Treatment of Refractory Crohn’s Disease by Intensive Granulocyte and Monocyte Adsorption Apheresis: A Report on Two Drug Refractory Cases

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Abstract

Granulocyte and monocyte adsorption apheresis (GMA) is one therapeutic option for induction of remission in patients with inflammatory bowel diseases. Recently intensive GMA (2 sessions per week) was reported to be strikingly better than weekly GMA, both in remission rate and time to remission. Here we report two cases of Crohn’s disease refractory to weekly GMA who responded to intensive GMA. One patient had not received immunosuppressive therapy while the other had been refractory to combination therapy with infliximab and azathioprine. Intensive GMA induced remission in these 2 patients. Intensive GMA may represent a therapeutic choice for remission induction and maintenance with infliximab.

Key words: Crohn’s disease, granulocyte and monocyte adsorption apheresis, intensive therapy

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Introduction

Crohn’s disease (CD) and ulcerative colitis (UC) are the major forms of inflammatory bowel diseases (IBD), which afflict millions of people throughout the world including many young individuals. However, no curable treatment has been developed due to poorly understood disease pathology. Induction of remission and maintenance of remission is the goal of therapy. Many therapeutic trials have been performed. Extracorporeal granulocyte and monocyte adsorption (GMA) has become one therapeutic option for induction of remission. The therapeutic mechanism of GMA is considered to be depletion of elevated/activated granulocytes and monocytes/macrophages which are sources of inflammatory cytokines including TNF-α (1).

Recently, GMA was approved for the treatment of CD in Japan. However, inadequate clinical response is sometimes experienced with the routine, one GMA session/week protocol (2, 3). Further, in patients with UC, intensive GMA (2 sessions per week) was reported to be strikingly better than weekly GMA, both in remission rate and time to remission (4). Here we report the first two cases of refractory CD being successfully treated by intensive GMA.

Case Report

Case 1: A 21-year-old female was admitted to our hospital complaining of bloody diarrhea, abdominal discomfort and weight loss. Hospital records showed she had developed CD limited to her colon for two years. Conventional treatment with 3 g/day 5-aminosalicylic acid (5-ASA) and 900 kcal elemental diet (ED) had been initiated, but the patient relapsed while under conventional medication. The patient refused to receive corticosteroid, biologics or immunosuppressives, saying she was intolerant to these medications. After 4 weekly GMA sessions, her CD activity index (CDAI) score increased from 229 to 305, instead of an expected decrease. We obtained informed consent to treat her with intensive GMA. After an 8 GMA sessions, the CDAI score decreased from 305 to 136 (remission level). Then, she agreed to receive maintenance infliximab (IFX) and has...
remained in remission (Fig. 1A). After intensive GMA, her Hb level was increased in spite of a decrease in the frequency of intravenous iron infusion. However, CRP titer also increased after intensive GMA as well as after weekly GMA.

Case 2: A 28-year-old male with CD affecting the colon and the small intestine was under maintenance IFX (5 mg/kg/infusion), at an 8-week interval together with 50 mg/day azathiopurine (AZP). However, the patient’s CDAI started to increase and reached 379 points indicating that IFX had lost its efficacy in this patient. We obtained informed consent to treat him with intensive GMA. We decided to start GMA to keep the patient’s CD in mild active state (under CDAI 220). Figure 1B shows the changes in this patient’s CDAI with time following addition of GMA to the ongoing medications (IFX+AZP). After 3 GMA sessions in the weekly protocol, the patient’s CDAI did not fall markedly, but after intensive GMA, CDAI decreased to below 150 points. To ascertain the contribution of intensive GMA to the decline in CDAI, we changed back to the weekly GMA which was associated with a rise in CDAI and worsening of the patient’s clinical symptoms. Again we changed to intensive GMA and there was a sustained fall in CDAI to clinical remission level (Fig. 1B). The patient could be kept in mild active state after 5 weeks of intensive GMA. We were unable to estimate the CDAI score after 6 weeks due to lack

Figure 1. Changes in CDAI, hemoglobin (Hb) and CRP in a refractory CD case treated by intensive GMA. (A) Case 1 was an AZP, steroid and IFX free patient who achieved a sustained remission when weekly GMA was changed to intensive GMA. Hb level increased after intensive GMA in spite of a decrease in the frequency of intravenous iron. CRP titer decreased during weekly and intensive GMA. (B) Case 2 was on AZP plus IFX maintenance therapy, but the patient’s CDAI started to rise indicating the loss of response to IFX in this patient. Further, in this case as well, weekly GMA appeared to be inadequate and a sustained fall in CDAI to remission level was achieved when the patient was treated in the intensive GMA protocol. Hb level increased after intensive GMA. CRP titer decreased during intensive GMA, but not during weekly GMA. Closed circles, CDAI; closed triangles, Hb; closed squares, CRP; open triangles; intravenous iron (80 mg) infusion.
of hematocrit value. Hb level was increased after intensive GMA, but the CRP titer decreased during intensive GMA and not during weekly GMA.

**Discussion**

By using an intensive GMA protocol, we could treat two CD patients who were found to be refractory to the routine, weekly GMA protocol. These cases are the first CD patients who responded well to the intensive GMA protocol. The former case was IFX, AZP and steroid free, while the latter case was a patient in whom IFX was losing its efficacy and the addition of weekly GMA seemed to be ineffective, indicating that a more intensive treatment schedule might be essential to see the full potential of GMA. Therefore, in case one, only intensive GMA with no additional medication induced remission. Likewise, intensive GMA appeared to have a major contribution to the induction of remission in the patient refractory to combination therapy (IFX+AZP+weekly GMA), case 2.

Patients with inflammatory bowel disease (IBD) have activated leucocytes of the myeloid lineage which infiltrate the colonic mucosa in very large numbers during active disease (5). Myeloid leukocytes such as CD14(+) CD16(+) monocytes are major sources of TNF and therefore, selective depletion of these leukocytes by GMA is expected to promote remission or enhance the efficacy of pharmacologics (6). However, clinical studies in UC have reported contrasting efficacy outcomes, ranging from an 85% to a statistically insignificant level (7, 8) suggesting that certain UC patients benefit, while others not so, depending on the patients’ demography (7, 9). Additionally, the effect of intensive GMA was not tested (8). Hb level after intensive GMA increased, but intensive GMA was not associated with a sustained fall in CRP. Before GMA, we could not carry out colonoscopy beyond the sigmoid colon due to edematous colon and deep ulcers in case 2. After intensive GMA, we could perform double balloon enteroscopy up to the ileum. However, mucosal healing was not observed. In fact mucosal healing is a time-dependent process and may follow the fall in CDAI.

**Conclusion**

Intensive GMA appears to be an ideal choice for remission induction therapy, and it is favored by patients for its excellent safety profile.

The authors state that they have no Conflict of Interest (COI).

**References**


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