Sulfate for IFI at our institution

We describe a case series of patients who received isavuconazonium

the CYP51A enzyme needed for fungal cell membrane formation

Isavuconazonium sulfate is a new broad spectrum triazole, targeting
dysregulation increase the risk for opportunistic invasive fungal

Prolonged neutropenia, immunosuppression and immune
dysregulation increase the risk for opportunistic invasive fungal

CASE #1: 2 y/o Female W/Rhizopus sinusitis

Severe aplastic anemia
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 transaminits which improved with 10% dose reduction and resolved upon discontinuation

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. 1Death; 2Discharge home

CASE #3: 8 y/o Male W/Zygomycoses

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-UCBT of pneumonia
Disseminated disease with parenchymal lung lesions
Underwent a 2nd 5/8 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 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
Isavuconazonium sulfate was well tolerated, held for known drug interactions with chemotherapy, and dose reduced for side effects including nephropathy (rising BUN and/or creatinine), electrolyte abnormalities (hyperkalemia, hypernatremia and/or hyponatremia) 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, the primary care practitioner in addition to dose increase has been more successful given long drug half-life

REFERENCES