Meltdose Tacrolimus Pharmacokinetics

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ABSTRACT

Background. Nonadherence to immunosuppressive therapy contributes to the loss of grafts. One of the problem is the fractioning of immunosuppressive dose. In fact, it was demonstrated that a single daily dose (QD) is associated with an increased adherence to therapy compared with twice daily dosing (BID). Tacrolimus (TAC), calcineurin inhibitor, is one of immunosuppression pillar in organ transplantation and its action is strongly correlated with blood concentration and therefore the therapeutic drug monitoring is recommended in the guidelines. However, one of the critical points of TAC is the poor and variable bioavailability that influences immunosuppression, and is also responsible for adverse effects.

Methods. MeltDose® Technology is a new technology to improve efficacy and/or reduce side effects. This new technology applied to TAC (Envarsus® or LCP-TAC) has achieved 4 main objectives: (1) improved bioavailability, (2) reduced dose fractioning to one tablet per day, (3) limited variability concentrations of TAC, and (4) lower doses of TAC will be administered.

Results. We analyzed the pharmacokinetic profile, efficacy, and security of Envarsus®.

TACROLIMUS (TAC), calcineurin inhibitor, is a pillar of immunosuppression in organ transplantation and it has as an immediate release (IR) formulation requiring a twice daily dose regimen (BID). Its action is associated strongly with blood concentration and therefore the actual guidelines recommended therapeutic drug monitoring [1].

One of the critical points of TAC-IR, is the poor and variable bioavailability [2,3]. Because the maximum drug concentration (C_{max}) and area under the curve (AUC_{0-12}) are fundamental to immunosuppression, but are also responsible for adverse effects (nephrotoxicity, tremor and paresthesia, hypertension, hyperglycemia), these parameters strongly affect the graft and patient health [4].

A review showing the results of 10 cohort studies conducted on kidney transplants (KTx) indicates that, in transplant recipients, nonadherence to immunosuppressive therapy contributes to the loss of grafts. Published data indicate that it can be up to 36% loss of the graft, a 7-fold increase compared with compliant patients [5,6].

In KTx, poor adherence to therapy seems to be linked closely with the dose fractioning of the drug; that is, the higher the dose fractionation, the lower is the adherence. Therefore, a single daily dose (QD) is associated with an increased adherence to therapy compared with a BID schedule [7]. So the second type of TAC was a prolonged-released capsules (TAC-PR) administered as single daily dose. This new formulation, however, did not solve the problem of interindividual and intraindividual variability, which is linked with lesser bioavailability.

Nanotechnology and nanoformulations in medicine can overcome the problems of poor bioavailability by virtue of the nanosize of drugs [8]. An extended-release formulation of TAC designed for once-daily administration (LCP-TAC) is a new prolonged-release TAC formulation, using a drug delivery technology designed to enhance the bioavailability of drugs with low water solubility by creating a solid solution of the drug. This minireview analyzes the pharmacokinetic properties of LCP-TAC in transplant recipients, omitting aspects of efficacy and safety of the new formulation.

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METHODS

MeltDose® technology, a platform developed by Veloxis Pharmaceuticals A/S (Hørsholm, Denmark), a company founded in 2002, is a drug delivery technology used to enhance the oral bioavailability and control the release of a drug, especially low water-soluble or -insoluble drugs. The goal of this technology is to improve efficacy and/or reduce side effects. Particle size plays a vital role in bioavailability. Unlike conventional and nanocrystal drug delivery formulations, which use larger particles that are more difficult to absorb, MeltDose® technology enhances bioavailability by reducing the drug to the smallest possible particle size down to single molecules. The smaller particle size enables better dissolution and absorption. The particles of the active substance have been reduced as small as possible, passing from the size of 10 μm of the conventional drug, to a solution <0.1 μm diameter, to be organized into oral tablets. Fenofibrate, a lipid-regulating agent to control cholesterol and marketed as Fenoglide® in the United States by Shore Therapeutics (East Setauket, NY), was the first product approved in the United States using the MeltDose® technology [9]. The second application was to TAC (Envarsus® or LCP-TAC). This formulation improves oral bioavailability and reduces the daily dose by 30% from previous formulations.

RESULTS

The pharmacokinetic profiles of TAC have been recently studied by Garnok-Jones [10], who compared kidney transplant recipients (KTRs) and liver transplant recipients who were stable, treated TAC-IR and converted to LCP-TAC. The total daily dosage was 5.26 versus 7.39 mg comparing the LCP-TAC versus TAC-IR with a statistically significant difference in KTRs ($P < .05$) but not in LTRs (4.4 vs 6.1 mg). The AUC24 (ng · h/mL) was comparable in LCP-TAC and TAC-IR without significant differences (206.7 vs 212.1 ng · h/mL; in KTRs; 185.4 vs 196.41 ng · h/mL in LTRs). However, as reported by product characteristics, LCP-TAC presents an oral bioavailability of approximately 30% higher than TAC-IR in KTx recipients. The C_{max} of LCP-TAC is significantly lower than TAC-IR in KTRs and LTRs (KTRs, 12.6 vs 17.6 ng/mL [$P < .0001$]; LTRs, 11.8 vs 16.8 ng/mL [$P < .001$]), although the median trough level (C_{min}) was similar in KTRs (6.5 vs 6.8 ng/mL) and LTRs (5.9 vs 6.4 ng/mL). Consequently, LCP-TAC has a significant reduction of C_{max}/C_{min} fluctuation ratio, comparing with TAC-IR, (KTRs, 2.03 vs 2.75 [$P < .0001$]; LTRs, 2.1 vs 2.7 [$P < .001$]).

Because LCP-TAC is a prolonged-release formulation of TAC, it results an extended oral absorption profile with a median time to maximum blood concentration (T_{max}) of approximately 6 hours at steady state, compared with 1.8 hours of TAC-IR in KTRs ($P < .0001$) and 1.5 hours of TAC-IR in LTRs ($P < .001$). The differences between blood concentrations versus time of LCP-TAC and TAC-IR are presented in Fig 1.

A very interesting innovation is that, in KTRs and LTRs, the mean total daily dose of LCP-TAC is approximately 30% lower than that of TAC-IR to reach the same exposure levels at 7 days. Moreover, there is a good correlation between C_{min} and AUC_{0-12} at steady-state for LCP-TAC in KRTs ($r = 0.91$) and LTRs ($r = .94$), making therapeutic drug monitoring is possible with C_{min}.

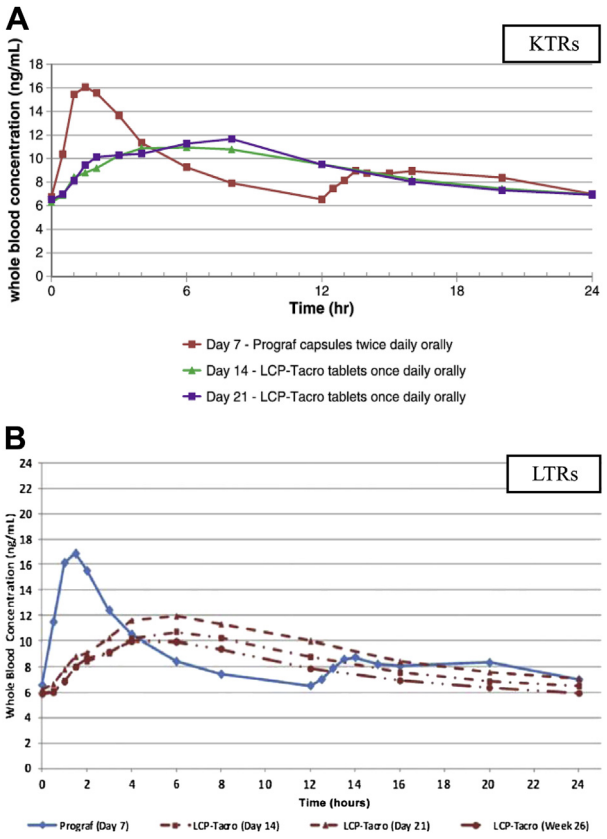

Fig 1. Mean whole-blood tacrolimus concentration in 47 kidney transplant patients (KTPs) on day 7, 14, and 21 versus time (**A**) and in 44 liver transplant patients (LTPs) on day 7, 14, 21, and 26 versus time (**B**). Dosage details are shown in paper. Reproduced from Gaber et al. [12] and Alloway et al. [13], with permission.

The blood sampling time must be in the morning before administration. LCP-TAC should generally be taken on an empty stomach to achieve maximal absorption. The other pharmacokinetics steps are stackable and have no significant differences compared with TAC-IR. TAC has a biphasic distribution and is extensively distributed. The steady-state volume of distribution of TAC is 47.6 L in healthy volunteers. TAC crosses the placenta and is excreted in breast milk. TAC is metabolized in the liver by cytochrome P450 3A4 and in the intestinal wall. The metabolites do not contribute to its pharmacologic activity in patients. The average total body clearance of TAC is 2.25 L/h in healthy volunteers and was 6.7 L/h in adult KTx recipients, with a mean half-life of approximately 30 hours in healthy volunteers.

DISCUSSION

TAC is a calcineurin inhibitor much more potent than cyclosporine, but its bioavailability is low and variable,

which this has often created problems of clinical efficacy. The LCP-TAC uses a MeltDose® technology and represents an innovation in the field of the immunosuppressive drugs. This new technology increases the amount of active ingredient that reaches the blood, ensuring the best therapeutic efficacy. Furthermore, the controlled release ensures a continuous absorption not only in the duodenum but also in the whole intestine, as demonstrated by Nigro et al. [11]. They studied a bowel scintigraphy immediately after dosing of LCP-TAC. Drug dissolution begins in the stomach and/or in the proximal part of the small intestine (time 0:02 hours), about 11 hours after the drug is found in ascending and transverse colon, and after 28 hours dissolution goes on in the transverse and descending colon. This new formulation of TAC ensures a continuous and consistent absorption through the gastrointestinal tract for 24 hours.

In a phase II study conducted on KTx stable recipients, there was a difference between blood concentrations of TAC after administration of TAC-IR BID regimen, obtained after 7 days after transplantation, and LCP-TAC QD under after 14 and 21 days after transplantation [12]. From a pharmacokinetic point of view, the following points present significant differences: (1) the total daily dosage (mg/d) is lower, the C_{max} is reduced with T_{max} delayed, the swing C_{max}/C_{min} is lower for LCP-TAC; (2) the C_{min} is comparable as well as the AUC_{0-24} between TAC-IR and LCP-TAC; and (3) there is a good correlation between the C_{min} and the AUC_{0-24} ($r^2 = 0.86$).

In a phase II study conducted on LTRs stable patients, pharmacokinetic data demonstrated consistent exposure (AUC) at the lower conversion dose. The C_{max}, C_{max}/C_{min} ratio, percent fluctuation and swing were significantly ($P < .001$) lower and T_{max} significantly lower ($P < .001$) for LCP-TAC versus TAC-IR [13].

In a 2014 paper by Grinyo et al. [14], the adjusted 1-year cumulative dose was statistically reduced for LCP-TAC compared with TAC-IR. The authors concluded that LCP-TAC significantly reduces the number of doses in the short and long term, with significant cost savings [14]. If used an official defined dial dose of TAC (IR and PR) and conversion rate of LCP-TACs (1 mg:0.7 mg) as the summary of product characteristics authorized by the European Medicines Agency, and LCP-TAC price is similar to TAC-PR cost, LCP-TAC therapy will cost less than TAC-PR. It is important to remember that many hospitals negotiate discounts on immunosuppressant drugs and competitive tendering processes are often in place for the various formulations and brands of TAC.

In a study by Bunnapradist et al. [15], the authors, on 162 stable KTx patients, found evidence of graft protection after 1 year of treatment with either TAC or LCP-TAC. The average trough concentration did not differ between the 2 treatments at 12 months (LCP-TAC, 5.19 vs TAC 5.07 ng/mL). However, the cumulative dose at 12 months was significantly lower (4.5 vs 4.8 for QD in BID; $P < .001$) [15].

The dosage should be based on clinical assessments (rejection and tolerability) and whole-blood TAC concentration monitoring. The therapeutic range is 5–20 ng/mL in de novo KTx recipients and 5–15 ng/mL in subsequent maintenance therapy (5–10 ng/mL, with concomitant treatment). The recommended starting dosage for TAC-PR in de novo KTRs or LTRs is 0.17 or 0.11–0.13 mg/kg, respectively, once daily in the morning, initiated within 24 hours of the completion of surgery [16].

Finally, allograft transplant patients maintained on TAC-IR BID or TAC-SR QD requiring conversion to QD TAC-PR should be converted on a 1:0.7 (mg:mg) total daily dose basis and the dose titrated against trough whole blood drug concentration. This difference reflects the higher bioavailability of TAC from LCP-TAC compared with TAC-IR such that doses of LCP-TAC that achieve the same whole blood trough concentrations at the end of the treatment period (and are therapeutically equivalent) are approximately 30% lower compared with TAC-IR.

In conclusion, LCP-TAC used in KTx and LTx transplants, compared with other formulations of TAC, shows (1) increased bioavailability, (2) a C_{min} and AUC_{0-12} comparable with TAC-IR and TAC-PR, (3) lower C_{max} with lower fluctuations in blood concentrations; and (4) the cumulative dose was lower than TAC-IR and TAC-PR. This new technology represents a fundamental innovation in the field of immunosuppressants and will be tested in other types of transplants. Obviously more studies must be done to confirm these results.

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