CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
103928Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)
Clinical Pharmacology and Toxicology Review of Technetium (99m Tc) fanolesomab (NeutroSpec), BLA
STN 103928

Sponsor: Palatin Technologies
Product: Technetium (99m Tc) fanolesomab (NeutroSpec)
Indication: Scintigraphic imaging of patients with equivocal signs of appendicitis who are 5 year of age or older
Date review completed: July 1, 2004

LeuTech is an anti-CD 15 monoclonal IgM antibody that is proposed for use to assist in the diagnosis of equivocal appendicitis. The biological product is a murine monoclonal antibody and consists of 100 ug (range 75 to 125 ug) drug substance to be conjugated with sodium pertechnetate Tc99 (10 to 20 mCi) for intravenous injection. The antibody binds to CD15 antigens that are found on human polymorphonuclear neutrophils (PMNs). The putative mechanism of action results from the accumulation of PMNs at the site of inflammation during the pathophysiological state. The CD15 antigen that is recognized by the antibody is a carbohydrate moiety, 3-fucosyl-N-acetyl-lactosamine and belongs to a family of antigens known as stage specific embryonic antigen-1 (SSEA-1), Lewis-X antigen or X-haptens. The antibody also reacts with various glycolipids and glycoproteins express predominately on neutrophils.

No significant binding of anti-CD15 was found to the circulating neutrophils of many common laboratory animals including monkeys (rhesus, cynomolgus and marmoset), rats, cats, guinea pigs, dogs, rabbits, sheep, and pigs.

No significant binding to RBCs were found when isolated blood samples were analyzed from human volunteers after 0.5 and 1.0 hour of labeling (Palatin Technologies Clinical Study Report 97-002). Using a Tc99m labeled antibody 80% and 82% of formalin fixed HL-60 cells or formalin fixed human neutrophils, respectively were bound.

Thakur, et al., (Nuclear Med Communications, 11: 37, 1990) assessed the performance of human neutrophils at various levels of antigen saturation the anti-CD15 antibody. When an average of 10% of the available surface antigens were bound, the phagocytic ability and nylon wool adherence of human neutrophils were decreased to 70% and 80% of controls. Opsonization by PMs to both gram positive and gram negative microorganism was also diminished in a dose dependent manner. At levels of 4% or less of antigenic saturation, no changes were observed in various cellular functions. The ability of PMNs to migrate towards E.coli in a broth was not diminished by binding at any degree of saturation. Given a uniform distribution of antibody over the available circulating PMNs in an adult, the 100 ug dose is expected to yield a level of saturation of approximately 0.4%. The toxicity of the anti-CD15 antibody was investigated, it was found that the antibody caused cellular lysis at a concentration of 1 ug/ml and higher. Lysis was depended on the presence of complement. Approximately, one half of the neutrophils from 2 donors were lysed at 1 ug/ml and all cells were lysed at concentrations between 2 and 5 ug/ml; little or no effect was found at 0.2 ug/ml.

Clinical Pharmacokinetics Study: Study title, “A safety Single-Center Clinical Study of Evaluate the Safety and Biodistribution of Technetium Tc 99m LeuTech in Normal Volunteers” protocol no. 97-002.

A non-randomized, open-label study of 10 normal subjects was conducted using LeuTech. Subjects were injected intravenously with Tc99 m labeled anti-CD15 antibody. A total dose of 8.9 to 10.7 mCi of technetium-99m and 68 to 128 ug of antibody were administered as a single dose. Blood samples were taken at 3, 5, 10, 15, 30, and 45 minutes and 1, 2, 4, 8, and 18 to 24 hours; blood samples were assayed for Tc99 levels. Urinary excretion was also determined. An evaluation for safety was performed as an integral part of the study. Both whole body, decay corrected radioactivity declined as a biphasic exponential curve. Elimination half-lives were estimated to be 0.3 (range 0.1 to 0.7) and 8.1 (range 3 to 18) hours. About 19% (range 5% to 42%) of radioactivity was associated with white blood cells at 0.5 hours and 25% (range 6% to
47%) at 1 hour post-injection. The collection of urine was limited to 30 hours. The mean cumulative radioactive dose recovered in the urine was 38% with a range of 32% to 46%. At 30 hours after injection, approximately 40% to 60% of the radioactive dose remained in the whole body. The liver was shown to have the largest single organ uptake of radioactivity which peaked at 45% to 50% of the total radioactive dose and was followed by spleen with 5% to 12%. No evidence of toxicity was found in the course of the study. Two other open literature references were included in the submission concerning biodistribution: Thakur, et al., J Nucl Med 37: 1789, 1996 and Gratz, et al., Eur J Nucl Med 25: 386, 1998.

A statistically significant decrease in WEC (p<0.1) was noted from 3 minutes post-injection through 1 hour post-injection. By 4 hours, a slight but significantly (p=0.016) greater than baseline rise in WBC occurred. WBC returned to baseline by 18 to 24 hours post-injection. Although the physiological basis for this change in WBC is not known, it is stated by the sponsor that these changes may represent the interaction of the white blood cells with the reticuloendothelial system of the liver.

Toxicology Studies

Two toxicology studies (X7F305G and X7F306G) were conducted using mice (CD-1) and rabbits (New Zealand White), respectively. Mice (10/sex/group) and rabbits (5/sex/group) were given a single intravenous dose of up to 500 ug/kg of decayed technetium bound antibody and monitored for 7 days. Mice were given doses of 0 (saline), 25, 125, 250, or 500 ug/kg; rabbits were given doses of 0 (saline), 25, 125, 250 or 500 ug/kg. Clinical observations, clinical chemistry, hematology, gross and microscopic anatomy for the control and high dose group were assessed. No effects were observed at the highest dose tested; therefore, the NOAEL is >500 ug/kg. Two pilot studies were also conducted using the antibody made by a different manufacturing technique (ascites) in which mice were given 1 ug/mouse and rabbits 25 ug/rabbits. No effects were observed.

Tissue Cross-reactivity Study

A human tissue cross-reactivity study was conducted on a panel of tissues at 2 concentrations (1 and 10 ug/ml). A wide variety of tissues bound the antibody including: resident histiocytes or Kupffer cells, alveolar macrophages, circulating monocytes and neutrophils, myelomonocytic progenitor cells, glial cells, perithelial cells, epithelial tissues/mucosal cells (eg., esophagus, tonsil, stomach), glandular cells (eg., pancreas, salivary gland), and mesothelial cells. Within the central nervous system binding occurred with not only glial cells but also cerebrum, cerebellum, spinal cord, posterior pituitary; no binding was found to peripheral neuronal tissue. An IgM antibody is not expected to cross the blood-brain-barrier and therefore, is unlikely to exert any effect.

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