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Short communication

Inflammatory bowel disease patients experiencing a loss of response to infliximab regain long-term response after undergoing granulocyte/monocyte apheresis: A case series

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ABSTRACT

Up to 50% of patients with ulcerative colitis (UC) or Crohn's disease (CD) experience a loss of response (LOR) to infliximab after an initial response to the drug. Granulocyte/monocyte apheresis (GMA) with the Adacolumn depletes the activated myeloid leukocytes that are known to exacerbate and perpetuate inflammatory bowel diseases, but GMA has hitherto not been applied to patients with LOR to infliximab. We report three cases (2 UC and 1CD) with LOR to maintenance infliximab therapy that received one GMA session/week for 3 consecutive weeks or more. The disease severity was assessed from the CD activity index or partial Mayo score, and the trough infliximab (TI) level was measured. Upon GMA therapy, all three patients achieved remission for up to 15 months with maintenance infliximab alone. The average plasma TI increased from 0.91 μg/mL to 1.46 μg/mL, with concomitant decreases of C-reactive protein (from 2.33 mg/dL to 0.78 mg/dL), interleukin-6 (from 8.4 pg/mL to 3.4 pg/mL), and interleukin-17A (from 0.21 pg/mL to 0.03 pg/mL). To our best knowledge, this is the first report of adding a non-drug GMA to restore the efficacy of infliximab. The outcomes, albeit in three cases, are relevant in therapeutic settings and should inspire further studies in a larger number of patients.

1. Introduction

In patients with ulcerative colitis (UC) and Crohn's disease (CD), the tumor necrosis factor-alpha (TNF-α)-inhibiting drug infliximab is applied to induce and maintain remission [1]. However, with time, many patients who initially responded to the drug may experience a loss of response (LOR) to it [2]. Attempts to restore adequate drug efficacy in patients with LOR include escalation of the dose, shortening of the infusion interval, or switching to another TNF-α inhibitor [3], but the adequacy of these strategies may be compromised by anti-drug antibodies [4,5]. Given that in patients with active inflammatory bowel disease (IBD), leukocytes are elevated as potential exacerbating and perpetuating factors, the selective depletion of these leukocytes by adsorptive granulocyte/monocyte apheresis (GMA) with the Adacolumn is expected to enhance drug efficacy [6]. Accordingly, in Japan and the European Union [6,7], GMA has become favorable among patients who wish to avoid pharmacological agents, including patients with a latent viral infection [8], pediatric patients [9,10], and the elderly [11]. In addition to depleting the extra load of myeloid leukocytes, GMA has been associated with a favorable immune profile, including a rise in regulatory T cells [12]. However, the efficacy of GMA in patients with LOR to infliximab has hitherto not been investigated.

2. Patients and methods

2.1. GMA treatment procedures

In the present study, we were interested to see the impact of GMA on the efficacy of infliximab in three patients (cases 1–3) who had experienced LOR to this TNF-α inhibitor. The GMA treatment was done as previously described [6,13]. In brief, the Adacolumn (JIMRO, Takasaki, Japan) and blood flow lines were primed with sterile saline to remove residual air bubbles from the column void volume and the circuit lines. A second priming of the system was done with heparinized saline. Blood was accessed through the antecubital vein in one arm and then returned from the column outflow to the patient via the antecubital vein in the contralateral arm. The duration of one GMA session was 60 min at a flow rate of 30 mL/minute. Patients received one GMA session per week until the CD activity index or the partial Mayo score started to fall, as described below for each case. Treatment was carried

Abbreviations: CD, Crohn's disease; CRP, C-reactive protein; GMA, granulocyte/monocyte apheresis; IL, interleukin; LOR, loss of response; TI, trough infliximab; TNF, tumour necrosis factor; UC, ulcerative colitis

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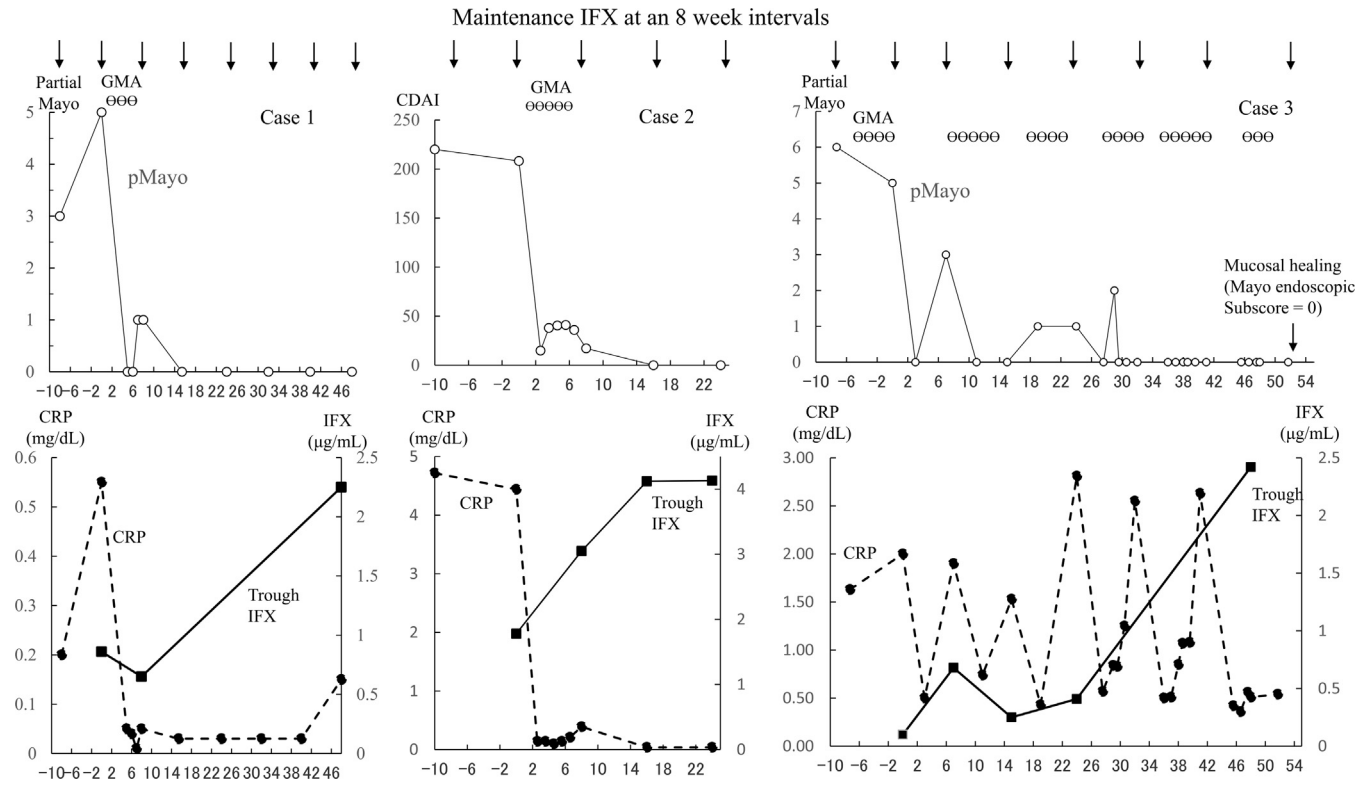

Fig. 1. The upper panels show changes in the partial Mayo endoscopic score or Crohn's disease activity index (CDAI) in Case 1 (A), Case 2 (B), and Case 3 (C) following the addition of Adacolumn GMA to the maintenance infliximab infusion (indicated by arrows). The lower panels show changes in C-reactive protein (CRP) and trough infliximab (IFX) levels in the same patients. Each Θ represents one GMA session. GMA = granulocyte/monocyte apheresis.

out in an outpatient or inpatient setting depending on the patient's IBD severity.

2.2. Patients and treatment outcomes

Case 1 was a 61-year-old woman with UC, diagnosed in October 2004. In November 2014, she received infliximab (5 mg/kg) at weeks 0, 2, and 6, followed by maintenance infliximab every 8 weeks. After 8.6 months, she experienced LOR that lasted for 3.2 months. She received three GMA sessions at one session per week over 3 consecutive weeks in combination with ongoing maintenance infliximab [13]. Her partial Mayo score decreased from 5 before GMA to 0 following the last GMA session, and her C-reactive protein (CRP) level likewise decreased. After a brief rebound, the partial Mayo score again fell to 0 and remained at this level without any additional GMA. Furthermore, the trough infliximab level had increased from 0.86 μg/mL at baseline to 2.25 μg/mL at week 48 (Fig. 1A). After achieving remission with the combination of GMA and infliximab, she continued to be in remission for 15 months on maintenance infliximab alone.

Case 2 was a 44-year-old man with CD diagnosed in 2005. In June 2013, he received infliximab (5 mg/kg) at weeks 0, 2, and 6, followed by maintenance infliximab every 8 weeks. After 26.4 months, he experienced LOR that lasted for 7.1 months, despite increase of the infliximab dose to 10 mg/kg. He received five GMA sessions at one session per week over 5 consecutive weeks, added to his maintenance infliximab. As seen in Fig. 1B, the patient's CD activity index fell to a remission level following five GMA sessions, and remained low up to week 24 on maintenance infliximab without further GMA therapy. The patient's CRP fell to a quiescent level, while the trough infliximab level increased from 1.78 μg/mL at baseline to 4.13 μg/mL at week 24.

Case 3 was a 65-year-old man with UC complicated by ankylosing spondylitis and diabetes as comorbidities. In June 2013, he received infliximab (5 mg/kg) at weeks 0, 2, and 6. After the 3rd infusion, he achieved clinical remission and then received maintenance infliximab every 8 weeks. After 12 months, he experienced LOR and was placed on azathioprine. After the combination of infliximab and azathioprine, he achieved clinical remission. In August 2015, he experienced LOR again that lasted for 17.4 months. Whether this was due to the comorbidities is uncertain, but we could not achieve a stable remission of his UC anytime soon after the initiation of GMA therapy, which was added to his maintenance infliximab at 8-week intervals. Fig. 1C shows that following the addition of GMA, both the CRP level and partial Mayo score initially fell, but then started to rise again. The man received a total of 25 GMA sessions and achieved stable remission (including mucosal healing) at week 52, with a partial Mayo score of 0. The patient's trough infliximab level, which was close to 0 before the addition of GMA, increased to 2.42 μg/mL at week 48. After the combination of GMA and infliximab, his UC remained in remission for 7.8 months.

2.3. Effects on cytokines

As additional measurements, we assayed the plasma interleukin (IL)-6 and IL-17A levels before GMA therapy and at week 7 or 8 post GMA. The data for these two proinflammatory cytokines are summarized in Fig. 2, showing decreases of both IL-6 (from 8.4 pg/mL to 3.4 pg/mL) and IL-17A (from 0.21 pg/mL to 0.03 pg/mL).

3. Discussion

In the first ever attempt of this kind, we added GMA to regular maintenance infliximab in three patients with LOR to the drug. All three patients achieved remission following this therapy, but the number of GMA sessions required to achieve remission ranged from 3 to 25. Likewise, the trough infliximab level rose following the addition of GMA, whereas the CRP level fell sharply, except in case 3. However, the most intriguing outcome was that cases 1 and 2 responded to infliximab