Clinical Aspects and Treatments for Pediatric Inflammatory Bowel Diseases

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The incidence of pediatric inflammatory bowel disease (IBD) is increasing worldwide, especially in the developing countries. It differs from adult disease in clinical manifestations, especially with regard to genetic predisposition in monogenic IBD. Pediatric disease also have a tendency to show more aggressive inflammation and greater extent of lesion. Newer drugs such as anti-tumor necrosis factor-α have been known to make a difference in treating pediatric IBD. Recent studies suggested that the patients with high risk factors might have some benefits from earlier use of biologics. To achieve treatment goals such as relieving symptoms, optimizing growth, and improving quality of life while minimizing drug toxicity, more research is needed to develop tools for risk stratification in the use of biologics for pediatric IBD.

Key Words: Pediatrics, Inflammatory bowel diseases, Crohn disease, Ulcerative colitis, Anti-tumor necrosis factor-α blockers

INTRODUCTION

Pediatric inflammatory bowel disease (IBD) is a growing concern in pediatric health care. Nearly a quarter of all patients with IBD develop the disease during childhood [1]. In recent decades, the incidence and prevalence of pediatric IBD have increased and the highest incidence has been reported from Canada, Norway, Sweden, Finland, the United Kingdom, and Ireland [2]. The incidence and prevalence of pediatric IBD in Singapore showed a 10-fold rise from 0.23 to 2.28 per 100,000 in the past 20 years, even though previously published data on the incidence of IBD in Asia showed differences among countries [3,4]. In Korea, recently published local data showed a rapidly rising trend in the incidence between 2011 and 2016; the incidence for all pediatric IBD increased from 0.86 to 3.33 per 100,000, with an increase from 0.67 to 2.78 for Crohn disease (CD) and from 0.19 to 0.56 for ulcerative colitis (UC) [5].
After the introduction of anti-tumor necrosis factor α blockers for use in IBD, pediatric IBD showed dramatically improved outcomes, similar to those in adults. However, it is still difficult for physicians to understand the current strategy for treatment of pediatric IBD, because of the lack of information and experience. In this article, clinical aspects and treatment of pediatric IBD will be discussed in the context of biologics.

**CHARACTERISTICS OF PEDIATRIC IBD**

**More aggressive disease course than in adults**

Childhood-onset IBD seems to be a more aggressive and rapidly progressive disease compared to adult-onset IBD [6,7]. CD is more prevalent than UC in children. The ratio of boys to girls is as high as 1.8:1. The most common type of disease distribution is pan-enteric or pan-colic. These cases were more often treated with systemic steroids and azathioprine and had a higher frequency of steroid dependence. The patients showed a more severe disease course compared to that in adults with IBD. These patients were more likely to have upper gastrointestinal involvement, extraintestinal manifestations, and strictureting and penetrating disease. Among pediatric IBD patients, 44% required surgery at some point, with a 34% risk within the first 5 years after diagnosis [7-10]. In CD, no differences were found when comparing corticosteroid responsiveness between pediatric and adult patients; however, the inflammatory phenotype is more common than the strictureting or penetrating phenotype in childhood [11,12].

**Strong genetic influences**

Among patients with IBD onset at a young age, 29% have one or more family members with IBD. The subgroup of children younger than 3 years of age with UC had the highest prevalence of first-degree relatives with IBD (44%) [13]. Several genetic defects that disturb intestinal epithelial barrier function or affect innate and adaptive immune function have incomplete penetrance of the IBD-like phenotype [14]. Monogenic defects, especially those affecting the interleukin-10 (IL-10) signaling pathway, result in severe or intractable disease [15]. Patients with IL-10 pathway defects often show initial presentation before 1 year of age. Intractable per-

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Table 1. Montreal and Paris Classification of Crohn Disease

| Characteristics          | Montreal                      | Paris                      |
|--------------------------|-------------------------------|----------------------------|
| Age at diagnosis (y)     | A1: <17                       | A1a: 0 to <17              |
|                          | A2: 17-40                     | A1b: 10 to <17             |
|                          | A3: >40                       | A2: 17-40                  |
|                          |                               | A3: >40                    |
| Location                 | L1: Terminal ileal±limited cecal disease | L1: Distal 1/3 ileal±limited cecal disease |
|                          | L2: Colonic                   | L2: Colonic                |
|                          | L3: Ileocolonic               | L3: Ileocolonic            |
|                          | L4: Isolated upper disease    | L4a: Upper disease proximal to Ligament of Treitz |
|                          |                               | L4b: Upper disease distal to Ligament of Treitz and proximal to distal 1/3 ileum |
| Behavior                 | B1: Non-stricturing non-penetrating | B1: Non-stricturing non-penetrating |
|                          | B2: Strictureting             | B2: Strictureting          |
|                          | B3: Penetrating               | B3: Penetrating            |
|                          | p: Perianal disease modifier  | B2B3: Both penetrating and strictureting disease either at the same or different times |
|                          |                               | p: Perianal disease modifier |
| Growth                   | Not available                 | G0: No evidence of growth delay |
|                          |                               | G1: Growth delay            |

Modified from Levin A et al. Inflamm Bowel Dis 2011;17:1314-1321 [21].
ianal fistula is a cardinal manifestation and diarrhea with bloody stools is also common with this defect [16,17]. There is no specific treatment for IL-10 pathway defects, except for hematopoietic stem cell transplantation [18,19].

**Paris classification for very-early-onset and monogenic IBD**

Very-early-onset IBD (VEOIBD) is usually defined when IBD occurs in children less than 6 years of age. A child less than 2 years of age can be classified as having infantile IBD [20]. However, in the Paris classification, which is a modified pediatric version of the Montreal classification and is frequently cited in textbooks, pediatric onset IBD is only classified as A1a and A1b, which occur at less than 10 years of age or between age 10 and 17 years, respectively (Table 1) [21]. Recent advances in translational research and next generation sequencing or whole exome sequencing have made it possible to change the diag-

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**Table 2. Pediatric Crohn's Disease Activity Index**

| History (recall, 1 wk) | Parameter | Detailed description | Point |
|------------------------|-----------|----------------------|-------|
| Abdominal pain         | None      |                      | 0     |
|                        | Mild (brief, does not interfere with activities) | 5     |
|                        | Mod/severe (daily, longer lasting, affects activities, nocturnal) | 10    |
| Stools (per day)       | 0-1 liquid stools, no blood | 0     |
|                        | Up to 2 semi-formed with small blood, or 2-5 liquid | 5     |
|                        | Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea | 10    |
| Patient functioning, general well-being (recall, 1 wk) | No limitation of activities | 0     |
|                        | Occasional difficulty in maintaining age appropriate activities | 5     |
|                        | Frequent limitation of activity, very poor | 10    |
| Laboratory             | Hematocrit (%) (use age-specific reference) | Normal | 0   |
|                        | mild decrease | 2.5   |
|                        | Mod/severe decrease | 5     |
| Erythrocyte sedimentation rate (mm/h) | < 20 | 0     |
|                        | 20-50 | 2.5   |
|                        | > 50  | 5     |
| Albumin (g/dL)         | ≥ 3.5 | 0     |
|                        | 3.1-3.4 | 5     |
|                        | ≤ 3.0 | 10    |
| Examination            | Weight | Weight gain or voluntary weight stable/loss | 0     |
|                        | Involuntary weight stable, weight loss 1%-9% | 5     |
|                        | Weight loss ≥10% | 10    |
| Height at diagnosis    | < 1 channel decrease | 0     |
|                        | ≥1, < 2 channel decrease | 5     |
|                        | ≥2 channel decrease | 10    |
| Height follow-up       | Height velocity ≥ −1 SD | 0     |
|                        | Height velocity < −1 SD, > −2 SD | 5     |
|                        | Height velocity ≤ −2 SD | 10    |
| Abdomen                | No tenderness, no mass | 0     |
|                        | Tenderness, or mass without tenderness | 5     |
|                        | Tenderness, involuntary guarding, definite mass | 10    |
| Perirectal disease     | None, asymptomatic tags | 0     |
|                        | 1-2 Indolent fistula, scant drainage, no tenderness | 5     |
|                        | Active fistula, drainage, tenderness, or abscess | 10    |
| Extraintestinal manifestions (n) | 0 | 0 |
|                        | 1 | 5 |
|                        | ≥2 | 10 |
nosis and treatment in VEOIBD. A gene panel or gene chip showed promising results in the diagnosis of VEOIBD [14]. The Clinical course of monogenic IBD, which is a subgroup of VEOIBD, is more severe than adolescent onset disease. The initial Pediatric Crohn’s Disease Activity Index (PCDAI) and Pediatric Ulcerative Colitis Activity Index (PUCAI) scores, the annual incidence of surgery, and the number of hospitalization per year were higher in the monogenic IBD group than that in other IBD groups [22]. There is no specific treatment for VEOIBD; however, a few reports showed that hematopoietic stem cell transplantation showed effectiveness in IL-10 receptor deficiency and XIAP mutations. VEOIBD could be useful in identifying the pathophysiology of IBD, because pediatric cases have a relatively stronger genetic background and less exposure to environmental and behavioral influences than adults [23,24]. As recent advances in VEOIBD make this category important in pediatric IBD, the Paris classification alone is unable to categorize all patient groups.

Treat to target

The traditional treatment strategy based on clinical symptom improvement does not improve long-term outcomes in CD and patients cannot avoid bowel damage. Therefore, the “treat to target” concept was introduced to incorporate use of biological markers and mucosal healing into IBD treatment [25]. This new method was adopted from the experience with rheumatic diseases, and can be tentatively regarded as an active approach to the severe disease group [26]. However, there are insufficient data with regard to optimal indications, biomarkers, and treatment strategies, especially in children. Early introduction of biologics in patients with poor prognostic factors, such as deep colonic ulcerations, extensive disease, marked growth retardation, severe osteoporosis, B2 and/or B3 behavior, and severe perianal disease, can be recommended to reduce bowel damage [27].

Scoring system

Endoscopic evaluation is the gold standard for diagnosis of CD in children. However, esophagogastroduodenoscopy and colonoscopy are more difficult and dangerous in children. To overcome the gap between the need to frequently evaluate disease severity and the difficulty of performing endoscopy in children, the PCDAI and PUCAI have been developed [28,29]. The PCDAI includes growth in children as an important parameter. These scoring systems are often used to determine treatment parameters in many clinical settings and investigational trials, as well as for insurance reimbursement (Tables 2 and 3).

### TREATMENT STRATEGY

The aims of therapy in pediatric IBD traditionally have been to relieve symptoms, optimize growth, and improve quality of life while minimizing drug toxicity [27]. To ensure growth in pediatric patients with CD, aggressive control of inflammation is

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**Table 3. Pediatric Ulcerative Colitis Activity Index**

| Item                          | Point |
|-------------------------------|-------|
| 1. Abdominal pain             |       |
| No pain                       | 0     |
| Pain can be ignored           | 5     |
| Pain cannot be ignored        | 10    |
| 2. Rectal bleeding            |       |
| None                          | 0     |
| Small amount only, in <50% of stools | 10    |
| Small amount with most stools | 20    |
| Large amount (>50% of stools) | 30    |
| 3. Consistency of most stools |       |
| Formed                        | 0     |
| Partially formed              | 5     |
| Completely unformed           | 10    |
| 4. Number of stools per 24 hours |     |
| 0-2                           | 0     |
| 3-5                           | 5     |
| 6-8                           | 10    |
| >8                            | 15    |
| 5. Nocturnal stools (any episode causing awakening) | |
| No                            | 0     |
| Yes                           | 10    |
| 6. Activity level             |       |
| No limitation of activity     | 0     |
| Occasional limitation of activity | 5    |
| Severe restricted activity    | 10    |

Sum of Pediatric Ulcerative Colitis Activity Index (0-85).
Fig. 1. Simplified treatment algorithm for pediatric CD according to risk factors. Dashed line indicates early use of biologics, that is, the “top down” strategy. High-risk factors in children for luminal CD are deep colonic ulcerations, extensive disease, marked growth retardation, severe osteoporosis, B2 and/or B3 behavior, and severe perianal disease [27]. Generally accepted risk factors are a history of more than 2 steroid courses, steroid dependence, hospitalization, chronic (>12 months) symptoms, need for immunosuppressants or need for surgery, terminal ileal location, structuring and penetrating behavior, smoking, positive serologic markers such as Anti-Saccharomyces cerevisiae antibody/perinuclear antineutrophil cytoplasmic antibodies, positive genetic markers such as NOD2/IBD5, and elevated C-reactive protein [30]. CD: Crohn disease, TNF: tumor necrosis factor, ASA: aminosalicylic acid.

essential. A recent consensus about the achievement of mucosal healing, especially in patients with poor prognostic factors, could not be fully supported because of the lack of evidence. It is difficult to identify patients with definite risk in order to initiate early aggressive immunotherapy and to define the necessary degree of mucosal healing and depth of transmural healing [27]. Current recommended strategy in pediatric CD is based on escalating medical therapy, beginning with nutritional intervention and/or steroids to achieve targets [30]. Overall, no differences in drug response were found when comparing pediatric and adult CD patients; therefore, current treatment options based on steroid responsiveness can be the same in adults and children. However, it is very important to avoid steroids in children as much as possible (Fig. 1) [27,30].

Nutritional intervention in pediatric patients is essential to control the disease, especially in CD. Exclusive Enteral Nutrition is recommended as first-line therapy to induce remission in children with active luminal CD. However, there is no evidence for the use of nutritional intervention in fistulizing CD or pediatric UC. The possibility of the development of colon cancer in pediatric IBD should be kept in mind. Even though pediatric colon cancer is very rare, children with VEOIBD can develop colon cancer at an earlier age than expected. In our institution, we reported a patient with VEOIBD and sigmoid colon cancer a few years ago [31].

TRANSITION TO ADULT CLINICAL CARE

The transition from pediatric to adult clinical care in IBD has been problematic. Transition requires careful coordination and collaboration among key persons in a multidisciplinary team, including the patient as well as the parents/caregivers and providers. Adult gastroenterologists who participate in the care of young adults should develop competence in key areas of adolescent and young adult care and should make an effort to collaborate with the pediatrician.
Providing adequate care for transitioning patients includes education for the development of self-management skills and developmental processes relevant to young adults with IBD [32]. Recent models suggested by European groups should be reviewed by Korean academic societies, and further prospective research is needed [33,34].

CONCLUSION

The incidence of pediatric IBD is increasing worldwide, especially in the developing countries. It differs from adult disease in clinical manifestations, especially with regard to genetic predisposition in monogenic IBD. To achieve treatment goals of relieving symptoms, optimizing growth, and improving quality of life while minimizing drug toxicity, more research is needed to develop tools for risk stratification in pediatric IBD.

REFERENCES

1. Kelsen J, Baldassano RN. Inflammatory bowel disease: the difference between children and adults. Inflamm Bowel Dis 2008;14 Suppl 2:S9-11.
2. Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, Griffiths AM. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. Inflamm Bowel Dis 2011;17:423-39.
3. Ng SC, Tang W, Ching JY, Wong M, Chow CM, Hui AJ, et al. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-pacific Crohn’s and colitis epidemiology study. Gastroenterology 2013;145:158-65.e2.
4. Ong C, Aw MM, Liwanag MJ, Quak SH, Phua KB. Rapid rise in the incidence and clinical characteristics of pediatric inflammatory bowel disease in a South-East Asian cohort in Singapore, 1994-2015. J Dig Dis 2018;19:395-403.
5. Hong SJ, Cho SM, Choe BH, Jang HJ, Choi KH, Kang B, et al. Characteristics and incidence trends for pediatric inflammatory bowel disease in Daegu-Kyungpook province in Korea: a multi-center study. J Korean Med Sci 2018;33:e132.
6. Van Limbergen J, Russell RK, Drummond HE, Aldhouse MC, Round NK, Nimmo ER, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. Gastroenterology 2008;135:1114-22.
7. Sauer CG, Kagathasan S. Pediatric inflammatory bowel disease: highlighting pediatric differences in IBD. Gastroenterol Clin North Am 2009;38:611-28.
8. Rinawi F, Assa A, Hartman C, Mozer Glassberg Y, Friedler VN, Rosenbach Y, et al. Incidence of bowel surgery and associated risk factors in pediatric-onset Crohn’s disease. Inflamm Bowel Dis 2016;22:2917-23.
9. Ruemmele FM, Turner D. Differences in the management of pediatric and adult onset ulcerative colitis: lessons from the joint ECCO and ESPGHAN consensus guidelines for the management of pediatric ulcerative colitis. J Crohns Colitis 2014;8:1-4.
10. Charpentier C, Salleron J, Savoye G, Fumery M, Merle V, Laberrenne JE, et al. Natural history of elderly-onset inflammatory bowel disease: a population-based cohort study. Gut 2014;63:423-32.
11. Jakobsen C, Bartek J Jr, Wewer V, Vind I, Munkholm P, Groen R, et al. Differences in phenotype and disease course in adult and paediatric inflammatory bowel disease: a population-based study. Aliment Pharmacol Ther 2011;34:1217-24.
12. Vernier-Massouille G, Balde M, Salleron J, Turck D, Dupas JL, Moutarde O, et al. Natural history of pediatric inflammatory bowel disease (IBD): analysis of a pediatric IBD consortium registry. J Pediatr 2015;166:35-40.
13. Jakobsen C, Bartek J Jr, Wewer V, Vind I, Munkholm P, Groen R, et al. Differences in phenotype and disease course in adult and paediatric inflammatory bowel disease: a population-based study. Aliment Pharmacol Ther 2011;34:1217-24.
14. Uhlig HH, Schwed T, Koletzko S, Shah N, Kammermeier J, Eldkadi A, et al. The diagnostic approach to monogenic very early onset inflammatory bowel disease. Gastroenterology 2014;147:990-1007.e3.
15. Glocker EO, Kotlarz D, Boztug K, Gertz EM, Schäffer AA, Noyan F, et al. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. N Engl J Med 2009;361:2033-45.
16. Shim JO, Hwang S, Yang HR, Moon JS, Chang JY, Ko JS, et al. Interleukin-10 receptor mutations in children with neonatal-onset Crohn’s disease and intractable ulcerating enterocolitis. Eur J Gastroenterol Hepatol 2013;25:1235-40.
17. Shim JO, Seo JK. Very early-onset inflammatory bowel disease (IBD) in infancy is a different disease entity from adult-onset IBD; one form of interleukin-10 receptor mutations. J Hum Genet 2014;59:337-41.
18. Engelhardt KR, Shah N, Faizura-Yeop I, Kocacik Uygun DF, Frede N, Muise AM, et al. Clinical outcome
in IL-10- and IL-10 receptor-deficient patients with or without hematopoietic stem cell transplantation. J Allergy Clin Immunol 2013;131:825-30.

19. Ko JS. Is infantile inflammatory bowel disease curable with hematopoietic stem cell transplantation? Korean J Gastroenterol 2013;62:313-4.

20. Snapper SB. Very-early-onset inflammatory bowel disease. Gastroenterol Hepatol (N Y) 2015;11:554-6.

21. Levine A, Griffiths A, Markowitz J, Wilson DC, Turner D, Russell RK, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. Inflamm Bowel Dis 2011;17:1314-21.

22. Kim KY, Lee EJ, Kim JW, Moon JS, Jang JY, Yang HR, et al. Higher Morbidity of monogenic inflammatory bowel disease compared to the adolescent onset inflammatory bowel disease. Pediatr Gastroenterol Hepatol Nutr 2018;21:34-42.

23. Tsianos EV, Katsanos KH, Tsianos VE. Role of genetics in the diagnosis and prognosis of Crohn's disease. World J Gastroenterol 2012;18:105-18.

24. Bianco AM, Girardelli M, Tommasini A. Genetics of inflammatory bowel disease from multifactorial to monogenic forms. World J Gastroenterol 2015;21:12296-310.

25. Bouguen G, Levesque BG, Feagan BG, Kavanaugh A, Peyrin-Biroulet L, Colombel JF, et al. Treat to target: a proposed new paradigm for the management of Crohn's disease. Clin Gastroenterol Hepatol 2015;13:1042-50.e2.

26. Kang B, Choe YH. Early biologic treatment in pediatric Crohn's disease: catching the therapeutic window of opportunity in early disease by treat-to-target. Pediatr Gastroenterol Hepatol Nutr 2018;21:1-11.

27. Ruemmele FM, Veres G, Kolho KL, Griffiths A, Levine A, Escher JC, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. J Crohns Colitis 2014;8:1179-207.

28. Hyams JS, Ferry GD, Mandel FS, Gryboski JD, Kibort PM, Kirschner BS, et al. Development and validation of a pediatric Crohn's disease activity index. J Pediatr Gastroenterol Nutr 1991;12:439-47.

29. Turner D, Otley AR, Mack D, Hyams J, de Bruijne J, Uusoue K, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. Gastroenterology 2007;133:423-32.

30. Danese S, Colombel JF, Reinisch W, Rutgeerts PJ. Review article: infliximab for Crohn's disease treatment: shifting therapeutic strategies after 10 years of clinical experience. Aliment Pharmacol Ther 2011;33:857-69.

31. Noh SY, Oh SY, Kim SH, Kim HY, Jung SE, Park KW. Fifteen-year-old colon cancer patient with a 10-year history of ulcerative colitis. World J Gastroenterol 2013;19:2437-40.

32. Philpott JR, Kurowski JA. Challenges in transitional care in inflammatory bowel disease: a review of the current literature in transition readiness and outcomes. Inflamm Bowel Dis 2019;25:45-55.

33. van Rheenen PF, Aloi M, Biron IA, Carlsen K, Cooney R, Cucchiara S, et al. European Crohn's and Colitis Organisation topical review on transitional care in inflammatory bowel disease. J Crohns Colitis 2017;11:1032-8.

34. Brooks AJ, Smith PJ, Cohen R, Collins P, Douds A, Forbes V, et al. UK guideline on transition of adolescent and young persons with chronic digestive diseases from paediatric to adult care. Gut 2017;66:988-1000.