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# Novel micelle carriers for cyclosporin A topical ocular delivery: in vivo cornea penetration, ocular distribution and efficacy studies.

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## Abstract

Cornea transplantation is one of the most performed graft procedures worldwide with an impressive success rate of 90%. However, for "high-risk" patients with particular ocular diseases in addition to the required surgery, the success rate is drastically reduced to 50%. In these cases, cyclosporin A (CsA) is frequently used to prevent the cornea rejection by a systemic treatment with possible systemic side effects for the patients. To overcome these problems, it is a challenge to prepare well-tolerated topical CsA formulations. Normally high amounts of oils or surfactants are needed for the solubilization of the very hydrophobic CsA. Furthermore, it is in general difficult to obtain ocular therapeutic drug levels with topical instillations due to the corneal barriers that efficiently protect the intraocular structures from foreign substances thus also from drugs. The aim of this study was to investigate in vivo the effects of a novel CsA topical aqueous formulation. This formulation was based on nanosized polymeric micelles as drug carriers. An established rat model for the prevention of cornea graft rejection after a keratoplasty procedure was used. After instillation of the novel formulation with fluorescent labeled micelles, confocal analysis of flat-mounted corneas clearly showed that the nanosized carriers were able to penetrate into all corneal layers. The efficacy of a 0.5% CsA micelle formulation was tested and compared to a physiological saline solution and to a systemic administration of CsA. In our studies, the topical CsA treatment was carried out for 14 days, and the three parameters (a) cornea transparency, (b) edema, and (c) neovascularization were evaluated by clinical observation and scoring. Compared to the control group, the treated group showed a significant higher cornea transparency and significant lower edema after 7 and 13 days of the surgery. At the end point of the study, the neovascularization was reduced by 50% in the CsA-micelle treated animals. The success rate of cornea graft transplantation was 73% in treated animals against 25% for the control group. This result was as good as observed for a systemic CsA treatment in the same animal model. This new formulation has the same efficacy like a systemic treatment but without the serious CsA systemic side effects. Ocular drug levels of transplanted and healthy rat eyes were dosed by UPLC/MS and showed a high CsA value in the cornea (11710 ± 7530 ng(CsA)/g(tissue) and 6470 ± 1730 ng(CsA)/g(tissue), respectively). In conclusion, the applied formulation has the capacity to overcome the ocular surface barriers, the micelles formed a drug reservoir in the cornea from, where a sustained release of CsA can take place. This novel formulation for topical application of CsA is clearly an effective and well-tolerated alternative to the systemic treatment for the prevention of corneal graft rejection.