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ORIGINAL RESEARCH

Nocturnal Asthma: Proof-of-Concept Open-Label Study with Delayed-Release Prednisone

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ABSTRACT

Introduction: Many inflammatory conditions, such as asthma, show circadian symptoms that are worse at night. Delayed-release prednisone was developed for bedtime administration to optimize inhibition of nocturnally elevated pro-inflammatory cytokines. A proof-of-concept study was undertaken to examine the impact of delayed-release prednisone on nocturnal awakenings in patients with asthma requiring treatment with oral steroids.

Methods: In this single-center, open-label study, patients receiving long-term treatment with conventional prednisone administered at 08:00 h were switched to 4 weeks of treatment with the same dose of delayed-release prednisone given at 22:00 h. The primary efficacy endpoint was the change in number of nocturnal awakenings during the final 2 weeks of each treatment phase.

Results: Seven patients received treatment with delayed-release prednisone. Mean nocturnal awakenings because of asthma decreased from 10.0 ± 5.45 with conventional prednisone to 2.1 ± 4.41 with delayed-release prednisone, a mean reduction of -7.9 ± 6.07 (82.7% reduction). Delayed-release prednisone was generally well tolerated, and there were no unexpected safety findings.

Conclusions: Although the size of the efficacy population was too small to detect any statistically significant changes in nocturnal asthma control, this proof-of-concept study suggests that nighttime administration of delayed-release prednisone provides better asthma symptom control compared with morning administration of conventional prednisone.

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INTRODUCTION

More than 60 years after their first clinical use, corticosteroids still form the mainstay of treatment for inflammatory conditions [1, 2]. With awareness of potential safety and tolerability issues arising from systemic exposure, topical corticosteroid preparations were developed, including inhaled formulations for use in inflammatory respiratory conditions (e.g., asthma). In other inflammatory conditions (e.g., rheumatoid arthritis or polymyalgia rheumatica), the chronic systemic nature or inaccessible location of the affected site precludes routine topical treatment and, therefore, administration of corticosteroids remains predominantly via the oral route. The need to improve the benefit:risk ratio for these patients continues to drive the development of this important class of treatment.

A common feature of many inflammatory conditions, including asthma, is the circadian pattern of symptoms [3, 4]. Recognition of this characteristic in rheumatoid arthritis prompted development of an oral formulation of prednisone that can be taken at bedtime, but releases the active ingredient approximately 4 h later, at the appropriate time to inhibit the nocturnal peak of pro-inflammatory cytokines that are associated with morning symptoms [5, 6]. In patients with rheumatoid arthritis, delayed-release prednisone reduces morning stiffness significantly more than the same dose of conventional prednisone (3–10 mg/day) taken in the morning, with benefit sustained over 12 months of treatment [7, 8]. Although in Europe, it is predominantly used to treat rheumatoid arthritis, in the USA and other countries the common nature of many inflammatory conditions is recognized in the approved indication of delayed-release prednisone as an anti-inflammatory or immunosuppressive agent for a range of conditions, including allergic and respiratory conditions.

The circadian nature of asthma symptoms is widely recognized by clinicians and patients alike. The involvement of clock genes located centrally and in the lung has been reported [4]. In the UK, 37% of patients with asthma reported frequent nighttime symptoms and in a large Europe-wide survey of patients with asthma, 54.5% reported one or more nights during the previous week with waking because of asthma [9, 10]. Nocturnal symptoms are usually indicative of poor asthma control [11]. Although adjustment of inhaled therapy may be sufficient for most patients, frequent nocturnal asthma symptoms are characteristic of severe persistent asthma that is difficult to treat [11, 12]. Patients with these symptoms usually require long-term treatment with oral corticosteroids in addition to inhaled therapy. In the USA, an estimated 4% of patients with asthma receive treatment with oral corticosteroids for at least 6 months, predominantly at doses up to 10 mg per day [13].

As in rheumatoid arthritis, there might be room to improve the optimal or preferred delivery of glucocorticoids and possibly improve the therapeutic ratio in patients with severe persistent nocturnal asthma who require longer term therapy. Delayed-release prednisone (also known as modified-release prednisone) once released in the gastrointestinal track behaves exactly like conventional (immediate-release prednisone) [5]. When taken orally at bedtime, prednisone peaks in the plasma approximately 6 h later [5]. This corresponds to the time when the

hypothalamic–pituitary–adrenal (HPA) axis is most active, and is the preferred time to deliver glucocorticoid therapy from both an efficacy (i.e., most heightened inflammatory period) and a safety perspective (least likely to dampen the HPA axis long term) [3, 5, 6]. As we report here, the Modified-Release Prednisone for Treatment of Nocturnal Asthma (MONA) study was an exploratory proof-of-concept study to evaluate the impact on nocturnal symptoms of a switch from conventionally administered immediate-release prednisone to delayed-release prednisone in patients with severe asthma.

METHODS

Patients

Patients included in the study were aged at least 18 years with a diagnosis of severe persistent asthma based on the American Thoracic Society (ATS) criteria [14], following monitoring for at least 18 months. All patients required continued treatment with oral corticosteroids for at least 12 months, in addition to standard therapy (high doses of inhaled steroids plus long-acting beta-2 agonist), and all patients had frequent nocturnal symptoms (at least three nocturnal awakenings because of asthma during the final screening week). Patients with hospital admission for asthma and/or lower airway infection in the 4 weeks before study entry were excluded from the study.

Study Design

This was a single-center, open-label, Phase IIa, sequential, single-treatment proof-of-concept study performed between July 2008 and May 2010. Eligible patients received treatment with conventional prednisone during a 4-week period (Weeks 0–4; treatment period 1) before switching to the same dose of delayed-release prednisone for 4 weeks (Weeks 4–8; treatment period 2). Conventional prednisone was administered at 08:00 h ± 30 min and delayed-release prednisone was administered at 22:00 h ± 30 min.

Assessments

Scheduled visits occurred at Week 0 and every 2 weeks to week 8. The primary efficacy endpoint was the change in the mean number of nocturnal awakenings during the final 2 weeks of each treatment phase. Secondary endpoints included changes in respiratory function measured by morning and evening peak expiratory flow (PEF), forced expiratory volume in 1 s (FEV_1), and forced vital capacity (FVC) at the end of each treatment period. The impact of asthma on patients was determined at the end of each treatment period, using the Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) [15, 16]. For the ACQ (which assesses asthma control over the previous week), a decrease in score corresponds to an improvement in asthma control [16]. For the AQLQ (which assesses the impact of asthma on health-related quality of life during the previous 2 weeks), an increase in score corresponds to an improvement in quality of life [15].

Safety

Safety and tolerability data were collected for all patients. Safety assessments included physical examination, vital signs, and laboratory and/or biological data. All adverse events (AEs) were recorded with information on their severity, relation to study medication, duration, and whether they were considered serious.

Statistical Analysis

All analyses were descriptive. The study was not designed or powered to detect statistical differences in endpoints. The study aimed to recruit a minimum of five and a maximum of 20 patients. The safety population comprised all patients dispensed any study medication. The efficacy population comprised all patients who completed both treatment periods.

Compliance with Ethics Guidelines

The study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by the local ethics committee/institutional review board, and all patients provided informed written consent prior to study-related procedures.

RESULTS

Study Population

Of 15 patients screened, a total of 12 patients were eligible to enter treatment period 1, receiving conventional prednisone; these patients constituted the safety population. During this period, five patients were withdrawn; the remaining patients entered the delayed-release prednisone treatment period (treatment period 2) and completed the study (efficacy population; Fig. 1). Patient demographics are shown in Table 1. Previous medical history in the study population included surgical procedures in 11 patients [mostly cesarean section or appendicectomy (58%)], history of infection (58%), gastrointestinal pregnancy or perinatal conditions, reproductive or breast disorders, respiratory disorders, vascular disorders, and phlebitis, which occurred in two (16.7%) patients each. Prednisone doses for the patients completing the study ranged from 5 mg to 45 mg/day with a median dose of 20 mg/day both before and after switch to delayed-release prednisone, indicating parity in the doses between both study arms.

Efficacy

Following the switch to delayed-release prednisone, the number of nocturnal awakenings because of asthma decreased from a mean (SD) of 10.0 ± 5.45 to 2.1 ± 4.41, a

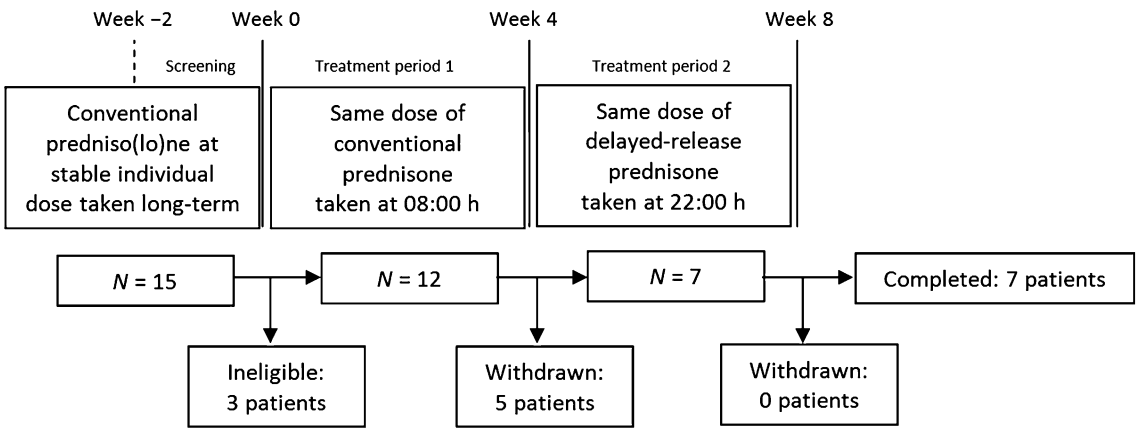

Fig. 1 Study design and patient disposition

Table 1 Demographics and baseline characteristics

Characteristics	Safety population ($N = 12$)	Efficacy population ($N = 7$)
Age (years)		
Mean ± SD	48.9 ± 14.4	46.1 ± 15.74
Median (range)	52.4 (22–68)	51.1 (22–63)
Female sex, *N* (%)	11 (91.7)	7 (100)
Body mass index (kg/m^2, mean ± SD)	27.0 ± 5.96	27.0 ± 5.89
Never smoked, *N* (%)	8 (66.7)	5 (71.4)
Time since diagnosis of asthma (years)		
Mean ± SD	26.2 ± 17.93	18.7 ± 13.56
Median (range)	20.7 (5–59)	15.6 (5–41)
Time since last asthma exacerbation (months)		
Mean ± SD	19.9 ± 40.28	10.0 ± 12.29
Median (range)	6.1 (3–144)	6.0 (3–37)
Time since last hospital admission for asthma, years		
Mean ± SD	4.4 ± 8.77	5.5 ± 11.62
Median (range)	1.6 (0.3–32)	1.2 (0.3–32)
Medication		
Number of patients with at least one previous asthma medication other than glucocorticoid (*N*/ %)	12 (100)	
Salmeterol/fluticasone	11 (91.7)	
Terbutaline	9 (75)	
Salbutamol	8 (66.7)	
Ipratropium	5 (41.7)	
Montelukast	3 (25)	
Budesonide	2 (16.7)	
Omalizumab	2 (16.7)	
Number of patients with glucocorticoid use	12 (100)	7 (100)
Equivalent daily prednisone dose		
Mean mg dose	17.22	18.57
Median mg dose	20	20

mean reduction of −7.9 ± 6.07 and mean relative reduction of −82.7% (Table 2). The number of nocturnal awakenings was reduced in six out of the seven patients (Fig. 2). Improvements were also seen in other measures of lung function (Table 3).

Table 2 Nocturnal awakenings

Statistic	Total nocturnal awakenings because of asthma in final 2 weeks of treatment		Absolute change	Relative change (%)
	Conventional prednisone ($N = 7$)	Delayed-release prednisone ($N = 7$)		
Mean (SD)	10.0 (5.45)	2.1 (4.41)	−7.9 (6.07)	−82.7 (36.88)
95% CI	5.0; 15.0	−1.9; 6.2	−13.5; −2.2	−116.8; −48.6
Median (range)	12 (1 to 15)	0 (0 to 12)	−10 (−14 to 0)	−100 (−100 to 0)

CI confidence interval, *SD* standard deviation

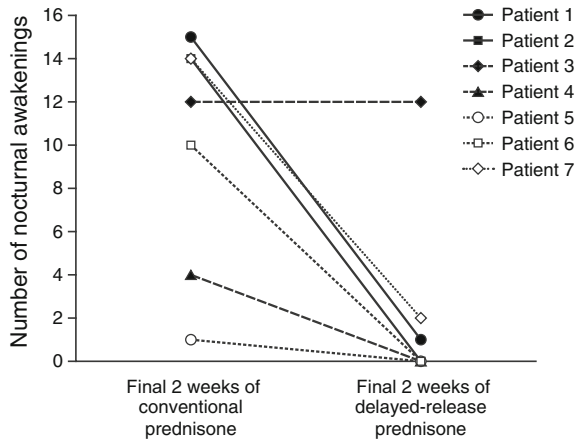

Fig. 2 Patient response: nocturnal awakenings

General asthma control, as assessed by the ACQ, improved from a mean (SD) of 18.7 ± 3.30 in the final week of conventional prednisone treatment to a mean (SD) of 11.4 ± 3.46 in the final week of therapy with delayed-release prednisone. Asthma-related quality of life scores (as measured by the AQLQ) improved from a mean (SD) of 130.9 ± 19.69 in the final 2 weeks of conventional prednisone treatment to a mean (SD) of 162.2 ± 25.97 in the final 2 weeks of delayed-release prednisone treatment. Improvements in these patient-reported outcomes were seen in six out of the seven patients (Fig. 3).

Table 3 Measures of lung function

Measure	Mean (SD) with conventional prednisone ($N = 7$)	Mean (SD) with delayed-release prednisone ($N = 7$)	Mean absolute change	Relative change (%)
Morning PEF (L/min)	284.2 (108.51)	300.2 (89.65)	16.0	12.0
Evening PEF (L/min)	280.1 (74.75)	327.5 (97.11)	47.3	17.2
FEV_1 (L)	2.05 (0.866)	2.09 (0.638)	0.04	9.2
FVC (L)	2.75 (0.912)	2.88 (0.779)	0.14	9.7
FEV_1/Predicted*	77.2%	78.9%		

FEV_1 forced expiratory volume in 1 s, *FVC* forced vital capacity, *PEF* peak expiratory flow, *SD* standard deviation

* FEV_1 end of week 4/predicted for conventional prednisone and FEV_1 end of week 4/predicted for delayed-release prednisone, pre-bronchodilator

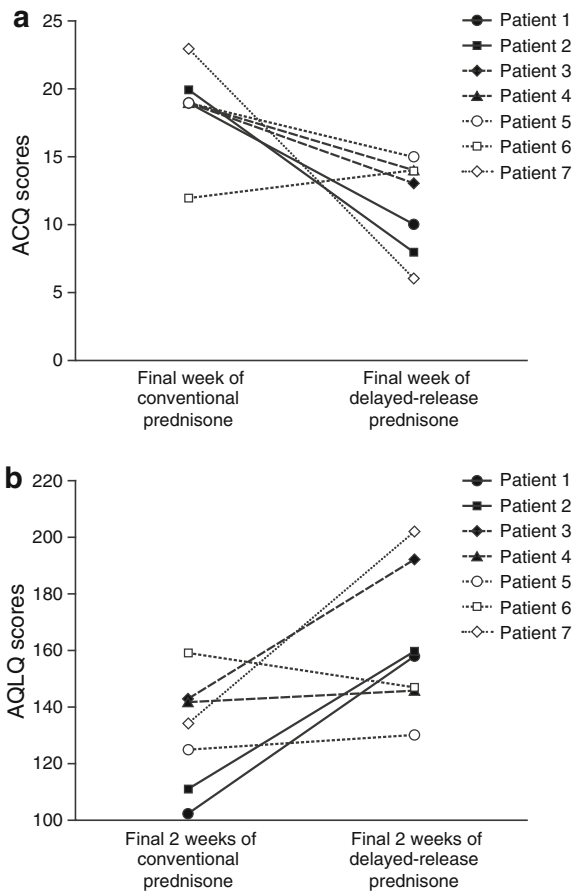

Fig. 3 Patient-reported outcomes. **a** Asthma Control Questionnaire (ACQ) scores; **b** asthma-related Quality of Life Questionnaire (AQLQ) scores

Safety and Tolerability

Most AEs reported during the study were of mild-to-moderate intensity and most were respiratory disorders. During the first treatment period (conventional prednisone), seven patients (58.3%) experienced at least one AE, with one considered serious (asthma exacerbation and arterial thrombosis). The most common AEs were reported in the Infections and Infestations category (33%). None of the AEs are considered related to study treatment. During the second treatment period (delayed-release prednisone), six patients (85.7%) experienced at least one AE, none serious. The most common AEs reported were in the Respiratory, Thoracic and Mediastinal Disorders category (42.9%). In two patients, the AEs (tremor and insomnia in one patient, and insomnia in one patient) were considered related to study treatment. There were no deaths or life-threatening AEs associated with study treatments. No clinically relevant changes in hematological or biochemical parameters, or vital signs were observed during the study.

DISCUSSION

Results from this small proof-of-concept study suggest that patients requiring oral corticosteroid treatments for severe nocturnal asthma benefit from a switch to delayed-release prednisone.

Nocturnal asthma is a variable exacerbation of the underlying asthma condition associated with increases in symptoms, need for medication, and worsening of lung function. These changes are related to sleep and/or circadian events [17]. Studies in patients with nocturnal asthma have demonstrated circadian changes in circulating eosinophils numbers that correlated with peak-flow variation [18, 19]. Fluctuating eosinophil inflammation was also observed in bronchoalveolar lavage fluid and in transbronchial biopsies of patients with asthma, with greater magnitude of increase in those with nocturnal symptoms [20, 21]. These data suggest that circadian activation of inflammatory cells has a pathogenic role in the development of nighttime airflow limitation. Therefore, as with other inflammatory conditions with circadian symptoms, an anti-inflammatory drug targeting this nocturnal peak in airway inflammation could show benefits over the same treatment used at other times of the day. This concept was explored more than 20 years

ago, although nocturnal corticosteroid administration was not investigated [22]. The impact on nocturnal asthma symptoms of inhaled steroid administration time is unclear [23]. In our proof-of-concept study, delayed-release prednisone given at 22:00 h was superior to conventional prednisone given at 08:00 h. The improvement in asthma control and nocturnal symptoms observed with delayed-release prednisone might result from the delivery of anti-inflammatory therapy at the most appropriate time to inhibit pathophysiological processes that result in symptoms.

Delayed-release prednisone was generally well tolerated, and there were no deaths or life-threatening AEs. There were no unexpected safety findings. These results are consistent with those with rheumatoid arthritis [7, 8, 24].

Although the size of the efficacy population was too small to detect any statistically significant changes, this proof-of-concept study suggests that delayed-release prednisone provides better asthma symptom control compared with standard morning administration of conventional prednisone. The limitations of an small, open-label, nonrandomized study such as this are well known and further study of delayed-release prednisone in patients with severe asthma is warranted to investigate whether switching to this treatment from the more conventional formulation improves outcomes and potentially allows a reduction in corticosteroid dose, as has been noted in the treatment of rheumatoid arthritis [25].

CONCLUSION

This proof-of-concept study suggests that nighttime administration of delayed-release prednisone provides better asthma symptom control compared with morning administration of conventional immediate-release prednisone. Timed delivery of prednisone during the peak inflammatory period (early morning sleeping hours) may be the most efficacious time to administer exogenous glucocorticoids to patients with nocturnal asthma.

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Disclosures. M. Aubier, C. Taillé, and L. Alavoine report no conflict of interest. S. Witte was previously an employee of Horizon Pharma GmbH, Mannheim, Germany. C. Knauer, J. Kent, and J. Ball are presently employees of Horizon Pharma, Inc and report having stock options.

Compliance with ethics guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

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