Clinical Immunology and Microbiology (CIM) - Innate Defense Regulators (IDRs) – Agnostic Therapy to Treat Bacterial Infections and Fight Resistance

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ABSTRACT

Background: Innate Defense Regulators (IDRs) are a novel class of synthetic peptides that enhance the control of microbial infections while attenuating tissue damage and modulating inflammation. IDRs target host innate immunity rather than the bacterium itself, evading antibiotic resistance mechanisms. IDRs act at key nodes in the intracellular signaling network of innate immune cells, and have demonstrated efficacy in preclinical and clinical models of bacterial infection with both gram-positive and gram-negative bacteria, whether administered therapeutically or prophylactically and whether administered as a stand-alone agent or in conjunction with antibiotics.

Material/Methods: The lead clinical IDR, dusquetide, was evaluated in an 84 subject single- and multiple-ascending dose Phase 1 study with concomitant evaluation of inflammatory responses and in a 111 patient double-blind, placebo-controlled, Phase 2 study treating oral mucositis in head and neck cancer (HNC) patients. Oral mucositis is a consequence of innate immune dysregulation causing excessive inflammation and provides an important framework for the clinical translation of IDRs. Dusquetide was administered as a 4-minute intravenous infusion in both studies. Incidence of infection in HNC patients was monitored throughout the Phase 2 study.

Results: Dusquetide was found to be safe and well-tolerated in the Phase 1 study with no serious or severe adverse events attributed to its use. Moreover, ex vivo evaluation of inflammatory stimulation of blood from the healthy volunteers with endotoxin revealed a more anti-inflammatory response in subjects administered dusquetide at doses of 0.15 – 2.0 mg/kg with higher doses (3.0 – 8.0 mg/kg) revealing a response similar to the placebo subjects. Similarly the Phase 2 study in oral mucositis revealed a statistically significant reduction in the median duration of oral mucositis at the 1.5 mg/kg dose level, primarily mitigating the inflammatory response prevalent in oral mucositis. The incidence of non-fungal (bacterial) infection in those oral mucositis patients was also significantly reduced in the HNC patients at both 1.5 and 6.0 mg/kg. The Phase 2 results were completely consistent with the results from both preclinical and Phase 1 clinical studies.

Conclusions: IDRs have been shown to “re-balance” the response of innate immune cells to innate immune stimuli occurring through most pattern recognition receptors. The interplay between anti-inflammatory, anti-infective and tissue healing responses yields a complex dose response where anti-inflammatory responses are increased at low doses and the anti-infective responses are increased across a wider dose response range. The advantages of IDRs include 1) the ability to use IDRs prophylactically without fear of genotoxicity, 2) the ability to use IDRs before the causative infectious agent is fully identified and 3) the ability to use IDRs irrespective of the bacterial pathogen. IDR action is independent of bacterial pathogen.

REFERENCES


RESULTS

CLINICAL STUDIES

Antibiotic Complementarity

Gram-positive, Antibiotic-resistant Bacteria

Male CD-1 mice were rendered neutropenic by 2 IP injections of cyclophosphamide (Cp) on Days -4 and -1 before infection (1,000,000 cfu of MRSA and P. aeruginosa, respectively). Dusquetide (50 mg/kg) was administered IV at 24 h before infection. Dusquetide (50 mg/kg) was administered IV at 24 h and 4 h before infection. MRSa (Catalog No. 33591, ATCC, 124 x10^9 cfu) was inoculated in the right thigh. Vancocycin (20 or 100 mg/kg) was given SC at 2 and 14 h after the bacterial inoculation. At 24 h after inoculation, the musculature of the right thigh were harvested.

Combination treatment with lung infection:

Male BALB/c mice (n=12/group) were infected intranasally. Dusquetide (50 mg/kg) or saline was administered IV 4 h prior to infection and every second day to Day 8. Dusquetidc (20 mg/kg) was administered orally upon infection and daily through Day 10. The combination of dusquetide + doxycycline was found to be more effective than the additive combination (p<0.0001).

RESULTS

Broad Spectrum Activity

Gram-positive, Antibiotic-resistant Bacterium (MRSA)

Dusquetide (5 mg/kg IV) or saline (IV) was administered at the indicated times to female Balb/c mice prior to or after infection via the tail vein with MRSA (USA300, 7.1 log10 cfu). Sub-optimal antibiotic treatment (amoxicillin, 0.25 mg/kg) was administered orally immediately after infection. Survival was monitored for 9 days.

Extended Pharmacodynamics

As expected for a peptide, dusquetide has a rapid pharmacokinetic half-life in plasma (mean residence time of 10 minutes). Despite this, the effect on the innate immune system is enduring. Anti-infective studies demonstrated no added benefit to repeated dusquetide administration within a 24-48 hour window, suggesting a pharmacodynamic response of 48-72 hours (North et al. 2016).

Chronic Tissue Injury (Oral Mucositis)

Fractionated radiation was administered to the everted cheek pouch of Golden Syrian hamsters on Days 0, 1, 2, 3, 6, 7, and 8. Dusquetide was administered on the indicated days and 2 h after radiation if applicable. OM was monitored by blinded scoring by 2 independent observers every second day throughout a 35 day window with OM reaching peak severity around Day 18.

CONCLUSIONS

• Dusquetide modulates the response of the innate immune system to a broad spectrum of triggers including infection, tissue damage and secondary inflammation.

• IDRs may significantly enhance antibiotic efficacy without increasing resistance.

• IDRs are effective when given prophylactically, pre-emptively or therapeutically.

• IDR action is independent of bacterial pathogen.

• A high degree of clinical translation was observed in recent Phase 1 and Phase 2 studies. A Phase 3 study in oral mucositis is currently recruiting.

REFERENCES


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