Introduction

Ischemia–reperfusion injury is a major issue in kidney transplantation, as it has become more and more evident that its clinical expression, delayed graft function (DGF), has a significant impact on graft survival [1–3]. How such an early and short-lasting event can influence long-term transplant outcome is being investigated, and the links between reperfusion injury and early rejection or chronic allograft dysfunction are progressively explained (see refs 4 and 5 for review). The mechanisms of reperfusion injury have been extensively explored in recent years and several therapeutic options are emerging. These mainly target the production of reactive oxygen radicals, but many studies have also concentrated on the importance of adhesion molecules and the interest of their blockade in prevention of the reperfusion syndrome. Reperfusion injury is the result of a cascade of events, making the allograft an inflamed organ. A central step in the process is the activation of the graft endothelium and of circulating leukocytes, that enable them to adhere on the endothelial surface and to emigrate into the interstitium. Leukoendothelial interactions are mediated by complementary adhesion molecules on both sides; experiments in animal models of reperfusion injury by clamping of the renal artery have shown that the blockade by monoclonal antibodies (Moab) or antisense oligonucleotides, of the most important of these adhesion molecules, mainly those responsible for the strong phase of adhesion, could prevent ischemic acute renal failure and its histologic lesions. The use of the anti-adhesion molecule Moab has already been extended to human transplantation, and experience with two Moab, targeting respectively ICAM-1 and LFA-1, suggests a protective effect towards reperfusion injury. A pilot study only has been reported with the anti-ICAM-1 Moab [6], but the anti-LFA-1 antibody, Odulimomab, has been extensively evaluated through several multicenter randomized trials, that will be summarized.

Experience with an anti-LFA-1 monoclonal antibody, Odulimomab, in human kidney transplantation

From 1990 to the present we have analyzed interest in an anti-LFA-1 Moab, Odulimomab, in kidney transplantation. The efficacy of the antibody in the
prevention of acute rejection has been evaluated through two main multicenter randomized clinical trials, that surprisingly suggested that the antibody could also have a beneficial effect on DGF.

Odulimomab is a murine IgG1 directed against the α chain of LFA-1 (CD11a), that interferes with the binding of ICAM-1 with the I domain of LFA-1. Odulimomab is able in vitro to inhibit T lymphocyte proliferation, T and NK cytotoxicity and antibody production [7]. The determination of the optimal dosage of the Moab has been performed in a dose-escalating study, based on measurements of Odulimomab circulating levels, analysis of saturation of LFA-1 molecules on monocytes and lymphocytes and inhibition of LFA-1-dependent adhesion [8, 9]. Accordingly, all the patients included in the subsequent studies received a loading dose of 30 mg, infused at least 2 h before surgery, followed by a 15 mg daily dose. Odulimomab was administered in a quadruple sequential induction regimen, during the first 10 postoperative days, in association with steroids and azathioprine. Cyclosporine A (CsA) was introduced on day 9 and maintenance treatment consisted of CsA bitherapy or tritherapy.

The efficacy of Odulimomab in the prevention of acute rejection has been assessed by comparison with the two reference treatments of initial immunosuppression in kidney transplantation, ATG in a similar quadruple sequential induction treatment [10] and CsA triple-therapy (manuscript in preparation). The first study, comparing Odulimomab and ATG, included 100 patients (49 under ATG, 51 under Odulimomab); the second, comparing Odulimomab and CsA, 301 patients (153 under CsA since the first day post-transplant, 148 under Odulimomab), all recipients of a first cadaveric kidney transplant, having less than 75% panel reactive antibodies. Efficacy data showed:

1. Similar graft survival with the Moab and the control treatments, 92% at 1 year for Odulimomab and 90% for ATG in the first study; 92% at 3 months for Odulimomab and 91% for CsA in the second study.
2. Similar patient survival, respectively 96% and 100% in the first study; 96% and 97% in the second.
3. The frequency of acute rejection episodes in the first 3 months post-transplantation was not statistically different in the three groups, 36% in the Odulimomab patients in the two studies versus 35% for those having received ATG and 37% for those having received CsA only. Rejection episodes were validated on clinical and histological grounds by a committee of outside experts.

In each trial, 11% of the treated patients showed rejection during the period of Moab infusions, as was also the case in the CsA group. Patients under ATG did not present acute cellular rejection during its administration, but some occurred very soon after the completion of the treatment, so that rejection incidence was the same as in the Odulimomab group at day 15. Rejection severity, estimated on the risk of recurrence, recovery of transplant function,