

Voriconazole vs Itraconazole for Primary Prophylaxis of Invasive Fungal Infection (IFI) in Allogeneic Hematopoietic Cell Transplant (HCT) Recipients

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Abstract

Background: Optimal antifungal prophylaxis following HCT is uncertain. The potential of oral VOR required prospective randomized evaluation.

Methods: Prospective, open label, multicenter study for primary IFI prophylaxis after allogeneic HCT. Patients ≥ 12 years were randomized (stratified by conditioning regimen intensity and donor type) to receive oral VOR or oral ITR from the day of HCT for at least 100 and up to 180 days. Primary composite endpoint: success of prophylaxis at Day 180, i.e. patient survived without developing proven/probable IFI or discontinuing prophylaxis for > 14 days during the first 100 days.

Results: 234 patients were randomized to VOR and 255 to ITR; all received > 1 dose of study drug. Success of prophylaxis was significantly higher with VOR than with ITR at Days 100 (55% vs 41%; adjusted 95% CI for difference: 6%, 24%; $p=0.0007$) and 180 (49% vs 35%; adjusted 95% CI for difference: 7%, 24%; $p=0.0004$). Significantly more VOR than ITR (54% vs 40%; $p=0.0014$) patients had sufficient days of prophylaxis (median: 97 vs 68 days). IFI incidence was low in both arms (VOR: 1.3%, ITR: 2.0%); no patients developed IFI while receiving VOR, compared with 3 ITR patients. There was no difference in 180 day survival (85% each). The most common treatment-related adverse events for VOR and ITR, respectively, were nausea (8% vs 15%), diarrhoea (4% vs 11%), hepatotoxicity (7% vs 2%) and visual impairment (6% vs 0%).

Conclusions: Primary prophylaxis with VOR is an effective, safe option for preventing IFI after allogeneic HCT.

Background

- Invasive aspergillosis (IA) is the major fungal threat in allogeneic HCT recipients
 - Voriconazole is an established and effective therapy for documented IA
- Optimal antifungal prophylaxis following allogeneic HCT is uncertain
- Oral antifungal agents have potential advantages but require testing in the allograft setting
- Oral voriconazole required prospective randomized evaluation as antifungal prophylaxis against an established oral agent that covers moulds

Prospective, Open-Label, Multicenter Study

- 489 patients \geq 12 years of age undergoing allogeneic HCT (myeloablative or reduced intensity)
- Randomized to primary IFI prophylaxis, stratified by conditioning regimen and donor type

Voriconazole (N=234)

- IV loading dose: 6 mg/kg BID
- PO maintenance dose: 200 mg BID for patients >40 kg and 100 mg BID for those <40 kg

Itraconazole (N=255)

- IV loading dose: 200 mg BID
- PO maintenance dose: 200 mg BID (Itraconazole capsules for total of ≤ 14 days only, ≤ 5 day periods suggested)

- Duration: at least 100 and up to 180 days
- Empirical therapy with non-study antifungal agent was permitted if signs of possible IFI developed

Participating countries: UK, Spain, France, Canada, Czech Republic, Portugal, Switzerland, Egypt, Greece, Russia, Turkey, Jordan

Primary Endpoint

Success of antifungal prophylaxis, defined as:

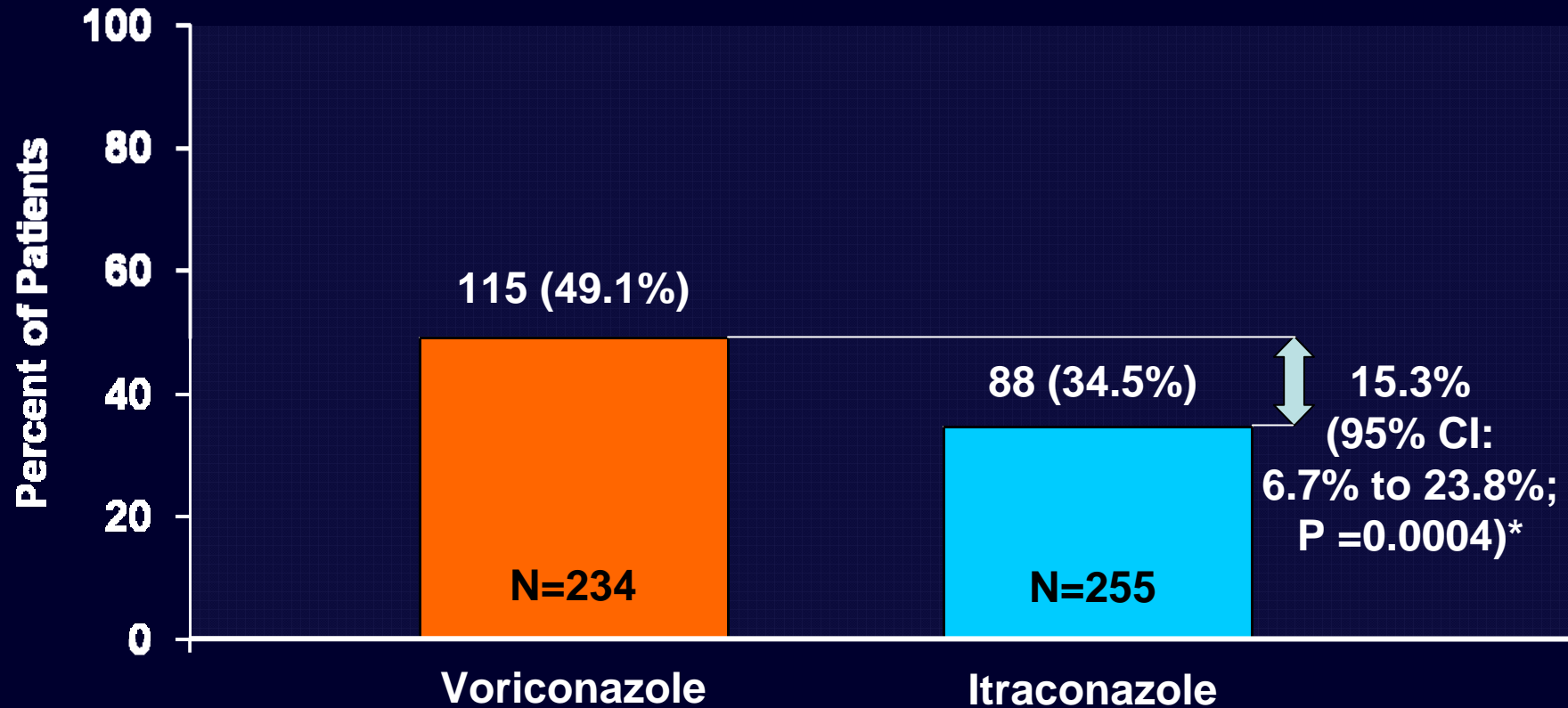
- Survival at 180 days post-transplant **AND**
- No proven or probable breakthrough IFI **AND**
- No discontinuation of study drug for >14 days during 100 day prophylactic period

Primary analysis was intended to demonstrate non-inferiority of voriconazole at Day 180. If non-inferiority was shown, superiority was tested.

Non-inferiority = lower limit of two-sided 95% confidence interval (CI) for difference in adjusted success rates is above -10%.

Superiority = two-sided 95% CI does not include 0% and is positive.

Success of Antifungal Prophylaxis at Day 180 (Primary Endpoint)



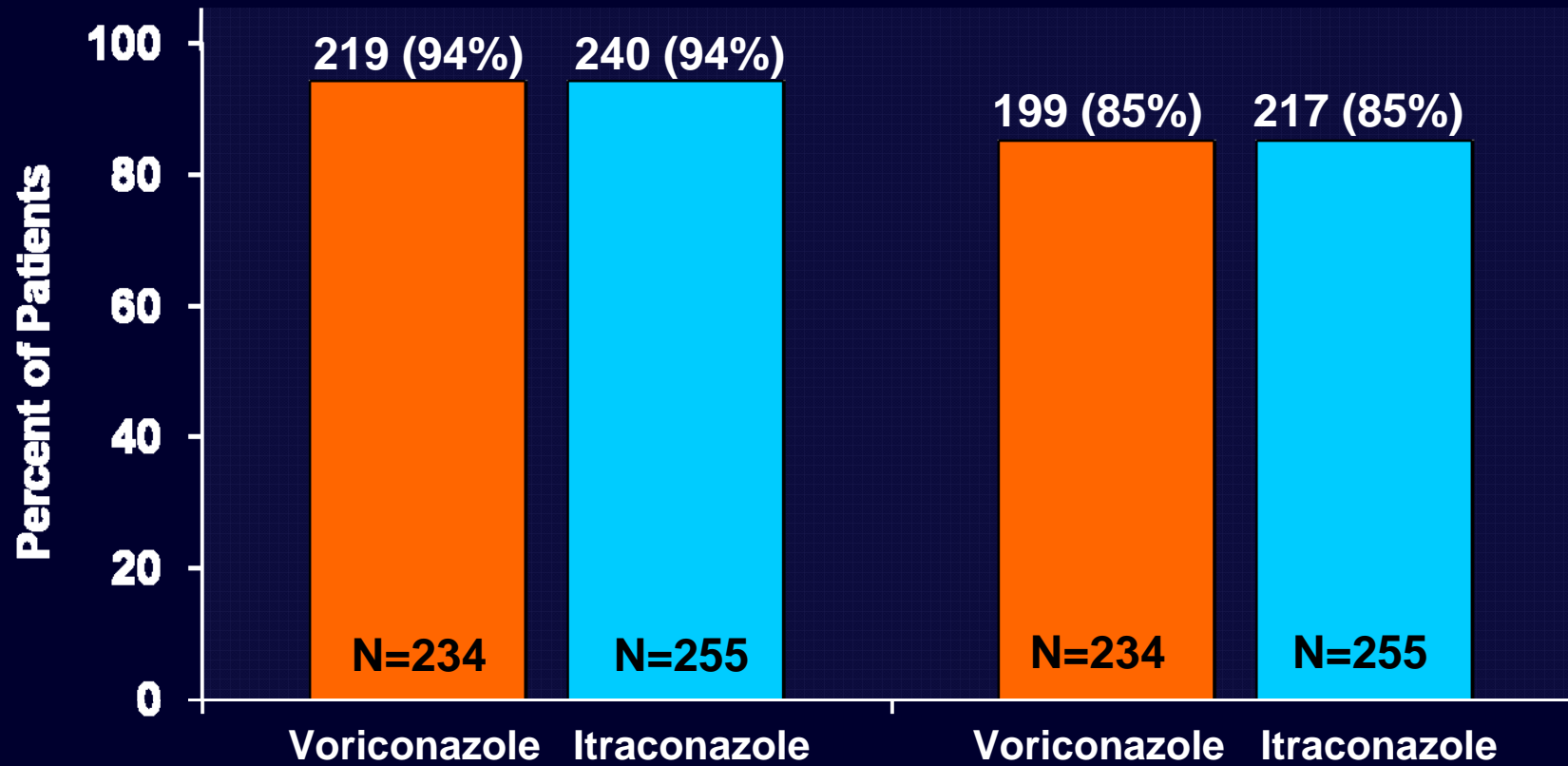
Voriconazole met criteria for non-inferiority and superiority

* Difference in proportions (Voriconazole – Itraconazole) adjusted for conditioning regimen (myeloablative vs. non-myeloablative) and relatedness of donor (matched related donor vs. mismatched/unrelated donor)

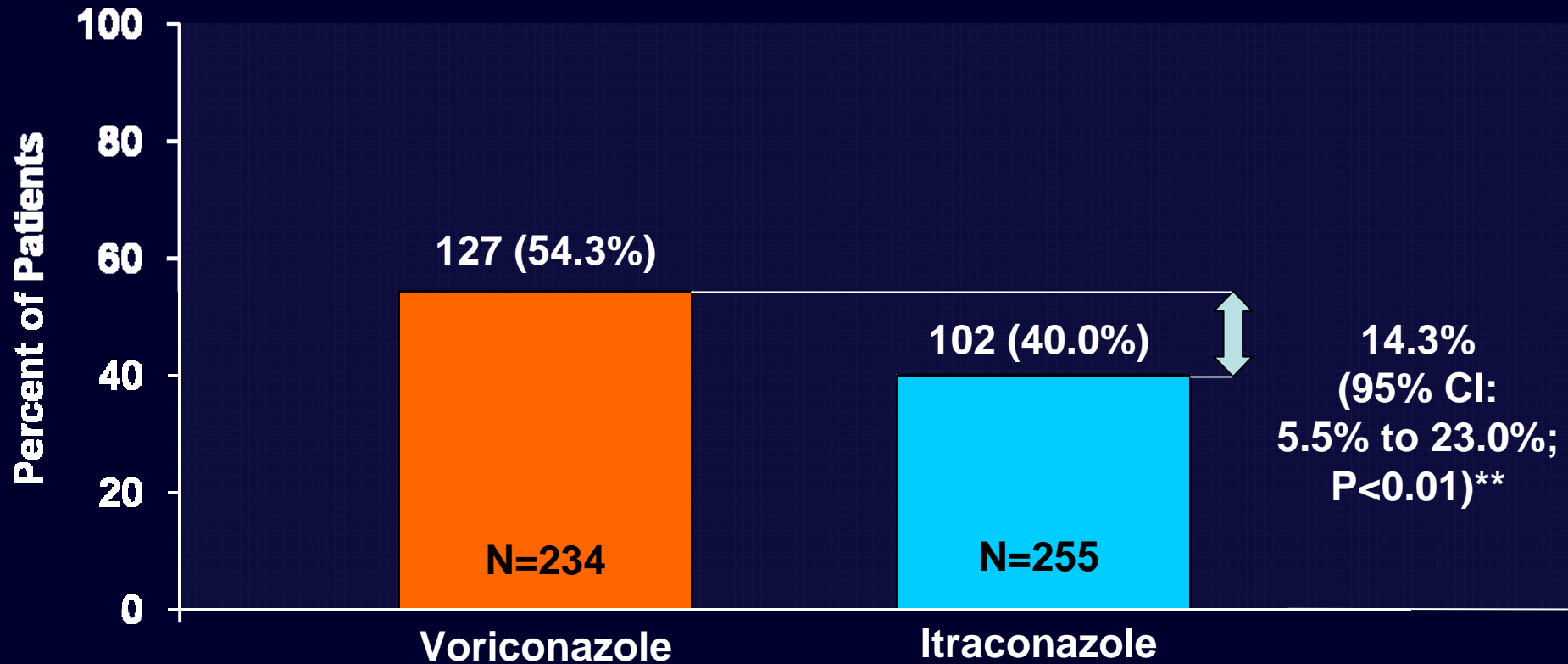
Survival

Day 100

Day 180



Sufficient Duration of Prophylaxis*



Median Duration of therapy: Voriconazole = 97 days; Itraconazole = 68 days

* Sufficient duration of prophylaxis = patient did not discontinue study drug for >14 days in total prior to Day 100

** Difference in proportions (Voriconazole – Itraconazole)

IFIs During Study

EORTC criteria	Treatment Emergent*	Pathogen	Body Site of IFI
3 in Voriconazole arm			
Proven	No	<i>Candida krusei</i>	Blood
Proven		<i>Candida parapsilosis</i>	Blood
Probable		<i>Aspergillus fumigatus</i>	Lung
6 in Itraconazole arm			
Proven	Yes	<i>Candida glabrata</i>	Blood
Proven	No	<i>Aspergillus fumigatus</i>	Lung
Probable	Yes	<i>Aspergillus</i> sp	Lung
Probable	Yes	<i>Aspergillus</i> sp	Lung
Probable	No	<i>Aspergillus fumigatus</i>	Lung
Probable	No	<i>Aspergillus</i> sp	Lung

*Treatment-emergent IFIs: occurring any time while patient was on study drug and for 7 days following treatment discontinuation.

Treatment-emergent IFIs: Voriconazole 0%, Itraconazole 1.2% (P=0.08 for difference).

Most Common Treatment-Related Adverse Events ($\geq 5\%$ in Either Group)

Adverse event	Voriconazole N=234	Itraconazole N=255	P value
Vomiting	9 (4%)	40 (16%)	<0.01
Nausea	18 (8%)	38 (15%)	0.01
Diarrhea	10 (4%)	28 (11%)	<0.01
Headache	11 (5%)	13 (5%)	0.84
Visual impairment	14 (6%)	0 (0%)	<0.01
Hepatotoxicity/Liver function test abnormality	29 (12%)	12 (5%)	<0.01

Summary of Major Findings

- Success of prophylaxis was significantly higher with voriconazole than with itraconazole in allogeneic HCT recipients
- There was no significant difference between the 2 treatments in terms of survival and IFI incidence
- The proportion of patients able to stay on prophylaxis for a sufficient duration was significantly higher with voriconazole than with itraconazole
- Hepatotoxicity was more common with voriconazole, but occurred at rates consistent with previous reports in this study population
- Long-term primary prophylaxis with voriconazole is an effective, safe option for preventing IFIs following allogeneic HCT

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