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LETTER TO THE EDITORS

Progression of liver fibrosis in HCV-positive liver transplant recipients randomized to everolimus with reduced calcineurin inhibitor (CNI) therapy or a standard CNI regimen

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Dear Sirs,

Three trials have recently been published in which *de novo* liver transplant patients were randomized to a standard CNI regimen or to everolimus with reduced CNI [1,2] or early CNI withdrawal [3–5]. Data from hepatitis C (HCV)-positive subpopulations treated with everolimus, however, remain largely unpublished [2] but would be welcome in this high-risk group of patients.

A planned subpopulation analysis of the H2304 study was undertaken in HCV-positive patients randomized at day 30 post-transplant to everolimus with low-exposure tacrolimus or a standard tacrolimus regimen [2]. Patients were stratified prior to randomization according to pre-transplant HCV status (based on the presence/absence of anti-HCV antibodies confirmed by serology or PCR).

In the EVR + Reduced TAC group and TAC control groups, 79/245 patients (32.2%) and 76/243 (31.3%), respectively, were HCV-positive. Baseline characteristics were similar, including viral load and the frequency of HCV genotype 1 [50/79 (63.3%) and 46/76 (60.5%)]. The composite efficacy endpoint of treated biopsy-proven acute rejection (tBPAR), graft loss, or death at month 24 occurred in 8/79 (10.6%) EVR + Reduced TAC subjects and 8/76 (11.6%) TAC control patients [$P = 0.850$, (Kaplan–Meier estimates)]. The difference between groups in adjusted mean change in estimated GFR (MDRD formula) from randomization to month 24 (ANCOVA) was [5.11 mL/min/1.73 m^2, 97.5% CI −4.59, 14.82] in favor of the EVR + Reduced TAC group.

Locally assessed Ishak–Knodell fibrosis scores were available at baseline and month 24 in 26/79 EVR + Reduced TAC patients (32.9%) and 30/76 TAC control patients (39.5%). The mean (SD) Ishak–Knodell staging score at month 24 was similar in the EVR + Reduced TAC and TAC control arms: 0.7 (0.9) vs. 1.1 (1.3) ($P = 0.450$), as was the mean (SD) change in staging score from baseline to month 24, adjusted for baseline score [0.2 (1.9) vs. 0.6 (2.0), respectively; $P = 0.450$]. The proportion of patients with clinically meaningful progression of fibrosis (defined as increase of ≥1 Ishak–Knodell fibrosis staging score from baseline, death, or graft loss) among patients with biopsy data, death, or graft loss at month 24 was not significantly different ($P = 0.087$) (Fig. 1). The overall necroinflammatory grading score and individual components of the score did not indicate any between-group difference. Adjusted values (ANCOVA) showed no significant difference in HCV viral load at month 24.

Antiviral therapy using an interferon-based regimen was administered to 23/71 EVR + Reduced TAC patients (32.4%) and 9/67 TAC control patients (13.4%).

This preplanned analysis of data for the two-year, randomized H2304 study detected no evidence that everolimus therapy with early reduction of TAC exacerbates the progression of liver fibrosis or HCV replication in HCV-positive liver transplant recipients. There was a trend to less fibrosis progression in the EVR + Reduced TAC patients

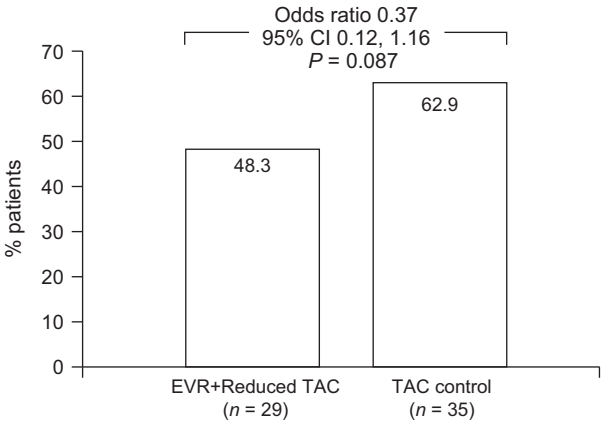

Figure 1 Progression of graft fibrosis from baseline to month 24. Progression was defined as an increase of ≥1 Ishak–Knodell fibrosis staging score, death, or graft loss. Patients with biopsy data at baseline and month 24 or in whom death or graft occurred by month 24 were included in the analysis. The logistics model included treatment, baseline score, and use of antiviral treatment as factors and recipient age as covariate.

but evaluation was hampered by the disappointingly low number of patients with paired biopsy samples. Longer term results in a larger population would be of interest.

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Conflict of interest

Faouzi Saliba has received speaker's fees and/or research funding from Novartis, Astellas, Roche, Genzyme, MSD, Gilead, Schering Plough, Gambro, and Vital Therapies. Frederik Nevens has received grant support from Ipsen, Roche, MSD, and Boston Scientific.

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