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Early combined immunosupression for the management of Crohn's disease

Khanna R, Bressler B, Levesque BG, et al. HYPERLINK "http://www.ncbi.nlm.nih.gov/pubmed/26342731" Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. Lancet 2015; 386: 1825-34.

Crohn's disease is a chronic inflammatory disorder of the gastrointestinal tract, with complications such as abscesses, fistulas, strictures, and extraintestinal manifestations. Treatment for Crohn's disease is still under discussion. One of the approaches of treatment is the conventional step-up treatment, which consists of using corticosteroids, antimetabolites, and anti-TNF consecutively. The second approach of treatment is top-down therapy that allows the clinician to start the treatment with the most effective drugs for this disease. Both approaches have advantages and limitations. The step-up therapy prolongs the exposure of corticosteroids, which makes the patient susceptible to the infections and also the side-effects of the corticosteroids. Unless two original trials 'TOP-DOWN' (1) and 'SONIC' (2) had shown that the top-down therapy is more effective than the conventional step-up therapy, due to some drawbacks of this highly effective therapy, such as infections, complexity of multidrug regimens, and cost, the step-up therapy is still the standard therapy for Crohn's disease.

Khanna et al. (3) presented a recent prospective trial, known as the 'REACT (Randomised Evaluation of an Algorithm for Crohn's Treatment)' trial, which was the largest randomized controlled evaluation of therapies for Crohn's disease. Although patients in the TOP-DOWN and SONIC trials were treatment-naive, disease durations of the patients in the REACT trial were at least 12 years. The authors targeted comparing the daily practice of the clinicians who treated patients with either conventional therapy or early combined immunosupression therapy (ECI) with an anti-TNF and antimetabolite. Gastroenterologists from Belgium and Canada participated in this study. These clinicians were randomly involved in the conventional therapy group or the ECI group. Patients in the conventional therapy group were treated according to their clinician's daily practice. Patients in the ECI group were treated according to the algorithm that added an anti- TNF and an antimetabolite after the first 4-week corticosteroid treatment in Canada and after 12-week treatment in Belgium, if patients did not undergo remission according to Harvey-Bradshaw index (HBI) scores. After randomization and exclusions, there were 18 gastroenterologists with their 729 patients in the ECI group and 17 gastroenterologists with their 675 patients in the conventional group who followed-up their patients for 24 months. The primary endpoint was the mean proportion of patients with corticosteroid-free remission (HBI ≤4) at the 12th month.

One of the results of this study was that patients in the ECI group were treated with anti-TNF and antimetabolites earlier than patients in the conventional group. There was no difference between the groups in the use of corticosteroids. As a primary endpoint, there was no statistically significant difference when comparing the proportion of remission between the groups at the 12th and 24th months (ECI 66% versus 61.9% and ECI 73.1% versus 65.1%, respectively). As one of the secondary endpoints, there was no difference in mean HBI scores at months 6, 12, 18, and 24 between the groups. In addition, there was no significant difference between the groups in admission to the hospital related to the disease. However, there was a statistical significance when comparing the other secondary outcomes. One of these outcomes was absolute risk reduction for surgical treatments. There were also significant differences when comparing major adverse events at month 24 and severe complications related to the disease between the groups. In the ECI group, there were two opportunistic infections and acute demyelinization related to adalimumab. One of these infections was pulmonary tuberculosis and the other was *Mycobacterium marinum* skin infection, and both infections were successfully treated. Acute demyelinization also recovered.

In the multivariate regression analysis, the factors that independently predicted the remission were male sex,

no previous surgery, low disease activity, remission at the beginning of the trial, and shorter disease duration. The factors that independently predicted the increased risk of major adverse events were conventional therapy, low caseload, high disease activity, perianal or fistulizing disease, corticosteroid therapy, younger age, and treatment in Belgium, in which there was a low case load and patients were treated with anti-TNF after 12 weeks of corticosteroid therapy compared with 4 weeks of therapy in Canada. SF-36 and EQ-5D scores were not significantly different between the groups. However, clinician satisfaction was better in the conventional group.

In the discussion part, the authors tried to explain why there was no difference in remission rates despite the presence of significant differences in the secondary endpoints between the groups. One of the explanations was that this trial was planned only on the patients' symptoms, and endoscopic findings and symptoms did not correlate all the times. The end points related to symptoms were not sensitive and specific for inflammation. Perhaps the differences in the secondary outcomes were related to inflammation. The answer will be provided in the second part of this trial, REACT-2, in which ileocolonoscopic findings will be added. The second explanation was that at the beginning of the trial, 55.5% of patients in both groups were under remission. Although there was no significant difference between the proportions, the rates of being under remission were greater in the ECI group than in the conventional therapy group at the 12th and 24th months. Use of anti-TNF and antimetabolites was started at the 24th month in the conventional therapy group; disease-related surgery and complication rates were better in the ECI group. Hence, timing of using the antimetabolites and anti-TNF becomes really important.

After the publication of this trial in 'Lancet,' some criticisms were made afterall. One of these criticisms was that at the beginning of the trial, 30% of patients already received an immunomodulator, 20% already received an anti-TNF, and 12% of patients received a combination of treatment (4). The patients in this study were not naive for immunomodulators and anti-metabolites and the mean disease duration before study enrollment was also more than 12 years. Because the study population in the REACT trial was not a newly diagnosed population and more than 60% of patients were already receiving some form of immunosuppression and another 47% had already undergone disease-related surgery at the time of enrollment, the appropriateness of assessing "early" combined immunosuppression is questionable. The second criticism was that although the top-down strategy is effective, there are some questions about the cost, long-term safety, and feasibility (5).

In conclusion, although this trial is valuable because of being the first cluster randomized trial and the largest randomized controlled evaluation of a therapy for Crohn's disease, some questions could be answered only after completion of the REACT-2 trial.

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