [1]. Surgery should where possible be planned early when it becomes evident of poor response to medical management. Surgery should be pursued in patients with toxic dilatation with impending perforation, intestinal perforation, massive haemorrhage, or longstanding colitis with intractability [1]. Patients who have been in hospital for more than eleven days and require surgery have an increased risk of mortality [1].

In this case, upadacitinib, an oral highly selective JAK1 inhibitor, was utilised for a young male with an ASUC flare with partial response to corticosteroids and infliximab salvage therapy. Given the effectiveness of upadacitinib as salvage therapy demonstrated in case series [4] and efficacy in managing moderate-to-severe UC [3], upadacitinib was offered to our patient after exhausting other medical treatment options. The aim was to respect the patient's wishes against surgery despite them being identified as a surgical candidate early in the admission. Unfortunately, the use of upadacitinib could not prevent the need for surgery and resulted in CMV reactivation.

Given the morbidity from colectomy in adults with ASUC is high, there remains an ongoing need for evaluation of novel medical therapies to prevent surgery. Tofacitinib, a pan-JAK inhibitor, as a treatment for ASUC, has been shown in a systematic review to have a colectomy-free survival at 30-days of 85%, 90-days of 86% and 180-days at 69% [5]. Main adverse effects included infectious complications [5].

The side effect of CMV reactivation in sequential salvage therapy was evident in our case. CMV was not detected on the initial flexible sigmoidoscopy PCR or histopathology. Subsequent detection of CMV on the histopathology from the surgical resection and viral load in the blood suggested CMV reactivation, which can be explained by the sequential immunosuppression. This highlights the higher infective risk of CMV reactivation if utilising a JAK inhibitor post corticosteroids and infliximab therapy.

Overall, this case suggests that upadacitinib as a sequential salvage therapy may not be effective and has potential side effects of CMV reactivation.

**Learning points/take home messages:**

- The initial mainstay of management in ASUC is high dose intravenous steroids, followed by medical therapies including cyclosporine or infliximab in patients with steroid non-response.
- There is some emerging evidence regarding the use of JAK inhibitors (Upadacitinib and Tofadacitinib) as primary and sequential medical therapy options in ASUC.
- Colectomy remains a management option for patients with inadequate response to medical therapies, and surgical consultation should be pursued early in patients presenting with ASUC.
- This case represents an example of the failed use of Upadacitinib as a sequential salvage medical therapy to avoid surgery and describes the additional adverse effect of CMV reactivation.

**Declarations**

**Conflicts of interest and funding:** None declared.

**Author contributions:** EC, and JYH contributed to the literature review and writing of the manuscript. AC contributed to the writing of the manuscript, collation and editing of manuscript, JPS conceived and supervised manuscript and provided revisions.

**Acknowledgements:** No acknowledgements.

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