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Tacrolimus trough concentrations after liver transplantation: back to the future.

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Abbreviations:

CNI: calcineurin inhibitor.

LT: liver transplantation.

TC: trough concentrations

Dear Sir:

We read with great interest the retrospective study by Di Maira et al[1] which failed to establish an association between early exposure to calcineurin inhibitors (CNI) and long-term outcomes among 432 patients who underwent liver transplantation (LT) in 2 centers. The authors suggested that early minimization of CNIs may have a limited prognostic impact.

Trough concentrations (TC) of tacrolimus are set higher within the first month after LT, with a progressive reduction thereafter. In clinical practice, most patients converge at TC around 4-5 ng/mL from the sixth postoperative month onwards. Therefore, the realistic window for a true minimization of tacrolimus is within the first months after LT. A systematic review and meta-analysis of 32 randomized trials comparing different targets of tacrolimus TC found a linear correlation between mean TC of tacrolimus within the first month and renal impairment rates at 1 year after LT.[2] Indeed, patients receiving mean tacrolimus TC>10 ng/mL showed twice higher renal impairment rates at 12 months.[2] Mean tacrolimus TC>10 ng/mL were also associated with increased risk of graft loss[3] and higher recurrence rates of hepatocellular carcinoma[4] in 2 independent observational studies. More recently, cumulative exposure to tacrolimus within the first 3 months after LT was associated with a more pronounced decrease of glomerular filtration rates,[5] which in turn is a widely renown surrogate of cardiovascular events.

The study by Di Maira et al. challenges this bulk of evidence, but there are several limitations to be taken into account. First, patients receiving tacrolimus and cyclosporine were analyzed together and subgroup analyses with patients receiving tacrolimus were clearly underpowered (the authors estimated minimum sample size at n=430 and there were only 243 patients receiving tacrolimus). Secondly, immunosuppression groups (i.e. high vs optimal vs low) were defined by median TC in

contrast with previous studies which used mean TC.[3,4] Mean TC would be more appropriate as they are sensitive to peaks of TC, which are thought to be especially deleterious and sufficient to increase the mortality rates due to infections, cardiovascular events and cancer.[3] In addition, as acknowledged by the authors, thresholds of tacrolimus and cyclosporine (monitored either with C_0 or C_2) may not be equipotent, thus resulting in a classification bias. Finally, a competing risk analysis would be needed to evaluate some outcomes such as cardiovascular events.

We agree with the authors that the true negative impact of CNI exposure, particularly for long term outcomes such as cardiovascular events or cancer, may be derived from cumulative exposure over time[5] rather than single measurements early after LT or intrapatient variability. However, we are concerned that the retrospective observation by Di Maira et al[1] may encourage physicians to increase tacrolimus trough concentrations early after LT, with a negative impact on renal impairment rates, and probably also on cardiovascular events and cancer. In contrast with the present study, future investigations should be aimed at determining the safest window for CNI minimization and at identifying immune-tolerant candidates for a complete withdrawal of CNIs.

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