ISAVUCONAZOLE IN PEDIATRIC PATIENTS WITH ONCO-HAEMATOLOGIC DISEASES AND HAEMATOPOIETIC STEM CELL TRANSPLANTATION

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INTRODUCTION

- ISA is a new triazole approved for treatment of invasive fungal infections (IFI) in adults with activity against both moulds and yeasts spp. and for mucormycosis when AmB is inappropriate
- The results from in healthy subjects showed a favorable linear PK and safety profile with excellent bioavailability after oral administration without relevant food or gastric pH effect, suggesting that the dose adjustment based on TDM may not be necessary
- However it was not possible to identify any thresholds that might support recommendations for C_{min} and C_{max} that could be used as clinical guide
- In children, ISA efficacy and safety have not been tested and the dosage and schedule have not been established. Notwithstanding, some reports describe its compassionate use in pediatric patients with severe or resistant IFD

PATIENTS AND METHODS

- This is a retrospective study involved 6 centers of the Italian Pediatric Hematology and Oncology Association (AIEOP). As it is not approved in pediatrics, its off-label use on single-patient basis required the approval of Ethics Committee and the written informed consent by the patient or parents.
- Data collection concerned patient characteristics, underlying disease, disease status at IFD diagnosis, type of allogenic HSCT, graft versus host disease (GVHD) incidence and prophylaxis, antifungal prophylaxis/treatment, IFD characteristics, reason to start ISA and diagnostic plan
- The monitoring of plasma ISA concentration, when performed, was applied by LC-MS/MS by using d-IS. The method was validated according to EMA/FDA guidelines before its introduction in the diagnostic service
- ISA plasma conc. was determined at steady state mainly as C_{trough}, but in some patients additional sampling times were carried out (at 1, 2, 3, 4, 6, 8, and 12 h post dose), according to the different clinical needs

RESULTS

TABLE 1: Patients' Characteristics S (n=29)

	Value
Age, yr, median (range)	14,5 (3-18)
1 to < 6 yr, n (%)	4 (14)
6 to < 12 yr, n (%)	5 (17)
12 to ≤18 yr, n (%)	20 (69)
Male sex, n (%)	20 (70)
Weight, Kg, median (range)	47 (15-80)
< 30 Kg, n (%)	7 (24.1)
≥30 Kg, n (%)	22 (75.9)
Isavuconazole used after, n (%)	
Chemotherapy	10 (34.4)
HSCT	19 (65.5)
Underlying disease, n (%)	
Acute lymphoblastic leukemia	16 (55)
Acute myeloid leukemia	8 (27.6)
Lymphoma	3 (10.3)
Congenital Bone Marrow Failure	1 (3.4)
MDS	1 (3.4)
Underlying disease status at IFI diagnosis, n (%)	
First complete remission	17 (63)
≥ Second complete remission	5 (18.5)
Relapse	5 (18.5)
Patient outcome, n(%)	
Alive	25 (86.2)
Dead	4 (13.8)
Cause of death, n (%)	
Relapse of underlying disease	2 (50)
IFD	1 (25)
Other[a]	1 (25)

Abbreviations: MDS, myelodiplasia; HSCT, hematopoietic stem cell transplantation; PP-IFD, proven/probable invasive fungal disease
[a] Transplant related multi organ failure

TABLE 2: HSCT Characteristics

	Value
Donor type, n (%)	
MFD	4 (21)
PMFD	10 (52.6)
MUD	5 (26.3)
GVHD prophylaxis during ISA treatment, n (%)	7 (36.8)
Ciclosporine	5
Sirolimus	2
Tacrolimus	1
Metilprednisolone	2
aGVHD grade, n (%)	
I-II	4
III-IV	2

Abbreviations: MFD, matched family donor; PMFD, partially matched family donor; MUD, matched unrelated donor; aGVHD, acute Graft Versus Host Disease; cGVHD, cronic-GVHD

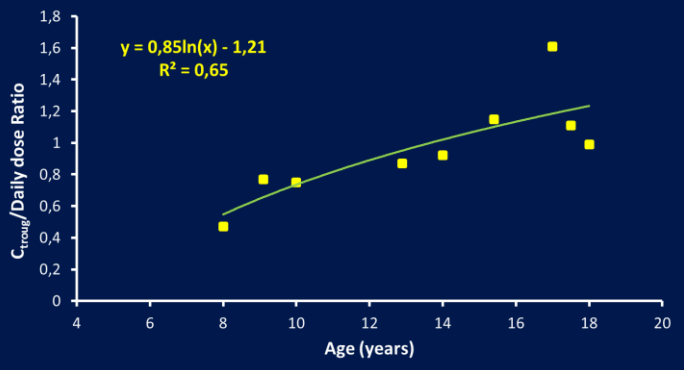
TABLE 3: ISA Dosage and and PK Data

	Value
ISA loading dose, n (%)	13 (44.8)
ISA dose, n (%)	
100 mg/day = pts < 30 kg	7 (24.1)
200 mg/day = Adult schedule	22 (75.9)
Median treatment, days (range)	75.5 (6-523)
1 to < 6 yr	46 (12-231)
6 to < 12 yr	86 (6-153)
12 to ≤18 yr	80 (6-523)
Dose/kg/day (mg/kg), median (range)	4 (2.50-6.67)
< 30 Kg BW	4,55 (3.57-6.67)
≥30 Kg BW	4 (2.50-5.71)
C_{trough} (mg/L), median (range) (n. 17)	4.91 (2.15-8.54)
< 30 KgBW	1,1 (0.73-2.15)
≥30 Kg BW	5 (2.48-8.54)
Conc/(Dose/Kg), median (range)	1.13 (0.47-3.42)
< 30 KgBW	0,75 (0.47-1.38)
≥30 Kg BW	1,38 (0.71-3.42)
AUC 0-24 h (mg*h/L), median (range) (n.6)	153.16 (86,31-169,45)

TABLE 4 : ISA Treatment Indication and Outcome

	Value
Indication to use ISA, n (%)	
Prophylaxis	5 (17.2)
First line therapy	4 (13.8)
Rescue treatment	20 (69)
IFD, n (%) (EORTC criteria)	
Possible	10 (41.7)
Probable	9 (37.5)
Proven	5 (20.8)
IFD outcome, n (%) (after follow up of 90 days)	
Complete remission	12 (50)
Partial remission	5 (20.8)
Stable disease	2 (8.3)
Progression	5 (20.8)
IFD attributable mortality, n (%)	1 (3.4)
Breakthrough infections, n (%)	0

RELATIONSHIP BETWEEN AGE AND ELIMINATION (C_{TROUGH}/DAILY DOSE) OF ISA



CONCLUSIONS

- Data in a large cohort of oncohematologic children affected by mucormycosis and aspergillosis, used as primary or secondary prophylaxis, including those treated with HSCT in which IFD are even more aggressive and difficult to treat
- ISA was used as rescue therapy because of treatment failure (n.18) or intolerance (n.2) to other antifungal drugs. The overall response rate in proven/probable IFD was high (64.3%), suggesting that ISA may be an effective salvage therapy also in case of aspergillosis and during treatment with azoles or combined therapy, and useful also as first line therapy, when other options are contraindicate. ISA efficacy was excellent also as prophylactic treatment
- The need for a TDM-based guided therapy is still controversial. The target C_{trough} level in adult is 2-4 mg/L, but TDM remains indicated only in special cases
- Our PK results showed that in pts >30 kg (ISA dose=adult) the C_{trough} was in line with the adult target, while younger did not achieve the threshold desired, confirming that ISA clearance is faster in younger, and a higher dose may be necessary. According to the relationship C_{trough}/dose ratio vs age (8-18 yrs), a patient of 8 yrs old needs a daily ISA dose (mg/kg) essentially doubled as compare to a patient 16 yrs old
- PK monitoring could help to identify optimal treatment individualization strategies especially in younger children