

Chronotherapy of asthma with inhaled steroids: The effect of dosage timing on drug efficacy

Diane J. Pincus, MD, Stanley J. Szeffler, MD, Lynn M. Ackerson, PhD, and Richard J. Martin, MD Denver, Colo.

Background: Studies in asthma with systemic corticosteroids given at 3:00 PM have shown a superior therapeutic benefit compared with dosing at other time points.

Objective: The study was designed to compare beneficial and systemic effects of 800 µg of inhaled triamcinolone once daily at 3:00 PM (QD group) versus 200 µg conventional four times a day dosing (QID group).

Methods: Efficacy outcome measures included forced expiratory volume in 1 second (FEV₁), peak expiratory flow rates, bronchial responsiveness, and use of β-agonist. Systemic effects were blood eosinophil and cortisol levels, 24-hour urinary cortisol, and evaluation for oral candidiasis and dysphonia.

Results: The baseline FEV₁ was comparable in the two groups: QD = 67% ± 2% and QID = 66% ± 2% of predicted value. After 4 weeks of treatment, FEV₁ increased similarly in the QD group to 77% ± 4% and in the QID group to 74% ± 4% of predicted value. Likewise, the improvement in morning and evening peak expiratory flow rates was not significantly different between the groups. Both QD and QID groups experienced comparable daily decrements in β-agonist use. The systemic responses to the two regimens as assessed by eosinophil count, morning serum cortisol, and 24-hour urinary cortisol were also comparable.

Conclusions: The single daily administration of inhaled triamcinolone at 3:00 PM has no increased systemic effects and produces similar improvement in efficacy variables. A dosing strategy based on once daily dosing should increase compliance of inhaled steroid use in the clinical setting. (*J ALLERGY CLIN IMMUNOL* 1995;95:1172-8.)

Key words: Asthma, inhaled steroids, chronotherapy, dose timing, triamcinolone acetonide

There is considerable evidence to support the concept that circadian rhythms influence disease manifestations of asthma. Specifically, patients with asthma demonstrate enhanced bronchial responsiveness at night, whether or not they have worsening of asthma symptoms or pulmonary function at night.¹ In addition, even in patients with

Abbreviations used

BID:	Twice daily
FEV ₁ :	Forced expiratory volume in 1 second
IQR:	Interquartile range
PC ₂₀ :	Provocative concentration (of methacholine) causing a 20% fall in FEV ₁
PERF:	Peak expiratory flow rate
QD:	Once daily
QID:	Four times daily
TEC:	Total eosinophil count

From the Department of Medicine and the Department of Pediatrics, National Jewish Center for Immunology and Respiratory Medicine; and the Pulmonary and Critical Care Section, University of Colorado Health Sciences Center, Denver.

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Reprint requests: Richard J. Martin, MD, National Jewish Center for Immunology and Respiratory Medicine, 1400 Jackson St., Room J116, Denver, CO 80206.

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very mild asthma without nocturnal symptoms, the late asthmatic response is more frequent and more severe after an allergen challenge given in the evening than after a daytime challenge.²

Assuming that inflammatory mediators are responsible for at least part of the pathophysiology, and hence disease manifestations of asthma, attention to time-related dosing of antiinflammatory

medication may be critical to the efficacy of pharmacologic intervention. In this regard, studies conducted in children with asthma³ and adults with nocturnal asthma⁴ have demonstrated that the efficacy of systemically administered corticosteroids is influenced by the timing of their administration. Specifically, both of these studies demonstrated improved pulmonary function as determined by peak expiratory flow rate (PEFR)³ and forced expiratory volume in 1 second (FEV₁)⁴ in asthmatic patients when the systemically administered corticosteroid was given at 3:00 PM as compared with 7:00 AM, 7:00 PM and 3:00 AM in one study³ and 8:00 AM and 8:00 PM in the other.⁴ Furthermore, Beam et al.⁴ also noted a 4:00 AM pancellular decrement in cytologic evaluation of bronchoalveolar lavage fluid after the 3:00 PM dose, an effect not observed at other times. These studies thus support the view that systemic corticosteroid administration at 3:00 PM may be critical to the interruption of the inflammatory cascade that is associated with the nocturnal exacerbation of asthma and with overall disease severity.

Studies evaluating the effect of dosage timing of inhaled steroids have been limited, and there are no studies that specifically compare the efficacy of medication given at 3:00 PM with other time points. Additionally, there are differences in the literature concerning the relative benefits of four times daily (QID) versus twice daily (BID) administration of inhaled steroids. The studies evaluating schedule differences frequently do not include mention of specific dose timing, and they vary considerably in patient population, entry criteria, and drug and dosage used. In some studies, BID dosing is found to be as effective as QID dosing,⁵⁻⁷ and in other studies QID dosing was found to be superior to BID dosing.⁸⁻¹⁰ This study was conducted to specifically determine whether the inhalation of steroids solely at 3:00 PM is associated with a clinical response comparable to that observed when the drug is given four times a day in a general asthmatic population with moderate to severe disease.

METHODS

Subjects

All subjects met the American Thoracic Society criteria for a diagnosis of asthma¹¹ and were required to have a history of cough or wheezing responsive to bronchodilators, spirometric confirmation of a 15% improvement in FEV₁ after inhalation of 180 µg of albuterol, and a concentration of methacholine causing a 20% fall in FEV₁ (PC₂₀) at 5 mg/ml or less. Additionally, a baseline FEV₁ between 50% and 80% of predicted value was

required. Exclusion criteria included a smoking history within 5 years, other pulmonary disease, and use of medication other than β-agonists or theophylline. Patients were also excluded from the study if they used cromolyn sodium or steroids, by any route, in the 4 weeks before entry. An upper respiratory tract infection delayed enrollment in the study for 4 weeks. However, once enrolled, development of an upper respiratory tract infection did not prohibit the subjects from completing the study if no change in corticosteroid medication was required during the course of the infection. All subjects with a history of seasonal allergy were skin tested to confirm sensitization. Patients could not enter the study if their allergen season started or ended during the course of the study or within 2 weeks before the study began. All subjects signed an Institutional Review Board–approved consent form before enrollment in the study. Thirty-two patients entered the study, and 30 patients completed it. Two patients did not complete the protocol because of unexpected relocations to other states.

Treatment regimens

Triamcinolone acetonide was used as a treatment drug. Each inhalation delivers 200 µg from the pressurized cannister and 100 µg from the built-in spacer. The treatment regimen consisted of either a total of 8 inhalations per day of the triamcinolone acetonide given as a single dose at 3:00 PM (QD group) or 2 inhalations at 7:00 AM, noon, 7:00 PM, and 10:00 PM (QID group). All patients were instructed to rinse their mouths after each dose of medication. Both groups received a total of 800 µg/day. The 4-week time frame of the study was selected because Tinkleman et al.¹² have shown nearly maximal improvement in FEV₁ with moderate dosage of inhaled steroids by 4 weeks of treatment. An 800 µg dose was chosen because this is a commonly used moderate dose of medication, which has previously been shown to produce improvement in pulmonary function in patients with asthma within 4 weeks.⁸

Study design

Patients were selectively randomized to the two treatment regimens on the basis of their baseline FEV₁ measurements so that an equivalent number of patients with moderate (FEV₁ = 66% to 80% of predicted value) and moderately severe (FEV₁ = 50% to 65% of predicted value) asthma were represented in both groups. In the week before randomization, all eligible patients underwent the following evaluations: three measurements of FEV₁ on separate days, from which a median value was obtained; a PC₂₀ in response to methacholine¹, morning serum cortisol between 7:00 and 8:00 AM¹³; morning blood eosinophil count; and a 24-hour urinary free cortisol excretion analyzed per gram of creatinine.¹³ At baseline, subjects also underwent oropharyngeal examination for candidiasis and auditory assessment for dysphonia. Patients kept daily medication

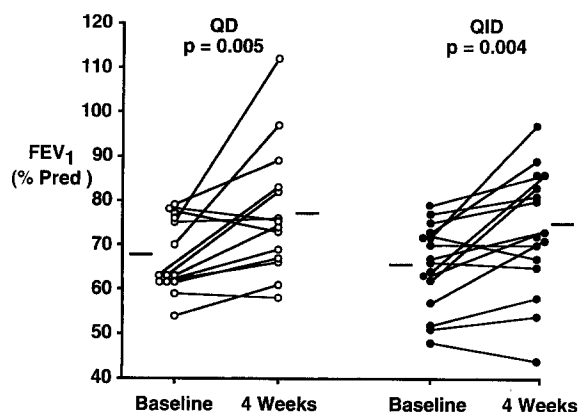


FIG. 1. FEV₁ at baseline and after 4 weeks of treatment for QD and QID groups. Both groups demonstrate significant improvement after inhaled steroid therapy. Between groups there are no significant differences at baseline or after 4 weeks of treatment.

diaries and measured their prebronchodilator PEFR in the morning and at bedtime, recording the best of three results. These diaries and PEFR measurements were then continued daily for the 4 weeks of the study. For each diary variable, (morning PEFR, bedtime PEFR, number of doses of β -agonist used per day), a mean value for the baseline week and a mean value for the fourth week were obtained for statistical comparison. At the conclusion of 4 weeks of treatment with medication, the FEV₁, PC₂₀, morning serum cortisol, 24-hour urinary cortisol per gram of creatinine, morning eosinophil count, and oropharyngeal examination were repeated. All measurements were obtained within the same hour of the day on every visit, and identical intervals between medicine administration before each test were maintained. No bronchodilator medication was taken for at least 4 hours before testing. Patients receiving theophylline at baseline continued to receive the same dose of theophylline throughout the study.

To assist with compliance, patients were given wristwatches with alarm settings for once a day or four times a day, whenever a medication dose was due. Compliance was monitored by weighing the triamcinolone cannisters at baseline and at the end of the 4-week period of use. A patient was deemed noncompliant if the weight of the cannister was greater than 10% of expected value at the end of the study.

Statistics

Summary statistics for the continuous variables are described with either mean $\pm$ SEM for normally distributed data, or median with interquartile range (IQR) (25th percentile to 75th percentile) for non-normally distributed data. Comparisons between groups were done with either a two-sample *t* test if the data were normally distributed or a Wilcoxon rank sum test for non-normally distributed data. All tests were two-sided. Comparisons within groups were

TABLE I. Baseline demographic and disease characteristics of patients

	QD group	QID group
Number of subjects	14	16
Average age (yrs)	27.0 $\pm$ 2.2	36.5 $\pm$ 2.0
Male subjects	9	7
Female subjects	5	9
Baseline FEV ₁ < 65%	5	7
Baseline FEV ₁ > 65%	9	9
Nocturnal asthma	8	9
In allergy season	4	3
Respiratory tract infections	2	2

done with either a paired-sample *t* test for normally distributed data or a Wilcoxon signed-rank test for non-normally distributed data. For a sample size of 14 in each group, with a type 1 error rate of 5% and a within-group standard deviation of 10.7 in percent predicted FEV₁, there is an 80% power of detecting a difference of 12 between groups in the mean group change from baseline.

RESULTS

Demographic information

The overall population consisted of 30 patients, 16 men and 14 women, with an average age of 32 years (range, 20 to 59 years). Eighty percent of patients were white, and the remaining population was black or Hispanic. These demographics were similar between groups (Table I). There were a similar number of patients in each group with nocturnally worsening asthma (defined as use of β -agonists on more than 2 nights a week) and an equivalent number in each group who were in their allergy season for the duration of the study. Four patients had respiratory tract infections during the study. None of these patients required increased inhaled steroids or addition of systemic corticosteroids. These patients were divided equally between QD and QID groups.

Lung function

The baseline FEV₁ values of the two groups of patients were comparable (*p* = 0.57). The QD steroid group had a mean baseline FEV₁ of 67.4% $\pm$ 2.2% of predicted value, which was not significantly different from the QID steroid group baseline mean FEV₁ of 65.5% $\pm$ 2.4% of predicted value. The absolute improvement within each group in the percent predicted FEV₁ was 9.9 $\pm$ 3.2 for the QD group (*p* = 0.008) and 8.0 $\pm$ 2.3 for the QID group (*p* = 0.003). The difference in improvement between the groups was not statistically

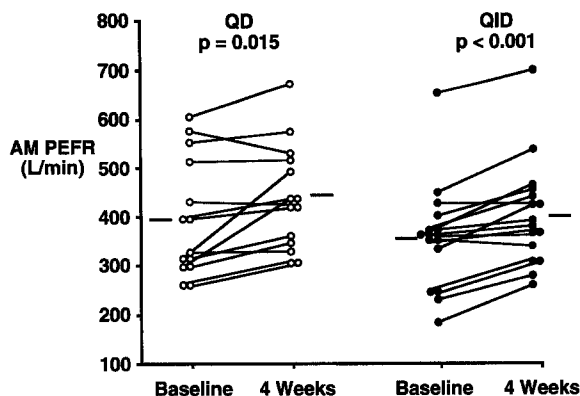


FIG. 2. Morning (AM) PEFR is shown at baseline and after 4 weeks of treatment for QD and QID groups. Both groups demonstrate significant improvement after inhaled steroid therapy. Between groups there are no significant differences at baseline or after 4 weeks of treatment.

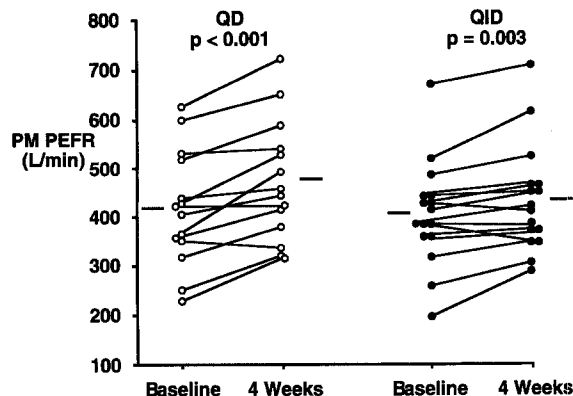


FIG. 3. Evening (PM) PEFR is shown at baseline and after 4 weeks of treatment for QD and QID groups. Both groups demonstrate significant improvement after inhaled steroid therapy. Between groups there are no significant differences at baseline or after 4 weeks of treatment.

significant ($p = 0.63$). Fig. 1 demonstrates the individual and group improvement after 4 weeks of treatment with inhaled steroids. The mean improvement, expressed as percent change from baseline in the QD group, was $14.7\% \pm 4.4\%$ ($p = 0.005$), and the mean improvement for the QID group was $12.1\% \pm 3.5\%$ ($p = 0.004$). The degree of improvement did not differ between groups ($p = 0.64$).

The baseline morning PEFR values in the two groups were not significantly different ($p = 0.33$). The QD group had a baseline mean morning PEFR of 396 ± 32 L/min compared with the QID group mean baseline morning PEFR of 354 ± 27 L/min. Fig. 2 demonstrates the significant improvement within both groups. The mean improvement for the QD group was 43 ± 15 L/min ($p = 0.015$), and the mean improvement for the QID group was 46 ± 9 L/min ($p < 0.001$). The baseline evening PEFR values in both groups of patients were also comparable ($p = 0.75$). The QD group had a mean baseline evening PEFR of 415 ± 32 L/min, which was not significantly different from the mean evening PEFR of the QID group, 402 ± 27 L/min. Both patient groups showed significant improvement, with QD mean improvement of 55 ± 12 L/min ($p < 0.001$) and QID mean improvement of 29 ± 8 L/min ($p = 0.003$) (Fig. 3). Although the degree of improvement in the morning PEFR did not differ between groups ($p = 0.89$), there was a trend toward greater improvement in evening PEFR for the QD group ($p = 0.07$) (Fig. 4).

The baseline PC_{20} was comparable between groups of patients ($p = 0.66$). The QD group had

a median baseline PC_{20} of 0.09 mg/ml (IQR, 0.04-0.20), and the QID group had a median baseline PC_{20} of 0.06 mg/ml (IQR, 0.04-0.18). The QD group PC_{20} median response to methacholine increased by 0.70 (IQR, -0.24-1.68) doubling dilutions of methacholine, which tended toward statistical significance ($p = 0.08$), whereas the QID group PC_{20} median response to methacholine increased by 1.77 (IQR, 0.77-2.21) doubling dilutions of methacholine ($p = 0.01$). Although the QID group demonstrated a significant improvement from baseline to 4 weeks of treatment, the degree of improvement compared with the QD group was not significantly different ($p = 0.18$).

β_2 -Agonist use

The baseline β -agonist use of the two groups of patients was comparable ($p = 0.80$). The QD group had a mean baseline β -agonist dose of 4.8 ± 0.9 actuations/day, which was not statistically different from that of the QID group mean baseline β -agonist dose of 5.1 ± 0.9 actuations/day. Both groups had a significant decrease in the amount of β -agonist use when inhaled steroids were administered. The QD group use of β -agonist decreased by 2.1 ± 0.5 actuations/day ($p = 0.001$), and the QID group use of β -agonist decreased by 1.7 ± 0.4 actuations/day ($p = 0.001$). The decrement in β -agonist use was not significantly different between groups ($p = 0.57$).

Systemic effects

The baseline total eosinophil counts (TECs) of the two groups were comparable ($p = 0.53$). The

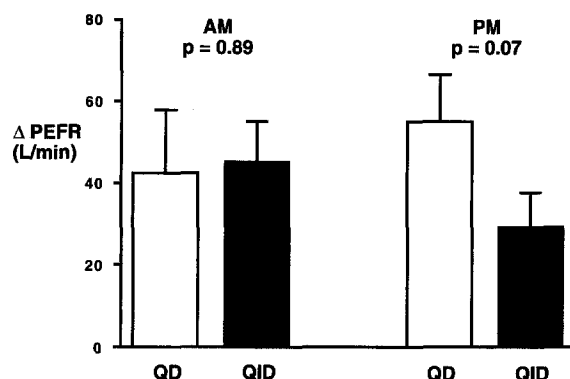


FIG. 4. The improvement in morning (AM) PEFR and evening (PM) PEFR is compared for the QD and QID groups. The improvement in morning PEFR was similar for each treatment group. There was a trend toward more improvement in evening PEFR for the QD group compared with the QID group.

QD group had a median baseline TEC of 476 (IQR, 132-690) cells/mm³, compared with the QID group median TEC of 282 (IQR, 75-674) cells/mm³. The QD group had a statistically significant change from baseline with a median decrease in TEC of 202 (IQR, -392 = -18) cells/mm³ ($p = 0.01$), a 42% decrease, whereas the QID group tended to but did not have a significant change from baseline, with a median decrease in TEC of 96 (IQR, -247 = 119) cells/mm³ ($p = 0.07$), a 34% decrease. The change in eosinophil count, when the two treatment groups were compared, was not significantly different ($p = 0.38$).

The median baseline morning serum cortisol levels were comparable between the treatment groups ($p = 0.12$). The QD group had a median baseline serum cortisol of 18.4 μg/dl (IQR, 13.6 = 27.6), which was not significantly different from the median baseline serum cortisol of the QID group, 12.9 μg/dl (IQR, 11.6 = 21.6). Neither treatment group had a significant change in median morning serum cortisol levels, and both groups demonstrated a slight increase in serum cortisol. The QD group had a median increase in morning serum cortisol of 0.2 (IQR, -5.4 = 4.5) μg/dl ($p = 0.86$), and the QID group had a median increase in morning serum cortisol of 2.7 (IQR, -2.2 = 7.8) μg/dl ($p = 0.32$). The degree of change from baseline of morning serum cortisol did not differ significantly between groups ($p = 0.35$). Both group median levels remained within the normal range of 5 to 20 μg/dl.

The baseline 24-hour urinary cortisol per gram of creatinine was comparable between groups ($p =$

0.62). The QD group had a median baseline value of 29.3 (IQR, 21.6 = 63.0) μg/gm, which was not significantly different from the median baseline value for the QID group of 42.7 (IQR, 20.1 = 73.0) μg/gm. Neither treatment group had a significant change from baseline in 24-hour urinary cortisol/creatinine. Neither group demonstrated a suppression in 24-hour urinary cortisol/creatinine, and the median values for both groups remained within the normal range of 20 to 90 μg of cortisol per gram of creatine. The QD group had a median increase in 24-hour urinary cortisol/creatinine of 29.6 μg/gm (IQR, -9.8 = 55.7) ($p = 0.10$), and the QID group had a median increase of 2.6 μg/gm (IQR, -33.2 = 16.3) ($p = 0.74$). Although the increment in 24-hour urinary cortisol/creatinine was not statistically significant for either group, the QD group median change was significantly greater than the QID group median change ($p = 0.053$).

No patient in either group had physical evidence of oropharyngeal candidiasis at any time during the study. One patient in the QID group had dysphonia unassociated with respiratory tract infection during the third and fourth weeks of inhaled steroid use, which resolved 1 week after inhaled steroids were discontinued.

Compliance outcomes

Cannister weight evaluation of medication compliance revealed that one patient in each treatment group had a final steroid cannister weight of 12% more than expected. All other patients had inhaled steroid cannister weight within 10% of expected weight. All patients were included in final data analysis.

DISCUSSION

The results of this study indicate that administration of triamcinolone acetonide at a total daily dose of 800 μg at 3:00 PM is comparable in efficacy to administration of the same total daily dose on a QID basis. Measures of medication efficacy, including FEV₁, morning and evening PEFR, and bronchodilator use revealed that 3:00 PM dosing produced improvement in all variables comparable to QID drug administration. Although only the QID group had a statistically significant reduction in methacholine-induced bronchial responsiveness, the difference in improvement between groups for this variable was not significant, and neither group achieved a clinically significant improvement of two doubling dilutions of methacholine.

Previous investigators, using either intramuscular or oral steroids for asthma therapy, have con-

sistently shown that there appears to be a benefit in timing of steroid administration to doses given at 3:00 PM.^{3,4} In previous studies that evaluated dose scheduling of inhaled steroids, QID dosing was found to be an optimally effective dosage schedule.⁸⁻¹⁰ In this study the finding of comparable efficacy for both the 3:00 PM and QID treatment schedules suggests that timing of drug administration at a critical period can facilitate a decrease in dosage frequency. Because 50% of the QID dosage in this study was given at noon and 7:00 PM, that time span may be sufficient to provide optimal drug efficacy. Evidence to support the possible importance of the noon to 7:00 PM time span can be found in several studies on steroid timing. In the only previous study in which timing of administration of inhaled steroids was clearly stated, QID dosing was superior to BID dosing.⁸ In that study 25% of the QID inhaled steroid was given at noon and 25% at 5:30 PM, whereas the less effective BID schedule included time points only at 8:00 AM and 10:00 PM.⁸ Likewise, in the study by Reinberg et al. in which parenteral steroid dose timing was evaluated, the outcome of treatment was definitely better with single dosing at both 3:00 PM and 7:00 PM than with single dosing at either 3:00 AM or 7:00 AM.³ Thus there may in fact be a window of time, likely between noon and 7:00 PM, during which it is most beneficial to administer inhaled steroids to patients with asthma, possibly even at a lower dose.

In this study systemic effects of inhaled steroids were monitored by measuring morning serum cortisol, 24-hour urinary cortisol corrected for creatinine, and blood eosinophil counts. Neither treatment group showed a statistically significant decrease in morning serum cortisol or 24-hour urinary cortisol/creatinine, and the degree of change was comparable between groups. The absence of adrenal suppression in both groups is reflected by an actual increase in morning serum cortisol and 24-hour urine cortisol/creatinine levels. Of interest, the blood eosinophil count was decreased to a significant degree only in the QD group, but the degree of change in eosinophil count was comparable between groups.

A previous study on systemic effects of oral corticosteroids by Nichols et al.¹⁴ demonstrated that administration of systemic corticosteroids at 4:00 PM does not produce increased adrenal suppression compared with administration at 8:00 AM, whereas dosing at midnight produces more adrenal suppression than dosing at 8:00 AM. Therefore it may be concluded that there is a combination of

factors that influence corticosteroid efficacy and systemic effects, one of which is dosage timing.

This study demonstrates that 3:00 PM dosing of inhaled steroids is as effective as QID dosing in a general asthmatic population. It should be stressed that our patients were not selected for nocturnal asthma and that patients with nocturnal asthma were equally distributed between treatment groups. In addition, the 3:00 PM dosing produced no increased adverse systemic effects during the 4-week period of administration. This schedule of medication could be considered as an alternative to the standard QID regimen, because QD treatment is likely to be associated with better patient compliance than multiple dose regimens.¹⁵ In addition, when multiple dose schedules are indicated, a portion of the treatment might be given in the afternoon rather than late in the evening to increase efficacy and decrease systemic toxicity. Further study is needed to determine whether indeed dosing between 5:00 and 6:00 PM might produce equal efficacy as dosing at 3:00 PM and thus further simplify the treatment regimen.

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