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RESEARCH ARTICLE

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Concurrent use of hydroxyurea and deferasirox in Californians with sickle cell disease

Trisha E. Wong[1] | Jhaqueline Valle[2] | Susan Paulukonis[2]

[1]Division of Pediatric Hematology/Oncology and Department of Pathology, Oregon Health and Sciences University, Portland, Oregon, USA

[2]Tracking California, Public Health Institute, Richmond, California, USA

Correspondence
Trisha E. Wong, Division of Pediatric Hematology/Oncology and Department of Pathology, Oregon Health and Sciences University, 3181 SW Sam Jackson Park Road, Mailstop CDRCP, Portland, OR 97230, USA.
Email: wong@ohsu.edu

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Abstract

Background and aims: When patients with sickle cell disease have appropriate indications, they can be prescribed hydroxyurea (HU) and deferasirox (DFX) concurrently despite little knowledge about how the two medications interact. We wished to analyze whether there was evidence of adverse interaction between HU and DFX when taken simultaneously and hypothesized that those who took both drugs together had similar clinical complications when compared to those who took only one or neither drug.

Methods: We conducted this retrospective cohort investigation between 2009 and 2016 of persons with SCD in the California Sickle Cell Data Collection Program, a validated database of Californians with SCD a statewide. People in the database who took HU and DFX simultaneously for at least 3 months as compared to those who took either HU or DFX alone or to matched persons who took neither drug were eligible.

Results: We identified 104 people who were prescribed both HU and DFX concurrently, 877 who were prescribed HU only, and 314 who were prescribed DFX only during the study period. We identified 416 matched controls who took neither HU nor DFX. People who took both HU and DFX concurrently had similar rates of ED and inpatient encounters and had similar rates and distribution of adverse effects compared to those who took either HU or DFX alone or took neither drug.

Conclusion: Three months of concurrent use of DFX and HU appears safe, but further studies are required to better understand the safety and effectiveness of this medication combination. (Funded by CDC, CDC Foundation, and others).

KEYWORDS
adverse effect, deferasirox, hydroxyurea, iron overload, sickle cell disease

1 | INTRODUCTION

Sickle cell disease (SCD) is an inherited red blood cell (RBC) disorder that results in polymerization of hemoglobin, sickle-shaped RBCs, anemia, pain, organ injury, and premature mortality. RBC transfusion is an effective therapy for SCD and many of its complications but is limited by eventual iron overload. To prevent iron overload and its significant complications, an iron chelator is often necessary in patients with severe SCD. Parenteral deferoxamine was the only iron chelator available until 2005, when enteral deferasirox (DFX) was approved in the

United States (US). DFX appears to have equivalent efficacy as deferoxamine but is better tolerated by patients and therefore patients are able to maintain improved adherence.[1,2]

Intermittent or chronic RBC transfusions were the only widely available treatment for SCD until the 1990s, when clinical trials confirmed that pharmacologic induction of fetal hemoglobin (Hb F) reduced complication of sickle cell anemia. Hydroxyurea (HU) was subsequently approved in 1998 in the United States for the treatment of adults with SCD to decrease the frequency of vaso-occlusive pain episodes, acute chest syndrome, transfusions, and hospitalizations and is routinely recommended for patients with severe SCD.[3,4]

HU and RBC transfusions are the current cornerstone of symptom management for SCD. As a result, patients with SCD are often prescribed HU and DFX concurrently despite little knowledge about how the two medications interact. The use of existing SCD therapies is a top research priority and sufficient concerns exist that clinical trials to date have not allowed study participants to take both drugs simultaneously.[5,6] Therefore, we wished to investigate whether there is evidence of increased adverse effect or evidence of toxicity between HU and DFX when taken concurrently. We conducted a retrospective, cohort investigation of persons with SCD in a statewide Medicaid-based database who took HU and DFX simultaneously as compared to those with SCD who took either HU or DFX alone or to matched persons who took neither drug. We hypothesized that individuals who took both drugs together had similar adverse effects when compared to those who took only one or neither drug.

2 | METHODS

2.1 | Cohorts

Included cohorts were validated and followed over time using data from the California Sickle Cell Data Collection Program (CA SCDC) as previously described.[7,8] In brief, those included in CA SCDC must either have been identified through newborn screening, confirmed by laboratory analysis to have SCD at one of six SCD clinical centers in California, or found in administrative data with three or more SCD-specific International Classification of Diseases-Clinical Modification (ICD-CM) codes over a 5-year period. People meeting this definition were then linked, using Social Security numbers (SSN) and date of birth to (1) the Patient Hospital Discharge and (2) Emergency Department Utilization databases from the California Office of Statewide Health Planning and Development, (3) vital records death files, and (4) Medicaid (Medi-Cal) claims. Inclusion criteria and data linking methodologies were previously validated.[9-11] Data collection and analysis were approved by the California Committee for the Protection of Human Subjects (the state's Institutional Review Board) and by each data steward (OSHPD, the Department of Health Care Services, and the California Center for Health Statistics and Informatics). CA SCDC received a waiver of consent.

We tracked utilization and discharge codes starting on the date of the first pharmacy fill claim of HU (HU Only cohort), DFX (DFX Only cohort), or whichever drug was started second in the Both Drugs cohort. To be included in the HU Only cohort or DFX Only cohort, the person had to be on the drug for at least 90 days, Table 1. Similarly, to be included in the Both Drugs cohort, a person with SCD had to be on both HU and DFX for at least 90 days. Those in CA SCDC that were on HU or DFX for <90 days or without an SSN listed in the Medi-Cal claims data were excluded. People were then tracked until the last day of the last prescription of the qualifying medication or for a maximum of 6 months, whichever was shortest.

Due to the high number of people in the database not on either drug, each subject in the Both Drugs cohort was randomly matched for age category, sex, and tracking start date to four control patients who never filled a prescription for either drug (Neither Drug cohort). Since this study aimed to compare outcomes in the Both Drug cohort to the other control cohorts, we did not compare the HU Only and DFX Only cohort to the Neither Drug cohort.

We wished to study whether taking both medications together increased the rate of adverse reactions or toxicity; therefore, known adverse reactions of HU and DFX as listed in Lexi-Drugs (Wolters Kluwer, Alphen aan den Rijn, Netherlands) were converted to International Statistical Classification of Diseases and Related Health Problems version 9 (ICD9) codes, Appendix A. For encounter data after September 30, 2015, when ICD10 was in use for administrative claims and encounter data, Centers for Medicare and Medicaid Services General Equivalence Mapping was used to map ICD9 to ICD10.[12] Lexi-Drugs categorize the adverse reactions by body system and these same body system categorizations are used in Table 2. In order to evaluate whether rates of adverse reactions increased or changed across cohorts, we analyzed all ICD9 or ICD10 discharge codes for individuals from ED and inpatient encounters, regardless of whether they were SCD-related, for a maximum of 6 months after start of tracking. These discharge codes were categorized by body system using their stem code and compared to the ICD9 and ICD10 codes of known adverse reaction. Using the tracking start and end date and the count of each outcome of interest, we calculated the rate per person year.

2.2 | Statistical analysis

Categorical variables were summarized using frequencies and percentages and compared for statistical significance using Chi-square tests. Continuous variables were summarized by means and rates, and analyzed using the Wilcoxon signed rank test for differences between the matched Both Drug and Neither Drug group and the Wilcoxon-Mann-Whitney test was used to test for differences between the Both Drugs compared to HU only or DFX Only. Analyses were done in SAS, version 9.4.

3 | RESULTS

Between 2009 and 2016, we identified 104 subjects in the Both Drugs cohort, 416 matched-controls in the Neither Drug cohort,

TABLE 1 Baseline patient characteristics

	Both drugs (n = 103)	Neither drug, matched (n = 412)	P-value	HU Only (n = 877)	P-value	DFX Only (n = 314)	P-value
Patients with an ED or hospital utilization within 6 months after follow up start, n (%)	58 (56)	214 (52)		506 (58)		112 (36)	
Patients with an ED or hospital utilization resulting in a known adverse reaction within 6 months after follow up start, n (%)	43 (42)	152 (37)		359 (41)		76 (24)	
Mean No. of ED & hospital encounters within 6 months after follow up start	1.89	1.83	.22[a]	3.16	.26[b]	1.07	<.001[b]
Mean No. of ED & hospital encounters resulting in an adverse reaction within 6 months after follow up start	1.43	1.71	.79[a]	2.17	.69[b]	1.05	.002[b]
Female, n (%)	53 (51)	213 (52)	N/A	425 (48)	.57[c]	172 (55)	.56[c]
Age, mean, years	26.6	27.2	N/A	27.8	.39[b]	25.2	.39[b]
Age groups, years			N/A		.25[c]		.17[c]
<7	0	0		27 (3)		10 (3)	
7 to 20.9	39 (38)	156 (38)		289 (33)		121 (39)	
21 to 40.9	46 (45)	184 (44)		387 (44)		145 (46)	
≥41	18 (17)	72 (18)		174 (20)		38 (12)	

Abbreviation: N/A, not applicable due to matching.
[a]Wilcoxon Signed Rank when compared to Both Drugs.
[b]Wilcoxon-Mann-Whitney when compared to Both Drugs.
[c]Chi-square when compared to Both Drugs.

TABLE 2 Discharge diagnosis by body system, No. of diagnosis (rate per person per year)

System	Both drugs (n = 103)	Neither drug, matched (n = 412)	*P*-value[a]	HU Only (n = 877)	*P*-value[b]	DFX Only (n = 314)	*P*-value[b]
Neurology	2 (0.04)	54 (0.26)	.0063	115 (0.26)	.3513	13 (0.08)	.7258
Ophthalmology	2 (0.04)	7 (0.03)	.8438	13 (0.03)	.9611	3 (0.02)	.6861
Cardiovascular	10 (0.19)	63 (0.31)	.5947	179 (0.41)	.1290	36 (0.23)	.6421
Pulmonary	32 (0.62)	123 (0.60)	.5849	409 (0.93)	.4036	37 (0.24)	.0589
Gastrointestinal	44 (0.85)	131 (0.64)	.0841	299 (0.68)	.1423	67 (0.43)	.0040
Liver	1 (0.02)	8 (0.04)	.5313	28 (0.06)	.6046	6 (0.04)	.6878
Renal	7 (0.13)	36 (0.17)	.8652	91 (0.21)	.9851	6 (0.04)	.0261
Hematology	3 (0.06)	41 (0.20)	.0183	47 (0.11)	.5299	54 (0.34)	.1900
Oncology	3 (0.06)	15 (0.07)	.5682	57(0.13)	.8636	22 (0.14)	.8515
Endocrine	0	6 (0.03)	.0625	17 (0.04)	.3834	6 (0.04)	.5756
Dermatology	2 (0.04)	12 (0.06)	.9018	31 (0.07)	.8755	13 (0.08)	.8488
Infectious Disease	13 (0.25)	44 (0.21)	.4765	120 (0.27)	.9467	46 (0.29)	.5817
Musculoskeletal	27 (0.52)	153 (0.74)	.2404	490 (1.12)	.1420	21 (0.13)	.0022

[a]Wilcoxon Signed Rank when compared to Both Drugs.
[b]Wilcoxon-Mann-Whitney when compared to Both Drugs.

877 controls in the HU Only cohort, and 314 controls in the DFX Only cohort, Figure 1. One individual from the Both Drugs cohort and the four matched-controls in the Neither Drug cohort were removed because the number of ED and inpatient encounters was greater than 4 standard deviations from the mean and accounted for more than 30% of the encounters. Patient characteristics for the four cohorts are described in Table 1. Age and sex distribution of the four cohorts were similar. The hospital utilization of the Both Drugs cohort compared to HU only and Neither Drug cohorts had similar ED and hospital encounters, Table 1. However, the Both

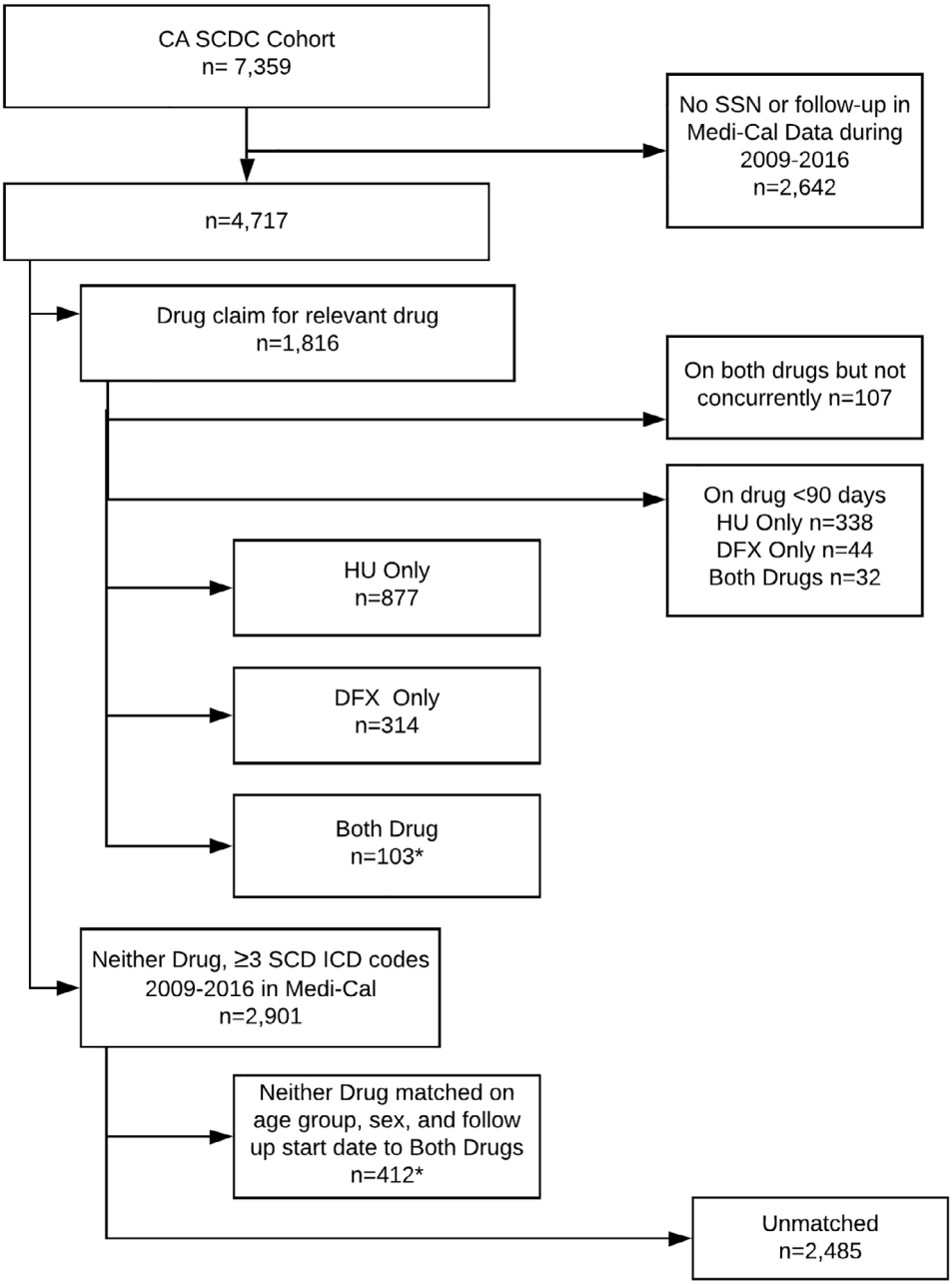

FIGURE 1 Selection of California Sickle Cell Data Collection Program (CA SCDC) participants for analysis

Drugs cohort had statistically more ED and hospital encounters (with or without an adverse reaction) compared to the DFX Only cohort. Of the 103 analyzed patients in the Both Drug cohort, 52 started HU first, while 51 started DFX first, and 97 (94%) filled prescriptions for both medications for the full 6-month analysis period.

As categorized by body system (ICD code stem), the rate of adverse complications captured during ED and inpatient encounters are reported in Table 2. There were no statistical differences in rate of adverse complications when comparing Both Drugs to HU Only cohort. However, the rate of gastrointestinal, renal, and musculoskeletal adverse complication was statistically higher in the Both Drugs cohort compared to the DFX cohort. Unexpectedly, the rate of neurological and hematological adverse reactions was statistically higher in the Neither Drug cohort compared to Both Drugs cohort. Not all other differences were statistically significant.

Asthma and pain, especially chest and abdominal pain, were common adverse effects across the cohorts, Table 3. The proportion of diagnosis codes for increased serum creatinine, renal tubular disease, acute renal failure, increased liver function test levels, skin changes, hearing or vision changes, leg ulcers, neutropenia, thrombocytopenia, or sepsis were no higher in the Both Drugs cohort compared to the three control cohorts (Data not shown). During the follow up period, 3 (2.9%), 11 (2.7%), 27 (3.1%), and 10 (3.2%) individuals had a malignant neoplasm diagnosis code in the Both Drugs, Neither Drug, HU Only, and DFX Only cohorts, respectively, which is similar to previous reported prevalence of cancer in those with SCD.[13]

TABLE 3 Top five adverse reactions, No. of adverse reactions (rate per person year)

Both Drug[a] (n = 122 Adverse reactions)		Neither Drug[a] (n = 568 Adverse reactions)		HU Only (n = 948 Adverse reactions)		DFX Only (n = 380 Adverse reactions)	
Adverse reaction	No. (rate per py)	Adverse reaction	No. (rate per py)	Adverse reaction	No. (rate per py)	Adverse reaction	No. (rate per py)
Abdominal pain	14 (0.27)	Asthma	47(0.22)	Asthma	139 (0.316)	Aplastic anemia	27 (0.17)
Asthma	13 (0.25)	Chest pain	36 (0.17)	Arthralgia	126 (0.28)	Abdominal pain	19 (0.12)
Constipation	12 (0.23)	Abdominal pain	39 (0.19)	Chest pain	113 (0.26)	Asthma	28 (0.18)
Chest pain	9 (0.17)	Back pain	17 (0.08)	Pain in extremity	68 (0.16)	Malignant neoplasm	20 (0.13)
Back pain	6 (0.11)	Pain in extremity	36 (0.17)	Back pain	70 (0.16)	Chest pain	170 (0.11)

[a]One patient was removed from Both Drug cohort (along with the four matched controls in the Neither Drug cohort) because the number of hospital and ED encounters was greater than 4 standard deviations from the mean.

4 | DISCUSSION

Based on this retrospective cohort investigation of a statewide Medicaid-linked database, persons with SCD who took both HU and DFX concurrently did not have higher rates for emergency or inpatient encounters when compared to cohorts who took HU alone or neither drug. ED and hospital utilization were higher in the Both Drugs cohort compared to the DFX Only cohort. This may be because people on DFX alone are possibly on a chronic transfusion regimen, which can reduce disease severity and organ dysfunction. When encountered either in the ED or inpatient setting, those on both HU and DFX had a similar rates and similar distribution of adverse complications compared to most controls. Furthermore, other frequent adverse reactions observed when HU or DFX are used as monotherapy did not appear to be increased when both medications were used concurrently.

Although clinicians prescribe HU and DFX together to patients with SCD, clinical trials have not allowed study subjects to take both concurrently, thereby complicating trial design and slowing progress in our ability to use established therapies optimally. To date, only one study enrolled 28 patients with SCD to a randomized trial of iron chelators and allowed concurrent HU use; this study concluded that ≤2 years of concomitant HU did not influence the efficacy, safety, and pharmacokinetic parameters of DFX.[14] A preclinical study of concurrent HU and DFX in mice also supports the safety of the combination and even proposes synergistic iron chelation.[15]

This is the largest analysis to date on the safety of concurrent HU and DFX use in people with SCD. Although we required only 90 days of combination HU and DFX therapy, 94% filled prescriptions for both drugs for the entire 6 months analysis. We opted to track cohorts for 6 months with the assumption that many adverse effects would be evident by then given the pharmacokinetic of both medications. Since many high-risk oral medications are prescribed 1 month at a time, requiring 3 months of refills increased our confidence that the person actually ingested the medication. However, as with all administrative database studies, this cannot be confirmed. Although we may see discharge coding that suggested signs of toxicity, our data would not capture whether either medication was discontinued due to perceived toxicity or intolerance and would not detect a small difference in adverse effects given our study size. Lastly, because our analysis required data on prescriptions filled, only individuals on Medicaid were analyzed. However, 62% of people tracked through CA SCDC are on Medicaid, therefore, the majority of Californians with SCD were captured.

As with any retrospective analysis, this work is susceptible to bias, particularly indication bias, where clinicians may prescribe RBC transfusion (with subsequent DFX) and HU to those with more severe SCD. If this was true, persons in the Both Drugs cohort might be expected to have a higher rate of encounters for ED or inpatient care and a higher rate of adverse events. However, we observe similar rates in the Both Drugs cohort compared to controls, which may strengthen our conclusion that concomitant HU and DFX appears safe. In addition, as is typical for other studies using administrative databases, our data is reliant on accurate and appropriate ICD9 and ICD10 coding. Although the case definition based on ICD coding used by CA SCDC has been validated, coding for transient and/or mild, but potentially clinically important, side effects is under-represented in claims data. This may be particularly important in this study with regard to transient lab abnormalities. Therefore, our study may underestimate the prevalence of mild adverse effects, specifically transient or mild changes in creatinine or liver function. However, this bias should be similar across all cohorts, and comparisons remain valid. As mentioned above, 3 months of prescription refills do not guarantee the person ingested the medication and therefore, sub-optimal adherence could also contribute to lower adverse reactions in the three medication cohorts.

In summary, prescribing HU and DFX together for at least 90 days appears safe in the short term. Future studies must further interrogate safety and effectiveness of concurrent use of HU and DFX in the short and long-term so that they can be given together in clinical trials, or be proven unsafe or ineffective so that clinicians stop prescribing them together. Ideally, this would be accomplished in a

prospective study that includes pharmacokinetics of both drugs and tracking medication adherence, adverse effects, and hospital utilization over years.

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CONFLICT OF INTEREST

The authors declare no competing financial interests.

TRANSPARENCY STATEMENT

Trisha Wong affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

AUTHORSHIP CONTRIBUTIONS

Conceptualization: Trisha Wong
Data curation: Jhaqueline Valle, Susan Paulukonis
Formal Analysis: Trisha Wong, Jhaqueline Valle, Susan Paulukonis
Funding acquisition: Susan Paulukonis
Investigation: Trisha Wong, Jhaqueline Valle, Susan Paulukonis
Methodology: Trisha Wong, Jhaqueline Valle, Susan Paulukonis
Project administration: Trisha Wong
Resources: Susan Paulukonis
Supervision: Susan Paulukonis
Validation: Jhaqueline Valle, Susan Paulukonis
Visualization: Trisha Wong, Jhaqueline Valle, Susan Paulukonis
Writing—original draft: Trisha Wong
Writing—review and editing: Trisha Wong, Jhaqueline Valle, Susan Paulukonis

All authors have read and approved the final version of the manuscript.

Trisha Wong had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

DATA AVAILABILITY STATEMENT

Data subject to third party restrictions.

ORCID

Trisha E. Wong https://orcid.org/0000-0002-5298-6217

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