Adjunctive therapies: adoptive immunotherapy for candidiasis

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Invasive infections due to *Candida* spp.

- 4th most frequent bloodstream infection
- High morbidity and mortality
- Most frequent in specific patient populations, ie immunocompromised pts, ICU, neonates
Medical Mycology: The Last 50 years

No. of drugs


Nystatin
Amphotericin B (1958)
Griseofulvin
5-FC
Miconazole
Ketoconazole
Fluconazole
Itraconazole
Terbinafine
ABLC
ABCD
L-AmB
Sordarins
Caspo
Posacon
Voricon
Ravucon
Micafun
Efungumab
Vo
Anidula
No. of drugs
Candida-attributable mortality is high:

12-17% in candidaemias treated by Amphotericin B or Fluconazole

Rex et al, NEJM 1994; 331: 1325-30 (fluconazole vs amphotericin B)
Rex et al, CID 2003; 36: 1221-8 (monotherapy 800mg fluconazole arm)

10% Candida-attributable mortality. A prospective observational study of candidaemia (n=1447)

Pappas et al, CID 2003; 37: 634-43

15-49% Candida-attributable mortality in case-matched studies

Morgan J, Infect Control Hosp Epidemiol 2005; 26:540-7
Zaoutis TE, Clin Infect Dis 2005; 41:1232-9
Issues for discussion

• Host immune response to *Candida* spp.
  – Innate immune response
  – Adaptive immune response

• Immunotherapeutic interventions
  – Growth factors
  – White blood cell transfusions
  – Antibodies

• Adoptive immunotherapy for candidiasis
  – Generation of anti-*Candida* T cells
  – Vaccination
Host immune response to *Candida* spp.

- Innate immune response
- Adaptive immune response
The structure of *C. albicans* cell wall
Cell populations and pattern-recognition receptors involved in *C. albicans* recognition

Netea et al. 6: 67, 2008
Recognition of *C. albicans* at the membrane level

Netea et al. 6: 67, 2008
Responses to C. albicans

Kim et al. Infect Immun  2005
Dendritic cells phagocytose fungal morphotypes through different phagocytic morphologies and receptors

- Conidia & blastoconidia - coiling phagocytosis
- Hyphae - zipper-type phagocytosis
Phagocytosis of yeasts: Involvement of dectin-1

zymosan

Antifungal host defense

Defensins
Lysozyme
Lactoferrin

Cytochrome b

O_{2}^-

NADPH

NADP^+

O_{2}

HOCl

H_2O_2

H_2O_2

Chloramines

H_2O_2

H_2O_2
Romani, Nature Immunol 2004

Adaptive immune response

Innate immunity

Mucosal surface

Fungus

PRR

Opsonin

Neutrophil

Macrophage

Inflammatory response

IL-10

IL-12

IL-16

Innate immune functions such as phagocytosis and neutrophil degranulation

Immature dendritic cell

Maturation

Draining lymph node

Antigen presentation

TCR

MHC

T cell

B cell

B cell

Antibody production

IFN-γ

TNF

IL-4

IL-5

T cell

T cell

Lymphocyte activation and cytokine release

T<sub>H1</sub>

IL-12

T<sub>H2</sub>

IL-4

T<sub>Reg</sub>

IL-10
Immunotherapeutic interventions

- Growth factors
- White blood cell transfusions
- Antibodies
- Adoptive immunotherapy
Augmentation of Antifungal Phagocytic Host Response by Th1 and Proliferative Cytokines

M-CSF
GM-CSF
G-CSF

IFN-γ
IL-12
IL-15
TNF-α

TNF-α, IFN-γ, IL-12

MIP1-α

Fungicidal activity & hyphal damage (oxidative and non-oxidative)
Clinical applications of CSFs in *Candida* infections

- Prophylaxis during neutropenia
- Therapy of febrile neutropenic patients and defined *Candida* infections
Antibody therapy
HSP90 as an anti-fungal target

- Hsp90 is a molecular chaperone present in the fungal cell wall and extra-cellular material

- Geldanamycin, a naturally occurring Hsp90 inhibitor, increases the in vitro sensitivity of *Candida* and *Aspergillus* to fluconazole and caspofungin

- Efungumab, a novel human recombinant antibody against hsp90, mimics geldanamycin activity
  
  Cowen, Science 2005

- Efungumab showed synergy with amphotericin B
  
  - against a broad range of *Candida* spp. in vitro
  - in animal models of invasive candidiasis

Study Objective

➢ To determine the efficacy and safety of L-amphotericin B alone and in combination with efungumab in treating adults with culture-confirmed invasive candidiasis

Study design

- Randomized, double blind, comparative, multicenter study
- Patients randomized in 1.1 ratio
- Patients stratified into *Candida albicans* versus *non-albicans*
- Intravenous treatment:
  
  Efungumab (1mg/kg) or placebo (saline) every 12 hrs for 5 days
  
  plus
  
  Abelcet (5mg/kg/day) or AmBisome (3mg/kg/d) for at least 10 d
Primary efficacy variable: Complete overall response Day 10

Efungumab + L-Amph B

Placebo + L-Amph B

47 (84%)

29 (48%)

p<0.001
Efficacy Variables

Efungumab L-amph B

Placebo +L amph B

p<0.001
Secondary efficacy variables - mycological clearance

Time Taken To Last Positive Culture

Kaplan-Meier Estimates (%)

- Placebo
- Mycograb

P=0.001
Conclusion

- *Efungumab (1mg/kg bid for 5 d) significantly enhances the clinical and mycological efficacy of Ampho B*
  - Complete Overall Response at Day 10 (84% vs 48%)
  - Clinical Response (86% vs 52%)
  - Mycological Response (89% vs 54%)
  - Rate of mycological clearance (Hazard ratio 2.3)
  - Candida-attributable mortality (4% vs 18%)

- *Efungumab is independent of the site of infection*
- *Efungumab was well tolerated*
Efungumab and caspofungin

• Synergy between efungumab and caspofungin

• *C. albicans* and several *Candida* spp.

• Efungumab increased the susceptibility of *Candida* to caspofungin and improved candidiasis in mice

• A clinical study is needed to study the synergistic efficacy of the two agents

Adoptive immunotherapy

• Generation of anti-*Candida* T cells to treat invasive candidiasis

  *Tramsen et al. J Infect Dis 196: 485, 2007*

• Vaccines to prevent invasive candidiasis

  *Spellberg et al. J Infect Dis 197: 967, 2008*
Anti-*Candida* T cell adoptive immunotherapy

- Allogeneic haematopoietic stem-cell transplantation and invasive candidiasis
- Adoptive transfer of specific anti-*Candida* T lymphocytes may be a therapeutic option
- The adaptive immune system has a major impact on the host response to *Candida* infection
- Reconstitution of adaptive cell immunity with Ag-specific T cells is a promising approach in patients undergoing allogeneic hematopoietic stem-cell transplantation

*Tramsen et al. J Infect Dis 196: 485, 2007*
Anti-Candida T cell adoptive immunotherapy

**Generation of anti-Candida T cells**
- Day 0: Incubation with *C. albicans* cell extracts
- Day 1: Cytokine secretion assay
- Day 14: Culture

**Characterization of anti-Candida T cells**
- Day 26: Rapid expansion protocol
- Day 38: Highly purified anti-Candida T cells (~3 x 10^7)
  - Intracellular cytokine cytometry
  - Phenotype
  - Intracellular cytokine cytometry
  - Alloreactivity
  - Proliferation
  - Anti-Candida activity
  - TCR spectratyping

*Tramsen et al. J Infect Dis 196: 485, 2007*
Loss of alloreactivity after enrichment and expansion of anti-\textit{Candida} T cells

Hyphal damage to *C. albicans* induced by anti-*Candida* T cells, PMNs and antigen-presenting cells alone or in combination.

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*Tramsen et al. J Infect Dis 196: 485, 2007*
Anti-*Candida* vaccination to prevent invasive candidiasis

- Vaccination of mice with rec N-terminus of candidal adhesin, Als3p plus Freund’s adjuvant protects mice from disseminated candidiasis
- Al(OH)$_3$ adjuvant plus rAls3p-N is also effective
- Neither B lymphocytes nor serum from immunized animals transferred protection to vaccine-naïve animals
- CD3+, CD4+, or CD8+ T lymphocytes from immunized animals transferred protection
- The vaccine was efficacious in IL-4-deficient but not in IFN-γ-deficient mice

*Spellberg et al. J Infect Dis 197: 967, 2008*
Survival of mice with disseminated candidiasis after vaccination with rAls3p-N plus Al(OH)$_3$

Adoptive transfer of T lymphocytes, but not B lymphocytes, transferred protection against disseminated candidiasis

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Conclusions-I

• Although conventional antifungal regimens are necessary for the treatment of yeast infections, immunomodulation shows promise as adjunctive therapy for patients with fungal infections.

• Growth factors and granulocyte transfusions could be considered in patients with invasive fungal infections not responding to appropriate antifungal treatment, in patients whose underlying cancer is still responsive to treatment and in whom severe neutropenia is expected to persist.
Conclusions-II

• Efungumab is a promising adjunctive antifungal compound and provides a new approach to the treatment of fungal infections

• Adoptive immunotherapy performed either as anti-\textit{Candida} T cell generation or as candidal vaccination is very promising