**GENETICALLY RECOMBINANT ANTIBODIES: NEW THERAPEUTICS AGAINST CANDIDIASIS**

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**ABSTRACT**

Genetically recombinant antibodies may represent a new approach to the treatment of candidiasis. The first such antibody has a broad spectrum of activity against Candida species. Preclinical studies demonstrate synergy with amphotericin B, both in vitro and in mouse models of candidiasis. It could also act synergistically with other cell-wall–active antifungal agents, such as caspofungin.

Thus far, combination therapy with amphotericin B and the antibody has been associated with regression of infection in 3 patients with culture-confirmed candidiasis. An ongoing phase 2 trial, begun last year, involves 60 patients with culture-confirmed invasive candidiasis who are receiving liposomal amphotericin B plus the antibody or placebo. Efficacy evaluations include clinical response and clearance of fungal cultures. The antibody was designed to be given with other antifungal agents to increase efficacy, reduce mortality, and reduce amphotericin B toxicity. It may also reduce the risk of resistance.

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CLINICAL OBSERVATIONS

The antibody was specifically designed to work with other antifungal agents in combination regimens to increase efficacy, reduce mortality, reduce amphotericin B toxicity, and reduce the risk of resistance. Thus far, the antibody has been given to 5 patients with culture-confirmed invasive candidiasis who were receiving a lipid-associated formulation of amphotericin B. Of these patients, 3 received 24 hours of treatment at the therapeutic dose. The first of these patients was a 53-year-old woman with invasive candidiasis that was complicating acute pancreatitis. She was not responding to amphotericin B lipid complex, but showed some clinical improvement (including cultures becoming negative) following 4 escalating doses of the antibody.

The second patient was a 45-year-old man who developed invasive candidiasis after bowel surgery, with multiple sites (including ascitic fluid) that were positive for C. albicans. He had fever, an elevated white blood cell count, and tachycardia, despite therapy with amphotericin B lipid complex. After 4 escalating doses of the antibody, his fever resolved, his white blood cell count decreased, and he improved clinically. Subsequent recovery was complicated by an episode of bacterial sepsis, which responded to antibiotics, and the patient made a full recovery.

The third patient was a 57-year-old man with C. albicans empyema. After 6 days of therapy with amphotericin B lipid complex, cultures taken from a chest drain were still growing Candida. The patient had an elevated white blood cell count and was deteriorating clinically. After 24 hours of treatment with the antibody, he made a full clinical recovery, and subsequent cultures were negative.

Pharmacokinetic and dose-ranging studies have determined that the optimal dose of the antibody is 1 mg/kg twice daily. Safety studies have found that the antibody is well tolerated, with no adverse changes in vital signs, hematologic variables, clinical chemistry values, and coagulation times.

CLINICAL TRIALS

A double-blind, placebo-controlled, phase 2 trial was initiated in England in 2001 and is expanding to include other countries. The 60 participating patients will have culture-confirmed invasive candidiasis being treated with liposomal amphotericin B. In addition, they will receive a 5-day course of either the genetically recombinant antibody or placebo. Evaluation of efficacy will include clinical response to treatment and clearing of fungal cultures. For further information regarding patient recruitment for this trial, please contact Prof Ruth Matthews via e-mail at dorene@labmed.cmht.nwest.nhs.uk; or Prof James P. Burnie at jburnie@labmed.cmht.nwest.nhs.uk.