Induction Therapy: Are We Picking Our Battles?

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Over the past 10 years the number of patients receiving induction therapy before transplantation has increased dramatically. United Network for Organ Sharing data indicate that while 8.6% of kidney transplants recipients received an induction agent in 1992, the percentage had increased to 59.7% by 2001 and continues to rise (1). The most popular induction agents currently being used are antithymocyte globulin, anti-IL-2 receptor antibodies, and most recently the anti-CD52 antibody, alemtuzumab, also known as Campath-1H.

While induction therapy has become more popular, several questions regarding the efficacy of different agents as well as the long-term consequences of induction therapy remain to be answered. The popularity of induction therapy has stemmed from its ability to tame the initial immune response, reducing the chances of acute rejection while lowering maintenance immunosuppression. The downside to induction therapy has been the increased potential for malignancies and infections, which is harder to quantify but still needs to be considered a very serious risk. Both recipient and donor populations have continued to change over recent years, with an increasing trend to transplant older patients who have more co-morbidities. In addition, the number of previously transplanted, sensitized patients who have returned to the waiting list has increased. At the same time, more and more organs from older and less ideal donors are being utilized for transplantation (2,3). Given the increasing heterogeneity of both recipients and donors, there is an increasing need to be more selective as to timing and type of induction therapy is used.

The pros and cons of induction therapy need to be balanced. Use of induction therapy decreases acute rejection episodes and improves short-term allograft survival (4). Steroid-free therapy or early withdrawal of steroids can be achieved with the protection of induction agents. Induction therapy permits the withholding of calcineurin inhibitors in the immediate posttransplant period, allowing the allograft to recover from delayed graft function while avoiding the potentially additive insult of vasoconstriction induced by these agents (5). This may be of particular importance when less than optimal organs are being transplanted (expanded criteria donor grafts or organs from non–heart-beating donors). In addition, use of some forms of induction therapy may be protective against delayed graft function itself (6). Sensitized and other high-risk patients appear to fare better in terms of acute rejection episodes and graft survival with induction therapy.

Despite these potential benefits, the risk of over-immunosuppression is a serious issue when utilizing induction therapy. The increased use of induction therapy coincides with an increase in the rate of development of BK nephropathy in kidney transplant recipients. Studies differ as to the importance of individual induction agents in the development of BK nephropathy, but there is a clear consensus that the degree of immunosuppression correlates with the incidence of reactivation of the BK virus (7). Equally serious, there has been a concern that use of induction therapy may result in higher rates of other infections as well as increased incidence of malignancies in the long term; these correlations, however, have also proved difficult to pin down. In addition, some studies indicate that there may be an associated, increased humoral response against the allograft associated with induction agents (8).

Two interesting articles in this issue of CJASN address questions regarding mechanisms and the balance of side effects and safety when using induction therapy. Lorenzo Gallon and co-workers from Northwestern University and Bergamo, Italy, analyzed cellular infiltrates after Alemtuzumab (Campath-1H) treatment. Campath-1H, initially popularized as a therapy close to inducing tolerance (propro tolerance), has gained popularity at some transplant centers (9). The authors characterized cellular infiltrates in 12 randomly chosen biopsies with typical features of acute rejection. Cellular infiltrates were dominated by macrophages and T cells of a memory phenotype despite peripheral T cell depletion. The time from transplantation to the occurrence of acute rejection ranged greatly from 7 to 225 days. Thus, it is possible that memory T cells dominated the cellular infiltrate due to insufficient depletion. However, it is also possible that the memory cells are present not because of resistance to depletion but because of homeostatic proliferation and repopulation that may occur when using T cell–depleting agents as induction therapy. This information might have a practical application in recipients with an increased ratio of memory T cells (e.g., older recipients).

In general, monoclonal IL-2R antibodies are associated with a limited potency as well as a reduced risk profile when compared with the polyclonal antithymocyte agents. However, there is at this point in time no clear clinical evidence to prefer one agent over the other. Piero Ruggenenti and co-workers from Bergamo, Italy, introduce a novel approach to balance...
safety and side effects when using induction agents. They present clinical data comparing the effects of an IL-2R Ab (Basiliximab) with low-dose rabbit antithymocyte globulin (RATG) (Thymoglobulin) to a standard-dose RATG treatment. While this study included patients with differing risk profiles (living related, sensitized, retransplanted, and those with delayed graft function), the authors observed reduced side effects with a comparable outcome (patient and graft survival, acute rejections) in addition to cost savings when using the IL-2R Ab and low-dose RATG combination.

With an increased armamentarium of immunosuppressants, including induction agents, and a better understanding of their effects and efficacy, we will have the opportunity to better tailor immunosuppression to the particular patient population or even to the organ being transplanted.

References