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Oral Encochleated Amphotericin B (CAMB) in the Treatment of Chronic Azole Resistant Mucocutaneous Candidiasis

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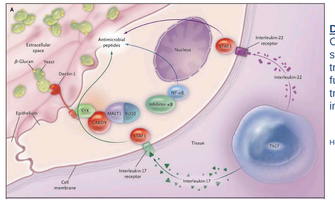
ABSTRACT

Azole resistant fungi are increasingly seen in immunocompromised hosts, especially those requiring intensive and/or chronic suppressive antifungal therapies. Amphotericin B (AMB) has broad antifungal activity, but available formulations can only be given parenterally and causes significant nephrotoxicity, electrolyte disturbances and infusion reactions. Encochleated Amphotericin B (CAMB) is a new oral formulation of AMB that is taken-up by macrophages, which then release AMB directly at the infected tissue. CAMB exhibited significant preclinical activity in mice with disseminated candidiasis and aspergillosis with minimal toxicity, thus showing promise for clinical development of CAMB. A phase 2A dose escalation study is currently underway to test the efficacy and safety of CAMB in patients with chronic mucocutaneous candidiasis (CMC) caused by primary immunodeficiencies, and who are azole resistant or azole intolerant. Here, we report the results from enrollment of two patients with STAT3 deficient Hyper IgE syndrome who suffer from chronic azole resistant CMC involving the oral and vaginal mucosa and nails for >20 years. Clinical efficacy criteria were met at 400mg (Pt. 01) and 200 mg (Pt. 02) of CAMB oral suspension twice daily with improvement primarily in the oral thrush on exam, clinical symptoms, and semi-quantitative fungal cultures. Clinical severity score for thrush (composed of oral pain, burning, dysphagia, odynophagia, and presence of plaques) for Pt. 01 decreased from 7 at baseline to 3 at the end of the study drug course. Vulvovaginal signs and symptoms also improved. C-AMB was well tolerated at the maximum drug dose for 4 weeks, without changes in kidney function, electrolytes, or gastrointestinal side effects. Oral thrush promptly returned after stopping C-AMB. Therefore, our preliminary clinical data indicate that C-AMB is promising as an oral systemically-absorbed broad-based antifungal without the toxicity of parenteral AMB. Enrollment of additional patients with CMC is ongoing to further evaluate the efficacy and safety of C-AMB.

INTRODUCTION

- Autosomal dominant Hyper IgE Syndrome (AD-HIES or Job's Syndrome) is caused by loss of function mutations in STAT3 and is characterized by eczema, recurrent skin and lung infections, mucocutaneous candidiasis, and multiple skeletal, connective tissue, and vascular abnormalities.
- AD-HIES is characterized by poor TH17 cell differentiation and thus, impaired IL-17 and IL-22 signaling, and abnormal antimicrobial peptide upregulation at epithelial surfaces. This leads to susceptibility to mucocutaneous candidiasis.
- Individuals with AD-HIES, as well as those with other immunocompromising conditions, are often maintained on chronic antifungals, which can lead to azole resistant *Candida* infections.
- Potent new oral fungicidal agents that can be safely administered to patients for prolonged periods of time without toxic drug-drug interaction are needed for immunocompromised patients.
- Amphotericin B is a broad spectrum fungicidal agent with little reported resistance, however its use is limited as a chronic treatment because of nephrotoxicity and the need for i.v. administration.
- Encochleated Amphotericin B (CAMB/MAT2203) is a lipid-crystal nanoparticle formulation of amphotericin B that is systemically absorbed and can be administered orally without the toxicities typically seen with i.v. amphotericin B.



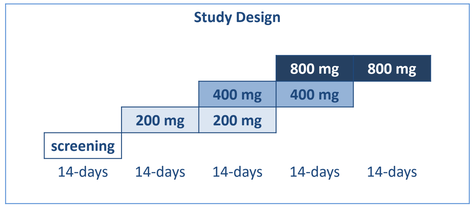
Defects in immunity to *Candida albicans*

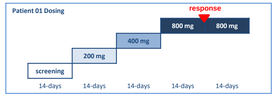
CMC results from defects that affect interleukin (IL)-17 signaling such as loss of function mutations in signal transducer and activator of transcription 3 (STAT3), gain of function mutations in signal transducer and activator of transcription 1 (STAT1) and loss of function mutations in interleukin-17 receptor A (IL-17RA).

Holland SM, Vinh DC, NEJM 2009; 361: 1798-1801

METHODS

- This is an open-label, phase 2a, efficacy safety, tolerability, and pharmacokinetic study of CAMB in patients with CMC who are refractory or intolerant to standard non-intravenous therapies





KEY INCLUSION CRITERIA:

A clinical diagnosis of at least one of the following: persistent oropharyngeal (OPC), esophageal (EC), or vulvovaginal candidiasis (VVC) documented by KOH or fungal stain and confirmed by culture to be azole resistant within the previous 6 months and/or intolerance to standard non-intravenous therapies or lack of improvement or worsening of after receipt of appropriately dosed oral azole therapy.

DEMOGRAPHICS & HISTORY

Two patients, female, white, aged 43 and 42, with long history of OPC, EC, VVC, BMI 44.6 (Patient 01) 20.5 (Patient 02)

ANTIFUNGAL SUSCEPTIBILITIES: SOURCE MOUTH

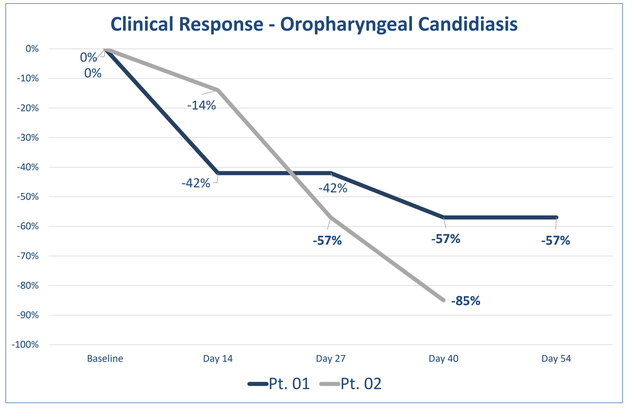
	Patient 01		Patient 02	
Antifungal	**MIC (mcg/mL)**	**Interpretation**	**MIC (mcg/mL)**	**Interpretation**
Amphotericin B	1	D1	1	D1
Anidulafungin	**0.5**	**I**	<=0.015	S
Caspofungin	**2**	**R**	0.03	S
Fluconazole	**128**	**R**	**32**	**R**
Flucytosine	2	D1	0.06	D1
Intraconazole	NA	NA	1	D1
Micafungin	**0.5**	**I**	0.015	S
Posaconazole	2	D1	2	D1
Voriconazole	**2**	**R**	**1**	**R**

S=susceptible I=intermediate R=resistant D1= no standardized susceptibility testing breakpoints for this drug

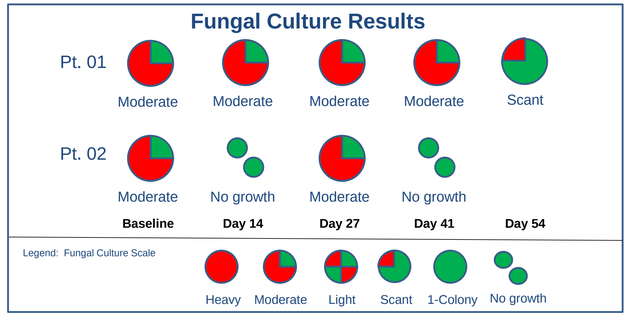
EFFICACY & SAFETY EVALUATIONS:

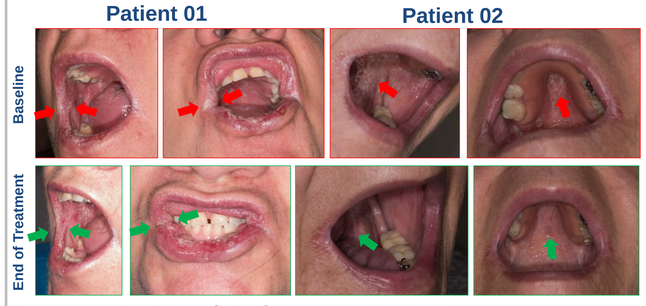
- Primary endpoint is Clinical Response after 14-days treatment at 800 mg/day (Pt. 01) and 400 mg/day (Pt. 02)
- Secondary endpoints include safety, mycology, and pharmacokinetics
- Clinical Efficacy Assessment
  - Clinical Cure: Absence of plaques or ulcers and absent or minimal symptoms
  - Clinical Improvement: Partial resolution (≥ 50%) of pretreatment signs and symptoms
  - Clinical Failure: No improvement (< 50%) or worsening of pretreatment signs or symptoms
  - Not evaluable: Subject not evaluable due to lack of follow-up visits.
- Symptoms evaluated for OPC/EC dysphagia, odynophagia, retrosternal pain, oral pain, burning of mouth
- Safety assessments include AE's and laboratory assessments

RESULTS



Both patients met primary endpoint (≥50 clinical response) after 14-days of treatment at Efficacious Dosage.



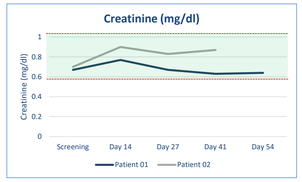


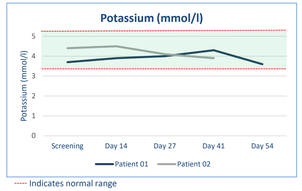
QUALITY OF LIFE (QOL)IMPROVEMENTS

Patients reported improved QOL as able to eat a greater variety of foods, including those that are acidic and spicy.

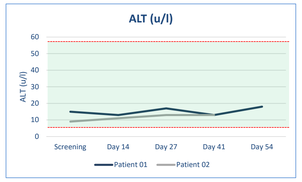
SAFETY

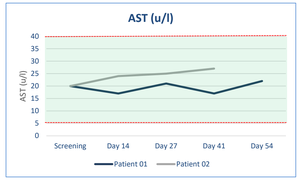
Renal





Hepatic





Indicates normal range

No Serious AE's reported; majority of AEs were mild and unrelated to CAMB

Incidence of Possible, Probably, or Definitely Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term				
System Organ Class	MedDRA PT	Relationship	Grade	CAMB
				N (%)
Any subject with an AE	Any			2 (100)
Metabolism/nutrition disorders	Any			2 (100)
	Decreased appetite	possible	1	1 (50)
	Hyponatremia	possible	1	1 (50)
Investigations	Any			2 (100)
	Blood bicarbonate abnormal	possible	1	1 (50)
Gastrointestinal Disorders	Any			1 (50)
	Nausea	possible	2	1 (50)
	Vomiting	possible	2	1 (50)
Nervous system disorders	Any			1 (50)
	Dizziness	possible	1	1 (50)
Skin and subcutaneous disorders	Any			1 (50)
	Hyperhidrosis	possible	1	1 (50)

Overall incidence of Treatment-Emergent Adverse Events	
	CAMB N (%)
Any TEAE	2 (100)
Grade 1	2 (100)
Grade 2	2 (100)
Grade 3	1 (50)*
Grade 4	0 (0)
Grade 5	0 (0)

Common Terminology Criteria for Adverse Events
Grade 1 = mild
Grade 2 = moderate
Grade 3 = severe or medically significant
Grade 4 = life threatening
Grade 5 = death related to AE
*left axilla abscess (unrelated)

CONCLUSIONS

- Two patients with AD-HIES with long-standing azole resistant mucocutaneous candidiasis responded clinically to oral treatment with CAMB.
- Response was improved compared to historical response with amphotericin B swish and swallow treatment.
- Oral Treatment with CAMB for up to 54-days was well tolerated. Reported adverse events were mostly mild in severity and unrelated to CAMB. There were no serious AE's reported.
- There were no signs of hepatoxicity, nephrotoxicity or hypokalemia after oral dosing for 54-days in Patient 01 and 41-days in Patient 02
- Additional studies of non-oral infections should be performed to demonstrate systemic efficacy.

*This research was supported by Matinas BioPharma and by the intramural research program of the NIAID.