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Clinical Research Article

Discontinuation of Drug Treatment in Cushing's Disease Not Cured by Pituitary Surgery

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Abstract

Objective: When transsphenoidal surgery (TSS) does not cure Cushing's disease (CD), 4 treatments are available: drug treatment (DT), second TSS (2nd TSS), bilateral adrenalectomy (BA), and pituitary radiotherapy (PR). DT is attractive but supposes long-term continuation, which we aimed to evaluate.

Design and Methods: Retrospective study, in a center prioritizing 2nd TSS, of 36 patients, including 19 with TSS failure and 17 with recurrence, out of 119 patients with CD treated by a first TSS, average follow-up 6.1 years (95% confidence interval 5.27-6.91). Control was defined as normalization of urinary free cortisol (UFC) and final treatment (FT) as the treatment allowing control at last follow-up. We also analyzed discontinuation rates of DT in published CD prospective clinical trials.

Results: Control was achieved in 33/36 patients (92%). DT was initiated in 29/36 patients (81%), allowing at least 1 normal UFC in 23/29 patients (79%) but was discontinued before last follow-up in 18/29 patients (62%). DT was FT in 11/29 patients (38%), all treated with cortisol synthesis inhibitors. Second TSS was FT in 8/16 (50%), BA in 14/14 (100%), and PR in 0/5. In published trials, discontinuation of DT was 11% to 51% at 1 year and 32% to 74% before 5 years.

Conclusion: DT allowed at least 1 normal UFC in 23/29 patients (79%) but obtained long-term control in only 11/29 (38%), as discontinuation rate was high, although similar to published data. Interestingly, a successful 2nd TSS was the cause for discontinuing efficient and well-tolerated DT in 5 patients. Further studies will show whether different strategies with cortisol synthesis inhibitors may allow for a lower discontinuation rate in patients not candidates for a 2nd TSS so that BA may be avoided in these patients.

Key Words: Cushing's disease, osilodrostat, ketoconazole, metyrapone, pasireotide, cabergoline

Cushing's disease (CD) is the consequence of the development of a pituitary corticotroph adenoma, responsible for hypersecretion of ACTH and cortisol, resulting in high morbidity and mortality. It is widely accepted that the best treatment for CD is removal of the pituitary adenoma: transsphenoidal surgery (TSS) by an expert neurosurgeon allows postoperative remission in 80% to 90% of the patients (1) with a 10% to 20% 10-year recurrence rate (2). TSS is thus the first-line therapy for most patients with CD, including those with a pituitary corticotroph microadenoma that remains invisible at magnetic resonance imaging (MRI) but whose existence is proved by bilateral inferior petrosal sampling (3). Second-line treatments are, however, required for the 10% to 20% patients who are not in remission after a first surgery, as well as for the 15% who develop a recurrence (4). For these patients, there are 4 treatment options: medical treatment using drugs (DT) that target either the secretion of ACTH by the pituitary adenoma or the synthesis of cortisol by the adrenal; a second TSS (2nd TSS); bilateral adrenalectomy (BA); and pituitary radiotherapy (PR), which has to be combined with another treatment until its efficacy is obtained (5).

Each of these second-line treatments has its own limitations and side effects. A 2nd TSS is possible only if there are good reasons to believe that a pituitary microadenoma that could not be entirely removed by a first TSS can still be removed by a second pituitary surgery, and 2nd TSS exposes the patient to the risk of pituitary insufficiency and other complications of pituitary surgery (1). BA has the great advantage to offer a nearly 100% remission rate of hypercortisolism but at the cost of total and permanent adrenal insufficiency, a disease that has its own morbidity and mortality (6). In addition, BA exposes the patient to the risk of developing corticotroph tumor progression (7). PR has a delayed and incomplete efficacy and carries a risk for long-term pituitary insufficiency,

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while the risk for development of meningioma and stroke, probably very low with modern techniques of PR, remains debated (5).

The limitations of 2nd TSS, BA, and PR, and the fact that DT can be rapidly effective and that it is reversible, explain why DT is such an attractive treatment for patients with CD not cured by a first TSS. Indeed, DT has generated a lot of attention in the past years as new drugs have been developed, including pasireotide (8, 9), osilodrostat (10-12), and levoketoconazole (13, 14), while other previously available drugs, such as ketoconazole (15), cabergoline (16), and mitotane (17), benefitted from new large retrospective studies that provided better evaluation of their efficiency. It should, however, be kept in mind that, with the exception of mitotane, which can result in some cases in irreversible adrenal insufficiency, persistence of the efficacy of DT supposes that the treatment be continued indefinitely: long-term control of CD with DT requires that the long-term discontinuation rate of DT be very low. This should put a focus on the discontinuation rates of DT for CD. In retrospective studies, evaluation of long-term discontinuation rates of DT in CD is uncertain, as it is difficult to be sure that there was no omission bias against patients who tried DT but abandoned it. This bias is not present in published prospective studies on different DTs for CD (8-14), where the data on the number of patients who were started on the drug but then abandoned it are available to all.

In the present study, we took advantage of a large monocentric series of 119 patients with CD treated by TSS, which included 36 patients who either were not in remission after TSS (19 patients, remission rate 84%) or recurred after remission (17 patients, recurrence rate 17%), with an average follow-up of 6.1 years in the 119 patients [95% confidence interval (CI) 5.27-6.91] and 6.7 year (95% CI 5.28-8.15, SD 4.41) in the group of 36 patients. We analyzed the different therapeutic strategies used in these 36 patients and their final treatment at last follow-up in order to better understand what can be expected from DT in the long term. We paid special attention to the discontinuation rate of DT in our series and also in published data from clinical trials on CD.

Methods

Patients

The patients' data were extracted from the medical record of patients referred to the Department of Endocrinology of the Grenoble Alpes University Hospital for pituitary surgery for CD between February 1, 2001, and September 30, 2020. Agreement of the National Commission on Informatics and Liberty was obtained through a delegation of the Innovation and Clinical Research Direction of Grenoble Alpes University Hospital ("Research not involving human beings" protocol), allowing the collection of personal and clinical data. In agreement with French law, an information letter was displayed in the Department of Endocrinology and an individual form was available to patients who do not consent to the use of their data. All 126 patients who benefitted from a first pituitary surgery for CD between February 1, 2001 and September 30, 2020, were considered for inclusion, but 7 patients were excluded for the following reasons: in 2 patients with no corticotroph adenoma found at surgery postoperative follow-up was consistent with pseudo Cushing's syndrome; in 2 patients a 2nd TSS was performed but the patients did not have the criteria for recurrence discussed later [they only had an elevated midnight cortisol or abnormal response to desmopressin stimulation but no urinary free cortisol (UFC) elevation]; in 3 patients TSS was performed in Grenoble but they were then followed in another center and it was not possible to obtain their follow-up data.

The 119 patients included in this study were 97 women (81.5%) and 22 men, and average age at TSS was 42.8 years (including 7 children 15, 15, 14, 10, 7, 6, and 6 years old; average age of adults 44.8 years). The follow-up in years (95% CI, SD) of the entire series of 119 patients was 6.1 years (95% CI 5.27-6.91).

As described in Cristante et al (3) and Lefournier et al (18), all patients presented clinical signs of CS. Diagnosis of ACTH-dependent CS was based on elevation of UFC, elevation of midnight salivary cortisol, absence of suppression of cortisol secretion after 1 mg of dexamethasone, and/or loss of cortisol circadian pattern, as well as an unsuppressed or increased ACTH level, as previously described (3). Pituitary origin was assessed by a corticotrophin-releasing hormone test, a desmopressin test, or an 8-mg dexamethasone test, combined with the identification of an adenoma in MRI. When MRI was not conclusive, bilateral inferior petrosal sinus sampling was performed by our neuroradiologists, as described in Lefournier et al (18), and CD diagnosis was established on either dynamic tests and a typical image of adenoma at MRI or a bilateral inferior petrosal sampling ACTH central to periphery gradient >2 or >3 after stimulation by corticotrophin-releasing hormone.

All patients were operated by the same expert neurosurgeon (E.G.) both for their first TSS and, when needed, for their second TSS.

In all patients, the therapeutic choices between DT, 2nd TSS, BA, and PR were made during multidisciplinary meetings of a pituitary team involving endocrinologists, a neurosurgeon, an endocrine surgeon, a radiotherapist. It has to be noted that our pituitary team has a "prioritizing TSS strategy" favouring TSS not only as a first-line therapy for most patients with CD but also as a second-line therapy when it is believed to have significant chances of success. This "prioritizing surgery strategy" does have consequences on the continuation rate of DT as, according to this strategy, a 2nd TSS will be proposed to patients treated by DT even when the patient is controlled by DT and has no intolerance to DT, as long as 2nd TSS is believed to have significant chances of success. Another strategy of this multidisciplinary group, which can be debated, is that PR was performed only in patients where a clear image of remnant/recurrency could be identified at MRI.

The follow-up of patients treated with DT and the choice of the drugs used was made mostly by 1 senior endocrinologist (O.C.).

Definition of Remission

Postoperative remission was defined as described previously in Cristante et al (3) by a serum cortisol level at 8:00 AM < 138 nmol/L (50 µg/L) in the days following pituitary surgery, using the former Endocrine Society guidelines (19) or by a normal UFC 3 months after surgery. We do recognize that both criteria are weak with regards to the recent update to the Endocrine Society Cushing guidelines (20), which now define remission typically as a postoperative cortisol

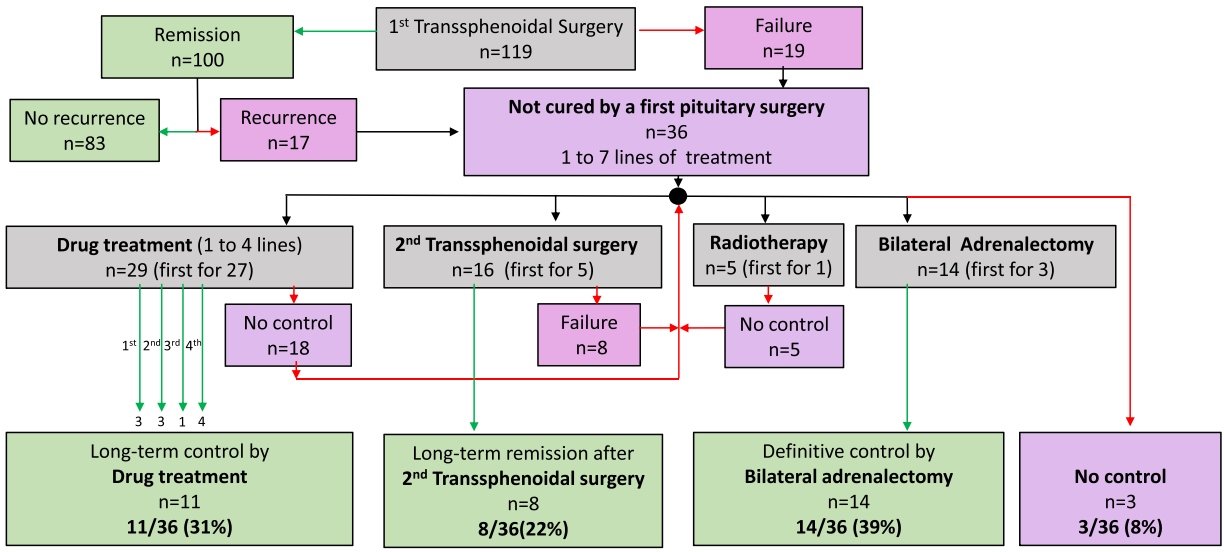

Figure 1. Flow chart of second-line treatments in 36/119 patients with CD not cured by a first TSS. A first TSS in 119 patients with CD resulted in 83 patients on long-term remission, while 19 patients were not in remission and 17 patients recurred. These 36 patients were treated by 1 or several second-line treatments, including drug treatment, second transsphenoidal surgery, bilateral adrenalectomy, or pituitary radiotherapy. Most patients had several consecutive treatments, including several different drug treatments. The red arrows show that in case of failure of a second-line treatment the patient was offered another second-line treatment, and this process could be repeated several times. The green arrows indicate that after 1 or several second-line treatments, the patient was finally controlled. This was not the case for 3 patients, who remained uncontrolled. For drug treatment, the numbers on the left of the green arrows indicate that control was achieved after trial of either a first, second, third, or fourth, while the numbers at the end of the green arrows indicate the number of patients in each of these first, second, third, or fourth drug trials. For each second-line treatment, the number of patients finally controlled is then related to the total number of patients not cured by a first TSS (36 patients).
Abbreviations: CD, Cushing's disease; TSS, transsphenoidal surgery.

<55 nmol/L while noting that occasionally, in specific situations, some patients can achieve remission without marked postoperative hypocortisolism.

Of note, a normal 3-month postoperative UFC does not rule out persistent mild hypercortisolism (a statement that also applies to any normal UFC obtained by DT). A normal 3-month postoperative UFC also does not rule out early recurrence, but, in this study, such recurrencies would be detected during follow-up.

Postoperative Recurrence

Recurrence was defined either as (1) an elevated 24-hour UFC with clinical Cushing syndrome or (2) 2 consecutive elevated 24-hour UFCs. In this latter case, the date for recurrence diagnosis was those of the second UFC.

Treatment Course and Disease Control

Four different treatment strategies were proposed to the patients not cured by a first TSS: DT, PR, 2nd TSS, and BA. Drug treatment used either cortisol synthesis inhibitors (metyrapone, ketoconazole, mitotane, osilodrostat) or drugs inhibiting ACTH secretion from pituitary corticotroph adenomas (cabergoline, pasireotide). When a given treatment strategy was not effective or not tolerated, an alternative treatment strategy was proposed to the patient. For DT, several drugs could be tried subsequently, so that during follow-up any given patient could receive up to 4 different treatment strategies including several drugs. Only 2 patients were treated for some period of time by bitherapy (ketoconazole and metyrapone). Disease control was defined as a normal 24-hour UFC. The final treatment was defined as treatment allowing disease control at last follow-up.

Statistics

Statistical analyses were performed with the RStudio Software (version 4.0.2).

Results

Short-term Control of CD With DT

Figure 1 illustrates the therapeutic course and outcomes of 119 patients with CD who underwent a first TSS in our institution between January 2001 and September 2020, resulting in long-term remission for 83 patients, while 36 patients were not cured by TSS. The follow-up in years of the entire series of 119 patients was 6.1 years (95% CI 5.27-6.91, SD 4.57), whereas the follow-up of the 36 patients not in remission or recurring was 8.50 years (95% CI 6.81-10.18, SD 5.16) and the follow-up of the different treatment groups were 2nd TSS: 8.92 years (95% CI 4.26-13.59, SD 6.73); BA: 10.11 years (95% CI 8.19-12.03, SD 3.66); DT: 7.04 years (95% CI 3.81-10.28, SD 5.41); PR 6.84 years (95% CI 5.02-8.66, SD 2.08); not controlled: 5.17 years (95% CI 0-10.65, SD 4.89).

Interestingly, DT was the treatment most frequently used in our 36 patients, as it was the first treatment initiated in 27 patients (75%), and, overall, 29 patients were treated by DT during follow-up (81%). By comparison, 2nd TSS was the first treatment in only 5 patients, BA in only 3, and PR in only 1 (Fig. 1 and Fig. 2). Most patients treated with DT received more than 1 drug during their follow-up (average 1.96 drug/patient), and, altogether, 23/29 patients treated with DT (79%) achieved control (normal UFC) at least 1 time during follow-up (Table 1, Fig. 2, Fig. 3A and 3B) demonstrating that, at least in the short term, DT is often efficient. Ketoconazole was the treatment most

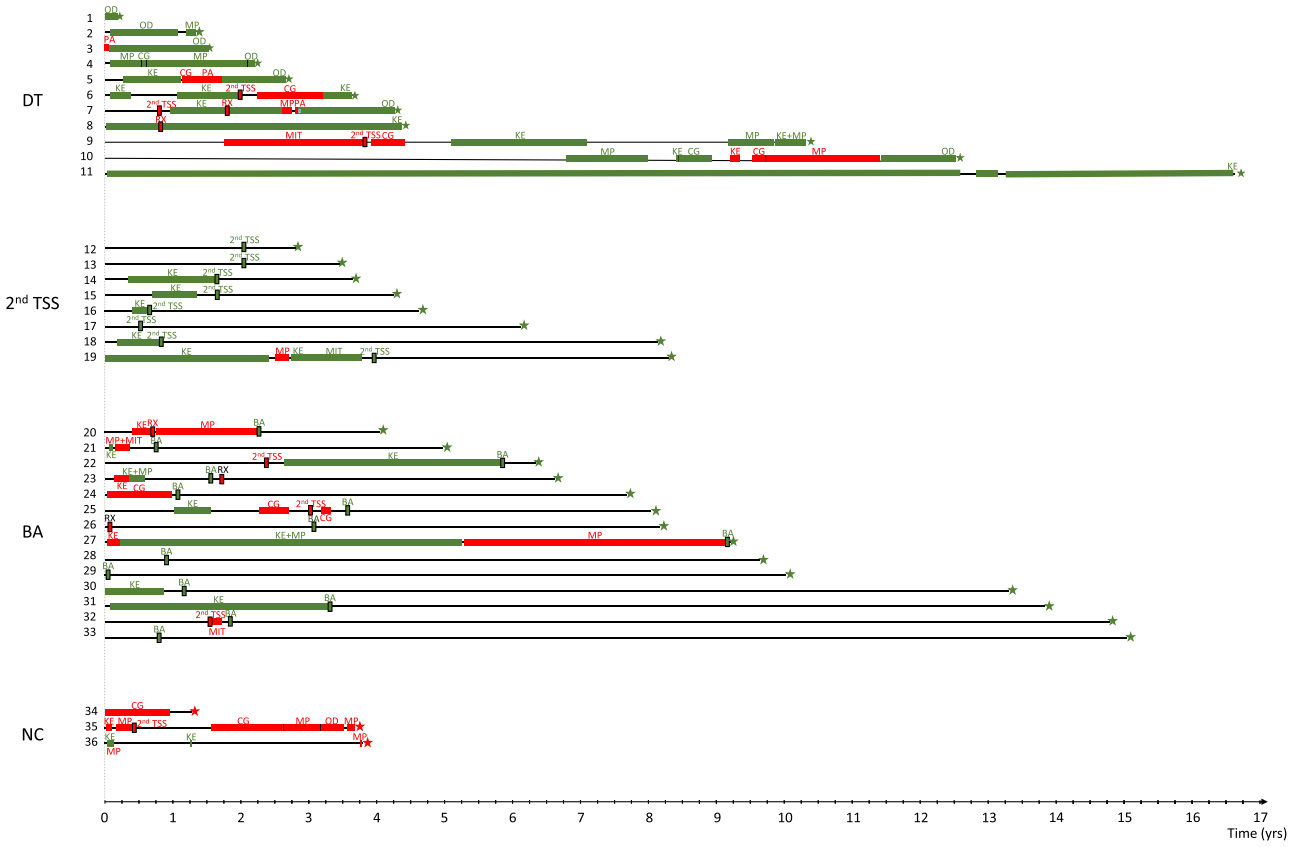

Figure 2. Time course of second-line treatments in patients with CD not cured by a first TSS. The follow-up of each patient is illustrated by an individual line that starts at the date of failure of the first TSS or at the date of recurrence and ends at last follow-up. The color of the line indicates that the patient is receiving a drug treatment that controls hypercortisolism (green line) or a drug treatment that does not control hypercortisolism (red line) or that he is receiving no drug treatment (black line). The color of the star at the end of the line defines whether the patient is controlled (green star) or not (red star). The abbreviation name of the drug treatment is written above the green or red lines. The occurrence of second TSS, BA, and PR are represented by small vertical bars included in the follow-up. The color of the vertical bar indicates whether the treatment was effective (green bar) or not (red bar). Abbreviations: BA, bilateral adrenalectomy; CD, Cushing's disease; CG, cabergoline; DT, drug treatment; KE, ketoconazole; MP, metyrapone; OD, osilodrostat; PA, pasireotide; PR, pituitary radiotherapy; TSS, transsphenoidal surgery.

frequently used, probably as it was perceived to be at least as effective as metyrapone and easier to take (fewer tablets) and for the longest duration (Table 1). Osilodrostat was the treatment most frequently efficient, but its efficacy could be evaluated only for a much shorter duration than ketoconazole, as it became available in France outside clinical trials only in 2019.

Long-term Control of CD With DT

Despite its high short-term efficacy, DT proved to control only 11 patients at last follow-up, who were all treated by cortisol synthesis inhibitors (6 with osilodrostat, 3 with ketoconazole, 1 with metyrapone, 1 with both ketoconazole and metyrapone) (Fig. 2). These 11 patients represent 38% of the 29 patients treated with DT or 30.5% of the 36 patients not cured by pituitary surgery (Fig. 1). Among the 18/29 (62%) patients treated with DT who abandoned DT before last follow-up, 5 were finally controlled by 2nd TSS and 10 by BA and 3 were not controlled at last follow-up. Comparison of Fig. 3A-3B and 3C illustrates how the initially high number of DT treated patients decreased, while the cumulated number of patients with either 2nd TSS or BA increased, as some patients treated with DT were switched to 2nd TSS or BA.

Discontinuation of DT for Lack of Efficiency, Poor Tolerance, or Unavailibility

The main causes for discontinuation of DT were lack of efficiency and/or poor tolerance. Table 1 summarizes the data regarding the choice of drugs, duration of exposure, and causes for discontinuation of the different drugs used in DT, while Fig. 2 presents all individual treatment courses of the patients, including the drugs used, their duration, and their effectiveness.

The main reason for discontinuation of ketoconazole was intolerance, reported in 12/22 (54%) patients (Table 1) for doses ranging from 400 to 1000 mg: cytolysis (elevation of alanine amino transferase or aspartate amino transferase hepatic enzymes at 3 to 8 times the upper limit of the normal range (6 patients), digestive disorders (3 patients), other symptoms (3 patients). Metyrapone was better tolerated but slightly less efficient at the dosage used, and the lack of efficiency was reported in 5 patients (42%) including 3 with overt Cushing's syndrome receiving doses of 2250 and 4000 mg. Metyrapone continuation was also affected by its temporary unavailability due to production issues in France and other countries in 2019. Osilodrostat was both efficient and well tolerated in 6 of the 8 patients who benefitted from this drug (Table 2). It is not possible to compare its long-term

Table 1. Efficacy and tolerance of the different drugs tested in the 29 patients with CD with failure of TSS or recurrence who received at least 1 drug treatment

Treatment	Ca	Pa	Ke	Me	Ke+ Me	Mi	Od	Any drug
n patients treated at least once by drug (% of 29 patients)	9 (31)	3 (10)	22 (76)	12 (41)	2 (7)	3 (10)	8 (28)	29[a] (100)
n patients controlled by drug at end of study (% who used the drug)	0	0	3 (14)	1 (8)	1	0	6 (86)	11 (19)
n patients with treatment stopped for lack of efficacy[b] (% patients with trial of the drug)	8 (89)	3 (100)	4 (18)	5 (42)	0	1 (33)	1 (12)	22 (57)
n patients with treatment stopped for intolerance[b] (% patients with trial of the drug)	1 (11)	0	12 (54)	2 (17)	1	2 (67)	1 (12)	18 (31)
n patients with treatment stopped for unavailibility				4 (33%)				
Duration of exposure (patient × months) (% of total exposure)	71 (7)	6 (0.6)	567 (54)	218 (21)	60 (6)	39 (4)	86 (8)	1047 (100)
Duration of efficacy (patients × months) (% of total exposure)	7 (10)	0	487.6 (86)	30.4 (14)	60 (100)	12.2 (31)	81.6 (95)	679 (65)

Abbreviations: CD, Cushing's disease; Ca, cabergoline; Ke, ketoconazole; Me, metyrapone; Mi, mitoane; Od, osilodrostat; Pa, pasireotide; TSS, transsphenoidal surgery.
[a]Total n patients for any drug is lower than the added n patients in each treatment, as many patients tried more than 1 treatment (average 1.55 drug/patient).
[b]Discontinuation of a treatment could be both for intolerance and for lack of efficacy. Transient discontinuations of a treatment for proven or suspicion of adrenal insufficiency are not counted.

efficacy and tolerance with the other drugs as it had a much shorter duration of exposure. Indeed, in France, it has been made available outside clinical trials only in 2019, when it benefitted from a temporary authorization of use due to the unavailability of metyrapone. Cabergoline and pasireotide were discontinued mainly for poor effectiveness.

Discontinuation of DT Despite Good Biological Efficiency and Tolerance

It should be noted that 4 patients ended with a final treatment other than DT although DT was efficient and well tolerated: patients 14 and 18 did have an efficient and well-tolerated DT but appeared as good candidates for a 2nd TSS, which, in agreement with our therapeutic strategy, was performed and proved successful (Fig. 2). Similarly patient 22 and 31 underwent BA although they were both biochemically controlled by DT, as defined by a normal UFC. For patients 22 and 31, the reason was that they still had clinical signs of CD despite a normal UFC, while patient 31 needed introduction of a cardiological drug that was not compatible with ketoconazole.

Final Treatments of Patients Discontinuing DT

Altogether, in addition to the 11 patients finally controlled by DT, the final treatment was 2nd TSS for 8 patients (which represents 50% of the 16 2nd TSS patients and 22% of the 36 patients with failure of pituitary surgery) and BA for 14 patients (which represents 100% of the BA patients and 39% of the 36 patients with failure of pituitary surgery) (Fig. 1, Fig. 2, Fig. 3C).

The 8 patients with a successful 2nd TSS included 6 patients with a recurrence and 2 patients with a first unsuccessful TSS.

Of the 14 patients treated by BA, there were 7 women of childbearing age who considered having a pregnancy in the future, including 6 women treated by DT prior to BA. The desire of pregnancy of these 7 women did certainly play a role in their decision to undergo BA, as no drug treatment for CD is approved during pregnancy. One could then consider that the inclusion of the 6 women treated by DT and with a desire for pregnancy should introduce a bias in the analysis of the efficiency of DT, as the desire for pregnancy might be a reason to discontinue DT even when it is effective. This is actually not the case, as none of these 6 women had obtained a normal UFC under DT. Of these 7 patients, 3 delivered a baby during follow-up. The 4 other patients did not have a baby, although at least 3 of them tried but failed to conceive (2 proved to have couple infertility conditions unrelated to CD with failure of medically assisted procreation and 1 developed metastatic colon cancer before she could conceive).

Pituitary Radiotherapy

The 5 patients treated by PR all had clear images of remnants or recurrencies. As already mentioned, only 1 patient had PR as a first treatment after failure of pituitary surgery and this patient (patient 26, see Fig. 2) was finally treated by BA. The 4 other PR patients (patients 7, 8, 20, 23; see Fig. 2) were first treated by DT, including 2 patients (patients 7, 8) finally controlled by DT and 2 (patients 20, 23) treated by BA. Altogether, none of the 5 patients treated by PR had their cortisol hypersecretion finally controlled by PR only, but none of

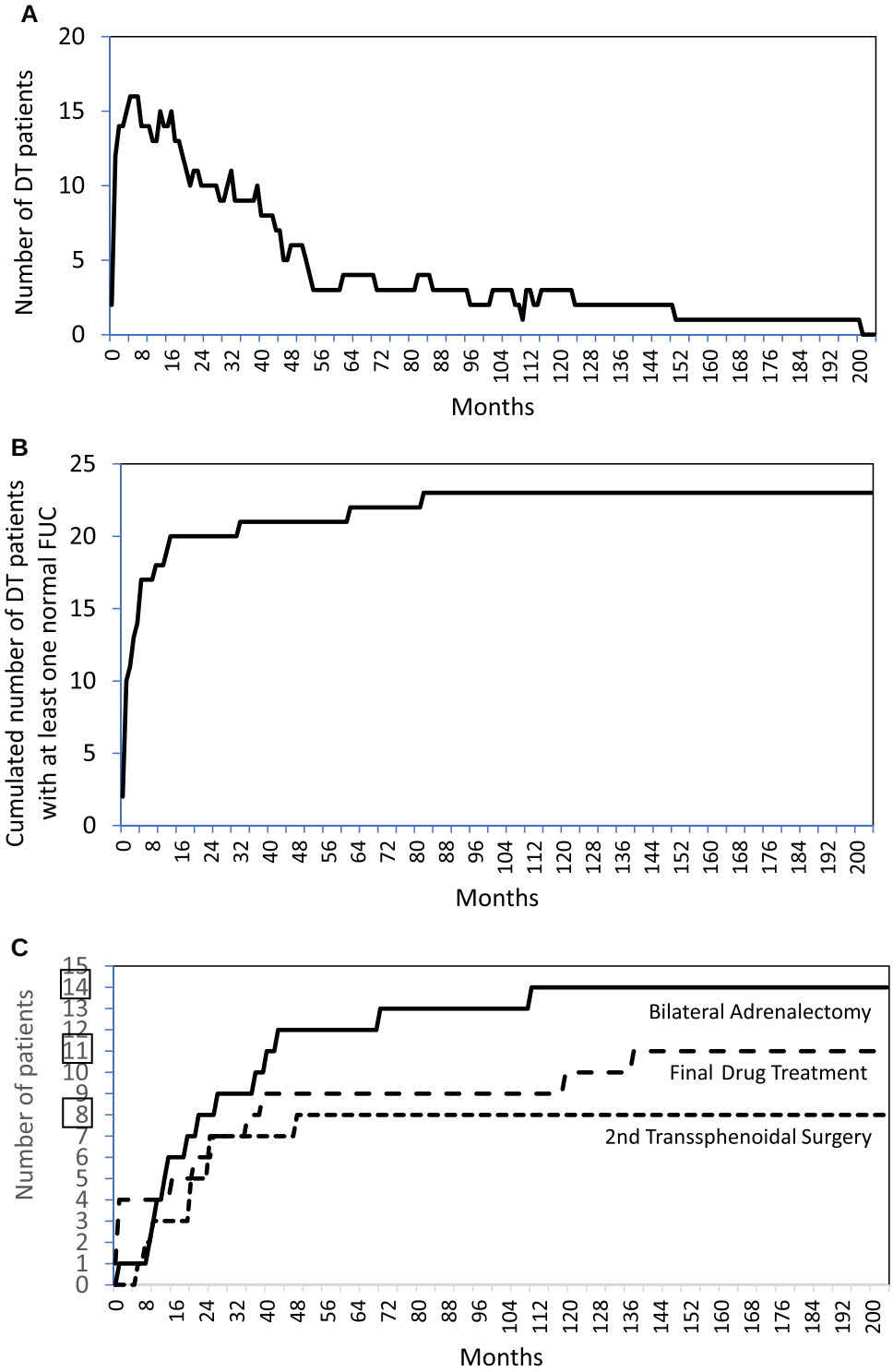

Figure 3. Evolution of patients treated with DT with time. (A) Evolution of the total number of patients treated by DT at any given period of time, including patients who never had a normal UFC. (B) Evolution with time of the cumulated number of patients treated with DT with at least 1 normal UFC. (C) Cumulated number of patients with either DT, second TSS, or BA as final treatment.
Abbreviations: BA, bilateral adrenalectomy; DT, drug treatment; TSS, transsphenoidal surgery; UFC, urinary free cortisol.

these 5 patients had tumoral progression of their corticotroph pituitary remnants or recurrencies, which is in favor of an antitumoral effect of PR.

Uncontrolled Patients

Finally, 3/36 (8%) patients (patients 34, 35, 36), all treated by DT were not controlled at the end of the study (Fig. 1, Fig. 2).

Clinical Results of Patients Treated by 2nd TSS or BA Despite Being Controlled by DT

Because our definition of DT efficiency was limited to a normal UFC, which can be criticized, we also analyzed the clinical evolution of patients who underwent 2nd TSS or BA despite having a normal UFC with DT. To the 4 patients already mentioned (patients 14, 18, 22, 31) in whom DT was both

Table 2. Clinical evolution of 7 patients with a normal UFC under DT who were still treated by 2nd TSS (5 patients) or BA (2 patients)

Patient	Sex	Age at 2nd TSS or BA	DT	Tolerance	UFC pre op nmol/24h	Treatment	BMI pre op	BMI 1 yr post op	BP pre-op (DDD)	BP 1 yr post-op (DDD)	HbA1c/Glyc. Pre-op (treatment)	HbA1c/ Glyc. Post-op	Overall evolution
14	F	51 (TSS)	Keto 600 mg/d	Good	50 n 28-138	2nd TSS	32.8	32.4	149/80 (0)	127/68 (0)	HbA1c 5.3%	HbA1c 5.8%	Stable
15	F	50 (TSS)	Keto 800 mg/d	Mediocre	237 n 120-240	2nd TSS	27.0	23.0	138/88 (3)	135/85 (0)	HbA1c 8% (metformin)	HbA1c 6.1%	Improved
16	F	41 (TSS)	Keto 800 mg/d	Mediocre	163 n 120-240	2nd TSS	28.2	25.0	148/80 (0)	122/76 (0)	HbA1c 7% (metformin)	HbA1c 5.8%	Improved
18	F	38 (TSS)	Keto 400 mg/d	Good	135 n 120-240	2nd TSS	25.5	25.9	130/80 (0)	113/58 (0)	Glyc 4.5 mml/L	Glyc 4.3 mml/L	Stable
19	F	20 (TSS)	Mitotane 3000 mg/d	Mediocre	39 n 28-138	2nd TSS	26.9	22.8	116/66 (0)	105/65 (0)	Glyc.4.1 mml/L	Glyc 4.2 mml/L	Improved
22	F	45 (BA)	Keto 800 mg/d	Good	72 n 28-138	BA	31.9	1 mth 30.8	140/100 (2)	140/100 (0)	HbA1c 6.6%	NA	Improved but Short follow-up
31	M	69 (BA)	Keto 800 mg/d	Mediocre	182 n 120-240	BA	31.8	30	145/90 (3)	130/90 (1)	HbA1c 6.4%	HbA1c 6.1%	Improved

Abbreviations: 2nd TSS, second transsphenoidal surgery; BA, bilateral adrenalectomy; CD, Cushing's disease; DDD, defined daily dose; DT, drug treatment; HbA1c, hemoglobin A1C; UFC, urinary free cortisol.
This table reports the clinical evolution of all 7 patients who, despite achieving biochemical controlled (a normal UFC) with DT, were still treated either by a successful 2nd TSS in 5 patients or by BA in 2 patients. The postoperative evolution (1 year after 2nd TSS or BA, except patient 22) of weight, blood pressure control, and glycemic control allows some comparison of the clinical benefits of CD control by DT vs clinical benefit of CD control by a successful 2nd TSS or by BA. The reasons for abandoning DT despite being biochemically controlled were as follows: patients 15, 16, 19, 31: poor tolerance of DT; patients 14, 18: the perspective to be freed from lifelong DT; patient 22: insufficient clinical control of CD despite a normal UFC.

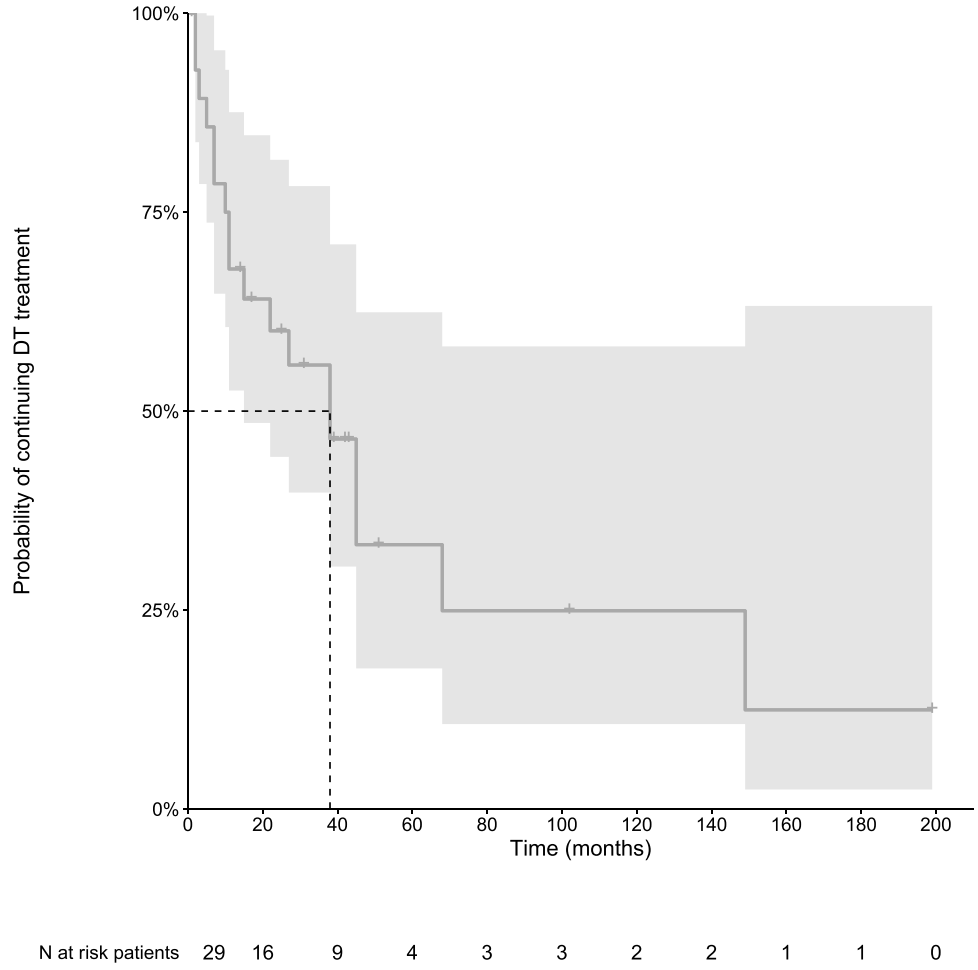

Figure 4. Kaplan–Meier analysis of continuation of DT in the 29 patients treated with DT. Out of the 36 patients with CD not cured by pituitary surgery, 29 patients received DT, including 27 with DT as their first second-line treatment and 2 who received DT after failure of a second TSS. Abbreviations: CD, Cushing's disease; DT, drug treatment; TSS, transsphenoidal surgery.

biochemically efficient and well tolerated, we added 3 patients who were biochemically controlled but did not tolerate DT (Table 2). Interestingly, at least 4 and maybe 5 of these 7 patients seemed to show a clinical benefit from 2nd TSS or BA despite being previously "controlled" by DT.

Discontinuation of DT in This Series and in the Literature

To better analyze discontinuation of DT, we plotted the discontinuation rate using Kaplan–Meier analysis, which allowed us to estimate that at 1 year the discontinuation rate was 30% while the median 50% discontinuation rate was achieved 38 months after initiation of DT (Fig. 4). Interestingly the 30% 1-year discontinuation rate is in the range of the 1-year discontinuation rates that can be calculated from the data available in publications of prospective clinical trials of DT on CD using pasireotide (8, 9), osilodrostat (10-12), and levoketoconazole (13, 14) (Table 3).

To try to determine whether discontinuation of DT was linked to specific characteristics of the patient, we compared the group of 11 patients with long-term control by DT to the group of 18 patients in whom DT had been abandoned (Table 4). The patients of the first group were all treated with cortisol synthesis inhibitors and were older than those of the second group (55.9 vs 47.9 years, $P = .04$). Both groups were similar with respect to initial UFC and percentage of women, but it is important to note that 12/15 women of childbearing age belonged to the group of patients who abandoned DT, in keeping with the fact that DT does not allow consideration of a pregnancy. Six patients who were not women of childbearing age discontinued DT: these patients seems to have higher UFC and more normal or uncertain MRI. The reason for discontinuation in this subgroup was mainly intolerance or inefficiacy (4/6 patients).

Discussion

When CD is not cured by pituitary surgery, DT is an attractive option both for the patient and his endocrinologist because the 3 other alternatives (2nd TSS, BA, or PR) each have their own difficulties to accept or to perform. Indeed 2nd TSS, which requires that a remnant or recurrence be clearly localized and accessible to surgery, has a lower remission rate than a first TSS and exposes the patient to the risk of pituitary insufficiency. BA imposes that the patient accepts abandoning his or her adrenals forever, taking a lifelong substitutive therapy, and being exposed to a lifelong risk for adrenal crises and a risk of corticotroph tumor progression. Finally, PR is hampered by a delayed and incomplete efficiency, and it imposes

Table 3. One-year and long-term discontinuation rates of different drug treatments for CD or endogenous Cushing's in prospective clinical trials

Study name and reference	Drug	Inclusion criteria	Study phase	n included	n final	n discont.	Maximal duration	Discontinuation rate	% discontinuation for lack of efficiency (%)	% discontinuation for adverse event (%)	% discontinuation for other or unspecified reasons (%)[a]
Pasireotide phase 3 (8)	Pasireotide short acting	CD	Initial	162	78	84	12 months	1 year 84/162 = 52%	31	44	25
Once-monthly Pasireotide phase 3 (9)	Pasireotide LAR	CD with UFC < 5 times n	Initial	150	104	46	12 months	1 year 46/150 = 31%	39	30.5	30.5
Linc 3 (10)	OsilodrOstat	CD	Initial	137	113	22[b]	48 weeks	<1 year 22/137 = 17%		59	41
Linc 4 (11)	OsilodrOstat	CD	Initial	73	65	8	48 weeks	<1 year 8/73 = 11%		37	62.5
SONICS (13)	Levoketoconazole	Endogenous Cushing's[a] (85% CD)	Initial	94	61	33	47 weeks	<1 year 33/94 = 35%	21	36	42
Once-monthly Pasireotide phase 3 extension (21)	Pasireotide LAR	CD with UFC < 5 times n	Extension	81	39	42	<36 months	<3 years 42/81 = 52%	29	21	50
Linc 3 study extension (12)	OsilodrOstat	CD	Extension	106	72	34	<197 weeks	<3,8 yrs 34/106 = 32%	3	35	62
Levo-ketoconazole extension (14)	Levoketoconazole	Endogenous Cushing's[a] (85% CD)	Extension	60	46[a]	14	12 months	1 year 14/60 = 23%	21	29	50

Abbreviations: CD, Cushing's disease; LAR, long-acting release.
The discontinuation rates were directly calculated from the data presented in the figure or tables describing patient disposition in the referenced publications. Regarding the different phases of the studies: "initial" is the phase of the study proposed to all patients included in the trial; "extension" is a subsequent phase proposed to patients willing to continue taking the drug in the frame of an extension trial;
[a]Other reasons include physician decision, patient decision, guardian decision, consent withdrawal, death, administrative reasons.
[b]24 actually discontinued this study but 2 discontinuations happened during the randomized withdrawal phase in the placebo arm.

Table 4. Comparison, for the 29 patients treated by DT, of the 11 patients with DT as final treatment vs the patients with either 2nd TSS (5 patients) or BA (10 patients) as a final treatment or not controlled (3 patients)

	Final treatment DT n = 11	Final treatment not DT n = 18		
		Total	Women of childbearing age (n = 12)	Other patients (n = 6: 4 women and 2 men)
UFC nmol/24 hours mean (95% CI)	602.6 (345-860)	781.1 (307-1255)	526.7 (308-745)	1247.4 (0-2513)
Age at start of care mean (95% CI)	48.0 (40.0-56.0)	35.1 (26.4-43.7)	26.2 (19.1-33.2)	52.8 (39.3-66.3)
% women	81.80	88.9	100	66.7
n women of childbearing age (</= 40 years old)	3	12	12	0
MRI				
Normal-uncertain (%)	18	39	25	67
Microadenoma image (%)	55	50	58	33
Macroadenoma image (%)	27	11	17	0
Average n drug tested mean (95% CI)	2.5 (1.8-3.3)	1.7 (1.2-2.1)	1.7 (1.1-2.2)	1.7 (1.0-2.3)
Average duration of DT years: mean (95% CI)	4.13 (1.49-6.77)	1.73 (0.74-2.72)	1.46 (0.84-2.08)	2.26 (0-5.07)

Abbreviations: 2nd TSS, second transsphenoidal surgery; BA, bilateral adrenalectomy; CI, confidence interval; DT, drug treatment; MRI, magnetic resonance imaging; UFC, urinary free cortisol.

acceptance of a risk of long-term pituitary insufficiency, while the risk for stroke or radiation-induced tumor is probably very low with modern techniques of PR but still a matter of concern.

Indeed, DT has 1 major advantage: unlike the 3 alternatives, DT is a reversible treatment, which can be tried before considering 2nd TSS, BA, or PR should DT prove to be not efficient, not tolerated, or not observed. We, like many other endocrinologists involved in the care of patients with CD, were very well aware of the potential interest in DT for treatment of our patients, and this explains why in our series DT was, by far, not only the most frequently used treatment but also the most frequent first second-line treatment: indeed, after failure of a first pituitary surgery or recurrence, the first treatment proposed to our patients with CD was DT in 27/36 (75%), whereas 2nd TSS was first proposed in 5/36 (14%), BA in 3/36 (8%), and PR only in 1/36 (3%), and during follow-up a total of 29/36 patients (80%) were treated at some time by DT (Fig. 1). However, the endocrinologists in our team who were following the patients had experienced that, for some patients, despite their best efforts in adapting the treatments, they eventually had to abandon DT and switch to either 2nd TSS or BA. This "clinical experience feeling" was the reason for performing this systematic evaluation of our series of 36 patients with CD not cured by a first pituitary surgery so that we could better evaluate what could be expected from DT in the long term. This evaluation led us to conclude that, out of the 29 patients treated with DT, only 11/29 patients (38%) were still controlled at last follow-up by DT while 18/29 patients treated with DT (62%) had switched to either BA or 2nd TS. This 62% discontinuation rate was higher than what we expected, which led us to question our ability to treat our patients with DT. Interestingly, however, our systematic analysis of the literature shows that the discontinuation rate in this series is actually very similar to the 1-year discontinuation rate observed in most prospective DT trials in CD (Table 2), which shows a 1-year discontinuation rate as high as 51% for pasireotide (8) and 35% for levoketoconazole (13), although it does seems lower for osilodrostat (11% and 17%) (10, 11). It can be argued that it is difficult to compare data from real-life patients to data from patients enrolled in a clinical trial, as a clinical trial imposes some specific rules to manage the drug that is tested. We think, however, that this comparison is still relevant as, in both a clinical trial or in real life, the main reasons for discontinuing a drug are a lack of efficiency and/or a lack of tolerance.

Still, to explain part of our high discontinuation rate of DT, we have to acknowledge that, as a result of our "TSS prioritizing strategy," we did perform a 2nd TSS in 2 patients (patient 14 and 18) who also had a normal UFC under DT but appeared good candidates for 2nd TSS and were indeed in remission after 2nd TSS. We also performed BA in 2 patients (patients 22 and 31) with a normal UFC under DT who seemed to still carry clinical signs of CD: if these 4 patients had kept DT and if DT was still effective at their last follow-up, then we would not have 11 patients with DT at last follow-up but 11 + 4 = 15 patients and the percentage of patients with DT as final treatment would then have been 15/29 (52%) rather than 11/29 (38%). Interestingly however, the clinical postoperative results of these 4 patients and of 3 additional patients in whom DT was efficient but poorly tolerated (Table 2) seem to validate our strategy and do question the validity of UFC as a sole parameter for evaluation of DT. This question has actually recently been addressed in the interesting HairCush study by Mohammedi et al, who demonstrated that patients with CD treated by DT with a normal UFC showed higher hair cortisone levels and higher late-night salivary cortisol and cortisone and proved to have a worse clinical score and a higher need for antihypertensive drugs than patients with CD in remission with TSS (22). Thus, the

clinical results of 7 patients from our study (Table 2) fit perfectly with the HairCush study to suggest that, in patients with CD treated by DT, a normal UFC is not sufficient to prove control of CD.

It has to be noted that, in our series, the discontinuation rates of the different drugs do not appear equivalent: first, all patients who were still on DT at last follow-up were treated by cortisol synthesis inhibitors rather than dopamine or somatostatin receptor agonists. This is likely related to a lower efficiency of the latter (Table 1). Of note, all but 1 of the 29 patients received at some time a steroidogenesis inhibitor, so that the fact that dopamine and somatostatin receptor agonists were discontinued more frequently did not significantly impact the final efficiency of DT. Second, among cortisol synthesis inhibitors, osilodrostat seemed to be continued more frequently than ketoconazole or metyrapone, which might suggest that osilodrostat could provide a lower discontinuation rate. It must be stressed, however, that in this retrospective study, no treatment was randomized and the duration of exposure to osilodrostat was much shorter than exposure to other drugs (Table 1), as osilodrostat was made available only recently. It must also be stressed that analysis of the literature on discontinuation of DT in the initial and extension phases of prospective studies (Table 2) shows that after a first year of treatment discontinuation rates run from 11% to 52% and, longer term, from 23% for levoketoconazole (14) to 52% for pasireotide monthly (21). For osilodrostat, 32% of patients abandoned the treatment during the extension period before 3.8 years and 47% before 4.7 years (12). It can be objected that these long-term discontinuation rates might be overestimated if some patients who abandoned the investigative drug during the extension period could receive the drug out of the extension protocol if the drug became commercially available. It might also be objected that the reason for discontinuation of a treatment in a clinical trial is theoretically not only lack of efficiency or adverse events but also other reasons such as "patient's or physician's or guardian's decision" (Table 3), but one can still hypothesize that in at least some cases the reason for these decisions to stop the treatment may still have a link with the efficacy or tolerance of the drug.

One should stress that there is another factor that has played a role in our 62% rate of discontinuation of DT: the fact that we have a general therapeutic strategy that prioritizes TSS over DT whenever TSS is believed to have interesting chances of success. This strategy is first validated by our good rate of remission at first TSS (100/119, 84%), and we believe it is also validated by the interesting results of remission at 2nd TSS (8/16, 50%).

There are at least 3 weaknesses in our study: its retrospective design, its monocentric design, and the relatively small number of patients with recurrence or absence of remission. Regarding the monocentric effect, therapeutic decisions regarding the choices between DT, 2nd SS, BA, and PR were made during multidisciplinary meetings involving endocrinologists, a neurosurgeon, an endocrine surgeon, and a radiotherapist. However, this multidisciplinary team may have developed with time an overall therapeutic strategy specific to this team, including both strengths and weaknesses. The strengths might include a resolute surgical strategy, which favors 2nd TSS whenever the location of the remnant or recurrence seems both clear and accessible, with a 50% chance of remission. On the contrary, our radiotherapy strategy may be considered somewhat weak as we do not perform radiotherapy when there is no clear MRI image of adenoma remnant or recurrence, whereas others advocate irradiation of the whole pituitary when there is no clear target (23) as long as the existence of a remnant/recurrency is certain. In our study, the candidates for PR were restricted to patients with a clear MRI target and not accessible to 2nd TSS. This explains the rather small number of patients (5/36, 14%) treated by PR in this study, while the rather poor results of PR in these 5 patients might be explained by the fact that our strategy probably selected more visible and more aggressive tumors and by the fact that in 3 patients PR was associated with BA, so that PR could not be considered a final treatment for control of CD.

It is possible that further studies will show that other teams may achieve better long-term continuation rates of DT and better control of CD by DT than what we achieved in this study. Indeed, the results of a medical treatment depends not only on the drug but also, to some extent, on the prescriber, who may induce a better adherence of the patients than what we achieved. A better adherence to DT might translate into a lower rate of BA, which would be an interesting goal, as BA imposes a risk for adrenal crises. Another possibility is that new strategies with DT might result in better clinical control rates and thus lower the need for BA: as we have seen in this study, some patients with a normal UFC under DT can still show significant clinical improvement when they are put in remission by a 2nd TSS or when BA is performed (Table 3). This indirectly indicates that a normal UFC is not the best parameter to evaluate control of CD and suggests that a better result may be achieved when a normal cortisol cycle is restored by 2nd TSS or even when hydrocortisone substitutive therapy after BA does not impose overexposure to cortisol in the evening and first part of the night. It has to be stressed that the strategy of titration using a steroidogenesis inhibitor with a medium or long half-life like ketoconazole or osilodrostat, which is the strategy that has been tested so far in clinical trials, cannot suppress exposure to cortisol during the evening and first part of the night unless it places the patient with cortisol levels also low in the morning, thus creating adrenal insufficiency. There are currently no strategies using DT that have been shown to achieve levels of cortisol that are at the same time low enough in the evening and in the first part of the night and high enough in the morning. Further studies would be needed to determine whether these goals might be better approached by new strategies, such as a "block and replace" strategy (using a cortisol synthesis inhibitor at a dosage sufficient to obtain a complete blockade of cortisol secretion and then adding a substitutive dose of hydrocortisone) or a "combination" strategy (adding a short-acting steroidogenesis inhibitor in the evening to a titrated dose of a longer acting steroidogenesis inhibitor in the morning).

It must be stressed, however, that BA will remain the only possible alternative in women of childbearing age who desire pregnancy. This explains that being of childbearing age was the main factor linked to discontinuing DT (Table 4), although it is possible that in patients not candidates for pregnancy, a higher UFC at baseline might also identify patients more likely to abandon DT for lack of efficiency. These women represented 7/14 (50%) of the BA patients and 7/36 (19%) of the whole group of 36 patients not cured by surgery, a significant group that will probably stay forever out of reach of any DT as one can expect that a woman with a strong desire

for pregnancy will choose to have her adrenals removed rather than to not have the prospect of a pregnancy. Finally, we do want to underline again the importance of considering a 2nd TSS: in this series, even though all our patients were operated on by the same expert neurosurgeon (E.G.) for their first pituitary surgery, a second pituitary surgery by the same surgeon was successful in 8/16 patients, so we feel that a repeat pituitary surgery by an expert surgeon should at least be considered in any patients with CD who show failure or recurrence after a first pituitary surgery.

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Data Availability

Some datasets generated or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

References

1. Pivonello R, De Leo M, Cozzolino A, Colao A. The treatment of Cushing's disease. *Endocr Rev*. 2015;36(4):385-486.
2. Petersenn S, Beckers A, Ferone D, *et al*. 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*. 2015;172(6):R227-R239.
3. Cristante J, Lefournier V, Sturm N, *et al*. Why we should still treat by neurosurgery patients with Cushing's disease and a normal or inconclusive pituitary MRI. *J Clin Endocrinol Metab*. 2019;104(9):4101-4113.
4. Braun LT, Rubinstein G, Zopp S, *et al*. Recurrence after pituitary surgery in adult Cushing's disease: a systematic review on diagnosis and treatment. *Endocrine*. 2020;70(2):218-231.
5. Castinetti F, Brue T, Ragnarsson O. Radiotherapy as a tool for the treatment of Cushing's disease. *Eur J Endocrinol*. 2019;180(5):D9-D18.
6. Hahner S. Acute adrenal crisis and mortality in adrenal insufficiency: still a concern in 2018! *Ann Endocrinol*. 2018;79(3):164-166.
7. Reincke M, Albani A, Assie G, *et al*. Corticotroph tumor progression after bilateral adrenalectomy (Nelson's syndrome): systematic review and expert consensus recommendations. *Eur J Endocrinol*. 2021;184(3):P1-P16.
8. Colao A, Petersenn S, Newell-Price J, *et al*. A 12-month phase 3 study of pasireotide in Cushing's disease. *N Engl J Med*. 2012;366(10):914-924.
9. Lacroix A, Gu F, Gallardo W, *et al*. Efficacy and safety of once-monthly pasireotide in Cushing's disease: a 12 month clinical trial. *Lancet Diabetes Endocrinol*. 2018;6(1):17-26.
10. Pivonello R, Fleseriu M, Newell-Price J, *et al*. 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*. 2020;8(9):748-761.
11. Gadelha M, Bex M, Feelders RA, *et al*. Randomized trial of osilodrostat for the treatment of Cushing disease. *J Clin Endocrinol Metab*. 2022;107(7):e2882-e2895.
12. Fleseriu M, Newell-Price J, Pivonello R, *et al*. Long-term outcomes of osilodrostat in Cushing's disease: LINC 3 study extension. *Eur J Endocrinol*. 2022;187(4):531-541.
13. Fleseriu M, Pivonello R, Elenkova A, *et al*. Efficacy and safety of levoketoconazole in the treatment of endogenous Cushing's syndrome (SONICS): a phase 3, multicentre, open-label, single-arm trial. *Lancet Diabetes Endocrinol*. 2019;7(11):855-865.
14. Fleseriu M, Auchus RJ, Greenman Y, *et al*. Levoketoconazole treatment in endogenous Cushing's syndrome: extended evaluation of clinical, biochemical, and radiologic outcomes. *Eur J Endocrinol*. 2022;187(6):859-871.
15. Castinetti F, Guignat L, Giraud P, *et al*. Ketoconazole in Cushing's disease: is it worth a try? *J Clin Endocrinol Metab*. 2014;99(5):1623-1630.
16. Ferriere A, Cortet C, Chanson P, *et al*. Cabergoline for Cushing's disease: a large retrospective multicenter study. *Eur J Endocrinol*. 2017;176(3):305-314.
17. Baudry C, Coste J, Bou Khalil R, *et al*. Efficiency and tolerance of mitotane in Cushing's disease in 76 patients from a single center. *Eur J Endocrinol*. 2012;167(4):473-481.
18. Lefournier V, Martinie M, Vasdev A, *et al*. Accuracy of bilateral inferior petrosal or cavernous sinuses sampling in predicting the lateralization of Cushing's disease pituitary microadenoma: influence of catheter position and anatomy of venous drainage. *J Clin Endocrinol Metab*. 2003;88(1):196-203.
19. Nieman LK, Biller BMK, Findling JW, *et al*. Treatment of Cushing's syndrome: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100(8):2807-2831.
20. Fleseriu M, Auchus R, Bancos I, *et al*. Consensus on diagnosis and management of Cushing's disease: a guideline update. *Lancet Diabetes Endocrinol*. 2021;9(12):847-875.
21. Fleseriu M, Petersenn S, Biller BMK, *et al*. Long-term efficacy and safety of once-monthly pasireotide in Cushing's disease: A phase III extension study. *Clin Endocrinol (Oxf)*. 2019;91(6):776-785.
22. Mohammedi K, Bertherat J, Raverot G, *et al*. Evidence of persistent mild hypercortisolism in patients medically treated for Cushing disease: the haircush study. *J Clin Endocrinol Metab*. 2023;108(10):e963-e970.
23. Losa M, Albano L, Bailo M, Barzaghi LR, Mortini P. Role of radiosurgery in the treatment of Cushing's disease. *J Neuroendocrinol*. 2022;34(8):e13134.