Pediatric Focused Safety Review Update of Exjade (deferasirox)

Peter Waldron MD
Kate Gelperin MD MPH
Office of Surveillance and Epidemiology
Division of Pharmacovigilance
Division of Epidemiology

Background

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- A focused pediatric review of deferasirox (DFS) identified an unexpected death of a 35 month old child
- The mother of this child testified about her child's experience with DFS
- The Cooley's Anemia Foundation asked for a label change "calling for cessation of the use of EXJADE when fever is present"

Development of review strategy

- Expansion of the PAC question, from fever as a risk factor, to fever or dehydration/hypovolemia
- Ability of FAERS to answer the PAC question with ultimate inclusion of other disciplines
- Identification of additional safety issues for children, and ongoing evaluations

Data Sources

- FDA Adverse Event Reporting System (FAERS)
  - We evaluated FAERS reports of fever and dehydration/hypovolemia in pediatric patients treated with DFS as possible risk factors for the development of serious hepatic/renal impairment
- Published Literature
  - DFS clinical trials
  - Reports of adverse events in the pediatric age group
  - Possible risk factors for adverse events
- Clinical Trial Data
  - We conducted an analysis of Study CICL670A0107 to evaluate whether signs or symptoms of fever or dehydration in children may be useful indicators for interruption of DFS to prevent severe nephrotoxicity or hepatotoxicity.
- Pediatric Nephrology Review
  - Clinical and pharmacology data submitted to NDA

FAERS Analysis

Renal or hepatic events in the setting of fever and/or dehydration in patients ages 2-15 years using deferasirox

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Case Selection: Fever and/or Dehydration

- Inclusion criteria
  - Patient was on DFS therapy and experienced fever, dehydration, or both
- Exclusion criteria
  - Duplicate
  - Sickle cell disease
  - Narrative does not support fever or dehydration
  - Insufficient information for further assessment
    - e.g., no narrative provided, conflicting temporal sequence, unclear exposure to DFS therapy at the time of fever or dehydration
- If a patient had multiple episodes of fever and/or dehydration within their report, all episodes were counted

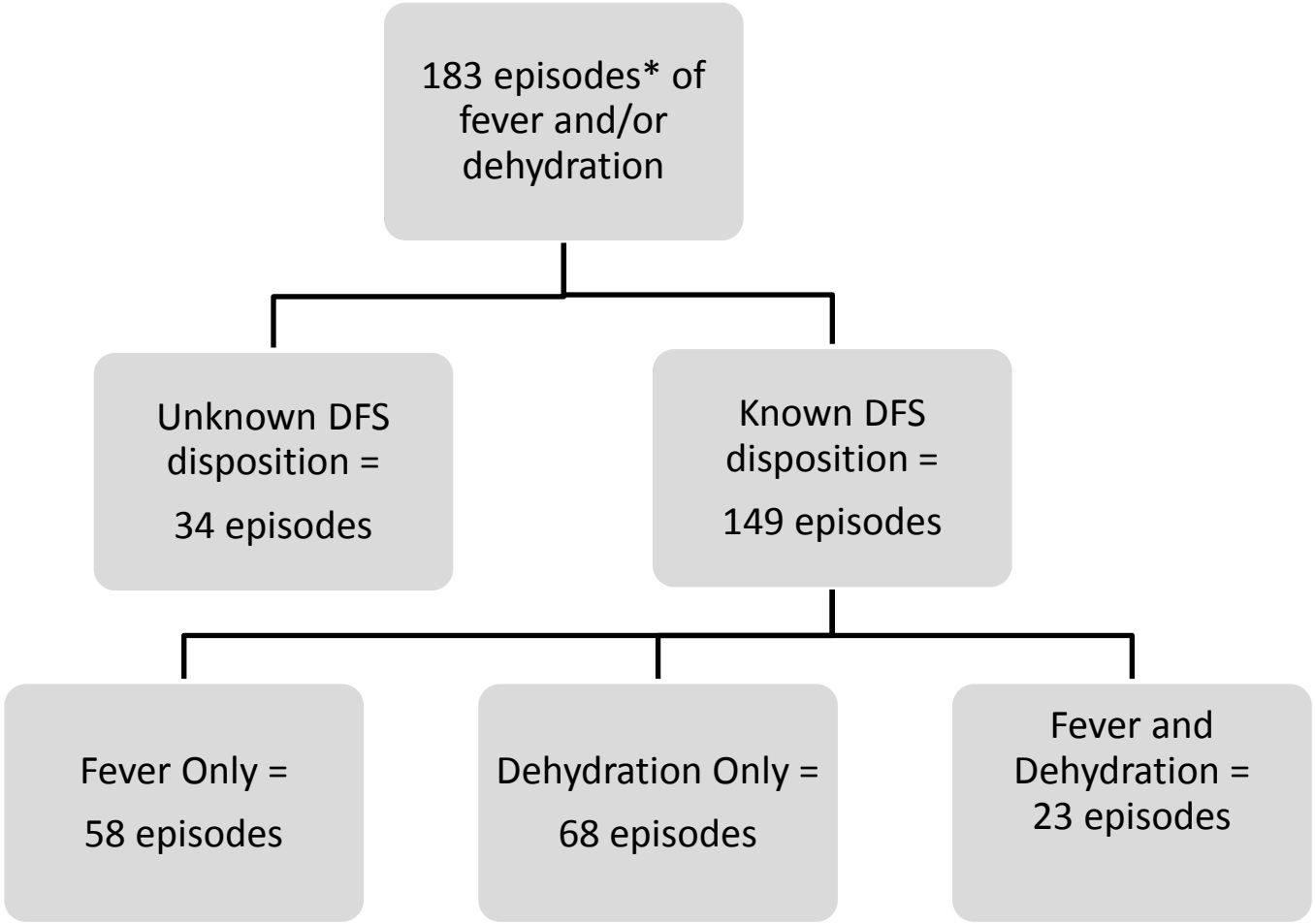
Fever and/or Dehydration Analysis

- DFS Disposition as Possible Risk Factor
  - Continue = received at least one dose of DFS during post-fever or dehydration event (intent-to-treat)
  - Discontinue = stopped DFS on the first day of the fever or dehydration event, whether this decision was due to a caregiver's discretion or under healthcare provider direction
  - Unknown = disposition was not clearly stated

- Patients with known DFS disposition were analyzed in 3 subgroups
  - Fever only
  - Dehydration only
  - Fever and Dehydration

- Outcomes
  - Renal or hepatic impairment (within 7 days prior to or 28 days after fever and/or dehydration)

Fever and/or Dehydration Episodes



* Out of 162 cases
DFS = deferasirox

Fever Only
(n=58 episodes)

	Continue DFS (n=34 episodes)	**Discontinue** DFS (n=24 episodes)
Renal or hepatic impairment	Yes event **4 (11.8%)** Renal 1 Hepatic 3 Both 0	Yes event **8 (33.3%)** Renal 2 Hepatic 6 Both 0
	No event **30 (88.2%)**	No event **16 (66.7%)**

Dehydration Only
(n=68 episodes)

	Continue DFS (n=37 episodes)	**Discontinue** DFS (n=31 episodes)
Renal or hepatic impairment	Yes event **12 (32.4%)** Renal 4 Hepatic 7 Both 1	Yes event **16 (51.6%)** Renal 7 Hepatic 4 Both 5
	No event **25 (67.6%)**	No event **15 (48.4%)**

Fever AND Dehydration
(n=23 episodes)

	Continue DFS (n=11 episodes)	**Discontinue** DFS (n=12 episodes)
Renal or hepatic impairment	Yes event **3 (27.3%)** Renal 0 Hepatic 2 Both 1	Yes event **10 (83.3%)** Renal 4 Hepatic 0 Both 6
	No event **8 (72.7%)**	No event **2 (16.7%)**

Limitations

- FAERS contains limited and incomplete information; it cannot be used to calculate incidence
- Active surveillance (e.g., clinical trial, patient assistance program) versus passive surveillance
- “Continue DFS” and “discontinue DFS” groups may have different risks for developing adverse events (e.g., historical or contemporary)
- Channeling bias (e.g., cases in “discontinue DFS” group may have been selected for discontinuation based on clinical status)
- Misclassification bias (e.g., “continue DFS” modeled after intent-to-treat approach; “discontinue DFS” has continued exposure due to drug half-life of 8-16 hours, particularly with renal and hepatic impairment)

Published Literature

- No reports attributed specific adverse events to fever
- No reports attributed events similar to the index case to respiratory syncytial virus
- Case reports attributed renal adverse events to dehydration, but they were confounded by prior or concomitant medications with nephrotoxicity risk
- Ongoing issues: dose iron-load imbalance, hyperammonemia, predictability of exposure, pharmacogenomics

Analysis of FAERS and Literature Reports

- FAERS data alone is not a reliable tool for determining the effect of DFS continuation/discontinuation in the fever and dehydration groups on subsequent renal/hepatic outcomes.
- Literature review did not identify evidence that fever or dehydration are indicators of subsequent increased risk of adverse events
- Due to the inherent limitations in measuring hypovolemia, and therefore in detecting and reporting it, we cannot exclude that hypovolemia increases the risk for renal or hepatic adverse events.

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Analysis of Clinical Trial Data Sources

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Analysis of liver or kidney injury after pediatric fever or dehydration adverse events in Study CICL670A0107

- The FDA review team conducted an analysis to evaluate whether signs or symptoms of fever or dehydration may be useful indicators for treatment interruption to prevent severe nephrotoxicity or hepatotoxicity in children, with a focus on Study CICL670A0107 for which complete clinical and laboratory safety data were available .
- Study CICL670A0107 is an open label phase 3 trial of the efficacy and safety of DFS compared to deferoxamine in β-thalassemia patients with transfusional hemosiderosis.
- Datasets for the analysis were extracted from a larger dataset that had been submitted by Novartis which identified fever or dehydration adverse events (AEs) among children (age 2 to 15 years) in Exjade clinical trials.

Analysis of liver or kidney injury after pediatric fever or dehydration adverse events in Study CICL670A0107

- The analysis dataset comprised 237 fever AEs and 126 dehydration AEs in 273 pediatric patients who received DFS during the double-blind portion and/or the long term extension of Study 0107.
- Laboratory values obtained after AEs of interest (fever or dehydration) were compared with lab values obtained before the event.
  - Serum creatinine (CREA)
  - Urine protein to creatinine ratio ($U_{P/C}$)
  - Alanine aminotransferase (ALT)
  - Total bilirubin (TBL)
- The proportion of fever AEs and the proportion of dehydration AEs with clinical laboratory evidence of liver or kidney injury and the distribution of "action taken" (i.e. interruption/adjustment vs continuation of DFS therapy) were assessed across several criteria levels for laboratory parameters.

Table 1: Proportion of **FEVER** AEs in Study 0107 with evidence of **LIVER** injury after interruption or dose adjustment of DFS therapy ***where ALT was within normal limits (WNL) prior to AE***

DFS dose was adjusted or withheld due to fever AE (action taken = 1)	Number (percent) of fever AEs followed by evidence of liver injury				
	No evidence of liver injury	ALT >ULN	ALT >2X ULN	ALT >3X ULN	ALT >3X ULN ***and*** TBL >2X ULN
Yes (n=23 AEs)*	19 (83%)	3 (13%)	0	0	0
No (n=134 AEs)**	109 (81%)	24 (18%)	10 (7%)	3 (2%)	0
Total (n=157 AEs)	128 (82%)	27 (17%)	10 (6%)	3 (2%)	0

All percentages are row percentages. Categories of lab values are not mutually exclusive.
Numbers are events from 107 unique pediatric patients with fever AEs from Exjade Study 0107.
* missing lab data for 1 event
** missing lab data for 1 event

Table 2: Proportion of **DEHYDRATION** AEs in Study 0107 with evidence of **LIVER** injury after interruption or dose adjustment of DFS therapy ***where ALT was WNL prior to AE***

DFS dose was adjusted or withheld due to dehydration AE (action taken = 1)	Number (percent) of dehydration AEs followed by evidence of liver injury				
	No evidence of liver injury	ALT >ULN	ALT >2X ULN	ALT >3X ULN	ALT >3X ULN ***and*** TBL >2X ULN
Yes (n=4 AEs)*	2 (50%)	1 (25%)	1 (25%)	1 (25%)	1 (25%)
No (n=87 AEs)**	70 (80%)	13 (15%)	3 (3%)	1 (1%)	0
Total (n=91 AEs)	72 (79%)	14 (15%)	4 (4%)	2 (2%)	1 (1%)

All percentages are row percentages. Categories of lab values are not mutually exclusive.
Numbers are events from 73 unique pediatric patients with dehydration AEs from Exjade Study 0107.
* missing lab data for 1 event
** missing lab data for 4 events

Table 3: Proportion of **FEVER** adverse events (AEs) in Study 0107 with evidence of **KIDNEY** injury after interruption or dose adjustment of DFS therapy ***where CREA was WNL prior to AE***

DFS dose was adjusted or withheld due to fever AE (action taken = 1)	Number (percent) of fever AEs followed by evidence of kidney injury			
	No evidence of kidney injury	CREA ≥ 25% increase ***or*** $U_{P/C}$ increase	CREA ≥ 33% increase ***or*** $U_{P/C}$ ≥0.4	CREA > ULN ***or*** $U_{P/C}$ ≥ 0.6
Yes (n=40 AEs)*	19 (48%)	20 (50%)	7 (18%)	2 (5%)
No (n=192 AEs)**	84 (44%)	102 (53%)	25 (13%)	14 (7%)
Total (n=232 AEs)	103 (44%)	122 (53%)	32 (14%)	16 (7%)

All percentages are row percentages. Categories of lab values are not mutually exclusive.
Numbers are events from 107 unique pediatric patients with fever AEs from Exjade Study 0107.
* missing lab data for 1 event
** missing lab data for 5 events

Table 4: Proportion of **DEHYDRATION** adverse events (AEs) in Study 0107 with evidence of **KIDNEY** injury after interruption or dose adjustment of DFS therapy ***where CREA was WNL prior to AE***

DFS dose was adjusted or withheld due to dehydration AE (action taken = 1)	Number (percent) of dehydration AEs followed by evidence of kidney injury			
	No evidence of kidney injury	CREA ≥ 25% increase ***or*** $U_{P/C}$ increase	CREA ≥ 33% increase ***or*** $U_{P/C} \geq 0.4$	CREA > ULN ***or*** $U_{P/C} \geq 0.6$
Yes (n=5 AEs)*	3 (60%)	1 (20%)	0	0
No (n=111 AEs)**	47 (42%)	57 (51%)	23 (21%)	9† (8%)
Total (n=116 AEs)	50 (43%)	58 (50%)	23 (20%)	9 (8%)

All percentages are row percentages. Categories of lab values are not mutually exclusive.
Numbers are events from 73 unique pediatric patients with dehydration AEs from Study 0107.
†Note: There were 9 events in 8 unique subjects where new onset kidney injury occurred after a dehydration AE (all were diarrhea) and continuation of DFS therapy. A similar injury pattern was not observed in the small number of subjects who had DFS dose interrupted or adjusted.
* missing lab data for 1 event
** missing lab data for 6 events

Analysis of liver or kidney injury after pediatric fever or dehydration adverse events in Study CICL670A0107

- Results showed that evidence of liver or kidney injury was observed commonly in Study 0107 after pediatric fever or dehydration AEs, regardless of whether or not DFS dose was interrupted/adjusted.
- Clinical laboratory abnormalities for CREA or $U_{P/C}$ in the range for which dose reduction/interruption are mentioned in the current DFS label were often observed after fever or dehydration AEs in this analysis.
- Of note, CREA >ULN or $U_{P/C}$ ≥0.6 were observed in 8 subjects with previously normal CREA when DFS therapy was continued during a dehydration AE (diarrhea). A similar injury pattern was not observed in the small number of dehydration AEs where DFS therapy was interrupted/adjusted.

Summary

Clinical Trials

- Following dehydration or fever events trial subjects frequently had lab values for CREA or $U_{p/c}$, which were in the range that the current DFS label uses to indicate dose reduction or interruption in treatment.

FAERS

- Analysis of FAERS data, with regard to interruption or continuation of DFS during fever or dehydration AEs, did not provide meaningful information for regulatory action

Medical Literature

- We identified no case reports of children receiving DFS, for which we could attribute a causal role to fever, RSV, or dehydration in the development of serious adverse events.

Pediatric Nephrology Review

Sources: Renal findings from pre- and post-marketing multi-disciplinary reviews completed for Exjade

Purpose: Determine if existing labeling language should be strengthened to enhance deferasirox safety in patients down to 2 years of age with fever, dehydration, or both

Pediatric Nephrology Review

Conclusion

- Fever with dehydration or dehydration alone may both increase risk of renal toxicity if DFS is continued

Recommendation

- Temporarily discontinue deferasirox in presence of clinical and/or laboratory evidence of dehydration

Concerns about safe use of deferasirox in young children

- Current labeling includes Boxed Warning for potentially fatal renal failure and hepatic failure and requires close monitoring of serum creatinine, transaminases, and bilirubin.
- Analysis of Study CICL670A0107 shows that subjects frequently had lab values for CREA or Up/c, which were in the range that the current DFS label uses to indicate dose reduction or interruption in treatment, following fever or dehydration events.
- FDA has received case reports of serious and fatal liver and kidney failure in young children taking DFS, several with elevated ammonia levels described.
- Can predictors of toxicity be better characterized and mitigated, especially in young children?

Ongoing analyses to address safe use of deferasirox in young children

- Hyperammonemia: 14 cases from FAERS
- Doses > 30 mg/kg/d for ages 2-6 years, and > 25 mg/kg/d when iron burden is low
- Review of Study CICL670A2411: A 5 year observational study of children aged 2 to <6 years at enrollment with transfusional hemosiderosis treated with DFS
- Pediatric dose modification with decreased renal function
- Predictability of exposure and pharmacogenomic effects

Concluding Remarks

- Measures to assure the safe use of DFS in children are being actively evaluated by both the FDA and the sponsor.
- Once FDA's safety review is complete, we will work with the sponsor to determine any appropriate updates to DFS labeling.


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BACKUP SLIDES (DEPI)

(n=8) from Study 0107 who developed CREA > UL
≥ 0.6 after dehydration AE where CREA was WNL

	Age	Sex	CREA before (mg/dL)	CREA after (mg/dL)	CREA ULN (mg/dL)	UPROTC before	UPROTC after	Days from AE to lab	Actu ((mg/
9	4	M	0.31	0.50	0.47	0.23	0.62	1	
5	14	F	0.43	0.59	0.96	0.4	0.68	18	
4	14	F	0.68	0.75	0.96	0.13	0.7	7	
5	12	F	0.57	0.82	0.96	0.09	0.6	27	
2	3	M	0.31	0.50	0.47	*	*	1	
3	10	M	0.49	0.73	0.73	0.14	0.12	11	
1	7	M	0.48	0.85	0.60	0.17	0.24	3	