First case report of using Ofatumumab in kidney transplantation AB0 incompatible

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ABSTRACT

Gli attuali protocolli di desensibilizzazione in campo di trapianti renali AB0 incompatibili combinano l'utilizzo della plasmaferesi con il Rituximab, anticorpo chimerico (umano e murino) anti-CD20. Nel 10% dei casi sono riportate reazioni da infusione alla somministrazione di Rituximab. Tali effetti avversi compromettono la riuscita del protocollo di desensibilizzazione, per cui è fondamentale valutare trattamenti alternativi per la deplezione linfocitaria B. Riportiamo il caso clinico di un uomo di 41 anni che, in seguito a reazione avversa a Rituximab, è stato sottoposto a protocollo di desensibilizzazione alternativo con Ofatumumab.

Ofatumumab essendo un anticorpo anti-CD20 completamente umanizzato sembrerebbe non indurre reazioni immunogeniche. Il paziente ha tollerato il farmaco senza effetti collaterali e con una buona efficacia clinica.

La nostra esperienza suggerisce come l'Ofatumumab possa rappresentare un valido agente alternativo di deplezione linfocitaria B nel protocollo di desensibilizzazione del trapianto AB0 incompatibile.

PAROLE CHIAVE: Ofatumumab, trapianto renale, AB0 incompatibile

ABSTRACT

Modern methods for desensitization protocol rely heavily on combined apheresis therapy and Rituximab, a chimeric (murine and human) anti-CD20 antibody used in AB0 incompatible kidney transplants. Severe infusion related reactions due to the administration of Rituximab are reported in 10% of patients. These adverse reactions may hinder the completion of the desensitization protocol. Therefore, it's useful to test alternative B cell depleting therapies. Our clinical case focuses on a 41-year-old male who developed an adverse infusion reaction following the administration of Rituximab and was given Ofatumumab as an alternative treatment. Ofatumumab is a fully humanized monoclonal anti-CD20 antibody. As a fully humanized antibody, Ofatumumab may avoid immunogenic reactions. The patient tolerated the administration of the drug showing no signs of adverse side effects and with good clinical efficacy. Our case report suggest that Ofatumumab is a valid alternative B cell depleting agent.

KEYWORDS: Ofatumumab, kidney transplant, AB0 incompatible

INTRODUCTION

Out of the millions of people who suffer from end stage renal failure worldwide every year, only a third are eligible for kidney transplants. The ability to perform transplants between donors and recipients with different blood types has increased the possibility of performing live donor transplants, made possible by effective new drugs being used during the desensitization process. Modern methods of desensitization are based on the application of apheretic techniques combined with immunosuppressive drugs such as Rituximab, a chimeric anti-CD20 antibody, which has a key role in B lymphocyte depletion. Severe infusion related reactions due to the administration of Rituximab are reported in approximately 10% of patients (1). Such reactions restrict the use of the drug. Therefore, it is common practice to test alternative B cell depleting therapies. We reported on the first clinical case of a patient undergoing desensitization protocol for kidney disease transplantation AB0 incompatible with Ofatumumab, a fully humanized monoclonal anti-CD20 antibody, given as an alternative B-cell depleting treatment.

Case report

A 41-year-old male diagnosed with end stage kidney disease due to nephroangiosclerosis was presented to our transplant center for live kidney donation accompanied by his mother: a potential, healthy, willing AB0 incompatible kidney donor. The patient was on regular, peritoneal dialysis for the last 18 months and also had ischemic heart disease treated with dual stent placement approximately one year before. Immunological tests [complement-dependent cytotoxicity lymphocytotoxicity crossmatches (CDC-LT, CDC LB), luminex DSA, Match-HLA], were performed in the recipients. Table 1 gives demographic and immunological data of the donor and recipient. After finding the donor and recipient eligible for transplantation, we proceeded with the desensitization protocol by using the Stockholm model (Tydel et al. AJ of Transplantation 2005; 5:145-148) (2) and the Johns Hopkins Hospital model (Montgomery et al. N Engl J Med 2011;365:318-326) (3) as a guideline. This protocol states that all AB0 incompatible recipients must have received the anti-CD20 antibody (Rituximab) for four weeks before the transplant. Then, two weeks before the patients must have received plasmapheresis to reduce the anti-ABO antibody. Most recipients received plasmapheresis 4 to 5 times (range, 2–9 times) until the isoagglutinin anti-ABO antibody ratio was ≤1:8.

Donor	**Recipient**
• Female • 67 years old • Mother • Blood type B	• Male • 41 years old • Child • Blood type 0 • Crossmatches negative • Luminex DSA negative • Match-HLA negative • IgG anti-B= 1:128

Table 1 - Demographic and immunological data of the donor and recipient

The qualifying patient was admitted to our department and administered Rituximab (375 mg/m^2 i.v.) as part of the desensitization protocol but despite the antihistamine, anti-inflammatory, and steroid i.v. premedication given prior (Methylprednisolone 250 mg, Chlorphenamine 10 mg and Paracetamol 1 g), he displayed an adverse infusion reaction: high fever, tremors, malaise and dyspnea.

Due to the impossibility of continuing the treatment with Rituximab, we decided to complete the procedure using another anti-CD20 antibody (Ofatumumab), after a period of clinical oversight. One month after the Rituximab reaction, the patient started a new desensitization therapy which consisted of Ofatumumab (300 mg i.v. 35 days before the transplant and 2000 mg i.v. 28 days before the transplant), six sessions of apheresis and a low dose intravenous immunoglobulin (0,5 g/Kg).

The intravenous dose of Ofatumumab was administered following doses of antihistamine, anti-inflammatory, and steroid i.v. premedication (Methylprednisolone 250 mg, Chlorphenamine 10 mg and Paracetamol 1 g). The patient tolerated the administration without reaction and it was possible to complete the cycle of desensitization without any side effects. The plasmapheresis sessions were performed on alternate days, up to the achievement of a sufficiently low antibody blood titer (≤1:8). In our clinical case six apheresis sessions (5 plasma-exchange and 1 cascade filtration) were necessary in order to achieve sufficiently low isoagglutinins levels and proceed to transplantation. The graphics 1 and 2 shows the pharmacological and apheresis procedural results: a progressive decrease in isoagglutinins levels.

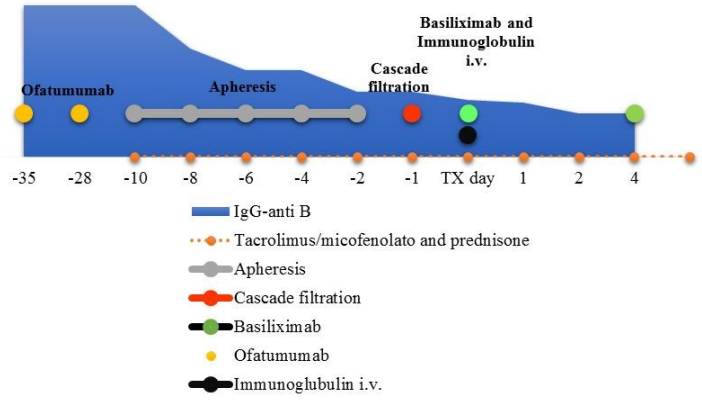

Figura 1. AB0 desensibilization protocol with Ofatumumab.

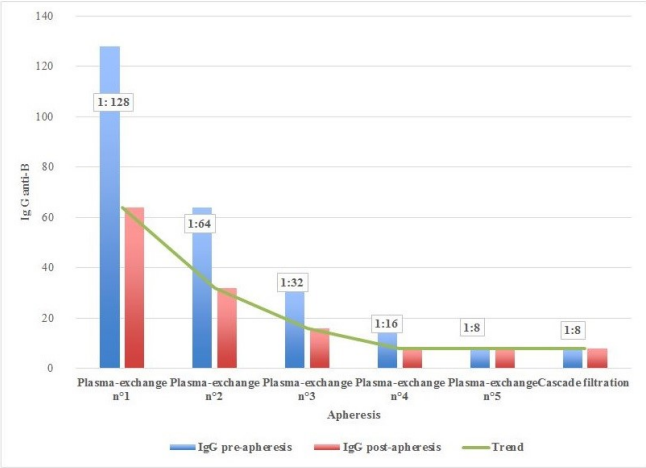

Figura 2. Isoagglutinin titer during apheresis treatment.

The triple immunosuppressive therapy was started on the first day of the plasmapheresis through oral administration of Tacrolimus (0,15 mg/Kg/day), Mycophenolic Mophetil (1000 mg x 2/day) and Prednisone (25 mg/day). On the day of the renal transplantation Basiliximab, an anti-CD25 antibody, was administered at a dose of 20 mg i.v., and then readministered on the fourth post-operative day as induction therapy.

After the desensitization protocol the patient underwent a renal transplant from an incompatible living donor with no surgical complications. The target trough level for tacrolimus was 10-15 ng/mL during the early postoperative period, but this decreased to 6-10 ng/mL after 3 months. Trimethoprim-sulfamethoxazole was used for prophylaxis for Pneumocystis jiroveci pneumonia for 6 months. No prophylaxis for CMV was performed because the patient was CMV-IgG positive.

The clinical course was characterized by a good functional recovery with creatinine values that reached 1.6 mg/dl after 1 month. Levels of IgG isoagglutinin anti-B were rechecked periodically after transplantation, and were at 1:2. Six weeks after transplantation, the patient developed a symptomatic reactivation of the cytomegalovirus for which he is undergoing antiviral therapy.

Discussion

The percentage of severe infusion reactions following treatment with Rituximab is approximately 10%. Ultimately, this side effect restricts the use of the drug. Rituximab, a chimeric monoclonal antibody (murine and human), consisting of a glycosylated immunoglobulin with a constant region of human origin and a variable region sequence of murine origin (4). The study of anti CD20 alternative is important in order to find alternative treatment options. Currently, three fully humanized anti-CD20 antibodies are available: Ofatumumab, Obinutuzumab and Ocrelizumab (5). There is no experience in the use of these drugs in renal transplantation.

Ofatumumab is a human monoclonal antibody (IgG1) that binds specifically to an epitope encompassing both the small and large extracellular loops of the CD20 molecule. The binding of Ofatumumab to the membrane-proximal epitope of the CD20 molecule induces recruitment and activation of the complement pathway at the cell surface, leading to complement-dependent cytotoxicity and resultant lysis of cells (6, 7). It was also observed that Ofatumumab can induce lysis in cells Rituximab-resistant expressing CD20. As a fully humanized antibody, Ofatumumab may avoid immunogenic reactions (8).

Today Ofatumumab is approved and used in malignant hematological disorders with encouraging results especially in those patients resistant or intolerant to treatment with Rituximab (9-13). In immune-mediated pathologies, there are sporadic clinical cases in which Ofatumumab treatment was administered. These include studies on pediatric Rituximab resistant nephrotic syndrome (14), treatment of lupus nephritis (15) and vasculitis ANCA-associated (8). In all these trials the Ofatumumab had a good clinical efficacy and is tolerated well. This is the first use of Ofatumumab in kidney transplantation protocol and our case report suggests that is a valid alternative B cell depleting agent, especially in patients who are intolerant to Rituximab due to infusion related reactions. Further studies are needed to secure and define the role of Ofatumumab and other emerging anti-B cell therapies in kidney transplantation.

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