Monoclonal Antibody Administration Provides Five Weeks of Pertussis Prophylaxis in Newborn Baboons: PoC for Passive Immunization to Protect Infants in the Developing World

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ABSTRACT

Background: Pertussis remains a significant health problem in the developing world, killing up to 200,000 infants annually. Maternal vaccination is currently the leading strategy to protect newborns, but is unlikely to capture all eligible mothers. We previously described the humanization of 1B7, a monoclonal antibody (mAb) that potently neutralizes pertussis toxin. Hu1B7 prevented disease symptoms in mice and mitigated disease when administered to weanling baboons after infection as part of a binary mAb cocktail. We hypothesize that hu1B7, given at birth, can protect newborns for several months, when the mortality rate is highest. Here we present a proof-of-concept study designed to determine if hu1B7 administered to newborn baboons could provide protection from pertussis infection 5 weeks later.

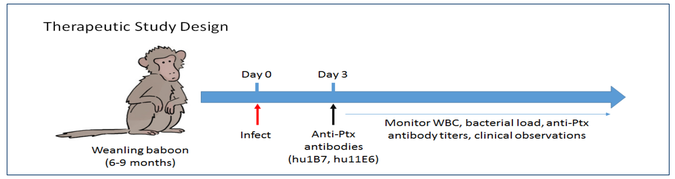
Material/methods: Neonates were recruited into the study after birth if they met the following criteria: normal gestational age (180 days +/- 10), normal birth weight (~1.0 kg), and anti-Fha titer <5 IU/ml (indicating no prior exposure to *Bordetella* species which can confound subsequent experimental infection). Two-day-old baboons assigned to the treatment group received hu1B7 (40 mg/kg, IV). Five weeks later, animals were infected with 10^8 cfu of *B. pertussis* strain D420 via intra-tracheal and intranasal infusions. Animals were monitored for clinical signs of disease, including leukocytosis, coughing, and bacterial colonization. The hu1B7 sera concentrations and anti-Fha responses were followed once- or twice-weekly for the duration of the study.

Results: To date, 6 controls and 7 treated animals have been enrolled. All animals were heavily colonized during the first week after infection as measured by *B. pertussis* in the nasopharyngeal wash fluid. All control animals developed significant leukocytosis, were observed to be coughing, and 3 required euthanasia. In contrast, white blood cell counts for all 7 of the treated animals remained within the normal range or were only modestly elevated, coughing was virtually absent, and all animals maintained normal activity. As expected for a humanized mAb in a non-human primate, hu1B7 had an elimination half-life of 12 ± 4 days.

Conclusions: mAb prophylaxis of newborn baboons with hu1B7 mitigated the clinical signs of pertussis, including leukocytosis and coughing, but did not prevent bacterial colonization. Assuming a half-life in humans of 3 weeks, mAb administration at birth could potentially provide 4 months of prophylaxis and is a viable strategy to complement maternal vaccination. We are currently expanding the study to include an extended half-life version of hu1B7, which could lower the dose and cost to further support developing world application.

BACKGROUND

Two humanized pertussis toxin-binding monoclonal antibodies, 1B7 and 11E6 [1] were previously tested for their therapeutic value in treating disease symptoms in B. pertussis infected weanling baboons [2].



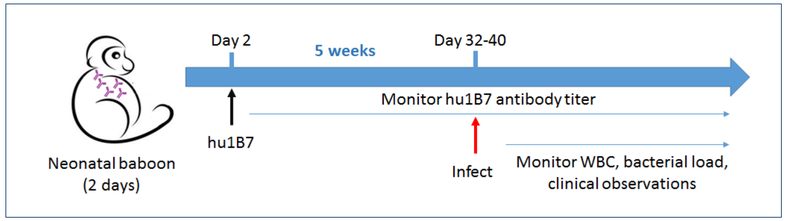
Antibody therapy rapidly reversed the leukocytosis, which subsequently normalized and resulted in clinical improvement in animals that suffered the most severe coughing [2].

These data demonstrated that the antibody cocktail, hu1B7 and hu11E6, provided a therapeutic benefit to *B. pertussis*-infected animals. Here, we tested the ability of pretreatment with hu1B7 five weeks prior to infection to protect neonatal baboons from pertussis pathophysiology.

RESULTS

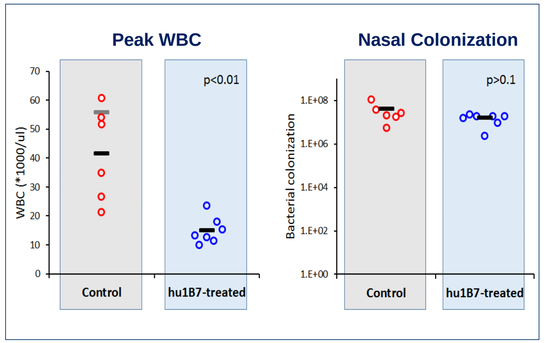
Prophylaxis Study Design

Two day old baboons assigned to the treatment group received hu1B7 (40 mg/kg, IV). Hu1B7 antibody levels were monitored weekly. Five weeks later animals were infected with *B. pertussis*. Leukocytosis, nasopharyngeal *B. pertussis* loads, and clinical symptoms were followed.



Antibody Prophylaxis Supressed Leukocytosis in Infected Baboons

Control animals infected at approximately five weeks of age exhibited marked elevations in peak white blood cell (WBC) counts. In contrast, animals treated with hu1B7 at 2 days of age and infected at 5 weeks had peak WBCs that either remained normal or were slightly elevated. Nasopharyngeal *B. pertussis* colonization was unaffected by antibody prophylaxis. Clinical symptoms of pertussis were ameliorated in all antibody-treated animals, while 3/6 control animals displayed symptoms severe enough to require euthanasia, including lethargy and/or coughing.



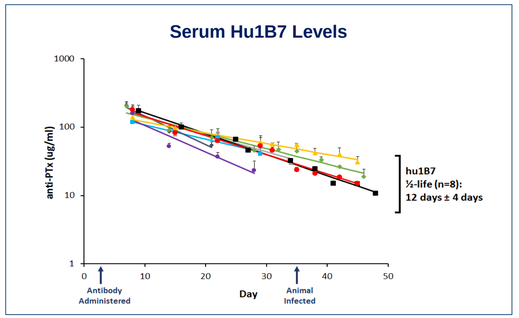
Peak WBC in hu1B7-treated animals (14.8 x 1000 cells/uL) were significantly reduced compared to controls (41.5 x 1000 cells/uL; p<0.01). Black bars indicate means from this study, gray bar, historical mean. Nasopharyngeal *B. pertussis* colonization was not significantly different in hu1B7 and control animals (p>0.1). Black bars indicate means.

Hu1B7 passive immunization functioned similarly to current human acellular vaccines in that it mitigated leukocytosis and prevented clinical symptoms and but did not prevent bacterial carriage.

These results provide proof-of-concept in a clinically relevant non-human primate model for the potential efficacy of neonatal antibody prophylaxis for the prevention of severe pertussis pathology.

Hu1B7 Antibody Half-Life in Neonatal Baboons

To assess the half-life of hu1B7 in the neonatal baboons, serum levels of the anti-pertussis toxin antibody was monitored by ELISA [1] at birth (pretreatment) and once or twice weekly for the duration of the study.



A two-phase elimination profile was observed with a beta-phase half-life of 12 ± 4 days (n=8). Data used to calculate the half-life (beta-phase) are displayed.

As hu1B7 is a humanized antibody delivered to a non-human primate, hu1B7 is predicted to have a longer half-life in humans. Assuming a half-life of 21 days in humans, antibody administration at birth could potentially provide 4 months of prophylaxis.

CONCLUSIONS

- Hu1B7 antibody prophylaxis suppressed leukocytosis and ameliorated clinical symptoms of pertussis in neonatal baboons
- Similar to the acellular pertussis vaccine, hu1B7 prophylaxis did not prevent nasopharyngeal bacterial colonization
- Hu1B7 half-life in baboons is 12 ± 4 days; the half-life in humans is expected to be longer
- Evaluation of an extended half-life version of hu1B7 in baboons is in progress

Pertussis prophylaxis using hu1B7, a humanized anti-pertussis toxin monoclonal antibody, may be a viable option to protect newborns for several months after birth when the risk of pertussis mortality is highest

REFERENCES AND DISCLOSURES

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