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Therapeutic drug monitoring and adverse events of delayed-release posaconazole tablets in patients with chronic pulmonary aspergillosis

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Background: Posaconazole delayed-release tablets offer better bioavailability than the liquid suspension, but no post-marketing data are available in immunocompetent hosts such as those with chronic pulmonary aspergillosis (CPA).

Objectives: To explore the pharmacokinetics and adverse event (AE) profile of posaconazole tablets in patients with CPA.

Methods: Patients started on posaconazole tablets at the National Aspergillosis Centre (NAC), Manchester, UK between February 2014 and October 2015 were identified from the NAC database and analysed retrospectively. The medical records were reviewed for factors that could affect posaconazole serum levels and the development of AEs.

Results: Seventy-two patients were included; 50 (69%) were male and the mean age was 48.5 ±12 years. Therapeutic levels (≥1 mg/L) were achieved in 90% of cases on 200 mg versus 90% of cases on 300 mg daily (P=not significant). Based on multivariate analysis, female sex (P=0.041), a 100 mg daily dose (P<0.001), asthma (P=0.01) and bronchiectasis (P=0.001) were associated with subtherapeutic levels. Forty-nine (68%) patients developed AEs, mainly fatigue (37%), dyspnoea (18%) and nausea (12%). AEs were present on 115/196 (59%) occasions on 300 mg/day and on 45/115 (39%) occasions on 200 mg/day (P<0.01). The mean level was 1.81 ±0.96 mg/L for patients reporting no AEs and 1.90 ±1.11 mg/L for those reporting AEs (P=not significant). Factors associated with AEs of grade ≥2 were a daily dose of 300 versus 200 mg (P=0.001) and asthma (P=0.008).

Conclusions: A lower-than-recommended posaconazole tablet dose achieved therapeutic levels in most patients and was better tolerated. Males were more likely to achieve a therapeutic level. Underlying conditions affected the degree and frequency of AEs.

Introduction

Posaconazole is a broad-spectrum azole used for prophylaxis and treatment of systemic fungal disease in immunocompromised patients, such as those with haematological malignancies or haematopoietic stem cell transplant recipients. It also has a role in immunocompetent hosts, such as those with chronic pulmonary aspergillosis (CPA).[1] Previously, posaconazole liquid suspension was the only orally available formulation. Its use was limited by a reliance on a high-fat meal to increase bioavailability and the need for multiple daily dosing due to satiable absorption. This resulted in subtherapeutic levels in a substantial number of patients.[2] More recently, a delayed-release tablet has become available, offering more consistent absorption and achieving improved drug serum levels.[3] The adverse event (AE) profile with this tablet is favourable, although its high cost remains a limitation. Therapeutic drug monitoring (TDM) is still recommended for the tablet formulation in haematological patients, as a number may still not reach therapeutic levels.[4] Use of proton pump inhibitors (PPIs), a higher BMI,

diarrhoea and graft versus host disease have all been associated with subtherapeutic levels in this population.[5,6]

In theory, the better bioavailability offered by the tablet could result in higher exposure and more AEs. However, the switch from liquid to tablet formulation did not result in increased toxicity in haematological patients[3,7–9] or lung transplant patients.[10] On the other hand, AEs have been reported in a few patients on tablets who achieved high serum drug levels: 3 out of 78 lung transplant patients developed fatigue, lethargy and weight loss with levels >2 mg/L, and 1 patient developed visual hallucinations with a level >10 mg/L.[11,12] In contrast, hepatotoxicity was not found to correlate with serum concentration in a study of cancer patients.[13]

Although posaconazole pharmacokinetics and tolerability have been studied extensively in the immunocompromised population and healthy volunteers, little information is available on immunocompetent patients such as those with CPA. Itraconazole and voriconazole are the first-line options for treatment of CPA, with posaconazole an alternative option, due to its high cost. Patients with CPA typically require more prolonged treatment than those with invasive fungal disease, making the issues of toxicity, resistance and cost more relevant. In addition, these patients may absorb the drug better and achieve higher posaconazole levels, as they generally do not have diarrhoea or mucositis, common in immunocompromised patients, and fewer are on PPIs. Non-transplant patients with pulmonary disease appear to achieve significantly higher levels than transplant patients.[14] On the other hand, some patients with advanced or extensive CPA have a very low BMI, making them potentially more susceptible to AEs.

In summary, the best approach for dosing and monitoring posaconazole tablets in immunocompetent patients is not known. The National Aspergillosis Centre (NAC) in Manchester, UK sees >120 new patients with CPA yearly and posaconazole tablets have been used for several years. We retrospectively analysed the pharmacokinetics and tolerability of posaconazole tablets in a cohort of patients with CPA.

Methods

The NAC database was searched for patients who were prescribed posaconazole tablets between February 2014 and October 2015. All patients were included irrespective of treatment duration. Current practice at the NAC is to start treatment with 300 mg of posaconazole daily in most patients or 200 mg daily in a subset of patients who, based on clinical judgement, are less likely to tolerate the higher dose, e.g. patients with low BMI, the elderly and those with high levels on a prior azole. Treatment is started without a loading dose as there is no urgency to achieve therapeutic levels in this patient population and, based on experience in the NAC, AEs leading to treatment discontinuation are more likely when a loading dose is used. Treatment is started in the outpatient setting in almost all cases. Patients have access to a Specialist Nurse by telephone to report any AEs and are seen in clinic according to clinical need.

After starting treatment, patients are normally reviewed in clinic at 4 weeks and then every 3 months. Samples are collected for TDM (random level), full blood count and renal and hepatic function tests a week before the clinic appointment. TDM is done using a validated bioassay by the NHS Mycology Reference Centre Manchester.[15] A level of ≥1 mg/L is considered therapeutic.[16] A level of <1 mg/L leads to a dose escalation by 100 mg/day. A level of >3.5 mg/L leads to a dose reduction of 50–100 mg/day, e.g. from 300 mg/day to 300 and 200 mg on alternate days. Reporting of AEs attributed to posaconazole leads to a reduction of dose provided the level can be kept ≥1 mg/L. Treatment is discontinued if the AEs are considered medically significant or debilitating.

Medical records were reviewed for patient demographics, underlying conditions, posaconazole blood levels, prescribed dose and changes, treatment discontinuation, use of PPIs, AEs clinically judged to be attributed to posaconazole and AE grade according to the common terminology criteria for AEs.[17] Statistical analysis was performed with SPSS version 23 for Windows. The effect of various risk factors on the probability of achieving a therapeutic level and on the development of AEs was assessed independently and in a multivariate model. Coefficient of variance (standard deviation/mean) was calculated to assess intra-patient variability of levels in patients who had seven or more measurements on the same dose. This study was a retrospective service evaluation and ethical approval was not required, as per UK Health Research Authority guidelines.

Results

Patient characteristics

Seventy-two patients were treated with posaconazole tablets during the study period. Fifty (69%) were male and the mean age was 48.5 ±12 years. Sixty-eight (94%) were white. All patients had previously been on at least one other oral mould-active triazole, but no one received concomitant antifungal therapy during posaconazole administration. Twenty (28%) patients had been previously treated for mycobacterial infection; 13 had TB and 7 had non-tuberculous mycobacterial infection. None of them was receiving concomitant antimycobacterial treatment. Twenty-four (33%) patients had a history of COPD, 18 (25%) had bronchiectasis, 11 (15%) had previous pneumothorax, 10 (14%) had asthma, 10 (14%) had allergic bronchopulmonary aspergillosis, 8 (11%) had previous lung surgery, 5 (7%) had severe pneumonia and 4 (6%) had sarcoidosis.

Posaconazole dosing and TDM

Posaconazole was administered for a mean of 381 days (range=5–1232 days). Sixty-one (85%) patients were started on 300 mg daily and 11 (15%) were started on 200 mg daily. In 14 (19%) patients TDM was not performed; 10 patients discontinued the drug due to AEs, 3 patients died before TDM was performed and 1 patient failed therapy with progression of the disease before levels were monitored. From those who stopped posaconazole due to AEs, seven had grade 3 AEs and three had grade 2 AEs. In 31 (43%) patients a dose adjustment was required; in 29 the dose was reduced.

A total of 384 measurements (mean of 5.3 per patient, range=0–15) were recorded. The overall mean posaconazole level was 1.94 mg/L (range=0.1–6.4 mg/L). Median and IQR levels for various dosing regimens are shown in Figure 1. The proportion of samples with a subtherapeutic level (<1 mg/L) for each dosing regimen and analysis for the factors associated with subtherapeutic levels are shown in Table 1. Significantly more measurements were below therapeutic level for doses of 100 and 200/100 mg, but no statistical significance was attained for the other comparisons. Eleven patients had seven or more measurements on the same dose (300 mg/day); the intra-patient variability is shown in Figure 2. For these patients, the mean coefficient of variance was 0.25 (range=0.12–0.46). No meaningful trend over time (i.e. upward or downward) in levels was observed in patients who had multiple measurements (data not shown).

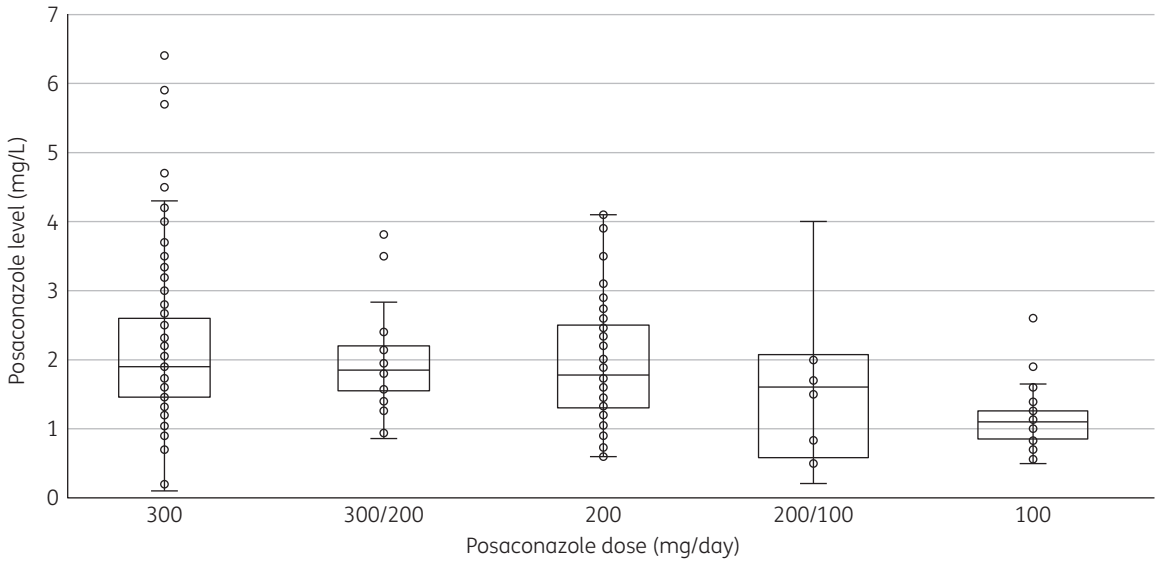

Figure 1. Median and IQR of posaconazole levels according to dosing regimen. Significant differences: 100 versus 200 mg/day ($P<0.001$), 100 versus 300/200 mg/day ($P=0.006$) and 100 versus 300 mg/day ($P<0.001$). The difference between 200 and 300 mg was not significant.

AEs

Forty-nine (68%) patients reported AEs attributed to posaconazole. Of these, 9 (18%) had grade 1 AEs, 22 (45%) had grade 2 AEs, 17 (35%) had grade 3 AEs and 1 (2%) had grade 4 AEs. AEs were: fatigue (37%), dyspnoea (18%), nausea (12%), headache (8%), peripheral neuropathy (8%), diarrhoea (6%), chest pain (6%), dizziness (5%), arthralgia (5%), dry skin (4%), hyponatraemia (4%) and hair loss (2%). Of the six patients who developed peripheral neuropathy with posaconazole tablets, three had previously had neuropathy with voriconazole and three developed neuropathy *de novo*. Seven patients who had previously had peripheral neuropathy with voriconazole ($n=5$) and itraconazole ($n=2$) did not experience worsening or redevelopment of peripheral neuropathy on posaconazole.

Forty-three of 61 (70%) patients started on daily doses of 300 mg, versus 5 of 11 (45%) patients started on 200 mg, developed AEs ($P=0.163$). AEs were present on 115/196 (59%) occasions in patients on 300 mg and on 45/115 (39%) occasions in patients on 200 mg ($P<0.01$). The mean level was 1.81 ± 0.96 mg/L for patients reporting no AEs versus 1.90 ± 1.11 mg/L for those with AEs ($P=0.661$). Seven patients (10%) had liver function test (LFT) abnormalities; five had grade 1 abnormalities and two had grade 2 abnormalities. In five of these seven, levels were measured as 0.8, 1.04, 1.63, 6.4 and 6.4 mg/L. In three cases, LFTs normalized when the dose was reduced from 300 to 200 mg, in one case they normalized with no change and in one case the drug was stopped. Risk factors for developing AEs of grade ≥ 2 are shown in Table 2.

Discussion

This is the first study, to our knowledge, examining the pharmacokinetics and side effect profile of the posaconazole tablet formulation in immunocompetent patients with CPA. Therapeutic levels were achieved in most patients, even with lower-than-recommended doses. A high frequency of side effects was observed, perhaps attributed to the higher levels obtained in this population compared with immunocompromised patients. Interestingly, we observed no relation between levels and toxicity; side effects appeared to correlate more closely with the prescribed dose than the level.

Approximately 1 in 10 patients, whether on 300 or 200 mg daily, did not achieve therapeutic levels. This shows that, even in this population of immunocompetent patients without mucositis or diarrhoea, TDM for posaconazole tablet treatment is still clinically relevant. On the other hand, the dose of 200 mg daily resulted in a similar proportion of subtherapeutic levels as the recommended 300 mg daily dose. This finding is supported by a population pharmacokinetic analysis by Petitcollin *et al*.,[18] which showed that a large proportion of patients with haematological malignancies can achieve adequate levels on 200 mg, especially if the level on the 300 mg dose is >1.5 mg/L. Interestingly, female patients were significantly more likely to achieve lower levels in our study, even when adjusted for other parameters such as body weight; this has been observed previously by Allegra *et al*.,[19] but not in other studies. It is possible that gender-related differences in drug metabolism, e.g. in the P-glycoprotein transporter, may play a role.[20]

More than half of patients reported side effects attributed by the treating physician to posaconazole. By far the most common side effect was fatigue. This has been reported previously in lung transplant recipients.[11] It is possible that this symptom might be due to the interaction of azoles with steroids, including inhaled steroids. This hypothesis is supported by the observation that patients with asthma reported fatigue more often than patients with other predisposing factors, such as those with previous TB, who are less likely to be on concomitant steroid inhalers. This association was not retained in multivariate analysis, however. Although every effort was made to switch to inhaled steroids that would be more compatible with posaconazole based on predicted drug interactions, the side effects still occurred frequently. Reversible adrenal insufficiency has been reported as a side effect of posaconazole.[21]

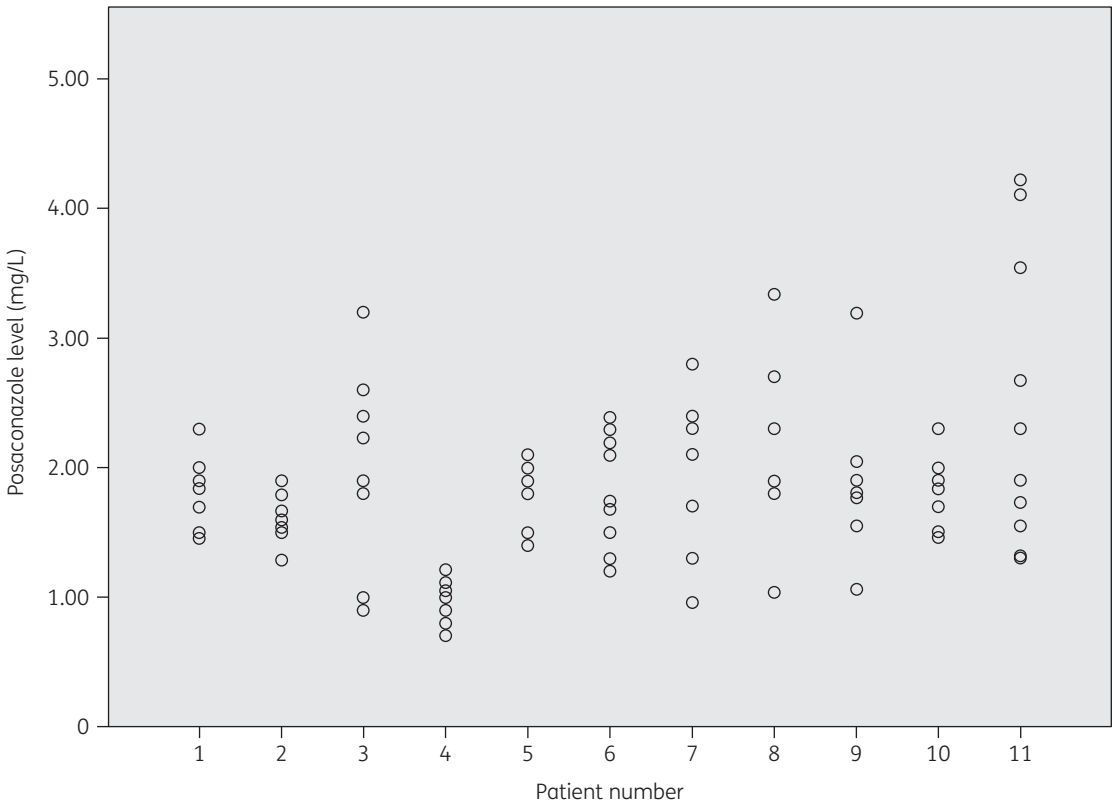

Figure 2. Posaconazole levels in patients with seven or more measurements on the same dose (300 mg/day).

Table 1. Risk factors resulting in a subtherapeutic posaconazole serum level

Risk factor	<1 mg/L	≥1 mg/L	*P* (univariate)	*P* (multivariate)
Dose (mg), *n*/*N* (%)				
300	19/189 (10.1)	170/189 (89.9)	reference	reference
300/200[a]	2/30 (6.7)	28/30 (93.3)	0.561	0.927
200	11/114 (9.6)	103/114 (90.4)	0.909	0.488
200/100[b]	3/8 (37.5)	5/8 (62.5)	0.029	0.053
100	15/43 (34.9)	28/43 (65.1)	<0.001	<**0.001**
Age (years), mean ± SD	59.88 ± 12.1	59.19 ± 11.4	0.69	
Weight (kg), mean ± SD	61.52 ± 14.75	67.61 ± 14.95	0.007	0.943
Sex, *n* (%)			0.004	**0.041**
male	27 (9.8)	248 (90.2)		
female	23 (21.1)	86 (78.9)		
Underlying condition, *n*/*N* (%)				
COPD	17/137 (12.4)	120/137 (87.6)	0.875	
TB	9/67 (13.4)	58/67 (86.6)	0.844	
asthma	12/47 (25.5)	35/47 (74.5)	0.011	**0.01**
bronchiectasis	3/73 (4.1)	70/73 (95.9)	0.011	**0.001**
PPI use, *n*/*N* (%)			0.516	
yes	18/122 (14.8)	104/122 (85.2)		
no	32/262 (12.2)	230/262 (87.8)		

P values retaining significance in multivariate analysis are shown in bold.
[a]Daily posaconazole dose alternating between 300 and 200 mg.
[b]Daily posaconazole dose alternating between 200 and 100 mg.

Table 2. Risk factors for developing AEs (grade ≥2) on posaconazole tablets

Risk factor	AEs	No AEs, *n* (%)	*P* (univariate)	*P* (multivariate)
Dose (mg), *n* (%)				
300	69 (34.3)	132 (65.7)	reference	reference
300/200[a]	0 (0)	30 (100)	0.998	0.998
200	19 (16.2)	98 (83.8)	0.001	**0.006**
200/100[b]	2 (25)	6 (75)	0.594	0.987
100	12 (27.9)	31 (72.1)	0.43	0.837
Age (years), mean ± SD	60.05 ± 10.91	59.00 ± 11.58	0.425	
Weight (kg), mean ± SD	65.13 ± 12.90	67.25 ± 15.65	0.221	
Sex, *n* (%)			0.889	
male	72/285 (25.3)	213/285 (74.7)		
female	29/112 (25.9)	83/112 (74.1)		
TDM level (mg/L), mean ± SD	2.01 ± 1.25	1.91 ± 0.91	0.451	
Underlying condition, *n*/*N* (%)				
COPD	41/142 (28.9)	101/142 (71.1)	0.279	
TB	11/69 (15.9)	58/69 (84.1)	0.049	0.061
asthma	20/48 (41.7)	28/48 (58.3)	0.008	0.141
bronchiectasis	21/76 (27.6)	55/76 (72.4)	0.661	
PPI use, *n*/*N* (%)			1.000	
yes	32/128 (25)	96/128 (75)		
no	69/269 (25.7)	200/269 (74.3)		

P values retaining significance in multivariate analysis are shown in bold.
[a]Daily posaconazole dose alternating between 300 and 200 mg.
[b]Daily posaconazole dose alternating between 200 and 100 mg.

It appears that prescribed dose was associated with the occurrence of side effects better than the measured level. This suggests that the serum concentration may not be the best predictor of toxicity, as it may not correspond to tissue concentration. Indeed, no correlation between levels and AEs, including liver toxicity and QT prolongation, was seen in two studies in haematological patients,[13,22] whereas Tverdek *et al*.[23] suggested a level of >1.83 mg/L as predictive of liver toxicity. In addition, side effects resolved in three patients when the level was brought down to <2 mg/L.[11] In our study, AEs were observed less often on the 200 mg daily dose compared with the usually recommended dose of 300 mg, although the number of patients starting with 200 mg was small. The possibility that 200 mg may be the optimal dose in CPA needs further study; this would be dramatically cost saving, with the cost of TDM being less than a single day of therapy at current UK prices.

This study has several limitations. Firstly, random rather than trough posaconazole levels were measured. Measuring random levels is more practical during routine clinical care as patients were seen in an outpatient clinic at different times of the day. However, the utility of measuring random levels in patients on long-term therapy is supported by the pharmacokinetics of posaconazole, which attains a steady-state after 1 week of administration and has a mean half-life of 29 h.[24,25] The timing of TDM was not identical in every patient, reflecting real-life limitations; however, samples were collected after at least 7 days of treatment in every case. Secondly, a cut-off of 1 mg/L was used according to recommendations,[16,26] although, in this patient group with chronic fungal disease and often a high fungal burden, e.g. in the form of aspergillomas, a higher level may be needed to prevent the emergence of resistance.[27] In addition, we did not correlate TDM with efficacy of treatment; this is much more challenging in patients with CPA who have more indolent disease compared with patients with invasive aspergillosis, and there are few well-defined criteria for clinical response. Finally, due to the retrospective nature of the study, AEs may have been missed or not documented fully in the medical notes. Also, weight rather than BMI was used for the analyses, as the latter information was not available.

In conclusion, in this real-life assessment of posaconazole tablet tolerance and TDM in a cohort of patients with CPA, a daily dose of 200 mg achieved similar levels to those obtained with the recommended 300 mg dose, but with a more favourable toxicity profile. Drug blood levels did not associate with side effects. Fatigue was by far the most common AE reported in this patient group. Interestingly, male patients appeared to achieve higher levels, an effect retained in multivariate analysis.

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This study was carried out as part of our routine work.

Transparency declarations

C. K. has received speaker and travel fees from Astellas. R. R.-R. has given lectures for Astellas, Basilea, Gilead and Pfizer, and has received conference attendance support from Astellas and Gilead. M. D. R. has received speaker fees from Gilead, Mylan, Astellas, MSD and Basilea, acts as a consultant for Gilead, Pulmocide, Pulmatrix and Pfizer, and is a long-standing member of

the ESCMID diagnosis and treatment guidelines writing groups. C. B. M has received travel support from Astellas, Pfizer and Gilead, has been paid for talks on behalf of Pfizer and has also received a research grant paid to the Mycology Reference Centre from Pfizer. D. W. D. and family hold Founder shares in F2G Ltd, a University of Manchester spin-out antifungal discovery company. D. W. D. acts or has recently acted as a consultant to Scynexis, Cidara, Quintiles, Pulmatrix, Pulmocide, Zambon, Roivant and Fujifilm, has been paid for talks on behalf of Astellas, Dynamiker, Gilead, Merck, Mylan and Pfizer in the last 3 years and is a long-standing member of the IDSA Aspergillosis Guidelines group, the ESCMID Aspergillosis Guidelines group and the British Society for Medical Mycology Standards of Care committee. I. R.-G.: none to declare.

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