ORIGINAL ARTICLE

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Combination Medical Treatment for Difficult-to-manage Cushing's Disease: A Single Tertiary Pituitary Center's Experience

Yönetimi Zor Cushing Hastalığında Kombine Medikal Tedavi: Tek Merkez Üçüncü Basamak Hipofiz Merkezi Deneyimi

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ABSTRACT

Aim: The primary treatment for cushing's disease (CD) is transsphenoidal surgery (TSS). However, in refractory cases where medical monotherapy fails, combination therapy may enhance efficacy through synergistic mechanisms and reduce side effects by using lower drug doses. This study aimed to evaluate the efficacy of mono- and combination therapies in difficult-to-manage patients with CD treated at our center.

Materials and Methods: This retrospective, single-center study included 55 patients with persistent CD treated between 2010 and 2025 with monotherapy or combination therapy after TSS. Clinical and biochemical parameters were compared between pretreatment and the last follow-up following mono- or combination therapy, and remission status was also assessed.

Results: Following TSS, all 55 patients received medical management [median duration of therapy: 21.0 (12.0-61.0) months]; therapy was initiated postoperatively in 44 patients (80%), while the remaining 11 (20%) continued their preoperatively initiated treatment. At the last follow-up, 77.5% of patients achieved remission. The most common regimens were pasireotide (30.9%), cabergoline + metyrapone (18.2%), and cabergoline + ketoconazole (14.5%). Overall, cabergoline (67.3%) and pasireotide (58.2%) were the most frequently administered agents across all treatment periods. Twenty-three patients (41.8%) required treatment changes, mostly due to lack of remission (23.6%). Medical therapy decreased baseline cortisol, adrenocorticotropic hormone, urinary free cortisol, late-night salivary cortisol, and adenoma size, with a significant reduction in dexamethasone suppression test (p=0.016). Monotherapy and combination therapy showed no significant differences in hormonal control, metabolic outcomes, remission rates, or adverse events.

Conclusion: Our findings suggest that medical combination therapy is a feasible, safe, and effective treatment option for the long-term treatment of CD in patients who could not achieve remission after TSS or who have persistent disease activity.

Keywords: Cushing's disease, medical therapy, monotherapy, combination therapy, remission, hypercortisolism

ÖZ

Amaç: Cushing hastalığının (CH) primer tedavisi transsfenoidal cerrahidir (TSS). Bununla birlikte, medikal monoterapinin başarısız olduğu dirençli olgularda kombinasyon tedavisi, sinerjistik mekanizmalar yoluyla etkinliği artırabilir ve daha düşük ilaç dozlarının kullanılmasına olanak sağlayarak yan etkileri azaltabilir. Bu çalışmada, merkezimizde tedavi edilen ve yönetimi güç olan CH hastalarında mono- ve kombinasyon tedavilerinin etkinliğinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Bu retrospektif, tek merkezli çalışmaya, 2010-2025 yılları arasında TSS sonrasında persistan CH nedeniyle monoterapi veya kombinasyon tedavisi uygulanan 55 hasta dahil edildi. Klinik ve biyokimyasal parametreler, mono- veya kombinasyon tedavisi öncesi ile son takip arasında karşılaştırıldı ve remisyon durumu da değerlendirildi.

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Bulgular: TSS sonrasında 55 hastanın tamamına medikal tedavi uygulandı [medyan tedavi süresi: 21,0 (12,0-61,0) ay]; 44 hastada (%80) tedavi postoperatif dönemde başlanırken, kalan 11 hasta (%20) preoperatif dönemde başlanmış olan tedavilerine devam etti. Son takipte hastaların %77,5'inde remisyon sağlandı. En sık kullanılan tedavi rejimleri pasireotid (%30,9), kabergolin + metirapon (%18,2) ve kabergolin + ketokonazol (%14,5) idi. Tüm tedavi dönemleri değerlendirildiğinde en sık kullanılan ajanlar kabergolin (%67,3) ve pasireotid (%58,2) idi. Yirmi üç hastada (%41,8) tedavi değişikliği gerekti ve bunun en sık nedeni remisyon sağlanamamasıydı (%23,6). Medikal tedavi başlangıca kıyasla kortizol, adrenokortikotropik hormon, idrar serbest kortizolü, gece geç saat tükürük kortizolü ve adenom boyutunda azalma sağlarken, deksametazon supresyon testinde anlamlı bir düşüş saptandı (p=0,016). Monoterapi ve kombinasyon tedavisi arasında hormonal kontrol, metabolik sonuçlar, remisyon oranları veya advers olaylar açısından anlamlı fark saptanmadı.

Sonuç: Bulgularımız, TSS sonrasında remisyon sağlanamayan veya persistan hastalık aktivitesi bulunan CH hastalarının uzun dönem tedavisinde medikal kombinasyon tedavisinin uygulanabilir, güvenli ve etkili bir tedavi seçeneği olduğunu göstermektedir.

Anahtar Kelimeler: Cushing hastalığı, medikal tedavi, monoterapi, kombinasyon tedavisi, remisyon, hiperkortizolizm

INTRODUCTION

Cushing's syndrome is a clinical condition that arises due to prolonged exposure of body tissues to excessive levels of glucocorticoids, regardless of the underlying cause. The most common endogenous etiology is an adrenocorticotropic hormone (ACTH) secreting pituitary adenoma. The disease predominantly affects women, with a female-to-male ratio ranging from 3/1 to 5/1[1]. Although cushing's disease (CD) is statistically classified as a rare disorder, it represents a clinical entity that is not actually uncommon[2]. The clinical manifestations of Cushing's syndrome are diverse and may vary significantly among patients. Traditionally, the disease is recognized by its distinct Cushingoid stigmata, which encompass a wide range of severe metabolic, cardiovascular, and neuropsychiatric comorbidities[3]. However, despite the well-defined nature of these classic signs, the clinical presentation of CD has evolved over the years. Contemporary patient profiles may deviate from the historical descriptions, often displaying a more variable phenotype rather than the classic symptoms.

Cushing syndrome can cause significant morbidity and mortality; however, early diagnosis and effective treatment can significantly improve outcomes. Therefore, comprehensive assessment of the disease's clinical features, diagnostic challenges, and treatment strategies is crucial to optimize patient management.

The primary treatment for CD is transsphenoidal surgery (TSS)[4]. However, surgical intervention alone may not always provide definitive disease control. When performed by an experienced neurosurgeon, remission can be achieved in approximately 80% of patients with microadenomas and 60% of those with macroadenomas[5]. In cases where remission is not achieved or disease recurrence occurs, secondary treatment options include repeat surgery, medical therapy, radiotherapy, and bilateral adrenalectomy (AX)[6]. Medical management plays an important role in controlling hypercortisolism, particularly in patients who are not suitable candidates for surgery or in whom surgical and radiotherapeutic interventions have failed. Available pharmacological options include adrenal steroidogenesis inhibitors (ketoconazole, metyrapone, mitotane, levoketoconazole, osilodrostat), dopamine agonists (cabergoline), somatostatin receptor ligands (pasireotide), and glucocorticoid receptor blocker (mifepristone)[7,8].

In certain patients, despite surgery and subsequent medical monotherapy, remission cannot be achieved. In such cases, combination medical therapy may be necessary to attain adequate disease control. Although specific standardized regimens for combination therapy have not been clearly defined, this approach represents a valuable therapeutic alternative, as no currently available single-agent treatment achieves complete normalization of cortisol levels or full reversal of hypercortisolism-related clinical manifestations and comorbidities[9]. Combination therapy may enhance the overall efficacy of individual drugs through synergistic mechanisms, allowing the use of lower doses for each agent and potentially reducing the risk of adverse effects[7]. In the present study, we aimed to evaluate the effectiveness, remission rates, and adverse effect profiles of medical monotherapy and combination therapy in patients with CD treated at our center.

MATERIALS AND METHODS

This retrospective, single-center study was conducted at the Pituitary Center of İstanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Endocrinology and Metabolic Diseases. Ethical approval was obtained by the İstanbul University-Cerrahpaşa Medical Research Ethics Committee (approval number: E-83045809-604.01-909825, date: 06.02.2024) and written informed consent was obtained from all participants prior to inclusion in the study.

Participants

Patients' data were scanned from the archives of the university and the hospital's electronic medical records between 2010 and 2025. The study included individuals aged 18 years or older with a confirmed diagnosis of CD who had undergone TSS but exhibited persistent disease requiring postoperative medical management (monotherapy or combination therapy). While some of these patients may have also received medical

treatment prior to surgery to control severe hypercortisolism, the primary inclusion criterion was the absolute necessity for post-operative medical therapy due to unremitting disease. Patients were excluded if they were pregnant, diagnosed with non-pituitary (ectopic or adrenal) cushing's syndrome, or if they achieved remission solely with surgical intervention and did not require any form of medical therapy during follow-up (Figure 1). All participants were evaluated from baseline to their last follow-up visit, and comparisons were made between pre-treatment and last follow-up clinical and biochemical parameters following mono or combination medical therapy.

Clinical Evaluation

The diagnosis of CD was made by evaluating clinical findings, biochemical tests, and radiological imaging. Initially, a one mg overnight dexamethasone suppression test (DST) was performed to biochemically confirm hypercortisolism. Patients with DST >1.8 mcg/dL underwent midnight serum cortisol levels x2, 24-hour urinary free cortisol x2 (UFC), and a late-night salivary cortisol (LNSC) test. Abnormal results in at least two of these tests were considered suggestive of hypercortisolism. To determine the cause of the endogenous cortisol excess, morning plasma ACTH levels were measured. Pituitary-mediated CD was suspected when ACTH levels were > 20 pg/mL. A high-dose DST and/or, if possible, a corticotropin-releasing hormone stimulation test were performed to confirm the diagnosis. Depending on availability, 1.5T or 3T contrast-enhanced pituitary magnetic resonance imaging (MRI) was used to determine the location of pituitary adenomas. In cases where adenomas were not detected on MRI or were suspected, bilateral inferior petrosal sinus sampling was performed to assess the central/peripheral ACTH gradient. Patients with pituitary ACTH excess detected through these methods were considered to have CD.

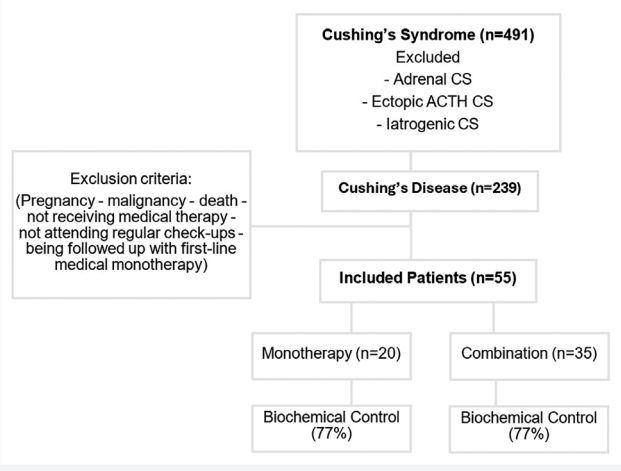

Figure 1. Flowchart of the study

CS: Cushing's syndrome, ACTH: Adrenocorticotropic hormone

Clinical data were retrospectively extracted from medical records at each follow-up visit. The parameters assessed both prior to and following medical therapy included demographic details, clinical characteristics, and history of surgical or radiotherapeutic interventions. Treatment-specific data, such as the regimen type (monotherapy or combination therapy) and treatment duration, were also recorded. Additionally, metabolic indicators comprising glycated Hemoglobin A1c, fasting plasma glucose (FPG), low-density lipoprotein (LDL) cholesterol LDL, triglycerides, systolic and diastolic blood pressure were also analyzed before the medical treatment and at the last follow-up. Biochemical and hormonal assays were performed using fasting blood samples obtained between 08:00 and 08:30 am LNSC samples were collected at 23:00 pm Hormonal parameters were measured via electrochemiluminescence immunoassay using the Cobas e801 platform (Roche Diagnostics GmbH, Mannheim, Germany). The institutional normal reference ranges for the evaluated biochemical parameters were as follows: serum basal morning cortisol, (N: 6.2-19.4 µg/dL); plasma ACTH, (N: 0-46 pg/mL); 24-hour UFC, (N: <140 mcg/day); and LNSC, (N: <0.276 µg/dL). As per standard guidelines, adequate suppression for the 1-mg overnight DST was defined as a serum cortisol level <1.8 µg/dL.

Clinical improvement and biochemical disease control were systematically documented. Systemic arterial hypertension was defined according to current clinical practice guidelines as a systolic blood pressure ≥140 mmHg and/or a diastolic pressure ≥90 mmHg, or the use of antihypertensive medication in patients with a prior diagnosis of hypertension[10]. Hyperlipidemia HL was diagnosed in individuals receiving lipid lowering therapy or exhibiting LDL levels exceeding 130 mg/dL and/or triglyceride levels above 200 mg/dL. The largest tumor size was determined using MRI, and surgical interventions were classified as TSS or TSS combined with AX. Patients who underwent radiotherapy were stratified by technique into Gamma Knife and Cyber-Knife subgroups.

Evaluation of Medical Treatment

Patients were categorized into two groups based on their entire treatment history. The "Monotherapy" group (n=20), comprising patients who received monotherapy throughout the study, and the "Combination Therapy" group (n=35), comprising patients who required more than one agent at any point during their follow-up. The efficacy of medical therapy was assessed by comparing serum cortisol, ACTH, UFC, DST, LNSC, adenoma size, HbA1c, FPG, LDL and triglyceride levels before and after treatment. Patients demonstrating biochemical improvement were classified as achieving adequate biochemical control, while those without improvement were defined as uncontrolled. Adequate biochemical control was determined based on UFC and, when available, LNSC levels. A UFC level

less than 1.5 times the upper limit of normal and an LNSC value within the reference range were considered indicative of adequate biochemical control. All patients were also evaluated for potential adverse effects of the medical therapy and for any new symptoms related to CD.

In our cohort, all included patients were classified as having persistent CD. Persistent CD was defined as the failure to achieve clinical and adequate biochemical control following the initial TSS, in accordance with established clinical practice guidelines[5]. Regarding surgical interventions, all 55 patients underwent TSS as the primary treatment; among them, 6 patients (10.9%) required a repeat TSS due to unremitting disease, and 6 patients (10.9%) eventually underwent bilateral AX. While all 55 patients were included in the overall demographic and safety analyses, 15 patients were excluded from the final adequate biochemical control calculation due to missing biochemical data at the final visit. Consequently, the biochemical control analysis was conducted on the remaining 40 patients.

Medical Treatment Protocol

Due to the retrospective and real-world nature of this study spanning 15 years, medical treatment was highly individualized rather than strictly standardized. However, our institutional approach to combination therapy consistently followed a stepwise, "add-on" strategy. When maximum tolerated doses of first-line monotherapy failed to achieve biochemical remission, or when dose escalation was precluded by adverse effects, a second complementary agent with a different mechanism of action was sequentially added to the regimen. The sequence of drugs was determined primarily by the patient's clinical severity, metabolic comorbidities (e.g., hyperglycemia), and national drug availability at the time.

The general posology for the most frequently used agents in our cohort was as follows: cabergoline was typically initiated at 0.5-1.0 mg/week and titrated up to a maximum of 3.0-4.5 mg/week. Subcutaneous pasireotide was started at 0.6 mg twice daily and increased up to 0.9 mg twice daily if tolerated. Metyrapone was initiated at 500-750 mg/day and titrated up to a maximum of 2000-3000 mg/day based on cortisol levels. Ketoconazole was generally started at 400 mg/day and increased up to 600-800 mg/day, with strict monitoring of liver function tests.

Statistical Analysis

Data analysis was conducted using SPSS 24.0 (SPSS, Inc, USA). Descriptive statistics for categorical variables were presented as frequencies and percentages, while continuous variables were summarized using the mean, standard deviation, median, minimum, and maximum values. To compare categorical variables such as disease control, gender, and disease severity (comparing biochemically controlled and uncontrolled groups), the chi-square (χ^2) test was applied. The normality of the variables was assessed with the Shapiro-Wilk test. For continuous variables with a normal distribution, paired sample t-tests were used to compare values before and after treatment. For non-normally distributed variables, the Wilcoxon signed ranks test was employed. Furthermore, for comparisons between the biochemically controlled and uncontrolled groups, the independent sample t-test was used for normally distributed parameters, while the Mann-Whitney U test was applied for those with non-normal distributions. In the correlation analysis, Pearson's correlation coefficient was used for normally distributed data, while Spearman's correlation coefficient was used for non-normally distributed data. Statistical significance was considered at $p<0.05$ with a 95% confidence level. Given the exploratory nature of this study and the large number of comparisons, we did not adjust for multiple testing; results should be interpreted as hypothesis-generating and p-values are nominal. Confirmation in independent cohorts is required.

RESULTS

The study included a total of 55 patients with difficult-to-manage pituitary CD. Of these, 45 (81.8%) were female and 10 (18.2%) were male, with a mean age of 39.63±13.65 years. The median duration of medical therapy was 21.0 (12.0-61.0) months. The median pretreatment UFC and LNSC levels were 162.45 (96.12-346.50) mcg/day and 0.47 (0.09-5.00) µg/dL, respectively. The median adenoma size on initial MRI was 8.0 (4.50-13.0) mm. General baseline characteristics are summarized in Table 1. All 55 patients underwent TSS and received medical management; therapy was initiated in the postoperative period for 44 patients (80%), while the remaining 11 patients (20%) continued their preoperatively initiated treatment (Table 1).

The most common reason for switching therapy was lack of remission in 13 (23.6%) patients (Figure 2). When the treatments received by the patients in different time periods were evaluated collectively, it was seen that a total of 37 (67.3%) patients were treated with cabergoline, 32 (58.2%) patients were treated with pasireotide and 18 (32.7%) patients received metyrapone (Table 1).

Regarding treatment patterns, 20 patients (36.4%) were treated exclusively with monotherapy, while 35 patients (63.6%) required combination therapy at some point during the study. At the last follow-up visit, although 35 patients had a history of combination therapy, 7 of these patients had been successfully tapered back to a single agent after achieving biochemical control. Consequently, at the final visit, 27 patients were receiving monotherapy and 28 were on combination therapy, as detailed in Table 2. At the last follow-up, among the 40 patients eligible for final efficacy evaluation, 31 (77.5%) achieved adequate biochemical control. Pasireotide emerged as the most frequently used monotherapy agent (n=17; 30.9%).

Table 1. Characteristics of patients

	n (%), mean ± SD or median (IQR)
Sex, female	45 (81.80)
Age (years)	39.63±13.65
Treatment duration (month)	21 (12-61)
Biochemical control (n=40)	31 (77.50)
Diabetes mellitus	11 (20.00)
Hyperlipidemia	17 (30.90)
Hypertension	25 (45.45)
Treatment modalities	
TSS	55 (100)
TSS + radiotherapy Gamma knife Cyber-knife	18 (32.7) 13 (23.6) 5 (9.1)
TSS + AX	6 (10.9)
TSS + multiple medical treatment modifications	23 (41.8)
Initiation of medical treatment Pre-op Post-op	11 (20.0) 44 (80.0)
Total patients' number of drugs use in time of periods Cabergoline Pasireotide Ketoconazole Metyrapone Fluconazole	 37 (67.3) 32 (58.2) 19 (34.5) 18 (32.7) 1 (1.8)

SD: Standard deviation, IQR: Interquartile range, TSS: Transsphenoidal surgery, AX: Adrenalectomy, Pre-op: Pre-operative, post-op: Post-operative

Among combination therapies, the most commonly preferred regimen was cabergoline + metyrapone (n=10; 18.2%) (Table 2).

In the overall cohort, while medical therapy led to observable reductions in basal cortisol, ACTH, UFC, LNSC, and adenoma size, these trends did not achieve statistical significance (p>0.05 for all). Conversely, a marked and statistically significant reduction was observed in DST values from baseline to the last follow-up [5.80 (3.17-13.00) vs. 2.83 (1.80-7.4), p=0.016] (Figure 3, Table 3). In contrast, metabolic parameters (FPG, HbA1c, LDL, triglyceride) showed clinical stability with no significant variations observed.

When stratified by adequate biochemical control status, patients in the biochemically controlled and uncontrolled groups displayed comparable biochemical profiles prior to treatment, with no statistical differences observed at baseline. However, at the last follow-up, a pronounced divergence was evident.

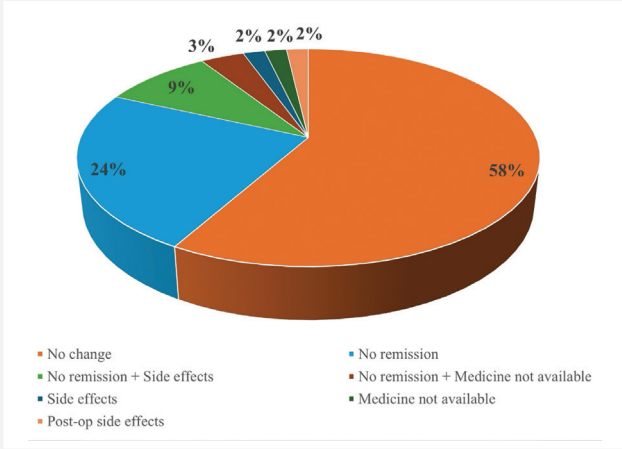

Figure 2. Reasons for changing medical treatment

Table 2. Medical treatments used in the last visit

	n (%)
Monotherapy	
Pasireotide	17 (30.9)
Cabergoline	3 (5.5)
Ketoconazole	3 (5.5)
Metyrapone	3 (5.5)
Fluconazole	1 (1.8)
Combination therapy	
Cabergoline + metyrapone	10 (18.2)
Cabergoline + ketoconazole	8 (14.5)
Cabergoline + pasireotide	4 (7.3)
Pasireotide + ketoconazole	2 (3.6)
Cabergoline + pasireotide + metyrapone	2 (3.6)
Cabergoline + metyrapone + ketoconazole	2 (3.6)

The biochemically controlled group demonstrated significantly lower serum basal cortisol (p=0.02), UFC (p<0.001), and LNSC levels (p=0.002) compared to the uncontrolled group (Table 4).

To evaluate treatment modalities, the cohort was divided into monotherapy and combination therapy subgroups. The groups were found to be comparable in demographic characteristics and treatment duration. The analysis yielded no statistically significant differences between the two therapeutic approaches in terms of hormonal efficacy, metabolic endpoints, biochemical control rates, or safety profiles (Table 5).

DISCUSSION

In this study, we examined the management strategies, medical treatment approaches, treatment combinations, medication related adverse effects and clinical outcomes of patients

diagnosed with pituitary CD which are difficult to manage and followed in our tertiary care center. We observed that combination medical therapies were required in the majority of patients, the rate of adverse effects leading to treatment discontinuation was low and biochemical control could be achieved even in difficult-to-manage cases when individualized combination therapy was implemented.

CD is known to occur predominantly in women[11]. Although the female-to-male ratio is commonly reported around 3:1, some studies have noted ratios as high as 4:1, 5:1, or even 8:1[12-14]. Consistent with the literature, our cohort also demonstrated a female predominance, with a female-to-male ratio of approximately 4:1. Most patients with CD present with microadenomas. Neurosurgical series have reported that microadenomas constitute 75% to 90% of all pituitary tumors in CD[15,16]. Similarly, in our study, 50 patients (90.09%) had microadenomas. The slightly higher percentage in our cohort may be related to earlier referral to specialized centers, improved MRI resolution, or selection bias inherent to tertiary referral centers, as patients with smaller tumors who fail initial management are more likely to be referred for advanced treatment and follow-up.

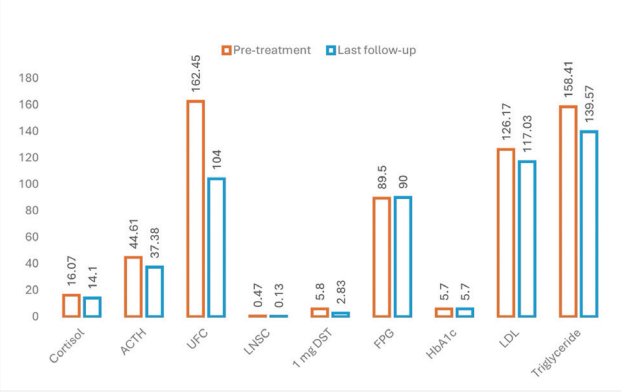

Figure 3. Comparison of patients' pre-treatment and last follow-up laboratory findings

ACTH: Adrenocorticotropic hormone, UFC: Urinary free cortisol, LNSC: Late-night salivary cortisol DST: Dexamethasone suppression test, FPG: Fasting plasma glucose, HbA1c: Hemoglobin LDL: Low-density lipoprotein

CD is associated with various metabolic comorbidities, including diabetes mellitus (DM), hypertension, and hyperlipidemia. In our study, one in five patients had diabetes, nearly half had hypertension, and approximately one in three had hyperlipidemia. Reported prevalence rates in the literature vary depending on diagnostic criteria and disease stage. When only the diagnosis of diabetes is considered, DM is present in approximately 20-45% of patients[17]. Hyperlipidemia has been reported within a broad range, from 12% to 72%, and hypertension in 49-78% of patients; moreover, hypertension may persist in up to 50% of cases even after remission[18,19]. In this context, metabolic comorbidity rates in our cohort were comparable to those reported in the literature. Differences between studies may be explained by variations in disease severity at presentation, duration of hypercortisolism prior to diagnosis, and heterogeneity in comorbidity definitions.

Remission rates in CD are influenced by several factors, including adenoma size and localization, type of intervention, surgical expertise, and management strategies used at high-volume centers. In patients undergoing first-line TSS, remission rates are approximately 80% in microadenomas and 60% in macroadenomas[5]. In cases where remission is not achieved with TSS, remission rates of around 75% may be obtained with postoperative medical therapy, and 64-80% remission

Table 3. Changes in laboratory parameters in patients receiving medical treatment for cushing's disease

	Pretreatment	Last follow-up	Difference*	p value
	Mean ± SD or median (IQR)			
Baseline cortisol (µg/dL)	16.07 (12.39-20.04)	14.10 (10.65-18.25)	-1.97	0.420
ACTH (pg/mL)	44.61 (24.64-67.22)	37.38 (24.22-61.21)	-7.23	0.216
UFC (mcg/day)	162.45 (96.12-346.50)	104.00 (68.85-191.01)	-58.45	0.249
LNSC (µg/dL)	0.47 (0.09-5.00)	0.13 (0.09-0.58)	-0.34	0.272
1 mg DST (µg/dL)	5.80 (3.17-13.00)	2.83 (1.80-7.44)	**-2.97**	**0.016**
The adenoma size in the pituitary MRI (mm)	8.00 (4.50-13.00)	6.00 (5.00-18.25)	-2.00	0.202
FPG (mg/dL)	89.50 (80.25-111.75)	90.00 (82.00-111.00)	+0.50	0.610
HbA1c (%)	5.70 (5.40-6.50)	5.70 (5.20-6.80)	0.00	0.353
LDL (mg/dL)	126.17±38.40	117.03±37.63	-9.14	0.340
Triglyceride (mg/dL)	158.41±70.43	139.57±68.54	-18.84	0.286

*Difference values represent median differences, except for LDL and triglyceride where mean differences are presented

ACTH: Adrenocorticotropic hormone, UFC: Urinary free cortisol, LNSC: Late-night salivary cortisol, DST: Dexamethasone suppression test, MRI: Magnetic resonance imaging. FPG: Fasting plasma glucose, LDL: Low-density lipoprotein, SD: Standard deviation, IQR: Interquartile range, HbA1c: Glycated hemoglobin

may be achieved with radiotherapy in patients who remain uncontrolled or experience recurrence[20,21]. In our study, all patients underwent TSS as the initial intervention, but the cohort consisted entirely of individuals who did not achieve remission after surgery and were therefore more challenging to manage. All received mono- or combination medical therapy, and a subset also underwent radiotherapy (32.7%). Despite the complexity of this population, 77.5% of our patients achieved biochemical control during follow-up, a rate consistent with the literature on multimodal and sequential treatment strategies. The comparable biochemical control rate, despite the inclusion of more refractory patients, may reflect individualized combination therapy, early treatment escalation, and close clinical monitoring in a tertiary referral center.

TSS is the first-line treatment for CD; however, medical therapy with or without radiotherapy is recommended for persistent or recurrent cases. In a real-world study by Broder et al.[22] using large US national datasets, 78.9% of patients underwent initial TSS, while 8.3% received radiotherapy and 7.8% required medical therapy during follow-up. Similarly, Giustina et al.[20] evaluated patients across nine international Pituitary Tumor Centers of Excellence. They reported a median medical therapy utilization rate of 13.3% (4.8-82.9%). In their cohort, the most frequently prescribed agents were ketoconazole (26.5%), metyrapone (17.2%), pasireotide (9.3%), cabergoline (2.8%), and osilodrostat (1.7%). In our study, medication preference patterns differed notably from these international cohorts. Throughout the follow-up period, cabergoline (67.3%) and pasireotide (58.2%) were the most frequently used agents. This variation is likely driven by several local factors, including restricted access to specific medications, variable insurance coverage, and fluctuating drug availability over time. Additionally, our patients received different agents across various treatment phases. This highlights the necessity for individualized therapy and stepwise treatment escalation in difficult-to-manage cases.

Preoperative medical therapy may be used in selected patients before TSS. This approach helps manage severe hypercortisolism and associated comorbidities (e.g., hyperglycemia, hypertension, infection, and thromboembolism risks) prior to surgery. Furthermore, it serves as a "bridge" treatment when surgery is delayed due to required stabilization, preoperative risk reduction, or logistical issues[23,24]. However, routine

Table 4. Clinical and laboratory characteristics of the biochemically controlled versus uncontrolled patients

	Biochemically controlled (n=31)	Uncontrolled (n=9)	p-value
	n (%), mean ± SD or median [IQR]		
Sex, female	23 (74.2)	7 (77.8)	0.601
Age, years	40.87±13.88	31±12.35	0.059
Treatment duration, month	42.29±38.26	32.33±32.30	0.448
Combination therapy	17 (54.8)	5 (55.6)	0.636
Pretreatment baseline cortisol (µg/dL)	15.05 (11.64-19.39)	19.31 (13.06-22.49)	0.215
Pretreatment ACTH (pg/mL)	58.24 (22.73-67.88)	61.30 (23.25-64.70)	0.849
Pretreatment UFC (mcg/day)	168.91 (100-371)	186 (92-340)	0.858
Pretreatment salivary cortisol (µg/dL)	0.35 (0.12-1.01)	3.60 (0.06-7.12)	0.878
Last follow-up baseline cortisol (µg/dL)	13.60 (9-16.60)	18.40 (11.80-31.09)	**0.002**
Last follow-up ACTH (pg/mL)	36.7 (24.16-53)	55.5 (23.9-130.37)	0.249
Last follow-up UFC (mcg/day)	92.75 (55.10-111.25)	381.90 (246.91-778.4)	**<0.001**
Last follow-up salivary cortisol (µg/dL)	0.11 (0.08-0.23)	4.38 (1.24-4.80)	**0.002**
The adenoma size in the initial pituitary MRI (mm)	10 (4.25-14)	6.75 (3.35-7.75)	0.368
Pretreatment FPG (mg/dL)	89.5 (81.75-127.5)	78.5 (67.75-105.5)	0.096
Pretreatment HbA1c (%)	5.8 (5.47-6.57)	5.9 (5.0-6.3)	0.409
Pretreatment LDL (mg/dL)	128.00±37.06	132.57±39.73	0.790
Pretreatment triglyceride (mg/dL)	164.36±76.53	155.14±44.74	0.691
Last follow-up FPG (mg/dL)	86 (82-120)	101 (78-107.5)	1.000
Last follow-up HbA1c (%)	5.8 (5.6-7.3)	5.3 (5.1-6.5)	0.257
Last follow-up LDL (mg/dL)	121.50±37.68	111.56±33.14	0.465
Last triglyceride (mg/dL)	140.56±58.91	148.00±90.59	0.823

SD: Standard deviation, IQR: Interquartile range, MRI: Magnetic resonance imaging, ACTH: Adrenocorticotropic hormone, UFC: Urinary free cortiso, LNSC: Late-night salivary cortisol, DST: Dexamethasone suppression test, FPG: Fasting plasma glucose, HbA1c: Glycated hemoglobin, LDL: Low-density lipoprotein

use of preoperative medical treatment is not supported by strong evidence; therefore, it should be reserved for selected cases. Notably, this preoperative intervention may suppress cortisol levels, thereby complicating the assessment of early postoperative remission. In a study by Valassi et al.[25] utilizing data from the European Register on Cushing's Syndrome (ERCUSYN), preoperative medical treatment was administered to approximately 20% of patients. Among these, ketoconazole was used in 62%, metyrapone in 16%, and their combination in 12%. Consistent with the ERCUSYN cohort, 20% of the patients in our study also required the initiation of preoperative medical treatment for similar clinical reasons.

Although medical therapy is an important option in patients with persistent or recurrent CD, combination regimens, despite being used less frequently, may provide an effective therapeutic alternative. Combination medical treatment can be preferred in patients with persistent hypercortisolism who fail to achieve remission after surgery, as a bridge therapy during the interval before radiotherapy becomes effective, in cases where monotherapy is insufficient, or to reduce adverse effects by using lower doses of each drug while achieving synergistic efficacy through different mechanisms of action[4,5,7,26].

A meta-analysis by Broersen et al.[27], involving 1520 patients from 35 studies, reported a cortisol normalization rate of

Table 5. Clinical and laboratory characteristics of patients received monotherapy and combination therapy

	Monotherapy (n=20)	Combination (n=35)	p-value
	n (%), mean ± SD or median (IQR)		
Sex, female	14 (70.00)	31 (88.60)	0.144
Age	38.15±16.20	40.50±12.08	0.577
Treatment duration	19.50 (11.25-42.75)	23.00 (13.00-71.50)	0.446
Radiothetapy	8 (40.00)	10 (28.57)	0.397
Biochemical control (n=40)	14 (77.77)	17 (77.27)	1.0
Side effects (n=45)	2 (10.52)	7 (26.92)	0.264
Diabetes mellitus	3 (15)	8 (22.9)	0.281
Hyperlipidemia	4 (20)	13 (37.1)	0.148
Hypertension	7 (35)	18 (51.4)	0.224
The adenoma size in the initial pituitary MRI (mm)	6.50±3.10	9.75±5.56	0.303
Pretreatment			
Baseline cortisol (µg/dL)	17.42 (11.50-20.02)	14.04 (12.66-20.08)	0.916
ACTH (pg/mL)	42.78 (31.30-68.99)	47.05 (20.25-67.66)	0.859
UFC (mcg/day)	226.57 (104.24-725.00)	129.30 (70.25-281.00)	0.162
LNSC (µg/dL)	0.47 (0.09-5.00)	0.36 (0.10-5.58)	0.902
1 mg DST (µg/dL)	8.46 (3.20-12.50)	4.97 (3.08-14.80)	0.772
FPG (mg/dL)	84.00 (75.50-97.50)	96.50 (84.00-130.50)	0.084
HbA1c (%)	5.65 (5.37-6.15)	5.90 (5.40-6.50)	0.493
LDL (mg/dL)	124.00±37.43	127.62±39.88	0.789
Triglyceride (mg/dL)	133.71±56.02	175.70±75.52	0.087
Last follow-up			
Baseline cortisol (µg/dL)	15.01 (11.25-18.45)	13.60 (9.00-18.40)	0.520
ACTH (pg/mL)	37.38 (24.55-47.35)	42.15 (20.70-70.96)	0.849
UFC (mcg/day)	109.00 (68.85-205.00)	100.10 (62.80-191.02)	0.892
LNSC (µg/dL)	0.10 (0.09-0.57)	0.14 (0.11-1.88)	0.332
1 mg DST (µg/dL)	4.12 (2.47-7.79)	2.05 (1.39-6.83)	0.164
FPG (mg/dL)	90.00 (82.00-102.00)	91.00 (81.75-141.25)	0.593
HbA1c (%)	5.80 (5.60-6.10)	5.65 (5.10-7.45)	0.681
LDL (mg/dL)	107.36±22.10	123.18±44.22	0.164
Triglyceride (mg/dL)	135.43±74.61	142.33±65.93	0.775

SD: Standard deviation, IQR: Interquartile range, MRI: Magnetic resonance imaging, ACTH: Adrenocorticotropic hormone, UFC: Urinary free cortisol, LNSC: Late-night salivary cortisol, DST: Dexamethasone suppression test, FPG: Fasting plasma glucose, HbA1c: Glycated hemoglobin, LDL: Low-density lipoprotein

49.4% with monotherapy. Notably, this rate increased to 65.7% in patients receiving combination therapy (≥2 agents). Regarding safety, the same study reported mild side effects in 24% of patients using cabergoline, 30.8% with metyrapone, and 58.3% with pasireotide. Interestingly, the incidence of mild side effects decreased to 18% in patients receiving combination therapy. However, serious side effects were observed in 20.9% of patients treated with multiple (≥2 agents) medications[27]. The literature indicates that combining ketoconazole with metyrapone or using a steroidogenesis inhibitor together with a tumor-targeted agent, may be beneficial due to complementary mechanisms that enhance adrenal steroid blockade or allow lower individual drug doses. Triple combinations such as cabergoline–pasireotide–ketoconazole or metyrapone–ketoconazole–mitotane have also been described; however, monitoring is advised due to the potential risk of QTc prolongation and hepatotoxicity[28,29]. Feelders et al.[30] added cabergoline to patients who failed to achieve UFC normalization after starting pasireotide therapy and compared the two groups. At follow-up, the mean UFC normalization was 50% (17 monotherapy, 17 combination), and the remission rate was similar in the two arms (50% each). In a study combining pasireotide, cabergoline, and ketoconazole treatments in 17 CD patients, the combination treatment resulted in UFC normalization in 15 (88.2%) patients, and clinical improvement was observed with reductions in body weight, waist circumference, and blood pressure[9]. Differences in response rates among studies may be related to variations in patient selection (treatment-naive vs. refractory cases), treatment sequencing, disease severity, and drug availability.

In our study, six different combination regimens were used at the last follow-up visit. The most commonly used combination was cabergoline + metyrapone, whereas pasireotide was the most frequently used monotherapy. At the last follow-up, adequate biochemical control was observed in approximately 77% of patients in both monotherapy and combination therapy groups, with no significant difference between them. However, basal cortisol, UFC, and one mg overnight DST levels were lower in the combination therapy group, suggesting that individualized combination therapy may provide better biochemical control than dose escalation of a single agent, particularly in more severe or refractory disease. Although treatment combinations changed during follow-up, major adverse effects were not observed. The most frequently reported side effects were nausea, diarrhea, and mild fasting blood glucose elevations, none of which required treatment discontinuation or regimen modification. The low side-effect rate in our cohort may be attributed to the stepwise escalation of therapy, use of lower doses in combination regimens, and close monitoring during follow-up.

Study Limitations

There are several limitations to our study. First, the sample size was relatively small, which limited the ability to compare the superiority of specific combination treatment regimens. Second, the retrospective nature of the study may have introduced selection and information bias. Third, difficulties in accessing certain medications during the study period sometimes prevented continuation of treatment according to the planned protocol or maintaining follow-up for the desired duration. Fourth, the retrospective chart-review design over a 15-year period resulted in missing granular data regarding the exact grading and precise quantitative severity of some drug-related adverse events. Finally, the inclusion of a heterogeneous patient profile, with a subset of individuals undergoing concurrent adjuvant treatments such as radiotherapy or subsequent bilateral AX, introduces potential confounding factors that may complicate the isolated assessment of medical treatment efficacy. For these reasons, prospective studies with larger patient populations and standardized treatment protocols are required to better evaluate combination treatment strategies.

CONCLUSION

Our findings indicate that while combination medical therapy does not demonstrate statistical superiority over monotherapy in our cohort, it represents a viable, comparable, and safe therapeutic alternative for patients with CD who do not achieve remission after TSS. Rather than a first-line medical approach, combination therapy provides a crucial step-up strategy when monotherapy fails or is limited by dose-dependent side effects, offering meaningful biochemical control without significantly increasing the rate of adverse events. This individualized approach facilitates effective disease management and may help reduce medication-related side effects. The success of combination therapy is further supported by close follow-up and multidisciplinary decision-making, which play a critical role in optimizing treatment outcomes and preventing complications.

Ethics

Ethics Committee Approval: Ethical approval was obtained the Pituitary Center of İstanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Endocrinology and Metabolic Diseases (approval number: E-83045809-604.01-909825, date: 06.02.2024). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: All participants provided written informed consent prior to enrollment.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.U.Ç., P.K., Concept: P.K., Design: M.U.Ç., P.K., Data Collection or Processing: M.U.Ç., Analysis or Interpretation: M.U.Ç., P.K., Literature Search: M.U.Ç., Writing: M.U.Ç.

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