Single center, open-label, randomized, controlled, cross over study to evaluate the pharmacokinetic and bioavailability of Envarsus® in comparison to Advagraf® in de novo liver transplant recipients

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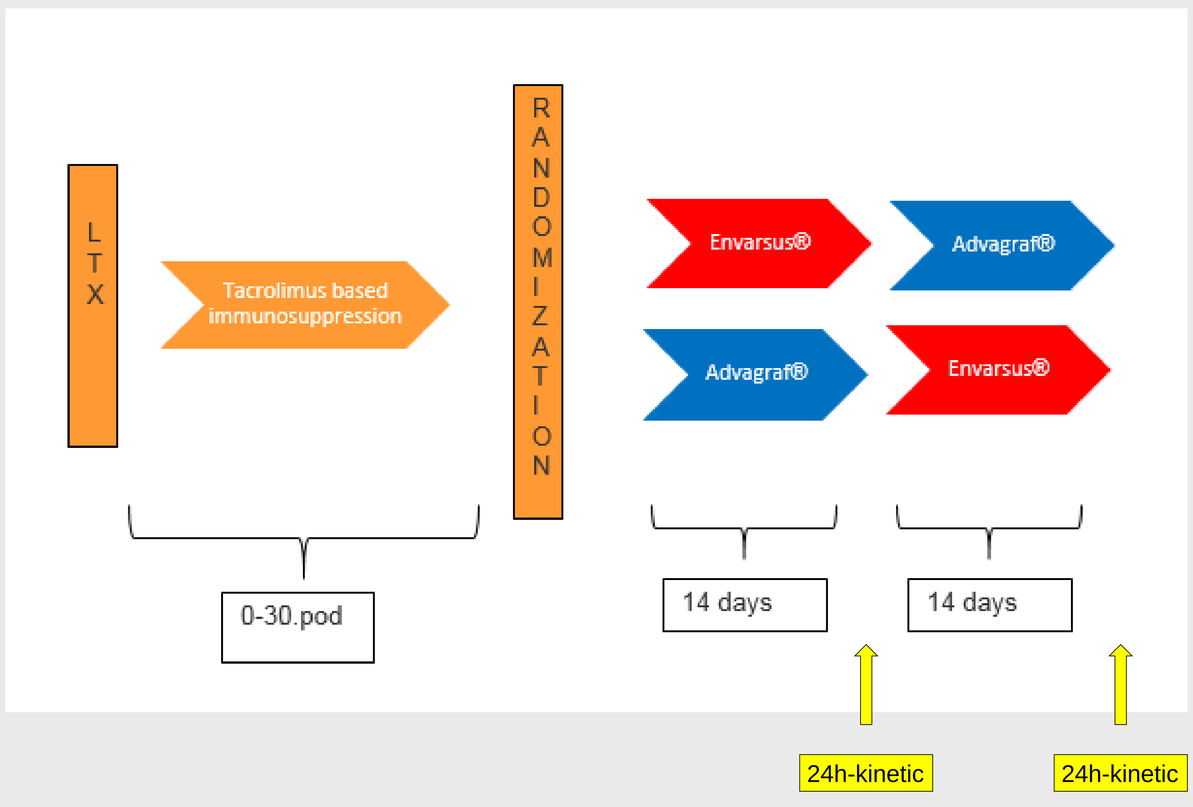
Background

- LCP-Tacrolimus (Envarsus®) is a novel, melt-dose, extended-release preparation of tacrolimus that has been developed for once-daily administration.
- First data after liver transplantation (LT) show improved pharmacokinetic (PK) properties with a higher bioavailability and a significantly lower peak-trough fluctuation, with the same effectiveness compared to standard twice-daily tacrolimus (Progaf®).
- Up to date the PK profile of Envarsus® has not been compared with once-daily tacrolimus (Advagraf®) in de novo LT recipients.

Methods

- Single center, open-label, randomized and controlled clinical cross over trial
- Patients were randomized in group 1 or 2 between LT and postoperative day 30 after LT. After LT all patients received standard twice-daily tacrolimus which was stopped and changed to Envarsus® or Advagraf® depending on randomization. Study medication was started the same morning for a period of 14 days with a target level of 6-10 mg/dL. 24h-PK sampling was done at the end of the period in the steady state of the medication, thereafter medication was switched again for a period of 14 days to Envarsus® or Advagraf® with terminal PK.



Results

- 20 patients were planned, screened and randomized for the study, thereof 2 patients withdrew their consent before change of medication, resulting in 18 patients with study medication = safety population
- 9 patients completed the study
- 9 patients with premature dropout
  - study reasons n=4 (e.g. lack of study medication, impossibility for 24h-kinetics due to very poor vein status)
  - Lack of adjustability study medication level n=2
  - medical complications n=2 (1x recurrent infection, 1x rejection)
  - consent withdrawn n=1

Results

The tacrolimus trough levels were comparable for both treatments arms at the start of PK profile (Envarsus® 6.9 ± 3.2 mg/dL; Advagraf® 6.0 ±1.6 mg/dL). $AUC_{0\text{-}24}$ (284.6 ± 164.7 mg*h/dL versus 242.3 ± 95.1 mg*h/dL) und C_{max} (23.9 ± 14.6 mg/dL versus 22.1 ± 14.3 mg/dL) were slightly higher for Envarsus® suggesting a higher bioavailability. However, it failed to reach statistically significance, may be due to the small sample size of 9 subjects in the PK population (originally 20 were planed). Concerning the administered doses, the ratio C0/doses is significantly higher for Envarsus® (adj. geoM ratio: 176.2% (CI: 131.6% – 235.8%)), which means that the administered dose in relation to trough level at steady state was lower for Envarsus® compared to Advagraf®. This applies in the same way for the $AUC_{0\text{-}24}$/doses (adj. geoM ratio: 176.5 (139.0, 224.1); likewise the administered dose to achieve the same AUC in steady state is lower for Envarsus® in contrast to Advagraf®. Also, the average cumulative dose (DAV) was lower for Envarsus® (adj. mean difference: 2.9 (CI: -0.1 - 5.9)).

The peak through fluctuation (PTF) was slightly higher for Advagraf® with adjusted geoM of 1.1 and 1.4, respectively (ratio: 84.3% (CI: 46.6% – 152.5%)).

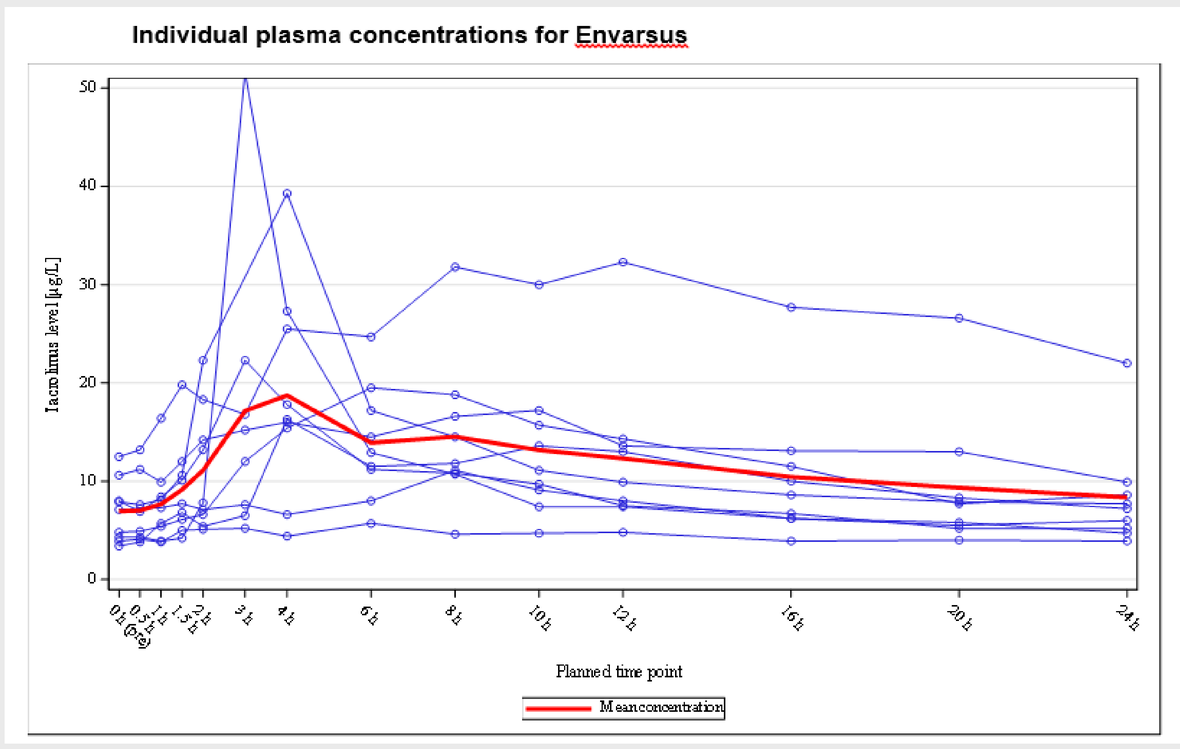
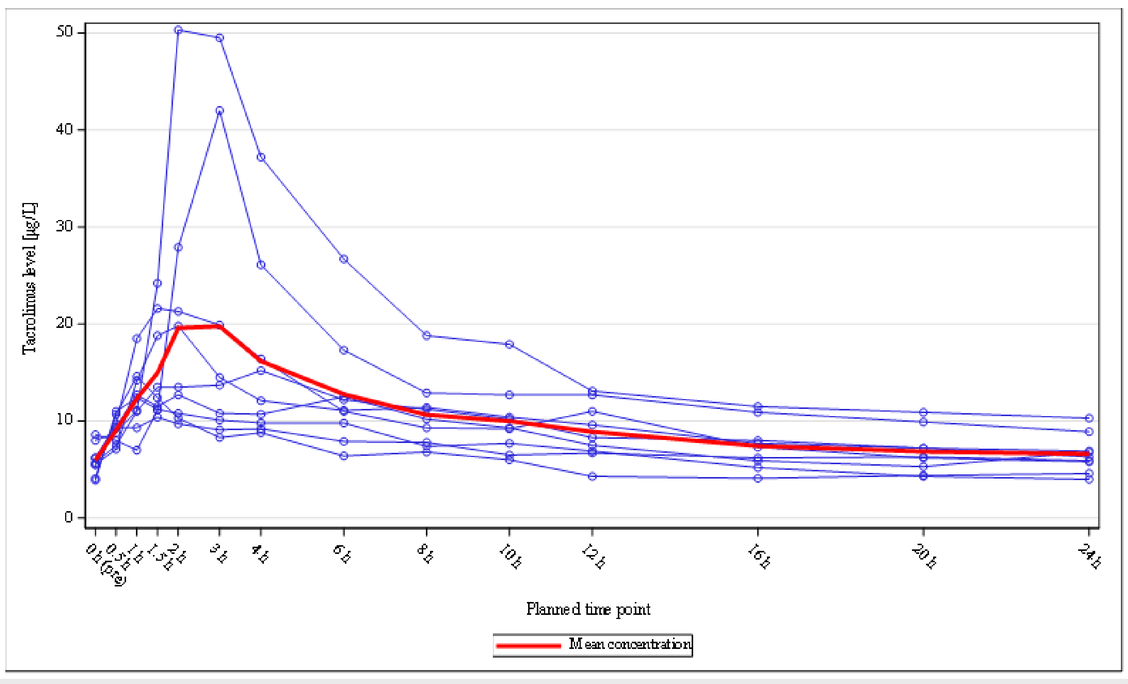


Figure 2 Individual plasma concentrations for Advagraf



Conclusion

Overall, we have found a preferable PK for Envarsus® in de novo LT patients and, in particular, a lower medication requirement to achieve equivalent trough levels.

* There are no commercial affiliations or consultancies of any author that could be construed as a conflict of interest with respect to the submitted data