Loss of Interleukin-10 Signaling and Infantile Inflammatory Bowel Disease – Implications for Diagnosis and Therapy

Kotlarz, D., Beier, R., Murugan, D., Diestelhorst, J., Jensen, O., Boztug, K., Pfeifer, D., Kreipe, H., Pfister, E.D., Baumann, U., Puchalka, J., Bohne, J., Egritas, O., Dalgic, B., Kolho, K.L., Sauerbrey, A., Buderus, S., Güng.r, T., Enninger, A., Koda, Y.K.L., Guariso, G., Weiss, B., Corbacioglu, S., Socha, P., Uslu, N., Metin, A., Wahbeh, G.T., Husain, K., Ramadan, D., Al-Herz, W., Grimbacher, B., Sauer, M., Sykora, K.W., Koletzko, S., Klein, C.

Gastroenterology 2012 April 28 [Epub ahead of print]

DONATA LISSNER
Charité - Universitätsmedizin Berlin
Department of Gastroenterology
Berlin, Germany

Donata Lissner
is currently performing her residency at Charité – Universitätsmedizin Berlin, and is interested in the immunological aspects of IBD, particularly the role of the innate immune system.

Introduction

Although identification of a single cytokine responsible for the pathogenesis of a chronic inflammatory condition seems promising for providing targeted curative treatment, this cannot be achieved for inflammatory bowel disease (IBD) with its complex and heterogeneous etiology. However, for a subgroup of IBD patients – children with very early onset IBD – one such cytokine seems to be Interleukin-10 (IL-10), known for its anti-inflammatory properties. First evidence for a role of IL-10 in IBD emerged yet nearly 20 years ago, when IL-10-/- mice had been shown to develop severe enterocolitis (1), an effect that could be reversed by IL-10 gene therapy (2). In 2009, three mutations in genes encoding for the IL-10 receptor (IL10R1 and IL10R2) were identified in children with early onset IBD (3). As a consequence, peripheral blood mononuclear cells (PBMCs) of affected children produced higher amounts of pro-inflammatory cytokines. As a proof of principle, one patient was successfully treated with allogeneic stem-cell transplantation, and sustained remission could be achieved.

What is this paper about?

Following up on these findings, the present study of Kotlarz et al. investigated the impact of mutations within the IL-10 pathway among children with IBD on the clinical disease course. Of 66 patients with disease onset < 5 years of age with a severe clinical course, 16 patients with loss-of-function mutations in IL-10 related genes were identified, with the majority affecting the IL-10 receptor (5 patients with mutations in the IL10RA and 8 patients with mutations in the IL10RB gene, respectively), and 3 patients with mutations in the IL-10 gene itself. All of these patients presented with perianal disease and onset of symptoms within the first three months of life. Endoscopic and histopathologic examination revealed close resemblance of these findings to Crohn´s disease (CD). Despite multimodal therapy including immunosuppressive therapy, exclusive enteral nutrition and surgical procedures, in none of the patients sustained clinical response could be achieved. In functional assays, defective response via the STAT-3 pathway was shown for mutations within the IL10R gene, resulting in diminished anti-inflammatory properties of IL-10 and thus production of high amounts of lipopolysaccaride (LPS)-stimulated TNFa by PBMCs. In 5 patients, hematopoietic stem cell transplantation (HSCT) was performed, of which 4 achieved sustained complete remission in terms of clinical and endoscopic response, with a median follow-up time of 2 years. In functional assays, reconstitution of the IL-10/STAT3 pathway was affirmed.

Conclusion

This study provides evidence for the importance of genotyping young children presenting with a severe refractory course of colitis with perianal affection, in order to offer a curative approach in treating a defined immunodeficiency rather than IBD. Hereby, it is important to distinguish between defective IL-10 on the one hand and mutations within the receptor on the other. The minority of children displayed loss-of-function mutations within the IL-10 gene. However, these patients would theoretically benefit from exogenous administration of functional IL-10. So far, this has only been examined in adult patients without having undergone genetic analyses before, and has – as we learned understandably – not been shown to be effective (4). With respect to mutations within the IL-10 receptor, further randomized trials are essential. One concern is that the induction therapy for HSCT, including chemotherapy and potent immunosuppressant drugs as well as gut decontamination, has contributed to the clinical response to a great extent, bearing in mind the possible uncontrolled immune response of IBD-patients to normal gut flora. Besides IL-10, IL10R2 is also a component of other receptors, namely IL-22, IL-26, IL-28, and IL-29 receptors. Thus, altered signaling in these pathways may equally contribute to the imbalance of pro- and anti-inflammatory signals.

According to the EuroKids register, only 1% of all paediatric IBD patients are diagnosed in infancy (5). In these children, Kotlarz et al. found mutations within the IL-10 pathway in not more than one third of patients. Thus, the reported important findings are merely applicable on a small, well-defined subgroup of patients. Nevertheless, for this group, defective IL-10 mediated immunomodulatory signaling is proven, and targeted curative therapy based on genetic findings is a promising option.

References

1) Kühn R, Löhler J, Rennick D, et al. Interleukin-10-deficient mice develop chronic enterocolitis. Cell 1993 Oct 22;75(2):263-74.
2) Lindsay JO, Sandison A, Cohen P, et al. IL-10 gene therapy is therapeutic for dextran sodium sulfate-induced murine colitis. Dig Dis Sci 2004 Aug;49(7-8):1327-34.
3) Buruiana FE, Solà I, Alonso-Coello P. Recombinant human interleukin 10 for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2010 Nov 10;(11):CD005109.
4) Glockner E, Kotlarz D, Boztug K, et al. Inflammatory Bowel Disease and Mutations Affecting the Interleukin-10 Receptor. N Engl J Med 2009;361:2033-45.
5) de Bie CI, Buderus S, Sandhu BK, et al. Diagnostic Workup of Paediatric Patients With Inflammatory Bowel Disease in Europe: Results of a 5-Year Audit of the EUROKIDS Registry. J Pediatr Gastroenterol Nutr 2012;54:374-380.