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TRANSPLANTOLOGY

Once– versus twice–daily tacrolimus: are the formulations equivalent?

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Tacrolimus is one of the most often used immunosuppressive drugs in organ transplantation. It was first approved in 1994 for use in liver transplantation, replacing cyclosporine A, due to better absorption properties regardless of bile secretion. Then it use was extended to other organs and nowadays more that 90% of kidney graft recipient in the United States receive tacrolimus as a basic immunosuppressant [1]. The use of tacrolimus is complicated by its narrow therapeutic index and wide intra– and interpatient pharmacokinetics variability, thus it dosage should be based on monitoring trough drug blood concentration. The main complications of drug overdosage are nephro– and neurotoxicity and metabolic disturbances like posttransplant diabetes mellitus and hyperlipidemia. On the other hand low, non–therapeutic drug blood level can lead to graft rejection and loss. Patients' noncompliance is the main cause of fluctuating tacrolimus blood concentration and in many cases could be the reason of acute graft rejection episodes. It is an important problem both in young, active but also in older kidney graft recipients and reduction of immunosuppressive drugs daily doses is one method to overcome this problem [2].
The once–daily (OD) extended–release formulation of tacrolimus (Advagraf, Astellas) was launched in 2007 in 0.5, 1, 3, and 5 mg doses. This drug formulation allows most of liver transplant and some kidney transplant recipients (on tacrolimus monotherapy or in dual therapy with prednisone) to use only one morning dose of immunosuppressants. Such therapy simplifies treatment protocol and increases patient compliance. Converting patients from twice daily (BID) to OD tacrolimus was proposed on equivalent daily dose but there was a concern of adequate blood levels after treatment switch. We observed in our center that OD tacrolimus doses had to be 10–15% higher than BID formulation to get the same trough blood drug concentration after conversion. In a multicenter, open–label, phase III study in stable adult liver transplant recipients converted from tacrolimus BID to OD (1:1 [mg:mg] total daily dose basis). Following conversion, mean tacrolimus trough levels were reduced by approximately 15% (7.5 ng/ml vs. 6.5 ng/ml; P <0.0001) but were more consistent, showing reduction between– and within–patient variability in trough levels [3]. However, in our retrospective analysis of 60 kidney graft recipients converted from tacrolimus BID to OD formulation in identical (1:1) daily doses in late posttransplant period trough blood drug concentration did not significantly differ pre and after conversion. OD tacrolimus doses were increased in 11 patients and decreased in 13 patients based on trough blood concentration during consecutive patient visits (unpublished data). OD tacrolimus is non inferior to BID formulation in long term effect in kidney transplant recipients. A systematic review of 6 randomized controlled trials and 15 observational studies revealed no significant differences in biopsy–proven acute rejection, patient and graft survival between the two formulations at 12 months [4].
However, there are some disadvantages of OD tacrolimus therapy. First, risk of overdose–related side effects is very high in first postransplant days and with BID tacrolimus formulation dose correction can be made with the evening dose. Secondly, only 1 mg OD tacrolimus capsules are reimbursed in Poland, making treatment rather difficult in case of higher daily doses.
In the present paper authors describe their experience with kidney transplant recipients from living donors who received OD tacrolimus [5]. They investigated tacrolimus pharmacokinetics and compared the dose of OD tacrolimus OD TAC to BD drug formulation. The study group is relatively small and there are some demographic differences between the groups that could affect pharmacokinetic parameters of the study drug: patients on OD tacrolimus were younger and were shorter time on dialysis. The

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authors compare daily doses and minimal concentration (Cmin) of both formulations, what is most important in clinical practice. However, detailed pharmacokinetic parameters are presented only for OD tacrolimus.

In conclusions OD tacrolimus appears to have efficacy and safety equivalent to that of BD formulation but a larger dose of OD tacrolimus compared to that of BD drug form may be required during the early period after kidney transplantation [5].

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