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A Pharmacokinetic and Pharmacodynamic Study of Delayed- and Extended-Release Hydrocortisone (Chronocort™) versus Conventional Hydrocortisone (Cortef™) in the Treatment of Congenital Adrenal Hyperplasia

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Abstract

Objective—Existing glucocorticoid treatment for congenital adrenal hyperplasia (CAH) is suboptimal and nonphysiological. We compared hormonal profiles during therapy with a new modified-release hydrocortisone (MR-HC), Chronocort™, to conventional hydrocortisone (HC), Cortef™, in patients with CAH.

Design and Patients—We conducted a Phase 2, open-label, crossover pharmacokinetic and pharmacodynamic study in 14 patients (7 males, ages 17 to 55) with classic 21-hydroxylase deficiency. One week of thrice daily HC (10 mg, 5 mg, 15 mg) was followed by one month of once daily MR-HC (30 mg at 2200 h). Twenty-four hour sampling of cortisol, 17-hydroxyprogesterone (17-OHP), androstenedione, and ACTH was performed at steady state.

Measurements—The primary outcome measures were 8- and 24-hour area under the curve (AUC) hormones and 0800 h 17-OHP.

Results—HC therapy resulted in three cortisol peaks. A single cortisol peak occurred at approximately 0600 h on MR-HC. MR-HC resulted in significantly ($P<0.001$) lower 24-hour, afternoon (1200 h to 2000 h), and night-time (2000 h to 0400 h) cortisol compared to HC. From 0400 h to 1200 h, when physiological cortisol is highest, cortisol was higher on MR-HC than HC ($P<0.001$). Patients on MR-HC had significantly ($P<0.05$) higher afternoon (1200 h to 2000 h) 17-OHP, androstenedione and ACTH, but significantly ($P=0.025$) lower 0800 h 17-OHP. No serious adverse events occurred.

Conclusions—MR-HC represents a promising new treatment for CAH. Overnight adrenal androgens were well-controlled, but rose in the afternoon with once daily dosing suggesting that a morning dose of glucocorticoid is needed. Further studies are needed to determine the optimal dosing regimen and long-term clinical outcome.

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Keywords

hydrocortisone; pharmacokinetic; circadian; Congenital Adrenal Hyperplasia; CAH

Introduction

Congenital adrenal hyperplasia due to 21-hydroxylase (21-OH) deficiency is an autosomal recessive disorder characterized by a defect in cortisol and aldosterone biosynthesis and androgen excess 1. In the 1950s, glucocorticoid replacement therapy was introduced and patients with CAH began to expect a normal lifespan 2. In spite of the progress made in the treatment of CAH, optimizing the treatment regimen for each patient is a dynamic and challenging process. The goal is to control the adverse effects of androgen excess while avoiding the unwanted complications of iatrogenic Cushing syndrome. No current glucocorticoid therapy is able to simulate the normal cortisol circadian rhythm and this may contribute to suboptimal clinical outcomes.

Many formulations of glucocorticoids are available to treat CAH and other forms of adrenal insufficiency. There is no standard treatment for CAH and physicians tailor treatment to the individual patient using short-acting, intermediate-acting or long-acting formulations 3. The timing of the doses varies depending on the physician and patient. Children with CAH are typically treated with hydrocortisone due to the short half-life in order to optimize childhood growth 4. After achieving adult height, patients are often switched to longer-acting glucocorticoid preparations that can be given once or twice daily to maximize convenience. Some physicians recommend using a reverse circadian pattern of glucocorticoid replacement to optimize androgen suppression 3, 5–7, because glucocorticoid given at bedtime suppresses the night-time surge of ACTH 7. Others advocate giving the highest glucocorticoid dose in the morning 8–10 or even waking the patient at 0300 h for a dose 10, 11, in an attempt to approximate the normal physiological timing of cortisol secretion. In healthy individuals, cortisol levels are low at night, begin to rise at 0200 h, peak in the early morning around 0800 h, and then decrease throughout the day 12.

The aim of this study was to compare Chronocort™, a novel modified-release formulation of hydrocortisone (MR-HC) designed to approximate physiological cortisol secretion, to Cortef™, the conventional immediate-release formulation of hydrocortisone (HC), in patients with CAH. Cortisol, ACTH, 17-hydroxyprogesterone (17-OHP), and androstenedione profiles were compared at drug steady state. In addition, 17-OHP measured at 0800 h, a biomarker commonly used to assess adrenal androgen control in patients with CAH, was evaluated. The use of a delayed- and extended-release formulation of hydrocortisone represents a new treatment approach to CAH, physiological cortisol replacement.

Subjects and Methods

This phase 2, open-label, crossover study compared hormonal steady state serum concentration profiles and pharmacodynamic responses of once daily MR-HC and thrice daily HC in patients with a diagnosis of classic CAH.

Study Subjects

Fourteen patients (7 females, 18 to 52 years, and 7 males, 17 to 55 years) with classic 21-hydroxylase deficiency (11 salt-wasting, 3 simple-virilizing) participated. Patients were 26.8 ± 3.8 years old with a BMI 29.2 ± 1.5 kg/m². The diagnosis and phenotype were confirmed with medical records and genetic testing. All patients were receiving glucocorticoid and

fludrocortisone therapy prior to entering the study. Seven patients were on dexamethasone (250-500 mcg/day), either once daily (6 patients) or twice daily (one patient). Three patients were on thrice daily HC (20-40 mg/day) and two patients were on twice daily prednisone (3.5-7.5 mg/day). All patients were older than 16 years (patients between 16-18 years demonstrated fusion of epiphyses on bone age X-ray), in good general health, and had a laboratory evaluation within 8 weeks of study entry with detectable 17-OHP and plasma renin less than 1.5 times the upper normal limit. Patients who were pregnant, lactating, had hepatic disease, renal disease, other significant medical or psychiatric illnesses, or were on medications that may induce hepatic enzymes and interfere with glucocorticoid metabolism were excluded. Sixteen patients were screened but two did not meet eligibility criteria. The study was approved by the Eunice Kennedy Shriver National Institute of Child Health & Human Development Institutional Review Board. Adult subjects and parents of participating adolescents gave written informed consent. All minors gave their assent.

Study Design

Up to eight weeks prior to the first visit, a screening 0800 h laboratory evaluation was performed (Fig 1). One week prior to the first visit, all patients were switched from their usual glucocorticoid medication to HC (10 mg at 0800 h, 5 mg at 1500 h, 15 mg at 2200 h; 14-22 mg/m²/day). In order to optimize the comparison conditions, we chose to use the same daily dose of HC as MR-HC.

On Day #1 of Visit #1, all patients had a baseline physical examination and underwent laboratory evaluation for electrolytes, liver and renal function tests, complete blood count (CBC) and pregnancy test (women only). Vital signs and orthostatic blood pressure were monitored during the duration of the stay. To evaluate drug profiles, 26 serum samples were obtained for assessment of steady state cortisol concentrations during the 24-hour period that began just before administration of the HC dose at 2200 h on day #1 of visit #1 (Figure 1). Blood samples were drawn every 30 minutes for the first two hours following each HC dose, and then every one to two hours until the next dose. Hourly samples were also analyzed for 17-OHP, ACTH and androstenedione. Patients were discharged to home on 30 mg (two pills of 15 mg) MR-HC as a single 2200 h dose for approximately 4 weeks. The dose of 30 mg per day MR-HC was chosen based on prior Phase 1 studies in healthy volunteers 13.

Patients were called weekly to assess for signs or symptoms of glucocorticoid excess or deficiency, and to monitor for adverse events. They also were asked to complete an outpatient evaluation that included vital signs to assess orthostasis. One dose adjustment was allowed for signs or symptoms of over- or under-treatment.

After 28 ± 3 days of MR-HC therapy, patients returned for visit #2 (Fig 1). Physical exam, laboratory tests, and vital signs were performed as they were in visit #1. To evaluate drug profiles, 23 serum samples were obtained during the 24 hours beginning just prior to the 2200 h administration of MR-HC, to assess steady state cortisol concentrations. Blood samples were drawn every 30 minutes for four hours following the MR-HC dose, and then every one to two hours for the remainder of the 24 hours. Again, hourly blood samples were also analyzed for 17-OHP, ACTH and androstenedione. Patients were discharged to home on their prior conventional glucocorticoid therapy. They were contacted at home up to one month following visit #2 to assess for further adverse events.

Study Medication

CortefTM (Pfizer, NY, USA) 10 mg and 5 mg tablets, and ChronocortTM (Phoqus Pharmaceuticals, Kent, UK) 15 mg and 5 mg tablets were used. ChronocortTM consists of a bilayer tablet, with an insoluble coating protecting all except one face. The unprotected face

has an outer non-drug layer which slowly erodes to expose the sustained-release hydrocortisone layer.

Hormonal assays

Serum concentrations of cortisol, androstenedione, and ACTH were measured using a competitive chemiluminescence immunoassay (ACM-Pivotal Global Central Laboratory, Rochester, NY). The cortisol assay has an analytical sensitivity of 5.5 nmol/L, with an intraassay coefficient of variation (CV) of 3.2% and interassay CV of 3.6%. The androstenedione assay has a sensitivity of 1.0 nmol/L, average intra- and interassay CVs of 6.4% and 7.7%, respectively, and normal reference ranges of 2.1 to 10.8 nmol/L for males and 1.0 to 11.5 nmol/L for females. The ACTH assay has a sensitivity of 1.1 pmol/L, intra- and interassay CVs of 7.7% and 8.5%, respectively, and a normal reference range of <10.1 pmol/L. 17-OHP was measured using Liquid Chromatography Tandem Mass Spectrometry at Quest Diagnostics Nichols Institute (San Juan Capistrano, CA). The assay has an analytical sensitivity of 0.12 nmol/L, interassay CV of 8.2% 14, and a normal reference range of 1.0 to 9.3 nmol/L for males and ≤ 8.6 nmol/L for females.

Statistical Analysis

Data are presented as mean $\pm$ SD, unless otherwise indicated, and were analyzed using Stata (v10, StatCorp LP, College Station, TX, USA). A p-value of less than or equal to 0.05 was considered statistically significant. The area under the curve (AUC) was computed using the trapezoidal rule for the entire 24-hour period and three 8-hour time periods (night-time 2000 h-0400 h; morning 0400 h-1200 h; afternoon 1200 h-2000 h), chosen to approximate physiological periods of low, high and intermediate cortisol secretion respectively. Peak plasma concentration ($C_{\max}$) and time to peak plasma concentration ($T_{\max}$) were determined using actual collection time points. Paired t-tests were used to compare treatments, as well as 0800 h MR-HC and 0800 h HC 17-OHP. Logarithmic transformation was performed for the 17-OHP and androstenedione data to achieve uniformity of variance and normal distribution.

Results

Pharmacokinetic Analysis

Twenty-four hour AUC cortisol was significantly higher when patients were receiving HC compared to MR-HC ($P < 0.001$; Table 1). $T_{\max}$ was greater for MR-HC than HC ($P < 0.001$), reflecting the delayed-release formulation. $C_{\max}$ also was higher for MR-HC ($P = 0.009$; Table 1).

24-hour Hormonal Profiles

At steady state HC, patients had three cortisol peaks in 24 hours representing the three doses of HC (Fig 2A). After MR-HC, a single cortisol peak occurred around 0600 h, 2 hours earlier than the cortisol peak previously observed in healthy individuals 13-15. ACTH levels were low overnight on MR-HC, but rose during the day, when cortisol levels were low or undetectable (Fig 2B). However, ACTH levels began to decrease around 1800 h, twenty hours after the MR-HC dose had been given, and four hours before the next dose was due. On HC, ACTH peaked at 0800 h. Similarly, 17-OHP levels were low overnight but rose during the day on MR-HC; on HC, 17-OHP rose to peak levels in the morning at 0800 h (Fig 2C). Androstenedione levels followed a similar pattern to 17-OHP but with less daily variation and between-treatment differences compared to the other hormones (Fig 2D).

8-Hour Hormonal Analysis

During the morning (0400 h to 1200 h) 8-hour period when physiological cortisol secretion is highest, cortisol AUC was higher on MR-HC than HC ($P<0.001$; Table 2). Conversely, during the night-time (2000 h to 0400 h) and afternoon (1200 h to 2000 h) periods when cortisol levels are physiologically low, patients had significantly lower cortisol AUC while on MR-HC compared to HC ($P<0.001$; Table 2).

ACTH AUC was significantly higher on MR-HC than HC during the night-time and afternoon time periods ($P<0.001$; Table 2).

During the night-time and morning 8-hour time periods, 17-OHP and androstenedione AUCs were similar in both treatment regimens (Table 2). However, during the afternoon, 17-OHP AUC ($P=0.039$) and androstenedione AUC ($P=0.012$) were significantly higher when patients were on MR-HC (Table 2).

0800 h 17-OHP Analysis

During MR-HC therapy, morning (0800 h) 17-OHP levels were significantly lower than during HC therapy (16.4 ± 27.9 vs. 86.9 ± 181.7 nmol/L; $P=0.025$). Morning (0800 h) 17-OHP levels obtained at screening when patients were on their usual glucocorticoid therapy were higher than during MR-HC therapy, but this difference was of borderline significance (78.7 ± 102.5 vs. 16.4 ± 27.9 nmol/L; $P=0.05$).

Adverse effects

All patients tolerated the change in glucocorticoid medication well. Three patients had dose adjustments during the course of the study and were on different doses of MR-HC for at least one week prior to Visit #2. Two patients had their MR-HC dose decreased to 25 mg at 2200 h due to trouble sleeping. One patient received an additional 5 mg MR-HC dose at 0800 h due to afternoon fatigue. There were no serious adverse events. Most common adverse events included headache, insomnia and fatigue (Table 3). The majority of symptoms remitted after one week on MR-HC, or with the dose adjustments mentioned. Two patients were excluded from analyses due to patient-related errors in medication dose.

Discussion

These data demonstrate that a delayed- and extended-release form of hydrocortisone can achieve good overnight and early morning control of ACTH and adrenal androgen secretion in patients with classic CAH. In our study, MR-HC, a novel formulation of hydrocortisone, given at 2200 h allowed for a delayed release and a single cortisol peak at 0600 h. During conventional HC, cortisol increased after each HC dose, and levels were undetectable by 0800 h, when physiological cortisol typically peaks. Morning 17-OHP measured at 0800 h, a biomarker commonly used to assess adrenal androgen control in patients with CAH, was lower when patients were on MR-HC compared to HC, reflecting improved early morning adrenal androgen control. However, this first attempt to approximate physiological cortisol secretion via oral medication failed to provide afternoon cortisol, leading to a rise in ACTH and 17-OHP in the afternoon and evening.

While mean 17-OHP levels over 24 hours were similar during the two treatment regimens, 17-OHP was higher from 1200 h to 2000 h when patients were on MR-HC. During this time period, cortisol reached very low levels, and was undetectable by 1400 h in most patients. Despite having undetectable cortisol for several hours, only one patient complained of afternoon fatigue. These low cortisol levels were associated with a rise in ACTH and higher 17-OHP levels observed in the afternoon and evening.

Interestingly, ACTH began to decrease a few hours before the 2200 h dose of MR-HC despite undetectable cortisol levels, suggesting persistence of an endogenous diurnal rhythm that is cortisol-independent. In healthy subjects, ACTH levels are highest in the morning (0600 h-0800 h) and lowest in the evening (1800 h-2000 h) 16, 17. This circadian rhythm was shown to be intact in six patients with simple-virilizing CAH who were withdrawn from cortisone therapy 7. In patients with Addison's disease treated with decreasing doses of cortisol, the diurnal rhythm in ACTH secretion was found to persist, with consistently lower levels in the evening despite chronic cortisol deficiency 17. This endogenous decline in evening ACTH suggests that full 24-hour cortisol coverage may not be needed to achieve 24-hour adrenal androgen control. It has been suggested that the diurnal variation of ACTH may be determined by the amplitude of secretory bursts, rather than the frequency of bursts, and does not necessarily require intact cortisol feedback 16. Other known factors involved in the regulation of ACTH secretion include corticotropin-releasing factor (CRF) and neurotransmitters, along with arginine vasopressin, oxytocin and angiotensin II 18, 19. As well, dopamine acts as an ACTH inhibitor 19.

Treatment of CAH is a challenging process. Glucocorticoid is typically given in doses sufficient to suppress adrenal androgen secretion without total suppression of the hypothalamic-pituitary-adrenal axis. It is often quite difficult to reduce excess androgen to acceptable levels without giving excess glucocorticoid 1. Androgen excess results in precocious puberty in children, impaired spermatogenesis or Leydig cell failure in adult males 20, 21, and infertility, hirsutism and amenorrhea in adult females. Glucocorticoid over-treatment can lead to low bone mineral density 22, 23 and Cushing syndrome 24. Both hyperandrogenism and hypercortisolism likely contribute to the impaired final heights observed in adults with CAH 25-28 and many patients suffer from signs and symptoms of both states. CAH patients have high rates of obesity 29. Children with CAH also have higher blood pressures along with elevated BMI 30. Adult women with CAH have been described as having high rates of insulin resistance and polycystic ovaries 31; this likely contributes to the fertility problems experienced by women with classic CAH 32. These risk factors put patients with CAH at higher risk for cardiovascular disease, the metabolic syndrome and type 2 diabetes.

Physiological cortisol replacement might improve control of adrenal androgens at lower glucocorticoid doses, thus decreasing the risk for development of these co-morbidities related to under- and over-treatment. None of the current glucocorticoid formulations mimics the natural circadian rhythm of cortisol release. Serum cortisol levels usually peak before wakening in the early morning 12 and then fall during the course of the day to a nadir in the late evening during sleep. Some physicians attempt to dose hydrocortisone to mimic this pattern with the highest dose in the morning. Others choose to use longer-acting formulations, decreasing the number of doses needed per day. However, long-acting glucocorticoid formulations often result in exposure to excess glucocorticoid, while shorter-acting preparations can lead to a build-up of androgens overnight 10.

Circadian infusion of hydrocortisone in patients with adrenal insufficiency has been promising. In a small study of patients with Addison's disease or CAH, ACTH levels were significantly lower with infusion therapy than with conventional three times a day hydrocortisone dosing 33. In the CAH patients, 17-OHP levels fell during the night-time infusion therapy and rose while receiving conventional therapy. Circadian hydrocortisone infusion in Addison's patients, via a subcutaneous insulin pump, has also yielded positive results by normalizing ACTH levels, improving subjective health scores and reducing the necessary effective glucocorticoid dose 34. These studies suggest that a more physiological therapy might improve management and the quality of life of patients with adrenal insufficiency. Chronocort™, the new modified-release tablet of hydrocortisone used in this

study, was designed to mimic the normal circadian pattern seen in serum cortisol levels of healthy patients. In a proof of principle study, Chronocort™ was shown to mimic the physiological circadian rhythm of serum cortisol levels in healthy volunteers 13. These subjects were adrenally suppressed with dexamethasone and given Chronocort™ 30 mg at 2200 h. Plasma cortisol samples revealed a nocturnal pattern very similar to that of physiological cortisol secretion. Subsequent mathematical modelling of an optimal MR-HC regimen suggested that twice daily medication could reproduce 24-hour physiological cortisol levels 15.

Our study is the first to use MR-HC in patients with adrenal insufficiency. Our CAH patients also displayed the expected overnight physiological pattern of cortisol release with a 2200 h dose of MR-HC. The resulting ACTH levels reflected this, and in turn, 17-OHP levels were low in the morning. The elevated afternoon ACTH and 17-OHP levels in patients receiving MR-HC indicates that increased daytime cortisol coverage would be needed. This could be achieved by adding a morning dose of MR-HC to the current 2200 h regimen, or by using a MR-HC with a longer half-life. Based on current data, most patients would require twice daily medication.

Our study was primarily designed to compare pharmacokinetic profiles of MR-HC to HC and to assess short-term safety and tolerability in CAH patients. The study therefore did not allow for flexible dosage adjustments that would be made in a routine clinical setting. Another drawback of this study was the small sample size and short duration of treatment. It is difficult to assess efficacy after only one month of treatment. In the clinical setting, following initiation of a new therapy, initial dose adjustments may occur based on clinical symptomatology, and dose adjustments based on hormonal evaluation are usually done after at least four to six weeks. As expected, patient-to-patient variability was observed, with respect to adrenal androgen control, and patient-specific dose adjustments would be needed with long-term therapy.

Overall, this new formulation of hydrocortisone was safe and well tolerated in our patients, with no serious adverse events and improved morning 17-OHP values. If a study allowed flexible dose adjustments and the administration of a morning dose of MR-HC, patients would likely display favourable cortisol, ACTH, 17-OHP and androstenedione profiles. A physiological cortisol profile with adequate adrenal androgen control would likely result in improved clinical outcome of CAH and could potentially improve the quality of life of patients with CAH and other forms of adrenal insufficiency. Such a study of longer duration, allowing dose adjustments and twice daily administration is indicated, but is not currently possible because the company manufacturing this MR-HC no longer exists. However, further development of MR-HC is being pursued. This first study in CAH patients using a novel form of hydrocortisone provides a foundation for future drug development that attempts to approximate normal physiology and improve treatment outcome.

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Figure 1. Crossover Pharmacokinetic Study. One week of HC at 10 mg at 0800, 5 mg at 1500 h, 15 mg at 2200 h, followed by one month of MR-HC 30 mg once daily at 2200 h.

Figure 2.

24-hour hormone profiles at steady state MR-HC and HC for A) cortisol, B) ACTH, C) 17-OHP, and D) androstenedione. To convert to conventional units, divide cortisol by 27.59 (mcg-hr/dL), ACTH by 0.22 (pg-hr/mL), 17-OHP by 0.0302 (ng-hr/dL) and androstenedione by 0.0349 (ng-hr/dL).

Table 1

Cortisol pharmacokinetic parameters for HC and MR-HC. All values are mean $\pm$ SE. *P<0.01, **P<0.001

	HC	MR-HC
AUC 24hr (hr*nmol/L)	5380 $\pm$ 414	3973 $\pm$ 166**
C _{max} (nmol/L)	651 $\pm$ 33	742 $\pm$ 47*
T _{max} (hours)	1.8 $\pm$ 0.3	6.7 $\pm$ 0.6**

Table 2

Hormone area under the curve (AUC) at steady state HC and MR-HC for three 8-hour time frames (night-time 2000 h-0400 h; morning 0400 h-1200 h; afternoon 1200 h-2000 h). All values are mean $\pm$ SE. P-values indicate differences between conventional hydrocortisone (HC) and modified-release hydrocortisone (MR-HC) for the specific time period. *P<0.05, **P<0.001. To convert to conventional units, divide cortisol by 27.59 (mcg-hr/dL), ACTH by 0.22 (pg-hr/mL), 17-OHP by 0.0302 (ng-hr/dL) and androstenedione by 0.0349 (ng-hr/dL).

Hormone AUC	Night-time 2000 h to 0400 h		Morning 0400 h to 1200 h		Afternoon 1200 h to 2000 h	
	HC	MR-HC	HC	MR-HC	HC	MR-HC
Cortisol (nmol-hr/L)	2262 $\pm$ 149	1186 $\pm$ 237**	1710 $\pm$ 157	2566 $\pm$ 188**	1435 $\pm$ 132	248 $\pm$ 39**
ACTH (pmol-hr/L)	245 $\pm$ 9	87 $\pm$ 12**	57 $\pm$ 16	41 $\pm$ 10	71 $\pm$ 28	228 $\pm$ 43**
17-OHP (nmol-hr/L)	103 $\pm$ 45	280 $\pm$ 113	292 $\pm$ 153	234 $\pm$ 122	239 $\pm$ 104	581 $\pm$ 226 *
Androstenedione (nmol-hr/L)	35 $\pm$ 13	52 $\pm$ 22	42 $\pm$ 15	45 $\pm$ 20	45 $\pm$ 20	66 $\pm$ 24*

Table 3

Adverse events reported by patients while receiving MR-HC.

Adverse Event	# Patients	Outcome (n)
Fatigue	4	Resolved spontaneously in 2-6 days (n=3); Resolved following dose increase (n=1).
Headache	4	Resolved in one day (n=1); Resolved following dose decrease (n=1); Resolved after return to conventional treatment (n=1); No resolution at close of study (n=1).
Acne	4	Resolved after 10 days (n=1); Resolved after return to conventional treatment (n=3).
Palpitations	3	Resolved spontaneously during first few days of treatment (n=3).
Insomnia	3	Resolved following dose decrease (n=2); Resolved following dose increase (n=1).
Moodiness	2	Resolved following dose decrease (n=1); Resolved after return to conventional treatment (n=1).
Decreased appetite	1	Resolved in 7 days.
Weight gain	1	Increase of 2 kg.
Paraesthesia	1	Resolved following dose decrease.
Irritability	1	Resolved following dose increase.