Everolimus for Primary Intestinal Lymphangiectasia With Protein-Losing Enteropathy

Michio Ozeki, MD, PhD, a Tomohiro Hori, MD, PhD, a Kaori Kanda, MD, a Norio Kawamoto, MD, PhD, a Takashi Ibuka, MD, PhD, b Tatsuhiko Miyazaki, MD, PhD, c Toshiyuki Fukao, MD, PhD a

Departments of aPediatrics, bGastroenterology, and cPathology, Gifu University Graduate School of Medicine, Gifu University, Gifu, Japan

Dr Ozeki contributed to the study conception and design, drafted the initial manuscript, and approved the final manuscript as submitted; Drs Hori, Kanda, and Kawamoto provided patient care, performed clinical data analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted; Dr Ibuka performed gastroenterological examinations, endoscopy, and clinical data analyses, reviewed and revised the manuscript; and approved the final manuscript as submitted; Dr Miyazaki carried out pathological examinations and analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted; Dr Fukao contributed to the study concept and design and critically reviewed the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: 10.1542/peds.2015-2562

Accepted for publication Nov 19, 2015

Address correspondence to Michio Ozeki, MD, PhD, Department of Pediatrics, Graduate School of Medicine, Gifu University, Yanagido 1-1, Gifu 501-1194, Japan. E-mail: michioo@gifu-u.ac.jp

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2016 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: This study was supported in part by a grant-in-aid 25461587 for Scientific Research from

Primary intestinal lymphangiectasia (PIL), also known as Waldmann’s disease, is an exudative enteropathy resulting from morphologic abnormalities in the intestinal lymphatics. In this article, we describe a 12-year-old boy with PIL that led to protein-losing enteropathy characterized by diarrhea, hypoalbuminemia associated with edema (serum albumin level: 1.0 g/dL), and hypogammaglobulinemia (serum IgG level: 144 mg/dL). Severe hypoalbuminemia, electrolyte abnormalities, and tetany persisted despite a low-fat diet and propranolol. Everolimus (1.6 mg/m²/day) was added to his treatment as an antiangiogenic agent. With everolimus treatment, the patient’s diarrhea resolved and replacement therapy for hypoproteinemia was less frequent. Hematologic and scintigraphy findings also improved (serum albumin level: 2.5 g/dL). There were no adverse reactions during the 12-month follow-up. To the best of our knowledge, this is the first report of everolimus use in a patient with PIL.

Lymphatic anomalies include cystic lymphatic malformation, generalized lymphatic anomaly, Gorham–Stout disease, lymphangiectasia, and central conducting lymphatic disorders. Lymphangiectasia occurs as a primary developmental lymphatic disorder with or without elevated systemic venous pressure due to lymphatic obstruction, and the condition must be distinguished from other lymphatic disorders. Depending on the site of the anomaly, lymphangiectasia may manifest as chylothorax, pulmonary lymphangiectasia, chylous ascites, protein-losing enteropathy (PLE), cutaneous vesicles, or superficial chylous leaks.

Primary intestinal lymphangiectasia (PIL), also known as Waldmann’s disease, is a rare exudative enteropathy characterized by morphologic abnormalities of the intestinal lymphatics without proliferation. Common symptoms of PIL are persistent diarrhea, peripheral edema, steatorrhea, lymphocytopenia, hypogammaglobulinemia, and hypoproteinemia. Treatment is generally symptomatic and may include a low-fat diet associated with medium-chain triglycerides, periodic intravenous albumin infusion, and corticosteroid administration. In a more severe case, octreotide, a synthetic analog of the naturally occurring hormone somatostatin (a potent inhibitor of the release of growth hormone, serotonin, gastrin, glucagon, and insulin), was successful. However, no curative therapy is currently available for PIL. A US Federal Drug Administration–funded prospective study of sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, in patients with complicated vascular anomalies has been underway (ClinicalTrials. To cite: Ozeki M, Hori T, Kanda K, et al. Everolimus for Primary Intestinal Lymphangiectasia With Protein-Losing Enteropathy. Pediatrics. 2016;137(3):e20152562

abstract

Departments of aPediatrics, bGastroenterology, and cPathology, Gifu University Graduate School of Medicine, Gifu University, Gifu, Japan

Dr Ozeki contributed to the study conception and design, drafted the initial manuscript, and approved the final manuscript as submitted; Drs Hori, Kanda, and Kawamoto provided patient care, performed clinical data analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted; Dr Ibuka performed gastroenterological examinations, endoscopy, and clinical data analyses, reviewed and revised the manuscript; and approved the final manuscript as submitted; Dr Miyazaki carried out pathological examinations and analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted; Dr Fukao contributed to the study concept and design and critically reviewed the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: 10.1542/peds.2015-2562

Accepted for publication Nov 19, 2015

Address correspondence to Michio Ozeki, MD, PhD, Department of Pediatrics, Graduate School of Medicine, Gifu University, Yanagido 1-1, Gifu 501-1194, Japan. E-mail: michioo@gifu-u.ac.jp

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2016 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: This study was supported in part by a grant-in-aid 25461587 for Scientific Research from
CASE REPORT

A 12-year-old Japanese boy presented to a municipal hospital with a 3-month history of progressive diarrhea, abdominal pain, lower limb edema, tetany, and weakness. He had no relevant family history or medical history. The patient was provisionally diagnosed with PIL and treated with a low-fat diet and infusions of albumin (4 infusions of 12.5 g) for infection prophylaxis. After 4 months, the patient was transferred to Gifu University Hospital to establish a definitive diagnosis and undergo additional therapy.

Physical examination on admission revealed an acutely ill patient with a puffy face and generalized edema. Laboratory findings revealed decreased levels of serum albumin (1.4 g/dL), total protein (2.8 g/dL), magnesium (0.9 mg/dL), and corrected calcium (8.1 mg/dL). Hypoalbuminemia was noted; at their nadirs, the IgM level was 60 mg/dL (normal: 45–300 mg/dL), IgA was 71 mg/dL (normal: 95–460 mg/dL), and IgG was 226 mg/dL (normal: 890–1850 mg/dL). The urinalysis results were within normal limits. The patient had a high fecal α1-antitrypsin clearance rate (494 mL/day; normal: <20 mL/day), indicating enteric loss of plasma proteins. Gastrointestinal endoscopy showed white villi and chyle leakage in the mucosa of the distal duodenum and ascending colon to the transverse colon (Fig 1A). Histologic examination of biopsy specimens from the duodenum and ileocecum showed diffusely dilated mucosal and submucosal lymphatic channels along the villi (Fig 1B). Staining for the lymphatic marker D2-40 was positive in the luminal cells (Fig 1C). Additionally, we found elevated nuclear and cytoplasmic immunohistochemical expression of mTOR in the lymphatic endothelial cells (Fig 1D). 99mTc-human serum albumin (99mTc-HSA) scintigraphy showed albumin leakage from the ascending colon to the transverse colon (Fig 2A). Scintigraphic examination showed no leakage in the stomach or small bowel. These results allowed for a definitive diagnosis of PIL and secondary PLE. Management of the patient’s hypoalbuminemia with a low-fat diet and infusions of albumin (12.5 g) with furosemide was unsuccessful. Because of this treatment failure, the patient was treated with oral propranolol (3 mg/kg per day divided every 8 hours). After 4 weeks, the patient’s symptoms persisted, and we decided to initiate treatment with an mTOR inhibitor. Because sirolimus was not available in Japan at that time, we chose another mTOR inhibitor, everolimus, which is approved for immunosuppressive therapy. The treatment was approved by the review board at our hospital, and written informed consent was obtained from the patient’s parents. Everolimus was started at 2 mg (1.6 mg/m2 per day). Dose adjustments were made to maintain the desired drug trough level of 5 to 15 ng/mL according to the literature. At the start of everolimus treatment, the serum albumin level was 1.6 g/dL and the IgG level was 217 mg/dL. After 4 weeks, the patient’s diarrhea had almost resolved and his serum albumin level was gradually increasing. Six months after initiation of everolimus, 99mTc-HSA scintigraphy showed no leakage of albumin from the gastrointestinal tract (Fig 2B). Fecal α1-antitrypsin clearance was markedly decreased (177 mL/day). However, the objective endoscopic findings in the duodenum were unchanged. The patient’s severe hypoalbuminemia gradually improved and the administration of immunoglobulin and albumin became less frequent, although the serum albumin level did not normalize (Fig 3). The patient’s treatment continued without any adverse effects during 12 months of follow-up.
The successful use of mTOR inhibitors in the treatment of a small collection of vascular anomalies has recently been reported. mTOR is a serine/threonine kinase regulated by phosphoinositide-3-kinase. It acts as a master switch for numerous cellular processes, including cellular catabolism and anabolism, cell motility, angiogenesis, and cell growth. In our patient, significant expression of mTOR was found in the affected tissues. Based on this finding, we propose that the enhanced mTOR expression seen within abnormal tissues affected by lymphangiectasia may explain the efficacy and mechanism of mTOR inhibitors in treating PIL lesions and may predict the efficacy of mTOR inhibitor therapy.

The etiology of PIL currently remains unknown. Several genes, including vascular endothelial growth factor receptor 3, prospero-related homeobox-transcriptional factor, forkhead transcriptional factor, and SRY (sex determining region Y)-Box 18 (SOX18), are involved in the development of the lymphatic system. Vascular endothelial growth factor is a key regulator in lymphangiogenesis and angiogenesis, and it acts as both a potential upstream stimulator of the mTOR signaling pathway and a downstream effector. Hokari et al. reported inconsistently changes in the expression of lymphangiogenesis regulatory molecules in the duodenal mucosa of patients with PIL. The lymphangiogenesis pathway is assumed to be involved in PIL, in which ligand binding-induced signaling through vascular endothelial growth factor receptor 3 on the surface of the lymphatic endothelium results in activation of the phosphoinositide-3-kinase /Akt/ mTOR pathway. Therefore, mTOR inhibitors are predicted to be effective agents for PIL.

The mechanisms of enteric protein loss in intestinal lymphangiectasia for lymphatic malformation and generalized lymphatic anomalies were recently described. However, propranolol did not show a therapeutic effect on the condition of our patient. We have presented a case of PIL with PLE treated with everolimus. This agent resulted in marked improvement in the patient’s symptoms and examination findings.

FIGURE 1
A. Enteroscopy revealed white villi and chyle leakage in the intestinal mucosa. B. Histopathology of intestinal tissue before treatment showed marked dilatation of lymphatic ducts along a villus (arrow) and involving the mucosa (hematoxylin and eosin stain, ×400). C. D2-40 immunostaining was positive in the luminal endothelial cells. D. Elevated nuclear and cytoplasmic immunohistochemical expression of mTOR was found in the lymphatic endothelial cells. Anti-mTOR immunohistochemistry manifested brown positive signals. The reference image in the bottom-right corner revealed normal intestinal mucosa.

FIGURE 2
A. 99mTc-HSA scintigraphy before treatment showed leakage of albumin from the ascending colon to the transverse colon (arrows). B. 99mTc-HSA scintigraphy after 6 months of everolimus administration showed no leakage of albumin from the gastrointestinal tract.
are not well understood, although increased pressure in the lymph channels has been suggested as a possible cause.\(^\text{14}\) Lymphatic hypoplasia results in obstruction of lymph flow, which leads to increased pressure within the lymphatics. This, in turn, causes dilation of the lymphatic channels in the intestine and leads to rupture of the channels with resultant loss of lymph into the bowel lumen.\(^\text{15}\) Lymphangiography is a valuable tool for the detection of lymphatic leakage. Recently published reports indicate that lymphangiography plays a therapeutic role in patients with lymphatic leakage.\(^\text{16}\) In our case, although lymphangiography was not performed, scintigraphy and \(\alpha\)-1-antitrypsin clearance showed lymphatic leakage and obvious improvement with treatment. However, there were no changes in the enteroscopic findings after treatment. Everolimus might have effects on the function of the lymphatic canals, but no apparent effects on endoscopic findings.

Everolimus has been approved for use in Japan as an immunosuppressant for the prevention of cardiac and renal allograft rejection.\(^\text{17}\) Practical experience has revealed that everolimus has some benefits over sirolimus. Although both substances are fairly similar chemically, the serum half-life of everolimus is shorter than that of sirolimus (28 vs 62 hours, respectively). Everolimus is more controllable because it reaches steady state earlier than does sirolimus (4 vs 6 days, respectively).\(^\text{18}\) Additionally, everolimus is reportedly associated with a lower incidence of hyperlipidemia.\(^\text{19}\) Although serious side effects are rare, it is necessary to monitor for their occurrence with any mTOR inhibitor therapy.

**CONCLUSIONS**

To the best of our knowledge, this is the first report of everolimus use in a patient with PIL. The clinical response to mTOR inhibitors such as sirolimus and everolimus may be related to inhibition of lymphatic endothelial cell growth and improvement in lymphatic canal function. Prospective studies are needed to determine the best systemic therapies for PIL with PLE and the optimal duration of treatment.

**ACKNOWLEDGMENTS**

We thank Dr Chiemi Saigo of Gifu University, Dr Hideki Matsumoto of Gifu Prefectural General Medical Center, and Drs Emi Kadoi and Kunihiro Shinoda of Gifu Municipal Hospital for their helpful comments. We also thank MT Yasuo Katagiri and MT Atsushi Nakagawa of Gifu University for technical assistance and the Department of Pediatrics at Gifu University for their contributions.

**ABBREVIATIONS**

mTOR: mammalian target of rapamycin
PIL: primary intestinal lymphangiectasia
PLE: protein-losing enteropathy
\(^{99m}\text{Tc-has:}\) \(^{99m}\text{Tc human serum albumin}\)


4. Vignes S, Bellanger J. Primary intestinal lymphangiectasia (Waldmann’s disease). Orphanet J Rare Dis. 2008;3(5). Available at: www.ojrnd.com/content/3/1/5


Everolimus for Primary Intestinal Lymphangiectasia With Protein-Losing Enteropathy
Michio Ozeki, Tomohiro Hori, Kaori Kanda, Norio Kawamoto, Takashi Ibuka, Tatsuhiko Miyazaki and Toshiyuki Fukao
Pediatrics 2016;137; DOI: 10.1542/peds.2015-2562 originally published online February 16, 2016;

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/137/3/e20152562

References
This article cites 15 articles, 2 of which you can access for free at:
http://pediatrics.aappublications.org/content/137/3/e20152562.full#ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Gastroenterology
http://classic.pediatrics.aappublications.org/cgi/collection/gastroenterology_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
https://shop.aap.org/licensing-permissions/

Reprints
Information about ordering reprints can be found online:
http://classic.pediatrics.aappublications.org/content/reprints

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since . Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2016 by the American Academy of Pediatrics. All rights reserved. Print ISSN:
Everolimus for Primary Intestinal Lymphangiectasia With Protein-Losing Enteropathy
Michio Ozeki, Tomohiro Hori, Kaori Kanda, Norio Kawamoto, Takashi Ibuka, Tatsuhiko Miyazaki and Toshiyuki Fukao
Pediatrics 2016;137;
DOI: 10.1542/peds.2015-2562 originally published online February 16, 2016;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/137/3/e20152562