Pediatric focused safety evaluation

Active ingredient: deferasirox

Peter Waldron, MD

Outline

- Background
- Division of Pharmacovigilance
- Office of Clinical Pharmacology
- Division of Pediatric and Maternal Health
- Division of Epidemiology

Background

US regulatory history: deferasirox (DFS)

- 2005 approved for transfusional iron overload age ≥ 2 years
- 2009 maximum Exjade dose increased from 30 mg/kg/day to 40 mg/kg/day
- 2010 Boxed Warning added for renal failure, hepatic failure, and gastrointestinal hemorrhage
- 2013 Exjade approved for non-transfusion dependent thalassemia age 10 years and older, maximum dose 20 mg/kg/day
- 2015 Jadenu tablet, film coated, and 2017 granule approved; 7 mg of Jadenu is equivalent to 10 mg of Exjade

2015 Pediatric Focused Safety Review

- January, 2015 pediatric focused safety review (PFSR) was triggered two years after approval of sNDA S-015: chronic iron overload in patients 10 years of age and older with non-transfusion dependent thalassemia (NTDT)

- September, 2015 PFSR was presented to Pediatric Advisory Committee

Case with fatal outcome presented to FDA Pediatric Advisory Committee Sept. 2015

- A 35 month (2 yr, 11 mo) old girl with transfusion dependent thalassemia
- RBC transfusion started at 7 mo. (28 mo. earlier)
- Chelation started at 24 mo.(11 mo. earlier)
- Concomitant medications: MVI, vitamin D, folic acid

Case Summary

- High dose (32 mg/kg/day) Exjade, with lower serum ferritin (SF) (655 mcg/L 42 days before the acute presentation)
- Acute hypovolemia and fever with RSV infection
- Acute kidney injury (AKI)/renal failure and acute liver failure (coagulopathy and encephalopathy)
- Later (12 hour), overt shock and respiratory failure
- Death due to cerebral herniation

Pediatric safety evaluation timeline

- Sept. 2015 Exjade PFSR presented to PAC
  - Testimony from the mother of the girl who died
  - Cooley Anemia Foundation testified about its membership's concern for use of Exjade during febrile illnesses, and requested that a Warning, to stop the use of Exjade for children who develop a fever, be added to the product information
- November 2015 Division of Pharmacovigilance (DPV) consulted, based on the request from PAC: “to acquire any data regarding safety of continued medication (administration) to children who have fever, and report back to the PAC”
- April 2016 Tracked Safety Issue opened: pediatric fever and dehydration
- March 2017 interim report to PAC
- April 2018 evaluation completed; May 2018 deferasirox labels updated

Questions identified by the Safety Issues Team

- Are there features of childhood illnesses, such as hypovolemia, that could interact with DFS use, to produce severe toxicity?
- Could continued drug use during periods of decreased glomerular function result in increased drug exposure?
- Is there an interaction between drug dose and body iron burden (BIB), such that at a high body iron burden a given dose may be associated with a lower rate of adverse reactions (AR), whereas that same dose at a lower BIB will be associated with an increased rate of AR?

FDA U.S. FOOD & DRUG ADMINISTRATION

Division of Pharmacovigilance

Fever and dehydration

Acute hepatic failure

FAERS Cases Of Renal Impairment After Episode Of Fever or/and Dehydration

	No renal impairment (%)	Renal impairment (%)	N total = 149
Fever only	95	5	58
Dehydration only	75	25	68
Fever and dehydration	52	48	23

Summary of FAERS and literature cases of acute hepatic failure

	Encephalopathy (E); Coagulopathy (C)	AKI	Hypo-volemia	Over-chelation	Causality	Outcome
FAERS N=13	E: 13 C:4; NR:7	Yes:10 NR:3	Yes: 11 NR:2	Yes: 7 NR:6	Probable: 8 Possible: 5	Recovery: 10 Death: 3
Literature N=3	E: 2 C: 3	Yes: 2 NR: 1	Yes: 3	Yes:3	Probable: 3	Recovery: 3

NR: no result reported

Summary of DPV findings

- There was a high frequency of indicators of renal impairment among children with dehydration risk, with or without fever
- An association between risk factors for hypovolemia and incidence of renal impairment indicators
- Reports of acute hepatic failure were associated with
  - Severe, acute kidney injury
  - Risk factors for hypovolemia
  - Overchelation

Introduction to next speakers

- Clinical Pharmacology: Olanrewaju Okusanya, Pharm D, MS
- DPMH: Mona Khurana, MD
- DEPI Nested Case Control Study: Steve Bird, Pharm D, PhD
- DEPI Clinical Trials analysis: Kate Gelperin, MD, MPH