Pruritus after discontinuation of cetirizine

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Abstract

Background: Intense pruritus or itching emerging after discontinuation of cetirizine has been the subject of postmarketing reports submitted to the U.S. Food and Drug Administration (FDA), published in the medical literature, and discussed on the internet. To better understand and further investigate this adverse event, we analyzed cases of pruritus occurring after discontinuation of cetirizine in the FDA Adverse Event Reporting System (FAERS) database and medical literature.

Methods: We conducted a retrospective study to identify and describe cases of pruritus occurring after discontinuation of cetirizine in the FAERS database and medical literature through April 24, 2017. Data collected from the reports included demographic information, reason for use, serious outcome, report source, duration of cetirizine use, time to onset of pruritus after cetirizine discontinuation, presence of associated urticaria, treatment for pruritus, concomitant comorbidities and medications associated with pruritus, rechallenge information, and patient outcome information.

Results: We identified 146 cases of pruritus after discontinuation of cetirizine. Reporting frequency increased starting in 2008. The median patient age was 38 years ($n = 141$), ranging from 6 to 71 years, and cases were predominantly reported in females ($n = 110$). Most cases ($n = 115$) were submitted directly to the FDA from consumers or healthcare providers. The median duration of use of cetirizine prior to discontinuation was 24 months ($n = 130$), ranging from 0.3 to 172.2 months. The median time to onset of pruritus from discontinuation was 2 days ($n = 91$), ranging from 0.5 to 5 days. Of the 55 cases that reported discontinuation of cetirizine again after restarting, 54 reported pruritus recurrence.

Conclusions: Our case series provided evidence of an association between the discontinuation of cetirizine and the development of pruritus. The mechanism by which cetirizine causes pruritus upon discontinuation is unknown. Patients and prescribers should have knowledge of this adverse event, given the widespread use and availability of cetirizine, and potential impact on patient quality of life.

Keywords: antihistamine, cetirizine, pruritus

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Introduction

Cetirizine is a second-generation antihistamine (SGA) indicated for the treatment of symptoms of allergic rhinitis and chronic idiopathic urticaria, including pruritus.[1] Cetirizine was approved as a prescription product in the United States in 1995 and has been available over-the-counter (OTC) since 2007. Intense pruritus or itching emerging after discontinuation of cetirizine has been the subject of postmarketing reports submitted to the U.S. Food and Drug Administration (FDA), published in the medical literature, and discussed on the internet.

To better understand and further investigate this adverse event, we analyzed cases of pruritus occurring after discontinuation of cetirizine in the FDA Adverse Event Reporting System (FAERS) database and medical literature.

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Methods

We conducted a retrospective study to identify and describe cases of pruritus occurring after discontinuation of cetirizine reported to the FAERS database and medical literature. The FAERS database contains adverse event reports submitted to FDA and is designed to support FDA's postmarketing safety surveillance program for drug and biological products. Patients, consumers, and healthcare professionals can voluntarily report adverse events directly to FDA *via* the MedWatch program or to product manufacturers, who are then required to submit the reports to FDA according to regulatory requirements. Adverse events in the FAERS database are coded using the Medical Dictionary for Regulatory Activities (MedDRA) international medical terminology developed by the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.[2] We searched the FAERS database through April 24, 2017, with the MedDRA Preferred Terms *Pruritus, Pruritus generalised, Urticaria, Dependence, Drug dependence, Drug withdrawal syndrome, Withdrawal syndrome*, and *Rebound effect*. We performed a literature search in PubMed and Embase with the terms *cetirizine* and *histamine h1 antagonists* matched against the terms *pruritus, rebound, withdrawal, withdrawal syndrome*, and *treatment withdrawal*.

For the purpose of this analysis, a case was defined as any report of pruritus following permanent or temporary discontinuation of continuous cetirizine treatment. To increase confidence that the appearance of pruritus following discontinuation was not due to the reappearance of pre-existing pruritus, we excluded reports in which the patient reported a prior skin condition (e.g., atopic dermatitis, pruritus, psoriasis, urticaria), treatment with cetirizine for a skin condition or unknown indication, or an alternative etiology for the development of pruritus. Alternative etiologies included concomitant medical conditions or medications associated with, and temporally related to, the onset of pruritus. We also excluded duplicate reports and FAERS reports associated with a nonserious outcome. Serious outcomes per regulatory definition (CFR 314.80) include death, life-threatening, hospitalization, disability, congenital anomaly, and other serious important medical events (or 'other')[3]; seriousness is determined by the reporter in reports submitted directly to FDA. Literature cases not reported to FAERS are not subject to coding of serious outcome; therefore, cases regardless of serious outcome were included.

Data collected from the cases included demographic information, reason for use, serious outcome, report source, duration of cetirizine use, time to onset of pruritus after cetirizine discontinuation, presence of associated urticaria, treatment for pruritus, concomitant comorbidities and medications associated with pruritus, rechallenge information, and patient outcome information. Positive rechallenge was defined as documented or suggested resolution of pruritus following reinitiation of cetirizine and reappearance of pruritus following subsequent discontinuation of cetirizine.

Results

We identified 146 FAERS and literature cases meeting inclusion and exclusion criteria.[4] Table 1 provides descriptive characteristics of these 146 cases. Cases in the FAERS database were initially sparse and primarily submitted by manufacturers until 2008; there was an increase in reporting thereafter, driven mostly by reports ($n = 115$) submitted directly to FDA from consumers or healthcare providers (Figure 1). Most FAERS cases were coded with the serious outcome 'other' ($n = 134$); details reported in these cases that may have been used to determine seriousness included quality of life issues, such as sleep disturbances and patient distress, or physical manifestations of pruritus, such as skin damage and bleeding.

The median patient age was 38 years ($n = 141$), ranging from 6 to 71 years of age, and cases were predominantly reported in females ($n = 110$). Itch was described as intense and unbearable; in some cases, the patient reported the itch started in the hands, feet, and scalp before spreading to the rest of the body. The indication for use reported in the 146 cases was hay fever, allergies, or symptoms of allergies ($n = 135$) or unapproved indications for use ($n = 11$), such as nonallergic rhinitis, sinus infection, and middle ear effusion. Reporters in 36 cases explicitly stated the patient did not have a history of similar symptoms (e.g., itching, urticaria, skin rash, dermatitis, 'skin issues') prior to initiation of cetirizine; most cases ($n = 33$) reported allergy-related indications for use.

Table 1. Descriptive characteristics of Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) and medical literature cases of pruritus reported after discontinuation of cetirizine, received by FDA through April 24, 2017 ($n = 146$).

Age (years)	Median	38
	Range	6–71
	Not reported	5
Sex	Male	36
	Female	110
Case source	Direct report*	115
	Submitted by manufacturer	28
	Medical literature	3
Serious outcomes coded in FAERS cases[$] ($n = 143$)	Disability	7
	Required intervention	3
	Hospitalization	1
	Other	134
Duration of use of drug prior to discontinuation attempt (months)	Median	24
	Range	0.3–172.2
	Not reported/unable to calculate[‡]	16
Time to onset of pruritus from discontinuation of drug (days)	Median	2
	Range	0.5–5
	Not reported/unable to calculate[§]	55
Case reported associated urticaria[‖]	Yes	30
	No	12
	Not reported	104
Treatment reported for pruritus[¶]	Taper	17
	Restart	86
	Alternative antihistamine	12
	Topical steroid	5
	Not reported	45
Case reported pruritus resolved with tapering cetirizine ($n = 17$)	Yes	1
	No	12
	Not reported	4
Case reported pruritus resolved with restarting cetirizine ($n = 86$)	Yes	56
	No	1
	Not reported	29
Response to Rechallenge[#] ($n = 55$)	Positive	54
	Negative	0
	Not reported	1

(Continued)

Table 1. (Continued)

Case reported by a physician or nurse practitioner	Yes	14
	No	132
Comorbidities associated with pruritus reported in the cases** ($n = 11$)	Hypothyroidism	7
	Anxiety	1
	Dry skin	1
	Depression	1
	Anemia	1
	Aluminum/Magnesium exposure	1
	None	91
	Past medical history not reported	44
Case reported concomitant medications labeled for pruritus‡‡	Yes	34
	No	23
	Unknown	2
	No concomitant medications	17
	Medications not reported	70

*Direct reports are adverse event reports submitted by patients, consumers, and healthcare professionals directly to FDA *via* the MedWatch program.
$Serious outcomes per regulatory definition include death, life-threatening, hospitalization, disability, congenital anomaly, and other serious important medical events. Literature cases not reported to FAERS are not subject to coding of serious outcome; therefore, cases regardless of serious outcome were included. A report may have more than one outcome.
‡Unable to calculate = non-numerical or nonspecific duration of use [e.g., 'years' ($n = 4$), 'months' ($n = 2$)].
§Unable to calculate = non-numerical or nonspecific time to onset [e.g., < 4 days ($n = 1$), < 1 week ($n = 1$), < 4–5 days ($n = 1$), 'few' days ($n = 2$), 'days' ($n = 1$)].
||Cases documented urticaria associated with pruritus after discontinuation of cetirizine.
¶A case may have more than one treatment.
#Positive rechallenge was defined in FAERS cases as documented or suggested resolution of pruritus following reinitiation of cetirizine and reappearance of pruritus following subsequent attempt at discontinuation of cetirizine. Positive rechallenge was counted in literature reports if specifically documented.
**Overall, 11 cases reported a comorbidity associated with pruritus (i.e., one that could potentially contribute to pruritus). A case may have more than one comorbidity associated with pruritus.
‡‡A case may have one or more concomitant medications labeled for pruritus. An 'unknown' concomitant medication is a medication not marketed in the United States or an unspecified medication (e.g., 'contraceptive unspecified').

The median duration of use of cetirizine prior to discontinuation was 24 months ($n = 130$), ranging from 0.3 to 172.2 months. The median time to onset of pruritus from discontinuation was 2 days ($n = 91$), ranging from 0.5 to 5 days. Urticaria was reported in 30 cases. Most cases ($n = 101$) reported one or more treatments for the pruritus, including restarting cetirizine ($n = 86$), tapering cetirizine ($n = 17$), use of an alternative antihistamine ($n = 12$), and use of a topical steroid ($n = 5$). Of the 55 cases that reported discontinuation of cetirizine again after restarting, 54 reported positive rechallenge, and one case did not report the outcome to rechallenge. Of the patients reporting past medical history ($n = 102$), 11 reported one or more comorbidities that could potentially contribute to pruritus, including hypothyroidism ($n = 7$), anxiety ($n = 1$), dry skin ($n = 1$), depression ($n = 1$), anemia ($n = 1$), and aluminum/magnesium exposure ($n = 1$); however, the report contained no mention of worsening or uncontrolled disease to suggest temporality with the pruritus and 8 of the 11 cases reported positive rechallenge to cetirizine. A total of 34 cases reported concomitant medications whose product labels list pruritus as an adverse event (Table 2).

Discussion

We identified 146 cases of pruritus after discontinuation of cetirizine that were associated with

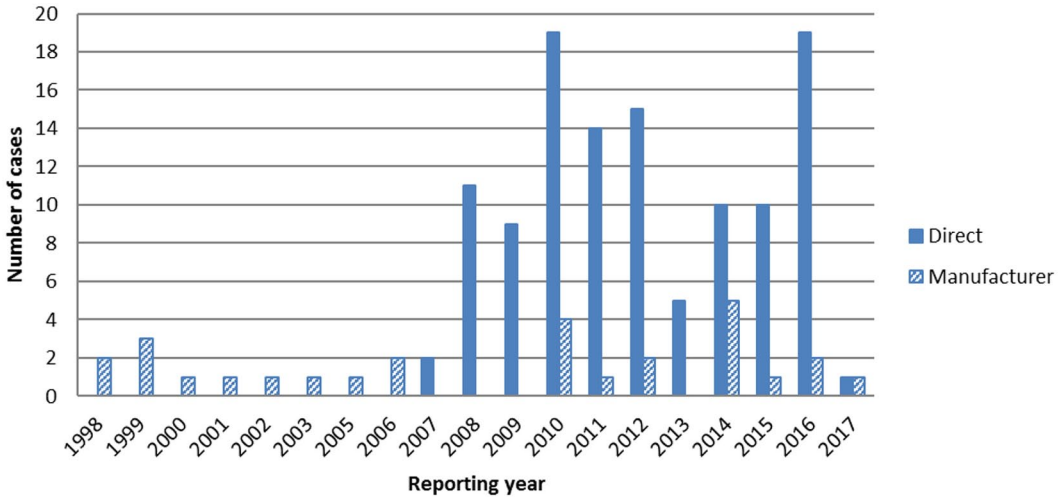

Figure 1. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) case counts of pruritus after discontinuation of cetirizine by case source, received by FDA through April 24, 2017, by year ($n = 143$).
This graph shows that cases in the FAERS database were initially sparse and submitted primarily by manufacturers until 2008; however, there was an increase in reporting thereafter, driven mostly by reports submitted directly to FDA. Cetirizine was approved as a prescription product on December 8, 1995 and for over-the-counter use on November 16, 2007. The data for 2017 was incomplete in the FAERS database.

serious outcomes. Some patients described the itch as so intense that it impacted their ability to work, sleep, or perform their normal daily activities; however, some cases that reported the serious outcome of 'other' did not contain sufficient case details to determine which aspect of the report was considered serious by the reporter. We excluded all cases in which patients reported a prior history or indication for use of skin conditions to minimize confounding by indication and increase confidence that the adverse event was not due to lack of effective therapy for pre-existing pruritus. The numerous cases with a strong temporal relationship and positive rechallenge provide evidence for an association between discontinuation of cetirizine and the development of pruritus.

The mechanism by which cetirizine induces pruritus upon discontinuation is unknown. A FAERS search using the same search criteria was performed for other oral SGAs such as levocetirizine, loratadine, desloratadine, and fexofenadine. There was insufficient evidence to support a class effect, though five cases meeting our inclusion and exclusion criteria were retrieved from FAERS and medical literature describing pruritus after discontinuation of levocetirizine, the R-enantiomer of cetirizine. The median duration of use of levocetirizine in the cases was 24 months ($n = 5$) and median time to onset was 1 day ($n = 3$); positive rechallenge was reported in all five cases. The indication for use reported in these five cases was hay fever ($n = 4$) and sinus disorder ($n = 1$). Likewise, we performed a search for hydroxyzine, a first-generation antihistamine that is metabolized to cetirizine, and retrieved only two cases that did not support a causal association. It has been theorized that high occupancy of H1 receptors by circulating antihistamine results in itch after discontinuation of antihistamines with shorter half-lives (such as cetirizine and levocetirizine).[4] Beyond half-life, there are other differences in the structure and pharmacokinetic properties of cetirizine and levocetirizine compared with other SGAs, including piperazine chemical structure, lower volume of distribution, and higher selectivity for H1 receptors.[5,6] It is unclear if any of these properties contribute to the mechanism by which post-discontinuation pruritus occurs.

Social media and other online resources are frequently used by patients to obtain and discuss health-related information.[7,8] Although patient-generated data from social media has limitations in postmarketing drug safety surveillance,[9,10] it may have contributed to reporting of adverse events to the FDA. Some of our cases reported finding similar experiences after searching for a

Table 2. Concomitant medications labeled for pruritus in Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) and medical literature cases of pruritus after discontinuation of cetirizine received by FDA through April 24, 2017 ($n = 34$)*.

Medication labeled for pruritus	Number of cases reporting medication
Amlodipine	2
Atomoxetine	1
Codeine/acetaminophen	1
Conjugated estrogens/medroxyprogesterone acetate	1
Duloxetine	1
Famotidine	1
Fexofenadine	1
Flunisolide Inhaler	1
Fluticasone Inhaler	1
Ibandronate	1
Indomethacin	1
Ipratropium	1
Isosorbide mononitrate	1
Lansoprazole	1
Levothyroxine	8
Lisinopril	1
Lisinopril/hydrochlorothiazide	1
Losartan	2
Methocarbamol	1
Metoprolol succinate	1
Montelukast	11
Niacin	1
Norethindrone acetate/ethinyl estradiol/ferrous fumarate	1
Omeprazole	4
Pantoprazole	2
Ramipril	1
Rosuvastatin	1
Sertraline	1
Simvastatin/ezetimibe	1
Sitagliptin	1
Terazosin	1
Theophylline	1
Valacyclovir	1
Zafirlukast	1
Zolpidem	1

*A case may contain one or more medications labeled for pruritus.

cause on the internet. Discussions about pruritus after discontinuation of cetirizine appear online as early as 2008, and some websites encourage patients to submit MedWatch reports to FDA.[11–13] Because cetirizine was approved for OTC use in November 2007, it is unknown if the increased reporting starting in 2008 (Figure 1) was a result of increased access, increased internet discussion, or both.

A major limitation of this study is that cetirizine is indicated for the treatment of disease states, such as chronic urticaria, that include pruritus as a symptom. To increase the potential that the adverse event was not due to removal of efficacious therapy, we utilized stringent exclusion criteria to minimize the contribution of underlying skin disease and pre-existing pruritus; however, this cannot be certain in all cases due to limitations of data in spontaneous case reports, such as incomplete reporting of data. We do note that most cases reported an indication for cetirizine of hay fever, allergies, or symptoms of allergies, which do not commonly present with generalized pruritus; atopy is a potential confounder given the indication for use in most cases was allergies or allergy symptoms. There were also nonallergic indications reported in our case series in which pre-existing pruritus is unlikely. Furthermore, a subset of cases (36/146 cases) confirmed the patient did not have similar symptoms prior to starting cetirizine, strengthening a possible association with cetirizine discontinuation. Another limitation is that a small number of cases that reported other comorbidities or concomitant medications associated with pruritus were included in the case series. These factors were unlikely the cause of pruritus after a critical analysis of the case narrative.

Conclusion

Our case series identified an association between discontinuation of cetirizine and the development of pruritus. Given the widespread use and availability of cetirizine and potential impact on patient quality of life, patients and prescribers should have knowledge of the association between the discontinuation of cetirizine and the development of pruritus. To further disseminate knowledge of this adverse event and facilitate recognition of cetirizine as a potential cause, cetirizine and levocetirizine prescription product labels were updated with information about pruritus after discontinuation of cetirizine in the Adverse Reactions section.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Disclaimer

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