EDITORIAL

INTESTINAL RESEARCH

pISSN 1598-9100 • eISSN 2288-1956
https://doi.org/10.5217/ir.2019.00124
Intest Res 2019;17(4):441-442

Tacrolimus in pediatric ulcerative colitis: does it have a role?

Seung Kim

Department of Pediatrics, Severance Children's Hospital, Yonsei University College of Medicine, Seoul, Korea

Article: Tacrolimus for ulcerative colitis in children: a multicenter survey in Japan **(Intest Res 2019;17:476-485)**

Inflammatory bowel disease (IBD) is becoming more common both in the Eastern and Western countries, and the increasing pattern is more rapid in children and adolescents than in the adult population.[1,2] Compared to patient with late onset UC, those with pediatric onset UC tend to show more severe and widespread disease location at diagnosis and a high rate of disease extension during follow-up.[3,4] In a population based European study, the 5-year colectomy rate was also higher among patients with pediatric onset UC (8.1%) than among patients with adult onset UC (4.1%).[5]

As steroids have a variety of side effects, such as growth impairments, pediatricians are often reluctant to use steroids; however paradoxically the proportion of steroid-dependent or refractory colitis is also higher in the pediatric age group than in adults.[6] Although new effective drugs with various mechanisms have begun to be used in adult UC patients, many of these drugs are not approved for use in children or not covered by insurance in some countries. Hence, there are more restrictions on the use of new effective drugs for pediatric UC patients. In order to overcome these obstacles while managing pediatric IBD patients, it is important to optimize the currently available drugs or therapies. Tacrolimus, an immunomodulatory, which act as a potent inhibitor of helper-T lymphocytes, is known to be effective in adult UC[7] and was suggested as one option of a bridging therapy to thiopurines or vedolizumab for pediatric UC in an evidence-based guideline from European Crohn's and Colitis Organisation and European Society of Pediatric Gastroenterology, Hepatology and Nutrition.[8] However, studies of pediatric UC patients treated with this drug are scarce and the optimal indication, dosage and treatment duration have not yet been clarified.

In the current issue of the *Intestinal Research,* Yanagi et al.[9] conducted a retrospective multicenter survey to evaluate the effectiveness and safety of tacrolimus for induction and maintenance therapy in Japanese children with UC. Data from 67 UC patients under 17 years of age who were treated with tacrolimus were included in this study. Thirty-nine patients were steroid-dependent and 26 were steroid-refractory; 20 had severe colitis, and 43 had moderate colitis. The initial tacrolimus dose was 0.09 mg/kg/day (range, 0.05–0.12 mg/kg/day), the highest blood trough concentration within 2 weeks was 12.4 ng/mL (range, 9.2–15.2 ng/mL), and the median tacrolimus treatment duration was 18.1 weeks (range, 10–41.4 weeks). Regarding short-term effects, the clinical remission rate was 47.8% (32 patients), and the clinical response rate was 37.3% (25 patients). Ten patients (14.9%) did not show treatment effect. However, among 57 patients who showed short-term remission or response, only 8 (14%) achieved long-term (1-year) remission without relapse or surgery. The remaining 49 required additional treatments, such as biologics (22 patients, 33%), tacrolimus re-administration (10 patients, 14.9%), prednisolone (4 patients, 6%) and colectomy (20 patients, 29.9%). According to the study, the mean dose of prednisolone was

Received October 1, 2019. **Revised** October 2, 2019. **Accepted** October 3, 2019.
Correspondence to Seung Kim, Department of Pediatrics, Severance Children's Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea. Tel: +82-2-2228-2054, Fax: +82-2-393-9118, E-mail: pedks@yuhs.ac

reduced from 19.2 mg/day at the onset of tacrolimus administration to 5.7 mg/day at week 8 ($P<0.001$), which reveals the steroid-sparing effect of tacrolimus administration. Although adverse events were identified during tacrolimus treatment in 36 patients (53.7%), most of the adverse events were mild and only 6 patients (9.0%) required discontinuation of tacrolimus owing to adverse events (renal impairment, myelosuppression, intestinal infection, and vomiting), which improved after discontinuation of tacrolimus or appropriate treatment.

These results suggest that appropriate use of tacrolimus is relatively safe in patients with pediatric UC and can be effective in a substantial number of patients with steroid-refractory or dependent UC, thus achieving steroid-sparing effects. However, as only a temporary effect is expected, efforts are required to connect subsequent treatments for the maintenance of remission. Further prospective studies are needed to establish the optimized strategy for using tacrolimus in the management of children and adolescent with UC.

FINANCIAL SUPPORT

The author received no financial support for the research, authorship, and/or publication of this article.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTION

Writing and approval of final manuscript: Kim S.

ORCID

Kim S https://orcid.org/0000-0003-4373-9828

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