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REVIEW

Induction immunosuppression in liver transplantation: a review

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Summary

Antibody therapy for induction is seldom used in liver transplantation in the United States, but continues to be used in approximately 10% of patients. The most commonly used antibody at the current time is basiliximab (Simulect, Novartis) and is used in adults with renal dysfunction at the time of liver transplantation with the intention of delaying introduction of calcineurin-inhibitors. In children, the same antibody is commonly used in order to reduce rates of acute rejection. Most patients, adult and pediatric, are treated with initially higher levels of tacrolimus rather than antibody induction.

Introduction

Induction immunosuppression is a prophylactic, perioperative course of intensive immunosuppression given to prevent acute rejection in the first months postoperatively, when the risk of rejection is highest [1]. Its potency is associated with more severe side effects than maintenance immunosuppression. Induction immunosuppression clearly offers protection against acute cellular rejection (ACR) in kidney transplantation [2]. However, the risk-benefit ratio of induction has been less apparent in liver transplantation, which has a lower incidence of acute rejection than kidney transplantation. A recent analysis of the UNOS database in the modern era of induction agents (2003–2009) demonstrated that induction immunosuppression in liver transplantation was related to significant improvements in graft and patient survival at 3 months, 1 year and 5 years post transplant, which prompts re-examination of the use of induction in liver transplantation [3].

Induction agents in the modern era of immunosuppression are broadly categorized as lymphocyte depleting or nondepleting. Thymoglobulin (Genzyme Corporation) is the most commonly used depleting agent in the US; it is a polyclonal rabbit-derived antibody preparation which targets multiple epitopes on T cells, resulting in nonspecific T cell depletion. Other anti-rejection properties are thought to include co-stimulation blockade, B-cell depletion and adhesion molecule modulation [1]. Thymoglobulin induces a dose-dependent lymphopenia, which suppresses T cells for up to 90 days. Alemtuzumab (Campath 1-H, Genzyme Corporation) is a monoclonal antibody, which selectively targets CD52, depleting mature lymphocytes for up to a year post administration [4, 5]. Nondepleting agents selectively target activated T cells by blocking CD25, the IL-2 receptor. Basiliximab (Simulect, Novartis) is a chimerized monoclonal antibody, which is currently the only nondepleting agent on the market. Effects are sustained for 1–2 months post administration [6]. Daclizumab

(Zenepax, Roche) is a humanized monoclonal antibody, which also targets CD25; it was withdrawn from the market in 2009 for commercial reasons.

In 2009 induction immunosuppression was utilized in 25% of patients after orthotopic liver transplantation (OLT). The use of induction in liver transplantation has increased over the past 10 years, as 15% of patients received induction in 2000 (Fig. 1) [7]. Basiliximab, daclizumab, and thymoglobulin have been the most commonly used induction agents since 2000. The use of prograf at higher doses in the immediate postoperative period is used in 90% of liver transplants currently, which provides the intensive immunosuppression usually associated with agents used solely for induction alone. Although some trials have examined the use of induction as an adjunct to conventional immunosuppression strategies, induction is most commonly employed after liver transplantation to facilitate calcineurin inhibitor minimization or steroid avoidance.

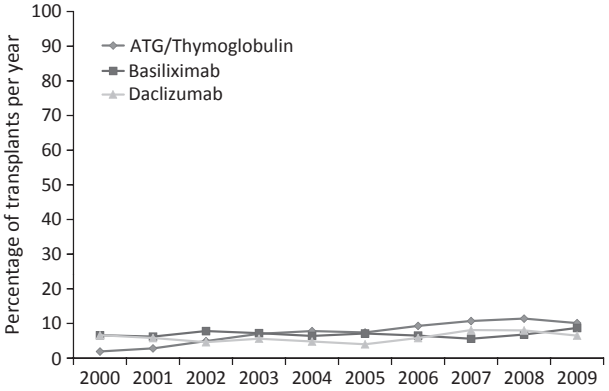

Figure 1 Immunosuppression use for induction, 2000–2009, recipients with liver transplants.

Methods

A literature search using PubMed was performed using the key words 'induction' 'liver transplantation', 'thymoglobulin', 'alemtuzumab', 'basiliximab', 'daclizumab', 'IL2RA', 'simulect', 'campath', and 'ATG'.

Induction as an adjunct to conventional immunosuppression

There are two randomized, prospective controlled trials comparing thymoglobulin induction as an adjunct to CNI-based immunosuppression strategies to CNI-based immunosuppression alone. Both failed to show any difference in ACR with thymoglobulin induction. Boillot and colleagues studied 44 patients post-OLT with thymoglobulin induction in combination with a standard regimen of tacrolimus, Table 1 mycophenolate mofetil (MMF), and steroids compared with 49 patients receiving tacrolimus, MMF, and steroids alone. There was no difference in ACR at 5 years post transplant (11% and 14%, respectively, P = NS) [8]. Bogetti and colleagues studied 22 patients post-OLT with or without thymoglobulin induction in addition to receiving tacrolimus and steroids; no difference in ACR was observed at 3 months post transplant [9]. There were no differences in infectious complications or malignancy in either study. While these are randomized controlled trials, the studies are limited by their small sample sizes. A retrospective review similarly examined the addition of thymoglobulin to a regimen of cyclosporine, azathioprine, and steroids provided no benefit against acute rejection after liver transplant [10].

A meta-analysis of randomized controlled trials comparing IL-2RA agents to existing immunosuppression regimens demonstrated a significant reduction in acute rejection within 1 year of transplantation with the use of induction immunosuppression (P = 0.04) [11]. Twelve

Table 1. Induction as an adjunct to conventional immunosuppression.

Reference	Induction	*N*	Maintenance immunosuppression	Follow-up	Graft survival	ACR
Boillot [8]	Thymoglobulin	93	Tacrolimus, MMF, steroids	5 years	(a) 77.3% (induction) (b) 87.8%	(a) 11% (b) 14.3%
Bogetti [9]	Thymoglobulin	22	Tacrolimus, steroids	3 months	(a) 100% (b) 100%	(a) 25% (b) 30%
Tchervenkov [10]	Thymoglobulin	73	Cyclosporine, azathioprine, steroids	1 year	(a) 65% (b) 81%	(a) 58% (b) 75%
Wang [11] (meta-analysis)	IL2 receptor antagonists	3,251	Tacrolimus, steroids, variable use of MMF	1 year	RR graft loss = 1.06	(a) 23% (b) 28% (P = 0.04)
Neuhaus [12]	Basiliximab	381	Cyclosporine, steroids	1 year	(a) 92.2% (b) 93.6%	(a) 39.4% HCV (–) 6 months 41% (P = 0.03) (b) 45.6%
Ramirez [15]	Basiliximab	92	Tacrolimus, steroids, ±MMF (both arms)	2 years	(a) 93.5% (b) 69.5% (P = 0.02)	(a) 7% (b) 34% (P = 0.001)

trials were included, eight of which used daclizumab for induction, and four used basiliximab. Subgroup analysis demonstrated no difference in rejection with trials using basiliximab ($P = 0.31$) compared with daclizumab ($P = 0.04$), however. There was no effect on mortality, graft loss, infection, or malignancy with the use of induction immunosuppression. This meta-analysis of high-quality randomized controlled trials is perhaps the strongest evidence in favor of the use of induction as an adjunct to conventional immunosuppressive regimens. Neuhaus and colleagues performed the largest trial included in this analysis [12]. Three hundred and eighty one liver transplant recipients were prospectively randomized to receive basiliximab or placebo induction immunosuppression in addition to a standard regimen of cyclosporine and steroids. While there was no significant difference in rejection episodes at 6 and 12 months between the two groups, the HCV-negative group treated with basiliximab did experience a statistically significant reduction in acute rejection at 6 months ($P = 0.03$).

Several retrospective reviews have demonstrated significant differences in ACR with basiliximab [13–15] or daclizumab [16] induction in addition to standard CNI-based regimens. Ramirez and colleagues performed the largest series in this group, examining 46 patients after OLT receiving basiliximab induction in the setting of a tacrolimus and steroid-based regimen, with or without MMF, compared with 46 historic controls receiving dual or triple standard immunosuppression. The group receiving basiliximab induction had an incidence of 7% ACR at 18 months, compared to 34% in the control group ($P = 0.001$) [15]. These studies are limited by their small sample sizes (less than 50 patients per treatment arm), retrospective case–control study design, and variable uses of MMF as an adjunct for CNI minimizing strategies [14, 15].

There are three case–control trials in the literature that investigate alemtuzumab as an induction agent for liver transplant. Alemtuzumab is administered with tacrolimus monotherapy as a CNI minimization strategy in each of these trials and compared with a conventional immunosuppressive regimen; none uses alemtuzumab as an adjunct to existing immunosuppressive regimens [17–19].

Induction to facilitate calcineurin inhibitor minimization

Although calcineurin inhibitors have markedly improved survival after liver transplant, their use is associated with an increase in renal failure [20–22]. The largest population-based cohort to date reported an 8% incidence of chronic renal failure 1 year post-OLT and 18% at 5 years post transplant. One large, retrospective review reported a 14.4% incidence of chronic renal failure at 10 years post transplant [23]. Chronic renal failure and end-stage renal disease (ESRD) after liver transplant is associated with significant morbidity and mortality [23, 24]. GFR at 1 year is predictive of late renal dysfunction [25] and an increased creatinine 1 month post transplant is associated with an increased risk of developing chronic renal failure [23]. In addition, postoperative acute renal failure is associated with a significantly increased risk of developing chronic renal failure or ESRD [24] Table 2. Given the correlation between CNI use, early renal failure, and mortality, many studies have examined the use of induction immunosuppression as part of a CNI-sparing strategy to preserve renal function.

The use of IL-2RA inhibitors as part of a CNI-sparing strategy has been the subject of many trials in the recent literature. Several single-center clinical trials performed in the early 2000s suggested IL-2RA inhibitors with delayed introduction of CNIs, or immediate initiation of low-dose CNIs resulted in improved renal function compared with the control arm (immediate full-dose CNI administration) with a similar [26] or significantly lower incidence of ACR [27–29]. These trials administered IL-2RA inhibitors to patients with pre-op renal dysfunction, and most used MMF in the experimental arm only. One trial demonstrated a significant reduction in ACR in the induction group independent of MMF administration, however [29].

Three multicenter, randomized control trials concerning the use IL-2RA inhibitors as part of a CNI-sparing strategy followed the earlier single-center trials. These trials differed from their predecessors in that patients included did not have significant renal dysfunction and both experimental and control arms used MMF. Each trial was adequately powered (>80%) to achieve statistical significance. The largest trial by Neuberger and colleagues examined three study protocols: immediate standard-dose tacrolimus (trough >10 ng/mL) and steroids, immediate low-dose tacrolimus (trough <8 ng/mL) with steroids and MMF, and Daclizumab induction, delayed (POD#5) low-dose tacrolimus with steroids and MMF. Each study arm comprised 168–181 patients who were followed until 1 year post transplant. Patients receiving IL-2RA induction had significant preservation of GFR compared with control arms without a significant difference in ACR. There was no difference in GFR or ACR between patients receiving immediate, low-dose tacrolimus with MMF and steroids compared with immediate standard-dose tacrolimus and steroids alone [30].

Yoshida and colleagues found that Daclizumab induction with delayed, low-dose tacrolimus, MMF, and steroids had significantly improved GFR at 1 month post transplant compared with controls receiving immediate, standard-dose tacrolimus, MMF, and steroids. There were no differences in ACR between the two groups. At 1 year post

Table 2. Induction to facilitate calcineurin inhibitor minimization.

Reference	Induction	*N*	Maintenance immunosuppression	Follow-up	Graft survival	ACR	Comments
Neuberger [30]	Daclizumab	525	(a) Induction, delayed (POD5), reduced dose tac, steroids, MMF (b) Immediate standard dose tac (>10 ng/mL) and steroids (c) Immediate reduced dose tac (<8 ng/mL), steroids, MMF	1 year	(a) 92.9% (b) 93.9% (c) 94%	(a) 19% (b) 27.6% (c) 29.2%	Patients receiving induction therapy had significant preservation of GFR at 1 year without a difference in ACR
Yoshida [31]	Daclizumab	148	(a) Induction, delayed (POD5), reduced dose tac (<8 ng/mL), steroids,MMF (b) Immediate, standard dose tac (>10 ng/mL), steroids, MMF	1 year	(a) 93% (b) 93%	(a) 23.2% (b) 27%	Patients receiving induction had significantly improved GFR which disappeared at 1 year; however neither group had significant pre-op renal dysfunction
Calmus [32]	Daclizumab	207	(a) Induction, delayed (POD5) standard dose tac, steroids, MMF (b) Immediate, standard dose tac (>10 ng/mL), steroids, MMF	1 year	(a) 98.9% (b) 96.6%	(a) 23.5% (b) 23.8%	No differences in GFR or ACR between groups; however, experimental group was standard dose tac and neither group had significant pre-op renal dysfunction
Soliman [41]	Thymoglobulin	391	(a) Induction, delayed (POD3) standard dose CNI, steroids (b) Immediate standard dose CNI, steroids	1 year	(a) 71.8% (b) 68% (5 years)	(a) 14.5% (b) 31.8% ($P = 0.0008$)	Serum creatinine, GFR significantly better with induction at 1 year; no pre-op renal dysfunction
Tchervenkov [42]	Thymoglobulin	298	(a) Induction, CNI (more likely delayed than control arm), MMF/AZA (more often than control) (b) CNI, MMF/AZA	1 year	(a) 73.9% (b) 75.5%	(a) 29.4% (b) 50% ($P = 0.02$)	Serum creatinine significantly lower with induction at 6 months; similar renal function between groups

transplant the immediate differences in GFR disappeared, and the authors theorized that the immediate differences in GFR noted would be more pronounced in patients with pre-op renal dysfunction, excluded from this study [31].

Calmus and colleagues examined a similar regimen of daclizumab induction, delayed standard-dose tacrolimus, MMF, and steroids to immediate standard-dose tacrolimus, MMF, and steroids. They found no differences in postoperative renal function or ACR between the two groups. These studies have demonstrated that delayed use of CNIs with IL-2RA induction does not increase the risk of rejection and may improve renal function, although improvement depends on using a lower dose of CNI rather than delaying standard-dose CNI administration [32].

Although the previous high-quality randomized controlled trials demonstrated improved or stable GFR without a difference in ACR with delayed, low-dose tacrolimus, and induction immunosuppression, similar findings have not been observed consistently in the kidney transplant literature. Borobia and colleagues retrospectively analyzed 57 patients after kidney transplant receiving basiliximab induction, steroids, cellcept, and tacrolimus immunosuppression. They found that tacrolimus troughs were significantly lower day 5 and 7 post transplant in patients with ACR within the first 3 months than those that had no episodes of rejection ($P = 0.009$, 0.006) [33]. Delaying tacrolimus in the setting of basiliximab induction had no effect on ACR or DGF in a randomized controlled trial conducted by Andres and colleagues, however ($n = 132$, each group) [34]. Barraclough and colleagues demonstrated a significant increase in ACR within the first month post transplant in patients in the lowest tertile of drug exposure POD#4 (as measured by AUC) to combined cellcept, prednisone and tacrolimus vs. the remainder of patients in the middle and highest tertiles of exposure ($P = 0.001$). Both groups received induction with basiliximab. Tacrolimus levels alone on post-op day 4 were not predictive of rejection by multivariate analysis, however [35]. Perhaps not surprisingly, day 4 tacrolimus levels were independently associated with delayed graft function.

In summary while some retrospective reviews correlate early postoperative exposure to tacrolimus with rejection, all patients received induction immunosuppression, and it follows that more immunosuppression is associated with

less rejection [33]. In addition, a higher quality randomized controlled trial found no differences in ACR with delayed tacrolimus with basiliximab induction compared with immediate tacrolimus without induction, a study design that parallels the CNI-sparing trials in the liver transplant literature [34]. Finally, kidney transplantation has a higher risk of acute rejection than liver transplantation, which confounds comparisons between the two organ systems [1].

Several studies have investigated the use of thymoglobulin and alemtuzumab (Campath 1-H) as part of a tolerogenic strategy that employs initial lymphocyte depletion with minimal doses of immunosuppression. These studies are limited by their small sample sizes and while the approach is notable, it is difficult to derive any meaningful conclusion from them. As a whole the tolerogenic approach has not been employed successfully after liver transplantation in the majority of trials investigating this strategy. Starzl and colleagues described a series of 14 patients after liver transplant that received a single dose of thymoglobulin and were maintained on standard-dose monotherapy until 4 months post transplant. After 4 months, patients without rejection episodes were reduced to once-daily tacrolimus dosing that was subsequently reduced to every other day down to once per week with average trough levels 2–4 ng/mL. Twelve patients remained on monotherapy at 1 year. Although the authors did not comment on frequency of rejection episodes, patients with rejection were managed with steroid boluses and increasing the frequency of tacrolimus administration [36]. A similar tolerogenic approach was described in a series of 76 patients who received campath induction, with tacrolimus monotherapy. These patients had a similar incidence of acute rejection compared with matched controls receiving conventional immunosuppression.

De Ruvo and colleagues achieved comparable results with a case–control trial that examined a similar tolerogenic regimen in hepatitis C patients. Twenty-three patients received Thymoglobulin induction with immediate tacrolimus monotherapy, with tacrolimus weaning beginning at 4 months post transplant. The control group ($n = 30$) received standard-dose tacrolimus with steroids (discontinued at 3 months). They found no difference in rejection at 1 year. Episodes of rejection were treated with steroids and reduction in the weaning schedule. There was similar HCV recurrence and survival at 1 year as well; renal function was not assessed [37].

Benitez and colleagues attempted a similar tolerogenic approach in a randomized controlled trial in patients after OLT without hepatitis C. Twenty-one patients were given thymoglobulin and immediate tacrolimus with weaning at month 3, compared with 16 control patients maintained on tacrolimus and steroids alone. The trial was stopped because of a markedly increased frequency of rejection in the experimental arm after attempted tacrolimus weaning (61 vs. 6.2%, $P = 0.001$) [38]. Although the induction regimen and average trough doses during weaning were similar to the other trials, which demonstrated success with tacrolimus weaning, this trial differed in that weaning was not stopped when rejection occurred. Similarly, trials that have attempted a tolerogenic strategy employing lymphocyte depletion with aggressive weaning have not been successful; thymoglobulin induction with sirolimus monotherapy did not allow complete withdrawal of immunosuppression at 6 months after liver transplantation [39], and attempts at stopping tacrolimus completely in a group of 18 liver transplant patients after thymoglobulin induction was unsuccessful [40].

Several retrospective reviews have demonstrated successful use of thymoglobulin induction with less aggressive CNI reduction than those trials investigating a tolerogenic approach. These reviews have shown improved renal function and similar or less frequent acute rejection compared with standard CNI regimens alone. Soliman and colleagues reported a single-center review of 262 patients after OLT who received thymoglobulin induction for 3 days with delayed, standard-dose CNI (POD#3) compared to 129 patients treated with immediate, standard-dose CNIs. Both groups received steroids. At 1 year, rejection was significantly improved in the group treated with thymoglobulin (14.5% vs. 31.8%, $P = 0.0008$). In addition, serum creatinine and GFR were significantly improved at 1 year in the experimental group ($P = 0.01$, 0.02), despite similar renal function between groups at the time of transplant [41]. While limited by its retrospective study design, there were no significant differences between experimental and control groups. This study is one of the largest reviews on this subject, although a power analysis was not performed.

Other retrospective reviews have reported similar results comparing thymoglobulin induction with delayed, standard-dose CNIs to immediate CNI administration alone. Both employed the use of MMF/Azathioprine [42] or MMF/steroids [43] in experimental and control arms. MMF/Azathioprine use was variable in the study reported by Tchervenkov and colleagues which confounds differences between groups [42]. Acute rejection at 1 year was either similar [42] or improved [43] between groups at 1 year post transplant, and renal function was significantly improved at 1 year and 6 months postoperatively [42, 43].

Induction to facilitate steroid avoidance and effects on hepatitis C recurrence

In addition to the adverse metabolic effects of steroid use, steroids have been implicated in hepatitis C recurrence,

a major cause of graft failure in patients transplanted for hepatitis C [44, 45]. Several trials have examined steroid-free protocols using induction immunosuppression to aid steroid avoidance. Eason and colleagues reported the first successful steroid-free protocol using thymoglobulin induction [46]. The authors described a single center, prospective randomized controlled trial in 71 patients after OLT. Thirty-six patients were randomized to receive two doses of thymoglobulin and 35 patients received a methylprednisolone bolus and steroid taper; both arms received standard-dose tacrolimus and MMF. By 3 months all patients were on tacrolimus monotherapy. With 18-month follow-up, the authors noted no difference in ACR between groups, although ACR that required steroid treatment was significantly lower in the thymoglobulin group ($P = 0.01$) Table 3. There was no significant difference in hepatitis C recurrence or metabolic effects of steroid use in either group. Although limited by small sample size, this was the first study to demonstrate successful steroid avoidance after liver transplant.

Many trials have investigated IL2-RA agents to facilitate steroid avoidance. With the exception of one trial which reported a significantly increased incidence of ACR in the steroid-minimizing arm [47], most have shown equivalent or improved efficacy in terms of ACR and hepatitis C recurrence.

Pageaux and colleagues described a multicenter, double-blind placebo controlled trial, which examined steroid minimization in the context of basiliximab induction. All patients received basiliximab induction, cyclosporine and IV steroids until POD#7, at which point patients were randomized to maintenance oral steroids, or a 7 day oral steroid taper that was discontinued POD#14. ACR at 3 months was significantly increased in the steroid-minimizing arm (38% vs. 24%, $P = 0.03$). There were no differences in hepatitis C recurrence or adverse metabolic effects such as hypertension or diabetes [47]. Strengths of this study include its prospective, randomized study design. Although a power analysis was not performed, each group was relatively large (approximately 80 patients per group).

Following this experience, trials have focused on complete avoidance of oral steroids in the steroid-minimization arm, rather than rapid tapering of oral steroids. Filipponi and colleagues reported a single-center, prospective randomized trial of 140 patients with hepatitis C after liver transplant. All patients received induction with basiliximab and azathioprine and cyclosporine for maintenance immunosuppression. Seventy-one patients received steroids, which were discontinued at 3 months; the remaining 66 patients did not receive steroids. Although the authors noted a significantly lower incidence of ACR in the steroid arm (24.3% vs. 39.4%, $P = 0.04$, power 80%), the incidence of ACR requiring treatment was the same at 1 year post transplant. In addition no differences in hepatitis C recurrence were noted in either group.

Two trials comparing IL2-RA induction and CNIs with CNIs and steroids (with or without IL-2RA induction) have demonstrated a similar incidence of ACR in each group and improved or similar hepatitis C recurrence without steroids. Both trials are high-quality prospective, randomized trials powered at >80%. Llado and colleagues studied 198 patients after OLT, randomized to receive basiliximab, cyclosporine and steroids or basiliximab and cyclosporine alone. MMF was added for renal insufficiency to reduce the CNI dose as needed. After 2 years there were no differences in ACR between groups. In hepatitis C patients there was a statistically significant increase in grade 4 portal inflammation, a marker of progression to fibrosis in hepatitis C recurrence, in the steroid-treatment group [48–50]. The authors also noted an increase in bacterial infections in the steroid-treatment arm ($P = 0.05$). Boillot and colleagues examined 351 patients after OLT who received Daclizumab induction with tacrolimus maintenance compared to 349 patients on tacrolimus and steroids alone. Each group received a single bolus of IV methylprednisolone at the time of transplant. At 3 month, the incidence of ACR was similar between groups, however, steroid-resistant ACR was significantly more common in the steroid group. Although hepatitis C recurrence was not measured, the authors reported significantly higher incidences of diabetes and CMV infection in the steroid group [51].

Two recent trials have reported significantly improved ACR using IL-2RA induction in combination with tacrolimus and MMF as compared with maintenance therapy with tacrolimus and steroids alone. Otero and colleagues reported a prospective, multicenter trial that randomized patients to daclizumab induction with tacrolimus and MMF ($n = 78$) or tacrolimus and steroids ($n = 79$) for maintenance immunosuppression without induction. Each group received a single dose of intraoperative IV steroids. They found a significantly decreased incidence of ACR in the induction arm ($P = 0.017$) with no difference in hepatitis C recurrence at 2 years post transplant (power > 80%) [52]. Similarly, Klintmalm and colleagues reported a prospective, multicenter trial with patients randomized to receive tacrolimus and steroids ($n = 80$), tacrolimus, steroids, and MMF ($n = 79$) or daclizumab induction with tacrolimus and MMF ($n = 153$) post-OLT. All patients were hepatitis C positive. At 1 year post transplant, the authors found a statistically significant lower incidence of ACR in patients in the induction arm as compared to the tacrolimus and steroid arm ($P = 0.01$), which retained significance when the two groups that did not receive induction were combined ($P = 0.03$). Hepatitis C recurrence was not significantly different between groups [53].

Table 3. Induction to facilitate steroid avoidance, and effects on hepatitis C recurrence.

Reference	Induction	*N*	Maintenance immunosuppression	Follow-up	Graft survival	ACR	Comments
Eason [46]	Thymoglobulin	71	(a) Induction, tacrolimus, MMF (b) Steroids, tacrolimus, MMF	18 months	(a) 89% (b) 89%	(a) 20.5% (b) 32%	No difference in hepatitis C recurrence in either group
Pageaux [47]	Basiliximab	174	(a) Induction, CSA, IV steroids until POD7 with 7 day oral steroid taper (b) Induction, CSA, IV steroids until POD7 with maintenance steroids	6 months	(a) 90.5% (b) 97.8%	(a) 38% (b) 24.4% ($P = 0.03$)	No difference in hepatitis C recurrence between groups
Filipponi [54]	Basiliximab	140	(a) Induction, CSA, azathioprine (b) Induction, CSA, azathioprine, steroids	1 year	(a) 84.8% (b) 72.9%	(a) 39.4% (b) 24.3% ($P = 0.04$)	No difference in hepatitis C recurrence in either group
Llado [49]	Basiliximab	198	(a) Induction, CSA (±MMF depending on renal function) (b) Induction, CSA, steroids (±MMF depending on renal function)	2 years	(a) 78% (b) 65%	(a) 17% (b) 21%	No difference in hepatitis C recurrence in either group, however increase in grade 4 portal inflammation steroid group ($P = 0.04$)
Boillot [51]	Daclizumab	698	(a) Induction, tacrolimus (b) Tacrolimus, steroids	3 months	(a) 90.5% (b) 92.2%	(a) 25.4% (b) 26.5%	Hepatitis C recurrence not measured; significantly higher incidence CMV and DM 2 in steroid group
Otero [52]	Daclizumab	157	(a) Induction, tacrolimus, MMF (b) Tacrolimus, steroids	2 years	(a) 89.7% (b) 88.6%	(a) 11.5% (b) 26.6% ($P = 0.01$)	No difference in hepatitis C recurrence between groups
Klintmalm [53]	Daclizumab	312	(a) Induction, tacrolimus, MMF (b) Tacrolimus, MMF, steroids (c) Tacrolimus, steroids	1 year	(a) 89.9 % (b) 88.1% (c) 84.8%	(a) 7% (b) 12% (c) 18.1% ($P = 0.01$ induction vs. c; $P = 0.03$ induction vs. b, c combined)	No difference in hepatitis C recurrence between groups

Although there are few trials investigating alemtuzumab (Campath) as an induction agent, one retrospective review suggested an increase in Hepatitis C recurrence associated with Campath induction, which lead to the abandonment of this strategy in hepatitis C patients.

In summary, the literature to date demonstrates that the use of steroid minimization in the context of induction immunosuppression is safe, as it does not result in an increase in ACR post transplant in the absence of oral steroids [47]. The incidence of ACR was improved in trials that compared steroid & CNI regimens with IL2RA induction, CNIs, and MMF, however, the use of MMF in the control arm only makes it difficult to attribute this improvement to the use of induction alone [52, 53]. Induction immunosuppression did not result in an increase in hepatitis C recurrence. It is worth noting, however, that the absence of steroids did not result in a lower incidence of hepatitis C recurrence, except for one study, which found an increase in peri-portal inflammation at 2 years post transplant in the steroid-treatment arm [49]. The adverse metabolic and infectious complications were noted in two studies reporting an increase in CMV, bacterial infections and diabetes in the steroid group [49, 51], although most studies with follow-up beyond the period of steroid treatment found no difference in metabolic complications between groups [47, 52, 54].

Side effects

Infection and malignancy are the most serious side effects associated with immunosuppressive medications, and the same is true for induction immunosuppression. In the modern era of induction immunosuppression and infectious prophylaxis, increased susceptibility to bacterial, fungal, or CMV infections in patients receiving induction therapy has not been observed in the recent literature [55]. No differences in infection were observed in studies that examined thymoglobulin as an adjunct to existing regimens [9, 51] or to facilitate CNI minimization [37, 38, 41]. Similarly, a meta-analysis of 12 randomized controlled trials examining IL2-RA induction as an adjunct to existing immunosuppressive regimens found no difference in infectious complications between groups [11]. The use of IL2-RA inhibitors as part of a CNI- or steroid-sparing strategy has not been associated with an increase in infectious complications [26, 27, 29–32] [47, 49, 52–54]. Although one retrospective review reported an increase in all infections with Alemtuzumab induction ($P = 0.03$) [56]. Other retrospective reviews with Alemtuzumab have shown no difference in infectious complications [18, 57].

Liver transplant recipients have a higher rate of de novo malignancy and cancer-related mortality than the general population [58]. Analysis of the effects of induction on de novo malignancy is complicated by changes in induction agents and duration of therapy over the past several decades; the incidence of post-transplant lymphoproliferative disorder, for example, has decreased in the last decade [59]. Large registry analyses concerning the effects of induction on malignancy post transplant with adequate follow-up exist in the kidney transplant literature and have not been performed in the liver transplant population. An analysis of 25 000 patients from the United States Renal Data System from 1996 to 2001 demonstrated induction therapy was associated with an increase in PTLD compared with patients that did not receive induction. When induction agents were analyzed separately, however, neither thymoglobulin nor IL2-RA inhibitors were associated with an increase in PTLD post transplant [60]. Although limited by small sample sizes and short (5 year) follow-up, single-center randomized controlled trials [8, 9] and retrospective reviews [42] concerning the use of thymoglobulin in liver transplantation have not demonstrated an increase in de novo malignancy after thymoglobulin induction. A meta-analysis of 12 randomized controlled trials similarly demonstrated no increased incidence of malignancy with IL2-RA induction [11].

International practices

The international use of induction immunosuppression in liver transplantation is similar to that which has been presented previously, namely to facilitate steroid avoidance or calcineurin inhibitor minimization. Several of the trials presented here are from centers in Europe [8, 12, 13, 47, 49, 52, 54, 61–64] and Asia [11, 14, 65]. One such CNI minimizing strategy is termed the 'bottom up' approach to patients with pretransplant renal insufficiency at a European center. The protocol consists of induction with basiliximab, maintenance therapy with MMF and steroids, and delayed introduction of sirolimus. A retrospective, case–control review demonstrated significantly improved renal function at 6 months in patients with 'bottom up' immunosuppression compared with controls ($P = 0.0006$) although sample size was small (15 in each group) [66, 67].

Pediatric liver transplantation

The principal induction agent used in pediatric liver transplantation is basiliximab (Simulect, Novartis). As induction, it is generally dosed at 20 mg intravenously on days 0 and 4 in children >35 kg, and at 10 mg intravenously on days 0 and 4 for those <35 kg [68]. Since children in particular benefit from steroid avoidance, basiliximab was evaluated as means of avoiding steroids altogether. Gras reported on 50 children treated with a steroid-free, tacrolimus-basiliximab-based immunosuppressive regimen and

compared them to 38 patients receiving conventional tacrolimus and steroids. Although patient and graft survival were the same, less rejection occurred in the basiliximab group ($P = 0.007$) as well as less viral infection ($P = 0.045$) and better growth scores [69]. Similar conclusions were reached in a randomized trial of basiliximab induction versus steroid therapy by Spada *et al.* comparing two groups of 36 patients each. Patients free from rejection were 87.7% in the basiliximab group compared to 67.7% in the steroid group ($P = 0.036$). Overall incidence of infection was 72.3% in the steroid group and 50% in the basiliximab group ($P = 0.035$) [70]. Thus, basiliximab is often used as induction in pediatric liver transplantation because of its steroid-sparing benefit and reduction in acute rejection. Since daclizumab is no longer available for clinical use as of 2009 when its marketing authorization was withdrawn, this anti-CD25 monoclonal antibody is no longer an alternative to basiliximab.

There is a paucity of publications on ATG induction use in pediatric liver transplantation in the past decade, and the principal comments published on the topic refer mostly to the increased incidence of malignancy, particularly PTLD, in children treated with depleting antibody such as ATG or OKT3. Since OKT3 has not been available since 2009 when it was voluntarily withdrawn from the market, it is no longer relevant to clinical decision-making. ATG has been used for rescue therapy in children with steroid-resistant rejection with good success, although 6 of the 14 children in whom it was needed had been induced with ATG or OKT3, suggesting that induction does not protect from steroid-resistant rejection [71].

Conclusions

Induction with antibody is used in only a minority, approximately 25%, of liver transplant patients in the United States at this time (Fig. 1). The most commonly used strategy of early immunosuppression is the drug tacrolimus (90%), with or without steroids and/or mycophenolate. About 15% of adults receive an anti-CD25 mAb as induction, and about 10% ATG. In children, basiliximab is used most often of the antibodies. Since tacrolimus is started with the goal of achieving relatively higher levels than are targeted at later time points, tacrolimus is being used with essentially the same intention as induction antibody use: that is, to provide initially potent immunosuppression at the time of the transplant when risk of rejection is highest, followed by subsequent lowering of dosage over time to achieve lower long-term maintenance levels.

As the risks associated with basiliximab are low, it is used most often in adults with renal functional impairment to allow delayed introduction of calcineurin inhibitors (CNI) and thus delay the renal insult of CNI therapy until renal function improves. In children, basiliximab is often used to reduce or avoid steroid therapy and its attendant effects on growth retardation, and also to reduce the incidence of acute rejection. These practices are supported by level III published data but reflect clinical practices prevalent in the United States in 2012.

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