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Motavizumab

Rec INN; USAN

Humanized Anti-RSV Monoclonal Antibody
Prevention of RSV Infection

A4B4L1FR-S28R
MEDI-524

Immunoglobulin G_1, anti-(respiratory syncytial virus glycoprotein F) (human-mouse monoclonal MEDI-524 γ1-chain), disulfide with human-mouse monoclonal MEDI-524 κ-chain, dimer

Immunoglobulin G_1, anti-(human respiratory syncytial virus glycoprotein F) humanized monoclonal MEDI-524; γ1 heavy chain [humanized VH (*Homo sapiens* FR/*Mus musculus* CDR)-*Homo sapiens* IGHG1] (223-213')-disulfide with κ light chain [humanized V-KAPPA (*Homo sapiens* FR/*Mus musculus* CDR)-*Homo sapiens* IGKC]; (229-229'':232-232'')-bisdisulfide dimer

CAS: 677010-34-3

EN: 292041

Abstract

Respiratory syncytial virus (RSV) is a major causative agent of viral bronchiolitis and pneumonia in infants and children. To date, palivizumab (Synagis®) is the only monoclonal antibody (MAb) approved for RSV prophylaxis. Palivizumab, however, does not offer complete protection to all recipients and is not effective in inhibiting RSV replication in the upper respiratory passages. Directed attempts to enhance the binding of palivizumab to F protein resulted in the production of motavizumab, a second-generation humanized MAb with vastly superior affinity and potency. *In vitro* studies have demonstrated that motavizumab binds to RSV F protein 70-fold better than palivizumab, with approximately 20-fold improvement in neutralization of RSV. Motavizumab has been shown to effectively inhibit RSV replication in the upper respiratory tract, with up to a 100-fold reduction in pulmonary RSV titers compared to palivizumab in the cotton rat model. A phase III trial with motavizumab in 6,635 preterm infants at high risk for RSV has been completed with the primary endpoint of establishing noninferiority *versus* palivizumab. Motavizumab was associated with significantly fewer RSV hospitalizations compared with palivizumab. Additionally, motavizumab demonstrated a statistically significant reduction in the incidence of RSV-specific outpatient lower respiratory infections compared with palivizumab. Drug-related adverse events and drug discontinuations were comparable between the two groups. MedImmune recently submitted a BLA with the FDA for motavizumab.

Background

Approximately 3% of all infants in the first year of life are hospitalized because of respiratory syncytial virus (RSV) infection (> 100,000 hospitalizations annually). The majority of these patients are healthy term infants (1). RSV infects nearly 70% of infants in their first year of life and almost all children by the age of 2 years (2). The development of a live attenuated RSV vaccine with reverse genetics or a vectored vaccine holds great promise for future control of the disease (3).

Children born prematurely, as well as those with chronic lung disease or congenital heart disease, are at the highest risk for severe RSV disease and associated hospitalization. Other high-risk groups include the elderly, those with underlying respiratory or cardiac disease, as well as immunocompromised patients, such as following transplants (4).

RSV is an enveloped RNA virus that primarily infects respiratory epithelial cells. The viral envelope glycoprotein F mediates fusion of the envelope with host cell membranes, followed by fusion of infected cells and the resulting formation of multinucleated masses called syncytia (5). The F protein sequence of RSV is similar across various viral strains and is therefore commonly targeted for therapeutic intervention (6). The symptoms and signs of RSV disease are caused by the direct viral cytopathic effect, as well as a host response to infection. Viral replication and the exaggerated immune response to RSV infection are closely interrelated. It has been suggested

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that the pattern of cytokine production elicited by RSV affects the balance between virus replication and host immune response, and this is what ultimately determines the manifestations of the disease (7).

Due to the lack of a broad-spectrum antiviral agent for the treatment or prophylaxis of RSV, passive immunoprophylaxis is relied upon as the most important method to reduce hospitalization rates and disease burden in high-risk infants (8). To date, palivizumab (Synagis®) is the only monoclonal antibody (MAb) approved for RSV prophylaxis. Palivizumab, however, does not offer complete protection to all recipients and is not effective in inhibiting RSV replication in the upper respiratory passages.

The humanized MAb motavizumab (MEDI-524, formerly known as Numax®) is a second-generation affinity-enhanced derivative of palivizumab that also targets the RSV glycoprotein F. It has been suggested that affinity maturation (arising from changes at three amino acid sites) during the development of motavizumab from palivizumab markedly increases the nonspecific binding of this MAb to various tissues. It is hypothesized that k_{on}-driven mutations are more likely to initiate nonspecific binding events than k_{off}-driven mutations. In effect, reversion of these three residues to the original sequences greatly diminished tissue binding. Motavizumab binds to RSV F protein 70-fold better than palivizumab, and exhibits about a 20-fold improvement in neutralization of RSV *in vitro*. Motavizumab was demonstrated to reduce pulmonary RSV titers to up to 100-fold lower levels compared to palivizumab, with additional inhibition of viral replication in the upper respiratory tract (9-11).

Preclinical Pharmacology

Motavizumab is the product of an evolution-based approach to improve the binding of the palivizumab molecule to F protein by manipulating both the on and off rates (k_{on}-driven mutations being more likely to initiate nonspecific binding events than k_{off}-driven mutations). In a mouse model, prophylactic administration of motavizumab has been shown to significantly reduce RSV replication, as well as local and systemic cytokine responses, especially those involving TNF-α, IL-1α, IL-12p70, keratinocyte-derived chemokine (KC), IL-10 and interferon gamma. This has been demonstrated to effectively prevent the development of acute clinical RSV disease (12).

Motavizumab has been shown to have superior neutralizing activity compared to palivizumab, with an additional reduction in RSV replication that translates into a significant reduction in clinical disease severity (10, 11, 13). In cotton rats, motavizumab was associated with up to 100-fold lower pulmonary RSV titers compared to palivizumab at equivalent doses (10).

Safety

Data from a pivotal phase III trial in 6,635 preterm infants (see below) demonstrated that both motavizumab and palivizumab were well tolerated. The incidence and severity of adverse events were comparable for both treatment groups and quite in line with prior experience with palivizumab. There were comparable rates of adverse events (n=298 or 9% on motavizumab *vs.* n=258 or 7.8% on palivizumab) and drug discontinuations (n=13 or 0.4% on motavizumab *vs.* n=10 or 0.3% on palivizumab) between treatment groups. Adverse events related to skin hypersensitivity reactions resulted in a low frequency of discontinuations (n=9, 0.3%) in motavizumab-treated patients, although no such events were noted in the palivizumab group. The overall mortality rates were not statistically different between the two groups (n=8 or 0.2% for motavizumab and n=4 or 0.1% for palivizumab). No deaths were considered to be related to the study drugs and there were no RSV disease-related deaths. Immunogenicity in the motavizumab arm was < 1% and consistent with prior experience with palivizumab (4).

Motavizumab was also well tolerated in a phase III trial in 1,410 full-term infants (see below), with a similar overall incidence and severity of adverse events in the motavizumab and placebo groups. The mortality rates were not statistically different between groups (0.4% in the placebo arm [n=2] and 0.3% in the motavizumab arm [n=3]) and were not attributed to the study medication. Similar to the phase III trial conducted in high-risk preterm infants, hypersensitivity-related skin rashes (within 2 days of dosing) were seen in about 1% of treated children in the motavizumab group (14).

Clinical Studies

Motavizumab has shown a similar safety and pharmacokinetic profile in phase I and II trials to palivizumab. In a pivotal phase III study involving 6,635 preterm infants at high risk for RSV, with a primary endpoint of noninferiority, motavizumab was associated with 26% fewer RSV hospitalizations compared to palivizumab (1.4% on motavizumab *vs.* 1.9% on palivizumab; $p < 0.01$ for noninferiority). Additionally, motavizumab demonstrated a statistically significant 50% reduction in the incidence of RSV-specific outpatient lower respiratory infections (2% on motavizumab *vs.* 3.9% on palivizumab; $p < 0.01$) (4).

In a phase III study in 1,410 full-term infants under 6 months of age in two Native American populations, motavizumab was shown to reduce hospitalizations due to RSV by 83% compared to placebo (8.3% in the placebo arm *vs.* 1.4% in the motavizumab arm; $p < 0.001$). An additional finding in this trial was a dramatic 71% reduction in the incidence of RSV-specific lower respiratory tract infections requiring outpatient management (9.5% on placebo *vs.* 2.8% on motavizumab; $p < 0.001$) (14).

MedImmune recently submitted a Biologics License Application (BLA) with the FDA seeking approval for motavizumab for preventing RSV infection (15).

Acknowledgements/Disclaimer

Dr. Madaan has no conflicts of interest to disclose.

Sources

MedImmune, Inc. (US); licensed to Abbott for marketing outside the U.S.

References

1. Peebles, R.S. Jr., Sheller, J.R., Collins, R.D. et al. *Respiratory syncytial virus infection does not increase allergen-induced type 2 cytokine production, yet increases airway hyperresponsiveness in mice*. J Med Virol 2001, 63(2): 178-88.

2. Shay, D.K., Holman, R.C., Newman, R.D. et al. *Bronchiolitis-associated hospitalizations among US children, 1980-1996*. JAMA – J Am Med Assoc 1999, 282(15): 1440-6.

3. Collins, P.L., Murphy, B.R. *New generation live vaccines against human RSV designed by reverse genetics*. Proc Am Thorac Soc 2005, 2(2): 166-73.

4. *Numax® achieves primary endpoint among high-risk infants versus current standard of care and shows reduction of medically attended outpatient RSV-related lower respiratory infections*. MedImmune, Inc. Press Release, May 8, 2007.

5. Harris, J., Werling, D. *Binding and entry of respiratory syncytial virus into host cells and initiation of the innate immune response*. Cell Microbiol 2003, 5(10): 671-80.

6. Openshaw, P.J., Tregoning, J.S. *Immune responses and disease enhancement during respiratory syncytial virus infection*. Clin Microbiol Rev 2005, 18(3): 541-55.

7. Mejías, A., Chávez-Bueno, S., Ríos, A.M. et al. *Anti-respiratory syncytial virus (RSV) neutralizing antibody decreases lung inflammation, airway obstruction, and airway hyperresponsiveness in a murine RSV model*. Antimicrob Agents Chemother 2004, 48(5): 1811-22.

8. American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn. *Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections*. Pediatrics 2003, 112(6, Pt. 1): 1442-6.

9. Wu, H., Pfarr, D.S., Losonsky, G.A., Kiener, P.A. *Immunoprophylaxis of RSV infection: Advancing from RSV-IGIV to palivizumab and motavizumab*. Curr Top Microbiol Immunol 2008, 317: 103-23.

10. Wu, H., Pfarr, D.S., Johnson, S. et al. *Development of motavizumab, an ultra-potent antibody for the prevention of respiratory syncytial virus infection in the upper and lower respiratory tract*. J Mol Biol 2007, 368(3): 652-65.

11. Mejias, A., Chavez-Bueno, S., Rios, A.M. et al. *Comparative effects of two neutralizing anti-respiratory syncytial virus (RSV) monoclonal antibodies in the RSV murine model: Time versus potency*. Antimicrob Agents Chemother 2005, 49(11): 4700-7.

12. Mejias, A., Chavez-Bueno, S., Raynor, M.B. et al. *Motavizumab, a neutralizing anti-respiratory syncytial virus (RSV) monoclonal antibody significantly modifies the local and systemic cytokine responses induced by RSV in the mouse model*. Virol J 2007, 4: 109.

13. Wu, H., Pfarr, D.S., Tang, Y. et al. *Ultra-potent antibodies against respiratory syncytial virus: Effects of binding kinetics and binding valence on viral neutralization*. J Mol Biol 2005, 350(1): 126-44.

14. *Motavizumab reduced RSV hospitalizations by 83 percent among high-risk Native American, full-term infants in placebo-controlled phase 3 study*. MedImmune, Inc. Press Release, August 23, 2007.

15. *MedImmune submits Biologics License Application to FDA for motavizumab*. MedImmune, Inc. Press Release, February 4, 2008.