New therapeutic approach by sirolimus for enteropathy treatment in patients with LRBA deficiency

Introduction

LPS-responsive beige-like anchor protein (LRBA) deficiency is a rare genetic disorder caused by biallelic loss-of-function mutations in the LRBA gene. This disorder is characterized by early-onset hypogammaglobulinemia, chronic diarrhea and autoimmune manifestations (1-4). Similar to common variable immune deficiency (CVID) patients, affected individuals show a reduced levels of immunoglobulin (Ig) isotypes and suffer from recurrent infections, hepatosplenomegaly, chronic pulmonary disorders as well as auto-inflammatory conditions including idiopathic thrombocytopenic purpura (ITP), autoimmune hemolytic anemia (AIHA) and enteropathy (1,5-9).

The enteropathy phenotype includes autoimmune enteropathy, inflammatory bowel disease (IBD)/IBD-like disease and non-infectious recurrent diarrhea. LRBA deficiency has been reported to be common among patients with CVID-like phenotype underwent genetic diagnosis (2,10,11). CVID patients and patients with LRBA deficiency resemble symptoms of enteropathy presenting in immunocompetent individuals, but the pathology is usually documented to be not similar and the symptoms often do not respond to the conventional therapies. In LRBA deficient...
patients, chronic diarrhea is characterized by duodenal villous atrophy and large bowel lymphocytic infiltration (5). Recent studies have reported that the chronic and severe diarrhea in patients with LRBA deficiency may not improve despite intravenous Ig (IVIg) treatment (6,12). Medical therapy typically with corticosteroids (budesonide and prednisone), empiric antibiotic therapy and gluten free diets have been used commonly (13). In patients refractory to corticosteroids, treatment with immunosuppressive drugs such as azathioprine, 6-mercaptopurine, tacrolimus, mycophenolate mofetil, infliximab, and rituximab have been reported. Side effects are commonly documented in administration of this group of medications, and maintaining remission has been reported to be unsuccessful in previous studies (5,14-16). sirolimus, also known as rapamycin, is a macrocyclic lactone antibiotic which also has a profound immunosuppressive property on the cellular immune response, particularly on T cells. sirolimus binds to the same intracellular receptor as tacrolimus and cyclosporine, however does not inhibit calcineurin. sirolimus blocks the "mammalian target of rapamycin" (mTOR) which subsequently interrupts signaling pathways for several cytokines and growth factors including interleukin 2 (IL2). Recent studies have suggested the effectiveness of sirolimus to reduce chronic diarrhea in patients with entopathy. Here, we report for the first time the successful use of sirolimus for management of entopathy in four patients with LRBA deficiency.

Case presentation

Case 1. A 14 years old female patient with LRBA deficiency was diagnosed at the age of five years old with hypogammaglobulinemia. She is a child of related (first cousin) parents. Her first manifestation was diarrhea which started at six months of age. The patient underwent antibiotic therapy for the diarrhea but there was no improvement in her symptoms. Other manifestations included splenomegaly, hepatomegaly and juvenile rheumatoid arthritis at the age of four. She underwent treatment for immunodeficiency at five years of age with IVIg, accordingly her diarrhea was controlled. Diarrhea became more severe since a year ago, up to 20 times during the day and 8 times during the night, and consequently six kilograms-weight loss was detected. Infliximab was administrated for five months, but no improvement was observed in diarrhea and weight loss symptoms. The pathological report of the colonoscopy showed edema and excess infiltration of lamina propria with lymphocytes and eosinophils. Focal micro-abscess formation and cryptitis were also detected. Her microscopic reports were conclusive of mild chronic gastritis, esophagitis and active colitis but no parasite or Helicobacter pylori infection was reported.

Case 2. A 21-year-old LRBA deficient female patient with re-
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**Discussion**

LRBA deficiency is characterized by combined immunodeficiency, enteropathy, and autoimmune complications. According to previously published studies, clinical features in patients with LRBA deficiency are heterogeneous, and first presentations of the disease often occur during childhood (2). The cohort study of Alkhairy et al. (2) divided the disease phenotypes into categories of RTI, autoimmunity, organomegaly, and enteropathy. They described the enteropathy phenotype as an overlapped group of autoimmune enteropathy, IBD/IBD-like disease and non-infectious diarrhea (6). In our study, all patients were early onset, and a broad range of complications including RTI and autoimmune manifestations were reported. Moreover, gastrointestinal complications including chronic diarrhea were seen in all patients.

Treatment of the autoimmunity, chronic diarrhea and associated colitis is challenging in patients with antibody deficiency (17,18). Uzzan et al. (19) reported that Ig supplementation does not significantly affect the course of non-infectious gastrointestinal disease in CVID patients. Currently available treatments including steroids and cyclosporine have resulted in remission only in a subset of patients, then large doses of steroids are often necessary to control active disease. Patients with autoimmune enteropathy commonly do not respond to conventional treatment or other non-specific immune suppression therapies, however autoimmune enteropathy has been reported with partial response to immunosuppressive drugs such as cyclosporine, azathioprine and 6-mercaptopurine (20). Tacrolimus has been used as a treatment option for enteropathies, especially in autoimmune patients. Its mechanism of action is similar to cyclosporine. Both drugs block the gene activation for cytokine production by inhibiting the antigenic response of helper T lymphocytes (21). Bousvaros et al. (16) in 1996 used tacrolimus for the first time as an alternative therapy for autoimmune enteropathy, and concluded that it can be efficacious when other immunosuppressive regimens fail (16). Mycophenolate mofetil has been also proposed as an alternative therapeutic option after the successful induction of remission in an infant with autoimmune enteropathy (22).

In the present report, we used sirolimus for clinical management of enteropathy in patients with LRBA deficiency. We showed that disease symptoms such as chronic diarrhea and weight loss were successfully controlled after administration of sirolimus. Massey et al. (23) reported effectiveness of sirolimus in treatment of refractory Crohn’s disease in an adult patient. Mutalib et al. (24) showed that sirolimus, by inducing both clinical remission and mucosal healing, is effective in children with severe IBD refractory to conventional therapies. In another study, Araki et al. (25) found that treatment of a severe refractory colonic and perianal Chrone’s disease with sirolimus may result in a marked improvement in symptoms of enteropathy. Yong et al. (26) also reported the impact of sirolimus in children with IPEX and IPEX-like enteropathy. Although satisfying results of ad-

<table>
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<tr>
<th>Parameters</th>
<th>Patient 1</th>
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<th>Patient 3</th>
<th>Patient 4</th>
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<td>7497</td>
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<td>4273</td>
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<tr>
<td>CD4+(cell/μL)</td>
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<td>363</td>
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<td>CD8+(cell/μL)</td>
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mination of sirolimus have been documented in patients with autoimmune enteropathy prior to our study (26,27), there was no evidence of using sirolimus in treatment of enteropathy in LRBA deficient patients. In the current study, for the first time, four LRBA deficient patients unresponsive to non-specific immune-suppressive agents underwent sirolimus therapy. Following administration of sirolimus, the frequency of diarrhea decreased and the patients’ weight gradually normalized. Therefore, sirolimus with its potential efficacy and immunomodulatory properties may be recommended for the treatment of severe enteropathy in LRBA deficiency. Further studies should be designed to provide evidence for the effectiveness of sirolimus administration in management of diarrhea in immunodeficient patients by providing detailed pathological and microbiological evidences after treatment.

References


