Corticosteroids and Kidney Transplantation

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The Karolinska Institute awarded Dr. Philip Hench a Nobel Prize in the 1950s for treating a patient who had rheumatoid arthritis with corticosteroids. In the 1950s, physicians saw corticosteroids as “miracle drugs” that offered dramatic relief for a diverse group of diseases. Physicians saw extraordinary benefits, such as rheumatoid arthritis patients’ throwing away their crutches or resolution of anaphylactic reactions. The medical community was delighted. The euphoria resulted in the uncritical use of these new agents. However, before long, the medical profession saw the downside of corticosteroid therapy with its diverse chronic toxicities. This two-edged sword has had an impact on solid-organ transplantation from its start in the 1960s until the present day.

In the early 1960s, Goodwin and Mims (1) reported that they had used corticosteroids to reverse acute rejection in a living-donor kidney transplant recipient. Starzl and Marchioro (2), in 1963, confirmed the efficacy with corticosteroids and the “almost miracle” effect. On the basis of a limited experience with living-donor transplantation, he suggested that a 100-mg/d dose as prophylaxis against early postoperative acute rejection was superior to treatment with 30 mg/d. One patient on the higher dosage did not have an acute rejection, whereas two on the lower schedule did. Today, these numbers are incredibly small, but we must remember that kidney transplant patients in the early 1960s were too few for any statistical analysis. To his credit, Starzl included a contemporaneous control group (n = 2) for comparison. Such a design often is absent even in current studies. Perhaps more remarkable for 1963, Starzl expressed concerns that the suppression of the first rejection episode might not be the best approach for eventual adaptation of the allograft to the host. This idea still is proposed today by some as a reason to favor protocols that withdraw corticosteroids soon after transplantation rather than months later.

In the United States, physicians quickly adopted the routine use of corticosteroids as standard therapy for all kidney transplantation. We have lived uncomfortably with this two-edged sword ever since. The anti-inflammatory effects were observed easily as fever that was associated with acute rejection quickly vanished after a single dose. It was not until years later that we learned that the mechanisms of action of corticosteroids reached beyond anti-inflammation to the immune system (3). Like many accomplishments in medicine, clinicians first published observational studies. Later, the apparent mechanisms were uncovered.

Despite the observation that corticosteroids worked and a mechanism for their function had been developed, some in the transplant community have questioned their use. As early as 1975, my group suggested a dose reduction to an alternate-day schedule (4). In Ireland, McGeown et al. (5) had excellent results for kidney transplantation using very low dosages of prednisone. Numerous abstracts and papers in the 1980s concerning alternate-day steroids would lead one to believe that it was common practice in the transplant community. It was not. Only the pediatric transplant community (where the benefits for growth were obvious immediately) seemed to adopt this approach to diminish exposure to corticosteroids (6). In the late 1990s, however, some prominent transplant centers again raised the question (7,8). This time the publications had more effect. The current report of the Scientific Registry of Transplant Recipients states that 22% of all renal transplant patients now (2005) are discharged without corticosteroids (9). This figure is nearly fourfold greater than the 6% frequency in 2001.

Why have the current reports had more impact than those 20 to 30 yr ago? The more recent reports from highly respected centers tend to include many more patients, and the rates for graft and patient survival are outstanding, with very low frequencies of acute rejection. Many studies have been sponsored by industry—with the positive and negative effects. Industry provides the finances and analytic tools to academic centers to improve the quality of the clinical trial. However, to the skeptic, such studies carry an industry bias to prove their “new drug” is “so good” that corticosteroids are unnecessary. It is possible that corticosteroids are as necessary or unnecessary as they were before the new drugs were introduced. It is only implied (not tested) that the “new agent” renders withdrawal possible. Industry-sponsored trials always must be analyzed with this bias in mind. Finally, the downside of corticosteroid therapy in adults was not as immediately obvious or as dramatic as it was in children. Now, transplant physicians who deal with long-term survival of adult transplant patients face adverse effects that are just as detrimental but simply require more time to manifest. As such, they see the risk/benefit ratio more as the pediatric transplant groups viewed it in the 1980s.

Gallon et al. presented such a single center comparison study in this issue of the CJASN. This study has the positive attribute of no industry sponsorship. It also included many patients with excellent results and lengthy follow-up. However, as the authors note, it has historical controls (sequential cohorts rather than contemporaneous) and is retrospective and not randomized. However, its strong conclusion that “the use of chronic
prednisone to maintain long-term kidney function and prevent acute cellular rejection is not justified” needs some caveats.

Many of the recent reports on this subject avoided randomized control subjects in favor of historical controls. Several blinded, randomized trials that included immunosuppression with cyclosporine (10) or tacrolimus (11) reported acute rejection after prednisone withdrawal. Indeed, the National Institutes of Health–sponsored study was halted by its safety committee because of the increased rate of rejection (12); the frequency was most increased among black patients but also was seen for all other groups of patients. Meta-analysis of controlled trials by different investigators published in 1993 (13), 2000 (14), and 2004 (15) all have noted statistically significant greater risk for acute rejection for patients who were withdrawn from corticosteroids. Some dismissed these findings because the withdrawal was “late” in many but not all studies.

Another caveat for the historical controls in the study by Gallon et al. is the significantly fewer living-related donors and older age of the donors in patients who received steroids; however, these recipients did as well as those in the lower risk group. Despite the authors’ conclusion that chronic prednisone is not justified, corticosteroid therapy was restarted eventually for 15% of the patients.

Despite these caveats, the findings of the study are impressive. Even if a contemporaneous, randomized, control group had been included in the study and that control group had better results than the rapid withdrawal group, it would still be difficult to justify corticosteroids for most patients because of the benefits of corticosteroid-free therapy. Therefore, physicians who deal with adult transplant patients may be catching up with the pediatricians who had a clearer vision of the risk/benefit ratio of chronic corticosteroid therapy.

In evaluating the current literature, it is puzzling and disappointing that there is a return the use of historical controls rather than the more rigorous approach with randomized control groups such as in the National Institutes of Health trial. Industry sponsorship of such studies must be viewed with a critical eye. Is there a hidden (and untested) commercial in the study? Some industry such as in the National Institutes of Health trial. Industry sponsorship was halted by its safety committee because of the increased rate of rejection (12); the frequency was most increased among black patients but also was seen for all other groups of patients. Meta-analysis of controlled trials by different investigators published in 1993 (13), 2000 (14), and 2004 (15) all have noted statistically significant greater risk for acute rejection for patients who were withdrawn from corticosteroids. Some dismissed these findings because the withdrawal was “late” in many but not all studies.

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References