European Journal of Endocrinology (2008) **158** 91–99 ISSN 0804-4643

CLINICAL STUDY

Ketoconazole revisited: a preoperative or postoperative treatment in Cushing's disease

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Abstract

Context: Although transsphenoidal surgery remains the first-line treatment in Cushing's disease (CD), recurrence is observed in about 20% of cases. Adjunctive treatments each have specific drawbacks. Despite its inhibitory effects on steroidogenesis, the antifungal drug ketoconazole was only evaluated in series with few patients and/or short-term follow-up.
Objective: Analysis of long-term hormonal effects and tolerance of ketoconazole in CD.
Design: A total of 38 patients were retrospectively studied with a mean follow-up of 23 months (6–72).
Setting: All patients were treated at the same Department of Endocrinology in Marseille, France.
Patients: The 38 patients with CD, of whom 17 had previous transsphenoidal surgery.
Intervention: Ketoconazole was begun at 200–400 mg/day and titrated up to 1200 mg/day until biochemical remission.
Main outcome measures: Patients were considered controlled if 24-h urinary free cortisol was normalized.
Results: Five patients stopped ketoconazole during the first week because of clinical or biological intolerance. On an intention to treat basis, 45% of the patients were controlled as were 51% of those treated long term. Initial hormonal levels were not statistically different between patients controlled or uncontrolled. Ketoconazole was similarly efficacious as a primary or postoperative treatment. Among 15 patients without visible adenoma at initial evaluation, subsequent follow-up allowed identification of the lesion in five cases. No adrenal insufficiency was observed. Adverse effects were rare in patients treated long term.
Conclusions: Ketoconazole is a safe and efficacious treatment in CD, particularly in patients for whom surgery is contraindicated, or delayed because of the absence of image of adenoma on magnetic resonance imaging.

European Journal of Endocrinology **158** 91–99

Introduction

Adrenocorticotropin (ACTH)-dependent Cushing's syndrome may be caused by a pituitary corticotroph adenoma (Cushing's disease (CD), 80–85% of cases), by an extrapituitary tumor (ectopic ACTH syndrome), or very rarely by a corticotrophin-releasing hormone (CRH)-secreting tumor (ectopic CRH syndrome). At the time of diagnosis, because of signs and symptoms of chronic endogenous glucocorticoid excess, most corticotroph adenomas are microadenomas (<10 mm in largest diameter). Complications of CD include hypertension, hypertrophic cardiomyopathy, diabetes, obesity, hyperlipidemia, osteoporosis, psychiatric, and cognitive manifestations (1).

Transsphenoidal surgery usually represents the first-line treatment of CD. In series reported by experienced surgeons, immediate success rates vary from 64 to 93%. Recurrence, frequently observed 5–10 years after surgery, occurs in 9–25% cases (2–4). Various treatments for recurrence have been proposed, but each of them implies specific risks: Nelson's syndrome after bilateral adrenalectomy (5), hypopituitarism, and radiation-induced brain tumors after radiotherapy (6, 7). Gamma Knife radiosurgery, though responsible for fewer adverse effects, is only effective in about 40–50% of cases (8–10).

Several medical treatments have been proposed in CD: despite its effectiveness, mitotane therapy is complicated by several side effects (11–13); metyrapone, which was mainly used in combination with aminoglutethimide, frequently induces hyperandrogenism (14, 15); only a small percentage of patients with CD is in remission with bromocriptine (15); and efficacy of glitazones is still a matter of debate with contradictory results in previously published series (16–18).

Ketoconazole is an antifungal agent with steroidogenesis inhibitor effects linked to inhibition of cytochrome P450 enzymes (19, 20). In addition to its blocking effects on steroidogenesis, ketoconazole has putative

DOI: 10.1530/EJE-07-0514
Online version via www.eje-online.org

extra-adrenal actions. At high concentrations, it has been shown to be an antagonist of the glucocorticoid receptor in cultured hepatoma cells (21) and it binds to glucocorticoid receptors in cytosolic preparations of human mononuclear cells (22). Earlier studies and case reports have described its effects in a total of about 100 patients, including 85 patients with CD (23–29). However, published studies were always based on few patients (<10) except one on 28 patients with CD previously treated with conventional radiotherapy (30). Moreover, all but one study had short mean follow-up not exceeding 8 months (31). We retrospectively studied the efficacy and adverse side effects of ketoconazole in 38 patients with CD, with a mean follow-up of 23 months.

Patients and methods

A total of 38 patients with active CD were treated with ketoconazole between 1995 and 2005 at the Department of Endocrinology of the University Hospital La Timone (Marseille, France). The diagnosis of CD was based on the association of clinical features of the disease, elevated 24-h urinary free cortisol level (UFC; mean of three samples to control for variability in cortisol secretion or urine collection), elevated serum cortisol and ACTH levels with a lack of response to a standard low-dose dexamethasone suppression test (2 mg/day for 2 days), and appropriate response to high-dose dexamethasone test (8 mg/day for 2 days). In the absence of an unequivocal image of pituitary adenoma at magnetic resonance imaging (MRI), inferior petrosal sinus sampling was performed. As ketoconazole is not currently approved in this indication in France, informed consent was obtained from each patient. All patients had received detailed information on side effects and potential benefits of ketoconazole used in a condition different from that of the marketed indication and had given an informed consent form allowing retrospective studies to be performed on their medical records for scientific purposes, as approved by the Ethics Committee of our institution.

Each patient had a complete clinical and hormonal evaluation before ketoconazole including 0800 and 0000 h ACTH and cortisol, and 24 h UFC. Plasma ACTH, cortisol, and UFC were measured by commercial RIA kits (Beckman-Coulter-Immunotech, Marseille, France). The ACTH immunoradiometric assay had a sensitivity of 1.2 pg/ml (at 95% probability), and intra- and inter-assay coefficients of variation of 6.9–9.1% and 6.2–9.6% respectively. The cortisol assay had a sensitivity of 10 nmol/l, and intra- and inter-assay coefficients of variation of 2.8–5.1% and 5.3–9.2% respectively.

Three patients had previously been treated by Gamma Knife radiosurgery before initiation of ketoconazole treatment. We divided the whole population in two groups: those who were not treated surgically before ketoconazole called 'No pituitary surgery group' and the others who had ketoconazole as an adjunctive treatment called 'After pituitary surgery group'.

Treatment with ketoconazole was always initiated at low dose (200–400 mg/day) with weekly control of aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), and γ-glutamyl transpeptidase (γ-GT) during the first month. The first evaluation of UFC (mean of three samples) was carried out after 1 month of treatment: if necessary, the dose of ketoconazole was increased by 200 mg per day every 10–15 days, with weekly liver function test controls. Urinary cortisol secretion was monitored until normalization at 1–4 month intervals, and ketoconazole dose was increased up to 1200 mg/day if necessary. Complete clinical evaluation was also periodically performed (clinical signs of hypercortisolism, weight, blood pressure) as well as standard biological evaluations including blood glucose and liver function tests (repeated at each titration step). Patients were considered controlled if they had normal 24-h UFC at two consecutive determinations. When the dose of ketoconazole was correct, hormonal control was checked at 3-month intervals. Patients who had immediate clinical or biological intolerance were considered uncontrolled and ketoconazole was stopped. None of our patients received sucralfate or acid-lowering agents during the period of treatment by ketoconazole, as stomach acidity is required for dissolution and absorption of the treatment. In patients with follow-up superior or equal to 36 months, dual energy X-ray absorptiometry was performed at the end of the treatment and compared with the pre-treatment evaluation. When ketoconazole was given awaiting possible later visualization of an intrasellar lesion, MRI was performed at 3-month and then 6-month intervals until treatment was stopped.

Statistical analysis was managed with SPSS version 13.0 (SPSS Inc., Chicago, IL, USA) for Windows. Comparison of means was evaluated with Student's *t*-test, and one-way ANOVA where possible. All statistical tests were two-tailed and $P<0.05$ was considered significant.

Results

Thirty-eight patients were included in this retrospective study (individual data reported in Table 1). Reasons for initiation of ketoconazole treatment were as follows: unsuccessful pituitary surgery ($n=17$ patients); lack of image of adenoma on pituitary MRI ($n=15$ patients); refusal (1 patient) or contraindication (1 patient) of surgery; and awaiting antisecretory efficacy of Gamma Knife radiosurgery (4 patients). Indeed, 21 patients were in the 'No pituitary surgery group' as they were treated with ketoconazole as a primary treatment and 17 in the 'After pituitary surgery group'. No patient was lost to follow-up.

Table 1 Individual data of the 33 patients treated with ketoconazole (excluding the 5 patients with immediate cessation of treatment because of intolerance). Control of the disease was defined by normalization of 24-h urinary free cortisol. Maximal dose in mg/day.

Patient	Sex/age	Group	Reason for treatment	Maximal dose	Outcome	Follow-up (months)
1	F/42	Surgery	Unsuccessful surgery	200	Controlled	72
2	F/32	No surgery	No MRI image	400	Controlled[a]	12
3	F/66	Surgery	Unsuccessful surgery	400	Controlled	30
4	F/73	No surgery	No MRI image	400	Controlled[a]	12
5	F/64	Surgery	Unsuccessful surgery	400	Controlled	36
6	F/26	Surgery	Unsuccessful surgery	400	Controlled	12
7	F/43	No surgery	No MRI image	400	Controlled	12
8	F/39	Surgery	Unsuccessful surgery	400	Controlled	12
9	F/50	Surgery	Unsuccessful surgery	400	Controlled	18
10	F/33	No surgery	No MRI image	400	Controlled[a]	12
11	F/55	No surgery	No MRI image	600	Controlled[a]	30
12	F/72	No surgery	GK latency	600	Controlled	12
13	F/47	Surgery	GK latency	600	Controlled	24
14	F/32	Surgery	Unsuccessful surgery	600	Controlled	18
15	F/50	Surgery	Unsuccessful surgery	800	Controlled	12
16	F/36	No surgery	No MRI image	1000	Controlled[a]	30
17	F/36	Surgery	Unsuccessful surgery	1000	Controlled	60
1	M/58	No surgery	No MRI image	600	Uncontrolled[b]	3
2	F/39	No surgery	No MRI image	600	Uncontrolled	2
3	M/52	No surgery	No MRI image	600	Uncontrolled	12
4	F/50	Surgery	Unsuccessful surgery	600	Uncontrolled	30
5	F/26	No surgery	Surgery refused	800	Uncontrolled	1
6	F/24	No surgery	No MRI image	800	Uncontrolled[b]	36
7	F/58	No surgery	No MRI image	800	Uncontrolled	6
8	F/26	No surgery	No MRI image	1000	Uncontrolled	6
9	F/44	Surgery	GK latency	1000	Uncontrolled	3
10	F/42	No surgery	No MRI image	1000	Uncontrolled	1
11	F/29	Surgery	Unsuccessful surgery	1000	Uncontrolled[b]	3
12	M/37	Surgery	GK latency	1000	Uncontrolled[b]	24
13	M/55	Surgery	Unsuccessful surgery	1000	Uncontrolled[b]	24
14	M/30	Surgery	Unsuccessful surgery	1000	Uncontrolled	6
15	F/34	No surgery	No MRI image	1200	Uncontrolled	1
16	F/18	Surgery	Unsuccessful surgery	1200	Uncontrolled	6

[a]Outcome: patient for whom a pituitary adenoma could be visualized after ketoconazole treatment.
[b]Patient with recurrence of hypercortisolism during ketoconazole treatment.

Ketoconazole was stopped in the first week of treatment in five patients (13%) because of clinical (five patients with nausea and diarrhea) or biological intolerance (one patient, fivefold increasing of γ-GT with normal ASAT and ALAT). All of these patients had initiation of treatment with 200 mg/day of ketoconazole. The remaining 33 patients were thus treated on a long-term basis by ketoconazole.

With a mean follow-up of 22.6 months, 17 patients were controlled (51.5% of those treated long term); doses of ketoconazole varied from 200 to 1000 mg/day (mean 529 mg/day). On an intention to treat basis, 44.7% of cases had thus normalized their UFC. Control of the disease was observed during the first month in eight patients and at 3 months after dose titration in nine patients.

The 17 biologically controlled patients also presented clinical regression of signs of hypercortisolism including lowering of blood pressure and loss of weight (mean loss: 1–2 kg 3 months after initiation of treatment, 5 kg 1 year after initiation of treatment). Blood pressure was normal in all controlled patients 3–6 months after initiation of ketoconazole. Mean systolo-diastolic blood pressure before ketoconazole treatment under anti-hypertensive treatment was 148/105 mmHg; mean systolo-diastolic blood pressure after 3–6 months ketoconazole treatment and the same anti-hypertensive drugs was 115/85 mmHg. However, anti-hypertensive drugs were not stopped despite blood pressure control in most of the patients, and none of the five patients in whom anti-hypertensive treatment was stopped had normalized blood pressure (anti-hypertensive drugs were reintroduced at the same dose).

In the five diabetic patients (they all belonged to the 'controlled group'), metabolic control on the basis of blood glucose and glycosylated hemoglobin (HbA1c) monitoring was improved. Two of the patients were treated by insulin: in the first one, the dose of insulin decreased from 160 to 140 units per day and HbA1c fell from 11.5 to 8% after 6 months of ketoconazole; in the second one, the dose of insulin fell from 90 to 60 units per day and HbA1c fell from 9 to 7.8% after 6 months of ketoconazole. The three other patients were treated with oral antidiabetic drugs (metformin alone or in combination with sulfonylurea). Antidiabetic treatment was not modified, but a 0.5–1% decrease in HbA1c was observed after 6–12 months of ketoconazole. One patient who had severe heart failure

had a marked regression of cardiac signs, with a drastic decrease of heart-protective treatments. In the three patients who were followed-up for more than 36 months, absorptiometry showed severe osteoporosis at the time of CD diagnosis: two patients presented with osteopenia at the end of the treatment (36 and 60 months after initiation) and one patient had normal absorptiometry according to her age 72 months after initiation of treatment.

In contrast, 16 patients (42.3% of the total cohort, 48.5% of those treated long term), treated for a mean period of 10 months with a mean dose of 890 mg/day (varying from 600 to 1200 mg/day), were uncontrolled at the end of the follow-up: five of them had initially been controlled, for a period of 3 months (two patients), 2 years (two patients), and 3 years (one patient), at doses varying from 600 to 1000 mg/day.

Of the 16 uncontrolled patients, 8 presented a significant decrease in UFC: 5 of them normalized high blood pressure without modification of their antihypertensive therapy (patients 2, 6, 7, 12, and 13 of the uncontrolled group). From the other eight patients with unchanged UFC, the blood pressure status was not modified including three patients with normal blood pressure at initiation of ketoconazole treatment (patients 1, 4, and 5 of the uncontrolled group). Half of the 16 uncontrolled patients also displayed clinical regression of signs of hypercortisolism with mean loss of weight similar to that of controlled patients.

Initial hormonal levels were not predictive factors of remission: initial 24-h UFC, UFC percent decrease at 1 and 3 months, 0800 or 0000 h ACTH and cortisol were not statistically different between controlled and uncontrolled patients (Table 2). None of our male patients were in the group of controlled patients. Doses of ketoconazole were obviously higher in uncontrolled patients, as they were systematically increased when there was no initial antisecretory efficacy. As shown in Fig. 1A and B, no clear dose–response relationship was found since higher doses were not systematically correlated with lower hormonal levels. We also tried to identify predictive factors in our population after exclusion of the five patients who ceased ketoconazole in the first week. However, none of the study parameters appeared to be associated with remission or therapeutic escape.

Ketoconazole was similarly efficacious in normalizing hormonal levels in the 'No pituitary surgery group' ($n=7$, 44% cases controlled) or in the 'After pituitary surgery group' ($n=10$, 59% cases controlled). Follow-up was significantly lower in the former than in the latter group, as ketoconazole was stopped in the patients primarily treated with ketoconazole when an adenoma became visible on MRI. There was no significant difference between both groups in terms of age, sex, or initial hormonal levels (Table 3).

Except for the five patients who discontinued ketoconazole in the first week, no other patient stopped treatment during follow-up because of adverse effects. Adverse effects were indeed rare: three patients had a moderate increase of γ-GT at initiation of therapy (not exceeding two- to threefold the upper limit of normal), spontaneously regressive at 3 months; two uncontrolled patients presented clinical intolerance (nausea, diarrhea) when increasing dose to 1200 mg/day; and one uncontrolled patient presented biological intolerance (eightfold the upper limit of normal of ASAT and ALAT) when increasing dose to 1200 mg/day. The symptoms subsided after dose was decreased to 1000 mg/day. It is important to note that no adrenal insufficiency or increase in size of previously visible lesions was observed.

Finally, ketoconazole was discontinued for a number of reasons: in one patient because of efficacy of Gamma Knife radiosurgery; in one patient surgery was decided because she wanted to be pregnant and ketoconazole is contraindicated during pregnancy; in four patients surgically treated with bilateral adrenalectomy after prolonged treatment (4–5 years) with ketoconazole and no adenoma on MRI; and interestingly in five patients surgically treated because of the later visualization of an adenoma on MRI after treatment (12–30 months after initiation of ketoconazole) although no lesion was visible on the initial MRI (Fig. 2).

Table 2 Comparison between controlled ($n=17$) and uncontrolled ($n=16$) patients in 33 patients treated with ketoconazole. Control of the disease was defined by normalization of 24-h urinary free cortisol. Extreme values are represented between brackets. Sex ratio is presented as number of female (F)/number of male (M). Number of patients in the 'No pituitary surgery group' (S−)/number of patients in the 'After pituitary surgery group' (S+). Percentage indicates the proportion of patients in each subgroup.

	Controlled	Uncontrolled	*P*
No. of patients	17 (51%)	16 (49%)	
Mean age (years)	47.1 (26–73)	38.5 (18–58)	NS
Sex ratio (F/M)	17F/0M	11F/5M	<0.05
No surgery group (S−)/after surgery group (S+)	7S−/10S+	9S−/7S+	NS
ACTH 0800 h pg/ml	67 (8–172)	61.4 (17–149)	NS
ACTH 0000 h pg/ml	62 (25–100)	65.1 (11–190)	NS
Cortisol 0800 h nmol/d	660 (269–1270)	628 (141–955)	NS
Cortisol 0000 h nmol/d	535 (135–1100)	513 (301–960)	NS
Initial UFC nmol/d	1560 (248–16700)	2409 (287–12500)	NS
Follow-up (months)	22.6 (6–72)	10 (1–36)	<0.05

UFC, Urinary free cortisol. $P<0.05$ was considered significant; NS, non-significant.

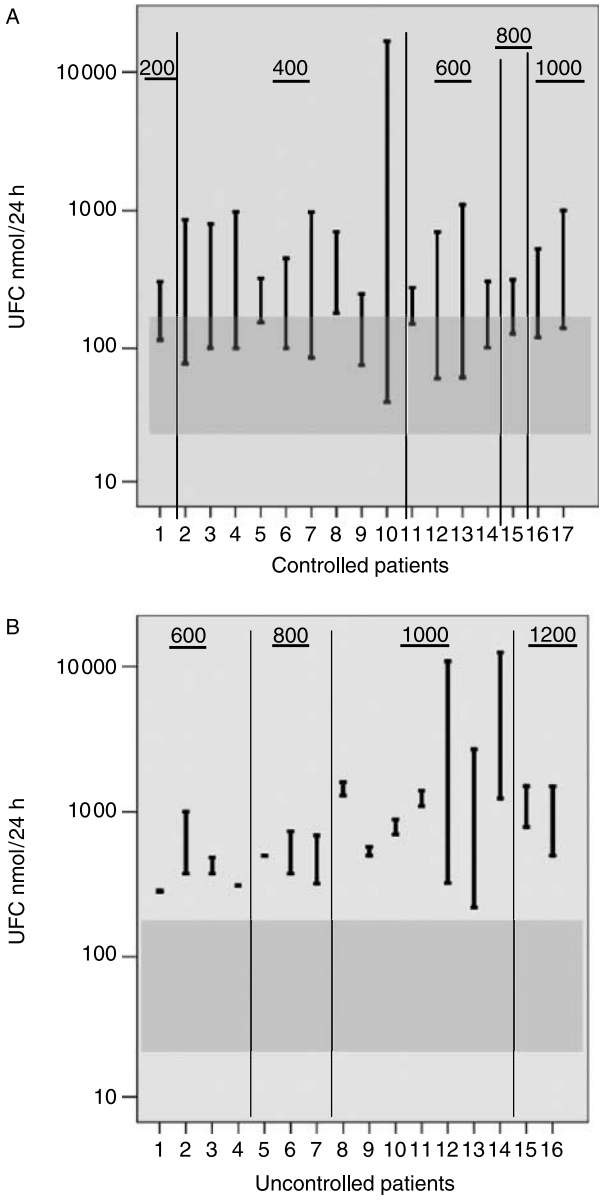

Figure 1 Urinary free cortisol (nmol/24 h) before initiation of and after the last evaluation on ketoconazole in Cushing's disease patients with controlled (A) or uncontrolled (B) hypercortisolism. In vertical bars, the upper point represents the initial level of urinary free cortisol (UFC), the lower point represents the final level of UFC after treatment with ketoconazole. Numbers in the upper part of the figure represent dose of ketoconazole in mg/day. Grey zone represents normal interval of urinary free cortisol (40–240 nmol/24 h). Remission was defined by normalization of urinary free cortisol.

Discussion

Transsphenoidal surgery remains the first-line treatment of CD (1). However, the rate of remission varies with the type of adenoma, estimated to be around 80% in microadenomas and about 50% in macroadenomas. Recurrence can be observed in 20–30% of cases, particularly in case of cavernous sinus invasion (2–4, 32–34).

Table 3 Comparison of the results of ketoconazole treatment in 'No pituitary surgery group' (S−) or 'After pituitary surgery group' (S+). Control of the disease was defined by normalization of 24-h urinary free cortisol. Extreme values are represented between brackets. Sex ratio: number of female (F)/number of male (M). Percentage indicates the proportion of patients in each subgroup.

	No pituitary surgery group	After pituitary surgery group	*P*
No. of patients	16 (49%)	17 (51%)	
Mean age (year)	44 (24–73)	42 (18–66)	NS
Sex ratio (F/M)	14F/2M	14F/3M	NS
ACTH 0800 h	54.4 (8–172)	76 (17–149)	NS
ACTH 0000 h	53.8 (11–93)	73 (17–190)	NS
Cortisol 0800 h	652 (141–1270)	637 (269–908)	NS
Cortisol 0000 h	547 (135–1100)	501 (186–960)	NS
Initial 24 h UFC	1792 (275–16700)	2124 (248–12500)	NS
Follow-up (months)	9.5 (1–30)	22.9 (3–72)	<0.05
Controlled	7 (44%)	10 (59%)	NS

UFC, urinary free cortisol. $P<0.05$ was considered significant; NS, non-significant.

The imidazole derivative ketoconazole reduces cortisol levels by inhibition of a variety of cytochrome P450 enzymes (19). In addition to its anti-steroidogenic effects, ketoconazole may also have extra-adrenal actions (as it was found to behave as a glucocorticoid receptor antagonist and to impair ACTH release *in vitro*) (21). With doses of ketoconazole varying from 200 to 1200 mg/day, about 50% of our patients with CD, treated as a first or as an adjunctive treatment were controlled at last evaluation, and only 15% revealed recurrence of hypercortisolism.

To our knowledge, this study currently represents the largest published about ketoconazole in CD. Earlier studies were based on fewer patients (23, 24, 26, 35–37), including one on 28 patients with CD, previously treated by conventional radiotherapy (30). In most cases, doses of ketoconazole were not increased beyond 1200 mg/day. Indeed, comparison with other series from the literature is difficult (Table 4): control of the disease varies from 0 to 100% of cases, but most of the studies had a low number of patients (between two and seven patients) (15). The only study with 28 patients, which described 93% of patients as controlled is biased by the fact that all patients had previously been treated with conventional radiotherapy, making a correct evaluation of ketoconazole alone impossible (30). Other medical treatments (mitotane (11–13), metyrapone (14, 38, 39), RU486 (40), bromocriptine (15, 41), etomidate (42, 43), peroxysome proliferator activator receptor (PPAR)-γ agonists (16–18)) or non-medical treatments (conventional radiotherapy (6, 7), Gamma Knife Radiosurgery (8–10), or bilateral adrenalectomy (5)) have been proposed as a treatment of CD, but they all have specific side effects, or were not evaluated in a sufficient number of patients (see Table 5 for comparative data).

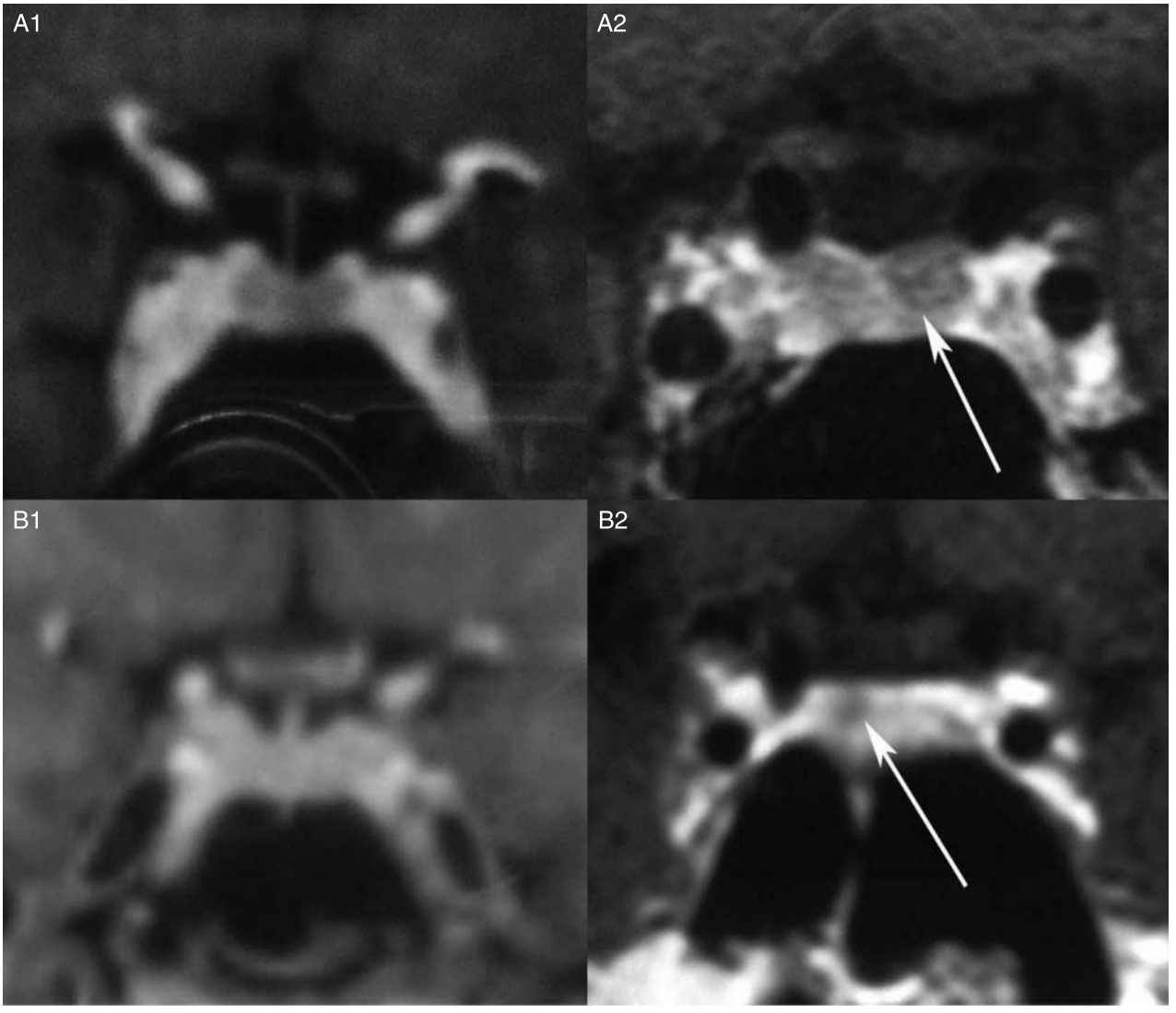

Figure 2 Pituitary MRI (sagittal, T1-weighted sequence after gadolinium injection) before and after ketoconazole treatment, disclosing the delayed visualization of an adenoma. (A1) Before ketoconazole treatment, heterogeneous pituitary without evident image of an adenoma. (A2) After 30 months of ketoconazole treatment, visualization of a left latero-sellar microadenoma. (B1) Before ketoconazole treatment, lack of pituitary adenoma image. (B2) After 12 months of treatment, a right latero-sellar microadenoma is visualized. In both cases, surgery was performed and allowed histological confirmation of the diagnosis and remission.

Interestingly, we did not find any significant difference in any of the parameters studied between patients in the 'No pituitary surgery group' and those in the 'After pituitary surgery group'. This point is particularly important in case of lack of visible adenoma on MRI. In this respect, our study illustrates the potential interest of a 'wait and see' attitude, which consists of giving ketoconazole first, and waits for the adenoma to possibly be visualized on MRI during subsequent follow-up. Indeed, in 5 out of the 15 patients without evident image on MRI, an adenoma could eventually be visualized after prolonged treatment (12–30 months), and these 5 patients were finally cured by transsphenoidal surgery. Although our data do not allow the claim that such a strategy is more effective than surgical exploration of the pituitary, they suggest that it represents a therapeutic option that may facilitate a second-line surgical approach.

No predictive factor of remission could be identified. In particular, initial hormonal levels and type of adenoma were not significantly different between patients controlled or not. Interestingly, none of our male patients were in the group of controlled patients. Although this difference was statistically significant, we did not manage to find any convincing hypothesis to explain this point. To our knowledge, gender differences in sensitivity to ketoconazole have never been described in CD. Moreover, among uncontrolled patients, three male patients with

Table 4 Efficacy of ketoconazole in previously published reports of the literature. Only studies including more than five patients are reported.

Author	Patients number	Mean follow-up (months)	Controlled patients (%)	Side effects (%)
Sonino (30)	28[a]	7	93	29
Loli (23)	6	8	100	0
Cerdas (35)	6	1	100	40
Mortimer (28)	8	0.5	100	25
McCance (36)	6	0.5	83	50
Engelhardt (37)	7	0.5	14	0
Our study	38	22.6	51.5	29
All studies	99	5.7	74	25

[a]Some of the studies included patients previously treated by conventional radiotherapy.

markedly elevated baseline UFC values (patients 12, 13, and 14) experienced a drastic fall in UFC reaching values approaching the upper limit of normal in two cases. As a consequence, male patients cannot be considered as non-responders to ketoconazole therapy.

The importance of the 3 months evaluation is worth underlying: all of our patients in remission were controlled within the first 3 months of treatment, not necessarily with the highest dose of ketoconazole. This means that ketoconazole is unlikely to be effective in case of uncontrolled hypercortisolism 3 months after the initiation of the treatment, if the dose was sufficiently increased. No predictive factor of later relapse of the disease could be individualized.

Five of our patients stopped the treatment during the first week because of clinical or biological intolerance, despite the use of a low dose at initiation of treatment (200 mg/day). No other patient stopped treatment during later follow-up. However, abnormal liver function tests were observed in one patient when ketoconazole was given at 1200 mg/day; this patient was not controlled and treatment had to be stopped anyway. All other adverse effects were transient and observed when increasing the dose of ketoconazole during the first week. Comparison with previous series is difficult as other treatments were sometimes associated. In the study by Sonino *et al.* ($n=28$ patients), ketoconazole was stopped during the first week for allergic reaction and acute liver toxicity in two patients (7% vs 13% in our series) (30). Other series did not evaluate enough patients to draw any firm conclusion. Few case reports described fatal hepatic cytolysis with ketoconazole (44–46). It is also necessary to stress that, as in another report based on three patients (31), three of our patients were treated for 60–72 months, with controlled hypersecretion and lack of adverse effects. This point confirms that intolerance is more likely to appear initially or at dose increase than during prolonged treatment at a stable dose. Close clinical and biological follow-up is necessary at titration steps on a weekly/monthly basis, while follow-up during long-term treatment with unchanged dose requires much less frequent controls. No Nelson's syndrome was observed in our study although secondary visualization of previously non-visible lesions might be considered as an equivalent of Nelson's syndrome in terms of mechanism.

To conclude, with 50% effectiveness and relatively few adverse effects, ketoconazole appeared as a valuable treatment in CD. When control of the disease was observed, it always occurred during the first 3 months of treatment. Side effects mainly occurred in the first week after initiation of treatment or in the case of dose increase, which makes it necessary to implement strict follow-up evaluations at each titration steps. In comparison with many other treatments of CD, ketoconazole also has the advantage of being less expensive. It can also be useful in case of lack of evident image on MRI, waiting for the adenoma to become visible to possibly allow easier secondary surgical removal. In such cases, if hypercortisolism is controlled, ketoconazole can be maintained during a prolonged period (up to 72 months in our study) without adverse effects.

Table 5 Comparison of different modalities of treatment of Cushing's disease in comparison with ketoconazole, based on the literature reports.

Treatment	Main mechanism of action	Controlled patients	Main adverse effect
Op'DDD (11–13)	11-β-hydroxylase inhibition	30–100%[a]	Hypercholesterolemia, liver alterations
Metyrapone (14, 38, 39)	11-β-hydroxylase inhibition	20–100%[a]	Hirsutism
Bromocriptine (15, 41)	Blockade of dopamine receptors	0–66%	Hypotension, nausea
Mifepristone (15, 40)	Glucocorticoid antagonist	50–80%[b]	Nausea, asthenia
Etomidate (42, 43)	11-β-hydroxylase inhibition	Case reports	
PPAR-γ agonists (16–18)	Bad defined	0–43%	Edema
Conventional radiotherapy (6, 7)		60–90%	Hypopituitarism
Gamma Knife Radiosurgery (8–10)		50–100%	Hypopituitarism
Bilateral adrenalectomy (5, 15)		84–91%	Nelson's syndrome
Transsphenoidal surgery (1–4, 32–34)		40–90%	
Ketoconazole	Cytochrome P450 enzymes inhibition	15–100%[a]	Liver function alterations

[a]Some of the studies included patients previously treated by conventional radiotherapy.
[b]Only few patients were treated by mifepristone making difficult a correct evaluation of this treatment.

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Received 15 October 2007
Accepted 16 October 2007