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INVITED COMMENTARY

Corticosteroid minimization after renal transplantation*

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Renal transplantation, as well as any other solid organ transplantation, is a real challenge in children. The achievement of a long-term survival with normal or near normal quality of life is the main attended goal. Chronic immunosuppression is, however, still mandatory and current protocols continue to include corticosteroid (Cs). Nevertheless, from a theoretical viewpoint, low-dose Cs or Cs-free immunosuppression could reduce or even avoid all kind of side effects, principally in infants and children [1].

Corticosteroid use can be associated with multiple side effects, including stretch marks, hypertrichosis, Cushingoid facies (''moon face''), obesity, seizures, pseudotumor cerebri, high blood pressure, increased susceptibility to infection, thromboembolism, pancreatitis, osteochondritis, avascular necrosis, osteoporosis, various degrees of adrenal insufficiency and growth disturbances [2].

The adverse effects of Cs depend on the type of formulation; time, dose, duration, route and regimen of administration; patient age and gender; underlying diseases; co-administration with other drugs that may interfere with their activities; and individual sensitivities. A certain dose of a certain Cs will produce different adverse effect profiles when administered to different individuals, probably due to differences in pharmacokinetics, different serum levels of proteins that bind and transport Cs and individual changes in clearance. This variable must be included when investigating any kind of Cs-reduction regimen.

Normal growth is probably the most important end point after paediatric renal transplantation. The chronic use of Cs certainly interferes with an enhanced growth in stature and any safe strategy to avoid this side effect should be evaluated. However, it should be noted that Cs-induced changes in growth and bone mineralization are fully reversible after treatment discontinuation [3], as long as patients are provided favourable conditions for mineralization to occur (i.e. conditions not always present in and ESRF patient). Discontinuation of Cs therapy is followed by a period of compensatory growth, which is at least partially due to an intrinsic mechanism at the epiphyseal plate. Compensatory growth occurs because decreased cell proliferation during Cs treatment preserves the proliferative capacity of chondrocytes, slowing maturation of the epiphyseal plate. After completion of treatment, the epiphyseal plate has not ''aged'' as far as it normally would; consequently, the growth rate may be increased. Duration of the growth period may extend beyond expected for age, a phenomenon known as catch-up growth.

Corticosteroid inhibits calcium resorption at the renal tubule and calcium absorption in the bowel through a vitamin D-independent mechanism, decreasing transcellular active calcium transport and normal calcium uptake by brush-border membrane vesicles, and decreases synthesis of calcium-binding proteins as well [4]. Cs therapy induces a redistribution of spontaneous PTH secretory dynamics by reducing the amount of PTH released in a tonic fashion and increasing the amount released as pulses. This change could have primary or secondary effects on bone metabolism in patients undergoing Cs treatment [5]. Cs inhibits

replication of osteoblast-lineage cells, decreases production of pre-osteoblasts and osteoblasts and induces apoptosis of mature osteoblasts and osteocytes. Furthermore, Cs hinders stromal cell differentiation into the osteoblast lineage and reduces the rate of terminal osteoblast differentiation, thus reducing mature osteoblast counts.

Corticosteroid also induces commitment of stromal cells to the adipocyte lineage, promoting adipogenesis at the expense of osteoblastogenesis. During Cs therapy, there is minimal nitrogen and no phosphorus retention; consequently, Cs-treated patients may develop a classic form of myopathy, which most commonly causes muscle weakness from the pelvic girdle to the distal muscles. This severe complication can lead to falls and contribute to the occurrence of fractures. Myopathy and muscle weakness may also play a role in bone loss by reducing physical activity, which encourages bone mass formation through muscle contractions [6].

Klare *et al.* [7] nicely described a normal and/or near normal adult stature among kidney transplant children who received a Cs course of just few months following surgery. This positive result was even much more evident in young children before their adolescence. This strategy was considered to be safe despite the absence of a control group receiving Cs or not receiving Cs at all. Even better results may be expected if a Cs avoidance regimen could be applied. As a majority of centres, patients included in these analysis were considered ''low risk'' patients, and unfortunately observations should be restricted to this selected category. Low-risk patients are normally patients with expected excellent long-term graft function. It is well documented that normal or near normal GFR is strongly related to normal growth. Excluding ''high risk'' patients with history of numerous rejections (i.e. theoretically lower GFR) is, in fact, a major bias, which should be at least discussed. Whether patients included in this study were recipients of living (LD) or cadaver donors was not detailed. Probably, LD recipients should be the best candidates for this Cs withdrawal policy.

As in the adult transplant population, the risk of acute rejection and chronic graft dysfunction should be considered before any decision on immunosuppression modulation (i.e. reduction). Current worldwide strategies strongly emphasize the importance of minimizing immunosuppression for a better long-term quality of life. Among these changes, Cs withdrawal or Cs avoidance is within the first line. Unfortunately, almost all trials are not capable of concluding whether these strategies are superior to conservative protocols because primary end points are mostly limited to acute rejection; current induction protocols can prevent acute rejection in almost 90% of patients, with or without the use of Cs. In addition, patients with impaired GFR and/or at increased risk of graft loss are generally excluded, impeding generalization of conclusions to other categories of recipients. Indeed, an important piece of information still lacking concerns graft fibrosis as well as anti-HLA antibody occurrence in Cs-free patients. These end points need to be prospectively evaluated in future minimization protocols.

If Cs should be given and withdrawal not recommended, the changes in growth and bone mineralization may be prevented with an adequate diet and calcium and vitamin D supplementation, physical exercise (enough to ensure normal mobility) and therapy directed at preserving the normal progression of puberty and maintaining the integrity of the GH-IGF-1 axis. One priority in caring for these patients should be the implementation of measures to speed up improvement of bone mineral density and prevent additional bone loss. Therefore, these risks must be continuously assessed and detected in all patients receiving long-term Cs therapy by means of clinical monitoring, assessment of dietary habits and physical activity, and serial DXA scanning [3,8,9].

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