



## SCIENTIFIC LETTER

### Cyclosporine treatment for severe steroid refractory immune-mediated colitis in a patient with ulcerative colitis<sup>☆</sup>



### Ciclosporina como tratamiento de colitis inmunomediada grave refractaria a esteroides en un paciente con colitis ulcerosa

Immune-mediated colitis (ImC) is the most frequent immune-related adverse effect in cancer patients treated with immune-checkpoint inhibitors (ICI). Diarrhoea is more frequent in patients receiving anti-CTLA-4 agents than anti PD-1/PDL-1 agents, and patients receiving ICIs for melanoma have more risk of ImC than those with other cancer. Treatment goes from symptomatic measures to withdrawal of the ICI, systemic steroids, biological drugs or even colectomy.<sup>1,2</sup>

We present the case of a 60-year-old man with medical history of ulcerative proctosigmoiditis (UC) treated with infliximab (IFX) in endoscopic and histologic remission since 2012 and with no other relevant comorbidities. A stage IV pulmonary cancer had been diagnosed in 2021 and pembrolizumab (PEM) (anti-PD-1 agent) was started in October 2021 with complete response at three months. IFX was maintained due to the deep remission achieved.

The patient was hospitalised in January 2022 because of severe bloody diarrhoea (>40 times/day), abdominal pain and defecatory urgency. Blood tests showed marked leucocytosis and reactive C protein (RCP) up to 20 mg/dl. *Clostridium difficile* and other bacterial infections were ruled out in stool culture. Symptoms had started four weeks earlier. A colonoscopy performed two days before admission revealed patchy areas of erythematous mucosa in rectosigmoid and ascending colon and normal mucosa in the transverse and descending colon. Suspecting a severe UC flare-up for IFX failure, systemic steroids (SS) and ustekinumab (UST) were started the same day of admission. After five days of treatment, the patient status remained unchanged. Histologic study showed chronic colitis alternating with normal mucosa in spared areas, cytomegalovirus (CMV) was negative. The patient was evaluated in a multidisciplinary committee; both inflammatory bowel disease (IBD) and ImC seemed possible diagnoses. Given the clinical severity, the failure to IFX and the SS refractoriness, cyclosporine (Cy) was preferred to vedolizumab (VDZ)

because of its more rapid effect and reversibility,<sup>3</sup> as a bridge until UST took full effect. After starting intravenous Cy (4 mg/kg/day), the patient experienced a rapid clinical and analytical improvement (see Fig. 1), persisting with rectal symptoms (tenesmus and defecatory urgency) so a rectoscopy was performed to evaluate the mucosa and take new biopsies which revealed CMV infection. Ganciclovir (5 mg/kg/12 h) was started achieving fully clinical remission.

The patient remained in clinical remission during the following 2 months. Cy was progressively tapered, leaving UST as maintenance treatment. Two weeks later the patient was rehospitalised due to severe watery diarrhoea. A relapse was suspected, and remission was reinduced again with Cy with successful results. Assuming UST failure, VDZ was started. Cy was again progressively tapered and the patient remained asymptomatic with VDZ for the next 6 months.

ImC was considered the most probable diagnosis and PEM was considered contraindicated and was no longer administered (last infusion had been 2 weeks before hospitalisation). The patient has remained clinically and radiologically stable of the oncologic disease without additional treatment.

Interestingly, the patient developed an ImC despite being treated with IFX, which is the first line treatment of steroid-resistant ImC. This fact forced us to use alternative drugs. Initially UST was preferred because, extrapolating data of IBD, has an apparently faster clinical effect than VDZ.<sup>3–5</sup> Despite the patient had been in deep remission for years with IFX and the finding of patchy mucosal lesions in the colonoscopy, UC flare up could not be totally ruled out, which is a limitation in this case.

Fangwen et al. recently published a study comparing the use of IFX, VDZ or both combined sequentially in ImC concluding that these therapies provide a shorter duration of SS use, fewer hospitalisations and lower ImC recurrence.<sup>6</sup> However, there are very few reported cases of ImC in patients with UC refractory to SS and IFX. We found one in a patient under IFX and other in a patient naïve to biologic treatment; both treated with VDZ.<sup>7,8</sup> No cases treated with Cy were found.

In conclusion, current case suggests that Cy may be a rapid and effective treatment for steroid-resistant ImC. This could be an important finding for corticoid and biologic refractory patients before colectomy. Even though more studies are needed, Cy may be used in patients with UC and severe ImC refractory to standard therapy.

<sup>☆</sup> The patient has given his informed consent to publish the information included in the article.

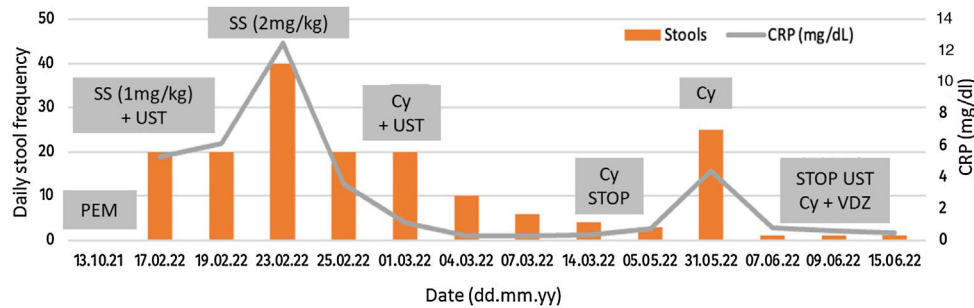


Figure 1 Evolution of the patient's stool frequency and RCP.

## Authors' contributions

Gerard Grau, Ariadna Altadill and Eduard Brunet reviewed the case and the available literature data and wrote the manuscript. Eduard Brunet and Xavier Calvet critically reviewed the text and provided important intellectual content. All authors definitively approved the submitted version.

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## Conflicts of interest

None of the authors have disclosed any conflict interest regarding the present case report.

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