

Elevated Serum IgE Prior to Acute Severe Infusion Reaction During Infliximab Maintenance Therapy in a Crohn's Disease Patient

To the Editor:

Intercepting tumor necrosis factor alpha (TNF- α) by antibodies to this cytokine, such as infliximab (IFX) and adalimumab, is currently the best hope for improving the treatment of patients with Crohn's disease (CD). However, formation of antibodies to IFX (ATI), episodes of infusion reaction (IR), as well as the loss of response to the currently available anti-TNF- α biologics by a significant fraction of patients are serious issues that limit the efficacy and safety of anti-TNF- α therapy. Accordingly, identification of a marker that can predict an IR episode is desirable. A 42-year-old male patient was referred to our hospital with symptoms including diarrhea, abdominal pain, and weight loss together with polyarticular arthropathy. He was diagnosed with colonic CD based on endoscopic findings, showing large longitudinal ulcers and classic cobblestone patterns in the colon without small bowel involvement. His arthritis was judged to be a type 2 polyarticular extraintestinal manifestation without joint destruction, seronegative for rheumatoid factor. The first therapeutic regimen for this patient in our hospital was oral prednisolone (PSL, 10 mg/day), oral mesalamine (5-ASA, 1500 mg/day), and methotrexate (16 mg/week). Two months later, methotrexate was withdrawn due to nausea and was switched to azathioprine (AZA, 50 mg/day). However, his

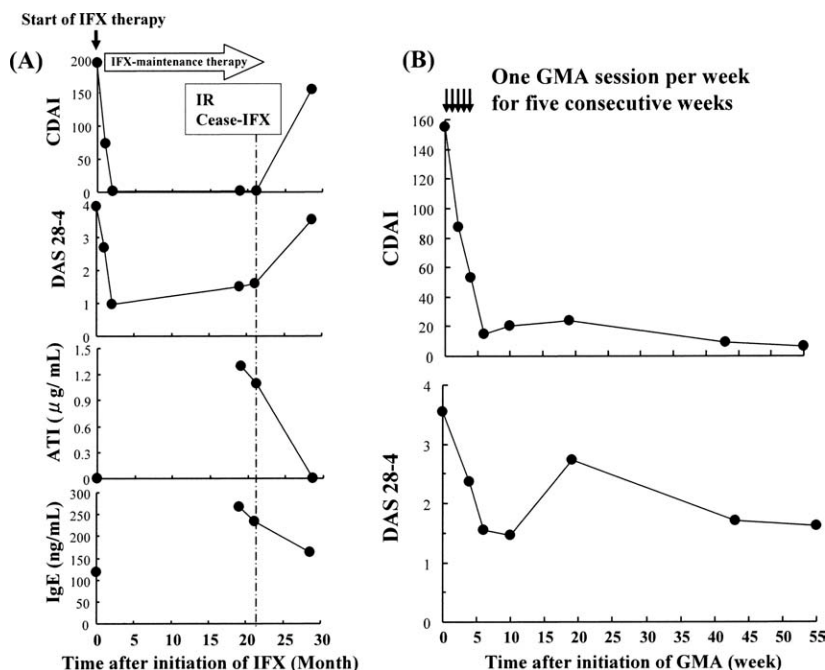


FIGURE 1. (A) Time course of disease activity scores, ATI, and serum IgE obtained before and after severe infusion reaction to IFX. CDAI <150, remission; DAS 28-4 <2.3, remission; ATI >1.69 μ g/mL, positive; IgE <408 ng/mL, normal. (B) Changes in CDAI and DAS 28-4 following GMA therapy.

CD Activity Index (CDAI) and disease activity score (DAS28-4) for arthritis¹ were 160 and 4.75, respectively. With these medications, neither the patient's colonic lesions nor joint symptoms reached the remission stage.

Subsequently, medication with IFX (5 mg/kg/day) was initiated together with 100 mg intravenous hydrocortisone and 50 mg intramuscular promethazine, administered 30 minutes before every scheduled IFX infusion (as a prophylactic measure). His CDAI and joint symptoms improved markedly (Fig. 1A). IFX infusion at 8-week intervals was continued as maintenance therapy in this patient. Twenty-one months after initiating IFX therapy the patient developed an acute severe IR and his blood pressure fell to below 90/60 mmHg, together with pallor, breathing difficulties, and hypoxemia (indicated by a dotted line in Fig. 1A). We decided to cease IFX therapy due to this severe IR. Additionally, AZA was discontinued due

to nausea after 22 months. The patient worsened with an increase in stool frequency and swollen/tender joint counts. We tried induction therapy with adalimumab at 24 months but the patient developed injection site reactions consisting of edema, erythema, and pruritus at the second adalimumab infusion and adalimumab was discontinued. Although the patient did not have any recorded history of allergic reactions such as pollinosis, he showed hypersensitivity reactions to both anti-TNF- α biologics.

We decided to look for serum factors potentially related to the infusion reaction. Stored sera at time 0 (patient naïve for IFX), 19 months (8 weeks before IR), 21 months (the day of severe IR), and 29 months (8 months after the cessation of IFX due to IR) were prepared for the measurement of IFX according to a new fluid-phase enzyme immunoassay.² In the same test samples, ATI was assayed by a double-antigen enzyme-linked immunosorbent

assay (ELISA) from Matriks Biotek Laboratories (Ankara, Turkey) and IgE was assayed using a human IgE ELISA kit obtained from Immunology Consultants Laboratory (Portland, OR). The outcomes are presented in Figure 1A (lower two graphs). ATI values at time 0, 19 months, and the day of IR (21 months) had increased from 0 $\mu\text{g/mL}$ to 1.3 $\mu\text{g/mL}$ and then to 1.1 $\mu\text{g/mL}$. Likewise, serum IgE levels at the same timepoints had increased from 119 ng/mL to 268 ng/mL and 233 ng/mL. At 29 months (8 months after the cessation of IFX therapy), both ATI and IgE levels had fallen to 0 $\mu\text{g/mL}$ and 162 ng/mL, respectively. At these timepoints serum IFX levels were undetectable.

Eight months after cessation of IFX therapy the patient's therapeutic regimen consisted of oral PSL (2 mg/day) together with oral 5-ASA (1500 mg/day). Further, the patient's CDAI and DAS28-4 scores were 155 and 3.54, respectively. As an alternative treatment option we decided to start granulocyte/monocyte adsorptive apheresis (GMA)³ with an Adacolumn

(JIMRO, Takasaki, Japan), which is an approved therapeutic intervention in Japan⁴ (Fig. 1B). GMA was applied at a flow rate of 30 mL/min for 1 hour (one GMA session) per week for five consecutive weeks. The patient responded well to GMA; at week 6 the CDAI and DAS28-4 scores had decreased to 15 and 1.54, respectively (well below the clinical remission levels). The patient achieved remission for both colonic lesions as well as for his joint symptoms. PSL was discontinued, leaving 5-ASA as the sole medication from week 39. At week 55, 1 year after the completion of the GMA course, the patient continued to be in stable remission: CDAI 6 and DAS28-4 1.61.

Our investigation identified IgE as a potential marker of IR, but a future study in a large cohort of patients is warranted to fully reveal the significance of IgE in the IR associated with IFX administration. Similarly, the therapeutic value of GMA as an alternative medication in patients who are intolerant to biologics is promising, but needs further evaluation.

Shingo Kato, MD, PhD
Taisuke Kobayashi, MD
Kazuhito Kani, MD
Hidehiko Takabayashi, MD
Ryuichi Yamamoto, MD
Koji Yakabi, MD, PhD

Department of Gastroenterology and
Hepatology, Saitama Medical Centre
Saitama Medical University
Saitama, Japan

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