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Clinical and Applied Immunology Reviews 5 (2005) 373–395

Clinical and Applied Immunology Reviews

Review

Desensitization protocols improving access and outcome in transplantation

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Received 1 August 2005; received in revised form 27 September 2005; accepted 13 October 2005.

Abstract

Sensitization to antigens of the HLA and ABO system has been the biggest barrier to access in renal transplantation and, increasingly, in transplantation of other organs. Additionally, antibody to donor antigens has been shown to result in injury to the graft ranging from catastrophic, irreversible hyperacute rejection to the slower, more insidious, chronic form of rejection. The problem of access has been recognized globally and has been the incentive for measures to overcome the disadvantage experienced by the sensitized patient. However, early attempts to reduce sensitization achieved only transient success. Newer immunosuppressive agents that affect B-cell function or viability have permitted the development of treatment protocols to eliminate and, potentially, downregulate donor-specific antibodies. The use of these protocols has achieved successful transplants that were HLA and/or ABO incompatible prior to treatment and, as such, has provided some patients with their only opportunity for transplantation.

Keywords: ABO incompatible transplantation; Desensitization; Double filtration plasmapheresis; HLA-specific antibody; Intravenous immunoglobulin (IVIg); Plasmapheresis; Sensitization; Transplantation

Abbreviations: ABO-DSA, antibody to donor ABO antigens; ABOi, ABO incompatible; AHG-CDC, antiglobulin enhanced complement-dependent cytotoxicity; AMR, antibody-mediated rejection; CDC, complement-dependent cytotoxicity; CMVIg, hyperimmune anti-CMV IVIg; CyA, cyclosporin; DFPP, double filtration plasmapheresis; DSA, donor-specific antibody; DSG, deoxyspergualin; HLA-DSA, antibody to donor HLA antigen(s); IVIg, intravenously administered, pooled human IgG; MMF, mycophenylate mofetil; OPTN, Organ Procurement and Transplantation Network; PP, plasmapheresis or plasma exchange; PRA, panel reactive antibody; RAPA, rapamycin; TAC, tacrolimus; XM, crossmatch.

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doi: 10.1016/j.cair.2005.10.002

1. Introduction

The single largest barrier to access to and outcome of a renal transplant is sensitization to donor antigens of the ABO and/or HLA systems. Sensitization to antigens of these 2 systems differs in important ways. Most individuals have antibodies to nonself ABO antigens that are proposed to result from exposure to environmental substances that cross-react with those antigens. In contrast, primary sensitization to HLA antigens occurs only after contact with HLA antigens as a result of transfusion, pregnancy, or transplantation. However, the identification of epitopes on microbial cell walls that are similar to those on some HLA antigens suggests that exposure of an HLA-sensitized individual to these microorganisms may provoke an anamnestic response or a broadening of the sensitization. Antibodies to the A and B blood group antigens are usually persistent throughout a person's lifetime while HLA-specific antibodies, particularly those provoked by transfusion or pregnancy, may weaken or disappear over time. Sensitization to antigens of the ABO system renders patients incompatible with a limited portion of the population which is maximum in blood type O patients. However, the multiple, antigen-encoding loci of the HLA system, the high polymorphism of the HLA loci, and the presence of multiple antigenic epitopes on individual molecules, many of which may be shared among different HLA antigens [1,2], can result in sensitization to all but HLA identical or very closely matched donors.

Several different protocols have been used in attempts to reduce or eliminate antibodies to ABO or HLA antigens. These can be grouped into 3 categories: (1) those that remove antibody through plasma exchange or immunoadsorption (IA); (2) those that block or downregulate antibody with intravenously administered, pooled human immunoglobulin (IVIg); and (3) those that use a combination of plasmapheresis (PP) and IVIg. These protocols differ in their efficacy, applicability, and cost. Comparisons of the efficacy of different protocols are difficult because of differences in the measurement of strength and specificity of donor-specific antibody (DSA), the immunologic risks of the patients, the number and types of PP applied, the dosage and specific product of IVIg, the immunosuppression regimen followed, additional types of treatment that may have been used, and the assessment of outcome. When treatment is applied prior to transplantation for patients who do not have a live donor, efficacy is measured as a reduction in the breadth of HLA-specific antibody often gauged by the percent panel reactive antibody (PRA), which is the percent of a panel of phenotypes with which a patient's serum reacts. Efficacy is measured as reduction in the titer of antibody to a specific donor in the case of preemptive treatment of patients with a positive crossmatch (XM) to a live donor or rescue treatment during an episode of antibody-mediated rejection (AMR). Despite these confounding factors, there is a degree of consistency of efficacy within each protocol category. These protocols have been used to increase access to transplantation by applying them to patients awaiting transplantation with the goal of reducing the breadth or strength of antibody. They have also been used to rescue kidneys in patients experiencing AMR, thus improving graft outcome. With growing appreciation of the detrimental effects of HLA-DSA on transplants of organs other than the kidney, these protocols are being used, increasingly, to improve transplantation of these other organs.

The mechanism(s) of action of these different treatment protocols may be substantially different. However, as in all areas of biology, it is likely that there are multiple mechanisms