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Medical management pathways for Cushing's disease in pituitary tumors centers of excellence (PTCOEs)

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Abstract

Purpose A recent update of consensus guidelines for the management of Cushing's disease (CD) included indications for medical therapy. However, there is limited evidence regarding their implementation in clinical practice. This study aimed to evaluate current medical therapy approaches by expert pituitary centers through an audit conducted to validate the criteria of Pituitary Tumors Centers of Excellence (PTCOEs) and provide an initial standard of medical care for CD.

Methods Based on the activities of nine international PTCOEs between 2018 and 2020, we evaluated patients under medical treatment and their biochemical control rates.

Results The median number of active patients with CD per center was 117 (35–279), with a median number of 10 new patients with CD managed annually in the endocrinology units of PTCOEs (4–42). The median percentage of patients with CD receiving medical treatment was 13.3% (4.8–82.9). Ketoconazole was the most frequently used drug, with a median rate of usage of 26.5% (5-66.7) of those receiving medical therapy. The median rates of metyrapone and pasireotide use were 17.2% (0–50) and 9.3% (0-51.7), respectively. For cabergoline and osilodrostat, therapy, the median rates of use were 2.8% (0-33.3), and 1.7% (0–25), respectively. Combination therapy was reported to be utilized in 13.6% (0-45.5) of medically treated patients. Mifepristone was used in a single center, representing 1.1% of its medically treated patients. Overall, the median control rate in patients with CD receiving medical treatment was 75% (10–100).

Conclusion Adrenal steroidogenesis inhibitors were the most commonly used medications amongst the centers. Despite the use of combination therapy, up to 25% of patients did not achieve disease control even in PTCOEs, highlighting the need for either more efficient combination therapies or novel therapeutic options.

Keywords Cushing's disease · Pasireotide · Ketoconazole · Metyrapone · Osilodrostat · Cabergoline · Mifepristone · Control rate · PTCOEs

Abbreviations

ACTH	Adrenocorticotropic hormone
CD	Cushing's Disease
COVID-19	Coronavirus disease of 2019
PTCOEs	Pituitary tumors centers of excellence
SSTR	Somatostatin receptor
UFC	Urinary free cortisol

Introduction

Cushing's disease (CD) is caused by an adrenocorticotropic hormone (ACTH)-producing pituitary adenoma and is the most common cause of endogenous Cushing's syndrome [1, 2]. The annual incidence of CD is 1.5/million, and the prevalence is 57 cases per million, with a female predominance [3, 4]. Despite its rare occurrence, the disorder is associated with commonly encountered comorbidities including hypertension, obesity, dyslipidemia, atherosclerosis, hypercoagulability, osteoporosis and fractures, impaired glucose

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metabolism, and immune and growth suppression [5–13]. Higher mortality rates reported in CD, mainly due to cardiovascular causes, were associated with persistent disease [14]. However, long-term sequelae of hypercortisolism may persist even years after successful CD treatment [15]. Hence, prompt diagnosis and management of the disease are essential to optimize patient outcomes [1]. The treatment goal is to achieve disease remission and long-term control ideally without occurrence of hypopituitarism [16]. The recommended first-line therapy is selective transsphenoidal surgical resection of the ACTH-secreting adenoma. Remission rates after surgery are dependent on surgeon expertise and may reach 83% for microadenomas and 68% for macroadenomas in PTCOEs [4]. A significant subset of adenomas is so small that they are not visible on high-quality imaging. Although surgical exploration after confirmation by bilateral inferior petrosal sinus sampling or corticotropin-releasing hormone/ high-dose (8 mg) dexamethasone suppression test is the first-line, medical treatment is an alternative option [1]. An expert endocrinologist is essential for personalized first and second-line treatment, including management of medical treatment and replacement, screening for recurrences and endocrine monitoring required after bilateral adrenalectomy, and radiation therapy. Current guidelines recommend that patients with CD should be followed in specialized PTCOEs wherever possible [1, 17–20].

Medical treatment options include steroidogenesis inhibitors (ketoconazole, metyrapone, osilodrostat, mitotane, etomidate), which block one or more steps in adrenal cortisol synthesis, pituitary targeted agents (cabergoline, pasireotide), which suppress ACTH secretion, and a glucocorticoid receptor antagonist, mifepristone [21, 22]. The recent development and approval of novel drugs achieving improved control rates have enhanced the increased role of medical management in CD. However, studies have been limited to clinical trials, especially for novel drugs, and real-world clinical practice data are limited [23]. Recent guidelines suggest adrenal steroidogenesis inhibitors as the first-line option due to longer experience with these drugs and their rapid action [1]. Personalizing treatment is a *sine qua non*, as determined by clinical CD features, to optimize outcomes including morbidity, mortality, and quality of life. In addition, a balance between long-term efficacy, cost, and side effects of therapy should be maintained [1, 22]. To date, there have not been reports of real-world medical treatment approaches and their efficacy in CD patients followed in PTCOEs.

The requirements for PTCOEs designation [17] were recently validated by assessing the activity of high volume globally recognized tertiary pituitary centers [24]. The aim of this study was to evaluate medical treatment approaches and their outcomes in centers that fulfilled the definition of PTCOEs, through previously collected data, to provide a real-life perspective on standards of CD medical care, as recently reported for acromegaly [25].

Methods

The study design has been described previously in detail [24, 25]. Nine centers across the world chosen by an expert scientific evaluating board and fulfilling PTCOE criteria volunteered to participate [24].

Surveyed centers were asked to provide number of patients with CD under active medical treatment. Moreover, centers were asked to report the number of medically treated patients in whom biochemical control was achieved according to current guidelines [20, 26]. Detailed medical treatment information were supplied by eight of nine participating centers. Results were reported as total and percentage or as median (min-max). Microsoft Excel, SPSS (version 27), and GraphPad Prism 10 were used for analysis.

Results

The median number of patients with CD per center was 117 (35–279). The median number of new patients with CD managed annually in the PTCOE endocrinology units was 10 (4–42).

Distribution of patients on medical treatment

13.3% of patients received medical treatment (median; range: 4.8–82.9). Surveyed centers reported a median of 15 medically treated CD patients per center (range: 3 to 100) [24]. Centers provided no data on mitotane treatment. Mifepristone was used in one patient at a single US center. When data on CD patients under medical treatment were analyzed, ketoconazole was the most frequently used drug, with a median rate of 26.5% (range: 5-66.7), (number of patients treated ranging from 1 to 30). Median rates for metyrapone and pasireotide use were 17.2% (0–50) and 9.3% (range: 0-51.7), (number of patients treated ranging from 0 to 24 and from 0 to 15, respectively). For cabergoline and osilodrostat, median rates of use were 2.8% (range: 0-33.3) and 1.7% (range: 0–25), (number of patients treated ranging from 0 to 8 and from 0 to17, respectively). Combination therapy was utilized with a median rate of 13.6% (range: 0-45.5), (number of patients treated ranging from 0 to 40) (Fig. 1).

Pasireotide and metyrapone therapies were provided in 6 centers with a median rate of use of 18.8% (range: 4.5–51.7) and 29.5% (range: 5.7–50) in those centers, respectively.

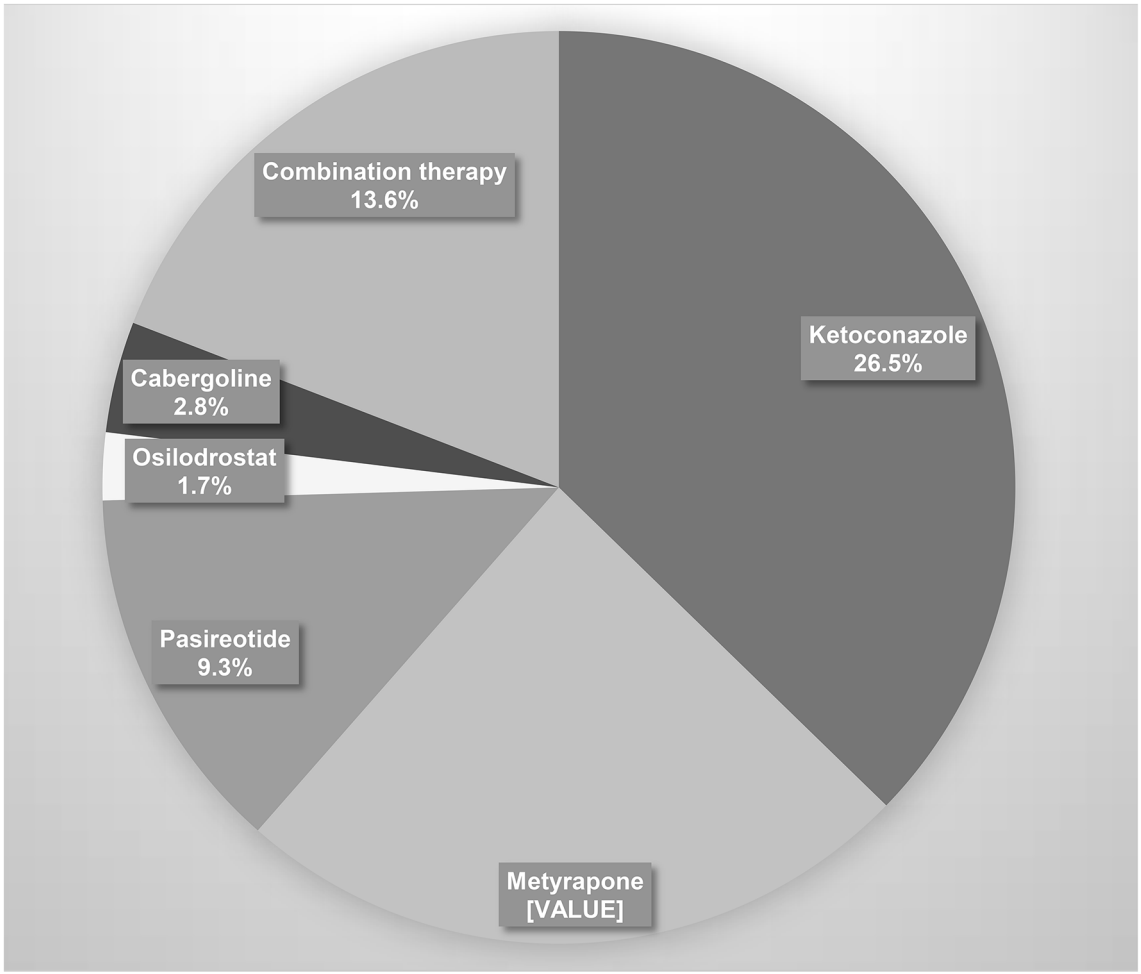

Fig. 1 Median rates of use of medical treatment options among all centers. * Mifepristone is not shown due to its limited use in only a single center

Data on osilodrostat and cabergoline were available for 4 centers, which used them at median rates of 18.5% (range: 3.4–25) and 9.2% (range: 5.7–33.3), respectively. Five centers reported the use of combination therapy, with a median rate of 25% (range:10-45.5). The only patient given mifepristone in a single center represented 1.1% of its medically treated population. (Fig. 2).

Control rates of patients receiving medical treatment

As reported [24], the overall median control rate of CD patients receiving medical treatment was 75% (10–100). The median biochemical control rate of ketoconazole provided by 7 centers was 76% (range: 20–100). Biochemical control rates with pasireotide and metyrapone, available from 5 centers, were 80% (range: 50–100) and 60% (range: 10–80), respectively. Rate of biochemical control with cabergoline varied between 40% in one center (5 patients) to 100% in another center (one patient), with a total median control rate of 90%, according to data provided by 3 centers (analysis limited by low patient numbers). The rate of biochemical control with osilodrostat and combination therapy provided by 4 centers were 65% (range: 33–100) and 73.8% (range: 50–100), respectively (Fig. 3).

Discussion

This study evaluated the medical treatment approaches used by internationally recognized PTCOEs for patients with CD. Medications for CD treatment are classified as adrenal steroidogenesis inhibitors, pituitary-targeted, and peripheral glucocorticoid receptor-targeted [23]. Adrenal steroidogenesis inhibitors are usually the first choice due to their effectiveness. Ketoconazole and metyrapone are reported to be the most common options since they have been available for many years [1]. In fact, our study demonstrated that in participant centers, ketoconazole therapy was the most frequently preferred medication in 26.5% of patients receiving

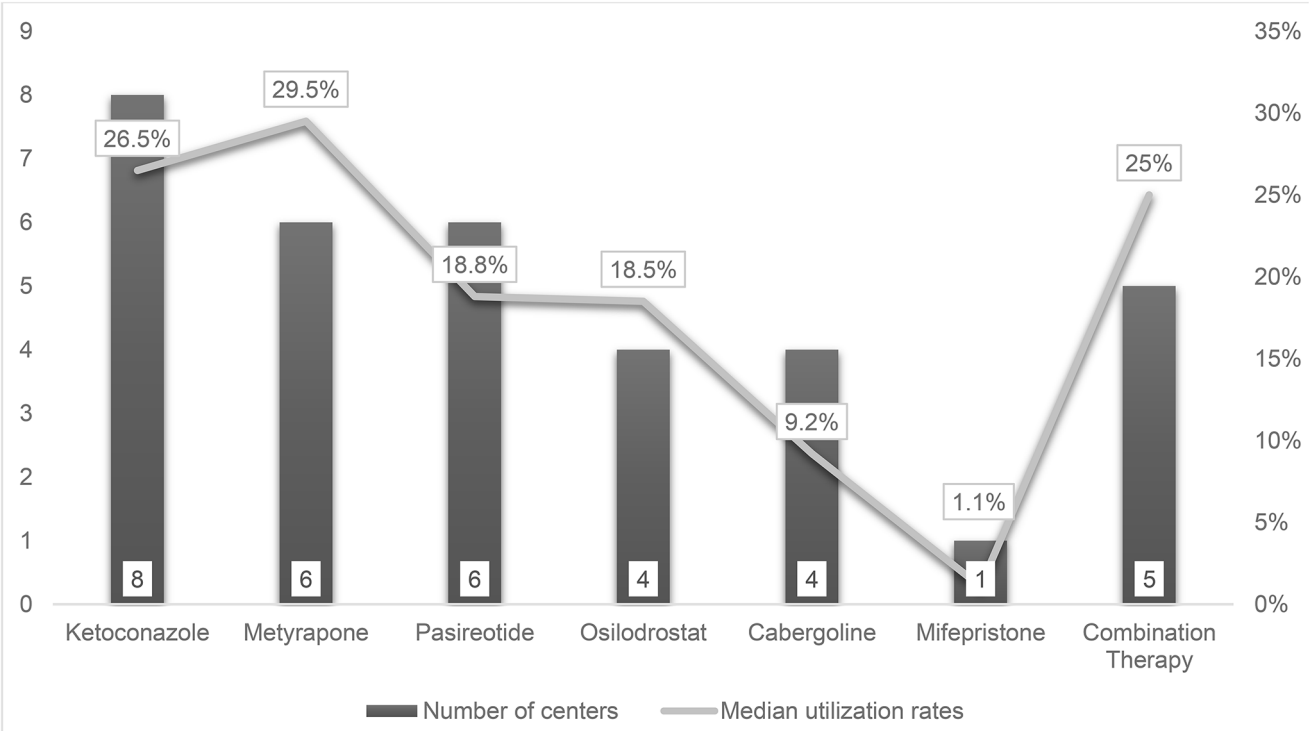

Fig. 2 Median utilization rates of medical treatment options among centers in which the specific medication is reported. Bar graphs show the number of centers that provided specific treatment option. Line graph showed the median utilization rates of each treatment options among centers that provided specific treatment options

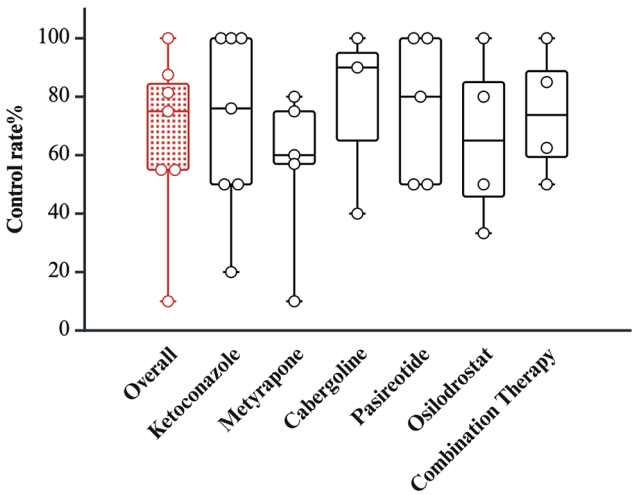

Fig. 3 Biochemical control rates by different medical treatment options. Boxplot graphs illustrate the biochemical control rates of centers for specific treatment options, with the red graph representing the overall biochemical control rates across centers. The crossbars inside each box indicate the median. Created in https://BioRender.com

medical treatment. This medication blocks multiple steroid biosynthesis pathways and has been reported to normalize urinary free cortisol (UFC) levels in 64.7% of patients with CD [23]. The outcomes of our study confirmed previously reported data, since ketoconazole use was reported in each center, and biochemical control was achieved in high percentage of patients (76%).

The second most frequently used drug in excellent pituitary centers was metyrapone, an 11ß-hydroxylase inhibitor, utilized in 17.2% of patients under medical treatment. Literature showed that the control rate with metyrapone varied between 45.4% and 100%, with a median rate of 75.5% [23] and escape from the response was reported in 18.7% of patients who initially responded to treatment [27]. The initial prospective study showed that metyrapone induced remission in 47% of patients, accompanied by a clinical improvement [28]. The reported median control rate with metyrapone by our surveyed centers was 60%. The more favorable response achieved with both ketoconazole and metyrapone in our study compared to previously published ones could be related to the effective escalation of the doses in expert endocrinology units.

Another novel adrenal steroidogenesis-targeted medication used in some PTCOEs was osilodrostat. This recently approved, oral 11ß-hydroxylase and aldosterone synthase inhibitor has a higher potency and a longer half-life than metyrapone and ketoconazole [29]. A phase 3 clinical trial demonstrated the efficacy and safety of osilodrostat by achieving control in 53% of patients without dose uptitration after week 12, and in 66.8% of patients regardless of dose increase at 24 weeks [30]. A subsequent phase

3 trial showed a complete response to osilodrostat in 77.1% of patients during the double blind period of the study with a dose escalation up to 20 mg twice daily at week 12, and in 80.8% of patients at week 36 during open label phase with a dose escalation up to 30 mg [31]. Of note, a long-term study reported a complete response in 50–88% of patients [32]. The overall median rate of osilodrostat use was 1.7% among the medically treated population. However, this rate increased to 18.5% in the four centers where this treatment option was available. Moreover, the surveyed centers reported a median control rate of 65% with osilodrostat, ranging from 33 to 100%. We should keep in mind that our study took part during the coronavirus pandemic of 2019 (COVID-19), and there was insufficient time to assess the true rate of use, since the drug was not approved or widely available until near the end of our data collection period in 2020, its use is expected to increase in the coming years. Our results were similar to those observed during the first period of phase 3 clinical studies, in which the dose escalation protocol was less effective than in the subsequent studies. Indeed, endocrinologists may have preferred lower doses to avoid adrenal insufficiency during the pandemic, as adverse events associated with hypocortisolism were reported primarily during the dose titration period of the clinical trials [33].

Pituitary directed medications, cabergoline and pasireotide, have demonstrated effective biochemical control of CD. Pasireotide has been approved for treatment of CD when remission could not be achieved by surgery, whereas cabergoline, a potent dopamine agonist with high affinity for dopamine type 2 receptors (D2), is currently used as an off-label therapy [23]. Among all the participating PTCOEs, 2.8% of medically treated patients received cabergoline. Indeed, only four centers used this option, in almost 10% of patients on medical treatment. Previous studies evaluating the efficacy of cabergoline included a limited number of CD patients, unsuccessfully treated by pituitary surgery, and demonstrated normalization of cortisol secretion in 25–40% of patients [34–36]. However, 28% of responders discontinued treatment due to loss of response or intolerance [36]. One of the participating centers reported a median 40% control rate with cabergoline treatment, whereas another center demonstrated control in the only patient. Consequently, the results showed that cabergoline could be effective in a subset of CD patients, with the advantage of oral administration and minimal side effects. However, the occurrence of escape and long lag time until achievement of control, combined with its off-label use, may have limited its use (therefore the power of our analysis) across audited centers. Pasireotide is a multitargeted somatostatin receptor ligand with a higher affinity to somatostatin receptor (SSTR) 5 than SSTR1, SSTR2 and SSTR3 [37]. In a 12-month, double blind, phase 3 study, biochemical control was achieved in 13% in the group treated with 600 µg pasireotide, and in 25% in the group treated with 900 µg pasireotide [38]. Patients with lower baseline UFC levels showed a higher rate of response. Early prediction of response is possible since when hypercortisolism was uncontrolled after the first 2 months of the study, it remained uncontrolled for the entire study period. Remarkably, a 50% response rate was achieved in patients with mild CD in this study. Adverse events were similar to other somatostatin receptor ligands, except for a higher frequency of hyperglycemia with pasireotide [38]. However, elevated glucose levels can be managed with anti-diabetic treatments [39], with a preference for glucagon-like peptide-1 based medications [40]. The results of the extension trial of the phase 3 study reported that disease control was achieved in 50% of patients after 12 months, and by 34.5% of patients after 24 months of treatment [41]. Recently, a multicenter study demonstrated that pasireotide treatment normalized UFC levels in 61.3% of patients with mild to moderate hypercortisolemia [42]. In addition, long-acting pasireotide normalized mean UFC levels in about 40% of patients with CD at month 7 and in 46.9% of patients at month 24 of the extension period [43, 44]. Long-term efficacy was reported to be 50% in a multicenter phase 2 study with either monotherapy or combination therapy with cabergoline [45]. In the literature long-term, real-world data on the effect of pasireotide in CD was scanty. In our study, the overall median utilization rate of pasireotide therapy was less than 10%, whereas among the subset of 6 which data on its use, the rate of utilization was close to 20%. Two participating centers reported 50% control rate with pasireotide, consistent with the literature, whereas the other 2 centers, each treating one patient, reported control, resulting in an overall median control rate of 80%. These results appear to indicate that pasireotide could be effective in a subset of CD patients who have mild to moderate disease, although our analysis was limited by the small number of patients. Moreover, the data may also suggest that PTCOEs could better identify CD patients with a higher response rate to this pituitary-directed drug that could be an effective treatment for CD similarly to other secreting pituitary adenomas [46, 47].

However, although a priori pituitary-targeted drugs may represent the ideal therapeutic option for CD management, their preference was limited among centers, with only approximately 10% of medically treated patients. This could be related to the more rapid action of adrenal-directed drugs, the limited need for adenoma mass reduction for microadenoma, and the long follow-up duration required for cabergoline to be effective. Nevertheless, due to the rapid action in disease control and the positive impact on both clinical features and the adenoma itself [23], pasireotide could be an attractive alternative. Although, its common

use within PTCOEs might have been expected, the limited implementation could be related to either a higher possible frequency of hyperglycemia or difficulties in maintaining injection regimens during the COVID-19 pandemic [11].

Mifepristone, the glucocorticoid receptor antagonist, improves signs and symptoms of CD rapidly. In fact, previous reports have shown improvements in glucose metabolism in 60% and in blood pressure in 38% of patients [48]. This drug was approved in the United States by the FDA for treatment of hyperglycemia secondary to Cushing's syndrome; hence, it is an on-label treatment option only in the USA. Another reason for its limited use could be the necessity of close clinical monitoring of response, since cortisol levels cannot be used to evaluate treatment response or the presence of adrenal insufficiency [1]. Only one surveyed center used mifepristone in one patient, reporting 100% control rate of symptoms.

Likely due to the side effects and rapid inactivation of cortisol requiring high doses of glucocorticoid replacement, none of the expert pituitary centers provided data on mitotane therapy.

Overall, 13.6% of medically treated patients were on combination therapy. Among the five surveyed PTCOEs that reported data on the use of this option, up to 25% of patients received combination therapy. Almost 25% of patients on medical monotherapy were not able to achieve biochemical control. Notably, prior studies report up to 90% percent control rates with combination therapy, especially when optimal dosages were employed [49, 50]. Regarding combination choices, use of an adrenal steroidogenesis inhibitor with a pituitary targeted agent was aforementioned [34, 49, 50]. Due to the information requested in our survey, no data were available on the combination alternatives selected by the centers. Given the frequent use of adrenal steroidogenesis inhibitors among centers, combination of ketoconazole/metyrapone with cabergoline might have been a possible option. In fact, the synergy between SSTR and D2 has recently shown to increase the therapeutic efficacy, particularly in the patients with moderate hypercortisolism at baseline [45]. It could be expected that centers might have initiated this option only in selected patients, in the light of their relatively limited preference. Triple combination options are effective, especially with the stepwise utilization of drugs differentially targeting SST5 and D2 receptors together with steroidogenesis inhibitors [50]. However, the combination of mitotane with other steroidogenesis inhibitors, reported to improve outcomes in severe CD [51], was not an option here, as none of the centers reported using mitotane.

Participating centers reported biochemical control rates with combination therapy reaching to 73.8%. The medical approach is affected by several clinical factors, including the side effect profiles, comorbidities, and concomitant medications. Furthermore, treatment cost, availability, and patient preferences may have an important impact on treatment decisions. As a result, it has been challenging to recommend the optimal combination therapy to overcome these limitations [27]. Noticeably, a degree of therapeutic inertia can also occur even in PTCOEs, as was demonstrated for acromegaly [25], since biochemical control could not be achieved in all medically treated CD patients with any of these therapies. The outcomes of the study showed an important need for a patient-centered approach that aligns with the consensus guidelines and the availability of novel medical treatment options. With growing knowledge of combination therapies, it is essential to establish more consistent protocols for when, how, and whom to start these options, particularly in PTCOEs.

Finally, the lack of detailed information on patient' characteristics, comprehensive clinical history, indications for therapy, modalities concerning specified combination treatment options, drug doses, and adverse events was the main limitation of this study. In addition, relatively small number of patients were under medical treatment especially for cabergoline and osilodrostat. Despite these drawbacks, our results inform choices and effects of several medical options for CD management in expert pituitary centers. Indeed, investigating implementation of recent progress in the era of medical treatment for CD in PTCOEs should lead to better understanding of both the benefits and disadvantages of these modalities for a real-world clinical approach. Moreover, it may serve as the first step for collaboration of PTCOEs to provide a basis for future guidelines of this rare disorder.

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Author contributions All authors contributed to the data collection process. M.M.U and S.F. reviewed data. M.M.U performed statistical analysis. M.M.U wrote the manuscript draft. A.G., F.C., and S.M. revised the manuscript. All authors reviewed the final version.

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Data availability The datasets generated and/or analysed during the current study are not public but are available from the corresponding author on reasonable request.

Declarations

Competing interests A. Giustina is the editor-in-chief in Pituitary.

References

1. Fleseriu M, Auchus R, Bancos I, Ben-Shlomo A, Bertherat J, Biermasz NR et al (2021) Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet Diabetes Endocrinol 9(12):847–875 Epub 2021/10/24. https://doi.org/10.1016/s2213-8587(21)00235-7
2. Melmed S, Kaiser UB, Lopes MB, Bertherat J, Syro LV, Raverot G et al (2022) Clinical Biology of the Pituitary Adenoma. Endocr Rev 43(6):1003–1037. https://doi.org/10.1210/endrev/bnac010PubMed PMID: 35395078; PubMed Central PMCID: PMCPMC9695123
3. Wengander S, Trimpou P, Papakokkinou E, Ragnarsson O (2019) The incidence of endogenous Cushing's syndrome in the modern era. Clin Endocrinol (Oxf) 91(2):263–270 Epub 20190527. https://doi.org/10.1111/cen.14014
4. Gadelha M, Gatto F, Wildemberg LE, Fleseriu M (2023) Cushing's syndrome. Lancet 402(10418):2237–2252 Epub 20231117. doi: 10.1016/s0140-6736(23)01961-x. PubMed PMID: 37984386
5. Arnaldi G, Angeli A, Atkinson AB, Bertagna X, Cavagnini F, Chrousos GP et al (2003) Diagnosis and complications of Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab 88(12):5593–5602. https://doi.org/10.1210/jc.2003-030871PubMed PMID: 14671138
6. Formenti AM, Maffezzoni F, Doga M, Mazziotti G, Giustina A (2017) Growth hormone deficiency in treated acromegaly and active Cushing's syndrome. Best Pract Res Clin Endocrinol Metab 31(1):79–90 Epub 20170309. https://doi.org/10.1016/j.beem.2017.03.002
7. Frara S, Allora A, Castellino L, di Filippo L, Loli P, Giustina A (2021) COVID-19 and the pituitary. Pituitary 24(3):465–481 Epub 20210503. https://doi.org/10.1007/s11102-021-01148-1
8. Frara S, Allora A, di Filippo L, Formenti AM, Loli P, Polizzi E et al (2021) Osteopathy in mild adrenal Cushing's syndrome and Cushing disease. Best Pract Res Clin Endocrinol Metab 35(2):101515 Epub 20210310. https://doi.org/10.1016/j.beem.2021.101515
9. Giustina A, Wehrenberg WB (1992) The role of glucocorticoids in the regulation of Growth Hormone secretion: mechanisms and clinical significance. Trends Endocrinol Metab.;3(8):306–11. https://doi.org/10.1016/1043-2760(92)90142-n. PubMed PMID: 18407116
10. Mazziotti G, Formenti AM, Frara S, Maffezzoni F, Doga M, Giustina A (2017) Diabetes in Cushing Disease. Curr Diab Rep 17(5):32. https://doi.org/10.1007/s11892-017-0860-9PubMed PMID: 28364356
11. Puig-Domingo M, Marazuela M, Giustina A (2020) COVID-19 and endocrine diseases. A statement from the European Society of Endocrinology. Endocrine.;68(1):2–5. doi: 10.1007/s12020-020-02294-5. PubMed PMID: 32279224; PubMed Central PMCID: PMCPMC7150529
12. Frara S, Melin Uygur M, di Filippo L, Doga M, Losa M, Santoro S et al (2022) High prevalence of vertebral fractures Associated with preoperative GH levels in patients with recent diagnosis of Acromegaly. J Clin Endocrinol Metab 107(7):e2843–e50. https://doi.org/10.1210/clinem/dgac183PubMed PMID: 35349698
13. Mazziotti G, Gazzaruso C, Giustina A (2011) Diabetes in Cushing syndrome: basic and clinical aspects. Trends Endocrinol Metab 22(12):499–506 Epub 20111011. https://doi.org/10.1016/j.tem.2011.09.001
14. Hakami OA, Ahmed S, Karavitaki N (2021) Epidemiology and mortality of Cushing's syndrome. Best Pract Res Clin Endocrinol Metab 35(1):101521 Epub 20210315. https://doi.org/10.1016/j.beem.2021.101521
15. Clayton RN, Jones PW, Reulen RC, Stewart PM, Hassan-Smith ZK, Ntali G et al (2016) Mortality in patients with Cushing's disease more than 10 years after remission: a multicentre, multinational, retrospective cohort study. Lancet Diabetes Endocrinol 4(7):569–576 Epub 20160602. https://doi.org/10.1016/s2213-8587(16)30005-5
16. Petersenn S, Beckers A, Ferone D, van der Lely A, Bollerslev J, Boscaro M et al (2015) Therapy of endocrine disease: outcomes in patients with Cushing's disease undergoing transsphenoidal surgery: systematic review assessing criteria used to define remission and recurrence. Eur J Endocrinol 172(6):R227–R239 Epub 20150119. https://doi.org/10.1530/eje-14-0883
17. Casanueva FF, Barkan AL, Buchfelder M, Klibanski A, Laws ER, Loeffler JS et al (2017) Criteria for the definition of Pituitary Tumor Centers of Excellence (PTCOE): a Pituitary Society statement. Pituitary 20(5):489–498
18. Frara S, Rodriguez-Carnero G, Formenti AM, Martinez-Olmos MA, Giustina A, Casanueva FF (2020) Pituitary Tumors Centers of Excellence. Endocrinol Metab Clin North Am 49(3):553–564 Epub 20200715. https://doi.org/10.1016/j.ecl.2020.05.010
19. Couselo M, Frara S, Giustina A, Casanueva FF (2022) Pituitary tumor centers of excellence for Cushing's disease. Pituitary 25(5):772–775 Epub 20220910. doi: 10.1007/s11102-022-01264-6. PubMed PMID: 36087228; PubMed Central PMCID: PMCPMC9587956
20. Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO et al (2015) Treatment of Cushing's syndrome: an endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 100(8):2807–2831 Epub 2015/07/30. https://doi.org/10.1210/jc.2015-1818
21. Mancini T, Porcelli T, Giustina A (2010) Treatment of cushing disease: overview and recent findings. Ther Clin Risk Manag 6:505–516 Epub 20101021. doi: 10.2147/tcrm.S12952. PubMed PMID: 21063461; PubMed Central PMCID: PMCPMC2963160
22. Fleseriu M, Varlamov EV, Hinojosa-Amaya JM, Langlois F, Melmed S (2023) An individualized approach to the management of cushing disease. Nat Reviews Endocrinol 19(10):581–599. https://doi.org/10.1038/s41574-023-00868-7
23. Pivonello R, De Leo M, Cozzolino A, Colao A (2015) The treatment of Cushing's Disease. Endocr Rev 36(4):385–486 Epub 20150611. doi: 10.1210/er.2013-1048. PubMed PMID: 26067718; PubMed Central PMCID: PMCPMC4523083
24. Giustina A, Uygur MM, Frara S, Barkan A, Biermasz NR, Chanson P et al (2023) Pilot study to define criteria for Pituitary Tumors Centers of Excellence (PTCOE): results of an audit of leading international centers. Pituitary 26(5):583–596 Epub 20230828. https://doi.org/10.1007/s11102-023-01345-0
25. Giustina A, Uygur MM, Frara S, Barkan A, Biermasz NR, Chanson P et al Standards of care for medical management of acromegaly in pituitary tumor centers of excellence (PTCOE).

Pituitary. 2024. Epub 20240604. https://doi.org/10.1007/s11102-024-01397-w. PubMed PMID: 38833044
26. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM et al (2008) The diagnosis of Cushing's syndrome: an endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 93(5):1526–1540 Epub 20080311. https://doi.org/10.1210/jc.2008-0125
27. Pivonello R, Scaroni C, Polistena B, Migliore A, Giustina A (2023) Unmet needs on the current medical management of Cushing's syndrome: results from a Delphi panel of Italian endocrinologists. J Endocrinol Invest 46(9):1923–1934 Epub 20230419. https://doi.org/10.1007/s40618-023-02058-8
28. Nieman LK, Boscaro M, Scaroni CM, Deutschbein T, Mezosi E, Driessens N et al (2021) Metyrapone Treatment in Endogenous Cushing's syndrome: results at Week 12 from PROMPT, a prospective International Multicenter, Open-Label, phase III/IV study. J Endocr Soc 5(Supplement1):A515–A. https://doi.org/10.1210/jendso/bvab048.1053
29. Varlamov EV, Han AJ, Fleseriu M (2021) Updates in adrenal steroidogenesis inhibitors for Cushing's syndrome - A practical guide. Best Pract Res Clin Endocrinol Metab 35(1):101490 Epub 20210206. https://doi.org/10.1016/j.beem.2021.101490
30. Pivonello R, Fleseriu M, Newell-Price J, Bertagna X, Findling J, Shimatsu A et al (2020) Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a double-blind, randomised withdrawal phase. Lancet Diabetes Endocrinol 8(9):748–761 Epub 20200727. https://doi.org/10.1016/s2213-8587(20)30240-0
31. Gadelha M, Bex M, Feelders RA, Heaney AP, Auchus RJ, Gilis-Januszewska A et al (2022) Randomized Trial of Osilodrostat for the treatment of Cushing Disease. J Clin Endocrinol Metab 107(7):e2882–e95. https://doi.org/10.1210/clinem/dgac178PubMed PMID: 35325149; PubMed Central PMCID: PMCPMC9202723
32. Fleseriu M, Biller BMK, Bertherat J, Young J, Hatipoglu B, Arnaldi G et al (2022) Long-term efficacy and safety of osilodrostat in Cushing's disease: final results from a phase II study with an optional extension phase (LINC 2). Pituitary 25(6):959–970 Epub 20221011. https://doi.org/10.1007/s11102-022-01280-6
33. Fleseriu M, Biller BMK (2022) Treatment of Cushing's syndrome with osilodrostat: practical applications of recent studies with case examples. Pituitary 25(6):795–809 Epub 20220824. doi: 10.1007/s11102-022-01268-2. PubMed PMID: 36002784; PubMed Central PMCID: PMCPMC9401199
34. Vilar L, Naves LA, Azevedo MF, Arruda MJ, Arahata CM, Moura ESL et al (2010) Effectiveness of cabergoline in monotherapy and combined with ketoconazole in the management of Cushing's disease. Pituitary 13(2):123–129. https://doi.org/10.1007/s11102-009-0209-8PubMed PMID: 19943118
35. Pivonello R, De Martino MC, Cappabianca P, De Leo M, Faggiano A, Lombardi G et al (2009) The medical treatment of Cushing's disease: effectiveness of chronic treatment with the dopamine agonist cabergoline in patients unsuccessfully treated by surgery. J Clin Endocrinol Metab 94(1):223–230 Epub 20081028. https://doi.org/10.1210/jc.2008-1533
36. Ferriere A, Cortet C, Chanson P, Delemer B, Caron P, Chabre O et al (2017) Cabergoline for Cushing's disease: a large retrospective multicenter study. Eur J Endocrinol 176(3):305–314 Epub 20161222. https://doi.org/10.1530/eje-16-0662
37. Ben-Shlomo A, Schmid H, Wawrowsky K, Pichurin O, Hubina E, Chesnokova V et al (2009) Differential ligand-mediated pituitary somatostatin receptor subtype signaling: implications for corticotroph tumor therapy. J Clin Endocrinol Metab 94(11):4342–4350 Epub 20091009. https://doi.org/10.1210/jc.2009-1311
38. Colao A, Petersenn S, Newell-Price J, Findling JW, Gu F, Maldonado M et al (2012) A 12-month phase 3 study of pasireotide in Cushing's disease. N Engl J Med 366(10):914–924 doi: 10.1056/NEJMoa1105743. PubMed PMID: 22397653
39. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM et al (2022) Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 65(12):1925–1966. https://doi.org/10.1007/s00125-022-05787-2
40. Colao A, De Block C, Gaztambide MS, Kumar S, Seufert J, Casanueva FF (2014) Managing hyperglycemia in patients with Cushing's disease treated with pasireotide: medical expert recommendations. Pituitary 17(2):180–186. https://doi.org/10.1007/s11102-013-0483-3
41. Schopohl J, Gu F, Rubens R, Van Gaal L, Bertherat J, Ligueros-Saylan M et al (2015) Pasireotide can induce sustained decreases in urinary cortisol and provide clinical benefit in patients with Cushing's disease: results from an open-ended, open-label extension trial. Pituitary 18(5):604–612. https://doi.org/10.1007/s11102-014-0618-1PubMed PMID: 25537481; PubMed Central PMCID: PMCPMC4560758
42. Pivonello R, Arnaldi G, Scaroni C, Giordano C, Cannavò S, Iacuaniello D et al (2019) The medical treatment with pasireotide in Cushing's disease: an Italian multicentre experience based on real-world evidence. Endocrine 64(3):657–672 Epub 20190409. https://doi.org/10.1007/s12020-018-1818-7
43. Lacroix A, Gu F, Gallardo W, Pivonello R, Yu Y, Witek P et al (2018) Efficacy and safety of once-monthly pasireotide in Cushing's disease: a 12 month clinical trial. Lancet Diabetes Endocrinol 6(1):17–26 Epub 20171012. https://doi.org/10.1016/s2213-8587(17)30326-1
44. Fleseriu M, Petersenn S, Biller BMK, Kadioglu P, De Block C, T'Sjoen G et al (2019) Long-term efficacy and safety of once-monthly pasireotide in Cushing's disease: a phase III extension study. Clin Endocrinol (Oxf) 91(6):776–785 Epub 20191001. https://doi.org/10.1111/cen.14081
45. Feelders RA, Fleseriu M, Kadioglu P, Bex M, González-Devia D, Boguszewski CL et al (2023) Long-term efficacy and safety of subcutaneous pasireotide alone or in combination with cabergoline in Cushing's disease. Front Endocrinol (Lausanne) 14:1165681 Epub 20231009. https://doi.org/10.3389/fendo.2023.1165681
46. Grottoli S, Maffei P, Tresoldi AS, Granato S, Benedan L, Mariani P et al (2024) Insights from an Italian Delphi panel: exploring resistance to first-generation somatostatin receptor ligands and guiding second-line medical therapies in acromegaly management. J Endocrinol Invest. Epub 20240529. https://doi.org/10.1007/s40618-024-02386-3. PubMed PMID: 38809458
47. Maffezzoni F, Formenti AM, Mazziotti G, Frara S, Giustina A (2016) Current and future medical treatments for patients with acromegaly. Expert Opin Pharmacother 17(12):1631–1642 Epub 20160628. https://doi.org/10.1080/14656566.2016.1199687
48. Fleseriu M, Biller BM, Findling JW, Molitch ME, Schteingart DE, Gross C (2012) Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing's syndrome. J Clin Endocrinol Metab 97(6):2039–2049 Epub 20120330. https://doi.org/10.1210/jc.2011-3350
49. Barbot M, Albiger N, Ceccato F, Zilio M, Frigo AC, Denaro L et al (2014) Combination therapy for Cushing's disease: effectiveness of two schedules of treatment: should we start with cabergoline or ketoconazole? Pituitary 17(2):109–117. https://doi.org/10.1007/s11102-013-0475-3PubMed PMID: 23468128
50. Feelders RA, de Bruin C, Pereira AM, Romijn JA, Netea-Maier RT, Hermus AR et al (2010) Pasireotide alone or with cabergoline and ketoconazole in Cushing's disease. N Engl J Med 362(19):1846–1848. https://doi.org/10.1056/NEJMc1000094PubMed PMID: 20463350

51. Kamenický P, Droumaguet C, Salenave S, Blanchard A, Jublanc C, Gautier JF et al (2011) Mitotane, metyrapone, and ketoconazole combination therapy as an alternative to rescue adrenalectomy for severe ACTH-dependent Cushing's syndrome. J Clin Endocrinol Metab 96(9):2796–2804 Epub 20110713. https://doi.org/10.1210/jc.2011-0536

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