Clinical Trial Design for Mould-active Agents: Time to Break the Mold

Aspergillosis in Neutropenic Patients

Elias Anaissie, MD, Vice-Chair, Myeloma Institute for Research and Therapy, UAMS, Little Rock, AR
Lecture Outline

- PET/CT: Show & Tell
- A Patient with Aspergillosis
- Immunity confounds assessment
- Aspergillus Galactomannan
  - For diagnosis
  - For outcome assessment
FDG-PET Scan For Diagnosing Infection

176 episodes, 153 patients

Various Sites:
- Respiratory (106): Pneumonia (99); Sinusitis (7)
- Vascular (21): Septic phlebitis (13); Implanted CVL (8)
- Discitis/osteomyelitis/septic arthritis: (21) Cellulitis (6)
- Periodontal abscess (10)
- Gastrointestinal (9): colitis (8), abscess (3) esophagitis (1)

Different Pathogens:
Bacteria 41, fungi 15 (IA), P. carinii: 2, viruses 2, mycob 2

Regardless of Immune Status:
Effective in severe immunosuppression: 37, (20%)
Clinically contributory in 84 patients (55%)
20 silent infections detected on PET for Ca staging

Mahfouz et al. J Clin Oncol 2004
Septic Thrombophlebitis

Miceli M, J Clin Oncol 22 (8); 1529-1531; 2004
Miceli M, Nucl Med Comm (8); 813-818, 2004
Miceli M, J Clin Oncol 22; 1949; 2004
FUO. Non-neutropenic. Normal LFTs.
A Patient with Aspergillosis

68 y.o male, MYELOMA
8/29/05:
Auto-Tx; fluco prophylaxis
9/2: ANC <100.
Fever, CT chest (-)
9/7: (+) GMI (x3 up to 6.0)
9/9: ANC>1000
Sputum (+) A. fumigatus
Ambisome
9/10: GMI (-)
9/11:↑SOB, O2↓ ICUCT: bil infilt, nodules

Management: Methylprednisone 1 mg/kg BID (9/11-13), Ambisome

Outcome: CR; CT (-); repeatedly (-) GMI; Alive and well 28 mo. later
The restored ability to mount an inflammatory response against the antigens of an existing opportunistic infection

TB Abscess as part of IRIS In HIV (+) patient
It Gets Worse Before it Gets Better
IRIS in Aspergillosis

25 Neutropenic patients with tissue-proven IPA

Day 0 3 7 14
Cm³ 0 11 37 47 34
PMN med 0 0 930 normal

4X↑Volume

Refractory

84% resolved

Caillot J Clin Oncol 2001
Immunity Confounds Outcome: P-IRIS

P-IRIS in Aspergillosis
- 19 Hem. ca. (04-06), neutropenia
- ≥ 2 consecutive (+) GM (OD ≥ 0.5)
- Aspergillosis (EORTC/MSG)

- Clinical/radiologic deterioration with
  - Neutrophil recovery and
  - Microbiologic response: normal GMI

- Complete response, survival at 3 mo
  - Same antifungal therapy
  - Addition of steroids in 2 pts.

- Implications:
  Serial GM testing to guide management

Miceli et al., Cancer 2007
Assessing Aspergillosis Response: Difficult

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>PR</th>
<th>Stable Dz</th>
<th>Failure</th>
<th>Indt*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>attributable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>signs &amp; symptoms</td>
<td>Gone</td>
<td>Improve</td>
<td>Minor or no improvement</td>
<td>Worse s&amp;s</td>
<td>Can't tell</td>
</tr>
<tr>
<td><strong>Radiological:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>attributable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>abnormalities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mycological:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eradication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not stated (+) histology or culture</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Need Sensitive and Specific Marker for Outcome

- Unable to assess response: inadequate diagnostic evaluation, conflicting clinical, radiologic or mycologic data (P-IRIS) or presence of other factors such as other infection, GvHD, etc.
Diagnosing Aspergillosis: even more Difficult with Serious Impact on Clinical Trials

100 Patients

2/3 Missed

34

1/4 Can't Confirm IA

21

10 % Can't Tell Outcome

19

Need Sensitive, Specific Marker for Diagnosis and Outcome

Subira, 2003; Maertens, 2001; Herbrecht 2002; Denning 2005; Cornely 2007
Galactomannan Index Improves Diagnosis (I)

GMI vs. Clinical/Radiologic Diagnosis

Before: 31/48 (65%)

-25
-8
-1

~1 wk before

Simultaneous: 5/48 (10%)

After: 12/48 (25%)

Galactomannan

Clinical Diagnosis

95% (+)

<table>
<thead>
<tr>
<th>Cut off</th>
<th>0.5</th>
<th>0.6</th>
<th>0.7</th>
<th>0.8</th>
<th>0.9</th>
<th>1.0</th>
<th>1.5</th>
<th>2 x 0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>97.4</td>
<td>92.1</td>
<td>92.1</td>
<td>86.8</td>
<td>84.2</td>
<td>81.6</td>
<td>76.3</td>
<td>92.1</td>
</tr>
<tr>
<td>Specificity</td>
<td>90.5</td>
<td>93.0</td>
<td>94.5</td>
<td>95.5</td>
<td>96.5</td>
<td>96.5</td>
<td>97.5</td>
<td>97.5</td>
</tr>
<tr>
<td>PPV</td>
<td>66.1</td>
<td>71.4</td>
<td>78.6</td>
<td>78.6</td>
<td>82</td>
<td>81.6</td>
<td>85.3</td>
<td>87.5</td>
</tr>
<tr>
<td>NPV</td>
<td>99.4</td>
<td>98.4</td>
<td>97.5</td>
<td>97.5</td>
<td>97</td>
<td>96.5</td>
<td>95.6</td>
<td>98.5</td>
</tr>
</tbody>
</table>
Serum GMI and Outcome

A Very Strong Correlation

Serum Aspergillus Galactomannan

- Improves Outcome Assessment of IA
- Qualifies as a Surrogate Endpoint
GMI Predicts Outcome and Survival

Survival of 56 pts with Hem. Ca and IA according to GMI

Aspergillus GMI (-)

Aspergillus GMI (+)

## Serum GMI, a “Validated” Surrogate Endpoint Using Stringiest Criteria (I)

<table>
<thead>
<tr>
<th>Biological Plausibility</th>
<th>✔</th>
</tr>
</thead>
<tbody>
<tr>
<td>In causal chain of disease, in proximity to clinical endpoint</td>
<td>✔</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome Prediction</th>
<th>✔</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captures net effect of intervention on clinical outcome</td>
<td>✔</td>
</tr>
<tr>
<td>Consistently sensitive to effects of the intervention</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Predicts clinical outcome:</strong> changes in mechanistically compatible direction, rate, temporal sequence</td>
<td>✔</td>
</tr>
</tbody>
</table>

**Experimental:** Quantitative and qualitative concordance between GMI and survival, histopathology and microbiology. Effects present in different species and sizes (rat, mouse, guinea pig, rabbit, dog) ✔

**Clinical trials:** Strong concordance with outcome (KCC) ✔

**Validated** in trials for a specific disease and population ✔

Anaissie E, Clin Infect Dis May 07
Serum GMI, a “Validated” Surrogate Endpoint Using Stringiest Criteria (II)

<table>
<thead>
<tr>
<th>Good Test Attributes</th>
<th>✔</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standardized, quantifiable, reproducible, non-invasive</td>
<td>✔</td>
</tr>
<tr>
<td>Short latency to observation of effects</td>
<td>✔</td>
</tr>
<tr>
<td>Generic: Tracks all therapies equally (all classes) *</td>
<td>✔</td>
</tr>
<tr>
<td>Representative of disease burden</td>
<td>✔</td>
</tr>
<tr>
<td>Dichotomous and quantitative</td>
<td>✔</td>
</tr>
<tr>
<td>Valid for all species/ infection sites</td>
<td>✔</td>
</tr>
</tbody>
</table>

Anaissie E, Clin Infect D is 2007

* Paradoxical effect with echinocandins: not so paradoxical after all

## Validating Surrogates

### Correlation Concordance

<table>
<thead>
<tr>
<th>Surrogate success</th>
<th>Surrogate failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical success</td>
<td>A</td>
</tr>
<tr>
<td>Clinical failure</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>D</td>
</tr>
</tbody>
</table>

Kappa coefficient of correlation:

- \( 0 < k < 0.4 \) = marginal (or no) agreement
- \( 0.4 \leq k < 0.75 \) = good agreement
- \( k \geq 0.75 \) = excellent agreement

John H. Powers, MD  
Lead Medical Officer  
Antimicrobial Drug Development and Resistance Initiatives  

[www.FDA.gov](http://www.FDA.gov)  

Validating Surrogates
Correlation Concordance Lit Review

% success with surrogate

Serum GMI vs. Aspergillosis
Literature review: 1994-2007

257 Pts: KCC 0.86
Woods G et al, Cancer 2007
## Validating Surrogates

### Correlation Concordance

| Hem. Cancer | Aspergillosis | \( \geq 2 \text{ cons. (+) GM} \) | Serial Testing | Arkansas Experience |

### Kappa Correlation Coefficient (KCC) GMI and Survival

- 56 pts: Auto-Tx (21), allo (3), other (32)
- KCC GMI & Survival:

<table>
<thead>
<tr>
<th></th>
<th>KCC (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>.8609 (.7093-1.000)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Neutropenic</td>
<td>.8271 (.6407-1.000)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Non-neutropenic</td>
<td>1.0</td>
<td>.0083</td>
</tr>
</tbody>
</table>

GMI Predicts Outcome incl. Survival

Survival of 56 pts with Hem. Ca and IA according to GMI

Aspergillus GMI (-)

Aspergillus GMI (+)

**Validating Surrogates Correlation Concordance**

<table>
<thead>
<tr>
<th>Literature</th>
<th>Proven/Probable IA</th>
<th>Sequential testing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(within 1 wk of outcome)</td>
</tr>
</tbody>
</table>

KCC between GMI and Survival Literature (27 pub):

- 257pts; Hem. Ca. auto-Tx, allo-Tx, oth.
- 3 outcomes:
  - Survival (survival/death)
  - Global (survival/death incl. autopsy)
  - Autopsy (autopsy findings only)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>KCC (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>.8737 (.8140-.9333)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Global</td>
<td>.9123 (.8617-.9629)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Autopsy</td>
<td>.8498 (.5608-1.000)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

KCC for all outcomes comparable across age groups (peds and adults) and treatment modalities including allo-HSCT.

Miceli M et al., Clin Inf Dis March 2008
<table>
<thead>
<tr>
<th>&quot;Limitations&quot; of GMI: False (+) &amp; (-) vs. diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td>- rarely available</td>
</tr>
<tr>
<td>- non-specific</td>
</tr>
<tr>
<td>- unvalidated</td>
</tr>
<tr>
<td>- transient</td>
</tr>
</tbody>
</table>

- Test Performance: always compare to Gold Standard

For Aspergillosis: Autopsy

- False (+): 1.3%
- False (-): 2.6%

Exceptions:
- Pip-Tazo, amox-clav
- Mould prophylaxis

Maertens J. JCM 199  Rovira M Transpl. 2004
Moragues MD Rev Iberoam Micol 2003
The Diagnosis & Management of IA is Difficult

Serum Aspergillus Galactomannan: excellent surrogate marker for diagnosis and surrogate endpoint for outcome assessment

Implications for patient care & novel trial strategies

Now is the time to break the mold of conventional clinical trials for Aspergillus-active agents

Anaissie E. Clin Infect Dis, May 07