Gone fishing for a solution

ST5 Microbiology & Infectious Diseases

Ian Blyth

FIS 2017
Case: Presentation

N.C 39yr old male, presented to his local hospital;

3wk history of headaches - Frontal
   - Increasing frequency/intensity

Nil fever/rigors/photophobia
Subjective weight loss
Case: Presentation

Nil significant PMH/DH
Homosexual male
Unemployed
Within 12hrs of presenting N.C began to complain of bilateral visual disturbance

Extremely agitated/disoriented
Required intubation.

CT Head - NAD
Case: Presentation

LP

Opening pressure >40mmHg
WCC 58  90% lymph
       10% polymorphs

Protein 0.42 Glucose 2.3 (<50% serum)
Case: Presentation

LP

Opening pressure >40mmHg
WCC 58  90% lymph
    10% polymorphs

Protein 0.42 Glucose 2.3

Gram stain - Yeast
Case: Presentation

Lumbar puncture

Opening pressure >40mmHg
WCC 58  90% lymph
  10% polymorphs

Protein 0.42 Glucose 2.3

Gram stain – Yeast  ID – Cryptococcus Neoformans
HIV test +ve

CD4 count 20
V/L 23234

Baseline resistance testing
T215E substitution (TAMS)
Case: Presentation

Diagnosis

Advanced HIV
Complicated by cryptococcal meningitis.
What induction therapy is advised by BHIVA in cases of cryptococcal meningitis in HIV?

1. Fluconazole 800mg PO OD
2. Voriconazole 6mg/kg IV BD
3. Liposomal Amphotericin B (4mg/kg/day) +/- Flucytosine (100mg/kg/day)
4. Lipid Amphotericin (1mg/kg/day)
5. Fluconazole 800mg PO OD + Flucytosine (100mg/kg/day)
What induction therapy is advised by BHIVA in cases of cryptococcal meningitis in HIV?

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Case: Treatment

Induction therapy
Ambisone 4mg/kg + Flucytosine
Induction therapy
Ambisone 4mg/kg + Flucytosine

ITU admission, while intubated
Initially required daily LP to maintain “safe” CSF pressure.

Unfortunately at time of extubation – Blind (cortical)

CD4 Count: 20    Viral load: 23,234
Case: Treatment

Patient received 4/52 of induction therapy

Ongoing LP for pressure maintenance.
Around every 72hrs - triggered by headaches

At end of induction:  
- CSF WCC 265 (100% lymph)  
- Protein 1.4  
- Gram -ve  
- Culture - sterile  
- CRAG 1:2560
Case: Treatment

2 wks into induction period, HAARVT initiated;

Truvada (TDF/FTC) T OD + Darunavir 800mg OD/ Ritonavir 100mg OD

CD4 Count: 20            Viral load: 23,234
Which of these is not a recommended regime for the consolidation phase, in the 2010 IDSA Crypto guidelines;

1. Fluconazole 800-1200mg 10-12wks
2. Weekly Liposomal amphotericin B 5mg/kg 10-12wks
3. Itraconazole 200mg Po BD 10-12wks
4. Lipid Amphotericin (1mg/kg/day) 4-6wks
5. Fluconazole 800mg Po OD + Flucytosine (100mg/kg/day) 6wks
Which if these is not a recommended regime for the consolidation phase, in the 2010 IDSA Crypto guidelines;

1. Fluconazole 800-1200mg 10-12wks
2. Weekly Liposomal amphotericin B 5mg/kg 10-12wks
3. Itraconazole 200mg Po BD 10-12wks
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5. Fluconazole 800mg PO OD + Flucytosine (100mg/kg/day) 6wks
Case: Consolidation phase

Ambisone/Flucytosine  ➔  Fluconazole
1200mg po od
Case: Consolidation phase

Ambisone/Flucytosine → Fluconazole
1200mg po od

LP requirement did not diminish

Transferred to our hospital, neurosurgical input.
EVD later converted to VP shunt
- Communicating hydrocephalus
1. Advanced HIV – Truvada/Darunavir/r
2. Cryptococcal meningitis
   Complicated by cortical blindness
   VP shunt due to communicating hydrocephalus
   Consolidative phase: Fluconazole

Stabilised
Discharged to OPD care

CD4 Count: 20      Viral load: undetected
Case: OPD

Two further admissions;
1. Investigation of recurrent vomiting
2. Investigation of fever/lymphadenopathy
Continued to receive Fluconazole 1200mg po od

As OPD:
- CSF WCC 24 (100% lymph)
- Gram - Yeast
- Cultures - sterile
- CRAG 1:2560

CD4 Count: 30  Viral load: undetected
Case: Readmission

Attended with tonic-clonic seizures (10 months after discharge from 1st admission)

At representation:
- CSF WCC 3
- Protein 8.4
- Gram -ve
- Culture - sterile
- CRAG >1:2560

CT venogram – No evidence of VST
No visible cryptococcoma

CD4 Count: 40    Viral load: undetected
Case: Re-intensification

Our options:

- Liposomal amphotericin + Flucytosine
- Voriconazole
- Fluconazole/Flucytosine
- Itraconazole
Case: Re-intensification

Our options:

- Liposomal amphotericin + Flucytosine
- Voriconazole
- Fluconazole/Flucytosine
- Itraconazole – suboptimal v fluconazole
Case: Re-intensification

Our options:

- Liposomal amphotericin + Flucytosine
- Voriconazole – Visual hallucination so discontinued
- Fluconazole/Flucytosine
- Itraconazole
Case: Re-intensification

Our options:

- Liposomal amphotericin + Flucytosine
- Voriconazole
- Fluconazole/Flucytosine
- Itraconazole

Ambisone 6mg/kg + Flucytosine 6/52
Case: Re-intensification

Ambisone 6mg/kg + Flucytosine 6/52

Onset: CSF  WBC 0  (-ve Gram/Sterile)
       Protein 8.4   CRAG >1:2560

3/52:   CSF  WBC 0  (-ve Gram/Sterile)
       Protein 6.65  CRAG >1:2560

6/52:   CSF  WBC 0  (-ve Gram/Sterile)
       Protein 7.52  CRAG >1:2560
Case: Re-intensification

Failed re-intensification
No improvement in CSF CRAG/Protein

Voriconazole intolerant
Previous failure on high dose fluconazole
No evidence of cryptococcoma

Still no reconstitution

What now?

CD4 Count: 60      Viral load: undetected
Isavuconazole

Novel Triazole
Broad spectrum of activity inc mucoraceous moulds
(Maintaining yeast and mould activity of early azoles)

Good oral bioavailability
Metabolism via CYP3A4 & UGT glucuronidation
TABLE 1 Pooled MIC distributions and ECVs for the *Cryptococcus neoforms*-*Cryptococcus gattii* species complex and isavuconazole using the CLSI M27-A3-RPMI microdilution method

<table>
<thead>
<tr>
<th>Species</th>
<th>No. of isolates</th>
<th>No. of isolates with an MIC$^a$ (μg/ml) of:</th>
<th>MIC range (μg/ml)$^b$</th>
<th>Mode (μg/ml)$^d$</th>
<th>ECV (μg/ml)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.008</td>
<td>0.016</td>
<td>0.03</td>
<td>0.06</td>
</tr>
<tr>
<td><em>C. neoforms</em> VNI$^e$ (AFLP1)</td>
<td>870</td>
<td>68</td>
<td>270</td>
<td>274</td>
<td>213</td>
</tr>
<tr>
<td><em>C. neoforms</em> (nongenotyped)</td>
<td>438</td>
<td>10</td>
<td>135</td>
<td>170</td>
<td>96</td>
</tr>
<tr>
<td><em>C. gattii</em>$^e$</td>
<td>406</td>
<td>23</td>
<td>78</td>
<td>106</td>
<td>87</td>
</tr>
</tbody>
</table>

$^a$ MICs were pooled from three or four of the six collaborating laboratories that submitted qualifying data for each cryptococcal group.

$^b$ MICs as determined by the CLSI broth microdilution method using standard RPMI 1640 broth.

$^c$ ECVs comprising ≥95% and ≥97.5% of the statistically modeled MIC population.

$^d$ Most frequent MIC.

$^e$ *C. gattii* comprises the VGI through VGIV (also known as AFLP4 through AFLP7 and AFLP10) genotypes.

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**Isavuconazole Treatment of Cryptococciosis and Dimorphic Mycoses**

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Case: Isavuconazole consolidation

Isavuconazole 200mg po od

Onset:  CSF  WBC 0 (-ve Gram/Sterile)
       Protein 7.5     CRAG >1:2560

2/12:   CSF  WBC 1 (-ve Gram/Sterile)
       Protein 4.9     CRAG 1:2560

4/12:   CSF  WBC 0 (-ve Gram/Sterile)
       Protein ND     CRAG 1:640

10/12:  CSF  WBC 0 (-ve Gram/Sterile)
       Protein ND     CRAG 1:640

22/12:  CSF  WBC 0 (-ve Gram/Sterile)
       Protein 6.58    CRAG 1:320
Case: Outcome

1. Advanced HIV – CD4 60 (8%) Undetectable V/L
   Failure to immune reconstitute
   Descovy (TAF/FTC) + Rezolsta (Darun/cobi)

2. Chronic Cryptococcal meningitis
   Complicated by cortical blindness/VP shunt
   Long term Isavuconazole therapy ?suppressive
Failure to reconstitute (Immunological non-responders)

CD4+ count increase, on attaining viral suppression is individually variable.

Subset of patients (10-15%) do not experience a significant increase in their counts. Termed immunological non-responders
Factors involved in non-response:

- Advanced disease at diagnosis
- Thymus exhaustion/Bone marrow failure
- Persistent T cell apoptosis
- Residual (“Privileged/reservoir site”) viral replication
  - lymphoid tissue
  - CSF
  - latently infected CD4+ cells
Case: The future

At home – living with 24hr care from father/sister
Ongoing investigation for lack of immune reconstitution.
Continue Isavuconazole indefinitely ??????
Thank you. Any question?