Use of various immunotherapies for refractory ulcerative colitis in a person living with HIV: a case report

Cecilia T. Costiniuk¹,²,³, Talat Bessissow⁴, Stéphane Isnard¹,³ and Jean-Pierre Routy¹,²,⁵,*

¹Chronic Viral Illness Service, McGill University Health Centre, Montreal, Quebec, Canada, ²Division of Infectious Diseases, McGill University Health Centre, Montreal, Quebec, Canada, ³ Research Institute of McGill University Health Centre, Montreal, Quebec, Canada, ⁴Division of Gastroenterology, Department of Medicine, McGill University Health Centre, Montreal, Quebec, Canada, ⁵Division of Haematology, McGill University Health Centre, Montreal, Quebec, Canada

*Correspondence address. Chronic Viral Illness Service, McGill University Health Centre, 1001 boulevard Décarie, Montreal, Quebec H4A 3J1, Canada. Tel: 1 (514) 934-1934 ext 53333; Fax: 1 (514) 843 2092; E-mail: jean-pierre.routy@mcgill.ca

Abstract

Cancer therapies include several immune checkpoint or anticytokine therapies whereas ulcerative colitis treatments consist of anticytokine therapies. The development of tolerance and immunological effects of these agents in people living with HIV are not well assessed as these persons are often excluded from clinical trials. Herein, we report a case of a Caucasian woman who received multiple sequential immunotherapies for severe ulcerative colitis. Due to steroid-refractory disease, receipt of maximal doses of mesalamine and initial repeated decline of surgical intervention, she went on to receive biologic immune inhibitors like tumor necrosis factor-α blockers infliximab and adalimumab, the α4β7 integrin blocker vedolizumab, anti-interleukin 12/23 blocker ustekinumab and Janus Kinase inhibitor tofacitinib without achieving remission. Only minor infectious complications were encountered and no significant changes in CD4 count nor CD4/CD8 ratio occurred. This case provides support for the safety and tolerability of the above immunotherapies in people living with HIV with suppressed viral load on antiretroviral therapy.

INTRODUCTION

In the management of ulcerative colitis (UC), one provides immunosuppressive therapy with the hope of tempering excessive inflammation while preserving immune function. However, if the proper balance between immunosuppression and immune preservation is not achieved, an individual will be tipped into immunodeficiency with increased infection risk. People living with HIV (PLWH) are often excluded from clinical trials involving biologics based on concerns of additive immunosuppression and infection risk. Consequently, little data are available to guide clinicians in managing PLWH who suffer from advanced inflammatory bowel disease (IBD). Herein, we present the case of young woman with HIV infection and extensive UC refractory to many therapies. Following repeated decline of surgical intervention, she was treated with multiple sequential immunomodulators and did not experience any major adverse effects.
CASE REPORT

A 36-year-old, Canadian-born Caucasian woman was diagnosed with HIV in 2008. She began antiretroviral therapy with tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg orally once daily and raltegravir 400 mg orally twice daily in 2012, when her CD4 count rapidly dropped to 86 cells/mm³. Later that year, she began experiencing frequent episodes of bloody diarrhea, with up to 20 stools daily, with cramping, rectal bleeding and elevated C-reactive protein (CRP). Stool was repeatedly negative for Clostridium difficile and ova and parasites. Colonoscopy demonstrated severe pancolitis and biopsies consistent with active UC with acute cryptitis, crypt abscesses with lymphoid hyperplasia, focal erosions, acute inflammatory exudate with architectural distortion. Hematoxylin and eosin stains for cytomegalovirus and histochemical exams for Herpes Simplex Virus I/II were negative. Despite high doses of oral prednisone (40–60 mg daily) and several emergency room visits to receive intravenous (IV) methylprednisolone for flares, she was deemed steroid-refractory.

Later that year, she received maximum doses of oral mesalamine and 6-mercaptopurine, as well as mesalamine suppositories and enemas. She then received infliximab (2012–2013), an antitumor necrosis factor (anti-TNFα) monoclonal antibody, until antibody formation. Despite maximum doses of adalimumab (2014), her UC remained refractory although no antibodies were detected using a drug-tolerant assay and medication levels were therapeutic (~12 μg/ml, the highest limit of detection). Attempts to taper her steroids resulted in flare-ups and a cushingoid feature. She declined colectomy as she felt this would interfere with her lifestyle, especially since she was getting married, and concerns about her future fertility.

One of the options explored was the use of vedolizumab, a monoclonal antibody against α4β7 integrin, via a clinical trial. However, due to the patient’s HIV infection she was not eligible to participate in any of the recruiting trials at the centre as HIV infection is frequently an exclusion criteria. Colonoscopy in 2015 revealed severe inflammation with ulcerations and friability consistent with Mayo 3 colitis, despite high-dose steroids and adalimumab, an anti-TNFω monoclonal antibody, at a dose of 80 mg weekly. By December 2015, vedolizumab was obtained through standard of care and initiated at 300 mg IV at weeks 0 and 2, 6 (loading dose) and then every 8 weeks thereafter as a maintenance dose. She was still bleeding from the rectum and had decreased weight, therefore daily prednisone 10 mg orally was maintained. She achieved clinical remission by March 2016 and steroids were stopped. Two months later, she developed right foot cellulitis following a minor trauma during a pedicure and required 48 hours of IV followed by oral antibiotics. Colonoscopy in June 2016, 3 months after stopping steroids, showed worsening condition with Mayo 3 colitis, so she was changed to vedolizumab 300 mg IV q 4 weeks and prednisone increased to 40 mg orally (po) daily. Anti-α4β7 antibodies were not detected. She was passing bright red blood per rectum 12 times in 24 hours and having five stools per 24 hours with lower abdominal cramping and rectal pain. Janus kinase (JAK) inhibitor, tofacitinib 10 mg po twice daily, was initiated October 2016 and prednisone 40 mg po daily maintained. Symptoms persisted requiring admission for IV prednisolone, but she continued to decline surgical colectomy. She also developed a bacterial vaginitis treated with metronidazole cream and later a skin furuncle, treated with oral antibiotics.

Following tofacitinib, she received interleukin 12/23 inhibitor ustekinumab March–September 2017. She gained 30 pounds in 1 year (body mass index 37), increased abdominal fat and bilateral cataracts due to cortisone. Attempts to decrease prednisone below 30 mg daily led to bloody diarrhea (12–17 bowel movements daily). She eventually accepted to undergo subtotal abdominal colectomy (pathology shown in Fig. 1) with rectal stump and temporary ileostomy by June 2018. She improved and was seen for follow-up a month post-op, at which time she was having increasing right lower quadrant pain and rising CRP. A computed tomography scan demonstrated inflamed subcutaneous fat surrounding the ostomy and a second collection centimeter with rim enhancement and fat stranding. These were drained and cultures grew E. coli and B. fragilis. She responded to IV antibiotics for 3 days followed by oral step-down antibiotics to complete 2 weeks. Eight months following her colectomy, she developed polyarthralgia in her interphalangeal joints, wrists, shoulders, knees and feet with a normal CRP and a negative Rheumatoid Factor while off prednisone, thought to be either inflammatory or mechanical polyarthralgia. Pathology on surveillance sigmoidoscopy March 2019 demonstrated chronic active proctitis with ulceration consistent with chronic idiopathic IBD. Throughout this entire time, her CD4 range was between 400 and 900 cells/mm³, with CD4/CD8 ratio of 0.41:1.12, and HIV viral load remained suppressed since November 2012.

DISCUSSION

Due to repeated decline of surgery in order to preserve her quality of life and fertility, this woman with HIV and refractory UC received all available conventional therapies including mesalamine, glucocorticoids, thiopurines, antagonists to TNF-α, IL-12/23 blockers and anti-α4β7 integrin. She also received a small-molecule JAK inhibitor, TNF-α inhibitors and α4β7 integrin blockers are used with extreme caution in PLWH due to concerns of additional immunosuppression and subsequent infection risk. However, during her 6 years of being on immunosuppressants, the patient only experienced one episode of cellulitis, bacterial vaginitis, a skin furuncle and peristomal abscesses, all of which were easily managed with traditional therapies. Another concern with the use of integrin receptor antagonists in PLWH, although rare, is the possibility of Progressive...
Multifocal Leukoencephalopathy due to John Cunningham (JC) virus [1]. Our patient underwent blood plasma JC virus testing prior to vedolizumab initiation and this polymerase chain reaction testing was negative. She also denied any neurological signs or symptoms throughout treatment.

This woman’s case demonstrates that the spectrum of drug classes available and sequential use of biologics for treatment of UC were safe in this patient with well-controlled HIV infection ART, including an TNF-α blocker, JK inhibitor, IL-12/23 blocker and the α4β7 integrin blocker vedolizumab. Our patient did not incur any significant changes in her CD4 count nor CD4/CD8 ratio during the course of her treatments and infections were relatively minor. Although we did not use combination biologics in this patient, their efficacy and safety for IBD and other and other inflammatory diseases associated was explored in a systematic review of observational studies which did not find any differences related to improvements in disease condition, adverse effects or infection rates in patients receiving combined treatment compared to placebo groups [2]. A clinical trial (NCT02764762) examining efficacy and safety of combined vedolizumab, adalimumab and oral methotrexate in patients with Crohn’s Disease is in progress [3]. Until evidence from clinical trials is available on efficacy and safety of biologics and combination therapy in PLWH, case reports and case series provide a channel for dissemination of these experiences within the medical community.

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CONFLICTS OF INTEREST STATEMENT

None declared.

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ETHICS APPROVAL

The authors received ethical approval for publication of the case report.

CONSENT TO PUBLISH

The patient provided informed written consent for the preparation of this case report and publication of data and pathological image in an open access journal. The participant understood that the details/images would be freely available on the internet and may be seen by the general public. A copy of the written consent is available for review by the editor of the journal.

GUARANTOR

Dr Costiniuk is the guarantor of the case report.

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