Cyclical caspofungin for chronic pulmonary aspergillosis in sarcoidosis

Abstract In sarcoidosis, chronic pulmonary aspergillosis (CPA) may be associated with significant morbidity, and treatment failure rates are often high, even with newer triazole antifungal agents. We report a treatment regimen of cyclical caspofungin infusions in 10 patients with sarcoidosis and worsening CPA despite oral triazoles.

Chronic pulmonary aspergillosis (CPA, including aspergilloma) complicates 3–12% of cases of sarcoidosis, and treatment failure rates remain high, even with newer triazole antifungals. We report a successful treatment regimen of cyclical caspofungin infusions in patients with sarcoidosis and worsening CPA despite oral triazoles.

Sarcoidosis and CPA were diagnosed in accordance with published criteria (described in the online supplement). Ten patients (six men; mean age 43.9±9.0 years) received treatment with caspofungin between 2008 and 2012. Nine patients were treated with oral triazoles (itraconazole n=5, voriconazole n=4) for a minimum of 4 months (up to 24 months) prior to caspofungin. Nine patients were receiving prednisolone (median dose 12.5 mg/day; range 7.5–20 mg), with four patients receiving additional immunosuppressive therapy (methotrexate n=1, azathioprine n=3). High-resolution CT (HRCT) demonstrated destructive fibrocavitary pulmonary changes (including aspergilloma) in all patients (figure 1). Detailed patient information (including treated disease course) is summarised in the online supplement.

Caspofungin was initiated due to progressive pulmonary fungal disease (including weight loss) in seven patients and triazole intolerance (rash, hair loss) in two patients. In the 12 months prior to caspofungin, all patients reported worsening respiratory symptoms (including recurrent haemoptysis in six patients), with deteriorating HRCT imaging in nine patients. Lung function deteriorated in seven patients, with a reduction in median total lung diffusion for carbon monoxide (DLco) from 42% (range 33–73%) to 34% (range 24–70%) (p=0.05) and a trend downward in spirometric lung volumes. Five patients lost weight (3–6 kg), and three patients were underweight (body mass index (BMI) 15.5–19.0) at the time caspofungin was commenced.

Caspofungin infusions were repeated every 12–16 weeks, with maintenance itraconazole (n=6) or voriconazole (n=4) between infusions. During a median follow-up of 16.5 (1–32) months, patients received between one and nine (median of six) cycles of caspofungin. Immunosuppression (including prednisolone) remained unchanged. In nine patients, symptoms (including haemoptysis) and inflammatory markers improved rapidly, with a decrease in median C reactive protein (CRP) from 31 (range 3–94) to 15 (range 3–23) (p=0.02) within 3 months, and sustained improvements in CRP at 6 months (CRP 4; range 1–14) and 12 months (median CRP 11; range 6–14). BMI normalised in two patients (with weight gain of 6 kg and 9 kg) and remained low (although improved) in one patient. In contrast with previous deterioration, HRCT appearances (assessed blinded to treatment) improved in four patients and remained stable in three. In two patients who did not undergo repeat HRCT, repeat chest radiographs stabilised. Follow-up imaging was unavailable in one patient, who died 1 month after caspofungin was commenced. In contrast with deteriorating pulmonary function tests in the 12 months prior to caspofungin, median forced vital capacity and DLco stabilised in the 12 months following caspofungin (see online supplementary table S1). Two patients died during follow-up (of progressive respiratory failure after 4 weeks and cor pulmonale after 32 months).

CPA in sarcoidosis is notoriously difficult to treat and is often associated with a dismal long-term prognosis. Our results suggest that caspofungin may offer a safe and effective therapy in patients with sarcoidosis and progressive CPA.

Gregory J Keir, Benjamin Garfield, David M Hansell, Michael R Loebinger, Robert Wilson, Elisabetta A Renzoni, Athol U Wells, Toby M Maher
Royal Brompton Hospital, London, UK

Correspondence to Dr Toby M Maher, Intestinal Lung Disease Unit, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK; t.maher@rbht.nhs.uk

Contributors GJK, BG and TMM performed data collection, analysis and prepared the manuscript. MRL, RW, EAR and AUM were involved in patient care, contributed to and reviewed the final manuscript. DMH provided radiology input and reviewed the final manuscript. GJK acts as guarantor for overall content of the manuscript.
Supplementary appendix

Diagnostic criteria for sarcoidosis and chronic pulmonary aspergillosis (CPA).

In the current study, a diagnosis of CPA was confirmed if the following criteria (proposed by Denning et al) [1] were fulfilled;

1. Progressive pulmonary cavitation with associated cavity wall thickening on chest radiography or cross-sectional imaging
2. Positive *Aspergillus* antibody titre or isolation or visualisation of *Aspergillus* species on a biopsy specimen from the lung or pleura
3. Elevated values for inflammatory markers (including CRP)
4. Constitutional or pulmonary symptoms lasting for at least 3 months
5. Exclusion of other possible causes that may mimic this syndrome (eg TB or malignancy)

This criteria also included the absence of significant systemic immunosuppression (eg prednisolone >7.5 mg/day) as a diagnostic criteria, although this criteria was not applied in the current study due to the co-existence of sarcoidosis and its requirement for immunosuppression to maintain disease control. Sarcoidosis was diagnosed in accordance with internationally accepted guidelines [2].

Monitoring response to therapy

Validated criteria with which to judge treatment response of CPA occurring in the context of sarcoidosis are not available. In the current study, response to therapy was based upon a composite of changes in symptoms, radiology, inflammatory markers and pulmonary function tests. Previously proposed criteria [1] for radiologic improvement include;

1. Reduction in cavity size/number
2. Reduction in pericavitary/pleural thickening

3. Loss of the intracavitary fungus ball.

In the current study, seven patients had improvement (n=4) or stability (n=3) of CT imaging (and stability of chest radiograph appearances in two additional patients without follow-up CT imaging) compared with deteriorating CT appearances in all patients in the 12 months prior to caspofungin commencement.

Pulmonary function tests (PFTs) were incorporated in assessing disease severity and monitoring treatment response. We hypothesized that a response to caspofungin may be associated with a reduction in airspace consolidation and interstitial change (as observed in HRCT imaging), which would be reflected in improvements in forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLco). Stabilisation of previously declining PFTs (prior to caspofungin) provides some support for this hypothesis, and changes in PFTs tended to parallel changes in radiology and symptoms.
References


Supplementary table 1.

Baseline patient characteristics, including immunosuppression, anti-fungal therapy and symptoms (including weight loss), in the 12 months prior to caspofungin initiation. Changes in radiology and pulmonary function testing are summarised for the 12 months before, and following commencement of caspofungin.

<table>
<thead>
<tr>
<th>Age/Gender</th>
<th>Ethnicity</th>
<th>Smoker (pk/yr)</th>
<th>Antifungals pre caspofungin</th>
<th>Immunosuppression pre caspofungin</th>
<th>Caspocycles</th>
<th>FU (mths)</th>
<th>Haemoptysis</th>
<th>Chronic sputum production</th>
<th>PTX</th>
<th>Weight</th>
<th>FVC%</th>
<th>DLco%</th>
<th>ΔFVC%</th>
<th>ΔDLco%</th>
<th>Radiology</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td>46.9 F</td>
<td>Afro-Caribbean</td>
<td>Ex (10 pk/yr)</td>
<td>itraconazole</td>
<td>pred 20 mg/day MTX 10 mg/week</td>
<td>8</td>
<td>32*</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>stable</td>
<td>HRCT worse</td>
<td>HRCT stable</td>
<td>-23.7</td>
<td>-14.8</td>
<td>54.0</td>
<td>28.0</td>
</tr>
<tr>
<td>39.3 F</td>
<td>Nigerian</td>
<td>never</td>
<td>voriconazole</td>
<td>pred15 mg/day</td>
<td>9</td>
<td>28</td>
<td>y</td>
<td>y</td>
<td>n</td>
<td>-3 kg</td>
<td>HRCT worse</td>
<td>HRCT better</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>37.6 M</td>
<td>Caucasian</td>
<td>Ex (6 pk/yr)</td>
<td>voriconazole</td>
<td>pred 15 mg/day</td>
<td>4</td>
<td>24</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>+2 kg</td>
<td>HRCT worse</td>
<td>HRCT stable</td>
<td>-6.9</td>
<td>-5.7</td>
<td>102.0</td>
<td>70.0</td>
</tr>
<tr>
<td>47.6 M</td>
<td>Afro-Caribbean</td>
<td>Ex (10 pk/yr)</td>
<td>itraconazole</td>
<td>pred 12.5 mg/day aza100 mg/day</td>
<td>8</td>
<td>19</td>
<td>y</td>
<td>y</td>
<td>n</td>
<td>-6 kg</td>
<td>HRCT worse</td>
<td>HRCT better</td>
<td>5.6</td>
<td>-6.3</td>
<td>51.0</td>
<td>31.0</td>
</tr>
<tr>
<td>39.7 M</td>
<td>Caucasian</td>
<td>never</td>
<td>itraconazole</td>
<td>pred 15mg/day</td>
<td>8</td>
<td>30</td>
<td>n</td>
<td>y</td>
<td>y</td>
<td>stable</td>
<td>HRCT worse</td>
<td>HRCT better</td>
<td>.</td>
<td>-2.6</td>
<td>89.0</td>
<td>61.0</td>
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<tr>
<td>60.2 M</td>
<td>Indian</td>
<td>never</td>
<td>itraconazole</td>
<td>nil</td>
<td>1</td>
<td>1*</td>
<td>n</td>
<td>y</td>
<td>n</td>
<td>-4 kg</td>
<td>HRCT stable</td>
<td>n/a</td>
<td>-18.8</td>
<td>-35.1</td>
<td>38.0</td>
<td>28.0</td>
</tr>
<tr>
<td>53.6 F</td>
<td>Caucasian</td>
<td>Current (30 pk/yr)</td>
<td>voriconazole</td>
<td>pred 7.5 mg/day</td>
<td>7</td>
<td>14</td>
<td>y</td>
<td>y</td>
<td>n</td>
<td>stable</td>
<td>HRCT worse</td>
<td>HRCT stable</td>
<td>-6.3</td>
<td>-22.9</td>
<td>51.0</td>
<td>34.0</td>
</tr>
<tr>
<td>31.1 F</td>
<td>Caucasian</td>
<td>never</td>
<td>voriconazole</td>
<td>pred 12.5 mg/day aza100 mg/day</td>
<td>4</td>
<td>12</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>-2.3 kg</td>
<td>HRCT worse</td>
<td>CXR stable</td>
<td>10.0</td>
<td>5.3</td>
<td>61.0</td>
<td>40.0</td>
</tr>
<tr>
<td>48.3 M</td>
<td>Caucasian</td>
<td>never</td>
<td>voriconazole</td>
<td>pred10 mg/day aza 50 mg/day</td>
<td>5</td>
<td>10</td>
<td>n</td>
<td>y</td>
<td>y</td>
<td>-6 kg</td>
<td>HRCT worse</td>
<td>CXR stable</td>
<td>-39.3</td>
<td>-38.5</td>
<td>38.0</td>
<td>24.0</td>
</tr>
<tr>
<td>35.1 M</td>
<td>Caucasian</td>
<td>never</td>
<td>voriconazole</td>
<td>pred 15mg/day</td>
<td>1</td>
<td>7</td>
<td>y</td>
<td>y</td>
<td>n</td>
<td>+5 kg</td>
<td>HRCT worse</td>
<td>CXR stable</td>
<td>16.0</td>
<td>12.5</td>
<td>56.0</td>
<td>54.0</td>
</tr>
</tbody>
</table>

* Patient deceased

Abbreviations:

F/U=follow-up, PTX=pneumothorax, FVC=forced vital capacity, DLco=diffusing capacity of the lung for carbon monoxide, pred=prednisolone, MTX=methotrexate, aza=azathioprine, HCQ=hydroxychloroquine, HRCT= high resolution computed tomography