Isavuconazonium sulfate use in multi-modal management of invasive Mucormycosis in four pediatric allogeneic hematopoietic cell transplant patients

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INTRODUCTION

- Prolonged neutropenia, immunosuppression and immune dysregulation increase the risk for opportunistic invasive fungal infection (IFI)[1]
- Isavuconazonium sulfate is a new broad spectrum triazole, targeting the CYP51A enzyme needed for fungal cell membrane formation
- We describe a case series of patients who received isavuconazonium sulfate for IFI at our institution

CASE #1: 2 Y/O FEMALE W/RHIZOPUS SINUSITIS

- Severe aplastic anemic
- Received 4 weeks of amphotericin B, posaconazole, surgical debridements with amphotericin
- Underwent 8/8 HLA-matched unrelated donor (MUD) allogeneic hematopoietic cell transplantation
- At week 9, isolate was found to be posaconazole resistant
- Started isavuconazonium sulfate with loading dose of 15 mg/kg IV Q12H for 4 doses, then maintenance dosing of 15 mg/kg/day
- Dose titrated to maintain trough >3 ug/mL
- After 11 weeks of *Rhizopus* therapy sinus endoscopy revealed resolution
- Isavuconazonium sulfate was well tolerated except for grade 1 transaminitis which improved with 10% dose reduction and resolved upon discontinuation[2]

CASE #2: 11 Y/O FEMALE W/RHIZOPUS SINUSITIS

- Severe congenital neutropenia on day +270 s/p 8/8 HLA-MUD alloHCT complicated by graft failure
- *Rhizopus* susceptible to amphotericin B & isavuconazonium sulfate
- Treated with amphotericin B irrigation, amphotericin, isavuconazonium sulfate and surgical debridement
- Target isavuconazole trough >3 ug/mL achieved on day 6
- Underwent a 4/8 HLA-haploidentical RIC HCT
- Weekly troughs were low requiring dose escalation
- Received 12 granulocyte infusions
- By day +43 post-haploHCT, she died from respiratory failure Despite absent findings of *Rhizopus* prior to her death, post-mortem evaluation revealed left sinus and nasal cultures positive for *Rhizopus*

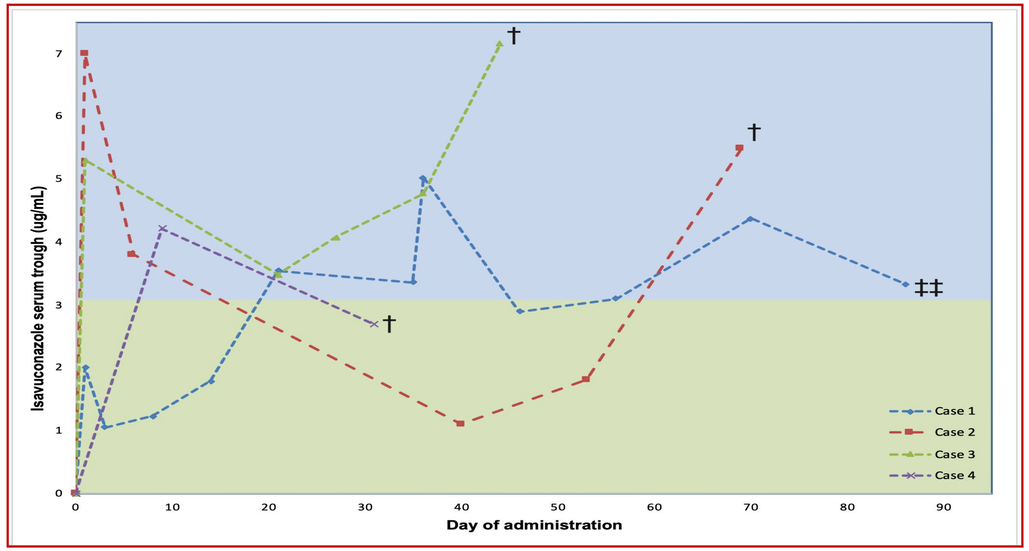

Figure 1: Isavuconazole serum trough goal achieved in majority of patients by day 21 of administration. Dotted line represents goal serum trough of 3 ug/mL. †Death; ‡‡Discharge home

CASE #3: 8 Y/O MALE W/ZYGOMYCES

- Adrenoleukodystrophy with palate ulceration on day +21 following a 5/8 HLA-matched umbilical cord blood transplant (UCBT) complicated by graft failure
- Disseminated disease with parenchymal lung lesions
- Treated with isavuconazonium sulfate and amphotericin
- Received 4 granulocyte
- Underwent a 5/8-HLA RIC haploHCT. For 2 weeks
- Despite achieving neutrophil engraftment, he died on day +22 post-haploHCT. Family declined post-mortem evaluation

CASE #4: 19MOS MALE W/RHIZOPUS ESCHAR

- MPS1 on day +52 post-5/6 HLA-matched umbilical cord blood transplant, complicated by graft failure
- Started amphotericin with surgical debridement
- Biopsy confirmed angioinvasive mucormycosis
- Isavuconazonium sulfate started
- Underwent a 2nd 5/6 HLA-matched RIC UCBT
- Variety of troughs obtained
- At last endoscopic sinus biopsy on day +38 post-2nd UCBT, fungal elements were absent
- Died on day +67 post-2nd UCBT of pneumonia
- Autopsy of revealed a healing ulcer with no fungal organisms

DISCUSSION

- 1 patient was discharged without evidence of IFI while others had negative cultures at death
- This series demonstrates the aggressiveness of Mucormycosis and the role of isavuconazonium sulfate in a multi-modal anti-fungal approach
- Pediatric dosing was extrapolated from adult literature although this approach was variably effective due to varying pharmacokinetics[3]
- Isavuconazonium sulfate was well tolerated, held for known drug interactions with chemotherapy, and dose reduced for side effects including nephrotoxicity (rising BUN and/or creatinine), electrolyte abnormalities (hyperkalemia, hypernatremia and/or hypocalcemia) and hepatic dysfunction (transaminitis)
- Steady state was not achieved until approximately 3 weeks after initiation
- In our report, case 2 was subtherapeutic for 39% of the duration, compared to others at an average of 29%, suggesting this target trough to be clinically relevant
- No toxicities or death were noted with supra-therapeutic troughs
- Variable time to therapeutic trough was noted in our cohort of pediatric patients and knowledge about pharmacokinetics unfortunately remains scarce

RECOMMENDATIONS

- Initiate isavuconazonium sulfate at a loading dose of 10 mg/kg every 8 hours for 6 doses followed by 10 mg/kg dosing every 24 hours, utilizing an individual max dose of 372 mg
- The use of a loading dose should be utilized to assist in reaching the steady state concentration sooner while a therapeutic drug level is in process
- If frequent monitoring is not possible, we recommend a first drug level at week 3 as week 2 levels have been misleading
- Once out of the acute phase – serum drug levels are monitored monthly, then every 2 months per provider comfort for infection control
- If dose increases are required, a partial reload in addition to dose increase has been more successful given long drug half-life

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