

Oral Abstract Book

Prolonged benefit of Reltecimod in treatment of patients with NSTI is independent of brief plasma half-life

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Background: Reltecimod (AB103) is a short CD28 receptor mimetic peptide that improves the host's ability to fight severe infections. In spite of a brief half-life in plasma (mice, pigs, humans), a single dose of Reltecimod suffices to provide sustained survival benefit in animal models of sepsis and long-term clinical benefit in patients with necrotizing soft tissue infections (NSTI). Reltecimod is currently being evaluated in a Phase 3 multicenter clinical trial in NSTI patients.

Hypothesis: Reltecimod's long-term efficacy benefit may be based on distribution to target sites and rapid intervention with signaling pathways, irrespective of its short residence time in plasma.

Methods: Male Balb/c mice (n=36) were administered a single IV dose of radiolabeled Reltecimod ([¹⁴C]valine, 5 mg/1000 mCi/kg). Whole blood, plasma and tissues were collected at 2, 4, 6, 8, 10, 20, 30 min and 1, 2, 4, 8, 24 h post-dose. Total radioactivity concentration in all tissues was determined, PK parameters were calculated, modeled and compared between mice and humans. Minimal time to observe efficacy was demonstrated using staphylococcal enterotoxin B-activated human peripheral blood mononuclear cells (hPBMCs), monitoring cytokine responses after different durations of exposure to Reltecimod (5min-9h).

Results: Fast clearance of Reltecimod from plasma was observed, 60.4 mL/min/kg, exceeding hepatic flow and approaching cardiac output, with a half-life of 2.65 min, consistent with parameters obtained after exposure of healthy human subjects and NSTI patients, fitting into a one-compartment elimination model. Reltecimod distributed rapidly across multiple highly perfused tissues/organs, but within 2 min targeted mainly lymphatic organs (lymph nodes and spleen, harboring T cells that express CD28). Peak accumulation was 20 min and 2 h, respectively, post dose in lymph nodes [26.4±11.3 ugEq/g, mean ± SEM] and spleen [9.61±1.93 ugEq/g, mean ± SEM] (Fig 1). Lymphatic concentrations were 22.1±9.7 fold higher than plasma at 20 min and remain so for several hours. Consistently, blood partitioning indicated that Reltecimod is preferentially and significantly enriched in WBC (6.8% after 2 h). Fast, long-lasting action of Reltecimod was demonstrated in hPBMCs, where a 5-min exposure was sufficient to attenuate IFN-g induction for at least 9h (Fig 2).

Conclusions: Our hypothesis is supported by (i) fast homing into target organs, where redistribution to systemic circulation may occur, leading to availability greatly exceeding plasma half-life; (ii) rapid onset of inhibition of inflammatory cytokine induction, independent of exposure time.