Induction treatment in renal transplantation

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Induction immunosuppression in renal transplant means the administration of large doses of immunosuppressive agents immediately before and/or after transplantation. Although conceptually total body irradiation, high doses of corticosteroids and even plasmapheresis carried out at the time of transplantation characterize induction treatments in renal transplantation, the term is more often employed to indicate the use of immunosuppressive biological agents, represented by monoclonal or polyclonal antibodies, in transplants considered of greater immunological risk.

Among biological immunosuppressants used as induction treatment in high immunological risk kidney transplant, antithymocyte globulin or thymoglubulin produced from the immunization of rabbits with human thymocytes (rATG), have been the agents of choice currently used by most centers, due to their favorable safety profile and efficacy.[1] rATG is a polyclonal antibody preparation with a high number of antigen specificities, including T and B surface lymphocyte antigens, NK cells, plasma cells, molecules associated with cell adhesion and chemokine receptors. These characteristics establish a broad spectrum of biological effects, many of which are secondary to mechanisms of action not yet fully understood.[2] The main biological effect observed after rATG administration is a rapid, intense and prolonged depletion of T lymphocytes from the peripheral blood.[3] T-cell depletion magnitude and duration are used to monitor rATG administration and dosing. Other biological effects include T-cell proliferative response modulation, reduced lymphocyte chemotaxis, interference with dendritic cell maturation, favoring the generation of a phenotype that facilitates immune tolerance and induction of regulator-T cell.[4,5]

Although rATG is considered a safe immunosuppressive agent, acute adverse reactions, such as acute cytokine release syndrome, and even severe and life-threatening ones, such as anaphylactic reactions, are described[6] and occur in less than 1% of the cases. rATG-induced serum sickness, characterized by fever and polyarthralgia, happens to about 7 to 27% of the cases, typically after the first week of rATG administration.[7] The mechanisms involved in these adverse reactions are not completely understood but may be related to the fact that rATG consists of a set of heterologous proteins (of rabbits) and also that a small fraction of antibodies found in the preparation has the ability to trigger cell proliferation, with consequent release of inflammatory mediators.[4] There are also increases in infections[8] and neoplasia.[9]

The selection of patients for rATG induction therapy is based on the stratification of risk for immune rejection. The number of HLA mismatches, the percentage of reactivity in the panel, the presence of specific donor anti-HLA antibodies and the prolonged time of cold ischemia, are all considered more frequently in this stratification. The definitions and the relative importance assigned to each of these risk factors by transplant centers have been variable, which is determining given the considerable non-uniformity still

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existing in relation to the rATG induction treatment indication or other biological immunosuppressants to treatment doses and durations, among recipients of kidney transplants.[10]

The study presented by Ribeiro Castro *et al.*[11] in this issue of JBN brings significant contributions on various aspects concerning the use of rATG, still considered widely controversial. Through a careful and comprehensive systematic review of the medical literature, they clearly point out the current state of the art regarding the use of rATG, not only as induction treatment, but also as a treatment for acute rejection in renal transplant recipients. Indicating, for instance, that the appropriate dose range is between 1 to 1.5 mg per kg per day, given in 4 to 6 days (total doses of 4 to 8 mg/kg) for most clinical situations; It clarifies that although not often used, infusion into a peripheral vein is a viable alternative to administration by central venous access, and the most appropriate time of rATG administration is prior to graft reperfusion. The authors also suggest that the best way to monitor the scheduled dose administration is through lymphocyte counts in the peripheral blood. rATG administration should be suspended when the number of lymphocytes is less than 100/mm3. The review also indicated that rATG reduces graft rejection incidence both compared to anti-IL-2R antibodies and in control groups.

The study results presented here are also surprising because they point out the relative lack of randomized trials, properly designed to answer several remaining questions in this field. In the 30-year period covered by the review, only a relatively small number of 26 studies evaluating the use of rATG in renal transplant recipients were randomized and were, therefore, eligible for inclusion in the analysis in question. This resulted in the fact that some recommendations received little support from studies, therefore having a low level of scientific evidence.

Although there is no consensus on the best induction treatment in renal transplantation, a large number of studies indicate that induction used as a biological treatment associated with conventional maintenance immunosuppression is superior to maintenance immunosuppression alone in recipients of renal transplantation with a high immunologic risk.[12] rATG has been the biological agent of choice for induction therapy in renal transplantation.

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