

WJG 20<sup>th</sup> Anniversary Special Issues (7): Liver transplant**Corticosteroid-free immunosuppression in liver transplantation: An evidence-based review**

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**Abstract**

Thirty-six randomized controlled trials and two meta-analyses were reviewed. With respect to adult patients undergoing first orthotopic liver transplantation (OLT), steroid replacement resulted in fewer cases of overall acute rejection in the corticosteroid free-immunosuppression arm. Initial steroid administration for two weeks and early tacrolimus monotherapy is a feasible immunosuppression regimen without steroid replacement, although further investigations are needed in view of chronic rejections. No significant differences were noted between the treatment groups in terms of patient and graft survival independently of steroid replacement. Renal insufficiency, *de novo* hypertension, neurological disorders and infectious complications did not differ significantly among steroid and steroid-free groups. Diabetes mellitus, cholesterol levels and cytomegalovirus infection are more frequent in patients within the steroid group. With respect to diabetes mellitus and hypercholesterolemia, the difference was independent of steroid replacement. In relation to transplanted hepatitis C virus patients, mycophenolate

mofetil does not appear to have a significant antiviral effect despite early reports. Male gender of donors and recipients, living donors, cold ischemia times, acute rejection, and early histological recurrence were related to the development of advanced hepatitis. There is sufficient scientific clinical evidence advocating avoidance of the *ab initio* use of steroids in OLT.

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**Key words:** Meta-analysis; Evidence based; Hepatitis C virus recurrence; Liver transplantation; Steroid withdrawal; Orthotopic liver transplantation

**Core tip:** Steroid replacement in orthotopic liver transplantation results in fewer cases of overall acute rejection in the corticosteroid free-immunosuppression arm. Tacrolimus monotherapy is a feasible immunosuppression regimen without steroid replacement, although further investigations are needed in view of chronic rejections. No significant differences were noted between the treatment groups in terms of patient and graft survival independently of steroid replacement. Male gender, living donors, cold ischemia times, acute rejection, and early histological recurrence are related to the development of advanced hepatitis. There is sufficient evidence advocating avoidance of the *ab initio* use of steroids in orthotopic liver transplantation.

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**INTRODUCTION**

During the last decades, patients undergoing liver trans-

plantation have had favorable outcomes, mainly due to the evolution of immunosuppressive agents. The use of steroids is still considered the mainstay of immunosuppression following liver transplantation as they decrease the risk of rejection. Nevertheless, they are also related to a large number of side-effects, as well as the potential recurrence of hepatitis C virus (HCV). The most common indication for liver transplantation is chronic HCV infection, accounting for about 40% of all transplants performed in the United States<sup>[1]</sup>. Initially, the main concern after liver transplantation has always been the prevention of rejection, but current challenges also include preventing toxicity from anti-rejection (immunosuppressive) agents, while providing adequate immunosuppression to preserve optimal results<sup>[2]</sup>. The advent of new agents addresses the need for immunosuppression to be more specific and free of the long-term side-effects of steroids. Immunosuppressive protocols currently focus on the avoidance of steroids and the use of a combination of different agents that reduce their respective toxicities. Many authors believe that early withdrawal of steroids can be made safely<sup>[3,4]</sup>, but the duration of steroid administration after liver transplantation and the initiation of steroid-free immunosuppression remain controversial.

A number of randomized control trials (RCTs) have been published concerning outcomes of steroid avoidance in liver transplantation. Two recently published meta-analyses (including RCTs published up to 2007) failed to draw robust conclusions owing to the heterogeneity of studies.

The different immunosuppressive regimens, varying follow-up periods, small sample sizes, and high percentages of failure of participants to undergo the allocated treatment were important bias factors in these meta-analyses.

Various sufficiently powered RCTs have been published in the last six years, addressing specific issues of steroid avoidance in liver transplantation.

The purpose of this review was to better define the role of the steroid-free immunosuppressive regimens in liver transplant recipients according to Evidence-based Medicine Levels of Evidence.

## RESEARCH

With the intention of identifying suitable studies, the electronic databases Medline, Embase, Pubmed and the Cochrane Library were used to search for articles from 1990 to 2013 in the English language literature which integrated the subsequent terms and/or combinations in their titles, abstracts or keyword lists: Randomized controlled trials, double-blind, liver transplantation, steroids, withdrawal, glucocorticoids, prednisone, methylprednisone, orthotopic liver transplantation and allograft. Where it was appropriate the above-mentioned terms were used in “(MESH)” (Pubmed and the Cochrane Library) otherwise the terms were combined with “AND/OR” and asterisks. Furthermore, the abstracts from national and international conferences were searched using

online search engines corresponding to the particular conference.

After the initial screen additional criteria were imposed: (1) no less than one treatment group had early withdrawal or no steroid administration and a second treatment arm in which the patients received at least 3 mo of steroids; (2) study analysis was by intention to treat; and (3) studies of pediatric patients or both pediatric and adult population were excluded.

The two authors separately chose studies for inclusion and exclusion and reached consensus when they did not agree in the initial allocation. The subsequent variables were recorded: authors, journal and year of publication, country of origin, trial duration, participant demographics and data concerning rejection, adverse events, complications, follow up and survival.

## CORTICOSTEROID-FREE IMMUNOSUPPRESSION IN LIVER TRANSPLANTATION

Thirty six RCTs<sup>[5-40]</sup> (some of which were updated versions of already published studies) and two meta-analyses<sup>[41,42]</sup> (including 19 and 21 of the above-mentioned RCTs, respectively) were reviewed. The evidence-based medicine levels of evidence and grades of Recommendation are shown in Tables 1 and 2. The baseline characteristics of the RCTs are summarized in Table 3. The strength and quality of the evidence is summarized in Table 4.

### Adult patients undergoing first OLT for any indication

**Rejection:** Steroid replacement is presented with fewer cases of overall acute rejection in the corticosteroid-free immunosuppression arm (level of evidence: 1a-, degree of recommendation: D).

In the meta-analysis of Sgourakis *et al*<sup>[42]</sup>, the corticosteroid-free immunosuppression group was equivalent to the steroid group in comparisons related to the following outcomes: acute rejection [mild: RR = 0.94 (0.69-1.29),  $P = 0.7$ ] [moderate: RR = 1.02 (0.83-1.27),  $P = 0.8$ ] [chronic rejection: RR = 1.52 (0.71-3.23),  $P = 0.2$ ] and [steroid-resistant rejection: RR = 1.34 (0.87-2.08),  $P = 0.5$ ]. Heterogeneity among studies in terms of acute rejection was observed. Considering overall acute rejection, in contrast to the results of meta-analysis (comparable results between treatment arms), metaregression showed that taking into account independently the RCT that replaced steroids [different regimens among studies *e.g.*, daclizumab (DAC), rabbit antithymocyte globulin, mycophenolate mofetil (MMF), or daclizumab and MMF], the outcome favored the corticosteroid-free immunosuppression arm [RR = 1.31 (1.09-1.58),  $P < 0.01$ ], while the reverse applied when steroids were not replaced. In the meta-analysis by Segev *et al*<sup>[41]</sup>, the rates of rejection within the first three months were somewhat higher among the steroid-free arms [RR = 1.31 (1.04-1.64),  $P = 0.02$ ] in studies where steroids were stopped, but not replaced. In contrast, the

**Table 1 Evidence-based medicine levels of evidence<sup>[43]</sup>**

| Level | Therapy/prevention, etiology/harm  | Prognosis  |
|-------|--|--|
| 1a    | SR (with homogeneity <sup>1</sup> ) of RCTs                                | SR (with homogeneity <sup>1</sup> ) of inception cohort studies; CDR <sup>2</sup> validated in different populations   |
| 1b    | Individual RCT (with narrow Confidence Interval <sup>3</sup> )             | Individual inception cohort study with > 80% follow-up; CDR <sup>2</sup> validated in a single population  |
| 1c    | All or none <sup>3</sup>   | All or none case-series  |
| 2a    | SR (with homogeneity <sup>1</sup> ) of cohort studies                      | SR (with homogeneity <sup>1</sup> ) of either retrospective cohort studies or untreated control groups in RCTs   |
| 2b    | Individual cohort study (including low quality RCT; e.g., < 80% follow-up) | Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR <sup>2</sup> or validated on split-sample <sup>4</sup> only |
| 2c    | "Outcomes" Research; Ecological studies                                    | "Outcomes" research  |
| 3a    | SR (with homogeneity <sup>1</sup> ) of case-control studies                |  |
| 3b    | Individual case-control study  |  |

<sup>1</sup>A systematic review (SR) that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level; <sup>2</sup>Clinical decision rule (CDR) (These are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category); <sup>3</sup>Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but now none die on it; <sup>4</sup>Split-sample validation is achieved by collecting all the information in a single tranche, and subsequently artificially dividing this into "derivation" and "validation" samples. RCTs: Randomized control trials.

rates of rejection were markedly lower in the steroid-free arms [RR = 0.67 (0.48-0.96),  $P = 0.03$ ] where steroids were replaced by other immunosuppressive agents. The rates of severe rejection also had a slightly higher trend, although not statistically significant, in studies where steroids were stopped, but not replaced [RR = 1.36 (0.63-2.93),  $P = 0.4$ ]. In studies in which steroids were replaced by another IS agent, severe rejection [RR = 0.37 (0.20-0.68),  $P = 0.001$ ] was markedly lower in the steroid-free arms.

The above-mentioned meta-analyses failed to provide a conclusive answer as many single studies resulted in a wide Confidence Interval and these meta-analyses had troublesome heterogeneity. Such evidence is inconclusive, and can thus only generate Grade D recommendations.

Four RCTs were published after these two meta-analyses<sup>[9,29,32,40]</sup>.

Steroid replacement by daclizumab + MMF resulted in fewer cases of biopsy proven acute rejection (BPAR) at 24 wk in the corticosteroid-free immunosuppression arm (level of evidence: 1b, degree of recommendation: A).

The study by Otero *et al*<sup>[29]</sup> [Tacrolimus (TACRO) + ST (3 mo) *vs* TACRO + Daclizumab + MMF - steroids replaced] enrolled 77 patients per treatment group which was required to provide 80% power to detect a difference

**Table 2 Grades of recommendation<sup>[43]</sup>**

|   |   |
|---|---|
| A | Consistent level 1 studies  |
| B | Consistent level 2 or 3 studies or extrapolations from level 1 studies          |
| C | Level 4 studies or extrapolations from level 2 or 3 studies                     |
| D | Level 5 evidence or troubling inconsistent or inconclusive studies of any level |

between the null hypothesis (a rejection rate of 40% in both groups) and the alternative hypothesis (a rejection rate of 16% in the modified therapy group) with a 2-sided significance level of 0.05 to allow for an estimated 20% discontinuation rate. Significantly more patients in the standard therapy group experienced BPAR at 24 wk in comparison with patients in the modified (steroids replaced) therapy group (26.6% *vs* 11.5%,  $P = 0.017$ ).

Initial steroid administration for two weeks and early Tacrolimus monotherapy is a feasible immunosuppression regimen without steroid replacement, although in view of chronic rejections, further investigations are needed (level of evidence: 1b, degree of recommendation: A).

In the study by Weiler *et al*<sup>[40]</sup> [TACRO + ST (steroids) for the first 2 wk followed by TACRO *vs* TACRO + ST (6 mo) - steroids not replaced], acute rejection after initiation of the study medication was comparable for both groups. Steroid-free immunosuppressive therapy leads to a higher rate of chronic rejection ( $P = 0.023$ ). This study was statistically powered (the initial scheduled sample size of 50 per treatment group was based on an estimated difference in the incidence of steroid side-effects of 15% between the primary study endpoints).

Ab initio tacrolimus monotherapy is a viable immunosuppressive approach in liver transplantation and is associated with lower rejection rates compared to microemulsified cyclosporine (CyA) (level of evidence: 2b, degree of recommendation: B).

Monotherapy (microemulsified CyA/TACRO) in both groups was used in the study by Cholongitas *et al*<sup>[9]</sup>. Patients in the TACRO group, as compared to those in the CyA group, had a significantly lower number of mild ( $P = 0.004$ ), severe ( $P = 0.006$ ) and total ( $P = 0.001$ ) rejection episodes per patient. Chronic rejection was observed in four (11%) patients receiving CyA. No patient receiving TACRO experienced chronic rejection ( $P < 0.001$ ). This study was not statistically powered.

**Adverse events:** Renal insufficiency, *de novo* hypertension, neurological disorders and infectious complications do not differ significantly among steroid and steroid-free groups (level of evidence: 1a, degree of recommendation: B).

In a meta-analysis by Sgourakis *et al*<sup>[42]</sup>, the corticosteroid-free immunosuppression group was equivalent to the steroid group in comparisons concerning the following outcomes: renal insufficiency [RR = 0.93 (0.78-1.11),  $P = 0.4$ ] and severe renal insufficiency [odds ratio (OR) = 0.98 (0.52-1.81),  $P = 0.9$ ] requiring hemofiltration, *de novo*

Table 3 Baseline study characteristics

| Ref.   | Indication                                | Recipients   | Regimens   | Outcomes  | Study duration                    | Rejection treatments protocols  |
|--|---|--|--|---|-----------------------------------|---|
| Belli <i>et al.</i> <sup>[6]</sup><br>2001   | HCV positive                              | Group A = 13<br>Group B = 11<br>Group C = 13   | RATG + AZA + CyA + ST (3 mo)<br>/RATG + AZA + CyA<br>/RATG + AZA + CyA + ribavirin   | Acute rejection, chronic rejection, HCV recurrence                                      | November<br>1997-November<br>1999 | NS  |
| Boillot <i>et al.</i> <sup>[7]</sup><br>2005   | Adult patients<br>undergoing first<br>OLT | Group A = 351<br>(103)<br>Group B = 347<br>(106)   | TACRO + daclizumab/TACRO + ST (3 mo)   | Acute rejection, corticosteroid resistant acute rejection, graft survival               | July<br>2000-February<br>2002     | Increasing TACRO dose and/or steroids   |
| Eason <i>et al.</i> <sup>[8]</sup><br>2003   | Adult patients<br>undergoing first<br>OLT | Group A = 59<br>(34)<br>Group B = 60<br>(31)   | RATG + TACRO + MMF/ST (3 mo) +<br>TACRO + MMF  | Patient survival, graft survival, rejection, adverse events, HCV recurrence             | December<br>1999-August<br>2002   | Increasing TACRO or adding MMF or sirolimus; steroids if no improvement after 48 h  |
| Filippini <i>et al.</i> <sup>[11]</sup><br>2004                                      | HCV positive                              | Group A = 74<br>Group B = 66   | Basiliximab + ST (3 mo) + CyA + AZA/<br>basiliximab + CyA + AZA  | HCV recurrence, patient survival, graft survival, treatment failure                     | October<br>1998-March 2001        | Methylprednisolone bolus for 3 d  |
| Kato <i>et al.</i> <sup>[14]</sup><br>2007   | HCV positive                              | 1 <sup>st</sup> Period<br>Group A = 15<br>Group B =<br>16/2 <sup>nd</sup> Period<br>Group A = 16<br>Group B = 23 | 1 <sup>st</sup> Period TACRO + daclizumab/TACRO<br>+ ST (3 mo)/2 <sup>nd</sup> Period TACRO +<br>daclizumab + MMF/TACRO + ST (3 mo)<br>+ MMF | Fibrosis stage, acute rejection, adverse events, predictors                             | November<br>1999-November<br>2001 | Methylprednisolone bolus ± taper; OKT3 for severe<br>or treatment-resistant rejection   |
| Klintmalm <i>et al.</i> <sup>[16]</sup><br>2007<br>(updated by<br>Klintmalm<br>2011) | HCV positive                              | Group A = 80<br>Group B = 79<br>Group C = 153  | TACRO + ST (3 mo)/TACRO + ST (3 mo)<br>+ MMF/daclizumab + TACRO + MMF  | Risk factors, rejection, HCV recurrence, treatment failure                              | NS                                | Methylprednisolone bolus ± taper; mild rejection<br>increasing tacrolimus ± antimetabolite (MMF or<br>azathioprine)<br>Antilymphocyte antibody for corticosteroid-<br>resistant rejection |
| Langrehr <i>et al.</i> <sup>[18]</sup><br>2002                                       | HCV positive                              | Group A = 27<br>Group B = 26   | TACRO + ST (3 mo)/TACRO + MMF  | Rejection, HCV recurrence   | NS                                | NS  |
| Lerut <i>et al.</i> <sup>[19]</sup><br>2004 (updated<br>by Lerut 2008)               | Adult patients<br>undergoing first<br>OLT | Group A = 50<br>Group B = 50   | TACRO + ST (3 mo)/TACRO  | Acute rejection, graft survival, adverse events   | NS                                | NS  |
| Lladó <i>et al.</i> <sup>[21]</sup><br>2006 (updated<br>by Lladó 2008)               | Adult patients<br>undergoing first<br>OLT | Group A = 102<br>(45)<br>Group B = 96<br>(43)  | Basiliximab + CyA + ST (3 mo)/<br>basiliximab + CyA  | Acute rejection, patient survival, graft survival, infection                            | April<br>2001-September<br>2004   | Methylprednisolone bolus for 3 d ± taper ± increase<br>in TACRO   |
| Lupo <i>et al.</i> <sup>[17]</sup><br>2005 (updated<br>by Lupo 2008)                 | Adult patients<br>undergoing first<br>OLT | Group A = 20<br>(9)<br>Group B = 21<br>(11)  | CyA + ST (3 mo)/CyA + Basiliximab  | Acute rejection   | NS                                | Methylprednisolone bolus for 3 d  |
| Margarit <i>et al.</i> <sup>[25]</sup><br>2005                                       | Adult patients<br>undergoing first<br>OLT | Group A = 28<br>(20)<br>Group B = 32<br>(15)   | TACRO/TACRO + ST (3 mo)  | Acute rejection, severe acute rejection, HCV recurrence, 3<br>yr-graft survival         | October<br>1998-September<br>2000 | Increasing tacrolimus dose; methylprednisolone<br>bolus for 3 d ± taper for severe rejection  |
| Moench <i>et al.</i> <sup>[26]</sup><br>2007 (updated<br>by Weiler<br>2010)          | Adult patients<br>undergoing first<br>OLT | Group A = 56<br>(15)<br>Group B = 54<br>(16)   | TACRO/TACRO + ST (6 mo)  | Patient survival, graft survival, acute rejection, chronic<br>rejection, adverse events | February<br>2000-August<br>2004   | Methylprednisolone; tacrolimus adjusted higher<br>level   |

| Author (Year)   | Study Design                                    | Group A (n)       | Group B (n)       | Regimen   | Primary Endpoints  | Secondary Endpoints | Follow-up                    | Significance   | Notes  |
|---|---|-------------------|-------------------|---|--|---------------------|------------------------------|----------------|--|
| Nashan <i>et al.</i> <sup>[27]</sup> 2001                       | Adult patients undergoing first OLT             | Group A = 25 (15) | Group B = 26 (15) | Basiliximab + CyA + ST (3 mo)/ Basiliximab + CyA + MMF                | Rejection, HCV recurrence  |                     | January 1999-December 2000   | NS             |  |
| Pagaux <i>et al.</i> <sup>[60]</sup> 2004                       | Adult patients undergoing first OLT             | Group A = 90      | Group B = 84      | Basiliximab + CyA + ST (6 mo)/ basiliximab + CyA + placebo            | Acute rejection, 6-mo graft and patient survival, treatment failure, recurrent HCV, adverse events   |                     | December 1999-August 2001    | NS             |  |
| Pelletier <i>et al.</i> <sup>[31]</sup> 2005                    | Adult patients undergoing first OLT             | Group A = 36      | Group B = 36      | TACRO + MMF + ST (3-6 mo) /TACRO + MMF                                | Rejection, HCV recurrence, graft survival patient survival   |                     | June 2002-May 2004           | Pulse steroids |  |
| Reggiani <i>et al.</i> <sup>[63]</sup> 2005                     | Adult patients undergoing first OLT             | Group A = 18      | Group B = 12      | TACRO + MMF + ST (3 mo)/TACRO + MMF                                   | Acute rejection, adverse events, pharmacokinetics of MPA   |                     | NS                           | NS             | NS/increasing tacrolimus for mild rejection; methylprednisolone bolus 3 d ± taper for moderate rejection; OKT3 for steroid-resistant rejection                                 |
| Samonakis <i>et al.</i> <sup>[64]</sup> 2006                    | HCV positive                                    | Group A = 27      | Group B = 29      | TACRO/TACRO + ST (3-4 mo) + AZA                                       | Acute rejection, survival, re-transplantation, adverse events  |                     | January 2000-January 2004    | NS             | Methylprednisolone bolus for 3 d   |
| Studnik <i>et al.</i> <sup>[65]</sup> 2005                      | Adult patients undergoing first OLT             | Group A = 19      | Group B = 20      | TACRO + dactizumab + ST (3 mo) + MMF/TACRO + dactizumab + MMF         | Acute rejection  |                     | February 2003-November 2004  | NS             |  |
| Tisonne <i>et al.</i> <sup>[67]</sup> 1999                      | Adult patients undergoing first OLT             | Group A = 22      | Group B = 23      | CyA + AZA + ST (3 mo)/CyA + AZA                                       | Graft survival, adverse events, HCV recurrence   |                     | NS                           | NS             | Methylprednisolone bolus for 3 d only for severe rejection duct damage   |
| Varo <i>et al.</i> <sup>[68]</sup> 2005 (updated by Otero 2009) | Adult patients undergoing first OLT             | Group A = 79      | Group B = 78      | TACRO + ST (3 mo)/TACRO + dactizumab + MMF                            | Acute rejection  |                     | NS                           | NS             | Up to 3 full courses of high dose steroids   |
| Washburn <i>et al.</i> <sup>[69]</sup> 2001                     | Adult patients undergoing first OLT             | Group A = 15      | Group B = 15      | TACRO + MMF + ST (15 mo)/ dactizumab + TACRO + MMF                    | Adverse events, rejection  |                     | April 1999-October 1999      | NS             | Increasing tacrolimus dose; steroid bolus for moderate rejection   |
| Manousou <i>et al.</i> <sup>[69]</sup> 2009                     | HCV positive                                    | Group A = 54      | Group B = 49      | TACRO/TACRO + AZA + ST (3 mo)   | Progression to Ishak S4, graft failure resulting in retransplantation or patient death, immunological failure, patient survival, acute rejection, chronic rejection, steroid-resistant rejection, recurrent HCV  |                     | January 2000-June 2007       | NS             | Pulse steroids   |
| Ramirez <i>et al.</i> <sup>[62]</sup> 2013                      | Adult patients undergoing first OLT             | Group A = 20      | Group B = 19      | Basiliximab + TACRO + EC-MPS + ST (6 mo)/basiliximab + TACRO + EC-MPS | Patient survival, graft survival, rejection, adverse events  |                     | February 2006-November 2007  | NS             |  |
| Neumann <i>et al.</i> <sup>[66]</sup> 2012                      | HCV positive                                    | Group A = 67      | Group B = 68      | TACRO + ST (3 mo)/TACRO + DAC   | Viral load of HCV at 12 mo, the incidence of BPAR, patient and graft survival at 12 mo, renal function, adverse events   |                     | June 2005-June 2008          | NS             | Increasing tacrolimus dose to trough levels of 15 ng/mL ± pulses of corticosteroids up to 1000 mg/d for 3 consecutive days   |
| Takada <i>et al.</i> <sup>[66]</sup> 2013                       | Living donor liver transplantation HCV positive | Group A = 35      | Group B = 40      | TACRO + ST (3 mo) /TACRO + MMF  | Event-free survival: histological recurrence of hepatitis C, BPAR resistant to 2 sets of steroid pulse therapy, hepatocellular carcinoma recurrence, Re-transplantation, Patient death   |                     | NS                           | NS             | Pulse steroids   |
| Lerut <i>et al.</i> <sup>[69]</sup> 2008                        | Adult patients undergoing first OLT             | Group A = 78      | Group B = 78      | TACRO + ST (64 d)/TACRO   | Graft and patient survival, incidences of TAC monotherapy and of low-dosage TAC monotherapy, renal insufficiency, diabetes mellitus, hypercholesterolemia, hyperuricemia, arterial hypertension, infectious, tumor complications, and performance status |                     | February 2000-September 2004 | NS             | Corticosteroid-sensitive rejection was treated with 3 to 5 oral or IV boluses of 200-mg Methylprednisolone. CRC was treated with a 10-d IV course of muromonab orthoclone OKT3 |

| Author et al [ref]                     | Study Design   | Group A = 305<br>Group B = 297 | TACRO + daclizumab/TACRO + MMF  | Rejection, overall survival and allograft survival, renal function  | March 2005-June 2007        | NS   |
|--|--|--------------------------------|---|---|-----------------------------|--|
| Becker <i>et al</i> [5] 2008           | Adult patients undergoing first OLT or split liver allograft transplantation | Group A = 36<br>Group B = 30   | CyA/TACRO   | Death   | January 1996-January 1997   | Acute rejection was treated with three 1 g/d methylprednisolone boluses  |
| Cholongitas <i>et al</i> [9] 2011      | Chronic liver disease  | Group A = 8<br>Group B = 13    | CNI/MMF vs a MMF/prednisone   | Renal function  | May 2003-May 2005           | “mild” rejection episodes were treated with steroid boluses<br>Steroid pulse therapy   |
| Gerhardt <i>et al</i> [12] 2009        | Adult patients undergoing first OLT  | Group A = 77<br>Group B = 72   | TACRO + ST (3 mo)/TACRO + ST (3 mo) + MMF/daclizumab + TACRO + MMF          | Acute rejection, HCV recurrence, survival   | NS                          | ACR was treated with an increase in TACRO to 15 ng/mL without a corticosteroid bolus and recycle. Moderate to severe ACR 4) was treated with a 1.0-g bolus of methylprednisolone, followed by a 6-d steroid taper of intravenous methylprednisolone or oral prednisone |
| Klntmalm <i>et al</i> [13] 2011        | HCV positive   | Group C = 146                  |   |   |                             |  |
| Lladó <i>et al</i> [21] 2008           | HCV positive   | Group A = 46<br>Group B = 43   | Basiliximab + CyA + ST (3 mo)/basiliximab + CyA                             | Acute rejection, patient and graft survival, adverse events (infections and metabolic decompensations), HCV recurrence  | April 2001-September 2004   | Methylprednisolone bolus for 3 d ± taper ± increase in TACRO   |
| Lupo <i>et al</i> [23] 2008            | Adult patients undergoing first OLT  | Group A = 21<br>Group B = 26   | CyA + ST (3 mo)/CyA + Basiliximab   | Acute rejection, patient and graft survival, HCV recurrence, medical and surgical complications, infections   | November 2002-November 2005 | Methylprednisolone bolus for 3 d   |
| Otero <i>et al</i> [29] 2009           | Adult patients undergoing first OLT  | Group A = 79<br>Group B = 78   | TACRO + ST (3 mo)/TACRO + Daclizumab + MMF                                  | Acute rejection, time to rejection, patient and graft survival, HCV status, hepatic and renal function  | May 2002-December 2003      | Up to 2 courses of high dose steroids for 3 d<br>Corticosteroid-resistant rejection episode was treated with anti-lymphocyte therapy   |
| Weiler <i>et al</i> [40] 2010          | Adult patients undergoing first OLT  | Group A = 56<br>Group B = 54   | All patients TACRO + steroids for the first 2 wk<br>TACRO/TACRO + ST (6 mo) | Patient survival, organ survival, steroid side-effects, acute rejection, chronic rejection, HCV recurrence  | February 2000-August 2004   | Methylprednisolone; tacrolimus adjusted higher level   |
| Junge <i>et al</i> [15] 2005           | Recipients with autoimmune hepatitis   | Group A = 14<br>Group B = 16   | TACRO + steroids/TACRO + MMF  | Graft and patient survival, acute rejection, liver functions, glucose metabolism, bone density, blood pressure, renal function, drug-related side-effects, infections | NS                          | Mild or moderate rejection: methylprednisolone pulse therapy<br>severe rejection: high-dose steroids + monoclonal antibody   |
| Bonaccorsi-Riani <i>et al</i> [8] 2012 | HCV positive   | Group A = 14<br>Group B = 21   | TACRO + steroids (2 mo)/TACRO + placebo                                     | 1 and 5 yr survival; HCV recurrence, retransplantation, death   | NS                          | NS   |

Numbers within brackets in the third column show the number of hepatitis C virus (HCV) transplanted patients; CyA: Cyclosporine; TACRO: Tacrolimus; ST: Steroids; RATG: Rabbit antithymocyte globulin; AZA: Azathioprine; MMF: Mycophenolate mofetil; OKT3: Murine monoclonal IgG2a antibody; EC-MPS: Enteric-coated mycophenolate sodium; BPAR: Biopsy-proven acute rejection; S4: Stage 4; CRC: Corticosteroid-resistant rejection; OLT: Orthotopic liver transplantation; BPAR: Biopsy proven acute rejection; NS: Non-significance.

Table 4 Summary of the strength and quality of the evidence

| Intervention   | Level of evidence | Degree of recommendation |
|--|-------------------|--------------------------|
| Studies including adult patients undergoing first OLT for any indication   |                   |                          |
| Steroid replacement results in fewer cases of overall acute rejection in the corticosteroid-free immunosuppression arm   | 1a-               | D                        |
| Steroid replacement by daclizumab + MMF results in fewer cases of BPAR at 24 wk in the corticosteroid-free immunosuppression arm   | 1b                | A                        |
| Initial steroid administration for two weeks and early tacrolimus monotherapy is a feasible immunosuppression regimen without steroid replacement, although in view of chronic rejections, further investigations are needed | 1b                | A                        |
| Ab initio tacrolimus monotherapy is a viable immunosuppressive approach in liver transplantation and is associated with lower rejection rates compared to microemulsified cyclosporine                                       | 2b                | B                        |
| Renal insufficiency, de novo hypertension, neurological disorders and infectious complications do not differ significantly among steroid and steroid-free groups   | 1a                | B                        |
| Diabetes mellitus, cholesterol levels and CMV infection had a higher incidence in the steroid group. The differences in cases of diabetes mellitus and hypercholesterolemia are independent of steroid replacement           | 1a-               | D                        |
| Hypertension, thrombocytopenia, renal impairment and overall incidence of infections do not differ significantly among steroid and steroid-free groups (steroids replaced by daclizumab + MMF)                               | 1b                | A                        |
| Early tapering down of steroids to tacrolimus monotherapy is possible with significantly fewer cases of diabetes and hypercholesterolemia  | 1b                | A                        |
| Side-effects related to monotherapy with microemulsified cyclosporine or tacrolimus are comparable   | 2b                | B                        |
| Complete corticosteroid avoidance in adult OLT using basiliximab induction with CNI and EC-MPS maintenance is as safe and as effective as standard corticosteroid containing immunosuppression                               | 2b                | B                        |
| No significant differences were noted between treatment groups in terms of patient and graft survival regardless of steroid replacement  | 1b                | A                        |
| Actuarial 5-yr patient and graft survival related to monotherapy with microemulsified cyclosporine or tacrolimus are comparable  | 2b                | B                        |
| Steroid withdrawal should be attempted in OLT recipients with underlying autoimmune hepatitis  | 2b-               | D                        |
| Which immunosuppression regimen? Both, tacrolimus-based regimens with daclizumab induction or the addition of MMF, allow for avoidance of steroid treatment  | 1b                | A                        |
| Studies addressing exclusively transplanted HCV patients   |                   |                          |
| A significant reduction in HCV recurrence independent of steroid replacement may be expected in steroid-free groups  | 1a-               | D                        |
| MMF does not appear to have a significant antiviral effect despite early reports   | 1b                | A                        |
| Male gender of donors and recipients, living donors, cold ischemia times, acute rejection, and early histological recurrence are related to the development of advanced hepatitis  | 1b                | A                        |
| Donor age, grade 2 inflammation at day 90 or one-year liver biopsy and diagnosis of acute hepatitis may be associated with the development of bridging fibrosis or cirrhosis   | 2b                | B                        |

CMV: Cytomegalovirus; MMF: Mycophenolate Mofetil; OLT: Orthotopic liver transplantation; EC-MPS: Enteric-coated mycophenolate sodium; BPAR: Biopsy-proven acute rejection; CNI: Calcineurin inhibitor; HCV: Hepatitis C virus.

hypertension development [RR = 1.07 (0.9-1.27),  $P = 0.4$ ], neurological disorders [OR = 0.76 (0.51-1.13),  $P = 0.2$ ] and infectious complications [RR = 1.07 (0.96-1.2),  $P = 0.2$ ].

In a meta-analysis by Segev *et al*<sup>[41]</sup>, the corticosteroid free-immunosuppression group was equivalent to the steroid group in comparisons related to the following outcomes: cumulative risk of hypertension [RR = 0.84 (0.69-1.02),  $P = 0.08$ ] and infection [RR = 0.97 (0.88-1.08),  $P = 0.6$ ].

Degree of recommendation “B” was extrapolated because data used in the included studies were clinically different despite the fact that there was no heterogeneity or wide Confidence Intervals among outcomes in both meta-analyses.

Diabetes mellitus, cholesterol levels and cytomegalovirus (CMV) infection showed a higher incidence in the steroid group. The differences in cases of diabetes mellitus and hypercholesterolemia were independent of steroid replacement (level of evidence: 1a-, degree of recommendation: D).

The development of post-transplant diabetes mellitus [RR = 1.86 (1.43-2.41),  $P < 0.001$ ], cholesterol levels at 6 mo [weighted mean difference (WMD) = 19.71 (13.7-25.7),  $P < 0.001$ ] and CMV infection [RR = 1.47 (0.99-2.17),  $P < 0.05$ ] favored the corticosteroid-free immunosuppression group as reported by Sgourakis *et al*<sup>[42]</sup>.

Similar results were published in the meta-analysis by Segev *et al*<sup>[41]</sup>: Significant reductions in cholesterol [standard mean difference = -0.41 [(-0.62)-0.20],  $P < 0.001$ ] and the risk of CMV infection [RR = 0.52 (0.35-0.76),  $P = 0.001$ ], were observed in the steroid-free groups.

Both meta-analyses had statistically significant heterogeneity of studies, especially in CMV infection and some studies had wide Confidence Intervals.

Metaregression analysis in the former<sup>[42]</sup> disclosed that there was no difference between studies that replaced or did not replace steroids in the corticosteroid free-immunosuppression group ( $P = 0.087$ ). The latter<sup>[41]</sup> also supports that the risk of diabetes [RR = 0.29 (0.18-0.47),  $P < 0.001$ ], was markedly lower in the steroid-free arms.

Four RCTs were published after these two meta-

analyses<sup>[9,29,32,40]</sup>.

Hypertension, thrombocytopenia, renal impairment and overall incidence of infections do not differ significantly among steroid and steroid-free groups (steroids replaced by daclizumab + MMF) (level of evidence: 1b, degree of recommendation: A).

In the sufficiently powered study by Otero *et al.*<sup>[29]</sup> [TACRO + ST (3 mo) *vs* TACRO + daclizumab + MMF - steroids replaced], although more patients in the standard therapy group reported hypertension (26.6% *vs* 20.5%), thrombocytopenia (15.2% *vs* 12.8%), new-onset diabetes mellitus (13.9% *vs* 9.0%), and renal impairment (27.8% *vs* 19.2%), these differences were not statistically significant. Overall infections occurred in 19.2% of the modified therapy group *vs* 11.4% of the standard therapy group ( $P = 0.172$ ).

Early tapering down of steroids to a tacrolimus monotherapy is possible with significantly fewer cases of diabetes and hypercholesterolemia (level of evidence: 1b, degree of recommendation: A).

In the sufficiently powered study by Weiler *et al.*<sup>[40]</sup> [all patients TACRO + steroids for the first 2 wk followed by TACRO/TACRO + ST (6 mo) - steroids not replaced], statistically significant differences in diabetes (53% in the steroid group *vs* 30%,  $P = 0.024$ ) and hypercholesterolemia (41% in the steroid group *vs* 10%,  $P = 0.002$ ) were demonstrated at six months. A statistical difference in the osteoporosis rate was insignificant.

Side-effects related to monotherapy by microemulsified cyclosporine or tacrolimus are comparable (level of evidence: 2b, degree of recommendation: B).

Monotherapy (microemulsified CyA/TACRO) in both groups was used in the study by Cholangitas *et al.*<sup>[9]</sup>. Twenty-eight (77%) patients in the CyA group developed renal dysfunction (defined as GFR < 60 mL/min) at least once, compared to 45 (36%) in the TACRO group ( $P < 0.001$ ), although this difference remained at the margin of significance at five years. Side-effects related to immunosuppression were similar between the two groups at one, two and five years after liver transplantation.

Complete corticosteroid avoidance in adult OLT using basiliximab induction with calcineurin inhibitor and enteric-coated mycophenolate sodium (EC-MPS) maintenance is as safe and as effective as standard corticosteroid containing immunosuppression (level of evidence: 2b, degree of recommendation: B).

In the study by Ramirez *et al.*<sup>[32]</sup> [Basiliximab + TACRO + EC-MPS + ST (6 mo) *vs* basiliximab + TACRO + EC-MPS], mean cholesterol levels were similar in both groups from baseline to 12 mo post-OLT. Mean arterial pressure levels were significantly higher in the corticosteroid group as opposed to the corticosteroid-free group at three and 12 mo post-OLT.

**Graft and patient survival:** No significant differences were noted between treatment groups in terms of patient and graft survival regardless of steroid replacement (level of evidence: 1b, degree of recommendation: A).

In the meta-analysis by Sgourakis *et al.*<sup>[42]</sup>, relevant

comparisons were equivalent among the corticosteroid-free immunosuppression group *vs* the steroid group in terms of the following outcomes: overall number of deaths during follow-up [RR = 0.9 (0.72-1.13),  $P = 0.36$ ], one-year patient survival [OR = 0.1 (0.69-1.45),  $P = 0.9$ ], one-year graft survival [OR = 0.8 (0.56-1.15),  $P = 0.2$ ], retransplantation [OR = 0.82 (0.45-1.52),  $P = 0.6$ ], deaths up to 6 mo [RD = -0.01 (-0.04-0.02),  $P = 0.5$ ] and 3-mo graft survival [OR = 1.24 (0.79-1.25),  $P = 0.4$ ]. Only 7 studies<sup>[7,9,10,26,28-30]</sup> gave detailed information on the percentage of patients in each treatment arm which had received the allocated regimen. The corticosteroid-free immunosuppression group was superior in terms of the number of patients receiving the allocated intervention [OR = 1.55 (1.17-2.05),  $P = 0.003$ ].

No differences between steroid-free and steroid-based protocols were observed in terms of death [RR = 0.95 (0.73-1.24),  $P = 0.7$ ] and graft loss [RR = 0.95 (0.76-1.19),  $P = 0.6$ ] in the meta-analysis by Segev *et al.*<sup>[41]</sup>.

Both meta-analyses included some studies with wide Confidence Intervals, while data in the latter meta-analysis have not been extrapolated to the specific time period.

In the sufficiently powered study by Otero *et al.*<sup>[29]</sup> (steroids replaced) no significant differences emerged between treatment groups in terms of patient and graft survival; however, the time to rejection for patients in the standard therapy group was significantly shorter than that noted in the modified therapy group ( $P = 0.044$ ).

In the sufficiently powered study by Weiler *et al.*<sup>[40]</sup> (steroids not replaced), patient ( $P = 0.236$ ) and graft survival ( $P = 0.509$ ) was similar in both groups. In total, eight patients (7.3%) were retransplanted within 5 years, four (7.1%) from the placebo group, and four (7.4%) from the steroid group.

In the study by Ramirez *et al.*<sup>[32]</sup>, no significant differences in patient and death-censored graft survival rates between the two groups (corticosteroids and corticosteroid-free) were observed. The 1-, 3-, and 5-year patient survival were as follows: 100% *vs* 95%, 85% *vs* 63%, and 80% *vs* 63%. The 1-, 3-, and 5-year graft survival rates in the corticosteroid and corticosteroid-free groups were as follows: 100% *vs* 95%, 85% *vs* 63%, and 75% *vs* 63%, respectively.

Actuarial 5-year patient and graft survival related to monotherapy with microemulsified cyclosporine or tacrolimus are comparable (level of evidence: 2b, degree of recommendation: B).

Monotherapy in both groups was used in the study by Cholangitas *et al.*<sup>[9]</sup>. Actuarial survival according to Kaplan-Meier curves at five years was 72% for TACRO and 70% for CyA. Graft survival at five years was 59% for TACRO and 57% CyA. Neither patient survival nor graft survival differed statistically between the groups. Only two patients in the TACRO group required a second LT, compared to five (14%) in the CyA group ( $P = 0.007$ ).

**Liver transplant recipients with autoimmune hepatitis:** Steroid withdrawal should be attempted in OLT recipients with underlying autoimmune hepatitis (level of



evidence: 2b-, degree of recommendation: D).

Only one RCT<sup>[13]</sup> exclusively analyzed patients with autoimmune hepatitis (AIH). The 2-year survival in the prednisone group was 93% *vs* 100% in the steroid-free group who received MMF. No differences were observed with regard to graft function, acute rejection, renal function, and infectious complications. The prednisone group showed significantly elevated glucose levels with higher HbA1c and insulin requirements. The mean serum cholesterol level was significantly lower and bone density showed significant improvement in the MMF as opposed to the prednisone group (both outcomes:  $P < 0.01$ ). The authors suggested that steroid withdrawal should be attempted in OLT recipients with underlying AIH. This is a low sample size study, where the randomization procedure and patient allocation were not disclosed.

**Which steroid-free regimen?** Both, TACRO-based regimens with DAC induction or the addition of MMF, allow for avoidance of steroid treatment (level of evidence: 1b, degree of recommendation: A).

In the large sufficiently powered, multicentre, randomized, open-label, parallel group, phase III trial conducted by Becker *et al*<sup>[5]</sup>, 602 patients were enrolled and randomized to treatment: 305 patients were randomized to the TACRO/DAC group and 297 to the TACRO/MMF group. Approximately 70% of patients in each group completed the study. The overall estimated rate of patients free of BPAR that required treatment within 3 mo of transplantation was 81.5% in the TACRO/DAC group and 82.2% in the TACRO/MMF group. Differences were found in the incidence of causally related adverse events which was significantly lower in the TACRO/DAC group than that in the TACRO/MMF group: 76.1% and 82.8%, respectively ( $P < 0.05$ ). Conversely, renal disorders were more often reported as an adverse event in the TACRO/DAC group than in the TACRO/MMF group. The authors concluded that TAC monotherapy after DAC induction was associated with significantly less leucopenia and bacterial infection. Both TACRO-based regimens, DAC induction or dual therapy with MMF, allow for avoidance of steroid treatment, thereby eliminating risks associated with steroids, while providing satisfactory levels of immunosuppression.

### Results of studies addressing exclusively transplanted HCV patients

**HCV recurrence:** A significant reduction in HCV recurrence independent of steroid replacement may be expected in the steroid-free groups (level of evidence: 1a-, degree of recommendation: D).

In the meta-analysis by Sgourakis *et al*<sup>[42]</sup>, the corticosteroid-free immunosuppression group was equivalent to the steroid group in comparisons pertaining to the following outcomes: overall deaths in HCV patients [RR = 0.92 (0.52-1.65),  $P = 0.8$ ], deaths in HCV-recurrence patients {RD = 0.01 [-0.05]-0.07},  $P = 0.7$ }, one-year patients [OR = 0.63 (0.37-1.08),  $P = 0.1$ ] and one-year

graft survival [OR = 0.68 (0.42-1.08),  $P = 0.08$ ]. The corticosteroid-free immunosuppression group was superior in terms of the relative risk of HCV recurrence [RR = 1.15 (1.01-1.13),  $P < 0.05$ ], acute graft hepatitis [OR = 3.15 (1.18-8.40),  $P = 0.03$ ] and the number of patients failing treatment: collectively, patients with graft loss/deaths/withdrawal [OR = 1.87 (1.33-2.63),  $P = 0.0001$ ]. Metaregression analysis also disclosed that there was no difference between studies that replaced or did not replace steroids in the corticosteroid-free immunosuppression group in terms of HCV recurrence ( $P = 0.610$ ).

Significant reductions in HCV recurrence [RR = 0.90 (0.82-0.99),  $P = 0.03$ ] were observed in the steroid-free groups in the meta-analysis by Segev *et al*<sup>[41]</sup>.

The fact that both the above-mentioned meta-analyses included studies with less than 6 mo of follow-up and that HCV recurrence is defined in many different ways among studies (Ishak score, fibrosis, HCV RNA *etc.*) must be taken into consideration.

Eight RCTs exclusively addressed HCV transplanted patients after the publication of the two meta-analyses<sup>[9,15,24,28,29,32,36,40]</sup>, three of which involved deceased donors<sup>[15,24,28]</sup>, one a living donor<sup>[36]</sup> and the remaining four all etiologies of deceased donor transplantation<sup>[9,29,32,40]</sup>.

In the sufficiently powered study by Neumann *et al*<sup>[28]</sup>, patients who had received antiviral treatment during the study were excluded. The percentage of patients free of HCV recurrence at 12 mo was 19.1% for the TACRO/DAC steroid-free protocol and 13.8% for the TACRO/ST protocol, with a significant difference in survival curves between treatments ( $P = 0.020$ ). HCV recurrence censored for antiviral treatment favored the TACRO/DAC immunosuppression protocol at a rate of 20.2% *vs* 13.1% in the TACRO/ST group ( $P = 0.022$ ). The overall estimated rate of patient survival was significantly lower in the TACRO/DAC arm ( $P = 0.025$ ). The estimated rate of graft survival was numerically lower in the TACRO/DAC arm. The rate of graft loss was 19.4% in the TACRO/DAC arm and 8.8% in the TACRO/ST arm. The overall frequency of BPAR was significantly lower in the TACRO/DAC than in the TACRO/ST arm ( $P = 0.048$ ).

Although there was a tendency for later HCV recurrence and a lower incidence of rejection, the authors also observed a higher dropout rate and a lower patient survival rate with TACRO/DAC compared to the TACRO/ST arm and concluded that it is difficult to recommend a steroid-free protocol for HCV-positive patients due to the afore-mentioned study limitations.

In the study by Manousou *et al*<sup>[24]</sup>, antiviral treatment for HCV recurrence [after Ishak stage 4 was reached] was used in six out of 54 monotherapy (MT) and eight out of 49 triple therapy (TT) patients, with three in each group achieving sustained virological response. Overall mortality was not significantly different between the groups. The difference in reaching the primary endpoint (Stage 4 fibrosis) was significantly ( $P = 0.045$ ) in favor of triple therapy patients. Rejection episodes assessed by protocol biopsies that were histologically proven and/or required

methylprednisolone (30% *vs* 49%) were less frequent in the MT group. Retransplantation rates (7.8% for TT and 9.6% for MT) and chronic rejection rates (2% for TT and 3.8% for MT) were not different. This randomized trial supported the benefit of low-dose and slowly tapered steroids as well as azathioprine after liver transplantation for HCV-positive recipients.

MMF does not appear to have a significant antiviral effect despite early reports (level of evidence: 1b, degree of recommendation: A).

In the sufficiently powered study by Klintmalm *et al*<sup>[15]</sup>, clinically significant HCV in the three arms [TACRO + ST (3 mo)/TACRO + ST (3 mo) + MMF/daclizumab + TACRO + MMF] occurred in 69.5%, 75.9%, and 68.1% within 2 years. None of these differences was statistically significant. The 1- and 2-year patient and graft survival rates in the three arms were similar. The 2-year graft survival rates were 79.1%, 79.8%, and 85.1%, respectively (no significant differences). By day 730, clinically significant acute rejection had occurred in 14.3%, 12.5%, and 13.7% of the patients in the three arms. None of the differences among the groups was significant. The authors found no evidence that MMF influenced HCV progression.

With regard to living donor liver transplantation in the study by Takada *et al*<sup>[56]</sup>, antiviral treatment with interferon and ribavirin was considered for HCV recurrence. A sustained virological response was achieved in 44.4% of patients in the ST group and in 66.7% of patients in the MMF group ( $P = 0.16$ ). The 1-, 3-, and 5-year overall survival rates were 94.1%, 87.6%, and 82.7%, respectively, for the ST group and 92.5%, 84.5%, and 81.0%, respectively, for the MMF group ( $P = 0.28$ ). BPAR requiring treatment with an ST bolus injection occurred in four patients from the ST group and in 13 patients from the MMF group ( $P = 0.051$ ).

**Predictors of the development of advanced hepatitis:** Male gender of donors and recipients, living donors, cold ischemia times, acute rejection, and early histological recurrence are related to the development of advanced hepatitis (level of evidence: 1b, degree of recommendation: A).

In the sufficiently powered study by Klintmalm *et al*<sup>[15]</sup>, Cox Regression showed that male gender of donors and recipients, living donors, cold ischemia times, acute rejection, and early histological recurrence (grade 2 inflammation on the 90-d liver biopsy sample or stage 1 fibrosis at one-year biopsy) were related to the development of advanced hepatitis.

**Predictors of advanced fibrosis:** Donor age, grade 2 inflammation at day 90 or one-year liver biopsy and diagnosis of acute hepatitis may be associated with the development of bridging fibrosis or cirrhosis (level of evidence: 2b, degree of recommendation: B).

According to a multivariate Cox analysis, the donor age and grade 2 inflammation at day 90 or one-year liver biopsy were associated with the development of bridging fibrosis or cirrhosis; the administration of murine mono-

clonal IgG2a antibody or thymoglobulin approached significance<sup>[15]</sup>. In yet another study, two independent predictors of fibrosis stage  $\geq 4$  were significant: randomization to monotherapy [OR = 0.7 (0.066-0.847)] and diagnosis of acute hepatitis [OR = 3.59 (1.108-9.823)]<sup>[24]</sup>.

However, the former study<sup>[15]</sup> observed subjects for only 2 years after transplantation, and some patients refused liver biopsy in the second year. Thus, the authors could not dismiss the possibility that differences might have been observed if all subjects had been biopsied or the follow-up had been longer. The latter study<sup>[24]</sup> was not sufficiently powered.

## CONCLUSION

### Considering adult patients undergoing first OLT

It seems that steroid replacement results in fewer cases of overall acute rejection in the corticosteroid-free immunosuppression arm, although the evidence is of moderate quality. Steroid replacement by daclizumab plus MMF or early tacrolimus monotherapy after initial steroid administration for two weeks, are strong alternatives. In terms of patient and graft survival and regardless of steroid replacement, steroid-free immunosuppression is strongly recommended.

Adverse events such as renal insufficiency, *de novo* hypertension, neurological disorders and infectious complications did not differ significantly among steroid and steroid-free groups. Diabetes mellitus, cholesterol levels and CMV infection showed a higher incidence in the steroid group. The differences in cases of diabetes mellitus and hypercholesterolemia were independent of steroid replacement.

### Considering transplanted HCV patients

MMF does not appear to have a significant antiviral effect despite early reports. Male gender of donors and recipients, living donors, cold ischemia times, acute rejection, and early histological recurrence are related to the development of advanced hepatitis.

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