Use of Serum Infliximab Level Prior to Cyclosporine Salvage Therapy in Severe Ulcerative Colitis

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Abstract
Medical treatment options for severe, steroid refractory ulcerative colitis (UC) include infliximab (IFX) or cyclosporine (CSA), but general consensus has been that both agents should not be used together or even successively. We report a case of a 17-year-old male with severe UC refractory to IV steroids with successful sequential salvage therapy guided by serum IFX level. After primary lack of response to IFX, an undetectable serum IFX level and elevated IFX antibodies were followed by immediate transition to IV CSA. This case demonstrates the possibility of therapeutic drug monitoring of IFX levels when calculating the risk/benefit ratio for patients with steroid-refractory UC failing primary salvage therapy.

Introduction
Both infliximab (IFX) and cyclosporine (CSA) are effective for the treatment of severe ulcerative colitis (UC) that is refractory to IV steroids, but general consensus has been that both agents should not be used together or even successively. A recent randomized trial of these agents in IV steroid-refractory patients found no difference in efficacy, but 40% of patients did not respond to the therapy in either arm. Case series have reported significant infectious events when the 2 agents are used for salvage therapy in close succession. We report a case of severe UC with successive salvage therapy guided by serum IFX level.

Case Report
A 17-year-old male with a 6-month history of pan-UC presented to our center. He had primary non-response to 8 weeks of mesalamine and continuous oral prednisone. He was started on combination therapy with azathioprine (AZA) 50 mg per day and IFX 5 mg/kg IV at 0 and 2 weeks, but due to lack of response, received 7.5 mg/kg IV at 6 weeks. Despite this approach, he was unable to wean from prednisone with persistent disease activity characterized by 6–8 bloody loose stools per day with associated severe urgency and nocturnal bowel movements. He received his next IFX at 7.5 mg/kg 6 weeks later. When this failed to control his colitis, he transferred care to our institution and was admitted. At that time (2 weeks after his last IFX dose) admission labs (Table 1) and serum IFX level and antibodies to IFX (ATI) were ordered (electrochemiluminescence immunoassay [ECLIA]; Esoterix Endocrinology, Calabasa Hills, CA).

He was found to have Clostridium difficile (C. difficile) infection and was treated with oral vancomycin 125 mg 4 times daily, metronidazole 500 mg IV every 8 hours, and IV methylprednisolone 20 mg every 12 hours. He was maintained on dual therapy for C. difficile for 12 days with continuation of oral vancomycin monotherapy for an additional 18 days. Despite clearance of C. difficile (by negative PCR 7 days after initiating therapy), he continued to have frequent bloody stools and urgency. Colonoscopy confirmed the presence of diffuse moderate-
to–severe active colitis (Figure 1). Biopsies demonstrated no evidence of viral cytopathic change, and immunostains were negative for cytomegalovirus infection. Eight days after admission, IFX and ATI results showed that serum infliximab was undetectable, and ATI was 265 ng/mL (reference: <22 ng/mL). After discussion with the patient, we decided to pursue further medical management. CSA 2 mg/kg IV continuous infusion was started (goal serum level: 300–400 ng/mL) with standard antibiotic prophylaxis for Pneumocystis pneumonia with trimethoprim/sulfamethoxazole (TMP/SMZ) and continued IV steroids. After 4 days of CSA, the hematochezia had stopped and the diarrhea started to resolve. He was discharged from the hospital on oral CSA, prednisone, TMP/SMZ, and AZA (Figure 2). At the time of this report 9 months later, he remains in steroid-free remission only on AZA, and there were no adverse events.

Discussion

Medical options for hospitalized patients with severe, corticosteroid-refractory UC include IFX or CSA. Initial response rates for both CSA and IFX in this challenging patient population are similar, ranging from 62% to 83%, respectively, and 71% of patients at 3 months. In patients treated with either CSA or IFX who do not respond to therapy, options include colectomy or, in a selective cohort, successive salvage therapy with the other agent. Published experience with successive salvage medical therapy has been limited to several small case series. Manosa et al reported that 6 of 16 patients receiving IFX salvage after CSA (38%) required colectomy after a median follow-up time of 195 days, while in a similar cohort, Chaparro et al reported that 29% progressed to colectomy at 1 year. Maser et al reported a retrospective study of 19 patients with steroid-refractory UC who were treated with CSA or IFX within 30 days as sequential rescue therapy. At 1 year, 8 (42%) patients required colectomy; steroid-free remission was achieved in 40% of the IFX-salvage cohort and 33% in the CSA-salvage cohort without statistical difference between them. In the largest cohort published to date, Leblanc et al published a retrospective study of 86 patients in which 48 (56%) patients had a colectomy despite sequential salvage therapy.

Table 1. Patient Laboratory Admission Values and Normal Values

| Laboratory Parameter     | Admission Values | Normal Values       |
|--------------------------|------------------|---------------------|
| Sodium, mEq/L            | 140              | 134–149             |
| Potassium, mEq/L         | 4.0              | 3.5–5.0             |
| Chloride, mEq/L          | 104              | 95–108              |
| Bicarbonate, mEq/L       | 28               | 23–30               |
| Urea nitrogen, mg/dL     | 12               | 7–20                |
| Creatinine, mg/dL        | 0.9              | 0.5–1.4             |
| Glucose, mg/dL           | 85               | 60–109              |
| Calcium, mg/dL           | 8.9              | 8.4–10.2            |
| Total protein, g/dL      | 6.6              | 6.0–8.3             |
| Albumin, g/dL            | 3.7              | 3.5–5.0             |
| Total bilirubin, mg/dL   | 0.1              | 0.1–1.0             |
| Alkaline phosphatase, U/L| 67               | 100–390             |
| AST, U/L                 | 17               | 8–37                |
| ALT, U/L                 | 34               | 8–35                |
| White blood cells, K/uL  | 19.0             | 3.5–11              |
| Hemoglobin, g/dL         | 11.2             | 13.5–17.5           |
| Platelets, K/uL          | 391              | 150–450             |
| C-Reactive protein, mg/L | 27               | <5                  |

AST = aspartate aminotransferase; ALT = alanine transaminase

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at 1 year, while 22% of patients had steroid-free remission.

The decision to pursue sequential medical therapy must account for the risks of delaying surgical intervention and that dual immunosuppression raises the risk of infection. Maser et al reported 3 (16%) serious infectious adverse events, including 1 death from gram-negative sepsis in the IFX salvage group. Leblanc et al reported that their IFX salvage group suffered 9 (10.5%) serious infectious complications as well as 1 death due to post-colectomy pulmonary embolism, possibly related to delayed surgical intervention. Chaparro et al also reported an infection adverse event rate of 8.4%, including 1 death due to post-colectomy nosocomial pneumonia.

The significantly longer half-life for IFX (8–10 days) versus CSA (6–8 hours) has led some to suggest the use of CSA as a first approach to steroid-refractory UC; if CSA fails, a shorter wash-out period may allow for safer IFX use. A lack of experience with CSA by gastroenterologists has made this option impractical. There is increasing evidence that the primary non-response to IFX in severe colitis may be partially attributed to rapid metabolism or rapid clearance of the drug, with emerging reports of fecal elimination of the drug as a potential explanation.\textsuperscript{12,13}

This is the first report of the use of therapeutic drug monitoring to minimize toxicity and guide IFX/CSA salvage therapy. We believe that this patient’s lack of response to IFX was due to rapid clearance and anti-drug antibodies. We do not know if he was losing IFX through a protein-losing colopathy and this “pseudo-episodic” therapy resulted in immunogenicity against the drug, or if he already had ATI that neutralized the IFX. In either explanation, it was clear that the subtherapeutic drug level was contributing to his lack of response to this therapy. The undetectable IFX level provided reassurance for use of salvage CSA. We propose that therapeutic monitoring may be used in the assessment of salvage therapies for selected patients.

A practical limitation to this approach is the time required to obtain IFX and ATI levels with currently available clinical assays, which delays clinical and therapeutic decisions for the patient. We believe that waiting for these results is worthwhile, considering the risks of surgery that may be averted. In the future, we hope “point of service” assays and improved turnaround times—driven by volume and demand—will reduce waiting time and make this approach more practical.

Disclosures

Author contributions: CG Chapman and AC Stein were involved with patient care and wrote the manuscript. A. Bochenek was involved with patient care. DT Rubin was involved with patient care, reviewed and revised the manuscript, and is the article guarantor.

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