725-MP: Extended Release Tacrolimus in Kidney Graft Recipients – Pharmacokinetic and Economical Aspects

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Background: The use of once daily tacrolimus formulations in de novo kidney allograft recipients is common nowadays. Therefore, we were interested in pharmacokinetic and economical aspects of the use of Envarsus™ and Advagraf™ compared with Prograf™.

Methods: Recipients of a kidney allograft receiving a tacrolimus based immunosuppression were included in a single centre retrospective study. Therefore, participants of the LCP-Tacro 3002 study - ClinicalTrials.gov: NCT01187953 - (Envarsus™, Prograf™) and of the ITP-NODAT study - ClinicalTrials.gov: NCT01683331 (Advagraf™) were analysed. Clinical and laboratory results were retrieved from our data base TBase. For the calculation of tacrolimus costs the German list prices and most convenient number of tablets/capsules were used.

Results: We analysed the data sets of recipients of a *de novo* kidney transplantation who received Envarsus™ (n=21), Prograf™ (n=23) or Advagraf™ (n=36). Pharmacokinetic results are summarized in Table 1.

Table 2: Costs of Different Tacrolimus Formulations in *de novo* Kidney Allograft Recipients [€; median (IQR)]

	d1-10	d90	d180	d360
Envarsus™	531,30 (464,24-600,37)	20,99 (16,68-23,77)	16,68 (15,03-23,77)	16,68 (15,03-18,21)
Advagraf™	630,50 (550,69-702,21)	30,37 (19,77-36,54)	20,37 (18,30-35,14)	20,37 (14,77-31,72)
Prograf™	468,26 (424,44-664,18)	30,00 (25,30-45,74)	28,53 (18,90-40,56)	23,53 (17,06-40,74)
U-test (E vs. A)	P<0,01	P<0,01	P=0,066	P=0,060
U-test (E vs. P)	n.s.	P<0,01	P<0,05	P<0,01
U-test (A vs. P)	P<0,01	n.s.	n.s.	n.s.

d1-d10: cumulative costs of the first ten days on tacrolimus; d90, d180, d360: daily tacrolimus treatment costs on the respective day; E – Envarsus™, A – Advagraf™, P - Prograf™

The differences in costs are significant during the early treatment phase (in the hospital) and remain relevant over the first 12 months. Given the daily tacrolimus treatment costs at 12 months the estimated treatment costs per year add up to 6088 € for Envarsus™, 8588 € for Prograf™ and 7435 € for Advagraf™.

Table 1: Pharmacokinetic Parameters [median (IQR)] of Different Tacrolimus Formulations in *de novo* Kidney Allograft Recipients

	d10			d90			d180			d360		
	Dose (mg)	**Dose (mg/kg)**	**Trough level (ng/ml/mg total daily dose)**	**Dose (mg)**	**Dose (mg/kg)**	**Trough level (ng/ml/mg total daily dose)**	**Dose (mg)**	**Dose (mg/kg)**	**Trough level (ng/ml/mg total daily dose)**	**Dose (mg)**	**Dose (mg/kg)**	**Trough level (ng/ml/mg total daily dose)**
Envarsus™	10,0 (6,75-14,0)	0,12 (0,08-0,18)	0,99 (0,66-1,84)	4,5 (3,0-5,0)	0,06 (0,04-0,07)	2,24 (1,63-3,24)	3,0 (2,25-5,0)	0,05 (0,03-0,07)	2,50 (1,28-3,13)	3,0 (2,25-4,0)	0,04 (0,03-0,06)	2,18 (1,59-3,47)
Advagraf™	15,5 (13,0-18,75)	0,22 (0,18-0,26)	0,49 (0,38-0,69)	7,0 (4,0-8,5)	0,09 (0,06-0,14)	1,34 (0,96-1,94)	5,0 (3,5-7,5)	0,07 (0,05-0,11)	1,32 (0,87-2,08)	4,5 (2,75-6,75)	0,06 (0,04-0,11)	1,44 (0,92-2,35)
Prograf™	15,0 (10,0-20,0)	0,19 (0,14-0,24)	0,59 (0,40-0,69)	6,0 (4,75-11,0)	0,09 (0,07-0,13)	1,19 (0,74-1,75)	5,5 (3,63-9,5)	0,06 (0,05-0,11)	1,27 (0,79-1,88)	4,5 (3,0-10,0)	0,06 (0,04-0,11)	1,50 (0,88-1,89)
U-test (E vs. A)	P<0,001	P<0,001	P<0,001	P<0,01	P<0,01	P<0,01	P<0,05	P<0,05	P<0,05	P<0,05	P<0,05	P<0,05
U-test (E vs. P)	P<0,01	P<0,01	P<0,01	P<0,01	P<0,01	P<0,01	P<0,05	P<0,05	P<0,05	P<0,05	P<0,05	P<0,05
U-test (A vs. P)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

d10, d90, d180, d360 – day 10, 90, 180 and 360 after kidney transplantation; E – Envarsus™, A – Advagraf™, P - Prograf™t

All pharmacokinetic comparisons between extended-release once-daily tacrolimus formulations, i.e. Envarsus™ and Advagraf™, revealed significant advantages for Envarsus™. Apart from the immediate-release of tacrolimus from Prograf™ capsules, which requires twice-daily dosing, there were no significant disadvantages of Prograf™ compared with Advagraf™ from a pharmacological point of view.

Difficulties in reaching therapeutic tacrolimus trough levels immediately after transplantation were common in Advagraf™ patients. This led to extra dosing with Prograf™ in 12 of 36 patients and eventually to a Advagraf™-Prograf™-switch in two cases.

Biopsy proven acute rejections occurred in 18/80 patients (Envarsus™: n=4/21; Advagraf™: n=8/36 ; Prograf™: n=6/23; Chi-square-test: n.s.). Sub-therapeutic tacrolimus trough levels were evident in 10 of 18 cases with rejections (Envarsus™: n=1/4; Advagraf™: n=4/8; Prograf™: n=5/6).

Not surprisingly the differences in pharmacokinetic characteristics translate into significant differences in treatment costs (Figure 1, Table 2), given the roughly comparable prices per mg of the different tacrolimus formulations.

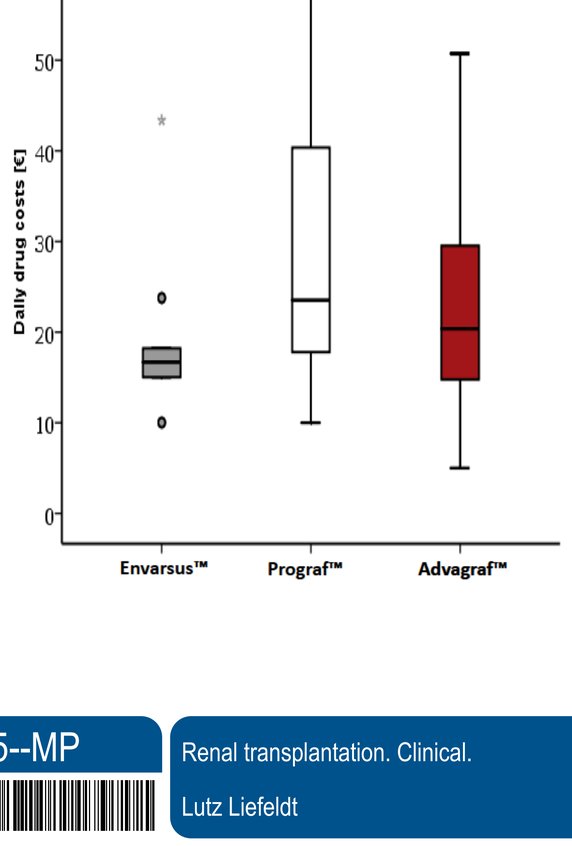

Figure 1:
Daily tacrolimus costs at 12 months after kidney transplantation (Kruskal-Wallis-Test: p<0,05)

High inter-individual differences in pharmacokinetic parameters (Figure 2) and thereby costs are evident. Obviously the inter-individual variability of the need for Envarsus™ is smaller (Figure 2 A, B) than for Prograf™ or Advagraf™. Despite higher doses of Prograf™ or Advagraf™ their tacrolimus exposure (Figure 2 C+D) is lower.

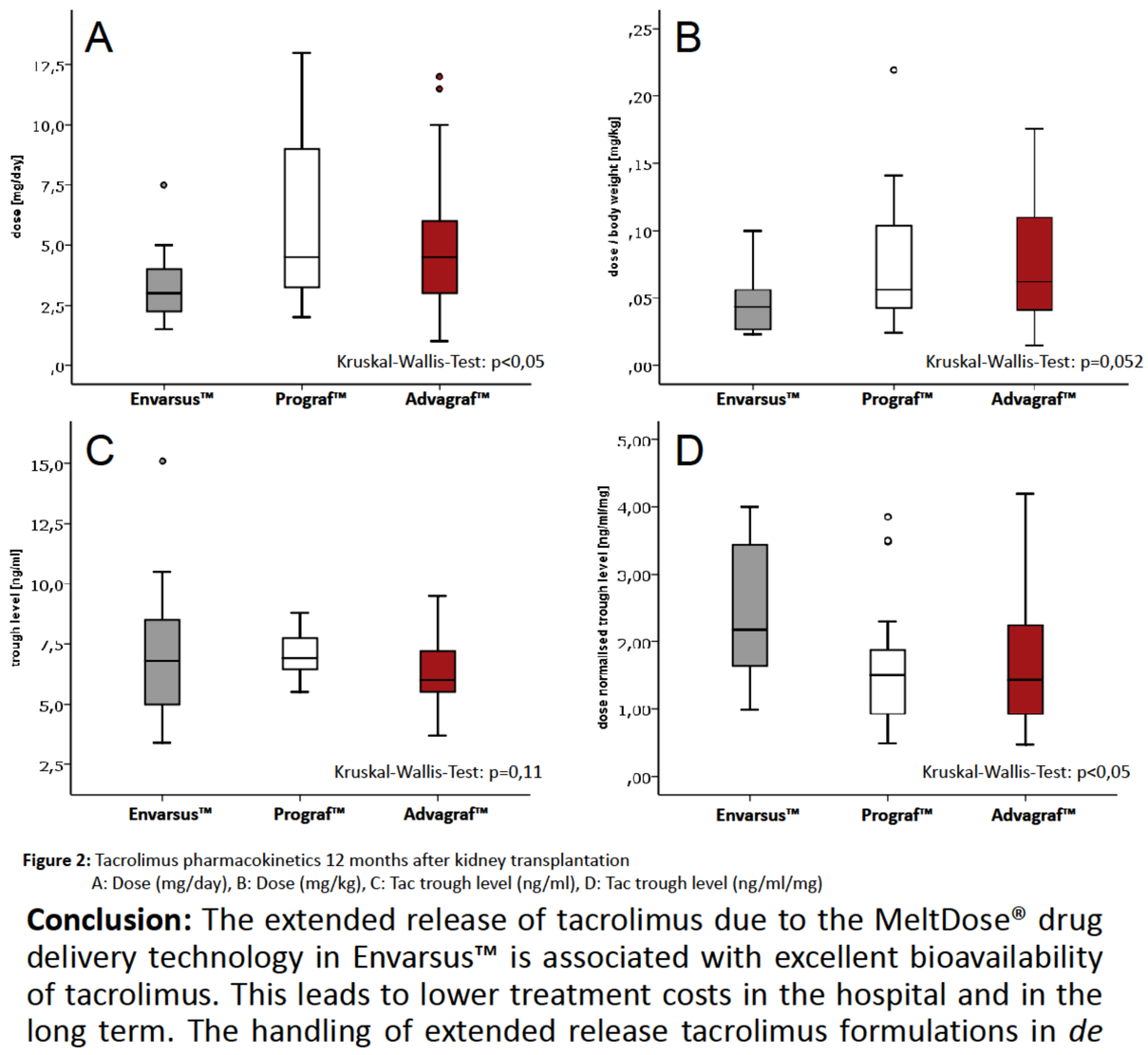

Figure 2: Tacrolimus pharmacokinetics 12 months after kidney transplantation
A: Dose (mg/day), B: Dose (mg/kg), C: Tac trough level (ng/ml), D: Tac trough level (ng/ml/mg)

Conclusion: The extended release of tacrolimus due to the MeltDose® drug delivery technology in Envarsus™ is associated with excellent bioavailability of tacrolimus. This leads to lower treatment costs in the hospital and in the long term. The handling of extended release tacrolimus formulations in *de novo* kidney transplantation requires a learning period. Diet-related changes of the absorption of tacrolimus as well as pharmacogenetic reasons may account for the phenomenon of highly variable tacrolimus exposure and require further studies.

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