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Treatment patterns in Cushing's disease patients in two large United States nationwide databases: application of a novel, graphical methodology

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Abstract
Purpose Data on real-world treatment patterns for Cushing's disease (CD) are limited. We used a novel graphical technique to analyze treatment patterns in CD patients in the United States.
Methods Two combined US claims databases were used to identify CD patients with claims with Cushing's syndrome diagnosis and either benign pituitary adenoma or hypophysectomy and newly-treated in 2008 (no treatment in prior 6 months). Patients were followed from first treatment day until end of enrollment or 12/31/2010. We compared summary statistics with a novel graphical methodology that simultaneously displays individual color-coded patient treatment histories.
Results Among 228 newly-treated CD patients, 180 (78.9 %) had surgery as first observed treatment, 42 (18.4 %) had pharmacotherapy, and 6 (2.6 %) had radiotherapy. In 42 patients who had pharmacotherapy as first treatment, dopamine agonists were used as first pharmacotherapy in 24 (57.1 %), ketoconazole in 17 (40.5 %), and mitotane in one patient (2.4 %). In 180 patients with surgery as first treatment, 15 (8.3 %) later had radiotherapy and 14 (7.8 %) had pharmacotherapy. In 42 patients who had pharmacotherapy as first treatment, 10 (23.8 %) later had surgery and 2 (4.8 %) had radiotherapy. Mean duration of first pharmacotherapy varied: 369.5 days for dopamine agonists, 157.1 for ketoconazole, and 30.0 for mitotane.
Conclusions This study addresses a need for US data on real-world treatment patterns for CD patients. The majority of CD patients undergo surgery as initial therapy. Patients using pharmacotherapy had limited persistence with treatment. Neither reasons for discontinuation of therapy nor the impact of a recent FDA warning on potentially fatal liver toxicity from ketoconazole could be assessed.

Keywords Cushing's disease · Treatment patterns · Population study · Insurance claims · Secondary data analysis · Graphical methodology

Introduction

Cushing's syndrome is a constellation of the signs and symptoms of excess glucocorticoid exposure. The causes of endogenous Cushing's syndrome are usually grouped into corticotropin-dependent (80–85 % of cases) and corticotropin-independent etiologies [1, 2]. Cushing's disease (CD) is caused by excessive adrenocorticotropic hormone (ACTH) due to a secreting pituitary tumor [3]. The incidence of CD is typically reported to range from 1.2 to 2.4 per million people annually in Europe [3–6] and up to eight cases per million population in people <65 years old in the United States [18]. CD is estimated to account for 70 % of all cases of Cushing's syndrome and is associated with substantial morbidity and mortality [1, 3, 7].

Incompletely controlled Cushing's syndrome is associated with an elevated mortality risk, making appropriate treatment crucial [4]. Once CD is diagnosed, the primary

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treatment is resection of the associated pituitary tumor, usually via transsphenoidal surgery, and overall remission rates range as high as 70–90 % [3, 8]. However, relapse rates of disease may reach 20–25 % at 10 years after surgery, requiring repeat surgical intervention, radioablation, or pharmacologic treatment [8].

Compared to the normal population and patients with non-secreting pituitary adenomas, patients with CD accrue significantly higher healthcare costs per annum [9]. However, to our knowledge no studies report combined surgical and nonsurgical treatment patterns at the population level in the United States. Therefore, our aim was to utilize population-level commercial health insurance claims databases in order to identify and characterize real-world clinical treatment pathways among US patients with CD. Additionally, we used a novel graphical technique that displays individual patient histories to depict CD treatment patterns. The benefits of using such graphical methodology are that it permits visualization of treatment patterns in individual patients and identifies specific points in time at which treatment at the patient level has been changed.

Methods

Study design and data sources

We conducted a retrospective cohort study using two major US commercial administrative claims databases, Thomson Reuters MarketScan Commercial Claims and Encounters (Truven Health Analytics, Ann Arbor, MI) and IMS Health PharMetrics (IMS Health, Danbury, CT). Each database represents claims for over ten million covered lives per year from all regions of the United States. Both administrative claims databases are compliant with the Health Insurance Portability and Accountability Act (HIPAA) and contain de-identified adjudicated pharmacy claims (e.g., outpatient prescriptions) and medical claims (e.g., inpatient and outpatient services) submitted for payment by providers, healthcare facilities, and pharmacies. Claims in these databases include information on patient, provider, and hospital demographics, physician visit characteristics, medical procedures, hospitalizations, drugs dispensed, dates of service/prescription, number of days of medication supplied, and tests performed. Drug-related claims are only recorded for the outpatient setting. Healthcare costs (i.e., medical claims paid) are recorded in both databases.

Study cohort selection

To identify our CD patient cohort, we first identified patients who had a claim with diagnosis of Cushing's syndrome (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code: 255.0) in 2008. Among this population, eligible patients were required to have an associated benign pituitary adenoma diagnosis (ICD-9-CM: 227.3) or hypophysectomy [ICD-9-CM: 07.6x; Current Procedural Terminology (CPT): 61546, 61548, 62165] procedure between 2007 and 2010. They were also required to have a pertinent pharmacologic, surgical, or radiation treatment in 2008 (Electronic supplementary material), and we defined the first day of this treatment in 2008 as Day 1. Eligible patients could not have had prior treatment before Day 1 and were continuously enrolled for at least 6 months before Day 1 (washout period). No minimum follow-up time was required, allowing us to track patient treatment patterns across time for all available claims for CD-related treatments. Thus, patients with CD who were newly treated in 2008 were included and followed from the Day 1 until the end of enrollment or up to 12/31/2010, whichever occurred first (i.e., maximum of 3-year follow-up).

Study measures

We used all enrollment files, medical claims, and pharmacy claims submitted during the follow-up period to determine the study measures. Every claim for an individual's period of enrollment is included in the database, and we presumed that there were no missing data because a claim must exist in order for payment to be processed. Patient age and gender were identified in enrollment records. The ICD-9-CM procedure codes and CPT codes used to identify treatments used in CD patients in these databases are described in the Electronic supplementary material. We assessed surgery (e.g., adrenalectomy, hypophysectomy), radiotherapy, and pharmacologic treatments (e.g., dopamine agonists, ketoconazole, mitotane).

Analyses

We reported descriptive statistics, including means, medians, and standard deviations for continuous variables as well as patient counts and percentages for categorical variables, for all study measures where applicable. All data transformations and statistical analyses were performed using SAS® version 9.3 (SAS Institute, Cary, NC).

We conducted an additional analysis using GRAPHx™ (Partnership for Health Analytic Research, LLC, Beverly Hills, CA), a novel, proprietary graphics-based algorithm developed using R version 1.12. The GRAPHx method uses multi-colored line segments to represent different treatments received since the first day of treatment, plotting them over time, and images are reviewed manually for the presence and length of segments and change in colors and patterns over time to interpret treatment episodes. Each

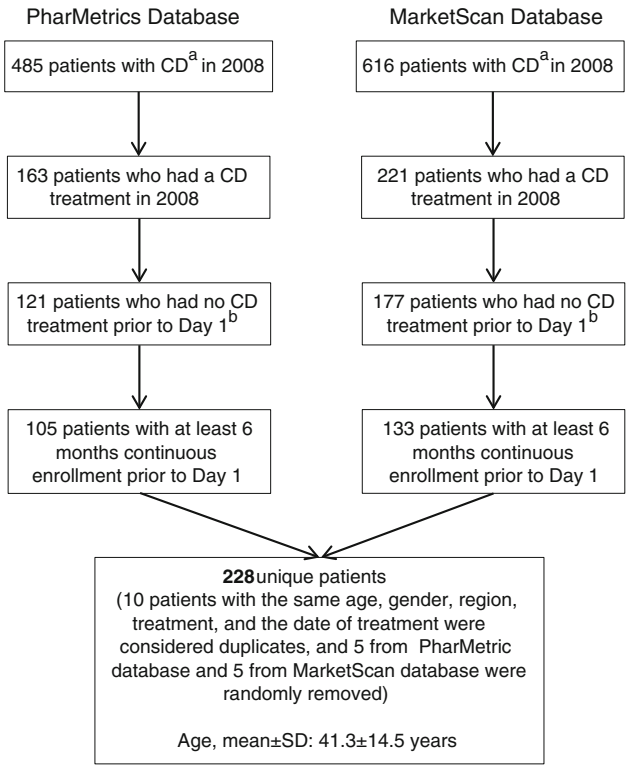

Fig. 1 Identification of newly treated patients with Cushing's disease. Day 1: first day of treatment. [a] Patients who had a Cushing's syndrome diagnosis in 2008 and had either benign pituitary adenomas diagnosis or hypophysectomy between 2007 and 2010. [b] First date of treatment in 2008

horizontal line in the graphical output represents an individual patient's treatment history in the follow-up period, while the height of each colored section is proportional to the number of patients. Gray areas represent periods of enrollment during which there were no claims for the treatments of interest. The treatment patterns for individual patients were sorted in the GRAPHx based on similar treatment patterns to facilitate the overall summary of these data.

Results

We initially identified 485 patients with CD in the PharMetrics database and 616 in the MarketScan database in calendar year 2008 (Fig. 1). Of these 1,101 patients, we excluded 863 patients: 717 did not have a CD treatment in 2008, 86 were not newly-treated (had a CD treatment before Day 1), and 60 did not have at least 6 months of continuous enrollment prior to Day 1. Finally, 10 patients with the same age, gender, region, treatment, and date of treatment in the two databases were considered duplicates. Five of these patients were randomly removed from the PharMetrics database and five were randomly removed from MarketScan. The final analytic sample included 228 newly treated CD patients with mean age of 41 years (SD: 14.5), of which 175 (76.8 %) were female.

Among the 228 CD patients, surgical treatment appeared most commonly (n = 180, 78.9 %), followed by pharmacologic therapy (n = 42, 18.4 %) and radiotherapy (n = 6, 2.6 %) as initial treatment (Table 1). Across the entire cohort, 38 (16.7 %) patients underwent a second treatment of any type during up to 3-years of follow-up. Among the 180 patients who underwent surgery initially, 26 (14.4 %) underwent a second treatment of any type. None of the radiotherapy patients subsequently had surgery. Twelve (28.6 %) of the 42 patients who initially underwent pharmacologic therapy underwent additional treatment.

Among 80 patients with at least 2-years enrollment, 58 (72.5 %) patients had single-modality treatment, primarily surgery (n = 40, 50.0 %), dopamine agonists (n = 10, 12.5 %), and adrenalectomy (n = 5, 6.3 %). Of the remaining 22 patients, ten underwent two or more pituitary surgeries and six underwent adrenalectomy after pituitary surgery. The mean number of days between two pituitary surgeries was 199.7 (median: 120). The mean number of days between initial pituitary surgery and adrenalectomy was 195.7 (median: 84).

Among pharmacologic agents, dopamine agonists were used most often (n = 24, 10.5 %), followed by ketoconazole (n = 17, 7.5 %), and mitotane (n = 1, 0.4 %). Mean duration of first pharmacologic therapy was greatest on dopamine agonists (mean: 369.5 days; median: 245), followed by ketoconazole (mean: 157.1 days; median: 30) and mitotane (mean and median: 30 days). For all pharmacologic treatments, the mean treatment duration was 275.4 days (median: 76).

Figure 2 depicts treatment patterns in newly treated CD patients as individual patient histories across 3 years of follow-up. Manual review of the figure demonstrated several findings. First, we noted that the majority of the cases featuring initial surgery were followed by gray space, indicating that relatively few claims for treatment after surgery were found. This is consistent with the 85.6 % of surgical patients without a second treatment claim identified during descriptive analysis. Second, we noted that the majority of the blue dots, representing follow-up pituitary surgery, were seen within 1 year of initial surgery. Finally, the GRAPHx figure demonstrated that patients treated initially with dopamine agonists appear to start and stop therapy more frequently than those who initiated ketoconazole first.

Discussion

The most recent consensus statement on CD states that transsphenoidal surgery is first-line treatment, since most

Table 1 Treatment patterns among newly treated Cushing's disease patients, stratified by first treatment (n = 228)

First CD treatment	1st treatment[a]		>1 treatment[b]		Interventions during entire period of observation, N (%)[b]					
					Any surgery		Any radiotherapy		Any pharmacologic treatment	
	Number	(%)	Number	(%)	Number	(%)	Number	(%)	Number	(%)
All	228	(100)	38	(16.7)	190	(83.3)	23	(10.1)	56	(24.6)
Surgery	180	(78.9)	26	(14.4)	180	(100)	15	(8.3)	14	(7.8)
Pituitary	172	(75.4)	26	(15.1)	172	(100)	15	(8.7)	14	(8.1)
Adrenalectomy	8	(3.5)	0	0	8	(100)	0	(0)	0	(0)
Radiotherapy	6	(2.6)	0	0	0	(0)	6	(100)	0	(0)
Pharmacologic treatment	42	(18.4)	12	(28.6)	10	(23.8)	2	(4.8)	42	(100.0)
Dopamine agonists	24	(10.5)	3	(12.5)	3	(12.5)	1	(4.2)	24	(100.0)
Ketoconazole	17	(7.5)	8	(47.1)	7	(41.2)	1	(5.9)	17	(100.0)
Mitotane	1	(0.4)	1	(100.0)	0	(0)	0	(0)	1	(100.0)

Bold font indicates totals and subtotals

[a] Column percent (i.e., percent in 228 patients)

[b] Row percent (i.e., percent in patients with the given first CD treatment)

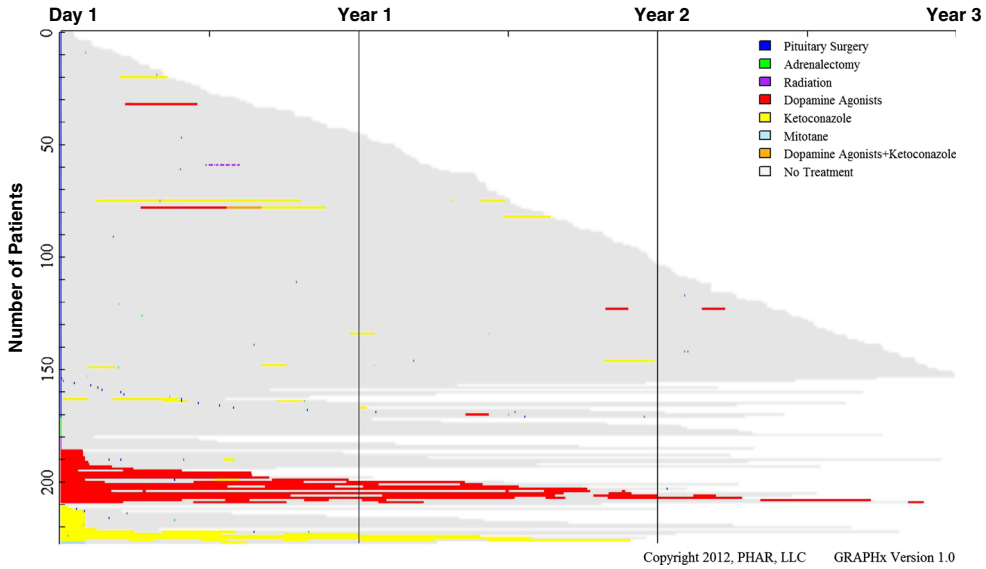

Fig. 2 Observed treatment patterns in newly treated Cushing's disease patients (n = 228) by first treatment observed during the 3-year follow-up period. Each *horizontal line* represents an individual patient's treatment history in the follow-up period; the height of each *colored* section is proportional to the number of patients. Each *multi-colored line* segment represents a different treatment received since the first day of treatment, plotted over time. Hence, *different color line* segments or *dots* (e.g., surgery) in an individual's *horizontal line* treatment history represent switches or instances of different treatments over time. *Gray* areas represent periods of enrollment during which there were no claims for the treatments of interest

cases are caused by discrete ACTH-secreting tumors rather than diffuse hyperplasia [10]. An analysis of the Nationwide Inpatient Sample (NIS) during 1993–2002 identified a 30.6 % complication rate among 3,525 patients, as well as an inpatient mortality rate of 0.7 % [11]. Retrospective case series comprise the current primary source of data suggesting 70–90 % long-term remission rates with initial surgical intervention [8, 12]. In the only other published study to date that reviewed an insurance claim database of CD patients, Swearingen et al. determined that healthcare costs and resource utilization were higher in CD patients relative to patients with nonfunctioning pituitary adenomas and population controls, without distinguishing between patients who received different therapeutic regimens [9].

This is the first study to describe real-world treatment patterns for CD in the United States, encompassing not only surgery but also pharmacologic therapy and radiotherapy. Using commercial insurance claims information

from two databases, we demonstrated that nearly four-fifths of 228 newly treated CD patients received surgery first. After up to 3-years of follow-up, 83.3 % of all patients and 85.6 % of the 180 surgical patients required no second treatment. These figures appear to be consistent with the review by Tritos et al. reporting recurrence rates of 2–26 % in surgical patients (with mean follow-up of 6–142 months) [8]. Further analyses of patient demographic, insurance status, and comorbidity characteristics in these patients would be of important epidemiologic interest.

The 42 patients initially treated with pharmacologic therapies had higher presumed failure rates. About 28.6 % of these individuals required a second therapy. One explanation is that these patients received surgical therapy outside of the observation period, and that these individuals are actually taking medication as second-line treatment. The graphical results provide another possible explanation: there was a substantial lack of persistence with therapy, particularly with dopamine agonists. Recent research suggests that long-term treatment with dopamine agonists over years, as opposed to short courses of 3–6 months, may be necessary to achieve and maintain remission in selected patients [13–15]. Insurance claims do not contain data on the reason for discontinuation of therapy, and both lack of efficacy and adverse effects may have contributed. A 2013 FDA announcement warns of serious hepatoxicity, including death, in patients who use ketoconazole for fungal infections (the drug is used off-label for CD), even among those with no history of liver disease. In addition, co-administration with certain anti-arrhythmic agents can result in potentially fatal QT prolongation [16]. The data in our study span 2008–2010, so the impact of these warnings on use of ketoconazole for CD is unknown.

This study has several limitations to consider. First, the limited duration of continuous patient enrollment and follow-up periods are characteristic of claims databases. This does not permit review of therapies that may have been provided under different health plans either before or after the included period of observation for each patient [17]. As a result, some of the patients in this study, particularly those receiving initial radiotherapy and pharmacologic therapy, may actually be receiving second-line interventions. Next, this study uses databases that lack detailed clinical information since these databases are not specifically generated for clinical or scientific aims; these clinical data, if available, could potentially explain findings such as inconsistent medication persistence in patients taking dopamine agonists. The commercial claims databases used in this study did not contain laboratory results data on biochemical control status of CD patients; we were consequently unable to determine whether medical therapy was associated with biochemical control. A chart review study in CD is currently underway with an aim to assess CD-related treatment use and disease status. Healthcare medication claims also represent medications purchased and not necessarily those actually consumed. Finally, this study only included patients with commercial insurance, representing the geographic distribution of the plans providing data to these databases. Thus, the results may not necessarily represent the general CD population, including those insured by other commercial health plans, uninsured patients, or those with Medicare coverage or other governmental plans.

Conclusion

This study addresses an unmet need for data on real-world treatment patterns for insured CD patients in the United States. The proportion of surgical patients requiring a second therapeutic intervention is consistent with previously published case series. Patient-level graphical analysis suggests persistence with pharmacologic therapy may be inadequate. The impact of a recent FDA warning on ketoconazole use could not be estimated in the current dataset.

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Conflict of interest Maureen P. Neary and William H. Ludlam are employees of Novartis Pharmaceuticals Corporation; Michael S. Broder, Eunice Chang, Dasha Cherepanov, and Gordon H. Sun are employees of Partnership for Health Analytic Research, LLC, a health services research company paid by Novartis to conduct this research.

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