EDITORIAL

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Could Early Anti-Tumor Necrosis Factor Therapy Change the Prognosis of Crohn's Disease?

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Article: Long-Term Clinical Outcomes of Korean Patient With Crohn's Disease Following Early Use of Infliximab **(Intest Res 2014;12:281-286)**

Anti-tumor necrosis factor (TNF) agents are used to treat chronic immune-mediated inflammatory disorders, and are the first biologic agents used to target a specific inflammatory mediator for the treatment of IBD. Considerable change in the treatment of IBD has occurred since the approval of anti-TNF agents for CD in 1998. Infliximab (IFX) is the first anti-TNF agent used for IBD. It has been traditionally used for refractory cases, which were unresponsive to less potent drugs such as 5-aminosalicylic agents, corticosteroids, and immunomodulators (IM) including azathioprine (AZA) and methotrexate. In the prebiologic era, the cumulative probability of major abdominal surgery in CD patients did not change over the past four decades, suggesting no potential for disease modification by conventional therapeutic strategies.[1] Although thiopurine use was associated with a statistically significant reduction in the need for surgery in a few studies,[2,3] no definite conclusions could be made on the disease-modifying potential of thiopurines because of the retrospective nature of these studies, and the lack of a clear causal relationship. Moreover, early introduction of AZA in CD patients was no more effective than conventional management in two recent randomized controlled trials from France and Spain.[4,5]

Therefore, the need for early and even frontline use of anti-TNF agents has been proposed for CD patients. In a study that compared the efficacy of IFX monotherapy, AZA monotherapy, and a combination of the two drugs in adults with moderate-to-severe CD who were previously naïve to immunosuppressive or biologic therapies, patients treated with IFX monotherapy were more likely to have a corticosteroid-free clinical remission than those receiving AZA monotherapy after 26 weeks.[6] Moreover, in terms of mucosal healing, which is becoming more widely accepted as a relevant outcome marker rather than clinical activity indices,[7] IFX monotherapy was also superior to AZA monotherapy.[6] However, considering the insufficient evidence, and concerns surrounding cost-effectiveness and long-term safety, early aggressive therapy based on anti-TNF agents cannot be recommended for all CD patients. For the long-term course of CD, several factors such as early onset, small bowel involvement, perianal disease at diagnosis, endoscopic severe lesions, and complicated disease behaviors are considered to predict further poor outcomes.[7] Therefore, a top-down therapeutic approach, making early use of a combination of anti-TNF agents and IM for patients with poor prognostic factors, is currently recommended by many experts.[7]

However, the long-term efficacy of early anti-TNF therapy for CD has rarely been evaluated under realistic conditions. Recently, Ghazi et al. divided their CD patients into an "early anti-TNF group (initial treatment with anti-TNF agents)" (54 patients), and a "step-up group" (39 patients), and retrospectively compared disease activity, quality of life, use of cortico-

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steroids, number of hospitalizations, and surgeries between both groups.[8] Up to one year after treatment, early anti-TNF therapy did not improve disease activity or quality of life, and did not decrease the need for corticosteroids or CD-related surgeries.[8] However, due to its retrospective design, small number of study subjects, no adjustment for potential confounders, and limited follow-up duration, it is not possible to draw firm conclusions on the role of early anti-TNF therapy for CD from this particular study.[8]

In this issue of Intestinal Research, Kim et al. tried to explore the clinical efficacy of early IFX therapy in a population of Korean CD patients in a multicenter context.[9] They enrolled a total of 721 subjects from 12 university hospitals, and divided patients into two groups depending on the date of CD diagnosis; July 1987 to December 2005 *vs*. January 2006 to January 2012.[9] The time at which the use of anti-TNFs became reimbursable in Korea was used to divide the cohort into the two groups.[9] Despite significant differences in the cumulative probabilities of IM (P<0.001) and IFX (P<0.001) use, they could not find differences in the cumulative probabilities of operation (P=0.905) and reoperation (P=0.418) between the two groups using Kaplan-Meier estimation and the Log-rank test.[9] Moreover, they could not find significant differences in cumulative operation rates and cumulative reoperation rates after adjusting for possible confounding factors such as sex, smoking, disease duration, disease location, disease behavior, and concurrent use of other drugs.[9] Because previous studies on the efficacy of early anti-TNF therapy were conducted only in Western countries, this study could send a meaningful message to clinicians managing CD patients in Korea. The authors also evaluated the operation rate up to the five-year mark, which could represent the mid-term outcomes, and not just the short-term outcomes of CD patients, which were commonly evaluated in previous clinical trials. The fact that study subjects were enrolled only from university hospitals and not primary or secondary medical institutions could be a potential source of argument.[9] However, because most CD patients in Korea are given anti-TNF agents in referral centers and especially in university hospitals, the patient group of this study could reflect the general CD patient population of Korea.

As the authors admitted, a considerable proportion of the second group may have been given IFX only after developing a significant level of bowel damage, thereby showing no significant difference in the operation rate and reoperation rate during follow-up.[9] This could be inferred from the fact that 36.8% of patients in the second group already showed structuring or penetrating behaviors at the time of CD diagnosis, and that the actual criteria for the reimbursement of anti-TNF agents in Korea state that anti-TNFs can be reimbursed only after failure of conventional therapy.[9] Therefore, the second group in the study by Kim et al. may not represent the patients for whom IFX was given at the "early" stage of disease, although the duration of disease at starting IFX was not clearly presented.[9] In addition, the retrospective nature of this study, information bias, and detection bias could have influenced the results.[9] The results of this study are consistent with those of a previous Spanish study by Domènech et al., which compared two cohorts of newly diagnosed CD patients which were defined depending on the availability of IFX (1994–1997 cohort *vs*. 2000–2003 cohort).[10] In this retrospective study, the authors could not find any differences in the surgical requirements or the development of disease-related complications between the two groups.[10] However, similar to the study by Kim et al., this Spanish study could not answer the question concerning the efficacy of early anti-TNF therapy because most cases of the 2000–2003 cohort were given IFX in the setting of a step-up algorithm, and as a result did not represent an "early" IFX-treated patient group.[10] Therefore, Domènech et al. finally concluded that the currently available drugs, when used in the setting of a conventional algorithm, are not likely to change the natural history of CD, a conclusion which is also similar to that of Kim et al.[9,10]

In conclusion, further prospective randomized trials comparing the efficacy and safety of first-line anti-TNFs and conventional approaches for newly diagnosed CD patients could answer our question concerning the usefulness of a top-down strategy. Because Asian CD patients including Koreans are showing different features with respect to sex distribution, phenotype, and genetics, there also could be a difference in long-term prognoses. Therefore, we need to perform further well-designed studies to clarify the role of early anti-TNF therapy for Asian CD patients.

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