Preoperative medical treatment in Cushing's syndrome: frequency of use and its impact on postoperative assessment: data from ERCUSYN

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Abstract

Background: Surgery is the definitive treatment of Cushing's syndrome (CS) but medications may also be used as a first-line therapy. Whether preoperative medical treatment (PMT) affects postoperative outcome remains controversial.

Objective: (1) Evaluate how frequently PMT is given to CS patients across Europe; (2) examine differences in preoperative characteristics of patients who receive PMT and those who undergo primary surgery and (3) determine if PMT influences postoperative outcome in pituitary-dependent CS (PIT-CS).

Patients and methods: 1143 CS patients entered into the ERCUSYN database from 57 centers in 26 countries. Sixty-nine percent had PIT-CS, 25% adrenal-dependent CS (ADR-CS), 5% CS from an ectopic source (ECT-CS) and 1% were classified as having CS from other causes (OTH-CS).

Results: Twenty per cent of patients took PMT. ECT-CS and PIT-CS were more likely to receive PMT compared to ADR-CS ($P<0.001$). Most commonly used drugs were ketoconazole (62%), metyrapone (16%) and a combination of both (12%). Median (interquartile range) duration of PMT was 109 (98) days. PIT-CS patients treated with PMT had more severe clinical features at diagnosis and poorer quality of life compared to those undergoing primary surgery (SX) ($P<0.05$). Within 7 days of surgery, PIT-CS patients treated with PMT were more likely to have normal cortisol

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($P < 0.01$) and a lower remission rate ($P < 0.01$). Within 6 months of surgery, no differences in morbidity or remission rates were observed between SX and PMT groups.
Conclusions: PMT may confound the interpretation of immediate postoperative outcome. Follow-up is recommended to definitely evaluate surgical results.

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Introduction

Surgery is the first-line treatment in patients with Cushing's syndrome (CS), but preoperative medical therapy (PMT) is often given, in order to control cortisol excess and correct severe comorbidities prior to the surgical procedure (1, 2). PMT may also be used in those centers where, for any reasons (e.g. long waiting time for surgery, limited availability of a specialized surgeon, etc.), surgical intervention cannot be performed soon after diagnosis of CS (2).

It has been hypothesized that patients with Cushing's disease (CD) preoperatively treated with adrenal-directed medications (i.e. steroidogenesis inhibitors) might have a lower risk of intraoperative bleeding, and therefore, a better surgical outcome but no firm data confirm this hypothesis (1, 3). Clinical observation suggests that PMT may protect CD patients from the occurrence of hypoadrenalism in the immediate postsurgical period, an important information that is actually considered as the gold standard to diagnose remission of the disease (4, 5). However, PMT may also confound the correct interpretation of outcome early after transsphenoidal surgery due to the 'de-repression' of the normal corticotroph cells in the remaining pituitary gland (4, 6). As a matter of fact, data on the potential, beneficial impact of PMT on perioperative morbidity and the immediate surgical and long-term outcomes in CD patients are scant and inconclusive (3, 7, 8).

The ERCUSYN is the largest prospective database existing to date which collects information on diagnosis, management and long-term follow-up in CS (9). Because ERCUSYN includes data from 57 centers in 26 European countries, it reflects the 'real-life' clinical practice and allows ascertaining whether and how PMT is used before surgery across Europe.

The aims of this study where to (1) evaluate the prevalence of preoperative medical treatment (PMT) in CS patients throughout Europe; (2) determine any differences in preoperative characteristics of patients who receive PMT and those who undergo surgery directly (SX) and (3) determine if PMT influences postoperative outcome in patients with pituitary-dependent CS (PIT-CS).

Patients and methods

Description of the database

One-thousand three hundred forty-one patients with Cushing's syndrome (CS), included into the ERCUSYN database between January 1, 2000 and January 31, 2016, were analyzed (10). Patients were classified into four major groups: pituitary-dependent CS (PIT-CS), adrenal-dependent (ADR-CS; adrenal adenoma), CS from an ectopic source (ECT-CS) and CS from other etiologies (OTH-CS).

A detailed description of the database layout has been provided elsewhere (9). This study has interrogated data entered in the 'Diagnosis', 'Therapy' and 'First follow-up visit' sections.

The 'Diagnosis' section contains information at diagnosis: baseline demographic and anthropometric characteristics, etiology of CS and diagnosis date, delay between onset of symptoms and final diagnosis of CS, other specialists consulted for Cushing's symptoms before correct diagnosis, clinical features, comorbidities, bone status and two questionnaires on quality of life (CushingQoL and EuroQoL-5D). It also contains a subsection comprising diagnostic tests; for each of them, hormone concentrations, units and diagnostic interpretation ('supporting' or 'not supporting' the diagnosis) is required.

The 'Therapies' section includes specific information on any treatment received (medical, surgery, radiotherapy). In the 'medical treatment' section, participants are asked to enter information on any medication specifically used to treat hypercortisolism before surgery, including ketoconazole, metyrapone, cabergoline, mitotane, mifepristone, etomidate and aminogluthetimide. Starting and final date of medical treatment as well as starting and final dose of each drug is also required.

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The 'Surgery' section contains information on date and type of procedure, histology report and the clinical/biochemical outcome in the immediate, postoperative period. In particular, participants are requested to indicate, when available, the clinical status early (within 7 days) after surgery, by choosing between the options 'no benefit' or 'cure/remission'. Parameters on which outcome judgment was made were also asked for, namely 'serum/urine cortisol' ('low', 'normal', 'high'), 'clinical improvement' ('yes', 'no') and 'need for glucocorticoids' ('yes', 'no'). 'Low' cortisol levels refer to those values, which are below the lowest limit of the normal range on the assay used in each center. 'Normal' cortisol levels refer to values within the normal range. 'Clinical improvement' refers to recovery characteristics early – within the first week – after surgery (subjective well-being of patients, and prevalence of perioperative morbidity). The 'Follow-up visit' section contains several biochemical testing, including morning serum cortisol and overnight 1-mg dexamethasone suppression test (DST). Centers are asked to provide information on both the value of hormone measurement and its diagnostic interpretation, i.e., 'low', 'normal', 'high', according to whether the value is below, within or above the normal range of the assay used in each center. In this study, the cut-offs of 5 µg/dL (138 nmol/L) has been used for both morning serum cortisol and serum cortisol after an overnight DST (5).

Glucocorticoid replacement was withdrawn at least 24 h prior to cortisol evaluation at any time points. The patient's surgical outcome ('active hypercortisolism' or 'remission/cure') assessed at first visit after surgery is also collected. 'First visit after surgery' refers to the first visit performed after 7 and up to 180 days after surgical intervention (7, 11). In this time frame, patients did not receive any additional treatment for CS. Comorbidities are also collected, including hypertension, thromboembolism, hypopituitarism, dyslipidaemia, diabetes mellitus, cardiovascular diseases, osteoporosis, fractures and depression.

If a specific item is not available, participants are asked to select 'not answered' (i.e. when information was missing) or 'not known' (when a test or clinical evaluation had been performed but results were not available for any reason).

The ERCUSYN study was approved by the ethics committee (CEIC) of the Hospital Sant Pau, Barcelona, Spain, which is the coordinating center. In addition, the local ethics committee approval was obtained for each participating institution and all patients gave their written informed consent, depending on national legal requirements.

All the data reported into the system were carefully monitored for inconsistencies, queried when necessary and validated before statistical analysis.

Statistical analysis

SPSS for Windows, version 22.0 (SPSS) was used to perform data analysis. Data on blood pressure and QoL scores are expressed as mean ± S.D., all the other values, not normally distributed, are expressed as median (interquartile range, IQR). Comparison between two groups was carried out using the Mann–Whitney's *U* test or the Student's *t*-test (depending on data distribution) for quantitative variables, and the χ^2 for categorical variables. The diagnostic performance of the tests was compared calculating the likelihood ratio from contingency tables; significance was identified using the adjusted residual. Stepwise logistic regression was used to identify clinical variables and type of treatment – PMT or SX – that might predict cortisol levels and outcome in the immediate – 7 days – postoperative period as well as at first postoperative visit within 180 days of surgery, in PIT-CS patients. Statistical significance was defined as a two-tailed P value <0.05.

Results

General characteristics of the overall population

Of 1341 patients included, 904 (67%) had PIT-CS, 335 (25%) had ADR-CS, 80 (6%) had ECT-CS and 22 (2%) had OTH-CS. Specific etiologic information has been described in detail elsewhere (10). Briefly, 79% of patients were women, median age was 44 years (IQR, 21 years), and median time elapsed from clinical onset to diagnosis was 2 years (IQR, 3 years) (10).

First-line treatment

Of 1341 patients included, 1143 had information available on treatment (85%). Eight hundred and ninety-three (78%) underwent surgery without receiving prior medical treatment (SX group), while 226 (20%) took presurgical medical treatment (PMT group). Twenty-four (2%) additional patients received medical treatment only, without subsequent intervention and, therefore, were excluded from the analysis. Distribution of each modality of treatment according to CS etiology is shown in Table 1.

ADR-CS patients were more likely to undergo surgery as a first-line treatment in comparison to both PIT-CS and

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Table 1 Distribution of treatment modalities based on CS etiology.

Treatment group	PIT-CS	ADR-CS	ECT-CS	OTH-CS	Overall
Only surgery (SX)	583 (74)	262 (93)*	33 (56)	15 (94)	893 (78)
Presurgical medical treatment (PMT)	184 (23)**	19 (7)	22 (37)**	1 (6)	226 (20)
Only medical treatment (MT)	20 (3)	0	4 (7)*	0	24 (2)
Overall	787	281	59	16	1143

Percentages are shown in parenthesis.
*$P<0.001$ vs PIT-CS and ECT-CS; **$P<0.001$ vs ADR-CS.
ADR-CS, adrenal-dependent CS; CS, Cushing's syndrome; ECT-CS, CS from an ectopic source; OTH-CS, CS from other etiologies; PIT-CS, pituitary-dependent CS.

ECT-CS (262/281 (93%) for ADR-CS vs 583/787 (74%) for PIT-CS and 33/59 (56%) for ECT-CS; $P<0.001$). Both PIT-CS (184/787 (23%) and ECT-CS patients (22/59 (37%)) were more likely to receive PMT compared to ADR-CS (19/281 (7%); $P<0.001$) (Table 1). Countries where PMT was more frequently used in PIT-CS patients were the Netherlands (52%), Spain (41%), UK (39%), Russia (27%) and France (15%).

Characteristics of PMT: type, dose and duration

Two hundred and twenty-six CS patients (20%) were treated with PMT. Data on dose and duration of each treatment modalities are shown in Table 2. Most patients (142/226 (63%)) were preoperatively treated with KTZ alone, of whom 80% were PIT-CS, 11% ECT-CS and 9% ADR-CS. MTP alone was administered to 36 patients (16%), of whom 85% had PIT-CS, 9% ADR-CS and 6% ECT-CS. All 14 (6%) patients taking CAB had PIT-CS. MIF was taken by five patients, 4 with ECT-CS and 1 with PIT-CS.

The combination of KTZ and MTP was used in 28 (12%) patients, of whom 82% had PIT-CS, 11% ADR-CS and 7% ECT-CS. Combination of KTZ and CAB was administered to 12 (5%) patients, most with PIT-CS (92%). The combination of KTZ and MIF was taken by 5 patients, 3 with PIT-CS and 2 with ECT-CS. Combination of KTZ and either mitotane or aminoglutethimide was used in 2 PIT-CS patients. CAB or mitotane was added to a combination of KTZ and MTP in 2 PIT-CS patients.

Median (IQR) duration of PMT was 107 (98) days. No differences in maximum dose, mean dose and duration of treatment for any of the medications were found between the etiologic groups.

Preoperative characteristics

PIT-CS patients who received PMT had worse baseline clinical features as compared with those in the SX group (Fig. 1). In particular, the PMT group had higher mean (±S.D.) systolic and diastolic blood pressure than the SX group (145±21 vs 139±21 mmHg for systolic, $P=0.001$; 90±15 vs 86±14 mmHg for diastolic, $P=0.002$) (Fig. 1A). Prevalence of some hypercortisolism-related characteristics was greater in the PMT than in the SX group, including skin alterations (easy bruising, purple striae) (145/173 (84%)

Table 2 Type and dose of medications (single or in combination), and duration of medical treatment in 226 patients treated prior to surgery.

Type	*n* (%)	Maximum dose (mg/day)*	Mean dose (mg/day)*	Duration (days)	CUD (g)**
Single medication					
KTZ	142 (63)	600 (200)	600 (200)	97 (82)	51 (64)
MTP	36 (16)	1250 (1250)	1062 (917)	114 (129)	104 (195)
CAB	14 (6)	1 (0.65)	0.8 (0.5)	109 (193)	96 (224)
MIF	5 (2)	600 (100)	600 (100)	42 (188)	34 (112)
Combined medication					
KTZ+MTP	28 (12)	KTZ 600 (400) MTP 1500 (1250)	KTZ 600 (275) MTP 1453 (750)	KTZ 88 (145) MTP 101 (200)	KTZ 37 (82) MTP 126 (204)
KTZ+CAB	12 (5)	KTZ 700 (350) CAB 0.5 (0.5)	KTZ 650 (350) CAB 0.5 (0.5)	KTZ 113 (258) CAB 93 (54)	KTZ 43 (157) CAB 47 (146)
KTZ+MIF	5 (2)	KTZ 800 (400) MIF 400 (200)	KTZ 800 (400) MIF 400 (100)	KTZ 109 (311) MIF 35 (373)	KTZ 108 (243) MIF 14 (221)

Doses and duration are shown as median (interquartile range, IQR).
*Dose for cabergoline (CAB) is expressed as mg/week; **CUD for CAB is expressed as mg.
CAB, cabergoline; CUD, cumulative dose; KTZ, ketoconazole; MIF, mifepristone; MTP, metyrapone.

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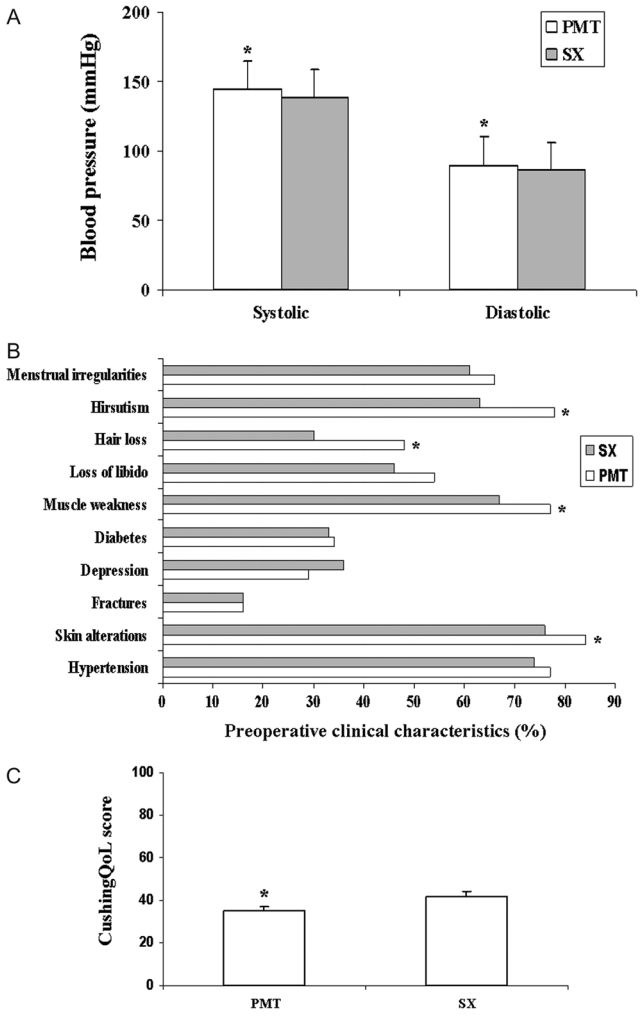

Figure 1

Preoperative clinical characteristics in PIT-CS patients who received presurgical medical treatment (PMT) and PIT-CS patients who were operated on without prior medical therapy (SX). (A) Systolic and diastolic blood pressure in PMT vs SX patients. *$P<0.01$, indicating more elevated systolic and diastolic blood pressure in PMT vs SX (145±21 vs 139±21 mmHg and 90±15 vs 86±14 mmHg, respectively). (B) Clinical features in PMT vs SX patients. *$P<0.05$, indicating greater prevalence of hypercortisolism-related features in PMT as compared with SX. (C) Quality of life (QoL), as measured using the CushingQoL questionnaire, in PMT vs SX patients. *$P=0.035$, indicating worse QoL in PMT than SX (35.6±17.3 vs 42±1, respectively).

vs 412/544 (76%); $P=0.026$), muscle atrophy/weakness (126/163 (77%) vs 331/497 (67%); $P=0.010$), hair loss (in women) (46/96 (48%) vs 100/334 (30%); $P=0.001$) and hirsutism (in women) (92/118 (78%) vs 260/411 (63%); $P=0.003$) (Fig. 1B). Mean (±S.D.) CushingQoL score was also lower in the PMT than the SX group, consistent with poorer quality of life in the former (36±1 vs 42±17, respectively; $P=0.035$) (Fig. 1C).

Table 3 Pituitary imaging in 688 PIT-CS patients receiving either PMT or SX.

MRI finding	PMT ($n=171$)	SX ($n=517$)	*P* value
Not seen	51 (30)	103 (20)	0.031
Microadenoma	84 (57)	295 (49)	0.093
Macroadenoma	36 (23)	119 (21)	0.67

Percentages are expressed in parenthesis.
MRI, magnetic resonance imaging; PMT, preoperative medical therapy; SX, surgery.

Data on pituitary imaging in PMT vs SX patients are shown in Table 3. PMT patients (51 of 171 (30%)) were more likely to have a negative MRI compared to SX patients (103 of 517 (20%)) ($P=0.031$).

No differences in the preoperative characteristics were found in the other etiologic groups.

Immediate postoperative evaluation in PIT-CS patients treated with steroidogenesis inhibitors as PMT

In the immediate postoperative period (within 7 days of surgery), 'cure' or 'remission', as defined by the ERCUSYN partners, was more frequently reported in PIT-CS patients who underwent SX as the only treatment as compared with patients who took steroidogenesis inhibitors (ketoconazole, metyrapone, mitotane) (344/459 (75%) vs 108/176 (61%); $P=0.003$). Patients who received SX were more likely to be classified as being in remission as compared with those who took PMT (OR 1.86 (95% CI 1.16–2.96); $P=0.009$). This significance remained after adjusting for preoperative features (skin alterations and muscle weakness), adenoma size, visualization of a pituitary adenoma on MRI and histology confirmation of an adenoma ($P=0.046$).

As expected, PIT-CS patients who received PMT were more frequently reported to have cortisol levels within the 'normal' range as compared with the SX group (40/176 (23%) vs 56/448 (13%); $P=0.006$). On the other hand, low or undetectable cortisol levels were more frequently reported in SX patients as compared with PMT patients (307/448 (69%) vs 106/176 (60%); $P=0.010$).

SX patients were more likely to have low/undetectable cortisol levels early after surgery compared to the PMT group (OR 0.48 (95% CI 0.30–0.76); $P=0.002$). This significance remained after adjusting for preoperative features (skin alterations and muscle weakness), adenoma

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size, visualization of a pituitary adenoma on MRI and histology confirmation of an adenoma ($P=0.017$).

Postoperative clinical improvement was more frequently reported in SX than in PMT patients (351/423 (83%) vs 123/161 (76%) ($P=0.040$)).

First postoperative evaluation within 180 days of surgery in PIT-CS patients treated with steroidogenesis inhibitors as PMT

The first postoperative visit after discharge from the hospital (>7 days after surgery) was performed within the selected period of 180 days in 723 patients. Mean (±S.D.) time for this visit was 96.3±84.2 days. In comparison to the observations within the first week after surgery, no difference in the prevalence of remission was found between SX (508/548 (93%)) and PMT (156/174 (90%)) patients; $P=0.21$. Prevalence of cortisol elevation above 5 µg/dL (138 nmol/L) after overnight 1-mg DST was slightly greater in the PMT than in the SX (19/30 (63%) vs 21/72 (29%); $P=0.048$). When the cut-off of 1.8 µg/dL (50 nmol/L) was evaluated, no differences in the responsiveness of cortisol were observed between the two groups.

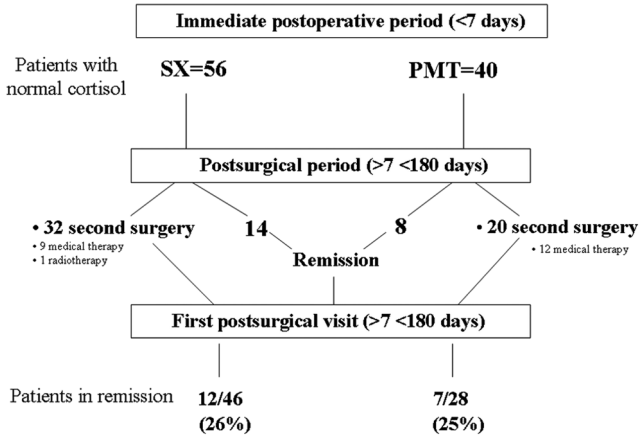

Figure 2

Outcome in 96 patients who had 'normal' cortisol levels in the immediate postoperative period (<7 days), within 180 postsurgical days. SX, surgery; PMT, preoperative medical treatment. To calculate the remission rate in each group, patients who underwent second-line medical therapy or radiotherapy (10 patients in the SX and 12 in the PMT group) were excluded. No differences were found in the rate of patients who underwent further treatment as well as in the remission rate between SX and PMT group ($P=0.27$ and $P=0.81$, respectively).

No differences in the prevalence of postsurgical morbidities, including thromboembolism and hypopituitarism, were observed at first post-discharge evaluation, between the PMT and SX groups.

When patients with normal cortisol levels immediately after the intervention were analyzed, 42 of 56 (75%)in the SX group vs 32 of 40 (80%) PMT patients ($P=0.27$) received further treatment within 180 postoperative days. Remission rate at first postsurgical visit was similar in both groups (26% for SX vs 25% for PMT; $P=0.81$) (Fig. 2).

Relationship between dose or duration of PMT and immediate postoperative outcome

A relationship between dose/duration of PMT and postoperative outcome could only be found for MTP. Thirty-six PIT-CS patients were treated with MTP alone and twenty-eight with MTP in combination with other drugs.

Median (IQR) cumulative dose (CUD) of MTP was significantly greater in patients with cortisol levels within the normal range ($n=21$ with data available) as compared with those having hypocortisolism ($n=29$) in the immediate postoperative period (223 (269) vs 72 (141) g; $P=0.017$). Similarly, patients classified as being surgical failures ($n=18$) received greater CUD of MTP as compared with those in remission ($n=34$) (223 (210) vs 95 (138) g; $P=0.026$), which might be a reflection of more severe disease.

Perioperative mortality

In the whole series, perioperative mortality (within one month of surgery) was not different in SX as compared with PMT group. Of 7 patients who died within one month of surgery, 4 (57%) received SX as a first-line treatment and the remaining three (43%) took PMT ($P=0.29$).

Discussion

These ERCUSYN data show that in Europe, one out of every five patients with Cushing's syndrome (CS) undergoes preoperative administration of steroidogenesis inhibitors prior to surgery (mostly ketoconazole, metyrapone or a combination of both) and, to a lesser extent, dopamine agonists (e.g. cabergoline) and glucocorticoid receptor antagonists (e.g. mifepristone). However, use varies in different countries, ranging from 52% in The Netherlands to no use in nine countries and depending on the underlying cause, being more frequently prescribed in

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patients with an ectopic (ECT-CS) (37%) or pituitary source (PIT-CS) (23%), than in ADR-CS (7%). Patients with more florid hypercortisolism at diagnosis and proteocatabolic signs, such as muscle atrophy and skin alterations, and more impaired quality of life, were more likely to receive PMT than those with a less aggressive clinical presentation. Thus, although we cannot exclude that some clinicians were prompted to use PMT due to long waiting time for surgery in their own center, our results suggest that most ERCUSYN participants tended to pretreat those patients with more severe hypercortisolism, attempting to control their comorbidities before undergoing the intervention.

Up to now, there is little evidence that PMT affects postsurgical outcome. On the one hand, those who defend its use argue that if hypercortisolism is treated, it will improve comorbidities and the patient's clinical condition, especially in severe disease, so that surgery is performed in more favorable conditions, potentially lowering the risk of perioperative complications (3, 6, 8, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21).

On the other hand, immediate evaluation in the first week after surgery to identify whether a patient is 'cured/in remission', as suggested in some guidelines (5), may be affected by PMT. Compared to patients who go directly to surgery, which remains the first-choice therapeutic option to quickly correct cortisol excess in CS (5), in PMT patients, clinical/biochemical improvements will more frequently have begun before surgery, so changes that take place in the first week after surgery may be less dramatic. This seems to be the case, since patients who underwent surgery without taking PMT were more likely to be classified as being 'in remission', compared to those who took PMT, in whom further clinical improvement was less evident in the immediate postoperative period. In fact, the PMT group was more likely to have 'normal' cortisol levels in the first week after adenoma resection than their counterparts treated with surgery as a first-line therapy. For the first time, this finding supports the hypothesis that PMT may protect from cortisol suppression in the immediate postoperative period (4). Based on clinical observations, it has been suggested that a sustained cortisol normalization induced by steroidogenesis inhibitors in the preoperative period may 'de-repress' the healthy corticotroph cells in the pituitary (whose function is suppressed by longstanding hypercortisolism), thus avoiding hypoadrenalism early after surgery (4). A few, small studies have been published to date on this topic, mostly retrospective, showing similar cortisol levels in the immediate postsurgical period, between patients who reached eucortisolism after PMT with steroidogenesis inhibitors and those who did not (7, 8, 22). Conversely, one report described postoperative cortisol suppression in 13 patients who had achieved eucortisolism after PMT, raising the hypothesis that pretreatment with adrenal-blocking agents may ameliorate intraoperative conditions (e.g. reduced bleeding), facilitating total adenoma resection and postoperative ACTH deficiency (3).

Additionally, postoperative 'normalization' of cortisol is generally considered a marker of persistent disease and a solid predictor of possible recurrence, although there is not widespread agreement on this point (22, 23, 24, 25, 26, 27). Although it is likely that most of the ERCUSYN participants relied upon the occurrence of hypoadrenalism to define early remission, establishing it with certainty is not possible due to the lack of a unique, standardized method for cortisol measurement throughout the centers. However, we have found that both 'normal' cortisol levels and a lower rate of early remission within 7 days of surgery, as described qualitatively, are associated with the administration of PMT with steroidogenesis inhibitors in PIT-CS, regardless of factors previously associated with surgical outcome, including adenoma size, visualization of a pituitary adenoma on MRI and histology confirmation (22, 28, 29, 30).

Of note, lack of visualization of an adenoma was more frequently reported in PIT-CS patients who received PMT as compared with those who were primarily operated on. This suggests that, in some cases, cortisol-lowering drugs have been offered within a 'wait and see' approach, when a successful resection of a nonvisible ACTH-secreting pituitary tumor was considered difficult to achieve early after the diagnosis of hypercortisolism (29). However, time interval between diagnosis of cortisol excess and surgery was similar between the two groups, indicating that starting PMT did not 'delay' the intervention in the ERCUSYN PIT-CS patients.

Clearly, PMT is highly recommendable in cases of an occult ectopic source of ACTH, in order to treat acute and potentially life-threatening morbidities associated with severe hypercortisolism (5, 31, 32); nevertheless, similar baseline clinical characteristics and visualization rate of an ectopic tumor in ECT-CS taking PMT vs those who underwent primary surgery were observed, possibly due to the limited sample size of ERCUSYN patients with this etiology.

It is reassuring, however, and demonstrated for the first time, that at first postoperative visit within 6 months of surgery, no differences were observed between the PMT and direct SX groups, as far as prevalence of postsurgical morbidities or remission rates. Moreover, thromboembolism

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was not more frequent in ERCUSYN patients with early postsurgical hypoadrenalism as compared with those having normal cortisol; these results are in line with previous observation that short-term medical therapy leading to biochemical remission does not improve the hypercoagulable state in CD patients (33). However, prevalence of thromboembolism may be underestimated in the ERCUSYN, depending upon intercentre differences in the monitoring strategy of postsurgical complications and different preventive protocols.

Clearly, many factors might influence this later postoperative outcome in PIT-CS patients, such as tumor size, invasion of local tissues, surgeon's expertise, disease duration and genetic defects, any of which might, in turn, overcome the potential impact of PMT on the occurrence of remission (2). Because cortisol dynamics have been shown to vary widely over the first 6–12 postoperative weeks, potentially leading to delayed stabilization of cortisol levels, later biochemical evaluation is essential to reliably distinguish the ultimate outcome of transsphenoidal surgery (7, 8, 34). Our data demonstrating that PMT is a further confounding factor for the proper interpretation of early surgical outcome in PIT-CS patients has important implications for decisions regarding the timing of additional therapy. In fact, early, detectable levels of postoperative cortisol in PMT patients might be misinterpreted as reflecting surgical failure and prompt some clinicians to refer them for further treatment. Instead, our data clearly support the need for retesting and long-lasting follow-up in all PIT-CS patients undergoing TSS.

The ERCUSYN design does capture information on changes of cortisol levels in patients taking PMT, and so, we could not assess the efficacy of this therapeutic approach and quantify how many patients achieved presurgical eucortisolism with PMT. Previous studies reported that rate of control of hypercortisolism ranges from 45% to 93% in CS patients taking KTZ (3, 8, 13, 16, 18), and from 35% to 72% in those treated with MTP (3, 8, 15, 21), depending on the assays used to define cortisol normalization, the maximum dose reached and genetically based differences in the individual responsiveness to these agents (35). Combination of both medications was reported to correct hypercortisolism in 45% of patients (8).

Limitations of this study include lack of both quantitative data and standardized methods to assess both presurgical and immediate postoperative biochemical status. This is due to both intra- and inter-centre differences in the assays used and lack of information on the normal range for each of them. Another limitation, which strictly pertains to the multicentric nature of ERCUSYN, is the heterogeneity in both the indications to use PMT and surgical success rate among the centers. While this may bias the results, it may also increase their external validity, allowing to generalize the conclusions and reflect real-life practice. Large, prospective, single-center studies should be performed to confirm the robustness of our data. In addition, ERCUSYN does not provide information on the safety of medications used as PMT or the effectiveness of such an approach to adequately reduce cortisol levels. Finally, variable time interval from surgery to first postoperative assessment among patients may have limited the detection of postoperative morbidity.

In conclusion, our study on 1143 CS patients entered in the ERCUSYN database has shown that cortisol-lowering medications are used, as a first-line treatment, in 20% of patients across Europe. Use of adrenal-blocking agents prior to pituitary surgery is independently associated with higher rate of cortisol 'normalization' and lower probability of hypoadrenalism, and consequently lower immediate postoperative identification of remission, compared to patients who go directly to surgery. Thus, caution is warranted when interpreting immediate postoperative status of PMT patients. However, at first postoperative visit within 6 months of surgery, no differences in remission rates or morbidities were seen between PMT and SX patients. Thus, benefits of preoperative improvements of hypercortisolism and consequent comorbidities attained by PMT, that are still to be evaluated, have to be confronted with the desire of immediate postoperative assessment as a prognostic marker of patients' longer term outcome, as suggested in current guidelines (5). However, long-term follow-up and repeated testing are still necessary in all patients, treated or not with PMT, in order to detect recurrences and conclusively establish surgical outcome and the most adequate long-term management strategy for each individual patient. A randomized trial assessing simple endpoints, such as length of hospital stay, surgical impression and adverse effects of surgery, is needed to conclusively demonstrate that PMT is a valid option in patients waiting for surgical correction of hypercortisolism.

Declaration of interest

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that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

1 Feelders RA & Hofland LJ. Medical treatment of Cushing's disease. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 425–438. (https://doi.org/10.1210/jc.2012-3126)

2 Pivonello R, De Leo M, Cozzolino A & Colao A. The treatment of Cushing's disease. *Endocrine Review* 2015 **36** 386–486.

3 van den Bosch OF, Stades AM & Zelissen PM. Increased long-term remission after adequate medical cortisol suppression therapy as presurgical treatment in Cushing's disease. *Clinical Endocrinology* 2014 **80** 184–190. (https://doi.org/10.1111/cen.12286)

4 Biller BMK, Grossman AB, Stewart PM, Melmed S, Bertagna X, Bertherat J, Buchfelder M, Colao A, Hermus AR, Hofland LJ *et al*. Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 2454–2462. (https://doi.org/10.1210/jc.2007-2734)

5 Nieman LK, Biller BMK, Findling JW, Murad MH, Newell-Price J, Savage MO & Tabarin A. Treatment of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism* 2015 **100** 2807–2831. (https://doi.org/10.1210/jc.2015-1818)

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6 Castinetti F, Guignat L, Giraud P, Muller M, Kamenicky P, Drui D, Caron P, Luca F, Donadille B, Vantyghem MC *et al*. Ketoconazole in Cushing's disease: is it worth a try? *Journal of Clinical Endocrinology and Metabolism* 2014 **99** 1623–1630. (https://doi.org/10.1210/jc.2013-3628)

7 Pereira AM, van Aken MO, van Dulken H, Schutte PJ, Biermasz NR, Smit JW, Roelfsema F & Romijn JA. Long-term predictive value of postsurgical cortisol concentrations for cure and risk of recurrence in Cushing's disease. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 5858–5864.

8 Valassi E, Crespo I, Gich I, Rodriguez J & Webb SM. A reappraisal of the medical therapy with steroidogenesis inhibitors in Cushing's syndrome. *Clinical Endocrinology* 2012 **77** 735–742. (https://doi.org/10.1111/j.1365-2265.2012.04424.x)

9 Valassi E, Santos A, Yaneva M, Toth M, Strasburger CJ, Chanson P, Wass JA, Chabre O, Pfeifer M, Feelders RA *et al*. The European Registry on Cushing's syndrome: 2-year experience. Baseline demographic and clinical characteristics. *European Journal of Endocrinology* 2011 **165** 383–392. (https://doi.org/10.1530/EJE-11-0272)

10 Valassi E, Franz H, Brue T, Feelders RA, Netea-Maier R, Tsagarakis S, Webb SM, Yaneva M, Reincke M, Droste M *et al*. Diagnostic tests for Cushing's syndrome differ from published guidelines: data from ERCUSYN. *European Journal of Endocrinology* 2017 **176** 613–624.

11 Valassi E, Biller BMK, Swearingen B, Pecori-Giraldi F, Losa M, Mortini P, Hayden D, Cavagnini F & Klibanski A. Delayed remission after transsphenoidal surgery in patients with Cushing's disease. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 601–610.

12 Jeffcoat WJ, Rees LH, Tomlin S, Jones AE, Edwards CRW & Besser GM. Metyrapone in long-term management of Cushing's disease. *BMJ* 1977 **ii** 215–217. (https://doi.org/10.1136/bmj.2.6081.215)

13 Loli P, Berselli ME & Tagliaferri M. Use of ketoconazole in the treatment of Cushing's syndrome. *Journal of Clinical Endocrinology and metabolism* 1986 **63** 1365–1371. (https://doi.org/10.1210/jcem-63-6-1365)

14 Tabarin A, Navarranne A, Guerin J, Corcuff JB, Parneix M & Roger P. Use of ketoconazole in the treatment of Cushing's disease and ectopic ACTH syndrome. *Clinical Endocrinology* 1991 **34** 63–69. (https://doi.org/10.1111/j.1365-2265.1991.tb01737.x)

15 Verhelst JA, Trainer PJ, Howlett TA, Perry L, Rees LH, Grossman AB, Wass JA & Besser GM. Short and long-term responses to metyrapone in the medical management of 91 patients with Cushing's syndrome. *Clinical Endocrinology* 1991 **35** 169–178. (https://doi.org/10.1111/j.1365-2265.1991.tb03517.x)

16 Sonino N, Boscaro M, Paoletta A, Mantero F & Ziliotto D. Ketoconazole treatment in Cushing's syndrome: experience in 34 patients. *Clinical Endocrinology* 1999 **35** 347–352. (https://doi.org/10.1111/j.1365-2265.1991.tb03547.x)

17 Moncet D, Morando DJ, Pitoia F, Katz SB, Rossi MA & Bruno OD. Ketoconazole therapy: an efficacious alternative to achieve eucortisolism in patients with Cushing's syndrome. *Medicina* 2007 **67** 26–31.

18 Castinetti F, Morange I, Jaquet P, Conte-Devolx B & Brue T. Ketoconazole revisited: a preoperative or postoperative treatment in Cushing's disease. *European Journal of Endocrinology* 2008 **158** 91–99. (https://doi.org/10.1530/EJE-07-0514)

19 Godbaut A, Manavela M, Danilowicz K, Beauregard H, Bruno OD & Lacroix A. Cabergoline monotherapy in the long-term treatment of Cushing's disease. *European Journal of Endocrinology* 2010 **163** 709–716. (https://doi.org/10.1530/EJE-10-0382)

20 Baudry C, Coste J, Bou Khalil R, Silvera S, Guignat L, Guibourdenche J, Abbas H, Legmann P, Pertagna X & Bertherat J. Efficiency and tolerance of mitotane in Cushing's disease in 76 patients from a single center. *European Journal of Endocrinology* 2012 **167** 473–481. (https://doi.org/10.1530/EJE-12-0358)

21 Daniel E, Aylwin S, Mustafa O, Ball S, Munir A, Boelaert K, Chortis V, Cuthbertson DJ, Daousi C, Rajeev SP *et al*. Effectiveness of metyrapone in treating Cushing's syndrome: a retrospective multicenter study in 195 patients. *Journal Clinical Endocrinology and Metabolism* 2015 **100** 4146–4154. (https://doi.org/10.1210/jc.2015-2616)

22 Invitti C, Pecori Giraldi F, de Martin M & Cavagnini F. Diagnosis and management of Cushing's syndrome: results of an Italian multicentre study. Study Group of the Italian Society of Endocrinology on the pathophysiology of the hypothalamic-pituitary-adrenal axis. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 440–448.

23 Shimon I, Ram Z, Cohen ZR & Hadani M. Transsphenoidal surgery for Cushing's disease: endocrinological follow-up monitoring of 82 patients. *Neuosurgery* 2002 **51** 57–61. (https://doi.org/10.1097/00006123-200207000-00008)

24 Hammer GD, Tyrrell JB, Lamborn KR, Apllebury CB, Hannegan ET, Bell S, Rahl R, Lu A & Wilson CB. Transsphenoidal microsurgery for Cushing's disease: initial outcome and long-term results. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 6348–6357. (https://doi.org/10.1210/jc.2003-032180)

25 Salenave S, Gatta B, Pecheur S, San-Galli F, Visot A, Lasjuaunias P, Roger P, Berge J, Young J. Tabarin A *et al*. Pituitary magnetic resonance imaging findings do not influence surgical outcome in adrenocortictropin-secreting microadenomas. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 3371–3376. (https://doi.org/10.1210/jc.2003-031908)

26 Atkinson AB, Kennedy A, Wiggam MI, Mc Cance DR & Sheridan B. Long-term remission rates after pituitary surgery for Cushing's disease: the need for long-term surveillance. *Clinical Endocrinology* 2005 **63** 549–559. (https://doi.org/10.1111/j.1365-2265.2005.02380.x)

27 Patil CG, Prevedello DM, Lad SP, Vance ML, Thorner MO, Katznelson L & Laws ER Jr. Late recurrences of Cushing's disease after initial successful transsphenoidal surgery. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 358–362. (https://doi.org/10.1210/jc.2007-2013)

28 Guillhaume B, Bertagna X, Thomsen M, Bricaire C, Vila-Porcile E, Olivier L, Racadot J, Derome P, Laudat MH, Girard F *et al*. Transshenoidal pituitary surgery for the treatment of Cushing's disease: results in 64 patients and long-term follow up studies. *Journal of Clinical Endocrinology and Metabolism* 1988 **66** 1056–1064. (https://doi.org/10.1210/jcem-66-5-1056)

29 Bochicchio D, Losa M & Buchfelder M. Factors influencing the immediate and late outcome of Cushing's disease treated by transsphenoidal surgery: a retrospective study by the European Cushing's disease Survey Group. *Journal of Clinical Endocrinology and Metabolism* 1995 **80** 3114–3120.

30 Rees DA, Hanna FW, Davies JS, Mills RG, Vafidis J & Scanlon MF. Long-term follow-up results of transsphenoidal surgery for Cushing's disease in a single centre using strict criteria for remission. *Clinical Endocrinology* 2002 **56** 541–551. (https://doi.org/10.1046/j.1365-2265.2002.01511.x)

31 Kamenicky P, Droumaguet C, Salenave S, Blanchard A, Jublanc C, Gautier JF, Brailly-Tabard S, Leboulleux S, Schlumberger M, Baudin E *et al*. Mitotane, metyrapone and ketoconazole combination therapy as an alternative to rescue adrenalectomy for severe ACTH-dependent Cushing's syndrome. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 1–9.

32 Corcuff JB, Young J, Masquefa-Giraud P, Chanson P, Baudin E & Tabarin A. Rapid control of severe neoplastic hypercortisolism with metyrapone and ketoconazole. *European Journal of Endocrinology* 2015 **172** 473–481. (https://doi.org/10.1530/EJE-14-0913)

33 van der Pas R, de Bruin C, Leebeck FW, de Maat LP, Rijken DC, Pereira AM, Romijn JA, Netea Maier RT, Hermus AR, Zelissen PM

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et al. Incidence of venous thromboembolism in patients with Cushing's syndrome: a multicenter cohort study. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 3525–3532. (https://doi.org/10.1210/jc.2011-1661)

34 Rollin GA, Feereira NP, Junges M, Gross JL & Czepielewski MA. Dynamics of serum cortisol levels after transsphenoidal surgery in a cohort of patients with Cushing's disease. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 1131–1139. (https://doi.org/10.1210/jc.2003-031170)

35 Valassi E, Aulinas A, Glad CAM, Johannsson G, Ragnarsson O & Webb SM. A common genetic variant in the CYP17A1 influences the therapeutic response to steroidogenesis inhibitors in patients with Cushing's syndrome. *Clinical Endocrinology* 2017 **87** 433–439. (https://doi.org/10.1111/cen.13414)

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