ISB[M]

Anti-asthmatic drugs: evaluation of possible targets for development of “best-in- class” drug

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FEV1 (Forced Expiratory Volume for 1 second) has been measured in framework of clinical trials of **Zileuton**

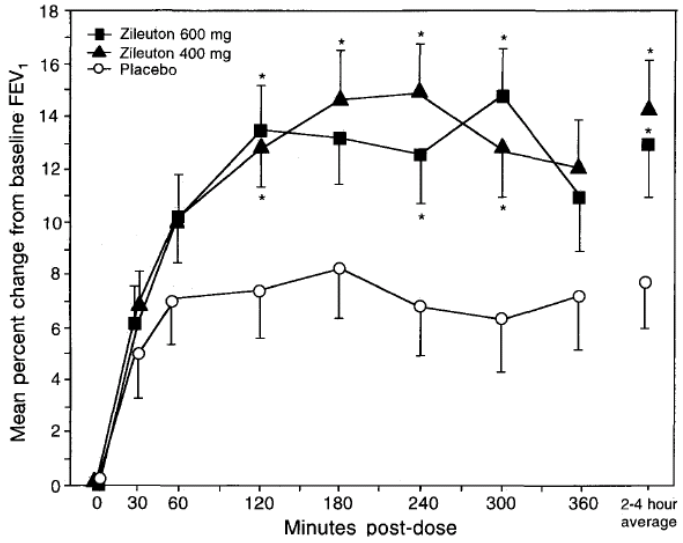


FIG. 2. First-dose effect of zileuton 600 mg, zileuton 400 mg, and placebo administered four times daily, expressed as mean percent change in FEV_1 from baseline between 0 and 360 minutes postdosing. $*p \leq 0.05$, zileuton vs placebo. The p values for zileuton 600 mg versus placebo were 0.012 at 120 minutes, 0.027 at 240 minutes, 0.003 at 300 minutes, and 0.025 for the 2 to 4 hour average. The p values for zileuton 400 mg versus placebo were 0.021 at 120 minutes, 0.015 at 180 minutes, 0.002 at 240 minutes, 0.022 at 300 minutes, and 0.006 for the 2 to 4 hour average. n = 122, 120, and 121 for the 600-mg zileuton group, 400-mg zileuton group, and the placebo group, respectively.

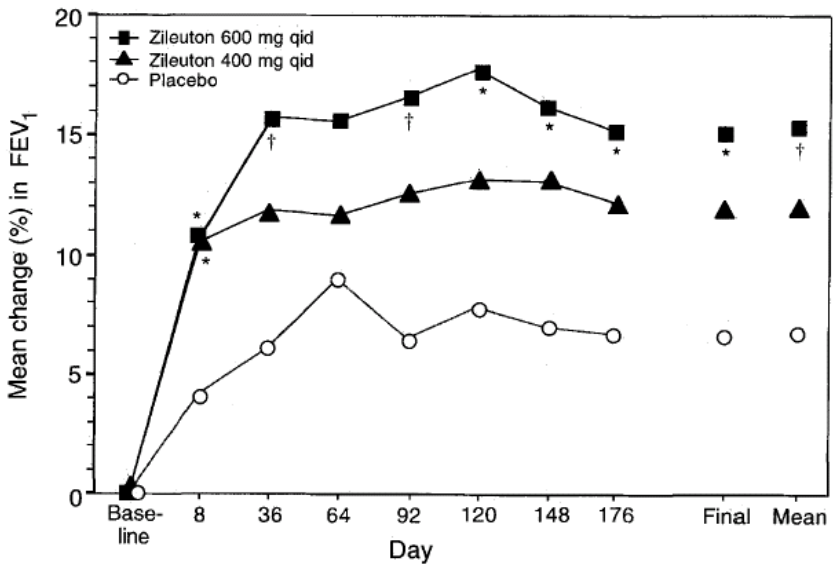


FIG. 3. Comparison of chronic trough effects of zileuton 600 mg and zileuton 400 mg, four times daily, with those of placebo, four times daily. The chronic trough effect was determined by measurement of FEV_1 before the first daily dose of zileuton at each of eight visits during the 26-week trial. $*p \leq 0.05$; $\dagger p \leq 0.01$.

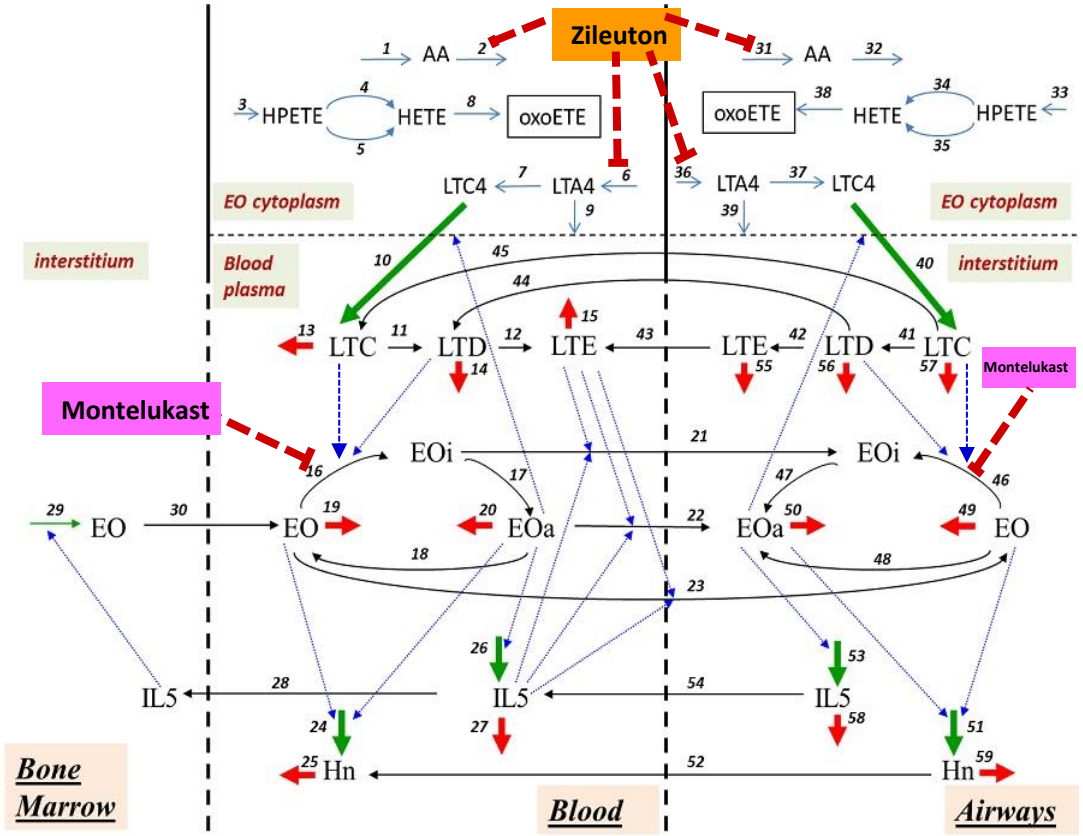
Observations :

- No dose-response up to 8 days when 400 mg and 600 mg is administered
- Separation in response after multiple doses

OBJECTIVES:

- To identify possible mechanisms underlying the observed complex relationship between the PK and PD (FEV1) of Zileuton
- To compare efficacy (in terms of FEV1 increase) of labeled dosages of Zileuton and Montelukast
- To evaluate potential benefit/risk of development of “best-in-class” drugs for “Zileuton” vs “Montelukast” targets

The scheme of the model



AA – Arachidonic Acid, **HPETE** – 5-hydroperoxyeicosatetraenoic acid, **HETE** – 5-Hydroxyeicosatetraenoic acid, **oxoETE** – 5-oxoeicosatetraenoic acid, **LTC4** – Leukotriene C4 (intracellular), **LTA4** – Leukotriene A4, **LTC** – Leukotriene C4 (extracellular), **LTD** – Leukotriene D4, **LTE** – Leukotriene E4, **EO** – non-activated Eosinophils, **EOi** – intermediate state of Eosinophils, **EOa** – activated Eosinophils, **IL5** – Interleukin-5, **Hn** – Histamine

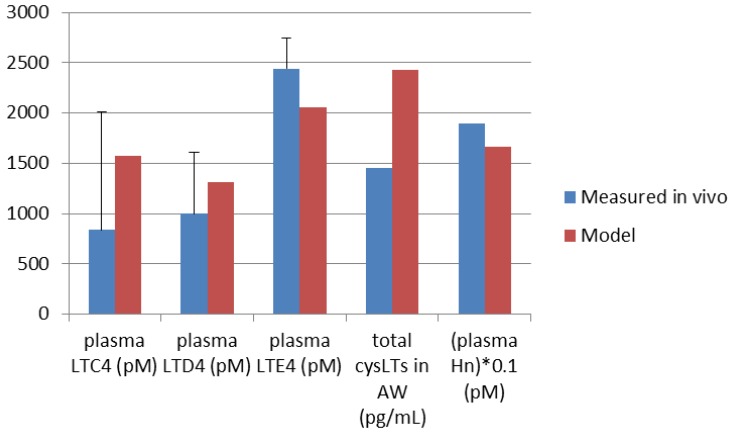
Binding, duffusion, transport

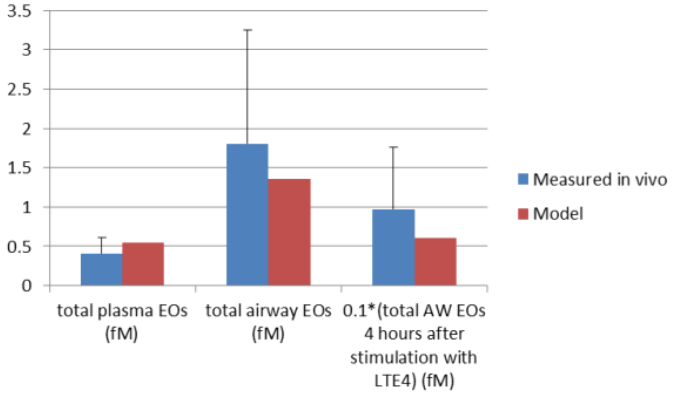
Biosynthesis, maturation

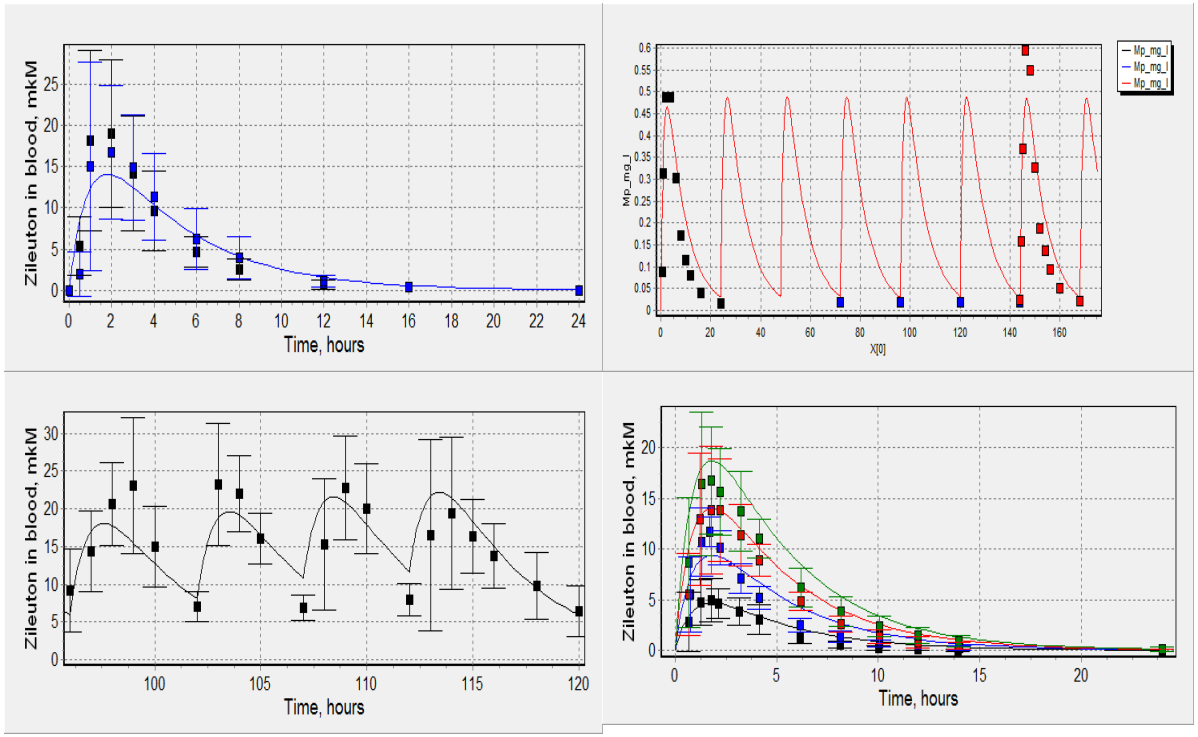
Cell death, degradation

Induction, stumulation

Model verification and validation



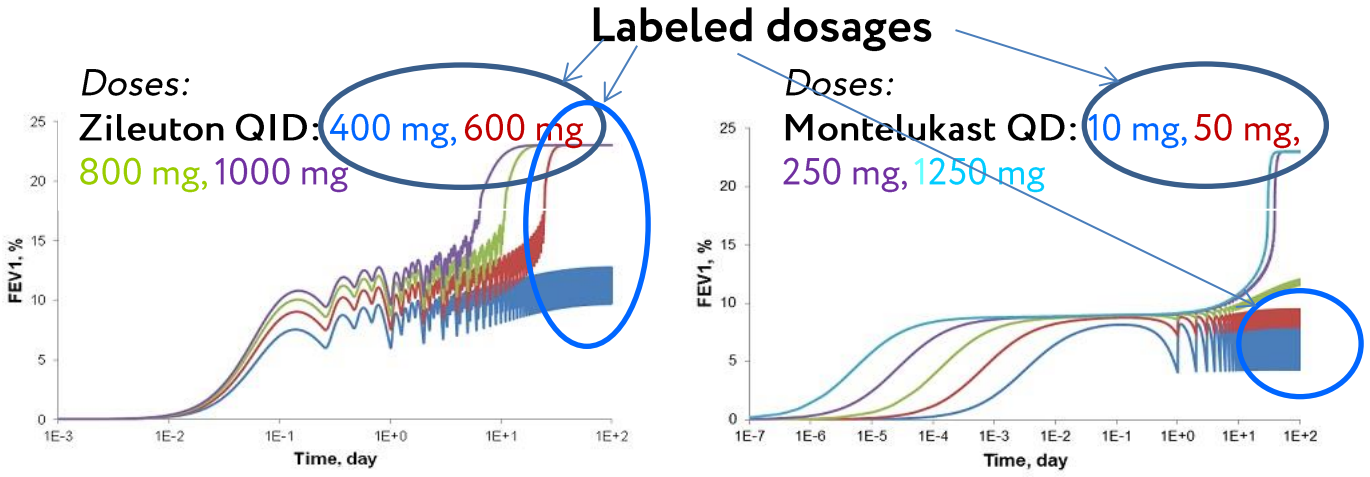




MODEL PREDICTIONS

Evaluation of potential benefit/risk of development of "best-in-class" drugs for "Zileuton" *vs* "Montelukast" targets.

STRATEGY: To evaluate potential benefits of development of more potent "best-in-class" drugs for *5LO* and *cysLT1R* we simulated FEV1 response resulted from administration of Zileuton and Montelukast dosages which are higher than labeled doses.



Conclusions

- To identify possible mechanisms underlying the observed complex relationship between the PK and PD (FEV1) of Zileuton.

  The fact that EOs number is regulated by two positive feedbacks (LT and IL5 mediated) results in existence of "critical" level of LTs. Exceeding (600 mg of Zileutone) or not exceeding (400 mg) of the "critical" level is responsible for "separation" effect in FEV-1. Delay in 8 days between start of Zileuton treatment and observation of "separation" effect is explained by lifespan of EOs.

- To compare efficacy (in terms of FEV1 increase) of labeled dosages of Zileuton and Montelukast

  Labeled dosages of Zileuton are more effective than labeled dosages of Montelukast.

- To evaluate potential benefit/risk of development of "best-in-class" drugs for "Zileuton" vs "Montelukast" targets

  Development of more potent cysLT1R blocker may results in substantial increase in FEV1 BUT there is no benefit in development of more potent 5LO inhibitor.

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