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ORIGINAL RESEARCH

Trough concentration of itraconazole and its relationship with efficacy and safety: a systematic review and meta-analysis

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Objectives: The optimum trough concentration of itraconazole for clinical response and safty is controversial. The objective of this systematic review and meta-analysis was to determine the optimum trough concentration of itraconazole and evaluate its relationship with efficacy and safety.
Methods: We searched PubMed, EMBASE, Web of Science, the Cochrane Library, ClinicalTrials.gov, and three Chinese literature databases (CNKI, WanFang, and CBM). We included observational studies that compared clinical outcomes below or above the trough concentration cut-off value which we set as 0.25, 0.5, and 1.0 mg/L. The efficacy outcomes were rate of successful treatment, rate of prophylaxis failure and invasive fungal infection (IFI)-related mortality. The safety outcomes included incidents of hepatotoxicity and other adverse events.
Results: The study included a total of 29 studies involving 2,346 patients. Our meta-analysis showed that compared with itraconazole trough concentrations (C_{trough}) of ≥0.25 mg/L, levels of <0.25 mg/L significantly increased the incidence of IFI for prophylaxis (RR =3.279, 95% confidence interval [CI] 1.73–6.206). Moreover, the success rate of treatment decreased significantly at a cut-off level of 0.5 mg/L (RR =0.396, 95% CI 0.176–0.889). An itraconazole trough level of 1.0 mg/L was associated with hepatotoxicity and other adverse events in a review of many studies.
Conclusion: An itraconazole trough concentration of 0.25 mg/L should be considered as the lower threshold for prophylaxis, and a target concentration of 0.5 mg/L should be the lower limit for effective treatment. A trough level of 1.0 mg/L is associated with increased hepatotoxicity and other adverse events (using High Performance Liquid Chromatography [HPLC]).
Keywords: itraconazole, trough concentration, efficacy, safety, meta-analysis

Introduction

Fungal infections exact a significant toll on human health and often compromise the clinical outcomes of patients. Prevalently, invasive fungal infection (IFI) is a leading cause of morbidity and mortality among neutropenic patients after intensive chemotherapy or hematopoietic stem cell transplantation, as well as in other immunocompromised populations.[1–3] Itraconazole is a first-generation triazole antifungal agent with broad-spectrum antifungal activity. In clinical practice, it is commonly used for fungal pathogen infections, such as *Candida spp., Cryptococcus neoformans, and Aspergillus spp.*[4] Itraconazole is often recommended as primary therapy for IFI[5–9] and as antifungal prophylaxis in immunocompromised patients.[10–12] Due to variable and unpredictable oral bioavailability and drug–drug interaction, a satisfactory pharmacokinetics profile cannot be developed with itraconazole in some conditions, making it difficult to determine the optimal dosing regimen.[13] Hence, therapeutic drug monitoring (TDM), a technique

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that timely and appropriately guides drug dosage modifications, is suggested to optimize the treatment.[14] Itraconazole trough concentration (C_{trough}) is a strong biomarker for drug exposure,[15] but most guidelines do not explicitly recommend an optimum trough concentration.

To our knowledge, there have been no randomized controlled trials on the target trough level, so there is no conclusive evidence on the relationship between the optimum trough concentration of itraconazole and its efficacy or safety. However, numerous observational studies have concluded minimum itraconazole level cut-off values, including 0.25,[16,17] 0.5,[18,19] and 1.0 mg/L.[20]A 2014 guideline from the British society for medical mycology recommended an itraconazole trough concentration of 0.5–1.0 mg/L to prevent and treat IFI,[21] which was based on some observational studies[22–30] and a previous meta-analysis in 2003.[31] This guideline also proposed an increased incidence of toxicity at higher itraconazole concentrations citing two studies which quantified itraconazole concentrations.[32,33]

Evidence for itraconazole target and critical trough concentrations described in these studies however, remains controversial and has significant limitations. For example, most of the observational studies which contributed to the aforementioned guideline were published more than 20 years ago. These studies often had no clear inclusion/exclusion criteria. Furthermore, the meta-analysis in the guideline[31] has drawbacks such as lack of standardized outcome definitions among included studies, no detailed itraconazole concentration data, no well-established methodology to perform quality assessment and subgroup analysis to explore the heterogeneity. More importantly, the previous and other meta-analyses[34,35] were all focused on the evidence of anti-mycoses efficacy or prophylaxis IFIs, rather than on the relationship between itraconazole concentration and efficacy or safety. Therefore, further evaluation of available literature is indicated to provide consistent recommendations for optimizing trough concentration. The objective of this systematic review and meta-analysis was to evaluate the relationship between the reported itraconazole trough concentration and the efficacy/safety of itraconazole.

Methods

Data sources

We performed this meta-analysis according to the Cochrane Handbook for Systematic Reviews and the Meta-analysis of Observational Studies in Epidemiology guidelines.[36] Two reviewers independently searched PubMed, EMBASE, Web of Science, the Cochrane Library, ClinicalTrials.gov, and three Chinese literature databases (CNKI, WanFang, and CBM) from inception until October 2017. We also examined reference lists of retrieved articles and related reviews. We used the search terms "itraconazole" and "concentration". We set no restrictions on language or study design.

Study selection

Two reviewers (JZ and YL) independently conducted initial screening and assessed titles, abstracts, and citations in greater detail. We included studies if: i) it was an observational study; ii) itraconazole was used for treatment or prophylaxis; iii) TDM was performed; iv) trough concentrations at steady state were reported for included patients; v) sufficient data about rate of treatment success, rate of prophylaxis failure, mortality or incidence of itraconazole-related adverse events (eg, hepatotoxicity) were reported; vi) sample size was ≥10 patients; and (vii) full text of the publication was available. The same reviewers retrieved and assessed the full text of potentially relevant articles using the same criteria. Disagreements were resolved through discussion.

Our exclusion criteria included: i) data came from simulated patients or pharmacokinetic models rather than from real patients; ii) concentrations were not troughs; iii) concentrations were not measured at steady state; iv) concentrations were measured by bioassay.

Cut-off value establishment

Previous studies[37–39] showed the MIC90 (MIC at which 90% of isolates were inhibited) of itraconazole for most yeasts and molds was between 0.25 and 1.0 mg/L. Some studies had shown a target itraconazole trough concentration of 0.25 mg/L.[16,17] A guideline[21] and other observational studies[18,19] suggested 0.5–1.0 mg/L as itraconazole trough concentration. Patients with C_{trough} of 1.0 mg/L were associated with a high level of clinical response according to Kim et al's 2014 study[20] and others.[40] Therefore, we established the stepwise cut-off values for itraconazole efficacy and safety as 0.25, 0.5, and 1.0 mg/L.

Data extraction and outcomes

The efficacy outcomes included were: IFI-related mortality, treatment success, and prophylaxis failure. Prophylaxis failure was evaluated by the incidence of IFIs, wherein, a high-risk ratio (RR) meant a high treatment success rate or prophylaxis failure rate. The major safety outcomes were hepatotoxicity and occurrence of adverse events. The pooled analysis for treatment success included only treatment studies, while the analysis for prophylaxis failure included only

prophylaxis studies, and the analysis of side effects included all studies.

Two authors extracted data independently (JZ and YL) and resolved any disagreements by discussion or by a third investigator (XN). We extracted study characteristics, participants' baseline characteristics, methods for measuring itraconazole concentration, type of trough concentration (initial, mean or maximum), cut-off value of itraconazole trough concentration, and pre-specified study outcomes of efficacy and safety from each study under review. If the study already contained a cut-off value, we considered patient groups below the pre-defined cut-off value as the intervention group, and those above the pre-defined cut-off value as the control. If studies contained no control group, we collected them into a single arm comparison. When individual patient data were available, we used all our pre-defined cut-off values to divide patients into two groups in the same way and extracted the number of events. When the trough concentration was measured multiple times for each patient, we used the mean value of multiple measurements, and we only used the median value when the mean was not available. If neither mean nor median was available, we used the reported trough concentration for that patient in the article. If there were multiple data for the same outcome in an article, we chose the outcome data measured at Day 14 considering itraconazole accumulates slowly and generally reaches concentrations steadily after 7–15 days of dosing.[41,42]

Quality assessment

Two independent reviewers (JZ and YL) completed the assessment. We applied the Newcastle–Ottawa Quality Assessment Scale to assess the quality of the included studies with control,[43] and used a star system (maximum of nine stars) to evaluate the methodological quality of each study. For observational studies without control, we applied a modified version of the Scale that does not evaluate the comparability part, and possible scores ranged from 0 to 6.[44] Higher scores indicated better quality. We resolved any disagreements between the reviewers through discussion. A third reviewer (XN) was available to settle any disputes.

Data analysis

We performed all analyses using the Open Meta-Analyst software (Tufts Medical Center, Boston, MA, USA). The I^2 statistic was used to assess heterogeneity among studies. I^2 values over 25%, 50%, and 75% represented low, moderate, and considerable heterogeneity, respectively.[45] To assess variations between studies in addition to sampling error within studies, we selected the fixed-effects model if I^2<50%, and the random-effects model when I^2≥50%. The DerSimonian–Laird or the Mantel–Haenszel method was used to calculate the PR or RR and 95% confidence interval (CI) for each study. The 95% CI of outcome among distinct groups did not overlap, showing that outcomes were statistically significant. P<0.05 was considered statistically significant.

Subgroup analyses

To explore the heterogeneity among different studies, we performed a subgroup analysis when more than two studies were included in the analysis of each cut-off level. For the treatment outcome, studies were stratified by: i) studies reporting single drug therapy compared with studies including patients on combination therapy (at least some patients on combination therapy); ii) studies located in Asian countries compared with in non-Asian countries. For the prophylaxis outcome, studies were stratified by location in Asian countries or European countries, or in America and Australia.

Sensitivity analysis

We performed sensitivity analysis to examine whether a single study substantially influenced the core results. We excluded each study and evaluated its effect on the summary estimates and heterogeneity of the main analysis, then reported the results for sensitivity analysis if the conclusions differed.

Results

Literature searches and study inclusion

The literature selection process is summarized in Figure 1. A total of 7,007 articles were initially identified. After initial screening, 68 full-text, potentially relevant articles were selected, 39 studies were excluded owing to inadequate clinical outcomes data, concentration was not a trough or at steady-state, or itraconazole alone, or measured by bioassay, among other reasons. Ultimately, 29 articles involving 2,346 patients were included for meta-analysis.[16–19,22–24,30,46–65]

Study characteristics

A summary of descriptions of included studies is reported in Table 1. Of these 29 studies, seven studies used itraconazole for treatment[30,46–51] and 22 studies used itraconazole for prophylaxis.[16–19,22–24,52–65] Fourteen were conducted in European countries, six were in Japan,[16,48,50,53,55,63] three were in China,[61,64,65] three were in America,[23,57,59] two in Australia,[18,62] and one in South Korea.[20] Among these, two studies were conducted in children who used itraconazole for prophylaxis.[54,56]

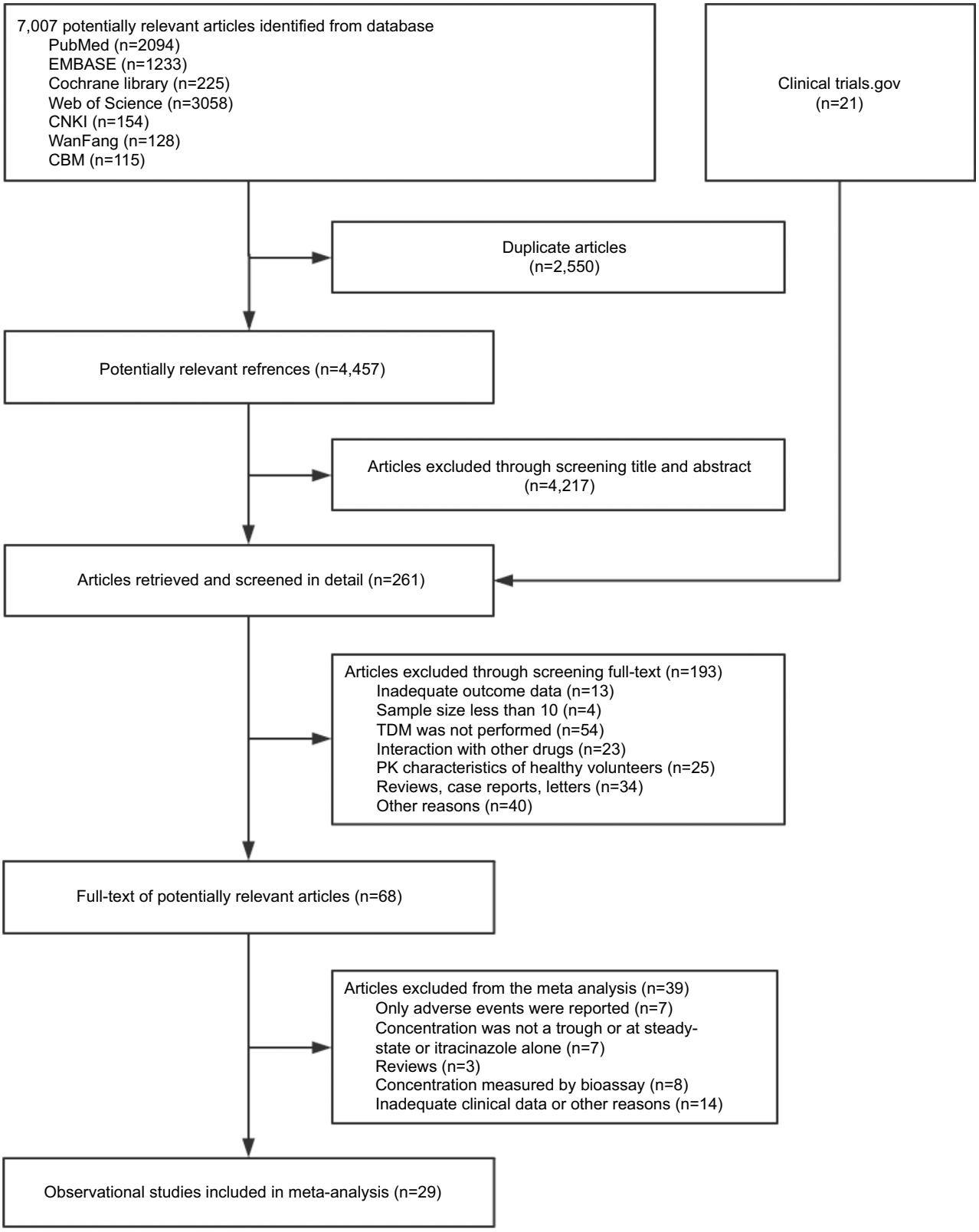

Figure 1 Flow chart of study selection.
Abbreviations: TDM, therapeutic drug monitoring; PK, pharmacokinetic.

Table 1 Characteristics of included studies

Itraconazole used for treatment									
First author year	**Country**	**Study design**	**Sample size (male/female)**	**Age (y)[a]**	**Main Disease (%)**	**Type of fungal infection (n)**	**Main site of infection**	**Duration**	**Combo therapy**
Cross et al 2000[30]	UK	prospective study	40 (9/31)	62 (29–81)	Candida-associated denture stomatitis	proven (36)	mouth	15 days	no
Lebeau et al 1994[46]	France	retrospective study	16 (9/7)	48 (8–86)	hematological disorder (38); cystic fibrosis (19); Hodgkin's disease (19)	proven (16)	lung	14–488 days	yes
[b]Havu et al 1999[47]	Finland	prospective study	129	NR	onychomycosis	NR	Fingernails, toenails	3 months	no
Matsumoto et al 1999[48]	Japan	prospective study	23 (13/10)	58.3±10.8	onychomycosis	Proven (15) probable (8)	Fingernails, toenails	NR	no
Caillot 2003[49]	France	prospective study	21 (13/8)	48 (25–78)	hematological malignancy	proven (21)	lung	14 weeks	yes
Yoshida et al 2012[50]	Japan	prospective study	24 (5/9)	64 (39–89)	respiratory disease	proven (64)	respiratory field, lung	51.7±34.0 days	no
Caillot et al 2001[51]	Belgium	prospective study	31 (20/11)	48 (25–78)	hematologic malignancies (87)	proven (31)	lung	14 (4–28) days	no
Itraconazole used for prophylaxis									
First author year	**Country**	**Study design**	**Sample size (male/female)**	**Age (y)**	**Main Disease %**	**Duration (d)**	**Follow-up (d)**		
Myoken et al 2002[16]	Japan	retrospective study	16	NR	acute leukemia	57 months	10		
Tricot et al 1987[23]	USA	prospective study	45 (27/18)	45 (9–78)	hematologic diseases	NR	NR		
Boogaerts et al 1989[22]	Belgium	prospective study	72 (40/32)	45 (9–78)	Hematological malignancies	42	NR		
Morgenstern et al 1999[52]	UK	prospective study	445 (276/169)	mean:44 ·5	hematological malignancies	90	30		
Harousseau et al 2000[17]	European countries	prospective study	281 (167/114)	48 (15–75)	Hematological Malignancy	19 (1–56)	NR		
Kageyama et al 1999[53]	Japan	prospective study	14 (8/6)	50 (25–79)	acute leukemia	(14–NR)	NR		
Brett et al 2013[18]	Australia	Retrospective study	57 (30/27)	NR	Heart and Lung Transplantation	(30–135)	NR		
Ceesay et al 2016[19]	UK	prospective study	53 (33/20)	52 (23–68)	hematological malignancies	NR	NR		
[c]Schmitt et al 2001[54]	France	prospective study	17 (10/7)	—	Hematologic Malignancy (71)	NR	NR		
Kanda et al 1998[55]	Japan	prospective study	18	NR	hematological malignancies	NR	NR		
Glasmacher et al 1999[24]	Germany	Retrospective study	150	54 (41–64)	hematological malignancies	21	NR		
Simon et al 2007[56]	Germany	prospective study	39 (20/19)	6.4 (0.7–11,5)	hematological malignancies	27 (6–246)	NR		
Marr et al 2004[57]	USA	prospective study	151 (75/76)	NR	allogeneic stem cell transplants	89	708		
Boogaerts et al 2001[58]	*Belgium*	prospective study	17 (9/8)	41 (19–60)	Hematologic Malignancy	21	NR		

(*Continued*)

Table 1 (*Continued*)

Itraconazole used for prophylaxis							
First author year	**Country**	**Study design**	**Sample size (male/female)**	**Age (y)**	**Main Disease %**	**Duration (d)**	**Follow-up (d)**
Winston et al 2002[59]	USA	prospective study	97 (51/46)	53 (24–72)	liver transplant	70	1y
Glasmacher et al 1998[60]	Germany	Retrospective study	47 (27/20)	57.0 (19–84)	Acute leukaemia	NR	NR
[d]Lin et al 2014[61]	China	prospective study	121 (76/45)	—	Allogeneic HSCT	—	180 (8–180)
Kim et al 2014[20]	South Korea	prospective study	181 (98/83)	54 (20–83)	hematological malignancies	14	NR
Lindsay et al 2017[62]	Australia	prospective cohort study	57 (36/21)	mean51.8 (18–76)	HSCT (81)	—	—
Liu et al 2015[64]	China	prospective study	35 (21/14)	37 (14–64)	Hemopathy	(NR-180)	NR
Toubai et al 2005[63]	Japan	prospective study	37 (21/16)	46 (16–77)	hematological malignancies	—	—
Liu et al 2013[64]	China	prospective study	112 (68/44)	37 (18–64)	acute myeloid leukemia	NR	NR

Notes: NR, not reported; HSCT, hematopoietic stem cell transplantation. [a]age was represented as median (interquartile range) or mean±SD. [b]Continuous treatment with itraconazole 200 mg once daily for 3 months were considered for this articl. [c]Ten patients in group 1 (aged 1.7 to 4.9 years; median, 1 year); and seven in group 2 (aged 6.2 to 14.3 years; median, 10 years). [d]The median age was 27.70 (12.2–52.9) years in the long-term arm and 23.60 (12.5–55.6) years in the short-term arm. The median duration of administration was 90 days (range, 4–96 days) in the long-term arm and 32 days (range, 9–35 days) in the short-term arm.

Ten studies used serum samples,[16,20,24,30,52,57,60–62,64] while the other 15 used plasma samples.[17,18,20,22,23,46–49,51,55,56,58,59,63] The remainder did not report whether serum or plasma sample was used. All the included studies measured itraconazole concentrations by HPLC.

Evaluation of efficacy

Table 2 displays a summary of outcomes for each study, and Tables 3–7 exhibit summaries of meta-analysis and subgroup analysis and sensitivity analysis for efficacy. Figures 2 and 3 and Figures S1–S10 show forest plots.

Our meta-analysis demonstrated there were no significant differences at all cut-off values for efficacy (without control arm) (Table 3). In comparing efficacy, including studies with control arm, we found a significant difference at the cut-off level of 0.25 mg/L for incidence of IFI (RR =3.279, 95% CI 1.73–6.206) (Table 4 and Figure 2). For treatment success, our meta-analysis based on two studies, showed that the success rate decreased at a cut-off level of 0.5 mg/L (RR =0.396, 95% CI 0.176–0.889) (Table 4, Figure 3). Only one study contributed data for IFI-related mortality so we were unable to pool the data.[60]

Subgroup analysis showed that the rate of prophylaxis failure significantly increased at a cut-off level of <0.25 mg/L in USA + Australia subgroup patients (PR =0.524, 95% CI 0.310–0.737) compared with other concentration regimens. There were no significant differences at other cut-off levels (Tables 5–7).

Sensitivity analysis

We identified moderate to considerable inter-study heterogeneity during some of the meta-analyses, so we used a random-effects model when $I^2 \geq 50\%$ and the source of heterogeneity assessed in subgroup analysis according to combination therapy and study location (Tables 5–7). The heterogeneity we observed may also be due to diseases, itraconazole dose, sample size, age, and/or the criteria used for assessment – these factors led us to also conduct sensitivity analysis. The trial by Caillot et al in 2001 with relatively small sample size or including complete and partial responders for outcome was omitted and analyzed again to test the stability of the final pooled results.[51] The results showed that, in ≥0.25 mg/L and ≥1.0 mg/L, I^2 was significantly decreased to less than 50%. When we removed another study with relatively small sample size or proven and possible IFI, there was a decline to less than 50% of I^2 in <0.5 mg/L range group.[63] Though I^2 decreased, the 95% CI did not change significantly, demonstrating that the meta-analysis results were robust. Sensitivity analysis results were summarized in Tables S1 and S2.

Evaluation of safety

Due to different reported safety outcomes and variable definitions of hepatotoxicity, we could not pool the data to perform a meta-analysis. In general, itraconazole was well tolerated in most patients.

Regarding treatment, Miller[66] reported that two of 13 patients with itraconazole C_{trough} <0.25 mg/L had adverse

Table 2 Outcomes and results of included studies

Itraconazole used for treatment				
First author year	**Type of C_{trough}**	**Cut-off value**	**Reported outcome**	**Definition of treatment success**
Cross et al 2000[30]	initial	all	treatment success	mycologically cured patients and non-cured patients
Lebeau et al 1994[46]	mean	0.5,1.0	treatment success liver function disorders	respond to therapy (recovery or improvement)
Havu et al 1999[47]	mean	≥0.25, <0.5, <1.0	treatment success	responders and non-responders
Matsumoto et al 1999[48]	mean	<0.25, <0.5,>1.0	treatment success adverse events	significant improvement and improvement
Caillot 2003[49]	mean	≥0.25, ≥0.5, <1.0	treatment success adverse events	complete or partial response
Yoshida et al 2012[50]	mean	≥0.25, ≥0.5, ≥1.0	treatment success liver dysfunction and other adverse events	Improvement (response)
Caillot et al 2001[51]	median	≥0.25, ≥0.5, ≥1.0	treatment success adverse events	complete or partial response
Itraconazole used for prophylaxis				
First author year	**Type of C_{trough}**	**Cut-off value**	**Reported outcome**	**Definition of occurrence of IFI**
Myoken et al 2002[16]	mean	0.25	occurrence of IFI	Positive cultures
Tricot et al 1987[23]	mean	0.25	occurrence of IFI	Positive cultures
Boogaerts et al 1989[22]	mean	0.25	Incidence of proven and suspected IFI	Positive cultures
Morgenstern et al 1999[52]	mean	0.25,0.5	proven fungal infections	clinical/radiological and mycological evidence, positive cultures
Harousseau et al 2000[17]	mean	0.25	occurrence of IFI adverse events	positive cultures
Kageyama et al 1999[53]	initial	all	occurrence of IFI	NR
Brett et al 2013[18]	initial	0.5	breakthrough IFI	EORTC/MSG, positive cultures
Ceesay et al 2016[19]	median	0.5	occurrence of IFI	EORTC/MSG, proven and probable IFI
[c]Schmitt et al 2001[54]	mean	1.0	occurrence of IFI	NR
Kanda et al 1998[55]	mean	≥0.25, <0.5, <1.0	pulmonary aspergillus infection	diagnosed by a computed tomography scan of the chest and by the detection of aspergillus antigen.
Glasmacher et al 1999[24]	initial	≥0.25, ≥0.5, <1.0	occurrence of IFI	clinical or radiological signs of infection, positive culture, include proven or highly suspected invasive fungal infections
Simon et al 2007[56]	mean	≥0.25, ≥0.5, <1.0	breakthrough IFI	NR
Marr et al 2004[57]	median	≥0.25, ≥0.5, <1.0	occurrence of IFI	EORTC/MSG, proven and probable IFI
Boogaerts et al 2001[58]	mean	≥0.25, ≥0.5, <1.0	occurrence of IFI abnormal AST/ALT value	NR
Winston et al 2002[59]	mean	≥0.25, <0.5, <1.0	occurrence of IFI liver function disorders	EORTC/MSG, positive cultures, proven
Glasmacher et al 1998[60]	median	≥0.25, ≥0.5, <1.0	IFI-related mortality occurrence of IFI hepatotoxicity and other adverse events	proven invasive fungal infection (1) Histological and/or microbiological proof (2) Radiological evidence and microbiological isolation of a fungus
[d]Lin et al 2014[61]	mean	≥0.25, ≥0.5, <1.0	Breakthrough IFI liver dysfunction and other adverse events	EORTC/MSG, Breakthrough IFI (proven, probable, and possible) .
Kim et al 2014[20]	mean	≥0.25, ≥0.5, ≥1.0	Breakthrough IFI hepatotoxicity and other adverse events	Breakthrough fungal infections, probable or proven
Lindsay et al 2017[62]	mean	≥0.25, ≥0.5, ≥1.0	occurrence of IFI liver function disorders	EORTC/MSG, Possible or probable IFI
Liu et al 2015[64]	mean	≥0.25, ≥0.5, <1.0	occurrence of IFI elevated aminotransferase value	NR
Toubai et al 2005[63]	mean	≥0.25, ≥0.5, <1.0	occurrence of IFI adverse events	clinical symptoms and positive cultures (proven and possible)
Liu et al 2013[64]	mean	≥0.25, ≥0.5, <1.0	occurrence of IFI adverse events	confirmed diagnosis, clinical diagnosis, suspected diagnosis

Abbreviations: C_{trough}, trough concentration; NR, not reported; EORTC-MSG, 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.

events grade 3 or 4 related to study treatment. Matsumoto et al[48] found patients with C_{trough} <0.25 mg/L experienced mild diarrhea (one case), mild drug eruption (one case), and abnormal GOT and GPT (one case). Lebeau et al[46] reported that two patients presented with liver function disorders with concentration 0.25–0.5 mg/L and 0.5–1.0 mg/L, respectively. Nine patients (43%) with C_{trough} 0.5–1.0 mg/L experienced severe adverse events in Caillot's study.[49] Among these nine cases, there was only one severe reaction definitely related to itraconazole treatment. In a study including a concentration more than 1.0 mg/L, researchers observed adverse events such as liver dysfunction in four patients and heart failure in five of a total of 24 patients in Yoshida et al's study.[50] In another trial,[51] only two events were considered definitely related to the treatment: rash in one patient and rigors during drug administration in another. Thirteen patients (42%) experienced adverse events possibly related to treatment. Together, these numbers are substantial in terms of adverse events results.

Regarding prophylaxis, of 97 patients on itraconazole with C_{trough} 0.25–0.5 mg/L, three patients had abnormal liver function tests possibly related to itraconazole, but no patients were removed from the study because of concerns about hepatotoxicity from itraconazole according to Winston and Busuttil.[59] In addition, we discovered from Toubai et al's study,[63] that there were no other obvious side effects caused by prophylactic itraconazole administration. For C_{trough} 0.5–1.0 mg/L, Boogaerts et al[58] reported three cases of abnormal rise in AST/ALT levels in 17 patients. Serious adverse events were reported in 26 (9%) patients in Harousseau et al's study.[17] Glasmacher et al,[60] in their study, claimed that there were no severe adverse effects (necessitating an interruption of prophylaxis) clearly attributable to itraconazole, especially no severe hepatotoxicity events. Lin et al's study[61] showed that drug-related adverse events occurred in 19 (15.7%) of the patients involved, including 15 with gastrointestinal disorders (12.4%), two with abnormal liver function (1.65%), one with hypokalemia (1/121), and one with hydrothorax (0.8%). In Liu's study there were 16 patients who withdrew from the study due to adverse reactions, including three cases of elevated aminotransferase.[65] Adverse events were observed in as many as 42 patients (14.1%) in Liu et al's study (transaminase elevation in two patients, drug withdrawal in 16, heart dysfunction in one).[64] For C_{trough} ≥1.0 mg/L, in Lindsay et al's research, there were eleven mild derangements of liver function tests and two moderate raised bilirubin in 57 patients.[62] Meanwhile, Kim et al's study[20] showed adverse events in 67 patients (32.8 %); specifically, hepatotoxicity (n=39, 19.1 %) and nephrotoxicity (n=8, 3.9 %) were common in this study and seven patients discontinued itraconazole therapy due to toxicity.

Table 3 Summary of meta-analysis for efficacy (without control arm)

Cut-off value (mg/L)	PR (95% CI)	Number of studies	Number of participants	I^2%
Rate of treatment success				
<0.25	0.498 (–0.204, 1.200)	2	22	93.32
≥0.25	0.527 (0.402, 0.652)	6	154	61.68
<0.5	0.549 (0.209, 0.888)	4	72	91.06
≥0.5	0.552 (0.373, 0.730)	5	104	73.96
<1.0	0.632 (0.478, 0.787)	5	108	67.24
≥1.0	0.480 (0.304, 0.657)	4	68	52.43
Incidence of IFI				
<0.25	0.183 (0.047, 0.319)	6	149	88.81
≥0.25	0.081 (0.053, 0.109)	19	1,726	85.9
<0.5	0.126 (0.052, 0.199)	7	251	71.28
≥0.5	0.077 (0.044, 0.110)	15	1,317	85.74
<1.0	0.101 (0.061, 0.140)	13	1,089	79.17
≥1.0	0.047 (0.021, 0.074)	4	245	0

Abbreviations: CI, confidence interval; IFI, invasive fungal infection

Table 4 Summary of meta-analysis for efficacy (with control arm)

Cut-off value (mg/L)	RR (95% CI)	Number of studies	Number of participants in experimental group	Number of participants in control group	I^2%
Rate of treatment success					
<0.25 vs ≥0.25	0.243 (0.018, 3.313)	1	3	33	NA
<0.5 vs ≥0.5	0.396 (0.176, 0.889)[a]	2	18	29	0
<1.0 vs ≥1.0	0.746 (0.462, 1.204)	2	33	14	0
Incidence of IFI					
<0.25 vs ≥0.25	3.279 (1.732, 6.206)[a]	6	149	419	0
<0.5 vs ≥0.5	1.214 (0.485, 3.306)	4	101	145	0
<1.0 vs ≥1.0	0.203 (0.026, 2.034)	2	20	7	0

Note: [a]Statistically significant difference.
Abbreviations: CI, confidence interval; IFI, invasive fungal infection; NA, not applicable.

Table 5 Summary of subgroup analysis for treatment success (without control arm)

Subgroup		Cut-off value (mg/L)	PR (95% CI)	Number of studies	Number of participants	I^2%
Combination therapy	Yes	<0.25	NA	NA	NA	NA
		≥0.25	0.605 (0.439, 0.770)	2	32	0
		<0.5	0.500 (0.010, 0.990)	1	4	NA
		≥0.5	0.682 (0.356, 1.008)	2	28	73.57
		<1.0	0.570 (0.395, 0.746)	2	30	0
		≥1.0	0.833 (0.412, 1.255)	1	2	NA
Combination therapy	No	<0.25	0.498 (–0.204, 1.200)	2	22	93.32
		≥0.25	0.493 (0.332, 0.653)	4	122	71.41
		<0.5	0.559 (0.166, 0.952)	3	68	94.02
		≥0.5	0.476 (0.264, 0.688)	3	76	74.12
		<1.0	0.654 (0.427, 0.881)	3	78	81.13
		≥1.0	0.414 (0.277, 0.550)	3	66	23.57
Study location	Asian location	<0.25	0.842 (0.678, 1.006)	1	19	NA
		≥0.25	0.435 (0.232, 0.637)	1	23	NA
		<0.5	0.842 (0.678, 1.006)	1	19	NA
		≥0.5	0.435 (0.232, 0.637)	1	23	NA
		<1.0	0.842 (0.678, 1.006)	1	19	NA
		≥1.0	0.435 (0.232, 0.637)	1	23	NA
Study location	Non-Asian location	<0.25	0.125 (–0.199, 0.449)	1	3	NA
		≥0.25	0.546 (0.339, 0.692)	5	131	67.21
		<0.5	0.438 (0.023, 0.854)	3	53	89.9
		≥0.5	0.584 (0.359, 0.809)	4	81	79.33
		<1.0	0.572 (0.437, 0.706)	4	89	40.23
		≥1.0	0.531 (0.249, 0.812)	3	45	68.29

Abbreviations: CI, confidence interval; NA, .

Table 6 Summary of subgroup analysis for prophylaxis failure (without control arm)

Subgroup		Cut-off value (mg/L)	PR (95% CI)	Number of studies	Number of participants	I^2%
Study location	Asian location	<0.25	0.053 (–0.050, 0.157)	2	16	0
		≥0.25	0.114 (0.062, 0.167)	8	761	77.25
		<0.5	0.174 (0.016, 0.332)	3	60	65.78
		≥0.5	0.097 (0.043, 0.150)	5	701	80.87
		<1.0	0.128 (0.070, 0.186)	6	579	71.45
		≥1.0	0.045 (0.015, 0.075)	2	182	0
Study location	European location	<0.25	0.172 (–0.012, 0.356)	3	112	92.61
		≥0.25	0.037 (0.010, 0.065)	7	639	78.45
		<0.5	0.095 (–0.071, 0.260)	2	76	81.2
		≥0.5	0.056 (0.013, 0.099)	7	394	79.96
		<1.0	0.062 (0.004, 0.119)	5	262	76.11
		≥1.0	0.167 (–0.132, 0.465)	1	6	NA
Study location	USA and Australia	<0.25	0.524 (0.310, 0.737)[a]	1	21	NA
		≥0.25	0.098 (0.066, 0.130)[a]	4	326	0
		<0.5	0.100 (0.046, 0.155)	2	115	0
		≥0.5	0.078 (0.016, 0141)	3	222	62.95
		<1.0	0.114 (0.074, 0.153)	2	248	0
		≥1.0	0.053 (–0.005, 0.111)	1	57	NA

Note: [a]There is significant difference in <0.25 vs other concentration groups in USA and Australia group.
Abbreviations: CI, confidence interval; NA, .

Table 7 Summary of subgroup analysis for prophylaxis failure (with control arm)

Cut-off value (mg/L)	Subgroup		RR (95% CI)	Number of studies	Number of participants in experimental group	Number of participants in control group	I^2%
<0.25 vs ≥0.25	Study location	Asian location	1.252 (0.086, 18.259)	2	12	16	0
		European location	0.225 (0.092, 0.549)	3	386	112	0
		USA	0.364 (0.138, 0.961)	1	212	21	NA
<0.5 vs ≥0.5	Study location	Asian location	0.750 (0.017, 32.676)	1	7	5	NA
		European location	1.046 (0.385, 2.845)	2	76	126	0
		Australia	5.526 (0.309, 98.923)	1	18	14	NA

Abbreviations: CI, confidence interval; NA, not applicable.

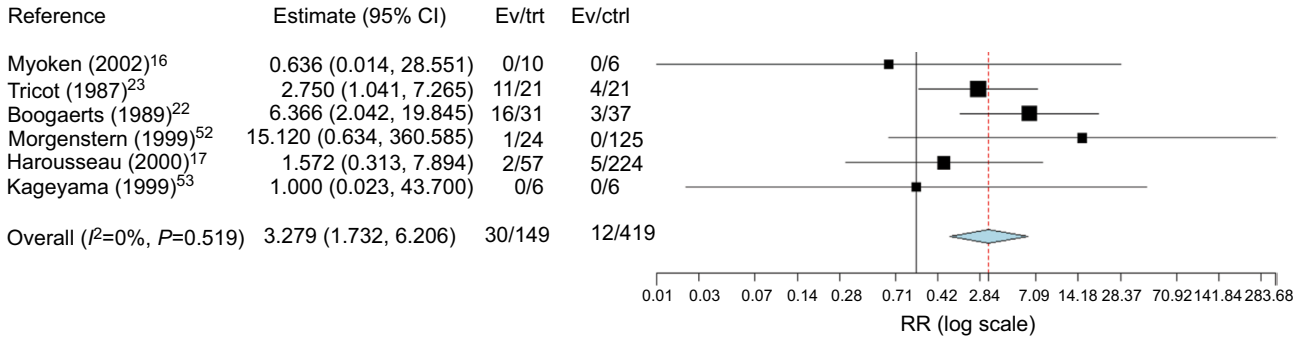

Figure 2 Meta-analysis for prophylaxis failure rate (trough concentration of <0.25 mg/L comparison with ≥0.25 mg/L, RR <1 favors C_{trough}<0.25 mg/L).
Abbreviations: CI, confidence interval; ctrl, control group; Ev, events; trt, treatment group.

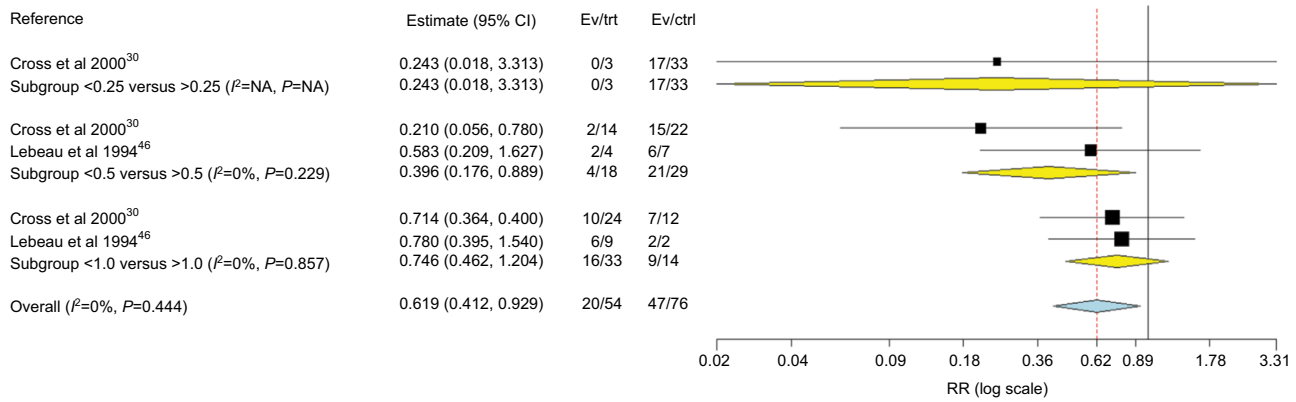

Figure 3 Meta-analysis for treatment success rate (trough concentration < cut-off value comparison with ≥ cut-off value, RR <1 favors ≥ cut-off value).
Abbreviations: CI, confidence interval; ctrl, control group; Ev, events; trt, treatment group.

Considering the myriad and prevalence of adverse effects in all these studies, an itraconazole trough level of 1.0 mg/L is associated with increased hepatotoxicity and other adverse events.

Evaluation when using the bioassay method

Due to the variation in measurements of blood itraconazole using bioassay (measures both itraconazole and hydroxy-itraconazole) vs HPLC (which measures itraconazole separately), it seems that concentrations measured by bioassay are 5-fold higher compared with HPLC/mass spectrometry.[67] Few studies have incorporated bioassay, so we excluded these studies from our meta-analysis. Accordingly, we have not identified any recommendations on itraconazole trough level measured by bioassay.

For treatment, Tucker et al[68] reported a trough concentration of 6.5±4.2 mg/L in 28 responders and 4.0±3.2 mg/L in eleven non-responders. Another, Sharkey et al's study, noted no elevations in hepatic enzyme values compared to baseline values in eight patients where two were <2 mg/L and the other six were >5 mg/L.[27] Galgiani et al[69] found 61 responded to itraconazole treatment in 97 patients with 6–8 mg/L and two adverse events could have been caused by itraconazole including

one case of elevated liver enzyme levels and one hypokalemia cased. Denning et al's study[25]determined that trough levels <2.5 mg/L in three responders and one non-responder, 2.5–5 mg/L in two responders and one non-responder, 5–10 mg/L in two responders; and finally >10 mg/L in three responders.

For prophylaxis, according to Lestner et al's study,[32] at C_{trough} <17.1 mg/L, 47 (31%) patients developed itraconazole-related toxicity; at C_{trough} ≥17.1 mg/L, 55 (86%) patients developed toxicity. Wheat et al[70] reported that, in their study, 39 of 42 patients with 6.8 mg/L achieved successful suppression, but 37 patients (88%) experienced grade 3 or 4 (severe or life-threatening) adverse events. One patient was removed from the trial entirely because of itraconazole. In addition, no patient receiving prophylaxis developed invasive aspergillosis and withdrew from the trial due to side effects, nor were toxicities attributed to rising cyclosporine levels associated with itraconazole (Patterson et al: 0.5 mg/L, six patients; 3.5 mg/L, six patients).[71] Denning's study also exhibited that patients with serum concentrations of 8 mg/L tended to have better clinical outcomes when using itraconazole for primary treatment of invasive aspergillosis.[72]

Quality assessment

Using a 9-point scoring system, most studies we analyzed scored between 7 and 9. In a 6-point scoring system, most studies scored between 4 and 6. The result showed that most studies did well in sample selection and comparability but failed in outcome due to short or inadequate follow-ups. Assessment of study-specific quality scores from the Newcastle–Ottawa Scale system is summarized in Table 8.

Discussion

As an antifungal agent, itraconazole has been widely used for the treatment of deep mycoses and prophylaxis of IFIs in patients with profound and prolonged neutropenia, bone marrow transplant recipients, solid organ transplant recipients, and other immunocompromised populations. Although many studies have analyzed itraconazole's efficacy compared with other antifungal drugs, researchers, so far, have drawn no definitive conclusions on the optimum trough concentration for treatment. Itraconazole exhibits high inter- and intra-patient variability in the pharmacokinetic profile following oral and intravenous doses, so TDM is suggested to optimize the efficacy and avoid toxicity.[21] Considering the lower power of individual observational studies and clinical needs, we conducted this systematic review and meta-analysis to provide a more reliable and explicit recommendation on the optimum trough concentration of itraconazole, with less random errors and more precise estimates.

To our knowledge, this is the first meta-analysis focusing on the relationship between itraconazole trough level and the efficacy/safety. After pooling available data from 29 included articles, the meta-analysis revealed that an itraconazole trough concentration of 0.25 mg/L is associated with successful prophylaxis of IFI. This conclusion differs from the 0.5–1.0 mg/L threshold that some publications have suggested, likely due to their limited study subjects.[73,74] We conducted a subgroup analysis by study location, thereby demonstrating that the rate of prophylaxis failure significantly increased at a cut-off level of <0.25 mg/L in USA + Australia subgroup patients compared with other concentration regimens. However, subgroup analysis results of the Asia and Europe subgroup were different and insignificant, suggesting a possibility that the concentration–efficacy relationship follows a different profile among different ethnicities. We recognize that the study number was limited and sample size was small in our meta-analysis, therefore further studies are needed to verify the differences in different ethnicities.

Our meta-analysis also demonstrated that a target value of 0.5 mg/L increased treatment success. It is similar to the guideline which recommends itraconazole trough concentration of 0.5–1.0 mg/L as it pertains to treatment of IFIs.[21] We divided our subgroups into combination therapy and study location. First, itraconazole inhibits CYP3A4, which leads to a number of clinically relevant drug–drug interactions. Combination therapy with amphotericin B or other drugs may change the profile of drug exposure,[14,75] which might explain why the combination therapy subgroup did not show significance at the 0.5 mg/L cut-off level. Second, each cut-off value of Asian location subgroup differed significantly. As there is only one study in every concentration group, we regard these subgroup analysis results as likely to be unreliable. Notably, the small number and size of included studies for treatment success limits the utility of this metric.[30,46]

During our meta-analysis, we observed heterogeneity in the results, some of which persisted even in subgroup analysis by combination therapy and study location. Nevertheless, sensitivity analysis resulted in a dramatic decrease in I^2 through removing method (Table S1 and S2). These results revealed that sample size and the criteria used for assessment could be the sources of heterogeneity. It is also possible that differences in disease, itraconazole dose, age and/or duration of disease or follow-up may be responsible for the heterogeneity we observed. Hence, future studies are needed to explore further causalities. However, though I^2 decreased, the 95% CI of each cut-off value only changed insignificantly, indicating the robustness.

Table 8 Quality of studies included in the meta-analysis

Study	Newcastle–Ottawa Quality Assessment Scale (cohort study)								Score
	Selection				Comparability	Outcome			
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	
Studies with control									
Cross et al 2000[30]	☆	☆	☆	☆	☆☆	☆	–	–	7
Lebeau et al 1994[46]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Myoken et al 2002[16]	☆	☆	☆	☆	—	☆	☆	☆	7
Tricot et al 1987[23]	☆	☆	☆	☆	☆☆	☆	–	–	7
Boogaerts et al 1989[22]	☆	☆	☆	☆	☆–	☆	–	–	6
Morgenstern et al 1999[52]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Harousseau et al 2000[17]	☆	☆	☆	☆	☆☆	☆	–	–	7
Kageyama et al 1999[53]	☆	☆	☆	☆	☆☆	☆	–	–	7
Brett et al 2013[18]	☆	☆	☆	☆	☆☆	☆	–	–	7
Ceesay et al 2016[19]	☆	☆	☆	☆	☆☆	☆	–	–	7
Schmitt et al 2001[54]	☆	☆	☆	☆	☆☆	☆	–	–	7
Studies without control									
Havu et al 1999[47]	☆	/	☆	☆	/	☆	☆	☆	6
Matsumoto et al 1999[48]	☆	/	☆	☆	/	☆	☆	☆	6
Caillot 2003[49]	☆	/	☆	☆	/	☆	☆	☆	6
Yoshida et al 2012[50]	☆	/	☆	☆	/	☆	☆	☆	6
Caillot et al 2001[51]	☆	/	☆	☆	/	☆	–	–	4
Kanda et al 1998[55]	☆	/	☆	☆	/	☆	–	–	4
Glasmacher et al 1999[24]	☆	/	☆	☆	/	☆	–	–	4
Simon et al 200756	☆	/	☆	☆	/	☆	–	–	4
Marr et al 2004[57]	☆	/	☆	☆	/	☆	☆	☆	6
Boogaerts et al 2001[58]	☆	/	☆	☆	/	☆	–	–	4
Winston et al 2002[59]	☆	/	☆	☆	/	☆	☆	☆	6
Glasmacher et al 199860	☆	/	☆	☆	/	☆	–	–	4
Lin et al 2014[61]	☆	/	☆	☆	/	☆	☆	☆	6
Kim et al 2014[20]	☆	/	☆	☆	/	☆	–	–	4
Lindsay et al 2017[62]	☆	/	☆	☆	/	☆	☆	☆	6
Liu et al 2015[64]	☆	/	☆	☆	/	☆	–	–	4
Toubai et al 2005[63]	☆	/	☆	☆	/	☆	☆	☆	6
Liu et al 2013[64]	☆	/	☆	☆	/	☆	–	–	4

Notes: The data is presented using the Newcastle-Ottawa Quality Assessment Scale, "☆", represents the score; "–" the item(question) has no score; "/", not applicable. Q1: the exposed cohort was truly or somewhat representative? Q2: the non-exposed cohort was drawn from the same community as the exposed cohort? Q3: exposure was ascertained by secure record or structured interview? Q4: outcome of interest was not present at start of study? Q5: on the basis of the design or analysis, cohorts had comparability? (controls for the most important factor? controls for any additional factor?) Q6: outcome was independent blind assessment or record linkage? Q7: follow-up was long enough for outcomes to occur? Q8: follow-up of cohorts was adequate? A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability.
Abbreviation: Q, question.

There are too little study-contributed data for IFI-related mortality for us to have effectively pooled data in our review.[60] The clinical outcomes and definitions of safety in studies were various, wherein some studies reported adverse events grade 3 or 4,[66] some reported liver function disorders with different criteria,[46,50] some reported adverse reactions related to itraconazole treatment,[51,60] and various trials reported the adverse events and abnormal laboratory examination values without consistent standards.[17,48,58] Thus we could not combine results to forge a comprehensive meta-analysis. Most patients treated with itraconazole are already immunocompromised and undergoing chemotherapy, which each involves conditions with many adverse effects. The relationship between treatment and adverse events remains unclear, and most guidelines indicate an increased incidence of toxicity at higher itraconazole concentrations without explicitly recommending an optimum trough concentration for safety.[21,73] After reviewing many studies, we offer 1.0 mg/L as the cut-off value that is associated with increased hepatotoxicity and other adverse events. To fully elucidate this issue, further studies are needed.

Our meta-analysis and review has the following strengths. First, it is the first to focus on the relationship of itraconazole trough concentration with efficacy and safety, providing certain reference significance to clinical practice. Second, our meta-analysis compared commonly used cut-off levels in a single analysis for individual cut-off levels. Finally, we included Japanese articles in this meta-analysis to maximize the reliability considering the prevalence of the research in

Japan, while most English language reviews have not done this until now.

We acknowledge the following limitations to our work. First, the number of studies and sample sizes were relatively small, leading to potentially insufficient power to detect mild differences. Second, we were unable to perform subgroup analysis for the pediatric population because we only identified two studies designed for children. Besides, we could not analyze the influences of different pathogen and infection locations on the results. Third, the use of observational studies in a meta-analysis is prone to biases and confounding factors inherent in the original studies. Finally, although our subgroup analysis and sensitivity analyses explained some heterogeneity in the results, there is a clear need for further study.

Conclusion

In conclusion, our meta-analysis of published studies demonstrates that 0.25 mg/L is the lower threshold of the target itraconazole trough concentration during prophylaxis of fungal infections. Additionally, the target 0.5 mg/L is the lower limit for successful treatment. We have deduced that a trough level of 1.0 mg/L is associated with substantially increased hepatotoxicity and other adverse events (using HPLC).

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Disclosure

The authors report no conflicts of interest in this work.

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