173* Novel steroids with anti-inflammatory activity that stimulate immunity: implications for treatment of Cystic Fibrosis

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Pulmonary inflammation and abnormal eicosanoid production are important pathologic features of CF. 16α–bromoepiandrosterone (HE2000) is a synthetic steroid with demonstrated anti-inflammatory activity in man. HE2000 and its metabolite 5α androstan-3β,16α-diol-17-one (HE3151) significantly ($p < 0.05$) reduced numbers of neutrophils and pleural exudate volumes (~50%) in the murine model of carrageenan induced pleurisy. Both compounds increased survival (>25%) in an LPS murine shock model and reduced cell numbers (~30%) and accelerated the maturation (increased lymphocytes) of infiltrates in a murine model of LPS induced lung injury. HE3151 significantly ($p < 0.005$) reduced chronic inflammation in delayed-type hypersensitivity responses. In the gut corrected *Cftr*$^{-/-}$ mouse model of *P. aeruginosa* lung infection, HE2000 significantly ($p < 0.05$) reduced bacterial burden and accelerated the maturation of cellular infiltrates ($p = 0.056$). In the reporter antigen popliteal lymph node assay (immune toxicity) neither HE2000 nor HE3151 were found to be immune-suppressive. Ongoing studies hypothesize normalization of eicosanoid metabolism. Treatment of CF and other diseases associated with chronic inflammation of the lung with HE2000, HE3151, or another closely related analog, may provide anti-inflammatory benefit to patients without immune suppressive side effects.

174 Reduction of drug-dose and therapy-costs in the inhalation therapy with high dose tobramycin

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Aims: The pseudomonas effective inhalation in cystic fibrosis with high dose tobramycin (TOBI 2×300 mg/day) is very cost intensive. The in vivo study at hand shows how to realise a considerable reduction of drug dose and thus also a reduction of therapy costs without decreasing the tobramycin lung deposition.
Methods: Following a randomised cross-over scheme, twelve subjects inhaled 300 mg/5 ml (TOBI) with a LC PLUS and 160 mg/4 ml (GERNEBCIN) with a LC STAR, which is flow and breath controlled by means of the AKITA-system. The intrapulmonal drug depositions was ascertained by gamma-szintigraphy. Furthermore FEV_1 and serum levels of tobramycin were determined 1 h after each inhalation.
Results: The depositions of tobramycin in the lungs was 41±12 mg (TOBI/LC PLUS) and 43±5 mg (GERNEBCIN/AKITA). The tobramycin serum levels were 0.39±0.21 mg/L after TOBI and 0.56±0.19 mg/L after GERNEBCIN. None of these treatments showed a striking decline of FEV_1 after inhalation, which lasted comparably about 13 min. The costs for each inhalation, based on German pharmacy sales prices, were about 19€ for GERNEBCIN and 59€ for TOBI.
Conclusions: The inhalation-system AKITA allows a maximum drug utilisation and a high accuracy in dosing the drug. Therefore, the lower dosage of tobramycin formulation, GERNEBCIN for inhalation, is as sufficient as TOBI inhalation to reach the necessary depositions in the lung. This reduces the oropharyngeal drug exposure and thus the potential of bronchial irritations. Using GERNEBCIN/AKITA for high dose tobramycin inhalation helps to save therapy costs in Germany of about 80€ each day.

175 Dosing tobramycin in the inhalation therapy of Cystic Fibrosis – a comparison of LC PLUS used in breath triggered mode and EFLOW RAPID

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Introduction: This in vitro study compared the dosing of tobramycin with LC PLUS used in breath triggered mode and EFLOW RAPID. Therefore, the tobramycin commonly used for inhalation in Germany, GERNEBCIN, was nebulised in different doses.
Methods: The nebulisation of differently concentrated tobramycin solutions: (1) 80 mg/2 ml, (2) 160 mg/4 ml and (3) 320 mg/4 ml with the EFLOW RAPID was examined by breath simulation measurements. As a reference the nebulisation with the LC PLUS was performed with and without breath triggered inhalation. Especially the most relevant nebuliser-/drug-parameters like respirable dosage of tobramycin RD [mg] and time of inhalation IT [min] were ascertained.
Results: The generated RD with EFLOW RAPID and LC PLUS for all nebulised doses of tobramycin was (1) 8.5/8.5, (2) 28.3/27.3, (3) 57/54.2; the IT was (1) 1.3/4.2, (2) 3.9/11, (3) 4.3/11.5. If an inspiration triggered nebulisation is performed with the LC PLUS, the RD rises up to 22%. The EFLOW RAPID is not able to nebulise residual volumes and therefore (1) 56, (2) 80 and (3) 143 mg of tobramycin were wasted.
Summary: The EFLOW RAPID is generating the same RD for tobramycin solutions of different concentrations as the LC PLUS. IT with EFLOW RAPID is much shorter but the breath triggered nebulisation with LC PLUS enables significantly higher RDs. The potential of the EFLOW's membrane technology to reduce the necessary drug-dose is not used by the "RAPID"-model. By increasing the volume of the GERNEBCIN-solution, this problem can be antagonised partly. The dosage for nebulised GERNEBCIN can be oriented on the study data at hand.

176 Effects of tobramycin solution for inhalation in patients with *Pseudomonas aeruginosa* chronic colonization

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Background: *Pseudomonas aeruginosa* (PA) chronic colonization is a highly significant event in the course of CF as it heralds an increase in the morbid-mortality. In fact, the lung function of a CF patient declines by about 2–3% per year. Inhaled antibiotics are the recommended therapy, as parenteral administration cannot eradicate lung infection. Tobramycin solution for inhalation (TSI) allows higher concentration to be delivered direct to the lungs without systemic toxicity.
Methods: From the 120 patients in follow up in the Adult CF Unit, it was selected a cohort of patients >14 years with TIS therapy during at least a year, from mild to severe pulmonary disease, no colonized by other resistant microorganisms, PA chronic colonized and a decrease of lung function with other inhaled antibiotic therapies and no resistance nor hypersensitivity to tobramycin. FEV1, microbiology and weight have been analyzed one year before and after up to 3 years in TSI therapy.
Results: It was included 27 patients: age (mean±DS): 25±5.37 years (15–35 y); 70% male, 30% female; mean FEV1 at baseline: 2.83 L (66.51% predicted). 5 patients had FEV1 > 75% and the rest, between 25 and 75%. 2 patients were colonized by *Aspergillus fumigatus* during TSI therapy. There was no selection of other multirresistant microorganisms. Decreasing trend of FEV1 was reverted with TSI therapy with a significant improvement of the lung function ($p < 0.001$). FEV1% increased 9.58%, 4.5% and 5.1% over baseline after 1, 2 and 3 years of therapy. There was a light increase of weight and few adverse events.
Conclusion: TSI therapy improves significantly the lung function in a short and medium term in CF patients with bad response to other suppressive therapies.