Ineffectiveness of Rosiglitazone Therapy in Nelson’s Syndrome

A. Munir, F. Song, P. Ince, S. J. Walters, R. Ross, and J. Newell-Price

Academic Unit of Diabetes, Endocrinology, and Metabolism (A.M., F.S., R.R., J.N.-P.) and Neuropathology (P.I.), School of Medicine and Biomedical Sciences, Medical Statistics Group (S.J.W.), The University of Sheffield, Sheffield S10 2JF, United Kingdom

Background: Peroxisome proliferator-activated receptor (PPAR)-γ agonists have been proposed as therapy to lower plasma ACTH in Cushing’s disease. Cyclical secretion of ACTH may, however, explain some of the responses seen. Patients with Nelson’s syndrome have persistently high levels of ACTH and may be a better model for examining new therapies to elevated ACTH levels.

Objective: The objective of the study was to assess whether high-dose rosiglitazone therapy reduces circulating ACTH levels in Nelson’s syndrome, a model of ACTH hypersecretion for which no established medical therapy exists.

Design: The design was an open-label, prospective, nonrandomized study over 14 wk.

Setting: The study was conducted at a university teaching hospital.

Patients: Six patients with Nelson’s syndrome participated in the study.

Management of Cushing’s disease is a challenge. Transsphenoidal surgery (TpS) remains the primary means of definitive therapy in suitable cases: depending on classification, initial remission is achieved in up to 60–80% of cases but with a relapse rate of up to 20%, and thus, long-term remission is achieved in only approximately 60% of patients (1). Moreover, the rate of hypopituitarism after TpS can be as high as 50% (2) and cure rate very low in 60% of patients (1). Moreover, the rate of hypopituitarism is present in human corticotroph adenomas (5), data on the effectiveness of agonists for Cushing’s disease caused by macroadenomas (3). These data highlight the need for alternative therapies.

Recently interest in medical therapy has focused on the use of peroxisome proliferator-activated receptor (PPAR)-γ agonists as therapy to lower ACTH and cortisol (4). Animal data suggested that high-dose rosiglitazone retarded tumor growth and lowered ACTH and cortisol levels in a mouse model of Cushing’s disease. Although PPAR-γ receptor expression is present in human corticotroph adenomas (5), data on the effectiveness of agonists for Cushing’s disease in humans has been conflicting. Rosiglitazone at a dose of 8 mg/d (maximum licensed dose) normalized urinary free cortisol (UFC) at 30–60 d in six of 14 patients with active Cushing’s disease but with subsequent escape of control, whereas acute administration had no effect on plasma ACTH (6). Similar data were found in two patients with Cushing’s disease with rosiglitazone 8 mg given for 33 and 20 d, with a modest fall in UFC levels and urinary cortisol to creatinine ratio (7). Pioglitazone, a less potent PPAR-γ agonist, given at maximum licensed dose for 30 d in five patients with Cushing’s disease was not effective at lowering ACTH or cortisol levels (8). Problems with these studies include the potential cyclicity of ACTH secretion in Cushing’s disease because this may be interpreted as a response and the lack of withdrawal of drug to confirm the efficacy of the effects seen.

In contrast, plasma ACTH levels remain high in patients with Nelson’s syndrome, a condition that may occur in 8–38% of adults after bilateral adrenalectomy for Cushing’s disease and in which a locally aggressive pituitary tumor may develop (9). Patients can present with mass effects, headache, visual field defects, and external ophthalmoplegia and are characteristically pigmented with high ACTH levels. It remains controversial as to whether the tumor progression is a result of the lack of cortisol feedback after adrenalectomy or whether the progression reflects corticotroph tumors that were programmed to behave in an aggressive manner (9). Corticotroph tumor progression can be monitored by magnetic resonance imaging (MRI) and plasma ACTH levels, but no established medical therapy exists (1). Radiotherapy to the pituitary at the time of adrenalectomy has been shown.

Methods: Patients were assessed at −2, 0, 4, 8, and 12 wk. Rosiglitazone 12 mg/d was administered between 0 and 8 wk. PPAR-γ immunoreactivity was assessed in pathological tissue.

Outcome Measure: Plasma ACTH was measured before (0830 h) and 120 min after morning dosing with hydrocortisone (HC).

Results: One female withdrew prior to commencing therapy for personal reasons. There was no evidence that ACTH levels changed over time (P = 0.864). The average ACTH level was 1187 ng/liter (95% confidence interval 928–1446) for patients before the HC dose and 432 ng/liter (95% confidence interval 172–692) after the HC dose. PPAR-γ immunoreactivity was positive in three ACTH-secreting tumors available.

Conclusions: Rosiglitazone 12 mg/d did not change circulating ACTH over time, despite PPAR-γ receptor expression in the tumor tissue. However, this does not preclude the possibility that other patients may respond or that higher doses of rosiglitazone or more potent agonists might prove useful treatment. (J Clin Endocrinol Metab 92: 1758–1763, 2007)
has been shown to be of benefit in preventing the onset of Nelson’s syndrome in some series, but review of other series does not confirm this (9). Further pituitary surgery may be needed (10), but anatomical considerations, especially lateral invasion into the cavernous sinus, may preclude this. Routine clinical monitoring after bilateral adrenalectomy for Cushing’s disease includes measurement of plasma ACTH after dosing with morning glucocorticoid, and in Nelson’s syndrome ACTH levels fail to suppress to less than 200 ng/liter (11).

Bilateral laparoscopic adrenal surgery for Cushing’s disease is now being considered more frequently. It is likely that more patients will present with Nelson’s syndrome or at the very least with high plasma ACTH levels and corticotroph tumor progression on MRI. In the light of all these data, we studied the effect of high-dose rosiglitazone (12 mg/d) in Nelson’s syndrome. Our aims were to assess whether this dose would cause a reduction in plasma ACTH in this model of ACTH hypersecretion (and by inference retard tumor growth) to correlate any effect to PPAR-γ receptor status in tumor tissue and thus to ask whether this dose of rosiglitazone might be a potential effective medical therapy.

Patients and Methods

The study was approved by the North Sheffield Ethics Committee and the Medicines Agency of the United Kingdom. Written informed consent was obtained from the six patients recruited to the study. All had a previous diagnosis of Cushing’s disease according to standard diagnostic criteria (12), had undergone pituitary surgery, and had a corticotroph adenoma with positive immunostaining for ACTH. All had subsequently needed bilateral adrenalectomy to control cortisol hypersecretion. Nelson’s syndrome was defined as a plasma ACTH greater than 200 ng/liter 2 h after the maintenance dose of glucocorticoid given at 0830 h in the morning and had been demonstrated in all (11). Details of each of the patients are given below.

Patient 1 was a 36-yr-old male, originally presenting at age 13 yr with Cushing’s disease in 1982. Computed tomography scan showed a left suprasellar mass. He underwent TpS at age 15 yr. Histology confirmed an ACTH-positive adenoma. He was not in remission and underwent a second TpS and required glucocorticoid, GH, and testosterone replacement therapy. Postoperative cortisol levels were never undetectable. UFC levels were elevated 7 yr later and bilateral adrenalectomy performed. MRI revealed a left suprasellar 5-mm lesion (maximum diameter). Three years later cutaneous and tongue pigmentation was noted and Nelson’s syndrome diagnosed, with ACTH levels of 360 ng/liter after morning glucocorticoid treatment.

Patient 2 was a 66-yr-old male, originally presenting in 1998 with chronic hemorrhagic pancreatitis and Cushing’s disease. Pituitary macroadenoma was found on MRI and at TpS, histology confirming an ACTH-positive corticotroph adenoma. Postoperative recovery was complicated by a pulmonary embolus, and after anticoagulation he developed a large midline intracranial hematoma with hydrocephalus requiring craniotomy. He was not in remission and bilateral adrenalectomy was performed later that year. Three-field fractionated radiotherapy was completed 3 yr later (1991) due to concerns of tumor expansion (22 mm maximum diameter) on MRI. He was deeply pigmented with elevated plasma ACTH levels (ACTH 964 ng/liter after morning glucocorticoid treatment).

Patient 3, a 38-yr-old female, presented with Cushing’s disease in childhood in 1980 and underwent TpS and fractionated three-field radiotherapy in 1983. Highly active disease necessitated bilateral adrenalectomy in 1984. Nelson’s syndrome was subsequently diagnosed with pigmentation, ACTH levels of 314 ng/liter postglucocorticoid dose, and tumor recurrence on MRI. A second TpS was performed in 1993 in another center. In 1996 further TpS histology confirmed an ACTH-producing adenoma. In 1998 MRI demonstrated tumor encasing the left internal carotid (10 mm maximum diameter). She underwent y-knife stereotactic radiotherapy in 1999 and is on full anterior pituitary hormone replacement therapy.

Patient 4, a 39-yr-old female, presented in 1994 with Cushing’s disease and underwent TpS and radiotherapy 6 months later. Histology was ACTH positive. Continuing uncontrolled hypercortisolism necessitated bilateral adrenalectomy later that year. Twelve months later Nelson’s syndrome was diagnosed with cutaneous pigmentation, MRI revealing tumor surrounding the right internal carotid artery (18 mm maximum diameter), and ACTH levels of 315 ng/liter 2 h after morning glucocorticoid. She is on full anterior pituitary hormone replacement therapy.

Patient 5 is a 35-yr-old female with Cushing’s disease, with a rightsided pituitary adenoma. TpS was performed, and histology was an ACTH-positive corticotroph adenoma. Postoperative cortisol was 729 nmol/liter. Cushingoid features persisted, resistant to metyrapone and ketoconazole. MRI showed residual tumor in the right cavernous sinus. She underwent bilateral laparoscopic adrenalectomy, with stereotactic radiotherapy to the remaining pituitary tumor. However, progressive pigmentation was noted with enlarged tumor on MRI to 19 mm maximum diameter. Her postglucocorticoid plasma ACTH levels were elevated at 1033 ng/liter, confirming Nelson’s syndrome.

Patient 6 is a 35-yr-old female who presented with Cushing’s disease in 1998. MRI revealed a right-sided adenoma. She underwent TpS. Histology revealed an ACTH-positive corticotroph adenoma. Postoperatively persistent disease necessitated bilateral adrenalectomy. Four months later she presented deeply pigmented and was diagnosed with Nelson’s syndrome, with plasma ACTH levels 343 ng/liter postmorning glucocorticoid dose. MRI confirmed residual tumor (5 mm).

In summary, all six patients had radiological evidence of a pituitary mass lesion at the time of diagnosing Nelson’s syndrome. Before this study, suprasellar or infrasellar extension was present in two patients, with invasion laterally in three, and disease confined to the fossa in one patient. Macroadenoma (>10 mm in two planes) was noted in patient 2, whereas all the other patients had microadenomas on MRI (Table 1). Despite supras- and/or infrasellar extension of tumor in most cases, only patient 2 had neurological symptoms, secondary to postoperative complications. There were no detectable preoperative visual field defect or cranial nerve lesions in any patient. Anterior pituitary function was assessed at regular intervals. Hormone replacement was tailored individually. Eye examination/visual fields were assessed on routine physical examination.

Study protocol

The six patients entered an open-label study over 14 wk. Plasma ACTH was measured at 0830 h before and at 1030 h, 2 h after the oral dose of glucocorticoid in all patients. A totally successful response to treatment would be a fall of plasma ACTH into the normal range (5–51 ng/liter) at 120 min after the first dose of morning hydrocortisone (HC). In addition, the urea and electrolytes, glucose, liver biochemistry, and full blood count were measured at each visit. Patients attended the endocrine unit for five visits at 0830 h in the fasted state. Patients did not alter their glucocorticoid medication for the duration of the study. A dose of rosiglitazone 12 mg/d was administered during wk 0–8. The medication was purchased from the hospital pharmacy, and the patients were given monitoring diaries to record any symptoms or omitted medication, and packets were inspected to ensure compliance.

Justification of dose of rosiglitazone

Because the original study in mice had used a high dose of rosiglitazone, we wanted to use the highest dose known to be safe in man for all our patients (13). All patients received a dose of rosiglitazone 12 mg/d. This is 1.5 times the maximum licensed dose used for type 2 diabetes mellitus but has previously been shown to be well tolerated but without added improvement in glycemic control.

Assays

ACTH samples were taken in duplicate and flash frozen at −40 C and run in the same immunoradiometric assay (Nichols, San Juan Capistrano, CA), with a sensitivity of 0.04 pmol and inter- and intraassay coefficients of variants 2.4–8.5% and 3.9–9.9%, respectively.
radiotherapy; RT, external beam pituitary radiotherapy; M, male; F, female.

(H2O2) in methanol at room temperature for 20 min. Nonspecific binding of endogenous peroxidases were quenched with 2% hydrogen peroxide for normality. Intracellular cytoplasm or nuclei was defined as a positive result for PPAR-γ expression in tumor tissue.

Surgically excised human pituitary tumor tissue was available for three patients (patients 1, 2, and 5) after resection for their Cushings disease. Immunocytochemical analysis of PPAR-γ expression was performed. Tissue aliquots were fixed with 4% paraformaldehyde and processed for paraffin embedding. Sections were immunostained using avidin-biotin-peroxidase to PPAR-γ (Santa Cruz Biotechnology, Santa Cruz, CA) as used by Heaney et al. (4), and immunoreactivity in either intracellular cytoplasm or nuclei was defined as a positive result for PPAR-γ expression. In brief, 3-μm sections were cut and mounted on ProbeOn-Plus slides (Fisher, Houston, TX). The sections were deparaffinized with xylene and rehydrated by graded ethanol treatment. Endogenous peroxidases were quenched with 2% hydrogen peroxide (H2O2) in methanol at room temperature for 20 min. Non-specific binding was blocked with Power Block (BioGenex, San Ramon, CA) at a 1:10 dilution according to the manufacturer’s recommendations. Microwave antigen retrieval was performed in 300 ml citrate buffer (pH 6) for 10 min. Slides were incubated with 1:50 diluted primary antibody for 2 h at room temperature. All of the slides were subsequently washed in PBS, and then 1:500 diluted biotin-labeled secondary antibody was applied at room temperature for 30 min. Immunoreactivity was detected with the Vectastain Elite ABC immunoperoxidase system according to the manufacturer’s recommendations (Vector Laboratories, Burlingame, CA) by incubating sections for additional 30 min. Sections were counterstained with Gill’s hematoxylin and then dehydrated through graded alcohol into xylene and mounted under glass coverslips. Negative controls were obtained by omitting the anti-PPAR-γ specific primary antibodies. Negative controls were performed for each slide using non-immune serum.

Statistical analysis

Sample size and power. Assuming a within-person variability of ACTH levels of approximately 400 ng/liter for the pre-HC dose and 250 ng/liter post-HC dose, 15 patients are needed to detect a change of 200 ng/liter with a power of 80% with 5% significance. (For five subjects, a statistically significant change in ACTH levels would be >420 ng/liter with a sd 250.)

Analysis

The main aim of the analysis was to establish whether ACTH levels changed over time after high-dose rosiglitazone therapy. P < 0.05 was regarded as statistically significant. The ACTH data were longitudinal and consisted of five repeated observations over time (wk 2, 4, 8, and 12) on each of the patients. Therefore, a marginal generalized linear model for longitudinal data, with coefficients estimated using generalized estimating equations (14), with robust srs and an exchangeable autocorrelation matrix in STATA (version 9, 2005; StataCorp, College Station, TX) was used to analyze the ACTH levels and allow for the longitudinal nature of the data. Estimates for the coefficient(s) from these regression models are reported along with their associated 95% confidence interval (CI). The exchangeable correlation structure corresponds to an equal correlation model, meaning that the correlations between the ACTH levels at different time points are equal to each other. In this analysis the following assumptions have been made: the outcome, ACTH level, is a continuous variable; there is or potentially is a linear relationship between ACTH level and time; the ACTH measurements, within an individual, over time are correlated with each other so that the correlations between ACTH levels at various time points are the same. We assumed that the errors or residuals from the longitudinal generalized linear model were normally distributed, and this was examined by plotting a histogram of the residuals and by a Shapiro-Wilk test for normality.

Results

The patients were diagnosed with Nelson’s syndrome between the years 1993 and 2002. The mean duration between prior unsuccessful TpS for Cushing’s disease to total bilateral adrenalectomy was 2.66 yr (range, 4 months to 10 yr). The median time taken to diagnosis of Nelson’s syndrome was 1.5 yr (range, 2 months to 3 yr). Pituitary irradiation had been prescribed in patients 2–5. One had received standard three-field fractioned radiotherapy at the time of adrenalectomy; the other three received conventional three-field fractioned radiotherapy at a later date, and two underwent stereotactic radiotherapy (y-knife) (Table 1). Five patients completed the study without complication or adverse events. One (patient 6) withdrew for personal reasons before taking any study drug. Patient 3 independently reported a reduction in cutaneous pigmentation while on the treatment with rosiglitazone at visit 3, but there was no change in plasma ACTH levels.

Figure 1 shows how the pre- and post-HC dose ACTH levels vary over time for the five patients. There appears some fluctuation in individual plasma ACTH values, but there were no consistent changes. The longitudinal model suggested there was no interaction between pre-HC dose and post-HC dose and time (P = 0.163), i.e. the relationship be-

### TABLE 1. Summary of patient characteristics

| Patient | Age (yr) | Sex | Basal plasma ACTH (ng/liter) | Year of NS | Pituitary MRI | Pituitary irradiation | Interval from bilateral adrenalectomy to NS (months) | Daily hormone replacement therapy |
|---------|----------|-----|-------------------------------|------------|--------------|----------------------|-----------------------------------------------------|----------------------------------|
| 1       | 36       | M   | 1554.6                        | 2001       | Left suprasellar extension, 5 mm | Nil                  | 6                     | Hydrocortisone, fludrocortisone, T4                |
| 2       | 66       | M   | 762.4                         | 2002       | Invasion of sphenoid air cell, 22 mm | RT for NS            | 2                     | Hydrocortisone, fludrocortisone, T4                |
| 3       | 38       | F   | 1160.9                        | 1993       | Invasion of left internal carotid, 10 mm | RT at ADRX and SRT  | 36                    | Hydrocortisone, fludrocortisone, T4, cycloprogynova, GH |
| 4       | 39       | F   | 756.9                         | 1996       | Invasion of right carotid internal carotid, 18 mm | RT for NS            | 4                     | Prednisolone, fludrocortisone, T4, GH             |
| 5       | 35       | F   | 1165.9                        | 2002       | Invasion of right cavernous sinus, 19 mm | SRT for NS           | 7                     | Hydrocortisone, fludrocortisone, T4                |
| 6       | 35       | F   | 1222.4                        | 1998       | Right-sided microadenoma, 5 mm | Nil                  | 36                    | Hydrocortisone, fludrocortisone                   |

Size of tumor is maximum diameter. NS, Nelson’s syndrome; TBA, total bilateral adrenalectomy; ADRX, adrenalectomy; SRT, stereotactic radiotherapy; RT, external beam pituitary radiotherapy; M, male; F, female.
between ACTH level and time does not vary differently pre- and post-HC dose. There was no reliable statistical evidence to suggest that the residuals from the longitudinal model (containing time and treatment group) were not normally distributed ($P = 0.11$).

There was no evidence that ACTH levels changed over time ($P = 0.864$). So it appears that high-dose rosiglitazone therapy has no effect on changing ACTH levels over time in this sample of patients with Nelson’s syndrome. As expected from clinical experience and physiology, there was evidence from the longitudinal model of a difference between the pre-HC and post-HC dose ACTH levels ($P = 0.001$), with patients after the dose having significantly lower ACTH levels, 754 ng/liter (95% CI 485–1024), than pre-HC dose, but this is not of clinical significance other than confirming the presence of Nelson’s syndrome. The average ACTH level was 1187 ng/liter (95% CI 928–1446) for patients pre-HC dose and 432 ng/liter (95% CI 172–692) after the HC dose.

In the three patients (1, 2, and 5), paraffin-embedded tumor samples from their original TpS were available. In each of these, there was strong immunoreactivity for PPAR-$\gamma$, with predominantly cytoplasmic staining [as was also found by Heaney et al. (4) (Fig. 2)].

**Discussion**

Treatment of Cushing’s disease and complications such as Nelson’s syndrome remain a challenge. This is illustrated all too well by the case histories of the patients participating in this study. Here our main objectives were to use Nelson’s syndrome patients to test the efficacy of rosiglitazone therapy in decreasing ACTH levels. The results show that rosiglitazone has no effect on ACTH levels in this sample of patients with Nelson’s syndrome.
syndrome as a model for persistent ACTH hypersecretion and assess whether rosiglitazone (12 mg/d) could be used as a therapeutic to reduce ACTH levels and, by inference, control tumor growth. We chose this dose because it was higher than that licensed for type 2 diabetes mellitus but has previously been shown to be well tolerated (13). Documented side effects of licensed doses of rosiglitazone include hepatic dysfunction and edema, but there were no adverse effects in our patients. All patients in our study received the same dose, and the design included a drug-withdrawal phase to ensure that had there been any reduction in plasma ACTH, we could in all likelihood ascribe this to the effect of rosiglitazone. We used measurement of plasma ACTH before and 2 h after morning glucocorticoid therapy, which is the same as the routine monitoring used by us, and others, in clinical practice for patients who have undergone bilateral adrenalectomy for Cushing’s disease (11). Two other studies reporting the use of rosiglitazone in few patients with Nelson’s syndrome, at lower licensed doses of 4 and 8 mg/d, also failed to show a response (15, 16). Our data show, however, for the first time, that even when rosiglitazone is given at high nonlicensed doses (12 mg/d) over 8 wk does not affect ACTH levels in patients with Nelson’s syndrome, even though PPAR-γ is expressed in excised pituitary tissue. This is disappointing and reduces the likelihood that rosiglitazone may be used as a potential therapeutic in this condition. However, the patient numbers in this study are small, and it is possible this group had aggressive disease resistant to treatment. This is illustrated by the relatively short time to the development of Nelson’s syndrome in our patients and the multiple modalities of treatment that they had received in an effort to control their ACTH hypersecretion. Our patients who had received radiotherapy years before study entry had done so many years previously, and thus, even if an effect of rosiglitazone been observed, it is highly unlikely that this could have been ascribed to an effect of the radiotherapy over the study period.

Our data are consistent with others that failed to show an effect of PPAR-γ agonists in Cushing’s disease given at licensed doses (8). Even though ACTH secretion is pulsatile, the relatively consistent nature of ACTH secretion can be seen from the values in this study. The original data demonstrating the effective use of rosiglitazone to lower ACTH in mouse models of Cushing’s disease used very high doses (150 mg/kg/d) of drug (4). Clearly the doses used in human studies are 2 orders of magnitude lower than this. Thus, taking these considerations into account and the data presented here, and elsewhere, it seems likely that even when rosiglitazone is used at higher than licensed doses that is unlikely to have a major role to reduce ACTH in states of hypersecretion, such as Nelson’s and Cushing’s disease. This does not exclude, however, the possibility that PPAR-γ agonists in development with greater agonist activity will not be of use for this purpose in the future. Furthermore, it is possible that treatment may have to be extended for longer than the 8 wk used here and that individual response may be seen in some patients. This said, we did not see even a trend toward a response using rosiglitazone, and thus, it is unlikely that even more protracted periods therapy would be effective using this agonist, but this cannot be excluded. Recent data, however, have shown that rosiglitazone may exert antitumoral effects independent of PPAR-γ (17), and thus, it is possible that use of this compound may have beneficial effect on either tumor shrinkage or slowing tumor growth, independent of any action on lowering plasma ACTH.

We wanted to assess the PPAR-γ expression in the tumor tissue because this might have an influence on the effects seen. Our results show robust expression of PPAR-γ. We deliberately used the same antibody as used in the original report by Heaney et al. (4), in which a positive effect of rosiglitazone was shown in a mouse model of Cushing’s disease. Our tumor samples were, however, from pituitary specimens obtained at surgery for Cushing’s disease, before the development of Nelson’s syndrome. It is possible the development of Nelson’s syndrome, and an aggressive tumor phenotype, is associated with loss of PPAR-γ expression, abrogating the effect of rosiglitazone. Because we do not have tumor tissue from surgery performed for Nelson’s syndrome, we are unable to test this possibility directly, and it merits further study.

Medical therapy for prolactinomas and acromegaly is effective for hormonal and tumor control. Historically, medical therapy to lower ACTH in Cushing’s disease and Nelson’s syndrome has been disappointing. Apart from PPAR-γ agonists, other attention on oral therapy is currently focused on dopamine agonists and retinoic acid as possible therapy. Cabergoline given as short-term therapy at doses of 1–3 mg/wk may lower UFC in up to 40% of cases of Cushing’s disease, but longer studies are needed (18). For retinoic acid, work in vitro (19) and in dogs (20) has recently shown the potential for this therapy in Cushing’s disease, and trials in humans are awaited. Finally, the injected multiligand somatostatin analog SOM230 has been shown to reduce UFC in some patients with Cushing’s disease (21).

In conclusion, our data with high-dose rosiglitazone add to the weight of evidence that this drug is not effective in lowering plasma ACTH, and other therapies need to be developed for this purpose for the treatment of Cushing’s disease and its complications.

Acknowledgments

We thank Anita Doane and Vicky Ilbott on the endocrine unit for their assistance with this study and the patients for their participation.

Received September 12, 2006. Accepted February 14, 2007.

Address all correspondence and requests for reprints to: Dr. J. Newell-Price, Senior Lecturer and Consultant Endocrinologist, Academic Unit of Diabetes, Endocrinology, and Metabolism, The University of Sheffield, Room OU142, O Floor, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, United Kingdom. E-mail: j.newellprice@sheffield.ac.uk.

This work was supported by the Society for Endocrinology and Clinical Endocrinology Trust Clinical Training Fellowship (to A.M.).

Disclosure Statement: The authors have nothing to disclose.

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