INTRODUCTION

We published early results of a randomised trial in liver transplant recipients with HCV cirrhosis assessing tacrolimus monotherapy (MT) versus tacrolimus, azathioprine and prednisolone triple therapy (TT), which showed a slower onset of histological severe fibrosis and portal hypertension in the TT arm compared with tacrolimus alone, independent of other factors known to affect fibrosis. This was
contrary to the starting hypothesis that the lesser immunopoten-
ty with MT should result in less fibrosis.

However, despite our initial trial results and other consistent
data with more patients, including a possible benefit with
azathioprine, the optimal immunosuppression for HCV trans-
plant recipients is still debated. Indeed, immunosuppression
worsens the severity of HCV recurrence. Cyclosporine has no
advantage versus tacrolimus regarding stage progression despite
in vitro (but not in vivo) activity against HCV. Tacrolimus com-
pared with cyclosporine improves both patient and graft survival
including patients transplanted for hepatitis C cirrhosis and is
the preferred calcineurin inhibitor.

Therefore, we evaluated outcomes in our trial, after a median
of 8 years of follow-up, including the original end points as well as
differences in hepatic venous pressure gradient (HVPG) and
collagen proportionate area (CPA) as a quantitative measure of
fibrosis and clinical decompensation.

PATIENTS AND METHODS
Inclusion—exclusion criteria, randomisation and endpoints

From January 2000 to June 2007, at the Royal Free Hospital,
consecutive transplant recipients were randomised if they had
cirrhosis, were HCV RNA positive in serum and previous hist-
ology was compatible with HCV liver disease. Randomisation at
the Royal Edinburgh Infirmary and St Vincent’s University
Hospital was between 12/2003 and 5/2006. Inclusion and exclu-
sion criteria were published previously. The study protocol was
approved by the Hospital Ethics committees at each site.

Follow-up stopped at death, retransplantation or 1/2013. We
analysed the original primary endpoints—progression to Ishak
stage 4 and graft failure either resulting in retransplantation or
patient’s death. We also evaluated patients’ survival, acute cellular
rejection episodes, chronic rejection, recurrence of HCV (defined
by Ishak inflammation score ≥4), HVPG progression to 10 mm Hg,
CPA, fibrosis progression assessed by CPA and Ishak stage (for
comparison with other published studies), and time to first episode
of clinical decompensation defined as whichever occurred first,
of ascites/hydrothorax, variceal bleeding or encephalopathy.

For each patient, the following were evaluated: demographic
and clinical data (including concomitant hepatocellular carcino-
moma (HCC) and/or alcoholic aetiology), donor age/gender, cold/
warm ischaemia time, initial immunosuppression and subse-
dquent changes, occurrence and treatment of rejection episodes,
cytomegalovirus or other infections, histological episodes of de
novo hepatitis, genotype, viral load pre-LT and 1 year post-liver
transplantation (LT), antiviral treatment and sustained viro-
logical response (SVR), diabetes mellitus pretransplant and post-
transplantation (LT), human leucocyte antigen and blood group com-
patibility of donor/recipient, sex match/mismatch and tacrolimus
levels at 5, 15 and 30 days post-LT.

Immunosuppression regimens

The MT group received tacrolimus 0.1 mg/kg/day (two divided
doses). The TT group received the same tacrolimus dosing,
together with azathioprine—initially intravenously then orally—
1 mg/kg/day, and methylprednisolone (16 mg/day intravenous)
until oral intake was established (20 mg/day prednisolone).
Tacrolimus trough concentrations were evaluated on alternate
week days. The doses were adjusted to maintain a whole blood
level within 5–14 ng/mL (aiming for 5–10). Azathioprine was
continued at the same starting dose unless neutropenia devel-
oped: 16 patients discontinued azathioprine between 10 and
37 months (median 14 months) post-LT. Prednisolone was gradu-
ually tapered from 3 weeks onwards and then stopped between
3 and 6 months, according to each centre’s practice. Protocol
biopsies were undertaken to diagnose acute cellular rejection
between days 5 and 10. If moderate or severe rejection was
diagnosed, daily intravenous 1 gm methylprednisolone was
given for 3 days.9

Virological assays

Determination of HCV genotype was performed by reverse
transcription PCR and reverse hybridisation assay of the ampli-
sed sequence (InnoLipa HCV II, Innogenetics, Zwijnaarde,
Belgium). Qualitative tests were performed by a reverse transcrip-
tion PCR assay (AmpliCor HCV Roche Diagnostic Systems Inc,
Branchburg, New Jersey, USA—later Bayer Thermomechanical
Analyzer Component system, Berkeley, California, USA).11

Liver biopsies

Protocol liver biopsies were performed at yearly intervals and
also if clinically indicated. All liver biopsies were reviewed by
liver trained histopathologists in each centre, in a blinded
fashion.

Liver biopsy samples were formalin fixed, parafin embedded
and stained with H&E, Gordon and Sweet staining was used
for reticulin and Sirius red and Van Gieson stains were used in
Edinburgh. All biopsies at the Royal Free Hospital were
restrained with picroSirius Red to ensure comparable staining
for collagen quantification and determination of CPA by digital
image analysis. The stage of disease (fibrosis 0–6) and the grade
of necroinflammatory activity were evaluated according to Ishak
et al.12

The number of liver cores, length of biopsy (lengths of each
core summed), and portal tract number per core and in total
were recorded.13 Liver biopsies<12 mm long were excluded (29
of 310). Complete portal tracts were defined according to
Crawford and colleagues.14 The equipment used and CPA mea-
surement were performed as previously described.15

Acute cellular rejection was graded using the Royal Free
Hospital score.16 Histological de novo hepatitis (HDNH) C
term ‘histological acute hepatitis C’ previously1 2 was defined
as before as an increase in alanine aminotransferase levels (>2
upper normal limit), together with histological changes consist-
ent with hepatitis without diagnostic features of cellular rejec-
tion, duct loss or other cause of liver injury, including
alloimmune hepatitis (autoantibodies negative).2

Fibrosis progression in each patient was calculated by percent-
age change of fibrosis according to CPA (CPA in latest biopsy
subtracted from CPA at 1 year post-LT, divided by time in years
between the two biopsies: CPA%/year). Ishak stage progression
was calculated as in latest biopsy subtracted from stage in the
biopsy at 1 year, divided by time in years—stage ‘units’/year
between the two biopsies.

Statistical analysis

Results are expressed as median and ranges. Categorical vari-
ables were compared using the χ² or Fisher’s exact tests. Con-
ditional variables were compared by Student t test, or if not
normally distributed by the Mann–Whitney test. We compared
the two randomised groups for histological, virological and clin-
ic outcomes in a preplanned evaluation.

Statistical comparison was made by life tables (Kaplan–Meier)
and log rank testing. All the following variables associated with
HCV recurrence in the literature (table 1)—except IL28B—were
evaluated in the Cox regression analysis: donor age/gender, cold/
warm ischaemia time, initial and changes in immunosuppression
occurance and treatment of rejection episodes, cytomegalovirus or other infection, HDNH episodes, genotype, viral load pre-LT and 1 year post-LT, antiviral treatment and SVR, diabetes mellitus pre-LT and post-LT, human leucocyte antigen and blood group compatibility of donor/recipient, sex match/mismatch and tacrolimus levels at 5/15/30 days post-LT.

A p value<0.05 was considered statistically significant. SPSS V2.0.0 was used.

Patients were censored at the time of SVR, when analysing progression to HVPG≥10 mm Hg, to CPA cut-offs of 6% and 7.2%, to first clinical decompensation event, and survival. As reported previously, sample size was calculated to be 110 patients: S4 was estimated to occur in 35% by 3 years with a projected decrease to 10% with tacrolimus MT, and this required a sample size of 103 patients (89 Royal Free Hospital, eight Royal Edinburgh Infirmary and six St Vincent’s Hospital) were randomised as previously documented.29 29 women, 74 men; 30 had HCC and 22 concomitant alcoholic liver injury. In the last follow-up, there were only two alcohol relapsers, one in each randomised arm. Two patients were coinfected with hepatitis B or D virus (remained HBV–DNA negative in blood throughout the study).

By randomisation, 54 received MT and 49 TT. The groups were well matched at randomisation with no significant differences in preoperative, peri-operative or immediately postoperative variables: four were retransplanted early post-LT, two for hepatic artery thrombosis and one for primary non-function in the MT group; and one TT for hepatic artery thrombosis. Two MT patients were withdrawn within the first month post-LT because of side effects of treatment.

We analysed the remaining 97: 49 MT and 48 TT. Median follow-up was 96 months (range 1–146): 91.6 months MT and 98.7 months TT; 15/97 (15.5%) died within 3 years from randomisation. In all, 78/97 (80%) had a follow-up of more than 3 years, fulfilling the sample size calculation based on Log rank testing.

Clinical characteristics were well balanced and HCV genotypes were similarly distributed. In tacrolimus MT: 20 patients genotype 1 (41%), seven genotype 2 (14%), 16 genotype 3 (33%) and six genotype 4 (12%). In TT group, the distribution was 20 patients genotype 1 (41%), one genotype 2 (2%), 19 genotype 3 (40%), seven genotype 4 (15%) and genotype 5 (2%).

Median HCV RNA levels were not significantly different, pre-transplant or at 1 or 3 months post-LT.1 Antiviral treatment for HCV recurrence was used in 25 of 30 patients reaching stage 4 (19 MT, 11 TT), with six achieving SVR (18, 36 and 52 months MT; 36, 38 and 40 months TT). The median time to initiate therapy was the same in the two trial arms: 45 months for 19 MT patients and 51 months for 11 TT patients. All patients were treated with pegylated interferon α-2b 0.5 μg/kg weekly escalating to 1 μg/kg, and ribavirin 200 mg escalating to

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**Table 1** Variables evaluated in the univariate analysis for the different endpoints examined

<table>
<thead>
<tr>
<th></th>
<th>MT</th>
<th>TT</th>
<th>p Value</th>
<th>CPA≥6%</th>
<th>CPA≥7.2%</th>
<th>HVPG≥10 mm Hg</th>
<th>Decompensation</th>
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<td>Cold/warm ischaemia time (min)</td>
<td>68/046</td>
<td>68/841</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>49 (48)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Stopped azathioprine</td>
<td>NA</td>
<td>16 (33%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.012</td>
<td>0.013</td>
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<td>Tacrolimus trough concentrations (ng/mL)</td>
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<td></td>
<td></td>
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<tr>
<td>5 days</td>
<td>7.7</td>
<td>5</td>
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<td>0.002</td>
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<td>0.017</td>
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<td>15 days*</td>
<td>8.5</td>
<td>6.1</td>
<td>0.003</td>
<td>0.001</td>
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<td>0.001</td>
<td>0.01</td>
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<td>30 days*</td>
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<td>0.01</td>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.03</td>
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<td>Age</td>
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<td>Donor age</td>
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<td>44 years</td>
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<td>NS</td>
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<td>0.0033</td>
<td>0.04</td>
<td>0.033</td>
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<tr>
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<td>30</td>
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<td>0.01</td>
<td>0.03</td>
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<td>HDNH</td>
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<td>8</td>
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<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<td>10</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>Viral load logIU/mL (median)</td>
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<td>Pre-LT</td>
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<td>5.36</td>
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<td>3 m post-LT</td>
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<td>NS</td>
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<td>Genotype 1/1b</td>
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<td>41%</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>NS</td>
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<tr>
<td>Antiviral treatment</td>
<td>19</td>
<td>11</td>
<td>0.01</td>
<td>0.01</td>
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<td>SVR</td>
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<td>NS</td>
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<td>NA</td>
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<td></td>
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<tr>
<td>Pre-LT (last follow-up)</td>
<td>19</td>
<td>15</td>
<td>0.013</td>
<td>0.038</td>
<td>0.044</td>
<td>0.04</td>
<td>NS</td>
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</tbody>
</table>

*Median trough levels derived from all measurements up to days 15 and 30 post-LT.

**Hepatology**
Factors associated with reaching Ishak stage 4 or greater

At least stage 4 was reached by 19 MT patients at a median of 32 months: eight reached stage 4, eight stage 5 and three stage 6. Correspondingly, 11 TT patients reached stage 4 or greater at a median of 49 months (six reached stage 5, none stage 6). Patients receiving antiviral treatment or achieving SVR were not censored as treatment in all patients was initiated after reaching Ishak stage 4 or greater. In univariate and multivariate analyses, three factors were associated with fibrosis stage ≥4: randomisation to allocated MT treatment (p=0.001, OR 2.94, 95% CI 1.3 to 6.7), HDNH (p=0.015, OR 2.67, 95% CI 1.23 to 5.8) and discontinuation of azathioprine (p=0.036, OR 2.24, 95% CI 1.3 to 3.9). Patients who died without reaching stage 4 (four MT, one TT) were censored at the last biopsy with its Ishak stage. Hazard curves of MT/TT allocation (p=0.005 Mantel–Cox) and use/discontinuation of azathioprine (p=0.003 Mantel–Cox) are shown in figure 1.

Factors associated with CPA cut-offs

As previously published, CPA of 6% at 1 year biopsy post-LT was highly predictive of clinical outcome in a larger recurrent HCV population after liver transplantation and CPA of 7.2% was independently associated with portal hypertension, that is, HVPG ≥6 mm Hg.11 We used the cut-off of 6% of CPA and the time to first reach CPA ≥6% to compare the allocated treatments, including a multivariate analysis: 20 MT patients reached CPA ≥6% (20/37 or 54%) at a median of 41 months, while 13 TT reached CPA ≥6% (13/44, 30%) at a median of 49 months. In the multivariate analysis, allocated treatment with MT (p=0.007, OR 2.67, 95% CI 1.31 to 5.46) and HDNH (p=0.001, OR 3.27, 95% CI 1.61 to 6.6) were independently associated with CPA ≥6%. For CPA ≥7.2%, allocated MT treatment (p=0.004, OR 2.85, 95% CI 1.38 to 5.86), HDNH (p=0.006, OR 2.69, 95% CI 1.32 to 5.48) and discontinuation of azathioprine (p=0.011, OR 2.1, 95% CI 1.1 to 2.8) were independent factors. Hazard curves are shown in figure 2 for CPA cut-offs of 6% and 7.2% (p=0.002 and p=0.001 Mantel–Cox respectively).

Factors associated with portal hypertension

HVPG measurement was performed combined with transjugular biopsies in 33 MT and 31 TT patients. These represent 78% MT and 72% TT patients surviving at 1 year at the Royal Free Hospital as HVPG was not measured in Edinburgh or Dublin. There were 154 HVPG measurements post-LT: 64 at a median of 17 months, 41 at a median of 31 m, 30 at a median of 48 m, 15 at a median of 63 m and four at a median of 86 m. HVPG ≥10 mm Hg (clinically significant portal hypertension) was reached in 11 MT compared with four TT patients. Cox regression analysis revealed HDNH (p=0.015, OR 3.68, 95% CI 1.26 to 10.69) and allocated MT treatment (p=0.017, OR 4.13, 95% CI 1.28 to 13.29) to be independently associated with HVPG ≥10 mm Hg: hazard curves are shown in figure 3 (p=0.027 Mantel–Cox and 0.019 Breslow).
Factors associated with clinical decompensation

Decompensation occurred in 13 patients (all reached stage 5/6 at the time of decompensation) at a mean of 82 months: nine MT patients (seven ascites, one variceal bleeding, one encephalopathy) at a mean of 70 m and four TT patients (three ascites, one encephalopathy) at a mean time of 91 m. Hazard curves are shown in figure 3 (p=0.015 by Mantel–Cox, 0.037 Breslow).

In the Cox regression analysis, allocated MT treatment was the only statistically significant factor associated with clinical decompensation (p=0.047, OR 3.23, 95% CI 1.01 to 10.3).

Fibrosis progression rate

We evaluated 310 biopsies for Ishak stage and 289 biopsies for CPA due to inadequate material for restaining. The number of biopsies performed every year were: 74 in year 1 (34 MT/40 TT), 57 in year 2 (27 MT/30 TT), 53 in year 3 (26 MT/27 TT), 36 in year 4 (17 MT/19 TT), 34 in year 5, (18 MT/16 TT), 27 in year 6 (14 MT/13 TT), 21 in year 7 (11 MT/10 TT), 18 in year 8 (9 MT/9 TT), 4 in year 9 (2 MT/2 TT) and 5 in year 10 (3 MT/2 TT). Fibrosis progression according to CPA and stage progression over time are shown in figure 4. Median CPA fibrosis progression rate was 0.7%/year (0.74%/year MT, 0.67%/year TT). Mean stages per year (given for comparison with published studies) were: at 1 year (1.45), 2 years (2.1), 3 years (2.38), 4 years (2.86), 5 years (3), 6 years (3.2), 7 years (3.2) 8 years (3.47), 9 years (4) and 10 years (5). Mean stages for MT group were: 1.58, 2.37, 2.77, 3.18, 3.28, 3.66, 3.22, 4, 5 and 3, and for TT group were: 1.3, 1.9, 2, 2.57, 2.6, 2.77, 3, 2.87, 3 and 3 for years 1–10 post-LT respectively. Mean Ishak stage progression rate was 0.2 stage U/year (0.3 stage U/year in MT, 0.2 stage U/year TT).

Fibrosis progression rate was not significantly different between patients requiring steroids boluses for acute cellular rejection or not. Median CPA fibrosis progression rate was 0.72%/year in those requiring steroids boluses and 0.69%/year in those not treated for acute cellular rejection. Mean Ishak stage progression rate was 0.2 stage U/year in both groups.

Factors associated with early survival overall survival and graft survival

In the TT group three patients died within 3 months: one patient after retransplant (sepsis—2 days) and two at 1 month from sepsis and multiple organ failure. There were another four deaths: one due to non-liver related causes at 6 months, two from recurrent HCV disease (30 and 42 months) and one at 95 months from recurrent HCC.

In the MT group, 14 patients died: five from sepsis and multiple organ failure (0.3, 0.3, 0.6, 1 and 4 months), one from graft failure (0.5 months), one from pulmonary hypertension (0.2 months), one from ductopenic rejection (18 months) and one from recurrent HCV disease (30 months). Six more patients died in the current update: three from recurrent HCV disease (36, 37 and 72 months post-LT), one from embolic stroke (56 months) and one from lung adenocarcinoma (96 months).

Overall, mortality in the randomised 103 patients favoured TT patients (p=0.036) as well as the 97 currently evaluated (p=0.025). However, there was no statistically significant factor associated with mortality in the multivariate analysis, and no significant difference in deaths due to HCV recurrence.

Similarly, graft survival favoured the TT arm (p=0.019): 15 MT and seven TT patients died, and five MT/4 TT were retransplanted, but this difference was not due to recurrent disease.

Figure 1

Hazard curves of reaching stage 4. Hazard curves of reaching Ishak stage 4 in the two treatment arms (p=0.005 Mantel–Cox). In all, 19 MT patients reached stage ≥4 at a median of 32 months, while 11 TT reached stage ≥4 at a median of 49 months post-LT. Sixteen patients discontinued azathioprine between 10 and 37 months post-LT. MT, monotherapy; TT, triple therapy.

<table>
<thead>
<tr>
<th></th>
<th>patients exposed to risk</th>
<th>12 m</th>
<th>20 m</th>
<th>40 m</th>
<th>60 m</th>
<th>80 m</th>
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<tr>
<td>MT</td>
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<td>45</td>
<td>32</td>
<td>12</td>
<td>5</td>
<td>4</td>
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<td>TT</td>
<td>patients exposed to risk</td>
<td>45</td>
<td>40</td>
<td>27</td>
<td>17</td>
<td>8</td>
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<tr>
<td>still on AZA</td>
<td>patients exposed to risk</td>
<td>29</td>
<td>26</td>
<td>18</td>
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<tr>
<td>discontinued AZA</td>
<td>patients exposed to risk</td>
<td>16</td>
<td>14</td>
<td>9</td>
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DISCUSSION

In this final evaluation of our randomised study, the median follow-up was just over 8 years, the longest published to date following liver transplantation in a randomised trial concerning HCV cirrhosis, and given the numbers who either died within 3 years or survived more than 3 years (used for sample size calculation), this allowed a robust evaluation of clinical outcomes of recurrent HCV disease. Our outcomes included first clinical decompensation event (evaluated for the first time), HVPG and fibrosis progression defined by CPA and Ishak stage.

Fibrosis progression after liver transplantation for hepatitis C related cirrhosis has been studied several times mainly by assessing changes in Ishak/Metavir scores. Fibrosis progression is well recognised to have prognostic significance before and after transplantation. The overall rate of increase of disease stage described by changes in Ishak staging in our total trial population is similar or lower than fibrosis rates previously described. The mean fibrosis Ishak stage was 1.45 and 2.1 in years 1 and 2 post-LT in our whole cohort, and 1.3 and 1.9 at years 1 and 2 post-LT respectively for the TT group, which are as low as those recently published in patients receiving sirolimus (which may have antifibrotic properties) compared with historical controls (0.62 and 1.15 metavir in year 1 and 2 biopsies, respectively).

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<td>TT still on AZA</td>
<td>patients exposed to risk</td>
<td>28</td>
<td>25</td>
<td>18</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>TT discontinued AZA</td>
<td>patients exposed to risk</td>
<td>16</td>
<td>13</td>
<td>8</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

![Hazard curves of collagen proportionate area (CPA) 6% and 7.2%.](image)

Hazard curves of reaching CPA 6% and 7.2% with those achieving sustained virological response censored (18 m MT, 36 m TT, 36 m MT, 38 m TT, 40 m TT, 52 m MT) in the two treatment arms (p=0.002 for CPA 6% and p=0.001 for CPA 7.2% by Mantel–Cox). Sixteen patients discontinued azathioprine between 10 and 37 months post-LT. MT, monotherapy; TT, triple therapy.
The relatively low overall rate of increase of disease stage in our trial population most likely reflects use of combined therapy of tacrolimus with azathioprine and steroids and/or the generally lower trough levels of tacrolimus achieved. Since our first publication, we have shown that CPA assessment in HCV post-LT patients correlates with both Ishak stage scores and HVPG, with greater percentage changes in CPA, compared with HVPG in early portal hypertension. Moreover, CPA at 1 year biopsy post-LT is highly predictive of clinical outcome in HCV transplanted patients and better than Ishak stage or HVPG. In the current update, MT and HDNH were independently associated with reaching CPA cut-offs of 6% and 7.2%, the latter corresponding to HVPG ≥ 6 mm Hg, reinforcing both the value of CPA and validating these cut-offs as endpoints.

As in our first publication, outcomes favouring the TT group are supported by HVPG measurements. There was more clinically significant portal hypertension (associated with advent of complications and worse survival) in the MT group (11 patients reached HVPG ≥ 10 mm Hg, compared with four TT) corroborating the more severe fibrosis found in MT patients.

The significance of HDNH is again confirmed by us and others as this was independently associated with Ishak stage 4, but also CPA cut-offs for decompensation and HVPG.

A limitation in this study could be the lack of evaluation of recipient IL28B polymorphism, which was also missing in the recent sirolimus study. Some studies suggest a higher recurrence rate of HCV hepatitis with the poor interferon response allele of IL28B in the recipient. However, randomisation will most likely have balanced out the more favourable polymorphism, which in any case is under represented in liver transplant populations. Moreover, IL28B was not significantly associated with either overall or liver related mortality in one study, and there has been a selection bias in most studies, as only patients with biopsies were evaluated, that is, not every patient with recurrent hepatitis C was biopsied. Moreover, no study evaluated immunosuppression when analysing severity of recurrence. Last, some studies do not show an association of recipient IL28B with worse HCV disease recurrence.

In conclusion, long term maintenance immunosuppression with tacrolimus, azathioprine and shorter term prednisolone in HCV cirrhosis recipients resulted in a slower onset of histological severe fibrosis confirmed by Ishak stage and CPA, less portal hypertension, and less clinical decompensation compared with tacrolimus alone. Our results support and extend our initial report. Given that our TT arm has the lowest fibrosis progression rate published so far—lower than sirolimus—and that there is some evidence that azathioprine is better than...
mycophenolate, our TT regimen could be considered as a first choice for patients transplanted for HCV cirrhosis, until other evidence proves otherwise.

Competing interests AKB and APD have an unrestricted educational grant from Pfizer.

Ethics approval The hospital ethics committees at each site.

Provenance and peer review Not commissioned; externally peer reviewed.

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