BREAK POINT

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FROM THE NEWSLETTER EDITOR'S DESK

Welcome to the October edition of ASA *Breakpoint.* In this issue, *IN THE NEWS* gives us cause, or pause, to reflect on treatment options of MDR-TB and the all conquering gonococcus. Jeong *et al.* then provide perspective on the clinical experience of the use of intravenous posaconazole following its availability through Merck's Named Patient Program. The matter of therapeutic drug monitoring with this formulation of drug is raised. An upcoming conference synopsis follow. As always, suggestions for inclusion of material in the newsletter is welcome.

Sharon Chen
ASA Breakpoint Editor

CONTENTS

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IN THE NEWS

A. Option for shortened MDR-TB regimen in updated WHO guidelines

The conventional treatment regimen for multidrug-resistant tuberculosis (MDR-TB) consists of a fluoroquinolone, an injectable agent, and at least 2 other core second-line agents for 20 to 26 months. *Updated WHO guidelines present the option of a shortened regimen for nonpregnant patients with MDR-TB who have no extrapulmonary disease, an isolate known to be susceptible to fluoroquinolones and injectable antituberculous agents, and no prior exposure to second-line agents for more than one mont*h [1]. The shortened regimen consists of an intensive phase (4 to 6 months of high-dose isoniazid, ethambutol, pyrazinamide, gatifloxacin [or moxifloxacin], kanamycin, prothionamide, and clofazimine) followed by a continuation phase (5 months of ethambutol, pyrazinamide, gatifloxacin [or moxifloxacin], and clofazimine). Support for this regimen comes in part from a large study from Bangladesh that reported high rates of favourable bacteriologic outcomes with a similar 9 to 12-month regimen [2]. The new WHO guidance also indicates that patients with rifampin monoresistance should be treated as for MDR-TB. Patients with known or suspected MDR-TB who do not meet criteria for the shortened MDR-TB regimen cannot be treated with the shortened course regimen.

B. Treatment failure of pharyngeal gonorrhea following combination antimicrobial therapy

Because of concerns about the decreasing susceptibility of *Neisseria gonorrhoeae* to several classes of antibiotics, combination antimicrobial therapy with ceftriaxone plus a second agent, preferably azithromycin, is the recommended treatment for uncomplicated gonorrhea. However, treatment failure following combination therapy has now been reported, in a heterosexual man from the United Kingdom who presented with both urogenital and pharyngeal infection [3]. Although the urogenital infection was successfully treated with ceftriaxone plus azithromycin, the pharyngeal infection persisted, and decreased susceptibility to both agents was detected in the post-treatment isolate. This report, in addition to surveillance reports suggesting increasing rates of decreased susceptibility to azithromycin in *N. gonorrhoeae* isolates in the United States, highlights the need for novel treatment strategies for gonorrhea in the face of rising antimicrobial resistance

1. World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis: 2016 update. WHO, Geneva 2016. http://www.who.int/tb/MDRTBguidelines2016.pdf?ua=1 (Accessed on May 17, 2016).

2. Aung KJ, Van Deun A, Declercq E, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. Int J Tuberc Lung Dis 2014; 18:1180.

3. Fifer H, Natarajan U, Jones L, et al. Failure of Dual Antimicrobial Therapy in Treatment of Gonorrhea. N Engl J Med 2016; 374:2504.

INTRAVENOUS POSACONAZOLE IN PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES: REAL WORLD EXPERIENCE

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Introduction

The efficacy of posaconazole suspension as antifungal prophylaxis in the haematology setting is well described.[1] However, its use remains challenging particularly in patients with poor oral intake and/or impaired gastrointestinal absorption. Whilst, the recent posaconazole tablet formulation may potentially overcome the bioavailability issue inherent to posaconazole suspension,[2] it may not be suitable in patients with limited oral access. In this patient cohort, intravenous (IV) posaconazole could be a potential alternative.

Between 1st July 2014 and 12th March 2015, patients suspected to have reduced posaconazole suspension absorption due to gastrointestinal disturbances and/or those unable to tolerate alternative antifungals were eligible to access IV posaconazole via the Merck Sharp and Dohme Australia Named Patient Programme (NPP). The recommended dose for IV posaconazole was 300mg twice daily as a loading dose on the first day followed by 300mg once daily thereafter for up to 14 and 30 days for prophylaxis and treatment of IFD, respectively. IV posaconazole was reconstituted in 150mL of 5% dextrose or 0.9% sodium chloride solution and administered through an in-line filter over 90 minutes via a central venous line. In this report, we retrospectively evaluate and describe the use of IV posaconazole, provided under the aforementioned scheme, in seven Australian tertiary teaching hospitals, which provide treatment for haematological malignancies.

INTRAVENOUS POSACONAZOLE IN PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES: REAL WORLD EXPERIENCE CONT'D

Results

A total of 61 patients received 70 courses of IV posaconazole through the NPP. Sixty-one courses of IV posaconazole was prescribed to 52 patients as prophylaxis against invasive fungal disease (IFD), primarily due to concern about impaired gastrointestinal function secondary to the management of their underlying haematological malignancies. Nearly all patients were receiving posaconazole suspension prior to IV posaconazole prophylaxis. IV posaconazole was administered for median (IQR) duration of 10 (6-15) days and was ceased following improvement in gastrointestinal function. Following cessation of IV posaconazole prophylaxis, posaconazole suspension remained the most commonly prescribed antifungal prophylaxis. No episode of breakthrough IFD was observed during and at cessation of IV posaconazole prophylaxis.

Nine courses of IV posaconazole were prescribed for [median (IQR)] 19 (7-30) days for the treatment of four proven, four probable and one possible IFD, which were defined using the European Organisation for Treatment of Cancer/Mycoses Study Group criteria.[3] Treatment outcomes, as determined using previously published criteria[4], appeared to be favourable whereby, improvement in signs and symptoms of IFD was observed in five cases at cessation of IV posaconazole and six cases at 30 days post-cessation (Table 1). IV posaconazole was mainly administered as mono-therapy, apart from the three cases of mucormycete infection, in which combination therapy with liposomal amphotericin B was used. Surgical debridement was also performed in two of the three cases. Importantly, given the debilitating nature of mucormycosis, early initiation of antifungal therapy, aggressive surgical intervention and correction of predisposing factors are critical to ensure good patient outcomes.[5]

Posaconazole trough plasma concentration (C_{min}) was measured in 39 courses.The median (IQR) of the first C_{min}, taken [median (IQR)] 4 (3-7) days post-initiation of IV posaconazole, was determined to be 1.16 (0.69-2.06) mg/L. Although the administration of IV posaconazole appeared to afford C_{min} above 1mg/L, this was not consistently achieved in all patients. In addition, inter- and intra-patient variability in posaconazole C_{min} was apparent despite administration of similar dosing regimen (Figure 1). As such, regular monitoring of IV posaconazole C_{min} may be beneficial. However, there is currently no recommendation on IV posaconazole dose adjustment in the event of sub-therapeutic C_{min}. Interestingly, neither administration of loading doses nor prior posaconazole suspension exposure appeared to result in higher posaconazole C_{min}.

Overall, our experience suggested that IV posaconazole was well tolerated, acknowledging the potential reporting bias given that only adverse events documented by treating clinicians in the medical records as attributable to IV posaconazole were included. Six courses of IV posaconazole was discontinued following concern about thrombocytopenia in one and abnormal liver function in five, although the thrombocyte count and liver function did not recover seven days after cessation

INTRAVENOUS POSACONAZOLE IN PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES: REAL WORLD EXPERIENCE CONT'D

of IV posaconazole. These adverse events were unable to be specifically attributed to IV posaconazole given the patients' complex underlying conditions and concurrent use of potentially liver toxic and/or myelosuppressive drugs. Neither infusion related reactions nor episodes of QTc prolongation were documented, although the latter was not regularly monitored.

Conclusion

Acknowledging the limitation associated with the retrospective study design and small sample size, IV posaconazole appeared to be safe and clinically effective in preventing breakthrough IFD in patients undergoing treatment for haematological malignancies. In addition, IV posaconazole in combination with liposomal amphotericin B may have a promising role in the management of mucormycosis. Therapetic drug monitoring should be considered during IV posaconazole therapy given the variability in C_{min}.

Reference:

1. Ananda-Rajah MR, Grigg A, Downey MT, et al. Comparative clinical effectiveness of prophylactic voriconazole/posaconazole to fluconazole/itraconazole in patients with acute myeloid leukemia/myelodysplastic syndrome undergoing cytotoxic chemotherapy over a 12-year period. *Haematologica* 2012; **97**(3): 459-63.

2. Cornely OA, Duarte RF, Haider S, et al. Phase 3 pharmacokinetics and safety study of a posaconazole tablet formulation in patients at risk for invasive fungal disease. *J Antimicrob Chemother* 2016; **71**(3): 718-26.

3. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008; **46**(12): 1813-21.

4. Segal BH, Herbrecht R, Stevens DA, et al. Defining Responses to Therapy and Study Outcomes in Clinical Trials of Invasive Fungal Diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer Consensus Criteria. *Clin Infect Dis* 2008; **47**(5): 674-83.

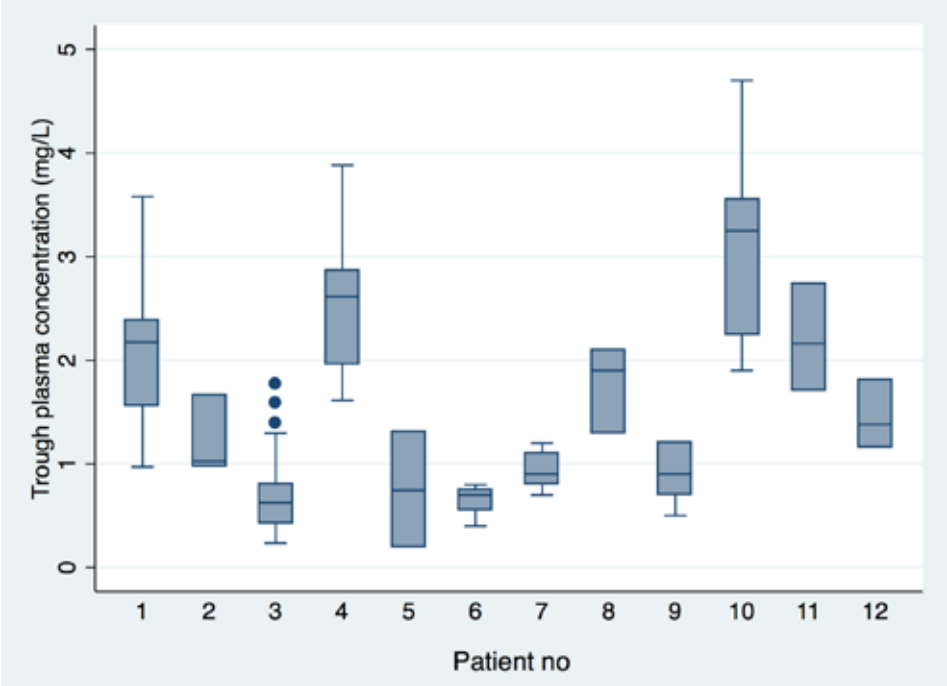
5. Spellberg B, Edwards Jr J, Ibrahim A. Novel perspectives on mucormycosis: Pathophysiology, presentation, and management. *Clin Microbiol Rev* 2005; **18**(3): 556-69.

INTRAVENOUS POSACONAZOLE IN PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES: REAL WORLD EXPERIENCE CONT'D

Table 1 Types of IFD and patient outcomes following IV posaconazole therapy

IFD classification	Fungal Organism	Patient outcomes	
		At cessation of IV posaconazole	30 days post-cessation of IV posaconazole
Proven	*Fusarium solani* complex	Partial response	Partial response
	Rhizopus oryzae	Stable response	Partial response
	Unspecified mucormycete	Complete response	Complete response
	Unspecified coelomycete	Stable response	Partial response
Probable	*Aspergillus fumigatus*	Partial response	Death (non-IFD)
	Aspergillus niger	Disease progression	Death
	Unspecified *Aspergillus sp.*	Stable response	Stable response
	Lichtheimia corymbifera	Partial response	Partial response
Possible	N/A	Partial response	Partial response

Figure 1 Inter- and Intra-patient variability in IV posaconazole trough plasma concentration in patients who had three or more measurements



2016 - 2018 MEETING CALENDAR

2016

16th Asia Pacific Conference on Clinical Microbiology and Infection (APCCMI)
30 Nov- 3 Dec 2016, Melbourne, Australia
Website: http://www.asainc.net.au

2017

ASA Annual Meeting, in conjunction with the StaphPath Meeting
23 - 26 February 2017, Adelaide South Australia
Website: www.antimicrobials2017.com

Australasian Society for Infectious Diseases
29 March – 1 April 2017, Blue Mountains, Australia
Website: www.asid.net.au

British Society for Microbiology Annual Meeting
3-6 April 2017, Edinburgh, Scotland
Website: www.microbiologysociety.org

27th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID 2017)
22-25 April 2017, Vienna, Austria
Website: http://escmid.org/dates_events/

ASM Microbe 2017
1-6 June 2017, New Orleans, LA
Website: www.asm.org/microbe2017

ICPIC 2017, 4th International conference on Prevention and Infection Control
20-23 June 2017, Geneva, Switzerland
Website: www.ICPIC.com

Transplant Infectious Diseases
2 September 2017, Montevideo, Uruguay
Website: http://www.tts.org/tid

Parasitology 2017
21-22 September 2017, Dallas, USA
Website: http://parasitology.cmesociety.com/

ID week 2016
Oct 4-8 2017, San Diego, CA
Website: www.idsociety.org

20th Lancefield International Symposium on Streptococci and Streptococcal Disease
16-20 Oct 2017, Fiji
Website: http://lisssd2017.org/

ICC 2017, International Congress of Chemotherapy
24-2 November 2017, Taipei, Taiwan
Website: http://www.ischemo.org/

2018

ASA Annual Scientific Meeting
22 - 24 February 2018 Sydney, New South Wales

28th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID 2018)
21-24 April 2018, Madrid, Spain
Website: http://escmid.org/dates_events/

ASM Microbe 2018
7-11 June 2018, Atlanta, GA
Website: www.asm.org/microbe2018