

Optimizing use of basiliximab in liver transplantation

Carlo B Ramirez
Adam Bozdin
Adam Frank
Warren Maley
Cataldo Doria

Department of Surgery, Thomas
Jefferson University, Philadelphia,
PA, USA

Abstract: Antibody induction therapy has not been part of standard immunosuppressive regimens in liver transplantation. However, in recent years there has been an upward trend in the use of antibody induction therapy in orthotopic liver transplantation (OLT), attributed mainly to the growing number of OLT recipients with renal dysfunction after the Model for End Stage Liver Disease (MELD) scoring system was adopted in 2002. Basiliximab, a chimeric monoclonal antibody, is the most frequently used induction antibody in OLT. Basiliximab targets the alpha chain of interleukin-2 receptors in activated T-lymphocytes, inhibiting T-lymphocyte proliferation responsible for acute cellular rejection. Basiliximab (given in two 20 mg doses intravenously on post OLT day 0 and 4) has an excellent efficacy and safety profile. Basiliximab induction also allows early steroid withdrawal or avoidance, as well as delayed introduction and minimization of calcineurin inhibitors (CNI) in the setting of renal insufficiency. Although its long-term effect on hepatitis C virus (HCV) recurrence post OLT is currently unknown, studies using basiliximab induction in steroid-free protocols suggest no harmful effect on histologic HCV recurrence and survival rates. Basiliximab is a well tolerated, effective and safe anti-rejection drug in pediatric and adult OLT recipients when given in conjunction with a CNI-based immunotherapy.

Keywords: liver transplantation, basiliximab, acute cellular rejection, immunosuppression, steroids

Introduction

Orthotopic liver transplantation (OLT) is recognized as the standard therapy for end stage liver disease secondary to chronic and acute liver diseases. Currently, the adjusted 1- and 5-year patient and graft survival rates after deceased-donor OLT are 87% and 73% and 83% and 68%, respectively.¹ Despite major advances in immunosuppression, acute cellular rejection (ACR) remains a significant postoperative problem. Although single episodes of acute rejection do not have a deleterious effect on graft function,² long-term, recurrent episodes may result in permanent damage to the liver and may compromise long term graft survival.³

Induction therapy with antibodies is generally used in organ transplantation to decrease the incidence and delay the onset of acute rejection in the immediate post-transplant period, when the risk of rejection is the highest. In OLT, however, antibody induction therapy has not gained widespread use and typically has not been part of immunosuppressive regimens until recently. In fact, from 1997 to 2003, the number of transplant centers using antibody induction therapy in OLT has increased from 7% to 20%.⁴ Basiliximab was the most frequently used (in 7% of OLT recipients) induction

Correspondence: Carlo B Ramirez
Division of Transplantation, Department
of Surgery, Thomas Jefferson University,
605 College Bldg., 1025 Walnut St.,
Philadelphia, PA 19107, USA
Email carlo.ramirez@jefferson.edu

agent, followed by rabbit anti-thymocyte globulin (RATG) and daclizumab (both in 6% of OLT recipients). This trend may be attributed to the growing number of OLT recipients with renal insufficiency or end stage renal disease (ESRD) since the Model for End Stage Liver Disease (MELD) scoring system was adopted in 2002. Induction agents have been used to delay the introduction of calcineurin inhibitors (CNI), primarily to avoid CNI neurotoxicity or nephrotoxicity in the setting of renal insufficiency. Another potential setting in which induction therapy may prove useful in OLT is in early steroid withdrawal or steroid avoidance regimen, to minimize known steroid adverse effects, while maintaining adequate immunosuppression. Therefore, selecting an immunosuppressive regimen that not only minimizes the risk of severe acute allograft rejection but also decreases the risk of complications (ie, renal insufficiency) and other adverse drug effects is important to achieve long term graft survival after OLT and improve quality of life.

Two types of antibodies currently used in clinical transplantation for induction therapy are polyclonal and monoclonal antibodies. Polyclonal antibodies are gamma globulins produced by several clones of animal cells (horse or rabbit) immunized with human thymocytes or lymphocytes. Consequently, they have nonspecific immunosuppressive effects resulting mainly from massive lymphocyte depletion. The major adverse effects of polyclonal antibodies include serum sickness, anti-idiotypic antibody formation, leucopenia and thrombocytopenia, cytokine release syndrome (due to mass release of cytokines after opsonization and destruction of mature T-cells), and significantly increased risk of infection and malignancy.⁵

On the other hand, monoclonal antibodies, such as the chimeric interleukin-2 receptor (IL-2R) antibody (basiliximab) and the humanized IL-2R antibody (daclizumab), selectively block the α -chain (CD25) of IL-2 receptors (IL-2R), which are expressed only on activated T-lymphocytes, and prevent ACR by inhibiting IL-2 driven T-lymphocyte proliferation. Therefore, they offer a more specific immune response and less adverse effects than polyclonal antibodies. Several studies comparing IL-2R monoclonal antibody (basiliximab) and rabbit-derived polyclonal antibody (anti-thymocyte globulin, or ATG) in renal transplant recipients showed that basiliximab offered considerable advantages over ATG in terms of convenience of administration (two-dose regimen) and lower incidence of adverse effects (leucopenia, thrombocytopenia, and CMV infection), with no evidence of cytokine release syndrome.⁶⁻⁸

The immunologic process of ACR is mainly a result of T-cell activation and proliferation. The immune process

begins with foreign antigens from the graft binding to antigen-presenting cells which subsequently activate T-cells. These cells then release IL-2 which binds to IL-2 receptors (IL-2R). This binding initiates an immune response characterized by cell proliferation and clonal expansion of activated T-cells as well as the generation of cytotoxic T-cells specific for graft antigens.⁹ Damage to the graft occurs when other T and B-cells are then activated causing occlusion of the graft vasculature and release of pro-inflammatory chemotactic chemicals that recruit even more lymphocytes as well as macrophages.¹⁰

Methods

This review article provides a synopsis of the efficacy and safety of basiliximab use in adult and pediatric OLT. The authors searched PubMed, Cochrane database, and Ovid Medline for studies published between 1950 and 2009, with the following search terms: basiliximab, Simulect, monoclonal, antibody, interleukin-2 antibody, and liver transplantation.

Mechanism of action

Basiliximab (Simulect®; Novartis, Basel, Switzerland) was approved by the Food and Drug Administration (FDA) in May 1998 for prophylaxis against rejection in adult and pediatric kidney transplant patients in combination with dual (CNI and steroids) or triple (CNI, azathioprine, or mycophenolate mofetil, and steroids) maintenance immunosuppression.

Basiliximab is a chimeric (75% human and 25% murine) monoclonal antibody derived from an IL-2R α (CD25)-specific parental murine monoclonal antibody, RFT5 γ 2a. Using genetic engineering technology, the variable region genes of the murine antibody are fused to the constant region genes of the human antibody. IL-2R α (CD25) antibody specificity and affinity are maintained since the murine variable region remains unchanged. However, this chimeric antibody is less immunogenic in humans because the murine constant region is replaced with the human equivalent. The purified preparation is formulated as a lyophilizate and meets all quality control criteria for monoclonal antibodies intended for use in humans.^{11,12} basiliximab binds with similar affinity as IL-2 to the α -chain (CD25) of IL-2R on the surface of activated T lymphocytes. Consequently, the drug effectively competes with IL-2, and inhibits IL-2 driven T-lymphocyte proliferation, which is a critical phase of allograft rejection.

Pharmacokinetic profile

Several clinical studies in adult and pediatric OLT recipients have evaluated pharmacokinetic properties of basiliximab in

conjunction with a number of maintenance immunosuppressive regimens.^{13–15} This drug has been shown to have biphasic and slow clearance with a long terminal half-life. This drug is characterized by a volume of distribution within the plasma compartment as well as outside the circulatory system, and is slowly broken down and eliminated from the body by intracellular proteolysis.

Basiliximab has a high volume of distribution (Vd), consistent with plasma volume of distribution almost completely saturating IL-2R on peripheral T lymphocytes within 24 hours after a single dose of 2.5 mg to 25 mg as described in renal transplant recipients.^{8,13} In OLT, the Vd in the plasma compartment is reported as 5.7 ± 0.9 L in adults and 2 ± 0.9 L in children, while the steady state volume (Vs) is reported as 9.7 ± 4.2 L in adults and 4.1 ± 3.9 L in infants and children.^{13–15}

Complete IL-2R α saturation is achieved when serum basiliximab concentration is reported to be ≥ 0.1 ug/ml (by ELISA) in liver transplant recipients.¹⁴ The duration of IL-2R α receptor saturation and suppression was 23 ± 7 days and 27 ± 11 days in adult and pediatric OLT recipients, respectively.^{13,15} It was observed that the incidence and onset of ACR was independent of basiliximab clearance and duration of IL-2R α saturation. There was no difference in the duration of IL-2R α saturation between recipients who developed ACR compared to those who did not.^{15,16}

Total body clearance was significantly faster for OLT recipients compared to renal transplant recipients (75 ± 24 vs 46 ± 16 ml/h, $P = 0.0001$) while the terminal elimination half life was shorter (4.1 ± 2.1 vs 5.8 ± 2 days, $P = 0.007$).¹⁵ Since it is expected that a large antibody like basiliximab cannot filter through the kidneys unless there is significant proteinuria, these differences in clearance were attributed to non-renal routes, such as ascitic drainage and post-operative blood loss.¹⁴ Although ascitic drainage accounted for only 20% of total basiliximab clearance, in the presence of massive ascitic drainage, basiliximab clearance may be clinically significant, warranting individualized drug dosing in specific cases. On the other hand, increased blood loss seen in OLT has little contribution to basiliximab clearance; therefore there is no evidence to support basiliximab dose adjustments based on volume of postoperative bleeding.^{13,14}

The suggested basiliximab dosing is generally the same in OLT as in kidney transplantation. However, the first dose is given within 4 hours after liver graft reperfusion, to avoid drug losses from blood loss and massive ascites. The second dose is given on the fourth day after transplantation as in kidney transplant recipients. An additional basiliximab dose of 10 to 20 mg depending on the recipient body weight may be

recommended on postoperative day 7 for ascitic drainage >5 to 10 L within the first week post OLT.¹³

In adult OLT recipients, the recommended dose of basiliximab is two 20 mg doses infused via a central or peripheral intravenous line over 20 to 30 minutes. In infants and children less than 9 years of age ($n = 30$), basiliximab clearance was reduced by 50% compared with adult OLT recipients. This finding was independent of age up to 9 years old, weight up to 30 kg, and body surface area to 1 m². Clearance in children 9 to 14 years of age and adolescents was similar to that of adults. Therefore, the recommended basiliximab dose for pediatric recipients ≤ 35 kg is 10 mg, and 20 mg for recipients ≥ 35 kg, given in 2 doses with the first given on day of transplant and second on the fourth post-transplant day.^{15,16} Routine monitoring of serum levels is not currently recommended for basiliximab. The pharmacokinetic characteristics of basiliximab are summarized in Table 1.

Efficacy studies

Results of large, multi-center, placebo-controlled, randomized clinical trials, which were conducted mainly in renal transplant recipients, have demonstrated the efficacy and safety of basiliximab induction in preventing rejection.^{12,17–19} In these trials, the incidence of ACR was significantly reduced by 12% to 14% in the basiliximab induction group compared to placebo. Furthermore, the incidence of corticosteroid-resistant ACR (requiring antibody therapy) at 6 and 12 months was significantly lower in the basiliximab compared to placebo group (10% vs 23.1%, $P < 0.001$) in the European/Canadian trial.¹² Similarly, significantly fewer recipients in the basiliximab than in the placebo group (25% vs 42%, $P = 0.001$) experienced steroid-resistant ACR that required antibody therapy and/or azathioprine, Tac, or MMF.¹⁷ However, despite reduction of early ACR episodes,

Table 1 Pharmacokinetic profile of basiliximab

Pharmacokinetic characteristic	Adult > 35 kg	Pediatric < 35 kg
Dose		
1st dose: OLT day 0 (mg)	20	10
2nd dose: OLT day 4 (mg)	20	10
Volume of distribution (L)	5.7 ± 0.9	2 ± 0.9
Steady state volume (L)	9.7 ± 4.2	4.1 ± 3.9
Elimination half life (days)	8.7 ± 6.7	7.6 ± 4.6
Total body clearance (mL/h)	55 ± 26	19.3 ± 6.5
Duration of IL-2R α saturation (days)	23 ± 7	27 ± 11

Abbreviation: OLT, orthotopic liver transplantation.

the 12-month graft and patient survival rates were similar in the two treatment groups.

Experience with the use of basiliximab induction in liver transplantation is less extensive.

Adult OLT recipients

A large, multi-center, double-blind, randomized trial involving 381 OLT recipients, stratified by hepatitis C (HCV) seropositivity, compared basiliximab to placebo in conjunction with cyclosporine (CsA) and steroid maintenance therapy.²⁰ In this study, the incidence of ACR episodes at 6 months post OLT was significantly lower in the basiliximab (35% vs 44%) compared to the placebo group. The reduction in ACR rate was more pronounced in the HCV-negative cohort, with much smaller difference seen in the HCV-positive cohort. Furthermore, the incidence of corticosteroid-resistant ACR was lower in the basiliximab compared to the placebo group at 6 months post OLT (18% vs 25%, $P=0.09$) and at 12 months post OLT (18% and 26%, $P=0.05$). The 1-year graft and patient survival rates in the basiliximab group were similar to those of the placebo group (84% vs 80% and 87% vs 84%, respectively).

In a multi-center, single-arm, open-label study, Calmus et al²¹ investigated the efficacy and tolerability of basiliximab induction with CsA, Azathioprine (AZA) and steroid maintenance immunosuppression in their first 101 OLT recipients. The authors reported an ACR rate of 23% at 6 months, none of which was labeled histologically as severe and required antibody therapy. Furthermore, there was no difference in grade of rejection between the HCV-positive and HCV-negative groups. The 1-year graft and patient survival rates were 88% and 90%, respectively.

A prospective, randomized, single-center study conducted in 47 adult OLT recipients compared basiliximab and CsA to steroids and CsA.²² They demonstrated a lower ACR rate (15% vs 29%, respectively) and a higher cumulative survival at 36 months post OLT (84% vs 61%, respectively) in the basiliximab and CsA group compared to the steroid and CsA group.

Several single-center experiences with the use of basiliximab induction in conjunction with dual (CNI and steroids) or triple (CNI, mycophenolate mofetil, or MMF, and steroids) maintenance immunotherapy in adult deceased-donor and living-donor OLT recipients, reported lower ACR rates of 7% to 27% and similar 1-year graft and patient survival rates of 88% to 93% and 90% to 94%, respectively.^{23–26} In a single-center, retrospective analysis of 42 consecutive deceased-donor, adult OLT recipients who received basiliximab induction with maintenance tacrolimus (Tac), MMF and early

steroid taper, Ramirez et al²⁵ reported a 93% rejection-free patient and graft survival rate after a 2-year follow-up.

Pediatric OLT recipients

In the pediatric OLT population, several single-center trials using basiliximab induction have consistently shown significant reduction in ACR episodes.^{27–33} Several studies comparing a steroid-free immunosuppressive regimen with basiliximab induction to a steroid-containing regimen showed a significantly higher growth catch up post OLT in the basiliximab group.^{27,29}

In a prospective randomized trial, Reding et al²⁷ compared 20 pediatric OLT recipients who received basiliximab induction and Tac, to 20 matched historical control group patients who received steroid induction and Tac. At 1 year post OLT, they observed a significantly higher growth catch up starting in the first week post OLT in the basiliximab group, and growth delay in the steroid group until the introduction of alternate day steroid treatment. They also noted a significantly higher rejection-free 1-year survival in the basiliximab group as compared to the steroid group (75% vs 50%, respectively).

Spada et al²⁸ conducted a prospective randomized study on 72 pediatric OLT with recipients equally distributed between those treated with basiliximab and Tac to those treated with steroids and Tac. The basiliximab group had a statistically significant lower incidence of rejection and infection. Although not statistically significant, the 1-year patient (91% vs 89%) and graft (86% vs 80%) survival rates favored the steroid arm.

In another prospective study, Gras et al²⁹ treated 50 pediatric OLT recipients with a steroid-free, Tac-based immunosuppression and compared the outcome to a historical control group of 34 pediatric OLT recipients treated with Tac and steroids. They reported a 3-year rejection-free graft survival rate of 72% and 41% ($P=0.007$) in the basiliximab and steroid groups, respectively. The incidence of viral infections was significantly less in the basiliximab group compared to the steroid group. Furthermore, there was growth catch up in the basiliximab group starting at 3 months post OLT. At 3 years post OLT, their height has reached the average of nontransplant children of the same age and gender. In contrast, patients in the steroid group had only significant growth improvement at 2 years and 3 years post-OLT. At 3 years post OLT, the mean height of recipients in this group was below the average of non-transplant children of the same age and gender.

Ganschow et al³⁰ compared the outcomes of 54 pediatric OLT recipients (transplanted in 1999 to 2000) who received basiliximab, CsA and steroids to a historical group of

54 pediatric OLT recipients (transplanted in 1997 to 98) who received CsA and steroids only. They reported a significant reduction of ACR rate in the basiliximab group compared to the historical group (16% vs 54%, respectively), after a follow-up period of 22 to 46 months. The incidence of steroid resistant rejection, chronic rejection, infection, PTLT, and patient survival were not statistically different.

Table 2 summarizes selected published efficacy studies on basiliximab use in adult and pediatric OLT.

Safety profile

The safety profile of basiliximab was studied extensively in several randomized trials conducted mainly in renal transplant patients. Data from the US and European/Canadian multicenter prospective randomized trials have all reported no significant difference in the type, incidence, and severity of adverse events in patients who received basiliximab compared with placebo.^{12,17–19} Similar findings were reported in studies conducted on OLT recipients.^{20–22} In both clinical studies comparing basiliximab to placebo²⁰ and basiliximab to corticosteroids,²² there was no reported difference in the incidence of infection and other adverse events between treatment groups.

Basiliximab is better tolerated and safer to use than Muromonab OKT3. Basiliximab has not been shown to cause cytokine release syndrome which consists of fever, chills, headache, and pulmonary edema. This syndrome is commonly observed with Muromonab OKT3 administration and was seen in comparative studies of the two agents.^{12,19}

Despite the 305 murine variable region sequences in basiliximab, it is surprisingly minimally immunogenic demonstrating an anti-idiotypic sensitization of only 0.4% to 1.4%.^{12,19} Even with the detection of these anti-idiotypic antibodies, there was no association with increased risk of ACR or adverse events.³⁴

Hypersensitivity reactions due to anti-idiotypic IgE antibody formation occurs rarely.³⁵ In a postmarketing surveillance conducted in October 2000, a total of 17 cases of hypersensitivity reactions, including anaphylaxis, occurred after exposure or re-exposure to basiliximab. Further cases of anaphylactic shock reactions occurred mainly in pediatric recipients who were re-exposed to basiliximab after re-transplantation.^{35,36}

The incidence of infections was similar in renal transplant recipients who received basiliximab compared to placebo in the US (73% vs 75%) and European trials (85% vs 86%).^{12,17} The incidence of cytomegalovirus infections in renal transplant recipients was likewise similar in the basiliximab and placebo groups in the European/Canadian (21% vs 27%) and the US (7% vs 9%) studies. Furthermore, the overall incidence of

malignancy, and post-transplant lympho-proliferative disease (PTLD) in the first post-transplant year was similar (0.3% and 0.6%) in the basiliximab and placebo groups, respectively. In the combined European/Canadian trials, 2 neoplasms (both breast cancer) developed in the basiliximab group, and 6 neoplasms (3 basal cell carcinomas, one squamous cell carcinoma, one hypernephroma, and one lymphoma) developed in the placebo group.¹² In the US trials, 5 neoplasms were recorded during the 12-month follow up period, 3 in the basiliximab group (1 melanoma, 1 adenocarcinoma, and 1 cerebral glioma) and 2 (1 multiple myeloma and 1 Kaposi's sarcoma) in the placebo group.¹⁷

Basiliximab has been reported to cause a number of adverse effects including pain, hypertension, nausea, anemia, peripheral edema, headache, as well as hyperkalemia, yet there has not been any reported drug interaction with this induction agent.¹² Due to the lack of animal reproduction studies with basiliximab there are no good data on its effect on fertility or the fetus itself. Due to the absence of adequate studies in pregnant women, the FDA has assigned basiliximab to category B. It is currently accepted that basiliximab should be avoided in pregnancy at this time because we know that IgG crosses the placenta, theoretically putting the fetus at risk.

Specific uses of basiliximab in liver transplantation

Induction therapy may have benefits in OLT recipients by allowing steroid avoidance/minimization and by allowing CNI minimization in the setting of renal dysfunction.

Steroids have always been part of standard post-transplant immunosuppression either for prophylaxis or treatment of ACR. However, susceptibility to infection, obesity, hypertension, hyperlipidemia, diabetes, osteopenia, cataracts, and growth retardation in children, are all well recognized long-term adverse effects of steroids. Steroids are also implicated in accelerating HCV recurrence post-OLT.^{37,38} Currently, HCV is the most common indication for liver transplantation, accounting for about 40% of all liver transplant cases.³⁹ Due to long-term steroid adverse effects, strategies to minimize steroid exposure ranging from early steroid reduction and withdrawal to complete steroid avoidance post OLT have been adopted. In recent years, several prospective clinical trials using basiliximab induction to facilitate early steroid withdrawal^{40,41} or complete steroid avoidance have been successfully conducted in adult^{22,42–45} and pediatric^{27–29} OLT recipients.

Although the long term impact of basiliximab on HCV-associated recurrence is currently unknown, complete steroid avoidance protocols utilizing basiliximab induction suggest

Table 2 Selected published efficacy studies on basiliximab use in adult and pediatric OLT

Reference	Study type	No. of pts.	OLT type	Treatment groups	ACR rate	Graft survival (1 year)	Patient survival (1 year)
OLT – adult							
Neuhaus et al ²⁰	MC,PR	188	DD	CsA, Ste, Bas	35	84	87
		193		CsA, Ste, pl	44	80	84
Calmus et al ²¹	MC,PR	101	DD	CsA,AZA, Ste, Bas	23	88	90
Lupo L et al ²²	PR	26	DD	CsA, Bas	15		
		21		CsA, Ste	29		
Grannas et al ²³	R	102	DD	CsA, Ste, Bas	27	93	94
Marino et al ²⁴	PR	50	DD	Tac, Ste, Bas	12	75 (3 y)	88 (3 y)
Ramirez et al ²⁵	R	42	DD	Tac, MMF, Ste, Bas	7	93 (2 y)	93 (2 y)
Gruttadauria et al ²⁶	R	60	LD	Tac, Ste, Bas	5	76 (3 y)	82 (3 y)
Filipponi et al ⁴⁴	MC, PR	70	DD	CsA,AZA, Bas, Ste	24	73	85
		70		CsA,AzAa, Bas, pl	39	82	89
OLT – pediatric							
Reding et al ²⁷	PR	20	DD	Tac, Bas	94	75	75
		20		Tac, Ste (historical)	74	50	50
Spada et al ²⁸	PR	36	DD	Tac, Bas	11	80	89
		36		Tac, Ste	31	86	91
Gras et al ²⁹	PR	50	DD	Tac, Bas	28	94 (3 y)	96 (3 y)
		34		Tac, Ste (historical)	59	88 (3 y)	91 (3 y)
Ganschow et al ³⁰		54	DD, LD	CsA, Ste, Bas	17	98	98
		54		CsA, Ste (historical)	54	94	94
Asensio et al ³¹	R	13	DD	Tac, Ste, Bas	30	80	80
		21		Tac, Ste	63	80	80
Kovarik et al ¹⁴	R	37	DD	CsA, Ste, Bas	55		
Strassburg et al ³²	R	12		CsA, Ste	42		100
		9		CsA,AZA, Ste	66		100
		21		CsA, Ste, Bas	33		100
		12		Tac, Ste	42		100
Gibelli et al ³³	R	32	DD, LD	Bas, CsA, Ste	57.1		
		28		CsA, Ste (historical)	67.8		

Abbreviations: MC, multicenter; R, retrospective; PR, prospective; DD, deceased donor; OLT, orthotopic liver transplantation; LD, living donor; Bas, basiliximab; Tac, tacrolimus; CsA, cyclosporine; AZA, azathioprine; MMF, mycophenolate mofetil; Ste, steroids; pl, placebo.

no significant difference in the incidence of histologic HCV recurrence and overall survival rates.^{42–45}

Llado et al⁴² looked at the use of CsA with basiliximab in an open-label prospective randomized trial to evaluate the efficacy of a steroid free regimen, specifically in HCV recipients. They found that there was no significant difference in ACR observing a 17% and 21% rejection rate in the nonsteroid and steroid groups, respectively. Patient survival was also not significantly different between the two groups. They did, however, find significantly less bacterial infection in the steroid-free group (38% vs 59%). They also saw 97% biopsy-proven HCV recurrence in both treatment groups.

Further evaluation was done by Lupo et al²² who conducted a prospective randomized control trial using CsA in both groups with two doses of 20 mg of basiliximab in one group and 200 mg hydrocortisone each day in the other group. They found similar findings as above demonstrating no significant differences in ACR, graft and patient survival, rejection-free survival, as well as infection rates.

In a 2-year, prospective, randomized trial, Ramirez et al⁴³ compared steroid-free to standard steroid therapy in 39 OLT patients treated with basiliximab, Tac, and enteric-coated mycophenolate sodium (EC-MPS). There were no significant differences between the steroid and steroid-free

group in regard to hypertension, cholesterol levels, infection rates, or HCV recurrence from baseline to 1 year, although there was a trend toward lower weight gain in the steroid-free group. There was no CMV and malignancy observed in either group. Furthermore, the ACR rate (5% in each group), as well as patient and graft survival rates were similar in the steroid and steroid-free group (100% vs 95%, respectively). The authors concluded that complete steroid avoidance with basiliximab, CNI, and EC-MPS, is as safe and effective as standard steroid therapy in adult OLT recipients.

Filippini et al⁴⁴ examined a steroid-free regimen in 140 HCV-infected transplant recipients in a double-blinded, randomized clinical trial. Both groups received 2 doses of 20 mg of basiliximab, CsA, and azathioprine with appropriate dose adjustments. One group then received a tapering regimen of methylprednisolone and oral prednisone while the other group received placebo. They found no significant differences in 12-month HCV histologic recurrence (41.2% vs 37.5% in steroid and placebo groups, respectively). However, a lower treatment failure rate (defined as death, graft loss, or study discontinuation for adverse events) was observed in the steroid-free group as compared to the placebo group (16% vs 28%, respectively). They did also find that biopsy-proven ACR was lower in the steroid group (24.3% vs 39.4%; $P=0.04$); however, there was no significant difference in treated ACR.

Segev et al⁴⁶ conducted a meta-analysis of randomized control trials looking at steroid avoidance in adult post-OLT patients, including 4 trials using basiliximab induction. It was shown that there were no significant differences in graft loss, death, and infection. They did, however, find a significant decrease in serum cholesterol levels and CMV infection. The relative risk (RR) for CMV in steroid-free groups was 0.52 ($P=0.001$). In studies where they replaced steroids with an alternate immunosuppressive agent, they found a RR of 0.29 for new-onset diabetes in the steroid-free groups ($P<0.001$), decreased rejection rates with a RR of 0.68 ($P=0.03$), as well as decreased severe rejection with a RR of 0.37 ($P=0.001$). In those studies where steroids were just removed from a regimen without replacement, rejection was found to be higher in the steroid-free arm, the RR being 1.31 ($P=0.02$). Despite no significant reduction in HCV recurrence within any individual trial, this meta-analysis demonstrated a RR of 0.90 ($P=0.03$) in HCV recurrence in the steroid-free groups. Given the data shown above, it has been demonstrated that steroid-free immunosuppressive regimens in OLT recipients can be safe and efficacious, and basiliximab appears to be an effective substitute in the induction phase of postoperative therapy.

Currently, renal insufficiency and ESRD after OLT represent extremely serious challenges facing OLT recipients, complicating patient management, and increasing risk of morbidity and mortality. OLT recipients have the highest incidence of ESRD of all nonrenal organ transplant recipients apart from intestinal transplants affecting more than 20% of OLT recipients.^{47,48} Furthermore, recipients who develop ESRD after OLT have a 4-fold higher risk of death and significantly lower survival rates compared to those without ESRD (28% vs 55%).^{47,48} The most common cause of ESRD after OLT is CNI-induced nephrotoxicity (75%) followed by progression of underlying renal disease (11%), hepato-renal syndrome (7%), and focal sclerosing glomerulosclerosis (7%).⁴⁹

The impact of CNIs on renal function and the fact that early kidney dysfunction is a predictor of late chronic renal failure after OLT,⁵⁰ have led to a number of studies exploring the use of antibody induction to delay or minimize CNI exposure.^{51–56} In a prospective, open-label, nonrandomized study using basiliximab induction followed by delayed initiation (median delay 36 hours) and reduced dose (trough level of 5 to 10 ng/mL) of Tac with maintenance MMF and steroid taper, Lin et al⁵⁴ demonstrated a “renal-sparing” effect of basiliximab induction in adult living donor OLT. They reported a significantly lower incidence of renal insufficiency at the third post-OLT month in the basiliximab group compared to the control (no induction) group (26% vs 67%) with similar incidence of ACR, CMV infection, and new-onset diabetes mellitus. Another clinical trial in 25 OLT recipients using basiliximab induction with low-dose Tac (trough levels 4 to 5 ng/mL), reported recovery of renal function in more than 80% of recipients without increasing the incidence of infections or adverse effects, and an ACR rate of 28%.⁵⁶

More than 90% of OLT recipients who develop ACR respond to standard steroid regimen consisting of methylprednisolone intravenous bolus followed by tapering doses of the drug. The conventional treatment for steroid resistant ACR includes the use of T-cell antibodies, such as anti-thymocyte globulin and murine monoclonal antibodies (OKT-3). However, these drugs are associated with potentially significant side effects, such as cytokine release syndrome, and increased risk of infection and malignancy, particularly PTLN in children.⁵⁷ Another rescue treatment protocol that has been tried successfully was high-dose Tac,⁵⁸ although its nephrotoxic adverse effect has been a major limiting factor to its use.

Several studies have shown the potential of basiliximab as a safe and effective alternative to OKT-3 and high-dose

Tac for rescue therapy in steroid resistant rejection.^{59–61} In a study on 7 pediatric OLT recipients with biopsy-proven steroid resistant ACR who were given basiliximab in 2 doses 3 to 7 days apart, only 2 recipients did not respond to rescue therapy and progressed to chronic rejection, while 5 recipients were treated successfully and were rejection free at a median follow up of 22 months (range: 5 to 32 months).⁵⁹ Another study described their experience with the use of anti-IL2-R antibodies (daclizumab or basiliximab) as rescue therapy for steroid-resistant rejection in 25 adult OLT recipients. In this study, the median time from OLT to onset of steroid-resistant rejection was 25 days. Twelve patients (48%) had complete resolution of rejection, with aspartate transaminase levels normalizing at a median of 37 days (range: 1 to 168 days). A total of 13 patients (52%) developed progressive liver dysfunction leading to death with graft failure (n = 3), retransplantation (n = 4) and chronic rejection (n = 6). Looking at the liver graft biopsy findings, all patients who were treated successfully had ACR, while those who responded poorly already had chronic rejection histologically.⁶⁰

Pharmacoeconomic evaluation

The use of the standard two 20 mg doses of basiliximab induction to the immunosuppressive regimen would entail an additional US\$3,000 to the total medical cost after transplantation. However, pharmacoeconomic studies conducted in kidney transplant recipients showed that basiliximab use is cost-effective compared to placebo, and this is attributed to reduction in the incidence of ACR, graft loss or delayed graft function, and consequent shorter hospital stay, decreased need for dialysis, and reduced hospital admission to treat ACR.^{62–64} The US multicenter trial comparing basiliximab, CsA and steroids vs placebo, CsS and steroids in 346 kidney transplant recipients demonstrated a significant reduction in ACR rate (38% vs 55%) and fewer hospital admissions to treat ACR in the basiliximab vs placebo group, respectively.¹⁷ The cost analysis showed lower total first-year medical costs (US\$28,927 vs US\$32,300, difference of US\$3,373), and lower first-year hospital costs (US\$9,328 vs US\$10,761, difference of US\$1,433) for treating ACR in the basiliximab compared to the placebo group, although the differences were not statistically significant.⁶² The pharmacoeconomic evaluation of 380 adult kidney transplant recipients in the European/Canadian multi-center trial.¹² demonstrated that basiliximab use generated a net cost savings of CAN\$1,554 (including drug cost) per patient in the first post-transplant year.⁶³

Conclusion

Induction with basiliximab, an anti-IL2-R monoclonal antibody, in combination with a CNI-based immunosuppressive therapy, is an effective and safe strategy for immunoprophylaxis in pediatric and adult OLT recipients. The high selectivity of this monoclonal antibody makes this drug an effective immunoprophylaxis in liver transplantation without increasing the risk of infection, HCV recurrence, malignancy, or other adverse effects. Basiliximab induction appears to be a safe substitute to steroids in early steroid withdrawal or complete steroid avoidance protocols. In the setting of renal insufficiency, basiliximab induction also allows for delayed introduction of CNIs to avoid CNI nephrotoxicity and preserve renal function without increasing the risk of rejection or compromising patient and graft survival in OLT recipients. Pharmacoeconomic analyses have also furnished evidence of the cost-effectiveness of basiliximab induction therapy. The combination of minimal dosing requirements without serum level monitoring, and proven therapeutic efficacy and excellent safety profile, makes this drug an ideal choice for induction therapy in OLT.

Disclosures

The authors disclose no conflicts of interest.

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