WS5.3  Wide pharmacokinetic variability of ciprofloxacin in patients with cystic fibrosis (CF) – a reason of treatment failure?


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Objectives: Ciprofloxacin (CIP) is used to treat CF patients and is partly metabolised in the liver by the CYP3A4 enzyme. We investigated the correlation between the enzyme activity and the metabolism of CIP. A Monte Carlo simulation was performed to predict eventual treatment failure.

Methods: We included 22 CF patients (21–53 yr) with chronic P. aeruginosa lung infections. The CYP3A4 activity was measured using the ERMBT. 500 mg CIP was given orally and blood samples were collected every half hour the first 3 h and at 6 and 12 h. The concentrations of CIP were calculated by using a biological assay. AUC, T_max and C_max were calculated. The Monte Carlo simulation was based on the MIC of 119 P. aeruginosa strains.

Results: A 14-fold variation, median (range), in AUC (mg.min/liter); 473.5 (138–1880) for CIP, a 30-fold variation in Cmax (mg/liter); 2 (0.25–7.6) and a 3 fold variation in Tmax (min); 91 (46–153) was found. We found an 8-fold variation in the CYP3A4 activity, with a median (range) of 0.8 (0.3–2.0), but no correlation with CIP metabolism was found.

Conclusion: We found a large variation in the metabolism of CIP and some patients may not have reached a high enough MIC/AUC ratio. We therefore recommend that plasma concentrations and MIC of the bacteria are measured regularly to avoid treatment failure.

WS5.2  Inhaled dry powder mannitol in cystic fibrosis (CF): impact on pulmonary exacerbations (PEs) in the Phase III studies (CF-301 & CF-302)

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Introduction: PEs in CF are linked to accelerated declines in lung function and mortality [1]. Two large phase III trials of inhaled dry powder mannitol (IDPM) have demonstrated sustained, clinically meaningful improvements in lung function from baseline over 26 weeks. The large population from these studies provides the opportunity to explore the impact of IDPM on PEs in CF.

Methods: Data were pooled from two similar, randomized (3:2, controlled, parallel group phase III studies in which a total of 600 pts received either IDPM (400 mg) or control (mannitol 50 mg) b.i.d. for 26 weeks. Protocol defined pulmonary exacerbations (PDPE) were assessed using Fuchs’ criteria [2].

Results: The incidence of pts with ≥1 PDPE was 29% lower (p=0.039) in the IDPM group than in the control group. Associated rescue antibiotic use incidence was reduced by 30% (p=0.033), in the IDPM group vs. the control. The supportive positive trend of a 22% reduction in PDPE-related hospitalization incidence did not reach statistical significance (p=0.219). The annualized PDPE rate was significantly lower in those patients treated with IDPM who had any improvement from baseline over 26 weeks in %predicted FEV1 (0.56 PDPE/year) compared to those who did not show FEV1 improvement (1.36/year) (p=0.03).

Conclusions: PEs are a key driver of worsening lung function in CF, which is not restored to pre-exacerbation levels in up to 25% of cases. IDPM has an important impact on the rate of PEs, with a reduced risk seen predominantly in those patients who had also shown an improvement in pulmonary function.

Reference(s):