

Growth Hormone in Cystinosis

By Dr. Craig B Langman

Cysteamine currently constitutes the primary treatment of cystinosis; it is used in order to reduce intracellular cystine levels to below 1-2 nmol ½ cystine/mg leucocyte protein. [1]. With this therapeutic end-point, a prolongation of native kidney function has been demonstrated in retrospective analyses of patient cohorts. [2] However, it remains uncertain that all manifestations cystinosis, which continue throughout life in this inborn error of metabolism, will be prevented with cysteamine therapy. [3] Further, the level of white blood cell cystine content that is optimal to achieve preservation of organ function in multiple body systems is uncertain as well, but levels lower than 2-2.5 nmol ½ cystine/mg protein seem to be protective. [3]

Loss of linear growth occurs, as does the kidney proximal tubule Fanconi syndrome, in almost all patients with infantile cystinosis. Initiating cysteamine treatment early, within in the first two years of life, rarely improves the Fanconi syndrome. [1]

Growth improves in cysteamine treated patients treated at this younger age, up to or above the 3rd percentile in many but not all. In general, the combination of adequate cystine depletion with cysteamine, adequate nutrition, and sufficient phosphate replacement to offset ongoing kidney losses allows for a normal growth rate, but seldom for catch-up growth. However, it is virtually impossible to improve the statural growth failure that is present in children first treated after 24 months of age with cysteamine alone to their genetic potential. For patients with remaining linear growth failure, recombinant human growth hormone (rhGH) is available.

Most patients with cystinosis have chronic kidney disease (CKD) and will eventually need a kidney transplant, and many will not have been diagnosed before two years of age. Thus, many patients with cystinosis will have linear growth failure that is unresponsive to cysteamine therapy alone. Kidney transplantation does not generally cure growth failure, although new protocols that spare or exclude corticosteroids may be of benefit in this regard. [4] Analyses from a single center have shown that there is acceleration of catch-up growth even five years after kidney transplantation with a corticosteroid- avoidance protocol. [5] This highlights the extent of growth deficit that occurs with CKD itself, even without the additional negative impact of cystinosis on linear growth. Additional reasons that children with CKD have linear growth failure include chronic metabolic acidosis, nutrient disturbances (poor nutrient and caloric intake), the bone disease unique to CKD (now termed CKD-Mineral Bone Disorder (CKD-MBD)), and a disorder of the growth hormone axis. At the level of the growth hormone axis, there are multiple abnormalities as noted in the following Table :

Table taken from a recent review [6].

Both in Europe and the United States, there is government approval for the use of recombinant human growth hormone (rhGH) in children with CKD of any cause, including cystinosis, who have growth impairment. Such approval is supported by contemporary evidence-based

medicine guidelines. [7] While initially it was felt that rhGH therapy should be restricted to patients older than 24 months of age, this view has been challenged both by more recent scientific data and by clinical experience. [8] Importantly, there is good evidence that there is no diminution of the adolescent growth spurt, during which final adult height is achieved, in children with CKD treated with rhGH sufficiently early, as rhGH is an effective agent in reducing or eliminating the defect in linear growth, especially if used prior to the need for maintenance dialysis. [6]

At present, rhGH therapy for linear growth deficits is not used in the early post-kidney transplant period for fear of possible rejection, or introduction of post-transplant lymphoproliferative disease. [9] In fact, in the United Kingdom, the National Institute for Clinical Excellence recommends, "In children with chronic renal insufficiency, treatment [with growth hormone] should be stopped and not restarted for at least a year." Clinical experience has included careful and highly individualized approaches to kidney transplant patients with growth failure in the pediatric age range after the first year of kidney transplantation. Accordingly, rhGH therapy does have a role in the treatment of post-transplant growth failure, but must be assessed on a patient-by-patient basis.

Once final height is achieved, rhGH therapy cannot increase height further. However, one may ask whether there are any other possible uses for rhGH in the adult patient with cystinosis. At present, there are no randomized prospective studies published to address this specific question, but there are some preliminary studies in humans to address possible benefits and risks of rhGH in adults with CKD or on maintenance dialysis.

Cardiovascular disease is the leading cause of death in patients with CKD, on dialysis, and with a functioning kidney transplant. The pathogenesis of the heart disease is multi-factorial, but includes systemic inflammation, endothelial dysfunction, lipid abnormalities, and CKD-MBD, and others. [10] Human experimental treatment with rhGH in adults with CKD or those on maintenance dialysis have indicated that there are beneficial effects on microcapillary blood flow, reductions in LDL-cholesterol, and other factors that might ameliorate the heart disease. [11] However, all studies to date are short-term, and it remains unknown if long-term therapy that would be required in patients with CKD or on maintenance dialysis would be sustained with rhGH treatment. Importantly, corticosteroid-sparing regimens in kidney transplantation may help reduce the burden of long-term cardiovascular morbidity and mortality by counteracting, in part, the occurrence of hypertension, diabetes, lipid disorders, and obesity that is prevalent in this population.

When corticosteroids are used, rhGH therapy may counteract some of the long-term negative effects of that therapy on body composition, as seen in Table 2 below. The use of rhGH is largely untested and its results, unknown in adult patients with CKD, on maintenance dialysis, or with a kidney transplant.

Table 2. Metabolic effects of long-term GCs vs. GH/IGF-1

From [12].

Despite the lack of data on patients with cystinosis, there is some information on the use of rhGH in growth hormone deficient adult patients, adults with Prader-Willi syndrome, patients with HIV, and elderly patients with muscle weakness or aging-related symptoms. GH replacement in such adult patients appears to improve the impaired cardiac function, exercise performance, muscle strength and exercise capacity. The side effects of rhGH in adults are mostly dose-related; despite a proportionally smaller dose used in adults compared to children, adult patients complain more about edema, arthralgias, joint swelling, myalgias and carpal tunnel syndrome. There are also at least theoretical concerns for a potential diabetogenic effect of rGH as well as possible increased risk of cancer. [13]

Conclusion: For the treatment of linear growth failure in patients with cystinosis and CKD, rhGH has been shown to increase height. It is best used earlier in the course of CKD and cystinosis than at the time of maintenance dialysis in this population, but even in patients receiving dialysis, there has been improved linear growth. Its use in the growth-stunted patient with growth potential after kidney transplantation should be limited to use > one year after transplantation, and only after consultation with subspecialists with direct clinical experience in treating this issue.

In distinction to its use in pediatrics, there is no general consensus for the use of rhGH after cessation of linear growth in adults with cystinosis and varying degrees of CKD, including after kidney transplantation. We would encourage investigators to conduct clinical trials that would address the needs of adult patients with cystinosis who may benefit from the judicious use of rhGH.

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