

Management of Primary Nonresponders and Partial Responders to Tumor Necrosis Factor- α Inhibitor Induction Therapy among Patients with Crohn's Disease

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Keywords

Crohn's disease · Infliximab · Expert opinion · Primary nonresponder · Partial responder

Abstract

Induction therapy with tumor necrosis factor- α (TNF- α) inhibitors is highly effective for the treatment of Crohn's disease. However, there are primary nonresponders (PNR) of TNF- α inhibitors without clinical response during the induction period. In addition, there are partial responders (PR), who show some efficacy, but clinical remission is not achieved by induction therapy. To date, the definition and clinical management of PNR and PR have not been established. This report summarizes the opinions of 36 Japanese experts attending the Japan Round Table Discussion on IBD Meeting regarding how to determine PNR and PR of TNF- α inhibitors and how to manage these patients in clinical practice. PNR, who do not show any initial improvement of clinical

symptoms and serum C-reactive protein (CRP) levels, require re-assessment of intestinal complications. PR can be determined either by clinical symptoms, serum CRP levels, or imaging results. PR need intensification of the treatment with TNF- α inhibitors either with or without optimization of immunomodulators. Optimization of initial TNF- α inhibitor therapy may improve long-term outcomes, but more evidence is required to improve the use of TNF- α inhibitors for the prevention and management of PNR and PR.

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Introduction

Crohn's disease (CD) is a chronic inflammatory disease of unknown etiology in inflammatory bowel disease (IBD) characterized by transmural granulomatous inflammation in the digestive tract and sometimes complicated by fistulas and abscesses [1, 2]. Tumor ne-

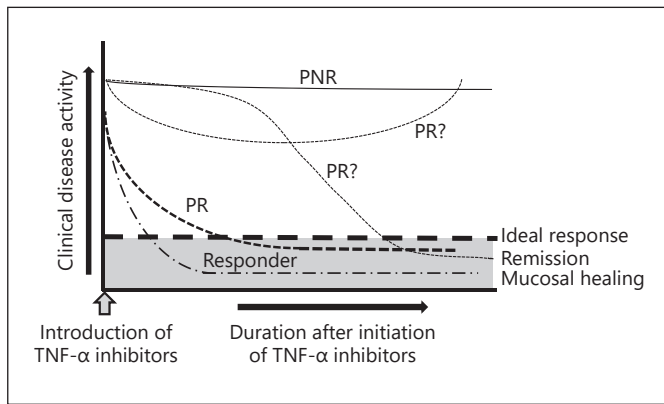


Fig. 1. Concept of primary nonresponders (PNR) and partial responders (PR) after the induction of TNF- α inhibitors.

crois factor- α (TNF- α) inhibitors, such as infliximab (IFX) and adalimumab (ADA), improve treatment efficacy and long-term outcomes in patients with CD. Although TNF- α inhibitors are highly effective in patients with CD [3, 4], there are primary nonresponders (PNR), who do not respond at all to induction therapy with TNF- α inhibitors. In randomized controlled trials and cohort studies of IFX for patients with CD, primary nonresponse rates were 8–42% and primary nonremission rates were 30–52% [5, 6]. Thus, in clinical settings, there are partial responders (PR) categorized as neither PNR nor responders, who display a partial response without satisfying effects in the induction phase of TNF- α inhibitors. Primary treatment failure of TNF- α inhibitors can be associated with poor long-term outcomes, including a high risk of surgery or sustained active disease despite medical interventions [7]. Patients who failed to obtain an ideal initial response show poor outcome, while Buhl et al. [8] reported that the population with deep remission increased to 25% at 2 years after IFX initiation among patients who had partial response after 1 year of IFX treatment. These results suggested that the initial response to TNF- α inhibitors can be associated with long-term outcomes, but some patients may show good long-term outcomes even when the initial response to TNF- α inhibitors was partial (Fig. 1). Thus, management of PR is important to improve the long-term efficacy.

To date, the definitions of PNR and PR are different among studies and not well established. In addition, the treatment strategy for PNR or PR is not well discussed. In order to minimize the populations of PNR and PR, it is important to optimize the usage of TNF- α inhibitors

Table 1. Issues discussed regarding PNR and PR in this meeting

- | | |
|-----|---|
| 1. | Definition and management of PNR |
| 1.1 | Definition of PNR |
| 1.2 | Management of PNR |
| 2. | Definition and clinical management of PR |
| 2.1 | Definition of PR |
| 2.2 | Proportion of PR who started infliximab and their clinical background |
| 2.3 | Management of PR |
| 2.4 | Management of patients who are still PR after treatment intensification |
| 2.5 | PR prevention |

PNR, primary nonresponders; PR, partial responders.

and concomitant medications. It may also be important to select the patient populations and timing of judging efficacy for TNF- α inhibitors. In this report, we summarized the expert opinions from the Japan Round Table Discussion on IBD (JRT) Meeting, which was attended by 36 Japanese IBD experts. Here, we characterized the PNR and PR to TNF- α inhibitors among the CD population and discussed the factors influencing the efficacy of induction therapy with TNF- α inhibitors. We also discussed how to manage PNR and PR to TNF- α inhibitors.

Process of the Round-Table Meeting

Thirty-six Japanese IBD experts attended the JRT held in Tokyo, Japan, on August 25, 2018. Before starting the group discussion, a short review lecture (30 min) was given about the proposed concept of PNR and PR and current information regarding the factors associated with therapeutic responses to TNF- α inhibitors as described in the Introduction [1–8]. Participants attended the round-table group discussion in 4 different groups (110 min) regarding the 7 issues related to PNR and PR, which were determined by the core members of this meeting (Table 1). In each group discussion, there was 1 moderator in each group, and the opinions of the attendees (8 attendees in each group without organizers) were accumulated. After completing the group discussion, opinions and comments from each group were presented. These opinions were discussed by all participants and were summarized by the chairman and attendees (80 min).

Table 2. Management of PNR to TNF- α inhibitors

| Management | Group 1 (n = 8) | Group 2 (n = 8) | Group 3 (n = 8) | Group 4 (n = 8) |
|---|--------------------|--------------------|--------------------|--------------------|
| Reassessment of intestinal complications | 8 | 8 | 8 | 8 |
| Switch TNF- α inhibitor to another TNF- α inhibitor | 3 | – | 7 | 8 |
| Switch TNF- α inhibitor to ustekinumab | 8 | – | 2 | – |
| Dose optimization of TNF- α inhibitors | – | – | 5 | 8 |
| Addition or dose optimization of immunomodulators | – | – | 5 ^a | – |
| Hospitalization with total parental nutritional therapy | 8 | – | – | 8 |
| Addition of enteral nutrition therapy | 8 | – | – | – |
| Addition of metronidazole | 1 ^b | – | – | – |

Number of participants who agreed to the proposal for the management of PNR is shown. PNR, primary nonresponders; TNF- α ; tumor necrosis factor- α ; –, not discussed. ^a In cases of mild disease activity. ^b In cases with colonic lesions.

Summary of the Meeting

Definition of PNR to TNF- α Inhibitors

PNR after the initiation of TNF- α inhibitors need to be assessed early due to their poor prognosis [7]. However, the response rate can gradually increase from the first to the third administration of TNF- α inhibitors [4, 9]. Therefore, it is premature to evaluate PNR soon after the first injection, as more accurate evaluations are made after the third injection. Thus, PNR are patients in whom clinical symptoms and serum C-reactive protein (CRP) levels do not improve at all or worsen after 3 injections of TNF- α inhibitors (8–10 weeks after initial IFX administration or 6–8 weeks after initial ADA administration). Intestinal complications (e.g., stenosis, internal fistula, abscess, and perianal disease) are risk factors for PNR [10, 11].

Management of PNR to TNF- α Inhibitors

Intestinal complications, such as stenosis, internal fistula, and abscess, can develop during the course of CD even if they were nonexistent at the time of diagnosis. Patients need to be (re-)evaluated for intestinal complications by using imaging modalities when they are suspected to be PNR. If complications, such as severe strictures, fistulas, and abscesses, are detected during examination, surgery should be performed if applicable. The experts felt that primary nonresponse was rare when severe intestinal complications were absent as some extent of efficacy can usually be observed in patients with CD in the absence of intestinal complications. Intestinal complications are usually assessed by imaging modalities before starting TNF- α inhibitors, and these patients would not be treated with TNF- α inhibitors in the clinical practice

of Japanese experts. Therefore, it was difficult to reach a consensus due to the limited experience of PNR management. For PNR without apparent intestinal complications that require treatment, medical treatment options, such as switching TNF- α inhibitors, proposed in the discussion of each group are listed in Table 2.

Definition of PR to TNF- α Inhibitors

PR are patients in whom some therapeutic effects are observed but clinical remission is not achieved by induction therapy with TNF- α inhibitors. If the patients meet one of the following conditions after 3 injections of TNF- α inhibitors (8–10 weeks after initial IFX administration or 6–8 weeks after initial ADA administration), they can be classified as PR: (1) both serum CRP levels and clinical symptoms decreased or improved, but did not become negative or disappear; (2) clinical symptoms were absent, but serum CRP levels were positive; and (3) even if patients' symptoms were absent and serum CRP levels were negative, active inflammation was observed on imaging (e.g., computed tomography [CT], magnetic resonance imaging [MRI], and ileocolonoscopy). Clinical activity can be evaluated using a quantitative clinical activity index, such as Crohn's disease activity index (CDAI), but the calculation of CDAI is time consuming and not clinically practical. Therefore, clinical activity is usually determined by the patients' symptoms assessed by the physicians and blood tests, such as serum CRP levels. In particular, when patients have clinical symptoms, it is necessary to evaluate if symptoms are caused by the active intestinal inflammation of CD or not. For that purpose, intestinal disease activity should be assessed using imaging modalities such as CT and MRI. In addition, serum

albumin and hemoglobin levels are useful for evaluating PR since these blood markers reflect the nutritional and inflammatory status. PR can be determined by endoscopy (ileocolonoscopy, capsule endoscopy, and balloon-assisted enteroscopy) in the absence of clinical symptoms and elevated CRP levels. In such cases, the optimal timing to evaluate PR for mucosal lesions has not yet been determined.

Proportion of PR to TNF- α Inhibitors and Their Clinical Background

The experts felt that the proportion of PR after the initiation of TNF- α inhibitors was approximately 20–30% based on their clinical experience. Patients with extensive small intestinal lesions, peri-anal lesions, and intestinal complications, such as strictures and fistulas, may be prone to becoming PR as they are considered to be resistant to TNF- α inhibitors compared to those without these lesions. Intensification of treatment may not always be necessary for all PR, and the population who required intensification was discussed. As a result, if CRP levels and clinical symptoms do not improve or worsen at the time of the fourth injection (10–14 weeks after IFX initiation or 6–8 weeks after ADA initiation) compared to the prior injection, treatment needs to be intensified. If clinical symptoms and CRP levels improve from the prior administration, treatment intensification is not necessary. However, in such cases, the condition of the patient should be observed carefully. The proportion of PR who requires treatment intensification was estimated to be about 50–60%, based on the experience of the experts.

Management of PR to TNF- α Inhibitors

Low serum drug concentrations of TNF- α inhibitors can be a factor for PR. Dose optimization needs to be performed to increase the concentration of TNF- α inhibitors. Dose optimization of IFX can include not only increasing the dose of IFX to 10 mg/kg in 8-week intervals, but also shortening the administration interval to 4 weeks. For cases of ADA treatment with 40 mg biweekly, the dose should be increased to 80 mg biweekly or shortened to 40 mg weekly, although weekly 40 mg injection of ADA is not approved in Japan. Some experts experienced that altering IFX injection to 5 mg/kg with 4-week intervals was sometimes effective in patients initially administered 10 mg/kg IFX at 8-week intervals. Shortening of the interval can be more effective than increasing the dose because the serum concentration of TNF- α inhibitors is maintained at stably high levels [12–14]. Although dose

optimization based on the serum trough level is ideal, it is not covered by Japanese national health insurance and can only be measured in limited institutions. In addition, the dose and timing of TNF- α inhibitor injections cannot be flexibly changed in Japan. In patients who are not taking immunomodulators (IM), it is worth considering the addition of IM at the time of TNF- α inhibitor dose optimization. Before using IM, risks of IM need to be estimated by the examination of *nudix hydrolase 15 (NUDT15)* genetic polymorphisms in order to screen high-risk patients for severe side effects, such as severe leukopenia and alopecia [15].

Management of Patients Who Are Still PR after Dose Intensification of TNF- α Inhibitors

When dose optimization of TNF- α inhibitors does not result in the improvement of clinical activity, switching between TNF- α inhibitors with the same mechanism of action is not expected to have high efficacy. In such cases, it will be better to switch to a drug with a different mechanism of action, such as ustekinumab, which inhibits the interleukin-12/23 p40 subunit. Using vedolizumab may also be an option, but it was not approved for use at the time of the meeting. The addition of enteral nutritional therapy or cytophoresis (in cases with colonic involvement) can also be considered, but evidence is scarce, and their efficacy may not be sufficient.

Interventions and Pretreatments to Prevent PR for TNF- α Inhibitors

As smoking is a significant risk factor for worsening disease activity of CD and induces unresponsiveness to drug treatment [16, 17], we need to instruct patients to stop smoking if the patient is a smoker. Previous studies have shown the benefit of using IM in combination with TNF- α inhibitors to prevent the development of anti-drug antibodies [3]. Therefore, it would be better to use concomitant IM at the initiation of TNF- α inhibitors, especially when using a chimeric antibody, such as IFX. In cases of severe disease activity, it may be effective to conduct total parental nutrition therapy (TPN) for a certain period before the initiation of TNF- α inhibitors in order to reduce intestinal inflammation. Some experts perform TPN in very severe cases and believe it is effective, but it is sometimes difficult to obtain the patients' consent to perform TPN with long-term hospitalization. Therefore, more evidence needs to be accumulated to determine the efficacy of combinatorial therapies.

Discussion/Conclusion

The Japanese IBD experts discussed about the evaluation and management of PNR and PR after the initiation of TNF- α inhibitors. The discussion described in this report was mostly based on the daily clinical practice of experts working in major Japanese high-volume IBD centers but not based on high-level evidence. We did neither propose a systematic list of questions nor use methodologies for qualitative data collection, which are used to represent a meta-analysis or a guideline based on a strict process. However, the content can be useful information for the consideration of treatment strategies when physicians do not achieve ideal outcomes, such as clinical remission and mucosal healing, after the initiation of TNF- α inhibitors. More evidence needs to be accumulated in order to improve the efficacy of TNF- α inhibitors to prevent and manage PNR and PR.

Appendix

JRT Group

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Statement of Ethics

The authors have no ethical conflicts to disclose. This study was a report of a IBD specialist meeting not related to either a study using human data and samples or animal study which needs approval from the ethical committee.

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Author Contributions

H.I. was involved in the drafting and critical revision of the manuscript. T.K., M.N., S.S., K.K., Y.S., M.W., and T.H. critically revised the manuscript for important intellectual content. All authors had major roles in the round table discussion and approved the final manuscript.