Cryptococcal Meningitis Treatment: What’s on the horizon?

Tom Harrison
Professor of Infectious Diseases, St Georges University of London
21st July 2020
Current recommendations

  Preferred: A short course (1 week) induction with AmB + 5FC
  Alternative: 2 weeks fluconazole 1200 mg/d + 5FC
    both followed by fluconazole consolidation and maintenance and ART at 4-6 wks

• Early infection - Asymptomatic CrAg-positive cases identified during screening:
  Recommend LP; if LP declined (majority of cases), or CSF CrAg negative:
  fluconazole 1200 mg/d 2 weeks, followed by fluconazole consolidation/maintenance and ART at 2 wks

AmB = amphotericin B deoxycholate; 5FC = flucytosine. ART antiretroviral treatment, CrAg = cryptococcal antigen, CSF = cerebrospinal fluid.
Current recommendations

Both based RCT mortality benefit data:
Symptomatic meningitis - ACTA
Molloy et al. NEJM 2018 378:1004
long term follow-up data CID 2020;70:521

Screening – REMSTART

Approx half mortality benefit due screening
The future? Optimising use of Liposomal Amphotericin B: The AMBITION-CM trial

Liposomal amphotericin (L-AmB, Ambisome) – in prior trials, no more effective but less toxic (renal impairment, anaemia) than conventional amphotericin B deoxycholate; even longer half life; excellent brain levels

Even better suited than conventional AmB to short course high dose induction treatment (as used in ACTA) – aimed at loading brain compartment

**IF** one / few doses effective, could be cost effective due shorter admission, less monitoring; and feasible to implement

**Phase II RCT**
Single 10 mg/kg/d dose: Safe, safer than Deoxy AmB
As rapid clearance as daily dosing for 2 weeks

The AMBITION-CM trial: Phase-III study – clinical endpoint non-inferiority trial

• Liposomal-AmB 10 mg/kg day 1 (single dose) plus 5FC plus fluconazole (for initial 2 weeks) vs
• Amphotericin B deoxycholate 1.0 mg/kg/d 7 days plus 5FC (“control arm” new WHO standard – from ACTA)
• All patients fluconazole 800 mg/d to 10 weeks, 200 mg/d thereafter. ART initiated 4-6 weeks
• Endpoints: Primary: All-cause mortality within 10 weeks
• Secondary: Early Fungicidal Activity (EFA); 2-week mortality; tolerability and adverse events; cost-effectiveness

>650 of target of 850 participants already enrolled
Results expected early 2021
Wide access to Flucytosine, and Modified-Release Flucytosine

- Access to 5FC is increasing and costs of 5FC are coming down:
  UNITAID AHD programme (launched Jan 2019)
  South African access programme, 5FC in routine use from May 2019:
    24% in-hospital mortality first 335 patients, with 1 week AmB+5FC regimen, compared with 35% from long term surveillance data in South Africa. Govender N et al ICASA Dec2019

- Major (Mylan) and multiple manufacturers committed

- Funding secured for development of easier to use modified release formulation that could be given twice rather than 4 x daily (EDCTP – DNDi and partners)

- In fact, progress since release of ACTA results showing that 5FC is an essential part of best treatment has been rapid
The future? More effective antifungal treatment for those testing CrAg-positive during screening

- Those testing CrAg positive have continued high mortality, despite fluconazole
- And a significant proportion 30-40% CrAg positives have subclinical CM (defined by +ve CSF CrAg) if they agree to LP
- A high CrAg titre predicts subclinical CM; and a high titre and subclinical CM are both associated with higher mortality

*We need to study more effective antifungal therapy for those who are CrAg+ve*, in the context of a bundle of diagnostics and ART adherence support for all
More effective antifungal treatment for those testing CrAg-positive: EFFECT and ACACIA trials

• EFFECT trial – funded MRC WT DFID Global Health Trials
  • From ACTA we know Fluconazole plus flucytosine (2 wks) is safe and effective and could be sustainable, cost-effective oral option for CrAg +ve, that may preclude need for LP and i/v Rx
  • South Africa, Tanzania, pragmatic trial, within screening programmes
  • 600 asymptomatic CrAg positive randomised to:
    • Fluconazole vs Fluconazole + flucytosine (first 2 wks)
    • All participants: ART adherence support, TB diagnostics

• ACACIA trial - Single Dose iv Liposomal Amphotericin for Asymptomatic Cryptococcal Antigenemia (ACACIA)
  Uganda, enrolling 2019 - 2023
Stratified management for those testing CrAg-positive according to CrAg titre

Semi-quantitative tests are in development:
**IMMY CrAgSQ (negative, 1+ to 4+)**

But may not be as easy to use in routine care as standard CrAg LFA - Depends relative intensity different test bands

**Biosynex Crypto PS (negative, 1+, 2+)**
Simple to use But sensitivity and specificity sub-optimal compared IMMY LFA. Tenforde et al, unpublished

Nevertheless prospect is that more aggressive antifungal treatment could be directed at those with higher blood titre, at greatest risk of poor outcome.

EFFECT and ACACIA can be analyzed by titre in retrospect in order to guide management pathways