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Editorial

Steroids in Pediatric Kidney Transplantation: A Balancing Act in Progress

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Interest in minimizing corticosteroid exposure is widespread given the potential associated morbidity. This morbidity may be greater in children where the hope for a lifetime of transplant benefit has been historically linked to the risks of long-term corticosteroids. Corticosteroids also compromise growth, a unique concern in children. Contrasting the potential benefit of less steroid exposure is the potential risk for increased rates of rejection and graft loss. Balancing all risks and benefits is critical.

In January 2001, the CCPT Study Group initiated a multicenter randomized double-blind placebo controlled study of steroid withdrawal at 6 months after transplantation. Positing more intensive immunosuppression would decrease early rejection and permit subsequent steroid withdrawal, the protocol combined Basiliximab induction, with cyclosporine or tacrolimus, sirolimus and steroids. At 6 months, rejection free subjects and those without another event resulting in discontinuation underwent a protocol biopsy. Subjects free from histologic evidence of rejection were randomized to a 6 month tapered steroid withdrawal or continued steroid maintenance. The trial was terminated in August 2004 due to 6.9% of subjects enrolled developing PTLD (1). The treatment assignments were unblinded, and a follow-up assessment initiated.

In this issue of *AJT*, Benfield et al. report the outcomes of the study (2). At termination, 274 of the anticipated 600 subjects were enrolled. Of the 132 that were randomized, 73 were assigned to withdrawal and 59 to maintenance. This represents the first peer reviewed controlled trial of steroid withdrawal in pediatric recipients. Despite enthusiasm for this report, one must recognize the challenges interpreting outcomes from studies having such a significant prerandomization selection, as well as any study terminated early. More limited enrollment compromises statistical power, impacting the potential for subgroup analysis and conclusions, especially for infrequent events. Both statistical and methodological errors may be introduced. Randomization may not have achieved appropriate balance for all important risk factors. Despite an overall 1:1 randomization design, there is a substantial imbalance in the arms due to block randomization. While the groups appear relatively comparable, the smaller sample size compromises the power of randomization. Additionally, unblinding introduces potential for subsequent reporting bias, particularly for subjective data.

Regarding the primary endpoint, withdrawal subjects had a greater standardized height velocity. The improvement observed was modest; at 18 months there was no difference in height z-score. There is baseline data on only 59 of 73 withdrawal subjects and 51 of 59 maintenance subjects. At 18 months, there was data on 35 and 28, respectively. This relatively low rate of reporting raises the potential for unknown, and potentially non-random, selection bias. It is interesting that the median age of withdrawal group (11.9 years) was lower than the maintenance group (13.5 years). Although age was a covariate in this analysis, it is unclear how pubertal status was accounted for. Given prepurbertal status is associated with better catch up growth, this difference may contribute to the observation. Conversely, the benefit of withdrawal may be less than expected given the withdrawal group was not steroid free until 12 months posttransplant. The impact may also have been attenuated by the relatively low steroid dose in the maintenance arm. Will this trend in height velocity continue and translate into clinically significant difference? Height data is only presented from 6 to 18 months while the study appears structured to provide 36 months of follow-up for other endpoints.

In evaluating other potential benefits of withdrawal, there was a lower Cushingoid assessment score, suggesting investigators could detect changes attributable to steroids. If some scoring was completed after unblinding, there is potential for bias. With respect to more objective data, there were no differences in lipid profiles or hypertension, potentially reflecting a Type II error, a lower risk associated with the dose of maintenance steroids, or attenuation of the benefit of withdrawal by 6 months of steroids treatment.

Regardless of the certainty or magnitude in this trial, there is enough evidence to believe that avoidance of steroids is associated with benefits. It is the potential balance of risk that causes concern. The authors report no differences in rejection rates or graft function. At 3 years, allograft survival was greater in the withdrawal group compared to the maintenance group (98.6% vs. 84.5%, respectively). Of note there were more deaths in the maintenance group, with four of the five plausibly linked to over immunosuppression associated with the protocol. Again, the results need to be interpreted with caution. The temptation to believe withdrawal is directly responsible for the increased graft survival, or conversely steroid therapy is worse, should be resisted. A reasonable interpretation might be that steroid withdrawal, in the setting of this specific protocol, was not associated with a large increase in risk of rejection or graft failure, acknowledging this trial was not structured to demonstrate noninferiority and the follow-up is 3 years.

Excellent results have been demonstrated in single center reports (3). Two additional multicenter randomized trials evaluating early steroid withdrawal and avoidance have recently completed (4,5) and hopefully will provide additional insight. Long-term follow up from all studies is essential.

This study represents a monumental undertaking started nearly a decade ago. Such large scale studies are vital if we are to improve care. The results must be viewed in context of the protocol utilized, which the authors clearly do not recommend. The study provides rationale to continue trials seeking to minimize steroid exposure, and frames many issues of study design in this challenging population. To achieve the right balance we must accurately determine the magnitude of all the risks and benefits, in both the short and long term.

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