IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 23, Issue 12, Series 03 (December. 2024), PP 60-65
www.iosrjournals.org

Single-Dose SUBA-Itraconazole's Bioavailability in Comparison to Conventional Itraconazole in Fed and Fasted Conditions

Dr. Mohammed Arif Chowdhury[1], Dr. Biswas Shaheen Hassan[2], Dr. Sumona Haque[3], Syed E. Shaude[4]

[1]*Associate Professor and Head, Department of Dermatology & Venereology, Ashiyan Medical College Hospital, Dhaka, Bangladesh*
[2]*Associate Professor, National Institute of Diseases of the Chest and Hospital, Dhaka, Bangladesh*
[3]*Health Officer, The United Nations International Children's Emergency Fund, Bangladesh*
[4]*Chief Coordinator, Department of Research and Development, International Network of Doctors Journal, Dhaka, Bangladesh.*

Corresponding Author: *Dr. Mohammed Arif Chowdhury, Associate Professor and Head, Department of Skin & Venereology, Ashiyan Medical College Hospital, Dhaka, Bangladesh.*

Abstract:
Background: *Conventional itraconazole (C-ITZ) has inconsistent absorption. SUBA-itraconazole (S-ITZ) demonstrates greater bioavailability than C-ITZ at steady state when taken with food, but no data are available comparing their performance in a fasted state.* ***Objective:*** *The aim of the study was to compare Single-Dose SUBA-Itraconazole's Bioavailability in Comparison to Conventional Itraconazole in Fed and Fasted Conditions.* ***Methodology:*** *This study was a comparative study which was conducted at Ashiyan Medical College Hospital during Jan'2023 to Jan'24. Sample size was 120. The study was for evaluating the relative bioavailability of a single oral dose of SUBA-itraconazole (S-ITZ) compared to Conventional itraconazole (C-ITZ) capsules when administered under fasted and fed conditions. Ethical clearance was given from the IRB board of the institution. Data were analyzed by SPSS 26.0 version.* ***Results:*** *Out of 120 people, 49 (41%) were male and 71 (59%) were female with male: female ratio of 4:6. The mean (+SD) age was 31.91 (+11.34) years. Service holder were the largest population 50 (41.67%) and 35 (29.17%) were day students. Under the fasted condition, the AUCinf and Cmax ITZ levels for S-ITZ were higher than those for C-ITZ (23 and 62%, respectively). Under fed conditions, S-ITZ exhibited a 5% lower AUCinf and a 20% lower Cmax compared to C-ITZ. Similar results were observed for OH-ITZ levels and are available in . There was no Tmax difference between formulations under fasted conditions; under fed conditions, the median Tmax for S-ITZ was 2.5 h longer compared to C-ITZ. The geometric mean S-ITZ/C-ITZ ratios for ITZ levels under fasted conditions were 122.76% (90% CI = 109.72 to 137.34%) and 161.75% (90% CI = 141.40 to 185.02%) for AUCinf and Cmax, respectively. Under fed conditions, the geometric mean S-ITZ/C-ITZ ratios for ITZ were 94.67% (90% CI = 85.35 to 105.01%) and 80.26% (90% CI = 67.61 to 95.27%) for the AUCinf and Cmax, respectively. The geometric mean S-ITZ/C-ITZ ratios for OH-ITZ under fasted conditions were 125.77% (90% CI = 111.40 to 141.99%) and 143.40% (90% CI = 128.19 to 160.42%) for the AUCinf and Cmax, respectively. Under fed conditions, the geometric mean S-ITZ/C-ITZ ratios were 91.86% (90% CI = 79.26 to 106.47%) and 84.25% (90% CI = 73.09 to 97.11%) for the AUCinf and Cmax, respectively. Decreased relative bioavailability in the presence of food was seen for S-ITZ and C-ITZ. The mean AUCinf and Cmax for both ITZ and OH-ITZ were lower (31 and 40% for AUCinf; 57 and 54% for Cmax) when S-ITZ was administered after the study meal; a similar decrease was seen in C-ITZ (10 and 18% for AUCinf; 14 and 22% for Cmax) for ITZ and OH-ITZ, respectively.* ***Conclusion:*** *Conventional itraconazole (C-ITZ) suffers from absorption variability. SUBA-itraconazole (S-ITZ) is more bioavailable than C-ITZ at steady state in a fed condition, but there are no data comparing the two under a fasted state. This study showed that S-ITZ exhibits reduced variability compared to C-ITZ capsules when administered under fasted conditions.*
Keywords: *SUBA-Itraconazole, Conventional Itraconazole, Bioavailability, Fed and Fasted Condition*

Date of Submission: 01.12.2024 Date of Acceptance: 20.12.2024

I. Introduction

Itraconazole (ITZ) is a broad-spectrum triazole antifungal effective against numerous medically significant fungi [1-4]. Conventional itraconazole (C-ITZ) is available in capsule and oral solution forms, but its absorption is inconsistent, leading to variable pharmacokinetics (PK) [5]. The impact of food on C-ITZ absorption varies significantly among patients, with interpatient variability reaching up to 15-fold [6]. As a result, unpredictable plasma levels of itraconazole (ITZ) and its major active metabolite, hydroxyitraconazole (OH-ITZ), can occasionally occur, leading to either subtherapeutic or super therapeutic levels. To address these limitations, a novel formulation known as Super Bio Available itraconazole (SUBA-itraconazole, or S-ITZ) was developed. S-ITZ demonstrates a relative bioavailability of 180% compared to conventional itraconazole (C-ITZ) and an absolute bioavailability of up to 90%. The 65-mg S-ITZ capsule is bioequivalent to the 100-mg C-ITZ capsule while producing fewer adverse events (AEs) [7,8]. The aim of the study was to compare Single-Dose SUBA-Itraconazole's Bioavailability in Comparison to Conventional Itraconazole in Fed and Fasted Conditions.

II. Methodology

This study was a comparative study which was conducted at Ashiyan Medical College Hospital during Jan'2023 to Jan'24. Sample size was 120. The study was for evaluating the relative bioavailability of a single oral dose of SUBA-itraconazole (S-ITZ) compared to Conventional itraconazole (C-ITZ) capsules when administered under fasted and fed conditions. Participants were healthy, aged 18 to 65 years, both male and female, nonsmokers, with body mass indices of 18 to 30, and without drug allergies who gave informed consent. Participants who were not willing to participate, severely ill patients were excluded from the study. Subjects in a fasted or fed state received S-ITZ 65-mg or C-ITZ 100-mg. No blinding of doses was performed. Blood samples were collected 60 min prior to dosing and prior to breakfast for subjects following the fed regimen and between 1 and 120 h postdose administration. ITZ and OH-ITZ plasma levels were measured by liquid chromatography with tandem mass spectrometry. The area under the plasma concentration over the dosing interval (AUCt), the area under the plasma concentration extrapolated to infinity (AUCinf), observed maximum plasma concentration (Cmax), the time to Cmax (Tmax), the elimination rate constant (kel), and the half-life (t1/2) were estimated based on plasma measurements. Ethical clearance was given from the IRB board of the institution. Data were analyzed by SPSS 26.0 version.

III. Result

Table 1. Age and Sex of the respondents (n=120)

Variable	N=120	Median (range)
Age (yrs) **Mean ± SD**	31.91±11.34	30 (18-90)
Sex		
Male	49 (41%)	
Female	71 (59%)	

Out of 120 people, 49 (41%) were male and 71 (59%) were female with male: female ratio of 4:6. The mean (±SD) age was 31.91 (±11.34) years.

Table 2. Distribution of the respondents' according to educational background (n=120)

Educational Level	N=120	%
Illiterate	3	2.5
Primary	10	8.3
SSC	20	16.67
HSC	60	50
Graduate or above	27	22.5
Total	120	100

Among all the respondents Illiterate 3 (2.5%), Primary level 10 (8.3%), SSC 20 (16.67%), HSC 60(50%), Graduate or above 27 (22.5%).

Table 3. Distribution of the respondents' according to response of Occupation of the study population (N=120)

Occupation Type	N=120	%
Transport worker	1	0.83
Industry worker	2	1.67
Service holder	50	41.67

Businessman	2	1.67
Housewife	30	25
Student	35	29.17
Total	120	100

Table 4. Distribution of the respondents' according to response of Treatment Received.

Study Period	Treatment Received
A	S-ITZ 65 mg × 1 dose under fasted conditions
B	S-ITZ 65 mg × 1 dose under fed conditions
C	C-ITZ 100 mg × 1 dose under fasted conditions
D	C-ITZ 100 mg × 1 dose under fed conditions

S-ITZ refers to SUBA-itraconazole, while C-ITZ represents conventional itraconazole. Under fasted conditions (Groups A and C), subjects received their dose following an overnight fast of at least 10 hours. Under fed conditions (Groups B and D), subjects were dosed within 30 minutes of consuming a high-fat, high-calorie meal (comprising 150 protein calories, 250 carbohydrate calories, and 500 fat calories) after an overnight fast of at least 10 hours. Post-dosing, all participants fasted for at least 4 hours during each period. A minimum of 14 days separated each dosing period. Subjects ingested one whole capsule with 240 mL of water at ambient temperature, with other fluids (except milk provided with the meal) restricted from 1 hour before to 1 hour after dosing. Foods and beverages containing caffeine were prohibited for 72 hours prior to dosing and throughout blood sample collection periods. Grapefruit consumption was not allowed for 7 days before the first dose and until the study concluded.

Parameter	**Itraconazole**				**Hydroxyitraconazole**			
	S-ITZ: fasted (65 mg ITZ)	**S-ITZ: fed (65 mg ITZ)Z**	**C-ITZ: fasted (100 m g ITZ)**	**C-ITZ: fed (100 m g ITZ)**	**S-ITZ: fasted (65 mg ITZ)**	**S-ITZ: fed (65 mg ITZ)**	**C-ITZ: fasted (100 mg ITZ)**	**C-ITZ: fed (100 m g ITZ)**
	N=30	N=30	N=30	N=30	N=30	N=30	N=30	N=30
Median T_{max} in h (range)	2.50 (1.50–5.00)	7.50 (4.50–24)	3.00 (1.50–4.52)	5.00 (2.50–11.00)	3.50 (2.00–6.00)	9.00 (4.50–24)	4.00 (1.50–5.50)	6.00 (2.50–12.00)
C_{max} (ng/ml)	111.910 (44)	50.299 (50)	74.362 (57)	62.224 (55)	180.514 (31)	85.902 (36)	133.969 (46)	70.224 (58)
AUC_{inf} (ng · h/ml)	1,006.534 (45)	684.773 (46)	879.762 (57)	754.350 (58)	1,934.418 (48)	1,186.126 (50)	1,656.887 (60)	954.350 (60)
T_{half} (h)	31.45 (23)	32.48 (26)	29.95 (22)	34.02 (30)	8.90 (47)	7.77 (38)	12.43 (45)	20.02 (35)

S-ITZ, SUBA-itraconazole; C-ITZ, conventional itraconazole; ITZ, itraconazole; C_{max}, maximum concentration; AUC_t, area under the plasma concentration over the dosing interval; AUC_{inf}, area under the curve extrapolated to infinity; k_{el}, elimination rate constant; T_{half}, half-life. C_{max}, AUC_t, AUC_{inf}, k_{el}, and T_{half} are expressed as the arithmetic mean (CV%).

Under the fasted condition, the AUC_{inf} and C_{max} ITZ levels for S-ITZ were higher than those for C-ITZ (23 and 62%, respectively). Under fed conditions, S-ITZ exhibited a 5% lower AUC_{inf} and a 20% lower C_{max} compared to C-ITZ. Similar results were observed for OH-ITZ levels and are available in . There was no T_{max} difference between formulations under fasted conditions; under fed conditions, the median T_{max} for S-ITZ was 2.5 h longer compared to C-ITZ.

Parameter	**Contrast in C_{max} (ng/ml)**			**Contrast in AUC_{inf} (ng · h/ml)**		
	RGM (%)	**90% CI**	**IS CV (%)**	**RGM (%)**	**90% CI**	**IS CV (%)**
Itraconazole						
S-ITZ fasted vs C-ITZ fasted	161.75	141.40–185.02	42	122.76	109.72–137.34	35
S-ITZ fed vs C-ITZ fed	80.26	67.61–95.27	55	94.67	85.35–105.01	32
S-ITZ fed vs S-ITZ fasted	42.87	36.61–50.20	50	69.42	63.76–75.58	26

C-ITZ fed vs C-ITZ fasted	86.40	74.38–100.37	48	90.01	79.34–102.11	40
S-ITZ fasted vs C-ITZ fed	187.20	164.23–213.40	41	136.38	122.81–151.46	33
Hydroxyitraconazole						
S-ITZ fasted vs C-ITZ fasted	143.40	128.19–160.42	35	125.77	111.40–141.99	38
S-ITZ fed vs C-ITZ fed	84.25	73.09–97.11	45	91.86	79.26–106.47	46
S-ITZ fed vs S-ITZ fasted	45.66	40.06–52.04	41	60.00	52.65–68.37	40
C-ITZ fed vs C-ITZ fasted	77.72	68.60–88.05	39	82.14	71.48–94.40	44
S-ITZ fasted vs C-ITZ fed	184.51	166.39–204.60	32	153.11	136.49–171.76	36

S-ITZ, SUBA-itraconazole; C-ITZ, conventional itraconazole; C_{max}, maximum concentration; CI, confidence interval; RGM, ratio of geometric means; IS CV, intrasubject coefficient of variation; AUC_{inf}, area under the curve extrapolated to infinity.

The geometric mean S-ITZ/C-ITZ ratios for ITZ levels under fasted conditions were 122.76% (90% CI = 109.72 to 137.34%) and 161.75% (90% CI = 141.40 to 185.02%) for AUC_{inf} and C_{max}, respectively. Under fed conditions, the geometric mean S-ITZ/C-ITZ ratios for ITZ were 94.67% (90% CI = 85.35 to 105.01%) and 80.26% (90% CI = 67.61 to 95.27%) for the AUC_{inf} and C_{max}, respectively. The geometric mean S-ITZ/C-ITZ ratios for OH-ITZ under fasted conditions were 125.77% (90% CI = 111.40 to 141.99%) and 143.40% (90% CI = 128.19 to 160.42%) for the AUC_{inf} and C_{max}, respectively. Under fed conditions, the geometric mean S-ITZ/C-ITZ ratios were 91.86% (90% CI = 79.26 to 106.47%) and 84.25% (90% CI = 73.09 to 97.11%) for the AUC_{inf} and C_{max}, respectively. Decreased relative bioavailability in the presence of food was seen for S-ITZ and C-ITZ. The mean AUC_{inf} and C_{max} for both ITZ and OH-ITZ were lower (31 and 40% for AUC_{inf}; 57 and 54% for C_{max}) when S-ITZ was administered after the study meal; a similar decrease was seen in C-ITZ (10 and 18% for AUC_{inf}; 14 and 22% for C_{max}) for ITZ and OH-ITZ, respectively.

IV. Discussion

In This study was a comparative study which was conducted at Ashiyan Medical College Hospital during Jan'2023 to Jan'24. Sample size was 120. The study was for evaluating the relative bioavailability of a single oral dose of SUBA-itraconazole (S-ITZ) compared to Conventional itraconazole (C-ITZ) capsules when administered under fasted and fed conditions.

Out of 120 people, 49 (41%) were male and 71 (59%) were female with male: female ratio of 4:6. The mean (+SD) age was 31.91 (+11.34) years. Among all the respondents Illiterate 3 (2.5%), Primary level 10 (8.3%), SSC 20 (16.67%), HSC 60(50%), Graduate or above 27 (22.5%). Service holder were the largest population 50 (41.67%) and 35 (29.17%) were day laborers.

In this study Under the fasted condition, the AUCinf and Cmax ITZ levels for S-ITZ were higher than those for C-ITZ (23 and 62%, respectively). Under fed conditions, S-ITZ exhibited a 5% lower AUCinf and a 20% lower Cmax compared to C-ITZ. Similar results were observed for OH-ITZ levels and are available in . There was no Tmax difference between formulations under fasted conditions; under fed conditions, the median Tmax for S-ITZ was 2.5 h longer compared to C-ITZ. This study contributes to the growing evidence that S-ITZ achieves bioequivalence to C-ITZ in terms of exposure levels for both ITZ and OH-ITZ, as indicated by AUCt and AUCinf measurements [9-11]. The geometric mean S-ITZ/C-ITZ ratios for ITZ levels under fasted conditions were 122.76% (90% CI = 109.72 to 137.34%) and 161.75% (90% CI = 141.40 to 185.02%) for AUCinf and Cmax, respectively. Under fed conditions, the geometric mean S-ITZ/C-ITZ ratios for ITZ were 94.67% (90% CI = 85.35 to 105.01%) and 80.26% (90% CI = 67.61 to 95.27%) for the AUCinf and Cmax, respectively . The geometric mean S-ITZ/C-ITZ ratios for OH-ITZ under fasted conditions were 125.77% (90% CI = 111.40 to 141.99%) and 143.40% (90% CI = 128.19 to 160.42%) for the AUCinf and Cmax, respectively. Under fed conditions, the geometric mean S-ITZ/C-ITZ ratios were 91.86% (90% CI = 79.26 to 106.47%) and 84.25% (90% CI = 73.09 to 97.11%) for the AUCinf and Cmax, respectively. Decreased relative bioavailability in the presence of food was seen for S-ITZ and C-ITZ. The mean AUCinf and Cmax for both ITZ and OH-ITZ were lower (31 and 40% for AUCinf; 57 and 54% for Cmax) when S-ITZ was administered after the study meal; a similar decrease was seen in C-ITZ (10 and 18% for AUCinf; 14 and 22% for Cmax) for ITZ and OH-ITZ, respectively. Regarding intersubject variability, treatment C (C-ITZ under fasting conditions) showed the highest variability for ITZ parameters AUC and Cmax, with variances of 0.422 and 0.372, respectively. In contrast, treatment B (S-ITZ under

fed conditions) exhibited the lowest intersubject variability, with variances of 0.179 and 0.187, respectively. These differences, however, were not statistically significant. Similarly, for OH-ITZ, the highest intersubject variability for AUCt, AUCinf, and Cmax was observed in treatment C (0.456, 0.439, and 0.246, respectively), while treatment B showed the lowest values (0.214, 0.218, and 0.129, respectively). The only statistically significant difference in variability was for Cmax under fasting conditions, with a P-value of 0.0028.

Under fasting conditions, S-ITZ showed 23% higher AUCt and AUCinf values compared to C-ITZ, with geometric means falling within the broader bioequivalence range. In the fed state, S-ITZ demonstrated a 10% lower AUCt and a 5% lower AUCinf relative to C-ITZ capsules, remaining within the wider bioequivalence range as defined by the FDA [12]. The continued confirmation of bioequivalence for clinically significant pharmacokinetic (PK) parameters between S-ITZ and C-ITZ enables clinicians to make more patient-centered therapeutic decisions. These include considerations such as less restrictive administration requirements, reduced interpatient variability, and improved drug tolerability. In this study, administering the C-ITZ capsule formulation in a fed state resulted in decreased bioavailability. This finding contrasts with historical literature, which generally reports improved bioavailability for C-ITZ in the fed state compared to the fasted state [13,14]. though it is consistent with more recent data [9, 10]. We propose that this discrepancy highlights the challenges clinicians face in understanding the complex pharmacokinetics (PK) of C-ITZ. While super therapeutic levels are linked to increased adverse events, subtherapeutic levels are associated with suboptimal clinical outcomes [15,16]. To address the challenges associated with capsule administration, a C-ITZ oral solution was developed. However, its use is limited as many patients find it unpalatable and experience poor gastrointestinal tolerability [17]. S-ITZ has shown promising results in early trials and recent comparative studies against other ITZ formulations. Emerging research on the pharmacokinetics of S-ITZ indicates enhanced bioavailability and more flexible administration requirements [10]. The only comparison trial conducted in an at-risk patient population demonstrated a quicker achievement of therapeutic levels and a lower incidence of subtherapeutic levels among patients. Encouraging data continue to emerge as we await the results of MSG15, a trial evaluating S-ITZ versus C-ITZ in the treatment of endemic mycoses.

V. Conclusion

Conventional itraconazole (C-ITZ) suffers from absorption variability. SUBA-itraconazole (S-ITZ) is more bioavailable than C-ITZ at steady state in a fed condition, but there are no data comparing the two under a fasted state. This study showed that S-ITZ exhibits reduced variability compared to C-ITZ capsules when administered under fasted conditions.

References

[1]. Chapman SW, Dismukes WE, Proia LA, Bradsher RW, Pappas PG, Threlkeld MG, Kauffman CA, Infectious Diseases Society of America. 2008. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. *Clin Infect Dis* 46:1801–1812.

[2]. Wheat LJ, Freifeld AG, Kleiman MB, Baddley JW, McKinsey DS, Loyd JE, Kauffman CA, Infectious Diseases Society of America. 2007. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis* 45:807–825.

[3]. Galgiani JN, Ampel NM, Blair JE, Catanzaro A, Geertsma F, Hoover SE, Johnson RH, Kusne S, Lisse J, MacDonald JD, Meyerson SL, Raksin PB, Siever J, Stevens DA, Sunenshine R, Theodore N. 2016. Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of coccidioidomycosis. *Clin Infect Dis* 63:e112-146–e146.

[4]. Nett JE, Andes DR. 2016. Antifungal agents: spectrum of activity, pharmacology, and clinical indications. *Infect Dis Clin North Am* 30:51–83.

[5]. Ashley ESD, Lewis R, Lewis JS, Martin C, Andes D. 2006. Pharmacology of systemic antifungal agents. *Clinical Infectious Diseases* 43:S28–S39.

[6]. Poirier JM, Berlioz F, Isnard F, Cheymol G. 1996. Marked intra- and inter-patient variability of itraconazole steady state plasma concentrations. *Therapie* 51:163–167.

[7]. Mangalore RP, Moso MA, Cronin K, Young K, McMahon JH. 2018. Treatment of disseminated histoplasmosis in advanced HIV using itraconazole with increased bioavailability. *Int J STD AIDS* 29:1448–1450.

[8]. Thompson GR, III, Lewis P, Mudge S, Patterson TF, Burnett BP. 2020. Open-label crossover oral bioequivalence PK comparison for a 3-day loading dose regimen and 15-day steady-state administration of SUBA™-itraconazole and conventional itraconazole capsules in healthy adults. *Antimicrob Agents Chemother* 64:e00400-20.

[9]. Abuhelwa AY, Foster DJ, Mudge S, Hayes D, Upton RN. 2015. Population pharmacokinetic modeling of itraconazole and hydroxyitraconazole for oral SUBA-itraconazole and Sporanox capsule formulations in healthy subjects in fed and fasted states. *Antimicrob Agents Chemother* 59:5681–5696.

[10]. Lindsay J, Mudge S, Thompson GR, III. 2018. Effects of food and omeprazole on a novel formulation of super bioavailability itraconazole in healthy subjects. *Antimicrob Agents Chemother* 62:e01723-18.

[11]. Thompson GR, III, Lewis P, Mudge S, Patterson TF, Burnett BP. 2020. Open-label crossover oral bioequivalence pharmacokinetics comparison for a 3-day loading dose regimen and 15-day steady-state administration of SUBA-itraconazole and conventional itraconazole capsules in healthy adults. *Antimicrob Agents Chemother* 64:e00400-20.

[12]. Haidar SH, Davit B, Chen M-L, Conner D, Lee L, Li QH, Lionberger R, Makhlouf F, Patel D, Schuirmann DJ, Yu LX. 2008. Bioequivalence approaches for highly variable drugs and drug products. *Pharm Res* 25:237–241.

[13]. Lestner J, Hope WW. 2013. Itraconazole: an update on pharmacology and clinical use for treatment of invasive and allergic fungal infections. *Expert Opin Drug Metab Toxicol* 9:911–926.

[14]. Yun H-y, Baek MS, Park IS, Choi BK, Kwon K-i. 2006. Comparative analysis of the effects of rice and bread meals on bioavailability of itraconazole using NONMEM in healthy volunteers. *Eur J Clin Pharmacol* 62:1033–1039.
[15]. Lindsay J, Sandaradura I, Wong K, Arthur C, Stevenson W, Kerridge I, Fay K, Coyle L, Greenwood M. 2017. Serum levels, safety and tolerability of new formulation SUBA-itraconazole prophylaxis in patients with haematological malignancy or undergoing allogeneic stem cell transplantation. *J Antimicrob Chemother* 72:3414–3419.
[16]. Grigg AP, Brown M, Roberts AW, Szer J, Slavin MA. 2004. A pilot study of targeted itraconazole prophylaxis in patients with graft-versus-host disease at high risk of invasive mould infections following allogeneic stem cell transplantation. *Bone Marrow Transplant* 34:447–453.
[17]. Shbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. 2014. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. *J Antimicrob Chemother* 69:1162–1176.