New Therapeutic Approaches for Patients with Fabry Disease

Key words: acroparesthesias, renal failure, enzyme replacement therapy, gene therapy

Fabry disease is an X-linked metabolic disorder caused by a deficiency of α-galactosidase A (α-gal A) (1). Lack of this lysosomal hydrolase results in the accumulation of the metabolic intermediates globotriaosylceramide and galabiosylceramide in a number of organs, including kidney, nervous system and heart. A majority of hemizygous male patients develop severe multisystemic disease (classic form), dominated by renal failure, progressive neurological and cardiac involvement and cerebrovascular complications (2). In this respect, Fabry disease resembles processes such as atherosclerosis rather than a classic storage disorder, with a reduced likelihood of functional reversal once the primary defect is reversed. In contrast, some asymptomatic male patients retain sufficient enzyme activity and long remain asymptomatic: their main manifestation is hypertrophic cardiomyopathy (cardiac variant). Early manifestations of classic form are periodic crises of pain in the extremities (acroparesthesias), angiokeratoma, hypohidrosis, and corneal and lenticular opacities. Indeed, the clinical manifestations of Fabry disease reflect the cellular sites of substrate storage and resultant organ dysfunction. So, various atypical forms of Fabry disease can exist (3). Recently, a new phenotype of Fabry disease with intermediate disease severity between the classical form and cardiac variant was reported (4). In addition, a new phenotype of Fabry disease was reported in this issue of the journal; a 25-year-old male patient manifested intermittent acroparesthesias and renal involvement but did not manifest angiokeratoma, hypohidrosis, corneal and lenticular opacities, and cardiac involvement (5). α-gal A activity in his white blood cells was markedly decreased.

Recent clinical trials have demonstrated that enzyme replacement therapy with α-gal A constitutes a major clinical advance in the treatment of patients with Fabry disease (6-9). This new therapeutic approach has been shown to be well tolerated and effective in reducing levels of the storage products globotriaosylceramide and galabiosylceramide and in normalizing many of the debilitating manifestations of the disease; the replacement therapy significantly reduced neuropathic pain, increased creatinine clearance, improved glomerular histology, and reduced the QRS interval on electocardiography. Renal function stabilized, even in patients with renal insufficiency at the onset of the treatment. Moreover, patients under the enzyme replacement therapy showed a normalization of sweating and improvements in their level of energy and sense of well-being. Although it is a short-term treatment, these findings show that enzyme replacement therapy offers promise as an effective management strategy for Fabry disease. Long-term studies are necessary to evaluate the full potential of enzyme replacement therapy. Now, the introduction of enzyme replacement therapy necessitates increased awareness of Fabry disease and knowledge of disease-related complications. As the authors in this issue indicated, early diagnosis of the disease and starting the enzyme replacement therapy will be very critical to prevent serious organ involvement such as renal failure, hypertrophic cardiomyopathy, or cerebrovascular complications in patients with Fabry disease.

Enzyme replacement therapy may be effective but may have limitations for long-term systemic, cost-effective correction or possible immunological consequences. As an alternative, gene therapy has been pursued for the amelioration of Fabry disease (10). Targets cells are readily accessible and relatively low levels of enzyme correction may be sufficient to reduce the levels of the storage products. So, Fabry disease is a compelling disease for gene therapy. Mouse models of Fabry disease have been generated to assist gene therapy for human Fabry disease (11). In vitro and in vivo studies using α-gal A transduced hematopoietic cells from Fabry mice have demonstrated enzymatic correction, leading to reduced storage products in a number of clinically relevant organs (10). This corrective enzymatic effect has been enhanced upon pre-selection of therapeutically transduced cells prior to the transplantation. In the near future, safe and effective gene therapy will be established for the patients with Fabry disease. We have tried to treat Fabry disease for a long time. And now, we are entering to the garden with effective therapy for Fabry disease by the narrow door.

References


See also p 983.

Takashi Igarashi, MD, PhD
Pediatrics, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655

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