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Aerosol delivery of immune-suppressants in lung transplanted patients

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Introduction: Cyclosporine A (CsA) a lipophilic cyclic peptide acting as a calcineurin inhibitor reversibly inhibiting T-cell mediated immune response is established in transplantation medicine and even treatment of other diseases (e. g. severe asthma, severe rheumatical diseases). Patients after lung transplantation are at high risk for development of bronchiolitis obliterans syndrome (BOS; about 50 % within 5 years after transplantation) causing an ongoing graft rejection and corresponding high mortality. Usually, CsA is administered orally associated with substantial systemic toxicity, e. g. hypertension and renal toxicity. Inhalative administration would result in high local doses and reduced systemic toxicity.

Materials and methods: Publications on inhalation of CsA and other immune-suppressants (e. g. tacrolimus, sirolimus, mycophenolate mofetil) were analysed focusing on recent publications in patients after lung transplantation and publications investigating methods for aerosol preparation or delivery.

Results: Beginning at about 1990, i. e. shortly after approval of CsA first publications were found investigating aerosolized CsA for treatment of lung transplant recipients. Experimentally, aerosols were prepared from special solutions of CsA, e. g. in propylene glycol or CsA liposomes by means of different types of nebulizers, metered dose inhalers (MDI) and dry powder inhalers (DPI). Physicochemical and pharmacological characteristics of aerosols were subject of several publications. CsA inhalation studies in lung transplanted patients showed a closed dose-deposition relation, even deposition within the lungs and lack of systemic side effects with little blood concentrations of CsA after pulmonary deposition. CsA inhalation was well tolerated resulting in an improved rate of BOS and long term mortality. Currently, ongoing clinical studies (up to phase III) investigate inhalative CsA administration in lung transplanted patients. A number of laboratory studies was found for aerosolized tacrolimus investigating its physicochemical and pharmacological characteristics; however, clinical studies for this compound are sparse. In addition, only experimental data were found for other immune-suppressants.

Conclusions: Feasibility of CsA inhalation has been demonstrated in patients after lung transplantation and may serve for prevention and treatment of BOS in lung transplant recipients. However, further clinical studies should be performed to investigate effect and potential limitations of this type of treatment. In addition other types of CsA aerosols beyond solutions or liposomes as well as other aerosols of other immune-suppressants should be tested.