Original Article

BIOCHEMICAL CONTROL DURING LONG-TERM FOLLOW-UP OF 230 ADULT PATIENTS WITH CUSHING DISEASE: A MULTICENTER RETROSPECTIVE STUDY

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ABSTRACT

Objective: Cushing disease (CD) results from excessive exposure to glucocorticoids caused by an adrenocorticotropic hormone–secreting pituitary tumor. Inadequately treated CD is associated with significant morbidity and elevated mortality. Multicenter data on CD patients treated in routine clinical practice are needed to assess treatment outcomes in this rare disorder. The study purpose was to describe the burden of illness and treatment outcomes for CD patients.

Methods: Eight pituitary centers in four U.S. regions participated in this multicenter retrospective chart review study. Subjects were CD patients diagnosed at ≥18 years of age within the past 20 years. Descriptive statistical analyses were conducted to examine presenting signs, symptoms, comorbidities, and treatment outcomes.

Results: Of 230 patients, 79% were female (median age at diagnosis, 39 years; range, 18 to 78 years). Length of follow-up was 0 to 27.5 years (median, 1.9 years). Pituitary adenomas were 0 to 51 mm. The most common presenting comorbidities included hypertension (67.3%), polycystic ovary syndrome (43.5%), and hyperlipidemia (41.5%). Biochemical control was achieved with initial pituitary surgery in 41.4% patients (91 of 220), not achieved in 50.0% of patients (110 of 220), and undetermined in 8.6% of patients (19 of 220). At the end of follow-up, control had been achieved with a variety of treatment methods in 49.1% of patients (110 of 224), not achieved in 29.9% of patients (67 of 224), and undetermined in 21.0% of patients (47 of 224).

Conclusion: Despite multiple treatments, at the end of follow-up, biochemical control was still not achieved in up to 30% of patients. These multicenter data demonstrate that in routine clinical practice, initial and long-term control is not achieved in a substantial number of patients with CD. **(Endocr Pract. 2017;23:962-970)**

Abbreviations:
BLA = bilateral adrenalectomy; **CD** = Cushing disease; **CS** = Cushing syndrome; **eCRF** = electronic case report form; **MRI** = magnetic resonance imaging; **PCOS** = polycystic ovary syndrome

INTRODUCTION

Cushing syndrome (CS) results from excessive exposure to glucocorticoids. Cushing disease (CD) is CS caused by an adrenocorticotropic hormone–secreting pituitary tumor (1-4). International population-based studies have estimated the annual incidence of endogenous CS at 1.2 to 2.4 per million people (5,6), and a recent U.S.-based study

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estimated 8 CD cases per million people (7). Although it occurs in any sex at all ages, CD is most commonly seen in female adults aged 20 to 50 years (7).

Untreated CD results in elevated mortality risk and multiple morbidities (8), including hypertension, glucose intolerance and diabetes, obesity, thrombosis, infertility, osteoporosis, infections, memory impairment, depression, anxiety, and psychosis (4,9). The primary treatment advised for CD is pituitary surgery to remove the tumor, with high success rates reported if the operation is performed by an expert surgeon (10). For recurrent or persistent disease, repeat operation, radiotherapy, medical treatment, or bilateral adrenalectomy (BLA) may be used, but little is known about the outcomes of these treatments in routine clinical practice in the United States. As persistent or recurrent CD can be a chronic disease, often requiring multimodal therapy over time to achieve remission, information about the efficacy of available treatments is needed to enhance long-term outcomes. The aim of the current study was to characterize treatment outcomes in a large, diverse, multicenter cohort of patients receiving clinical care for CD.

METHODS

Study Design and Setting

In this study, the data were collected retrospectively from medical records of eligible patients at 8 United States pituitary/endocrine centers from August 20, 2014 to May 18, 2015: University of Miami and Jackson Memorial Hospital, FL; Massachusetts General Hospital, MA; Cedars-Sinai Medical Center, CA; Icahn School of Medicine at Mount Sinai, NY; Allegheny Endocrinology Associates, PA; Stanford Health Care, CA; University of Rochester Medical Center, NY; and Harbor-UCLA (University of California, Los Angeles) Medical Center, CA. Study sites included major referral centers and regional/local centers across four major U.S. census geographic regions (Northeast, Midwest, South, and West), which were selected based on adequate number of CD patients treated, varied geographic location, and diversity of patient populations. The study was approved by the Institutional Review Board at each site.

Patient Population

Each center was responsible for identifying the medical records of eligible patients meeting specific inclusion/exclusion criteria. Patients included in the study had documentation by a physician in the medical charts indicating a diagnosis or recurrence of CD in the past 20 years. CD diagnosis was confirmed by each site's principal investigator and the Endocrine Society guidelines (11). Eligible patients had to be ≥18 years old at the time of their diagnosis. Patients with CS caused by anything other than a pituitary tumor, who were <18 years old at the time of CD diagnosis, or who were diagnosed with CD or CD recurrence >20 years prior, were not included in this study. Eligible patients at each site were identified through existing CD patient databases and International Classification of Diseases coding. Sites made every attempt to enroll all eligible CD patients with sufficient data for abstraction into the study. Patients presented at the study sites at different points in their treatment timelines, so that some patients were not initially diagnosed or treated at the study sites, presenting there later for a second opinion.

Data Collection

A password-protected web-based electronic case report form (eCRF) was designed in conjunction with site investigators. Abstractors were endocrinology nurses or fellows, well acquainted with their site's patient charts and documentations styles. To ensure consistent data abstraction across sites, all abstractors were trained in applying inclusion/exclusion criteria and in entering data using the eCRF. Training entailed multiple webinars to ensure abstractors understood the patient eligibility criteria, every item in the eCRF, and the functionality of the abstraction tool. After the initial webinar, abstractors independently collected data from de-identified training medical records using the eCRF; their data entries were then verified by the research staff and discussed in a webinar. Only after the training was completed and the abstractors passed a test that confirmed their competency to interpret charts in a way that was consistent with the other abstractors were they able to begin real data collection using the eCRF. Data collected covered the interval from the earliest available data in the medical records at the study site until either (*1*) the date of institutional review board approval at the study site, or (*2*) the date the patient was last seen, whichever came first. Data quality assurance was conducted concurrently with data collection. The eCRF included automatic validity checks (e.g., invalid dates, illogical dates, or test values outside of physiologic ranges were flagged immediately). The research staff also conducted regular data quality checks for content, inconsistencies, and missing fields.

Data collected included patient demographics (birth year, sex, race/ethnicity) and key clinical milestones (date of first visit, suspicion of CS, diagnosis of CS, diagnosis of CD, and referral to pituitary surgery, outcome of surgery, date of recurrence, date of radiotherapy, medications used, date of adrenalectomy, and final disposition, such as death or transfer of care). Also recorded were conditions reported by the patient (i.e., symptoms), including dermatologic (e.g., acne, hair loss, bruising), genitourinary (e.g., amenorrhea, loss of libido, infertility), musculoskeletal, neurologic, psychiatric, and others (e.g., moon facies, fat pads, obesity). Conditions observed/reported by a physician (i.e., signs) were also captured, including dermatologic (e.g., acne, facial plethora, striae), musculoskeletal (e.g.,

peripheral muscle wasting), neurologic, psychiatric, and others. In addition to medical history and associated signs and symptoms, cardiovascular, endocrine, genitourinary, infectious, musculoskeletal, neurologic, psychiatric, and other comorbidities were collected based on the treating physicians' records and not based on specific definitions or guidelines for each diagnosis.

Outcome Measures

Pituitary adenoma details were recorded based on pituitary magnetic resonance imaging (MRI) before pituitary surgery. Given that the dates and types of CD treatments were captured, the first treatment reported was classified as the first CD therapy. CD treatments collected in this study included initial pituitary surgery, radiotherapy, pharmacotherapy, and adrenalectomy.

To examine the burden of illness of CD, presenting signs, symptoms, and comorbidities were assessed. Presenting signs, symptoms, and comorbidities were defined as those recorded at any time during the pretreatment period (on or before the first CD therapy). To examine treatment outcomes of CD, biochemical control was determined. Biochemical control was defined as follows, in patients: (*1*) following pituitary surgery, any morning (5 to 9 am) serum cortisol <5 μg/dL or ≤1.8 μg/dL after 1 mg dexamethasone (or, in patients with no serum cortisol or dexamethasone suppression tests, a 24-hour urinary free cortisol < lower limit of normal); (*2*) on pharmacotherapy or post-radiotherapy, either any value of 24-hour urinary free cortisol ≤ upper limit of normal or 11 PM to 1 AM salivary cortisol in normal range; (*3*) following BLA. Biochemical control was assessed based on the definition above after initial surgery and at the end of follow-up. If no laboratory values were available, control was considered "indeterminate." Patients taking mifepristone were classified as controlled based on their endocrinologist's assessment of improvement in their CD signs and symptoms.

Statistical Analysis

This study was a retrospective descriptive study; hence, no sample size calculations or hypothesis testing were conducted. All measures were reported as means, standard deviations, medians, and ranges, or as counts and percentages, as was deemed appropriate for the given variable. Descriptive statistics were reported for patient characteristic variables: demographics (age, gender, race, ethnicity, and weight at last visit), age at CD diagnosis, and time from presentation to CD diagnosis. Also reported were the prevalence of observed signs, symptoms, and comorbidities before treatment for CD was initiated. Finally, distribution of biochemical control was reported. All data transformations and statistical analyses were performed using SAS® 9.4 (SAS Institute, Cary, NC).

RESULTS

There were a total of 230 CD patients with median age of 39 years (mean, 40.5; range, 18 to 78 years) at diagnosis. Of these patients, 67% were Caucasian, 6% were African American, 1% were Asian, and 26% were other/unknown. Seventy-nine percent of patients were female. Of the 230 subjects, 76 (33.0%) patients had microadenoma and 64 (27.8%) had macroadenoma (for 90 patients, no MRI result was available). The study cohort had a mean length of follow-up of 3 years (SD, 3.7 years; median, 1.9 years; range, 0 to 27.5 years). Median time from presentation to CD diagnosis was 287 days, ranging from 1 day to 23.6 years (Table 1).

The most prevalent signs before initial CD treatment were facial rounding (51.0%), striae (46.3%), facial plethora (45.6%), posterior cervical or supraclavicular fat pads or central obesity (36.7 to 42.9%) (Table 2). Symptoms that were most prevalent before initial CD treatment included weight gain (68.0%), easy bruising (48.3%), fatigue (44.9%), muscle weakness (37.4%), hirsutism (34.7%), headache (28.6%), and anxiety (22.4%) (Table 3). Comparison of common conditions in Tables 2 and 3 suggests facial rounding, posterior cervical fat pads, and general and central obesity were all better recognized by physicians than patients. Comorbidities present at diagnosis included hypertension (67.3%), polycystic ovary syndrome (PCOS) (43.5%), hyperlipidemia (41.5%), obesity (29.3%), diabetes (27.9%), depression (22.4%), anxiety (13.6%), menstrual irregularities (12.2%), prediabetes (10.9%), sleep apnea (9.5%), and osteoporosis (9.5%) (Table 4; Fig. 1).

Table 1
Patient Characteristics

		n (%), unless otherwise indicated
Age, years	N	230
	Mean (SD)	47.0 (13.0)
	Median (min-max)	46 (23-85)
<34		41 (17.8)
35-44		66 (28.7)
45-54		65 (28.3)
55-64		33 (14.3)
≥65		25 (10.9)
Female		181 (78.7)
Race		155 (67.4)
White		
Black		14 (6.1)
Asian		2 (0.9)
Other		4 (1.7)

Continued on next page

Table 1 *Continued*		
More than one race		3 (1.3)
Unclear or unknown		52 (22.6)
Ethnicity		41 (17.8)
Hispanic or Latino		
Non-Hispanic or Latino		143 (62.2)
Unclear or unknown		46 (20.0)
Weight[a], pounds	n	226
	Mean (SD)	194.3 (51.2)
	Median (min-max)	189 (95-438)
Age at CD diagnosis, years	n	230
	Mean (SD)	40.5 (12.9)
	Median (min-max)	39 (18-78)
Time from presentation[b] to diagnosis of CD, days	n	149
	Mean (SD)	765.5 (1232.2)
	Median	287
Duration of follow-up, days	n	230
	Mean (SD)	1,113.2 (1,342.0)
	Median (min-max)	687 (1-10,040)

Abbreviation: CD = Cushing disease.
[a]At last visit during the study period.
[b]Defined as date of first visit with any symptoms, signs, or comorbidity later ascribed to CD.

Of all patients, 160 (69.6%) patients had one treatment, 64 (27.8%) patients had multiple treatments, and 6 (2.6%) had no treatment during the observation period. According to documentation in charts of the 6 untreated patients, it was determined that surgery was inappropriate for 4 of the patients, 1 patient refused surgery, and 1 patient underwent surgery after the study ended. First-line treatment was pituitary surgery in 220 patients (95.7%), and of these, 60 (27.3%) patients had subsequent pituitary surgery. Control after initial surgery was achieved in 91 (41.4%), not achieved in 110 (50.0%), and indeterminate in 19 (8.6%). Of 230 patients, 58 (25.2%) had pharmacotherapy, 29 (12.6%) patients had radiotherapy, and 16 (7.0%) patients had bilateral adrenalectomy over the period of observation. Of 91 patients in remission after initial pituitary surgery, 7 (7.7%) patients recurred by end of follow-up. Among 58 patients that received pharmacotherapy, ketoconazole was used most commonly (n = 40; 69%), followed by cabergoline (n = 16; 27.6%), pasireotide (n = 7; 12.1%), metyrapone (n = 5; 8.6%), mifepristone (n = 2; 3.4%), rosiglitazone (n = 2; 3.4%), bromocriptine (n = 1; 1.7%), and pioglitazone (n = 1; 1.7%).

Table 2
Prevalence of CD Signs[a] Prior to CD Treatment[b]

	All patients, n = 147
	n (%)
Dermatologic	
Striae	68 (46.3)
Facial plethora	67 (45.6)
Hirsutism	35 (23.8)
Bruising	32 (21.8)
Thin skin	25 (17.0)
Other skin changes	21 (14.3)
Acne	19 (12.9)
Hair loss	10 (6.8)
Fungal infections	2 (1.4)
Poor wound healing	1 (0.7)
Musculoskeletal	
Proximal muscle weakness	18 (12.2)
Extremity wasting	14 (9.5)
Lower extremity swelling	13 (8.8)
Neurologic	
Bitemporal hemianopsia	2 (1.4)
Psychiatric	
Anxiety	3 (2.0)
Depression	3 (2.0)
Cognitive impairment	1 (0.7)
Other	
Facial rounding	75 (51.0)
Fat pads, posterior cervical	63 (42.9)
Fat pads, supraclavicular	60 (40.8)
Obesity, central	54 (36.7)
Obesity, general	34 (23.1)
Other signs attributed to CD	20 (13.6)
Elevated blood pressure	8 (5.4)

Abbreviation: CD = Cushing disease.
[a]Conditions based on physician's assessment of a patient.
[b]Subgroup includes patients who had ≥1 visit before initiating CD treatment.

In 224 patients, at the end of the observation (which varied across patients from 1 day to 27.5 years; median, 1.9 years), control was achieved by using any treatment modality selected by the treating physicians in 110 patients (49.1%), not achieved in 67 (29.9%), and indeterminate in 47 (21.0%). Six patients had no treatment during the study observation period (described above). Differences in distributions of patient characteristics by final biochemical control status were insignificant (Table 5).

Table 3
Prevalence of CD Symptoms[a] Prior to CD Treatment[b]

	All patients, n = 147
	n (%)
Dermatologic	
Easy bruising	71 (48.3)
Hirsutism	51 (34.7)
Stretch marks	36 (24.5)
Acne	29 (19.7)
Plethora	27 (18.4)
Hair loss	20 (13.6)
Other skin changes	17 (11.6)
Poor wound healing	5 (3.4)
Fungal infections	2 (1.4)
Genitourinary	
Menstrual irregularities (includes amenorrhea)	37 (25.2)
Decreased libido	29 (19.7)
Erectile dysfunction or impotence	7 (4.8)
Infertility	3 (2.0)
Musculoskeletal	
Muscle weakness	55 (37.4)
Lower extremity swelling	16 (10.9)
Back pain	9 (6.1)
Extremity wasting	7 (4.8)
Neurologic	
Headache	42 (28.6)
Blurry vision	24 (16.3)
Other vision problems	12 (8.2)
Dizziness or vertigo	8 (5.5)
Psychiatric	
Anxiety	33 (22.4)
Depression	31 (21.1)
Memory problems	12 (8.2)
Other	
Weight gain	100 (68.0)
Fatigue	66 (44.9)
Other symptoms attributed to CD	51 (34.7)
Facial rounding	29 (19.7)
Insomnia	22 (15.0)
Obesity, central	20 (13.6)
Polydipsia	13 (8.8)
Fat pads, posterior cervical	11 (7.5)
Snoring or daytime sleepiness	8 (5.4)
Fat pads, supraclavicular	6 (4.1)
Obesity, general	4 (2.7)

Abbreviation: CD = Cushing disease.
[a]Conditions reported by the patient.
[b]Subgroup includes patients who had ≥1 visit before initiating CD treatment.

DISCUSSION

The goal of the current study was to characterize treatment outcomes in routine clinical practice for the first time in a large, diverse, multicenter U.S. cohort of CD patients. Only 41% of patients achieved remission with initial pituitary surgery. Many CD patients therefore required additional treatments, including more pituitary surgery, pharmacotherapy, radiation, and BLA. Despite these treatments, at the end of follow-up (median of 2 years), biochemical control was achieved only in about half of the patients, and nearly one-third of patients still had not achieved control.

Forty-one percent of this cohort had initial surgical remission, which contrasts with previous reports that showed surgical remission rates of 73 to 76% for microadenomas and about 43% for macroadenomas (1,10,12-14). Inclusion of a relatively large proportion of patients with macroadenomas in this cohort could have played a role in the low initial surgical remission proportion observed in this study. Although data were extracted at centers experienced with managing CD, for 49 of 220 patients, the initial pituitary surgery for CD had taken place elsewhere, with the patient possibly seen at the investigative site later for a second or subsequent opinion. Importantly, however, these findings illustrate that there are different surgical outcomes across a range of medical centers, surgeons, and geographic regions. This cross-sectional view of initial surgical remission rates in routine clinical practice contrasts with prior reports that typically described surgical remission rates from one expert surgeon or group (1,10,12-14). These data therefore provide a view of CD outcomes in a 'real-world' setting and suggest a need for improvement in surgical outcomes for patients with CD. Given recent data from Clayton et al (15) suggesting that pituitary surgery alone achieves a mortality outcome that is not different from the normal population, our findings underscore the importance of treatment at a center and with an experienced surgeon. Finally, it is conceivable that some or all of the patients with undetermined biochemical control status were actually under control. Combined with the 49% known to be in control, this would make a total of 70% controlled patients, which would be more consistent with data from prior studies.

Also unexpected was our finding that despite additional therapies beyond the initial transsphenoidal surgery, including more pituitary surgery, pharmacotherapy, radiation, or BLA, biochemical control was only achieved in about half of the patients after a median of 2 years of follow-up. Therefore, nearly one-third of the patients had residual, active disease. This finding underscores the chronic nature of CD and the need for multimodal therapy in some patients. Even after multiple therapies, many patients continued to have active disease, highlighting the need for more effective therapeutic options for patients with CD.

Consistent with previous studies, there was a high prevalence of comorbidities at diagnosis, including

hypertension, PCOS, hyperlipidemia, obesity, diabetes, and depression. Patients with active CD have a standardized mortality rate that is 1.7- to 4.8-fold greater than the general population (6,16-19). Mortality rate improves after successful treatment of CD, although whether it reverses to that of the general population is not clear (6,16-19). That many CD patients in our cohort did not achieve remission after initial or even subsequent treatment suggests that they remain at risk for comorbidities and increased mortality.

The study has several limitations that deserve mention. The retrospective nature of the data collection precluded complete biochemical data being available for all patients. As a result, in 21% of the patients, remission status at the most recent follow-up was unknown. These results are based on a convenience sample of patients with different lengths of follow-up, including patients with follow-up periods that are likely too short to observe treatment outcomes or patients with long periods of follow-up, so

Table 4
Prevalence of Comorbidities Prior to CD Treatment[a]

	CD patients, n = 147
	n (%)
Cardiovascular	
Hypertension	99 (67.3)
Hyperlipidemia	61 (41.5)
Coronary atherosclerosis	4 (2.7)
Deep venous thrombosis	3 (2.0)
Myocardial infarction	1 (0.7)
Endocrine	
Polycystic ovarian syndrome	64 (43.5)
Diabetes, type 2	41 (27.9)
Impaired glucose tolerance/prediabetes	16 (10.9)
Genitourinary	
Menstrual irregularities (includes amenorrhea)	18 (12.2)
Nephrolithiasis	10 (6.8)
Decreased libido	6 (4.1)
Infertility	5 (3.4)
Erectile dysfunction or impotence	2 (1.4)
Infectious	
Fungal infection, excluding skin and nails	2 (1.4)
Musculoskeletal	
Osteoporosis	14 (9.5)
Osteopenia	9 (6.1)
Neurologic	
Stroke	1 (0.7)
Psychiatric	
Depression	33 (22.4)
Anxiety	20 (13.6)
Memory impairment	2 (1.4)
Psychosis	1 (0.7)
Other	
Obesity	43 (29.3)
Obstructive sleep apnea	14 (9.5)

Abbreviation: CD = Cushing disease.
[a]Subgroup includes patients who had ≥1 visit before initiating CD treatment.

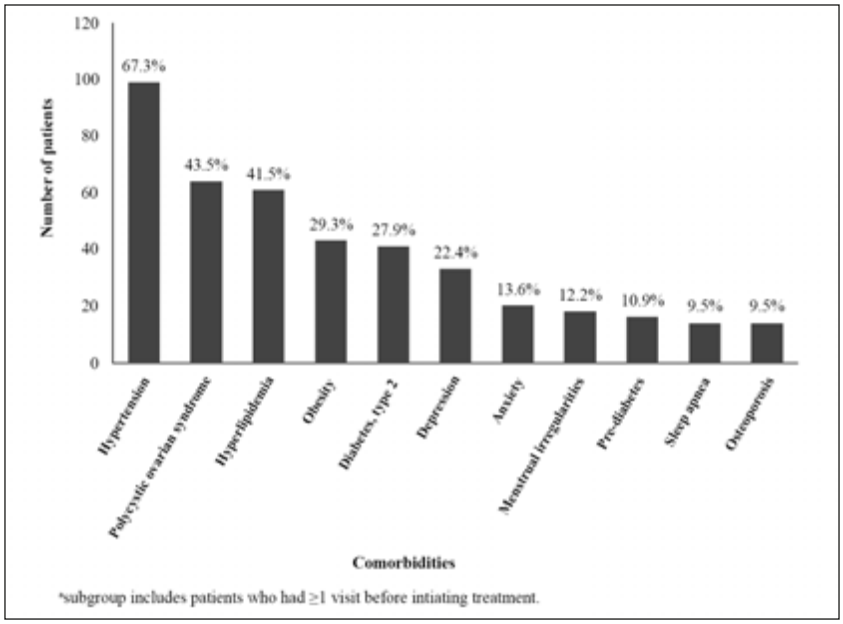

Fig. 1. Ten most prevalent comorbidities prior to CD treatment.[a]

Table 5
Patient Characteristics by Final Biochemical Control

	Final biochemical control			
	Control n = 110 (49.1%)	**No control n = 67 (29.9%)**	**Indeterminate n = 47 (21.0%)**	**All N = 224**
Female, n (%)	86 (78.2)	53 (79.1)	39 (83.0)	178 (79.5)
Age at CD diagnosis, in years mean (SD), [median] (range)	39.7 (11.9) [40] (19-78)	39.1 (13.6) [36] (18-71)	42.8 (14.0) [41] (18-73)	40.2 (12.9) [39] (18-78)
Weight, pounds[a], n, mean (SD), [median] (range)	110, 192.4 (51.4) [191] (100-438)	66, 196.6 (53.2) [185] (112-358)	44, 195.3 (51.0) [187] (95-315)	220, 194.3 (51.7) [188] (95-438)
Macroadenoma, n (%)	37 (33.6)	16 (23.9)	11 (23.4)	64 (28.6)
Microadenoma[b], n (%)	38 (34.5)	24 (35.8)	14 (29.8)	76 (33.9)
No adenoma size[c], n (%)	35 (31.8)	27 (40.3)	22 (46.8)	84 (37.5)
Number of years from presentation to CD diagnosis, n, median (range)	70, 0.9 (0.0-17.3)	44, 0.7 (0.1-11.8)	30, 0.8 (0.0-23.6)	144, 0.8 (0.0-23.6)
Number of years from CD diagnosis to first CD treatment, n, median (range)	99, 0.1 (0.0-1.2)	57, 0.1 (0.0-2.0)	42, 0.1 (0.0-1.8)	198, 0.1 (0.0-2.0)
Number of years from initial intervention to end of observation, median (range)	3.7 (0.0-19.3)	2.3 (0.0-21.1)	2.3 (0.0-27.3)	2.5 (0.0-27.3)
Number of years from last intervention to end of observation, median (range)	1.8 (0.0-15.3)	1.1 (0.0-16.1)	0.1 (0.0-14.6)	1.2 (0.0-16.1)

Abbreviation: CD = Cushing disease.
[a]At last visit during the study period.
[b]Microadenoma includes 9 patients with indeterminate magnetic resonance imaging (MRI) result and 35 with no visible adenoma on MRI.
[c]No MRI result was available.
All comparisons not statistically significant.

that changes in clinical care standards may have affected CD management over time. Given that patients were recruited from specific regional and tertiary care centers, including some patients who may have been enrolled in clinical trials and/or patients who were referred because they were particularly challenging, the cohort may not be representative of the general CD population. It should be noted that off-site care, including MRI scans, may not have been thoroughly documented in the patient charts. Also, since many patients with CD are initially misclassified as having PCOS due to overlapping presentations, likely many of these patients did not have a diagnosis of PCOS but instead had signs and symptoms of PCOS due to their CD. The fact that many CD patients are given a diagnosis of PCOS (either accurately or inaccurately) is important for clinicians to note. Finally, some data, including dosing and duration of treatment, were not captured in this study. We reviewed the historical mix of paper and electronic medical records entered by many physicians over 20 years of patient care across 8 referral centers. This methodology does not allow for a simple approach to a detailed, comprehensive analysis of the outcomes of Cushing disease management. With greater availability of electronic medical records, more uniform information might be captured to provide better data in the future. Despite these limitations, this study represents a large cohort of patients with CD, and for the first time, data are available across different geographic settings and practice types in the U.S.

Despite multiple treatments, at the end of follow-up, biochemical control was still not achieved in 30% of CD patients. These multicenter data demonstrate that in routine clinical practice, initial and long-term control is not achieved in a substantial number of patients with CD.

CONCLUSION

Further research is needed to identify effective new medical therapies that allow for long-term remission in patients with CD. Future study efforts should also entail the assessment of pituitary surgical re-intervention, radiotherapy, and pharmacotherapy for patients with persistent or recurrent disease.

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DISCLOSURES

M.P.N., Q.S., and Y.L. are employees of the Novartis Pharmaceuticals Corporation. Y.L. was affiliated with the Icahn School of Medicine at Mount Sinai throughout the study duration. M.S.B., D.C., M.E., and J.L. are employees of the Partnership for Health Analytic Research, LLC, a health services research company paid by Novartis to conduct this research. J.C. has been Principal Investigator (PI) of research grants to the University of Southern California from Novartis, Pfizer, and Cortendo, has received research support from Novartis, and has performed consulting for Novartis and Pfizer. B.M.K.B. has been the PI of research grants to Massachusetts General Hospital from Cortendo and Novartis and has performed occasional consulting for Cortendo, Ipsen, and Novartis. E.B.G. was the PI of a research grant to Mount Sinai Hospital from Novartis, is PI for clinical trials funded by Novartis and Strongbridge, and has performed occasional consulting for Strongbridge, Chiasma, and Novartis. A.A. has been PI of research grants to the University of Miami from Novartis and has performed consulting for Novartis, Pfizer, and NHT therapeutics. E.M. and I.S. have received honorarium from Novartis. K.P.L., V.B., R.S.S., and V.S. have no conflicts of interest to disclose.

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