Intravenous and Oral Posaconazole Pharmacokinetics in a Five-Year-Old With *Mucor*: A Case Report and Review of the Literature

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Posaconazole is a lipophilic triazole antifungal that exhibits variable absorption when administered orally. It possesses a broad spectrum of activity against various fungi, such as *Aspergillus* and traditionally resistant molds such as *Rhizopus* and *Mucor*, which carry a poor prognosis. Unfortunately, the tablet and suspension formulations of posaconazole are Food and Drug Administration approved for treatment of fungal diseases only in patients older than 13 years of age. Furthermore, the approval of the IV formulation is exclusively for adult patients. Nevertheless, the extended spectrum of activity and available dosage forms make it an attractive option for pediatric use. The data that exist to guide dosing of posaconazole in young pediatric patients are limited primarily to case series and case reports. Thus, we recommend therapeutic drug monitoring to ensure both safety and efficacy in pediatric patients. Herein we describe our experience with both oral and IV posaconazole in the salvage therapy of a 5-year-old female with extensive cutaneous *Mucor*. In contrast to previous reports, which show larger doses may be necessary to obtain therapeutic concentrations in pediatric patients as compared with adults, our patient reached targeted concentrations with weight-based dosing.

ABBREVIATIONS AUC, area under the curve; CT, computed tomography; IV, intravenous; MIC, minimum inhibitory concentration

KEYWORDS antifungal; nasogastric feeding tube; *Mucor*; pediatrics; posaconazole; therapeutic drug monitoring

J Pediatr Pharmacol Ther 2019;24(6):528–533

DOI: 10.5863/1551-6776-24.6.528

Introduction

Mucormycosis, formerly known as zygomycosis, is a fungal infection caused by rapidly growing fungi.¹ Commonly, infection is transmitted through inhalation of fungal spores or direct inoculation of the skin.² Those most at risk for infection include patients with the following risk factors: diabetes (particularly those with ketoacidosis), cancer, neutropenia, history of long-term use of systemic corticosteroids, transplant recipients (i.e., stem and solid organ), those with a history of IV drug abuse, prematurity, low birth weight, iron overload, and skin trauma (e.g., burns and surgical patients).^{3–5}

Roden et al³ found that the most commonly implicated pathogens related to mucormycosis are fungi in the *Rhizopus* and *Mucor* genera, with *Rhizopus* species causing a majority of cases. Less common pathogens include *Rhizomucor*, *Saksenaia*, *Cunninghamella bertholletiae*, and *Apophysomyces*. Infection with any of the *Mucor* species is defined by the location of one or more of the following: rhino-cerebral, pulmonary, gastrointestinal, cutaneous, and disseminated. Rarely occurring is endocarditis, osteomyelitis, peritonitis, and renal infections. Infection with *Mucor* accounts for 8.3%

to 13.3% of all fungal infections and is the third most common type of invasive fungal infection in hematopoietic stem cell transplantation.^{3,6–8} The prognosis for patients with severe infections of *Mucor* is poor, with reported mortalities that approach 70% to 96%. This severity is due to several distinct patient- and pathogen-specific factors, including the invasiveness of the infection, comorbid conditions, non-specific diagnostic symptoms, and inherent resistance to traditional pharmacotherapy.⁹ Herein we present an overview of the pharmacokinetics and therapeutic efficacy in a 5-year-old patient infected with an aggressive strain of *Mucor*.

Pharmacology/Pharmacokinetics

Posaconazole is a lipophilic triazole antifungal with a broad spectrum of activity against *Candida* species (including many that are traditionally resistant to azole antifungals), *Aspergillus*, and *Mucor*.^{10,11} The mechanism of action of posaconazole is similar to that of other triazole antifungals. The principal mechanism of action is through blockade of the cytochrome P450 enzyme 14- α demethylase in the synthesis of lanosterol to ergosterol,

resulting in decreased cellular growth and division.¹² The half-life of posaconazole is approximately 35 hours, with steady-state concentrations achieved between 7 and 10 days of therapy. Posaconazole exhibits saturable absorption, leading to a threefold increase in plasma concentrations with multiple daily dosing (every 6 hours), as compared with once-daily dosing.^{12,13} A variety of dosage forms are available, including oral tablets, suspension, and IV formulations, making it an attractive treatment option for pediatric patients infected with *Mucor*. However, the oral tablet and suspension are only approved in patients 13 years and older, while the IV formulation has labeled indications only for patients older than 18 years of age.¹²

Numerous food-drug and drug-drug interactions exist of which the clinician must be aware when including posaconazole as a part of antifungal therapy. The bioavailability of posaconazole was shown to increase 2.6- and fourfold when administered with a full meal and a high fat content meal, respectively. An acidic environment also enhances absorption and solubility. When used in conjunction with gastric suppressing agents such as proton pump inhibitors, the AUC has been shown to decrease by 32% and thus should not be used concomitantly with the oral formulation. In contrast, administration with an acidic beverage has been shown to increase the AUC by 70%. Medications that increase gastric motility must also be taken into consideration when prescribing posaconazole. Coadministration with metoclopramide showed a decrease in the AUC by 19% and thus should be avoided when possible. When administered with loperamide, the AUC of posaconazole exhibits a negligible increase of 11% but provides little benefit in achieving higher trough concentrations.¹⁴ This makes the IV route ideal for patients who are septic, those who cannot tolerate the oral formulation, and those in whom otherwise therapeutic concentrations cannot be achieved with oral formulations. At the time of this publication, no large-scale randomized, controlled trials have been conducted to define the ideal dosing regimen and frequency of IV posaconazole administration in young pediatric patients (<12 years of age). As a result of the large interpatient variability of established dosing regimens, we recommend that all pediatric patients receiving either oral or IV posaconazole therapy undergo therapeutic drug monitoring to ensure both efficacy and safety.

Posaconazole therapeutic drug monitoring is useful to ensure adequate drug exposure as a result of its high interindividual and intraindividual variation in bioavailability. While the optimal concentration associated with efficacy depends on patient conditions (e.g., immunosuppression) and fungal characteristics, such as MIC, clinical studies¹⁵ suggest that a trough target of 1.25 mg/L should be achieved for treatment of invasive fungal infections, and a trough target of 0.7 mg/L should be achieved for prophylaxis. Others¹⁶

proposed higher targeted trough concentrations based on AUC/MIC ratios. To date, posaconazole has shown no concentration-dependent adverse events; however, the European Medicines Agency suggests an upper boundary of 3.75 mg/L.^{16,17}

Data to guide IV dosing are limited to case reports and patient case series. A retrospective chart review by Teusink-Cross et al¹⁸ describes pediatric patients who received IV posaconazole with therapeutic drug monitoring. Of the 30 patients who were evaluated, 24 patients had at least one posaconazole serum concentration. Data collected included posaconazole concentration, liver function tests, serum creatinine and glomerular filtration rate, and concomitant medications. The median age was 11 years (range, 0.8–27 years), with a median weight of 31.25 kg (range, 5.6–93.9 kg). Eleven of 24 patients weighed less than 30 kg, and the remaining 13 patients weighed greater than 30 kg. The median dose required to achieve target concentrations (>1 mg/L) in patients weighing less than 30 kg was 10 mg/kg every 24 hours (range, 8.8–12.5 mg/kg/day). In those greater than 30 kg, a dose of 300 mg every 12 hours was required (range, 300–400 mg/dose) to achieve therapeutic concentrations. All patients in the study were reported to have tolerated the medication well, with no adverse reactions that could be attributed to the drug. A more recent case series published in May of 2018 by Strommen et al¹⁹ describes dosing with IV posaconazole for both empiric and definitive treatment of *Aspergillus* and suspected fungal infections in pediatric patients undergoing hematopoietic stem cell transplant. Loading doses ranged from 8.8 to 10 mg/kg every 12 hours for 1 day followed by maintenance doses as large as 8.4 mg/kg to 12.2 mg/kg daily to achieve therapeutic concentrations. To our knowledge, there have been no reported cases of treatment of cutaneous *Mucor* infection in a pediatric oncology patient with IV posaconazole.

Case

A 5-year-old, 22-kg Caucasian female with no significant past medical history was diagnosed with standard-risk B-precursor acute lymphoblastic leukemia and completed a standard 3-drug induction therapy. She presented to the emergency department at the end of induction therapy with fever and neutropenia complicated by worsening calf bruising and a swollen left knee. At the time of her emergency department she had completed 4 weeks of intensive chemotherapy, including vincristine and pegasparginase and 28 days of dexamethasone. Other pertinent home medications included diphenhydramine as needed for allergies/nausea, ranitidine for gastric prophylaxis while on prolonged steroids, and sulfamethoxazole/trimethoprim for *Pneumocystis jiroveci* pneumonia prophylaxis. Initial laboratory results included the following: absolute neutrophil count of 170/mm³, serum creatinine of

Table. Posaconazole Dosing, Frequency, Route, and Serum Concentrations

Date from initial presentation	Dose (mg/kg/dose)	Frequency (hrs)	Route	Duration of therapy before TDM (days)	Posaconazole Serum Concentration		
					Peak (mg/L)	Trough (mg/L)	Target (mg/L)
6 wks	9	every 6	NG-tube	7	1.12	0.93	Trough > 1.25
6 wks	5	every 12	IV	3	3.36	2.20	Trough > 1.25
2 mo	14	every 6	NG-tube	7	2.18	2.15	Trough > 1.25
5 mo	17	every 6	NG-tube	1	1.25	1.06	Trough > 1.25
6 mo	18	every 6	NG-tube	2	0.84	0.84	Peak > 0.7

NG-tube, nasogastric feeding tube; TDM, therapeutic drug monitoring

0.22 mg/dL, and potassium of 3.3 mEq/L. Based on the above findings, the patient was empirically started on IV cefepime and clindamycin for febrile neutropenia and presumed cellulitis. Surgery service was consulted the following morning (day 2 post–initial presentation) as a result of rapidly enlarging skin lesions on her left tibia and right distal thigh. At this time, no surgical intervention was recommended, but rather the plan was to continue pharmacological management with broad-spectrum antibiotics for presumed cellulitis. As a result of the patient's worsening lesions, clindamycin was discontinued and gentamicin was initiated to treat presumed ecthyma gangrenosum. Patient course was also complicated at this time by *Clostridium difficile* infection, and oral metronidazole was initiated.

Two days later (day 4 post–initial presentation), an emergency incisional biopsy and infectious disease consult were requested by the oncologist as a result of rapid progression of the leg lesion, documented as increased swelling, redness, and size. Vancomycin was added at this time to cover for resistant Gram-positive organisms, and a patient-controlled morphine analgesia pump was initiated for worsening pain. All blood cultures had remained negative for 72 hours at this time.

Five days post–initial presentation, the biopsy tested positive for mold, with concerns for mucormycosis. Liposomal amphotericin B (5 mg/kg/dose IV, once daily) was initiated. All other antibiotics were discontinued at this time since the patient was no longer neutropenic and a fungal infection was identified. The following day (day 6 post–initial presentation) the patient underwent a CT scan of her chest, abdomen, and sinuses to rule out disseminated infection. A nasogastric feeding tube was placed to optimize nutritional and medication administration.

The CT scan revealed 2 small pulmonary nodules in the right middle lobe and some mild mucosal thickening of the bilateral sinuses. The patient's course was further complicated by hypertension and hypokalemia. Two days (day 7 post–initial presentation) after starting liposomal amphotericin B, the dose was increased to 7.5 mg/kg/dose IV daily. She had multiple surgical debridements during her hospitalization, so eventually

clindamycin and ceftriaxone were initiated for cellulitis coverage.

Mercaptopurine and vincristine single dose with intrathecal methotrexate were initiated 2 weeks post–initial presentation after lesion stabilization. A new skin lesion was identified 1 week later, and 200 mg (10 mg/kg/dose) of oral posaconazole (Noxafil, Merck & Co., Inc, Whitehouse Station, NJ) every 6 hours was initiated at this time. New lesions continued to arise, so the liposomal amphotericin B dose was increased to 10 mg/kg/dose IV once daily and caspofungin 70 mg/m² IV once daily on day 1 followed by 50 mg/m² IV once daily was also initiated. Immunoglobulin G concentrations were assessed at this time based on concerns for hypogammaglobulinemia; concentrations were within normal limits. Posaconazole concentrations were obtained 7 days after initiation (day 31 post–initial presentation) to ensure that steady state had been reached (Table).

Therapeutic drug monitoring was used to optimize therapy since limited pediatric data are available in *Mucor* treatment and because oral absorption is erratic. Oral peak concentrations were drawn at 3 hours postdose, and trough concentrations were drawn prior to next dose (6 hours). Posaconazole concentrations on oral therapy were as follows: peak of 1.12 mg/L and trough 0.93 of mg/L, with a goal above 1.25 mg/L for the entire dosing interval. The dose was increased to posaconazole 300 mg (14 mg/kg/dose) every 6 hours, and repeat concentrations were planned for 5 to 7 days following the increase. However, because of a progressively worsening lesion, the patient was transitioned to posaconazole 110 mg IV every 12 hours (5 mg/kg/dose) 1 month post–initial presentation, and concentrations were obtained 3 days later. Every–12 hour dosing was chosen over once-daily dosing based on the severity of the patient's disease. Intravenous peak concentrations were drawn at 1 hour postdose, and trough concentrations were drawn prior to next dose (12 hours). Posaconazole concentrations on IV therapy were as follows: peak = 3.36 mg/L and trough = 2.2 mg/L, with goal above 1.25 mg/L for the entire dosing interval. Based on these concentrations, the patient was continued on the IV dosing.

After 1 week of IV therapy (6 weeks post-initial presentation), the lesions were clinically controlled. In preparation for discharge, the patient was transitioned to oral posaconazole at 300 mg (14 mg/kg/dose) every 6 hours based on previous pharmacokinetics data for home therapy. Concentrations were again drawn 7 days after restarting oral therapy and resulted in a peak of 2.18 mg/L and a trough of 2.15 mg/L. The patient was continued on this dosing, and no further concentrations were obtained during that admission. The patient continued on triple antifungal therapy for a total of 3 weeks and then transitioned to liposomal amphotericin B and posaconazole orally for an additional 2 weeks. She was sent home 2 months post-initial presentation on maintenance therapy of oral posaconazole 300 mg (14 mg/kg/dose) every 6 hours.

The patient was readmitted 10 days later (2 months post-initial presentation) as a result of new abscess lesion concerning for fungus on her right leg. The patient was reinitiated on triple therapy with oral posaconazole, liposomal amphotericin B, and caspofungin and was sent for surgical debridement. It was later discovered that family had been administering incorrect doses of posaconazole—200 mg (10 mg/kg/dose) instead of the intended 300-mg dose (14 mg/kg/dose). Posaconazole dosing remained at 300 mg (14 mg/kg/dose) orally every 6 hours and concentrations were not obtained at this admission since previous concentrations were within expected limits and because there was no change in organ function/clearance or with enteral feeding regimens that may alter bioavailability. After surgical debridement and triple antifungal therapy for 2 weeks (2.5 months post-initial presentation), the patient was discharged on posaconazole 300 mg (14 mg/kg/dose) orally every 6 hours with significant education to the family to ensure correct dosing. After being home for 1 week, the patient was readmitted for another new cutaneous lesion on her right leg, and triple therapy was reinitiated and surgical debridement was completed. She was monitored for about 2 weeks and discharged on triple therapy because of the recurrent lesions despite adequate posaconazole concentrations (3 months post-initial presentation). At this time, having completed 1 month of a reduced-intensity consolidation and another of standard maintenance chemotherapy, the patient was transitioned back to reduced-intensity interim maintenance with the Capizzi methotrexate rather than high-dose methotrexate.

While receiving Capizzi methotrexate (3 months post-initial presentation), the patient was found to have a new lesion on her right shin and was transferred to an outside institution because of insurance changes, and she was lost to follow-up for 1 month. Her chemotherapy was held for 2 months and she had no new lesions for a full month so chemotherapy was resumed with Capizzi methotrexate. Her posaconazole dose was adjusted while in an outside hospital to posaconazole 376 mg (17

mg/kg/dose) orally every 6 hours (5 months post-initial presentation). Her pharmacokinetic concentrations were performed when she returned to our institution for chemotherapy administration. Her peak was 1.25 mg/L and her trough was 1.06 mg/L, with a goal of 1.25 mg/L for the entire dosing interval; thus, posaconazole was increased to 400 mg (18 mg/kg/dose) orally every 6 hours and the patient was discharged (5 months post-initial presentation).

The patient's course was further complicated by septic shock secondary to *Enterobacter* and *Viridans streptococcus*, approximately 6 months post-initial presentation. Posaconazole pharmacokinetic concentrations were obtained after the patient was stabilized, with a corresponding peak of 0.84 mg/L and a trough of 0.84 mg/L (indicating an actual peak concentration between 2 and 6 hours). Her feeding regimen, dosing of posaconazole, timing of posaconazole, other changes in medications, and non-compliance were all ruled out as potential causes for the subtherapeutic concentrations. Based on these concentrations and her clinical status, posaconazole therapy was kept at 400 mg (18 mg/kg) every 6 hours as prophylaxis.

One year post-initial presentation the patient had no signs of fungal recurrence. The patient's interim maintenance therapy was completed and her leukemia remained in remission. She was able to receive appropriate delayed intensification chemotherapy. Currently she is receiving maintenance chemotherapy while on posaconazole antifungal therapy alone. Outpatient monthly posaconazole concentrations are being performed until therapy is completed at 1 year following her final lesion to ensure prophylactic coverage is maintained.

Discussion

Our patient initially achieved a therapeutic trough greater than 1.25 mg/L (2.20 mg/L) with an IV dose of 5 mg/kg/dose twice daily. An oral dose of 14 mg/kg/dose every 6 hours was necessary to achieve approximately the same trough (2.15 mg/L). Though a direct comparison or calculation of absolute bioavailability cannot be made, the concentrations in our patient illustrate that the difference in dosing necessary to achieve comparable trough concentrations between oral and IV can be substantial (5 mg/kg twice daily versus 14 mg/kg every 6 hours). A trough goal of 1.25 mg/L was targeted based on data indicating a greater degree of efficacy in active invasive fungal infections.^{14,20}

Intravenous posaconazole concentrations in pediatric patients reported by Strommen et al¹⁹ showed that larger doses in pediatric patients (as compared with adults) may be necessary to obtain therapeutic concentrations. In contrast, our patient obtained the targeted trough at comparable weight-based adult doses. Dosing differences between patients may be due to several factors, including drug-drug interactions

(i.e., *p*-glycoprotein inhibitors/inducers), differences in metabolism (e.g., UGT1A4 polymorphisms), sex, food, etc.^{21,22} Similar to the findings reported by Strommen et al,¹⁹ the patient experienced no adverse events that could be attributed to posaconazole, with peak concentrations reaching greater than 3 mg/L.

Conclusion

Both oral and IV posaconazole concentrations have high inter- and intraindividual variability. Very little information is available regarding IV posaconazole in pediatric patients. To our knowledge this is the first report describing both oral and IV posaconazole concentrations in a single patient. The changes in posaconazole concentrations resulting from conversion from oral to IV posaconazole are difficult to predict. Therapeutic drug monitoring is strongly recommended to optimize therapy. This case report supports previous literature in finding that larger doses of oral posaconazole in pediatric patients are necessary to achieve targeted concentrations, but the IV dose necessary was comparable to that associated with adult-based dosing.

ARTICLE INFORMATION

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Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all patient information in this report and take responsibility for the integrity and accuracy of the report.

Acknowledgments We would like to acknowledge the assistance of Dr. Charles Peloquin at the Infectious Disease Pharmacokinetics Laboratory and the University of Florida for their assistance in therapeutic drug monitoring.

Accepted April 15, 2019

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REFERENCES

- Ibrahim AS, Spellberg B, Walsh TJ, Kontoyiannis DP. Pathogenesis of mucormycosis. *Clin Infect Dis*. 2012;54(suppl 1):S16–S22.
- Skiada A, Lanternier F, Groll AH, et al. Diagnosis and treatment of mucormycosis in patients with hematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia (ECIL 3). *Haematologica*. 2013;98(4):492–504.
- Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis*. 2005;41(5):634–653.
- Petrikkos G, Skiada A, Lortholary O, et al. Epidemiology and clinical manifestations of mucormycosis. *Clin Infect Dis*. 2012;54(suppl 1):S23–S34.
- Walsh TJ, Gamaletsou MN, McGinnis MR, et al. Early clinical and laboratory diagnosis of invasive pulmonary, extrapulmonary, and disseminated mucormycosis (zygomycosis). *Clin Infect Dis*. 2012;54(suppl 1):S55–S60.
- Gleissner B, Schilling A, Anagnostopoulou I, et al. Improved outcome of zygomycosis in patients with hematological diseases? *Leuk Lymphoma*. 2004;45(7):1351–1360.
- Kontoyiannis DP, Marr KA, Park BJ, et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. *Clin Infect Dis*. 2010;50(8):1091–1100.
- Park BJ, Pappas PG, Wannemuehler KA, et al. Invasive non-*Aspergillus* mold infections in transplant recipients, United States, 2001–2006. *Emerg Infect Dis*. 2011;17(10):1855–1864.
- Katragkou A, Walsh TJ, Roilides E. Why is mucormycosis more difficult to cure than more common mycoses? *Clin Microbiol Infect*. 2014;20(suppl 6):74–81.
- Groll AH, Walsh TJ. Posaconazole: clinical pharmacology and potential for management of fungal infections. *Expert Rev Anti Infect Ther*. 2005;3(4):467–487.
- Sabatelli F, Patel R, Mann PA, et al. In vitro activities of posaconazole, fluconazole, itraconazole, voriconazole, and amphotericin B against a large collection of clinically important molds and yeasts. *Antimicrob Agents Chemother*. 2006;50(6):2009–2015.
- Noxafil (posaconazole) [package insert]. Whitehouse Station, NJ: Merck & Co Inc; 2015.
- Li Y, Theuretzbacher U, Clancy CJ, et al. Pharmacokinetic/pharmacodynamic profile of posaconazole. *Clin Pharmacokinet*. 2010;49(6):379–396.
- Krishna G, AbuTarif M, Xuan F, et al. Pharmacokinetics of oral posaconazole in neutropenic patients receiving chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome. *Pharmacotherapy*. 2008;28(10):1223–1232.
- Seyeedmousavi S, Mouton JW, Verweij PE, et al. Therapeutic drug monitoring of voriconazole and posaconazole for invasive aspergillosis. *Expert Rev Anti Infect Ther*. 2013;11(9):931–941.
- Dekkers BGJ, Bakker M, van der Elst KCM, et al. Therapeutic drug monitoring of posaconazole: an update. *Curr Fungal Infect Rep*. 2016;10:51–61.
- European Medicines Agency, Committee for Medicinal Products for Human Use. Assessment report Noxafil. EMA/159150/2014. <https://www.ema.europa.eu/en/medicines/human/EPAR/noxafil>. Accessed July 19, 2019

18. Teusink-Cross A, Davies SM, Chandra S, et al. Intravenous posaconazole is safe and effective in pediatric HSCT patients. *Biol Blood Marrow Transplant*. 2017;23(3):S166.
19. Strommen A, Hurst AL, Curtis D, et al. Use of intravenous posaconazole in hematopoietic stem cell transplant patients. *J Pediatr Hematol Oncol*. 2018;40(4):e203–e206.
20. Walsh TJ, Raad I, Patterson TF, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. *Clin Infect Dis*. 2007;44(1):2–12.
21. Ghosal A, Hapangama N, Yuan Y, et al. Identification of human UDP-glucuronosyltransferase enzyme(s) responsible for the glucuronidation of posaconazole (Noxafil). *Drug Metab Dispos*. 2004;32(2):267–271.
22. Allegra S, Fatiguso G, De Francia S, et al. Evaluation of posaconazole pharmacokinetics in adult patients with invasive fungal infection. *Biomedicines*. 2017;5(4):66. doi:10.3390/biomedicines5040066.