CMV infections after two doses of daclizumab versus thymoglobulin in renal transplant patients receiving mycophenolate mofetil, steroids and delayed cyclosporine A

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Abstract

Background. Cytomegalovirus (CMV) infection is a major complication after renal transplantation and is involved in graft rejection. The anti-interleukin-2-receptor antibody daclizumab reduces the incidence of acute rejection without increasing the incidence of CMV infection.

Methods. This multicentre, randomized trial compared safety and efficacy, at 1 year, of two doses of daclizumab (54 patients, group D) with thymoglobulin (55 patients, group T) plus delayed cyclosporine (CsA), MMF (mycophenolate mofetil) and steroids in first cadaver kidney transplant patients. Primary criterion was CMV infection/syndrome/disease. D+/R− patients received oral ganciclovir prophylaxis for 90 days.

Results. Status for CMV was identical in the both groups. The incidence of CMV infection/syndrome/disease was 39% in group D versus 51% in group T (NS). Time to onset of CMV replication was delayed in group D (P = 0.015) and mean number of pp65-positive cells was lower at 4 and 6 months (P < 0.001). Incidence of symptomatic CMV episodes was not reduced in whole group D (5.6% versus 16.4%, NS), but lower in D+/R− and D−/R+ patients without chemoprophylaxis, compared to group T (2.8% versus 21.6%, P = 0.028). Patient and graft survivals and incidence of biopsy-proven acute rejection were identical.

Conclusions. Limited dosing regimen of daclizumab with MMF, steroids and delayed CsA introduction was safe and effective. The incidence of CMV infection was not significantly different, but without chemoprophylaxis, clinical manifestations and viral replication were reduced with this regimen.

Keywords: cytomegalovirus; daclizumab; kidney transplantation; thymoglobulin

Introduction

Two main induction agents are commonly used to reduce the incidence of acute rejection after kidney transplantation: a depleting agent such as antithymocyte globulin (ATG) or a non-depleting agent such as monoclonal antibody against interleukin 2-receptor (IL-2R).

ATG (Thymoglobulin®) is associated with an increased incidence of short- and long-term complications, with patients being more susceptible to severe viral infections, particularly cytomegalovirus (CMV), post-transplant lymphoproliferative disease (PTLD) and other malignancies. ATG induction therapy is now preferentially used in patients with high immunological risk or for corticosteroid sparing.

Daclizumab is a humanized IgG1 monoclonal antibody that selectively targets the α-chain of IL-2R (CD25) expressed on activated T lymphocytes. In combination with cyclosporine (CsA), prednisone and mycophenolate mofetil or azathioprine (MMF/AZA), daclizumab significantly reduces acute rejection and improves patient survival compared to placebo [1,2]. Daclizumab is given as either five 1 mg/kg doses at 14-day intervals or as two doses (1 or 2 mg/kg for the first dose and 1 mg/kg for the second dose 10–14 days later). Treatment with daclizumab is well tolerated and does not increase the incidence of CMV...
intravenous infusions of Zenapax® for surgery. Patients in the daclizumab group received two
randomized (1:1) to one of the two treatment groups be-
after giving written consent, the patients were centrally
or malignancy and unlikely compliance with the schedule.
and living-donor renal transplant, patients who received
CMV serology (D−/R−) did not receive
chemoprophylaxis and were treated with IV ganciclovir
when pp65 antigenemia was positive according to local
practices. For CMV prophylaxis, D+/- patients received oral
ganciclovir 3 g/day, starting 10 days after transplantation,
with the dose being adjusted according to graft function
and continued for 14 weeks. Patients with low risk for
CMV infection (D+/-R+ and D−/-R+) did not receive
chemoprophylaxis and were treated with IV ganciclovir
when pp65 antigenemia was positive according to local
practices. After initial screening at baseline (Day 0) patients
were monitored at Days 7 and 14, Weeks 4, 6 and 8 and Months
3, 4, 5 and 6, and finally at 1 year post-transplantation.
CMV replication was tested for in all patients by detec-
tion of pp65 viral antigenemia at every visit, and carried
out when there were clinical or biological signs suggesting
CMV-related symptoms. CMV infection was defined as
positive pp65 antigenemia. CMV syndrome was defined as
pyrexia above 38°C for two consecutive days, associated
with a positive antigenemia with at least one of the fol-
lowing: malaise, leukopenia < 3 × 10⁹/L, thrombocytopenia
< 100 × 10⁹/L and transaminase levels at least twice
the upper limit of the normal range. CMV infection with
organ involvement was classified as tissue-invasive CMV
disease. Patients with CMV primo-infection or reactivation
were treated by intravenous ganciclovir according to local
practice.
Acute rejection episodes were suspected from clinical
signs (fever, oliguria) and/or an increase in the crea-
tininaemia level >20% over pre-rejection baseline level,
and confirmed by locally examined graft biopsy before
initiating treatment. A blinded centralized analysis
was carried out by two pathologists and rejection
was classified according to the modified Banff 1997
scheme. Acute cellular rejection episodes were treated
with five daily 8, 6, 4, 3, and 2 mg/kg boluses of methyl-
prednisolone, and then prednisone 1 mg/kg with taper-
ing according to local practice. A second episode was
in the same way as the first episode, except that
maintenance steroids were allowed. Patients with acute

disease [3]. Daclizumab can also be used with reduced
dose of calcineurin inhibitors (CNI) and to delay their in-
troduction [4,5], thus limiting their nephrotoxicity, as previ-
ously reported with ATG. Several randomized multicentre
studies have compared basiliximab with ATG induction
[6–9], but only two non-randomized single-centre studies
compared daclizumab to ATG in kidney and simultaneous
pancreas–kidney (SPK) transplantation [10,11], and a few
studies were reported in lung and cardiac transplantation
[12–15].
CMV remains a major cause of morbidity in solid or-
gan transplant recipients and may manifest as symptomatic
tissue invasive disease or CMV viral syndrome. CMV in-
fection has also been associated with indirect effects such as
opportunist infection, acute and chronic rejection and
allograft dysfunction.
We conducted this study in low immunological risk
patients to evaluate at 12 months after transplantation, the safety—particularly with respect to CMV infection/
syndrome/disease—and efficacy of two doses of da-
clizumab compared to ATG. Both the induction agents
were associated with MMF and delayed introduction
of CsA, with steroids being withdrawn during the
sixth month.

Subjects and methods

Study design

We undertook an open-label multicentre, randomized,
parallel-group trial in nine French centres (trial name: EC-
TAZ; protocol identification: 010624; date of registration:
16 July 2001). All patients were aged from 18 to 65 years
and had a first cadaver renal allograft. Inclusion criteria
were cold ischaemia time ≤36 h, panel reactive antibodies
(PRA) ≤20% in previous and current serum and female
patients of childbearing age agreeing to continue effec-
tive birth control during the study. The following were the
main exclusion criteria: donor and patient with negative
CMV serology (D−/R−), multi-organ transplantation, sec-
ond and living-donor renal transplant, patients who received
steroids for the treatment of an autoimmune or renal disease
during the 30 days before inclusion, significant liver disease
or malignancy and unlikely compliance with the schedule.
After giving written consent, the patients were centrally
randomized (1:1) to one of the two treatment groups be-
after surgery. Patients in the daclizumab group received two
intravenous infusions of Zenapax®: the first of 2 mg/kg
(range 100–200 mg) during the 24 h before transplant-
tion and the second of 1 mg/kg 14 days later. Pa-
ients in the ATG group received intravenous infusions of
Thymoglobulin®: the first of 1–1.5 mg/kg after transplan-
tation, with the following adjusted to obtain a CD2/CD3
count < 20/mm³ with at least four and no more than nine
total daily infusions, according to the delayed graft function
(DGF).
All patients received MMF (CellCept®, CsA (Neoral®)
and steroids. MMF treatment was started before surgery
at a single dose of 2 g and then continued at a dose of
2 g/day until the end of the trial. CsA was adminis-
tered at an initial dose of 2–4 mg/kg, starting at the latest
7 days post-transplantation depending on the presence or
absence of DGF. CsA was administered together with ATG
for two consecutive days only. CsA dose was progressively
adjusted to maintain whole blood trough cyclosporine lev-
els between 150 and 250 ng/mL from Day 7 until Month
2, 125 and 200 ng/mL from Months 3 to 6 and 125
and 175 ng/mL from Months 7 to 12. Steroids were ad-
ministered by an intravenous bolus of methylprednisolone
(250 mg) before and after transplantation. Prednisone was
administered from Days 1 to 7 at 1 mg/kg/day and then at
0.5 mg/kg/day from Days 8 to 14. The dose was then de-
creased by 5 mg steps per week until a dose of 20 mg/day
was reached, and then decreased by 2.5 mg steps per week
until 10 mg/day was reached. This dose was maintained
for at least 1 month and then was gradually decreased by
2.5 mg steps per fortnight, until treatment was dis-
continued 5 or 6 months after transplant. Corticosteroid
withdrawal was attempted in patients with no more than
one acute cellular rejection episode, no vascular rejection,
no vasculitis as the cause of end-stage renal disease, cre-
atininaemia < 20 µmol/L at Month 4 and proteinuria
< 1 g/24 h.
For CMV prophylaxis, D+/- patients received oral
ganciclovir 3 g/day, starting 10 days after transplantation,
with the dose being adjusted according to graft function
and continued for 14 weeks. Patients with low risk for
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was classified according to the modified Banff 1997
scheme. Acute cellular rejection episodes were treated
with five daily 8, 6, 4, 3, and 2 mg/kg boluses of methyl-
prednisolone, and then prednisone 1 mg/kg with taper-
ing according to local practice. A second episode was
in the same way as the first episode, except that
maintenance steroids were allowed. Patients with acute
rejection resistant to steroids were treated according to local practice.

**Primary and secondary endpoints**

The primary endpoint was to compare the safety of daclizumab with that of ATG at 12 months, in terms of asymptomatic CMV infections, symptomatic CMV infection (syndrome and disease) and treated CMV episodes.

The secondary endpoints were to compare the efficacy of daclizumab with that of ATG at 12 months with respect to the incidence and time of the first acute rejection episode, patient and graft survival, number of patients with steroid withdrawal, serum creatinine level and 24-h proteinuria. DGF was defined as the need for dialysis during the first week after transplantation, and/or a slow graft function with serum creatinine level in the absence of dialysis, above 250 µmol/L at Day 5, oliguria during 24 h or decrease in creatininaemia < 20% at Day 2 post-transplantation [7].

**Statistical methods**

The objective of the trial was to demonstrate the superiority of the daclizumab two-dose arm versus thymoglobulin on the primary endpoint, i.e. the number of patients (ITT) with cytomegalovirus infection/syndrome/disease episode during the first year post-transplantation. Calculation of \( \Pi \) was therefore based on a model of comparison of percentages and was performed according to the following hypothesis: estimation of \( \Pi_a \) (number of patients with CMV disease in the daclizumab group) at 12% [1,16,17] and \( \Pi_b \) (in the thymoglobulin group) at 37% [7]. The first type error was set at \( \alpha = 5\% \) and the second type error at \( \beta = 20\% \). Under these conditions, the number of per-protocol patients who needed to be randomized was 46 per arm. The number of patients excluded from the per-protocol population was estimated to be \( \sim 15\% \). The total number of patients to be randomized was therefore 55 per group. A total of 110 patients were therefore to be included in this trial.

The analysis calculated the number of patients with CMV asymptomatic infection, or CMV viral syndrome or CMV disease. The safety population was defined as all eligible patients who received at least one dose of study medication (daclizumab or ATG). The intent-to-treat (ITT) population was defined as all eligible patients who received at least one dose of study medication and who subsequently underwent transplantation. Data of patients receiving the intended treatment, without major deviation from the study protocol or with early graft loss for vascular or surgical complications, who were really exposed to the risk of global immunosuppression (on-therapy population), were analysed for the primary endpoint.

Quantitative variables were summarized by the mean and the standard deviation and qualitative variables by the frequency and the percentages of each modality. All the comparisons for efficacy and safety were two-tailed comparisons. The time to onset was analysed using the Kaplan–Meier method and was compared between groups by using a log-rank test. \( P \)-values of < 0.05 were considered to be significant.

**Ethics**

All patients gave written informed consent. The study conformed to the Declaration of Helsinki concerning medical research in humans (as amended) and to Directive 91/507/EC: Rules Governing Medicinal Products in the European Community. The approval of the Ethics Committee (CCPPRB) of Poitiers was also obtained before starting the study.

**Results**

**Patient selection**

Between June 2001 and April 2003, a total of 115 patients were enrolled. Eligible patients were randomly assigned to treatment by daclizumab (\( n = 58 \)) or by ATG (\( n = 57 \)). Three patients (one in the daclizumab group and two in the ATG group) were neither treated nor transplanted and were excluded from further analysis. Thus, the safety population contained 112 patients: 57 in the daclizumab group and 55 in the ATG group (Figure 1).

In the ITT population three more patients were excluded, all from the daclizumab group: two patients who received one dose of daclizumab but were not transplanted and one patient who received a poor quality graft due to ecstasy abuse [18]. Thus, the ITT population included 109 patients: 54 in the daclizumab group and 55 in the ATG group.

The on-therapy population excluded eight further patients for the following reasons: second dose of daclizumab omitted (one patient), MMF introduced 1 month after transplantation (one patient), cyclosporine not introduced (one patient), early graft loss due to venous (two patients) or arterial (two patients) thrombosis and primary failure due to haematoma (one patient). This population contained 101 patients: 50 in the daclizumab group and 51 in the ATG group.

**Baseline characteristics**

The two groups were well matched for age, sex ratio, HLA compatibilities, CMV serology status between donor and recipient, mean time on dialysis and cause of end-stage renal disease (Table 1). The mean cold ischaemia time was shorter in the daclizumab group but was < 24 h for both groups (ITT population analysis: \( P = 0.01; \) on-therapy population: \( P = 0.027 \)).

**Immunosuppression**

In the ATG group, the mean ATG dose was \( 61.5 \pm 19.6 \) mg per day, for a mean duration of \( 6.5 \pm 1.9 \) days.

The mean time to introduction of CsA was \( 3.2 \pm 2.5 \) days in the daclizumab group and \( 4.0 \pm 1.7 \) days in the ATG group (NS). Mean whole blood trough levels and daily doses were similar in both groups.
At Week 52, 79.6% and 88.6% of patients received MMF 2 g/day in the daclizumab and ATG groups, respectively. Mean doses of MMF were similar for the two groups at all time points, except at Week 8 in which the mean dose was lower for the ATG group: 1.68 ± 0.4 versus 1.92 ± 0.3 (P = 0.015).

Steroids were withdrawn in 75% and 77.3% of patients in the daclizumab and ATG groups, respectively, at 12 months.

**CMV infection**

In the ITT population, 45% (49/109) of patients presented an episode of CMV infection/syndrome/disease. All episodes (CMV infections 75.5%, CMV syndromes 18.4% and CMV diseases 6.1%) occurred in the first 6 months post-transplantation. The incidence of CMV episodes was not statistically different in the daclizumab group (21/54, 39%) compared to the ATG group (28/55, 51%) (Table 2). The incidence of symptomatic CMV infections in the daclizumab group (3/54: 5.6%) and in the ATG group (9/55: 16.4%) was not significantly different. However, pp65 antigenaemia was detected significantly later in the daclizumab group than in the ATG group (75 ± 46 versus 34 ± 26 days post-transplantation, P = 0.015) (Figure 2).
Table 2. CMV infection/syndrome/disease incidence

<table>
<thead>
<tr>
<th></th>
<th>ITT population</th>
<th>On-therapy population</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Daclizumab</td>
<td>ATG</td>
</tr>
<tr>
<td></td>
<td>n = 54</td>
<td>n = 55</td>
</tr>
<tr>
<td>CMV infections/syndrome/disease (%)</td>
<td>21 (39)</td>
<td>28 (51)</td>
</tr>
<tr>
<td>CMV infection</td>
<td>18 (33%)</td>
<td>19 (38%)</td>
</tr>
<tr>
<td>CMV syndrome</td>
<td>1 (2%)</td>
<td>8 (29%)</td>
</tr>
<tr>
<td>CMV disease</td>
<td>2 (10%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Treated with intravenous ganciclovir</td>
<td>7 (33%)</td>
<td>12 (43%)</td>
</tr>
<tr>
<td>Delay of onset of the first CMV episode</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (days)</td>
<td>75 ± 46*</td>
<td>34 ± 26*</td>
</tr>
<tr>
<td>Median (interval) (days)</td>
<td>57 (29–168)</td>
<td>29 (16–89)</td>
</tr>
</tbody>
</table>

*P (log-rank) = 0.015, **P (log-rank) = 0.023.

Fig. 2. CMV (infection/syndrome/disease)—free survival in the ITT population.

Table 3. CMV infection/syndrome/disease—events (12-month follow-up) according to CMV status

<table>
<thead>
<tr>
<th>ITT population</th>
<th>CMV episodes</th>
<th>Asymptomatic CMV episodes</th>
<th>Symptomatic CMV episodes</th>
<th>Time to positive pp65Ag (days)</th>
<th>Treatment ganciclovir IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>D+/R− (n = 37)</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>89</td>
<td>1</td>
</tr>
<tr>
<td>ATG n = 18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daclizumab</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D+/R+, D−/R+</td>
<td>26</td>
<td>18</td>
<td>7*</td>
<td>28 (13–45)</td>
<td>11</td>
</tr>
<tr>
<td>ATG n = 37</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daclizumab</td>
<td>35</td>
<td>15</td>
<td>1*</td>
<td>43 (29–125)</td>
<td>4</td>
</tr>
<tr>
<td>n = 19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>n = 35</td>
<td></td>
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</table>

*Fewer symptomatic CMV episodes in the daclizumab group compared to the ATG group [1/35 (2.8%) versus 8/37 (21.6%), P = 0.028] in low-risk (R+) recipients for CMV infection.

The overall incidence of CMV episodes (Table 3) was higher in R+ patients without chemoprophylaxis (56.9%) compared to D+/R− patients (21.6%) and symptomatic CMV infections in R+ patients were fewer in the daclizumab group compared to the ATG group (2.8% versus 21.6%, P = 0.028). The number of patients treated with intravenous ganciclovir was not significantly different in the daclizumab and ATG groups (33% versus 43%, respectively). The evolution of viral load studied with the pp65 antigenaemia showed a lower mean number of pp65-positive cells in the daclizumab group compared to the ATG group for R+ patients and ITT population (P < 0.001 at 4 and 6 weeks) (Figure 3).

We found no relevant differences between the ITT population and on-therapy population exposed to the risk of global immunosuppression for the primary endpoint.

Incidence of acute rejection

The global incidence of biopsy-proven acute rejection (BPAR) was 15.6% (17 patients) in the ITT population: 9 patients (16.7%) in the daclizumab group versus 8 patients (21.6%) in the ATG group.
Fig. 3. Mean number of pp65-positive cells in the ITT population and according to CMV status.
early withdrawal of steroids, in low-risk immunological
risk of PTLD [23]. Currently, according to the ‘Lisbon con-
prophylaxis with ganciclovir or acyclovir is to reduce the
CMV infections. Another potential advantage of extended
prophylaxis, symptomatic CMV infections were less fre-
tquent in the daclizumab group compared to the ATG group
(P = 0.028). Interestingly, the onset of CMV replication
was significantly delayed in the daclizumab group and both
mean pp65 antigenaemia value and peak of antigenaemia
were lower. Thus, our results suggest that induction with da-
cilizumab should be preferred to ATG to reduce the severity
of CMV infections in low immunological risk renal trans-
plant recipients. As most of CMV episodes occurred in low-
risk patients (D+/R+, D+/R+) CMV chemoprophylaxis
given in these patients could further reduce the incidence of
CMV infections. Another potential advantage of extended
prophylaxis with ganciclovir or acyclovir is to reduce the
risk of PTLD [23]. Currently, according to the ‘Lisbon con-
ference on the care of the kidney transplant recipient’, either
prophylaxis, pre-emptive therapy or only clinical observa-
tion depending on the immunosuppression regimen and the

The first BP AR episode usually occurred before Month
6 (72%), with no significant difference between the two
groups (daclizumab group: mean, 133 ± 107 days; ATG
13) in the ATG group. A slow graft function was observed
after transplantation, 74% of patients in the daclizumab
and 75% in the ATG group had serum creatinine levels < 250
µmol/L. Serum creatinine levels were identical between the
two groups at all time points in the study, with a mean value
of 143 ± 42 µmol/L 1 year after transplantation.

At Month 12, there was no difference in proteinuria be-
tween the two groups: 0.32 ± 0.74 g/24 h in the daclizumab
and 0.31 ± 0.92 g/24 h in the ATG group.

Safety. There was no significant difference between the
two groups in the number, cause and severity of the reported
adverse events. No new malignancy and no case of PTLD
were seen in either group at 1 year after transplantation.
Only five patients (two in the daclizumab group and three in
the ATG group) (4.9%) developed post-transplant diabetes
mellitus. Of these, two recovered normal glycaemia after
steroid withdrawal.

Discussion

This prospective, randomized, multicentre trial compared
two doses of daclizumab with ATG induction therapy, as-
associated with MMF with delayed introduction of CsA and
early withdrawal of steroids, in low-risk immunological
first cadaver renal recipients. Previous studies have shown
that induction treatment with anti-IL-2Rα antibodies was
equivalent to induction therapies with polyclonal antibodies
for patient and graft survival, although IL-2Rα antibodies
were associated with significantly fewer side effects [19].
Studies using five or two doses of daclizumab associated
with CNI and AZA/MMF did not increase the number of
infections, compared to placebo [1,16,20,21], particularly
for CMV infections [3,20]. Recent studies have shown a
tendency to lower the incidence of CMV infections with
basiliximab compared to ATG [7,9] except in one large
study of 277 patients where incidence of CMV was 13.2%
in the basiliximab group compared to 7.1% in the ATG
(group [8] [10]. In two non-randomized studies in kidney
to ATG, without details on CMV status or chemoprophy-
laxis, none of the patients in the daclizumab group (10 and
12 patients, respectively) developed CMV infection con-
trasting with 14% (5/35) and 17% (2/12), respectively, in
those treated with ATG. In lung and cardiac transplanta-
tion, viral infections were similar between groups receiv-
ing daclizumab or ATG [13–15], but only one randomized
trial reported a higher incidence of CMV infection in the
daclizumab group compared to the ATG group (18/25 ver-
sus 6/25, P = 0.03), but this was attributed to a higher
incidence of CMV mismatch [12]. The favourable effect
on the incidence of CMV infections is attributed to the
high selectivity of IL-2Rα antagonists on activated lympho-
cytes compared to massive lymphocyte depletion induced
by polyclonal antibodies. Randomized trials between da-
cilizumab and basiliximab regimens have not been directly
compared for efficacy and safety profile. One retrospec-
tive study suggests that a limited-dose daclizumab regimen
(two 1 mg/kg doses) may be as effective as and less costly
than a standard-dose basiliximab regimen [22]. In our study,
we compared low-dose daclizumab and ATG and did not
find a significant difference in the incidence of CMV in-
fecction/syndrome/disease between the two groups and in
the number of patients treated with intravenous ganciclovir.
The CMV serological status of donor–recipient pairs was
similar for both the treatment groups. Symptomatic CMV
infections were three times, but not statistically signifi-
cant, less common in the daclizumab group (P = 0.19).
However, in D+/R+, D−/R+ patients without chemopro-
phylaxis, symptomatic CMV infections were less fre-
fquent in the daclizumab group compared to the ATG group
(P = 0.028). Interestingly, the onset of CMV replication
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8 patients (14.5%) in the ATG group (NS). One patient in
the daclizumab group had two BPAR episodes. The Banff
grades of acute rejection were primarily IA (44%), IB (17%)
and borderline (17%).

The first BPAR episode usually occurred before Month
6 (72%), with no significant difference between the two
groups (daclizumab group: mean, 133 ± 107 days; ATG
8 patients (14.5%) in the ATG group (NS). One patient in
the daclizumab group had two BPAR episodes. The Banff

risk of CMV are recommended [24]. However, as Paya et al. [25] reported a 49% rate of positive viremia at 1 year post-transplantation despite 3 months valganciclovir or ganciclovir, long-term benefits of CMV chemoprophylaxis in these groups need to be confirmed.

Our results also show that two doses daclizumab plus delayed introduction of CsA are as effective as ATG plus delayed introduction of CsA for preventing acute rejection and for graft function with 16.5% incidence of BPAR in the daclizumab group versus 14.5% in the ATG group. These rates were similar to the 13.1% incidence, irrespective of the daclizumab dose regimen, in patients reported in the SRTR database [26]. Ahsan et al. [27] reported a BPAR in 6% of patients at 6 months treated with a single intra-operative dose of daclizumab (2 mg/kg) and in 16% of control patients with no induction treatment, with both groups also receiving tacrolimus/MMF/prednisone. More recently, Ekberg et al. in the CAESAR study reported a 25.4% incidence of BPAR at 1 year in the low-dose cyclosporine arm patients receiving five-dose daclizumab induction with MMF and steroids [28]. In our study, CMV infection/syndrome/disease and steroid withdrawal were not associated with a higher incidence of BPAR.

Steroid treatment can be reduced and withdrawn with IL-2R antagonists, with a success rate similar to that observed with ATG in selected low immunological risk patients [7,29,30]. Kuypers et al. [4] reported at 1 year post-transplant a 17.1% BPAR incidence with daclizumab (two doses) + tacrolimus (target 5–10 ng/mL) + MMF (2 g) and a low dose of steroids (stopped at 5 months), whereas it was 41.4% with the standard dose tacrolimus (target 10–15 ng/mL) + MMF (1 g) and steroids but without daclizumab. Rostaing et al. [5] reported a similar 16.5% incidence of BPAR at 6 months in patients treated with daclizumab/tacrolimus/MMF without steroids (88.8% of patients were steroid-free at 6 months) or with tacrolimus/MMF/steroids without induction. In our series, steroid withdrawal was achieved in >70% of patients after 1 year, in both the groups. We have previously shown a long-term high success rate of steroid withdrawal in selected patients treated with ATG/ALG induction, CsA and AZA/MMF regimen [31–33]. Further similar studies with longer follow-up are needed to establish long-term sparing effect of induction by IL2-R antagonists.

The patient and graft survival rates were comparable in both groups and renal function was not different.

In conclusion, two-dose daclizumab induction regimen appeared safe and effective for low immunological risk patients receiving a first cadaver renal transplantation and treated with CsA/MMF/prednisone. Its efficacy to prevent acute rejection was similar to ATG. The incidence of CMV infections was similar, but time to onset was delayed and severity was reduced, especially in D+/R+ and D−/R+ patients without chemoprophylaxis. This regimen allowed delayed introduction of cyclosporine and steroid withdrawal in most patients. A higher dose regimen (five doses) may be more appropriate for patients having a high risk of acute rejection [34]. These results need to be confirmed over a longer follow-up.

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References

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