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Microdose Therapytm demonstration disease clinical trial of cortisol-responding diseases

ENDOCRINE CONTROL OF INFLAMMATION: RHEUMATOID ARTHRITIS DOUBLE-BLIND, CROSSOVER CLINICAL TRIAL

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Summary: A dysfunction in the endocrine control system for inflammation in rheumatoid arthritis serves as the theoretical basis for chronic inflammation in the study design described. Eighteen patients with rheumatoid arthritis, who acted as their own controls, were brought to a minimum symptom state through conventional means, trained, and allowed to control subsequent flares by a patient-initiated, flare-response prednisone regimen. The six-month trial was double-blind with a crossover at midpoint. While continuing stable non-steroidal anti-inflammatory and disease modifying antirheumatic drug therapies, the patients averaged additional 57% and 75% reductions from baseline in tender joint count and total pain score, respectively, on the prednisone therapy. The prednisone therapy was differentiated by improvement from that of a placebo by six of the nine parameters evaluated. The adverse events were no more frequent with prednisone than with placebo use. The efficacy of prednisone was increased threefold while reducing consumption by 40% when compared to the predecessor 5-mg prednisone/day clinical trial.

Introduction

The plan described for the control of chronic inflammation is based upon the premises that it is a consequence of a dysfunction in the endocrine control system of inflammation, and its control can be achieved by timely hormone supplementation. The plan involves returning the patient to an asymptomatic state via the use of a glucocorticoid regimen commonly employed for this purpose, identifying and removing the inflammatory stimulus, if present and possible, and treating the subsequent, undesirable, acute-inflammation episodes with less intense, patient-controlled glucocorticoid regimens to re-establish and maintain the asymptomatic state.

The rationale arises from the hypotheses of Ingle and Ingle (2) that the restive state glucocorticoid concentration is permissive to stress reaction, and of Munck and coworkers (3) that the glucocorticoids function to turn off stress reactions preventing them from overshooting and damaging the host. When the stress reaction is inflammation, these hypotheses are consistent with and integral to the endocrine control of inflammation proposed by Garcia Leme (4,5) in which inflammation was proposed to induce hypophyseal axis activity, and the resultant liberation of glucocorticoids had a negative feedback effect on inflammation.

In support of the Garcia Leme proposal, Lewis rats which have a defect in their ability to synthesize corticotropin-releasing hormone in the hypothalamus were shown to have a defective stress reaction to inflammatory stimuli (6,7). In rat models of inflammation, animals that have been hypophysectomized cannot suppress an inflammatory challenge (8). These data suggest that inflammatory and autoimmune diseases may be exacerbated by a defective reaction to inflammatory stresses. Supporting evidence for this

hypothesis is provided by data which show the circadian rhythm of adrenal hydrocortisone secretion is markedly disrupted in patients with active rheumatoid arthritis (9).

Three extensions to the two already formulated hypotheses serves as the basis of the present clinical trial: inflammation is the primary defense reaction which is overshooting and damaging the host; chronic inflammation is the consequence of a reduced glucocorticoid pulse response which is inadequate to turn off this defense reaction; and the inadequate pulse can be corrected by external glucocorticoid supplementation. Without correction, the inflammation often outlives its cause. Parts one and three of our plan are examined in this study, and rheumatoid arthritis was selected as the (demonstration) disease.

Materials and methods

The efficacy and safety of the trial procedures were assessed in a double-blind fashion. The crossover design was implemented by the study coordinator in which half of the patients were selected to receive prednisone, then a placebo, while the other half received the placebo first. The duration of the double-blind trial was six months with the crossover occurring at midpoint. The protocol was approved by the institutional review boards of the University of North Dakota, North Dakota State University and the Dakota Medical Center, and all patients were required to sign an informed consent statement. The patients continued taking stable doses of either non-steroidal anti-inflammatory drugs (NSAID) or disease modifying antirheumatic drugs (DMARD) or both throughout the trial. An overview of the trial periods is presented in **Table I**.

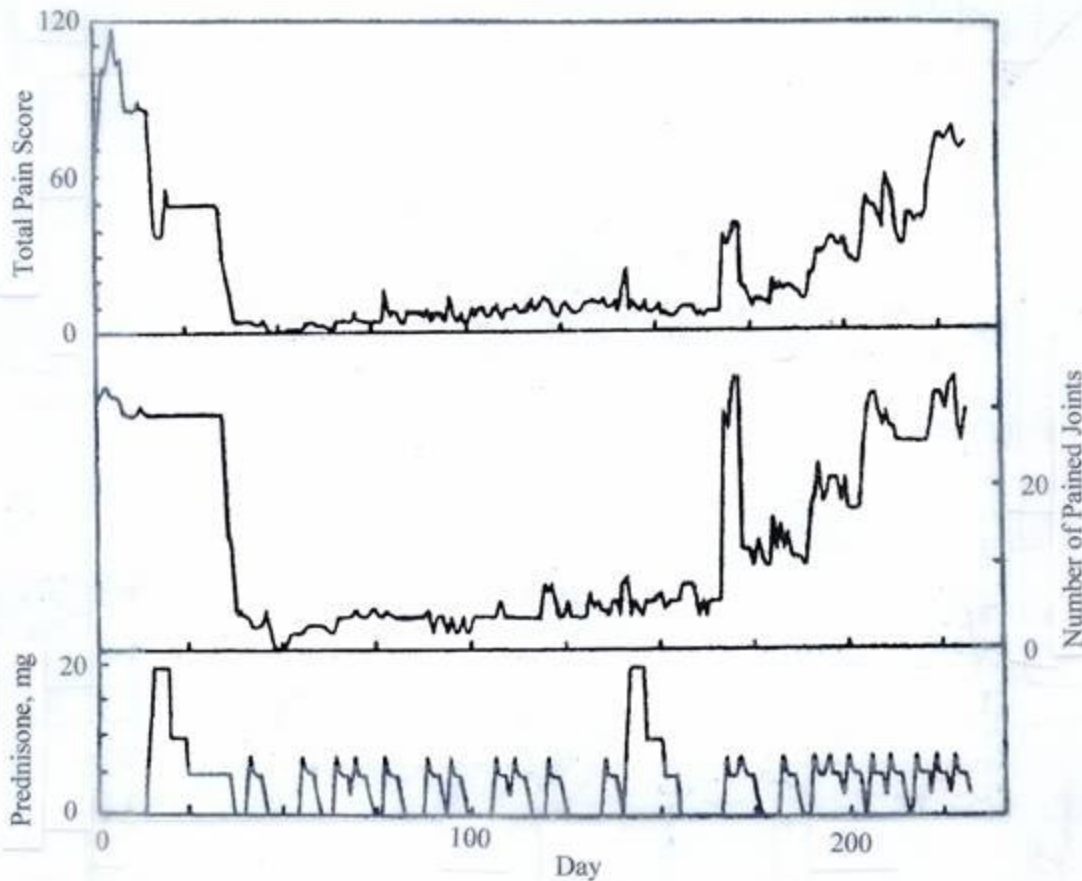
Table 1. *Overview of clinical periods*

Period	Days	New medication	Blinded
Baseline period	7	None	--
Induction period I	14	Prednisone, 170 mg	--
Therapy period I	90	Patient control of medication	+
Induction period II	14	Prednisone, 170 mg	--
Therapy period II	90	Patient control of medication	+

Patients were entered into the study, if they met the following inclusion criteria: 18 years of age or over, had rheumatoid arthritis according to American College of Rheumatology criteria, were able to give their informed consent and understand the instructions for use of the prednisone, and had active disease as defined by standard minima of swollen and tender joints, Westergren sedimentation rate (ESR), morning stiffness and global pain.

Exclusion criteria were: use of any glucocorticoid in the six weeks preceding the study, change in any slow-acting or investigational antirheumatic drug within the last six months, pregnancy, diabetes mellitus, active peptic ulcer disease, or the presence of any concurrent significant illness. Concurrent use of non-steroidal anti-inflammatory drugs or disease modifying antirheumatic drugs was allowed if the dose had been unchanged for the past month.

The qualifying medical examination and patient consent were obtained prior to entering into the baseline period. The baseline period established the disease activity prior to implementing the protocol of the trial.



During the seven days of the baseline period, the patients were trained to evaluate and record the individual joint pains and steroid use in the daily diary.

The induction period accomplished a reduced symptom state, namely, the minimal symptom state. Prednisone, in the form of 5-mg, centre-scored tablets was selected as the glucocorticoid of choice rather than the endogenous hydrocortisone because of reduced adverse events in its use. A modest, 175-

mg total, 14-day prednisone regimen was used to alleviate chronic inflammation from the patients during the induction period. The regimen consisted of a single morning ingestion of 20 mg for days 1-5, 10 mg each day for days 6-10 and 5 mg each day for days 11-14. If a patient did not achieve a 50% reduction of the total pain score from that of the baseline period to the last two days of the induction period, then the patient was discontinued from the trial. Patients were randomized into two groups for the therapy periods.

The objective of the therapy period was to maintain the minimal symptom state via patient control of the medication timing. For this trial, a flare was defined to be a 20% increase in pain in one or more joints. Each flare was to be quenched to re-establish the minimal symptom state via the use of a less intense, 25-mg, 5-day, prednisone regimen. The latter consisted of taking 7.5 mg of prednisone immediately upon identifying the onset of a flare on day 1, 5 mg between 07h00 and 08h00 on days 2-4 and 2.5 mg between the same hours on day 5. If a second flare occurred within the 5-day time treatment period of the first flare, the first regimen was to be discontinued and a second repeat, 5-day regimen initiated.

The crossover from prednisone (therapy period I) to placebo (therapy period II) or vice versa occurred at the midpoint of the trial and immediately after the induction period II. Crossover could occur earlier if the physician judged the treatment of the therapy period I to be ineffective. Neither the physician nor the patient knew in which therapy period the prednisone was being given.

Patient training was accomplished with the aid of videotapes to standardize the presentation. During the baseline period, the patients were taught to use the daily diary form. During the induction period, the patients were trained on the potential adverse effects of prednisone, the techniques of flare identification and quenching, the requirement of quenching the flare at its inception, and the objective 2.5 mg/day average daily ingestion of prednisone. The training was reinforced by telephone contact with the patients or during the physician visits as needed. Compliance was assessed by tablet counts during physician visits and by graphic displays of patient diary data (Fig. 1).

Fig. 1. The computer-assisted data presentation of a Type A rheumatoid arthritis patient of the trial. This patient used prednisone during therapy period I [days 37-140] and a placebo during therapy period II [days

155-231]. During therapy period I, this patient averaged 2.6 mg prednisone/day, had 93% symptom improvement from that of the baseline period and 3.2 flares/month.

Tender joint count, swollen joint count, duration of morning stiffness, time until fatigue, ESR, and haemoglobin were evaluated and recorded during visits of the physician. The physician's visits occurred seven times during the six-month trial: during the baseline period, the beginning, middle and end of each therapy period. Automated chemistry panels and complete blood counts were done at the end of each therapy period. Daily total pain score, number of painful joints, extent of morning stiffness, global assessment and medication used were recorded on the daily diary form by the patient at the same time of each day. The total pain score was defined as the numerical sum of the individual joint pain ratings each day recorded on the 0-9 basis. The number of painful joints was defined as the number of non-zero digit entries each day.

Total pain score, joint counts and medication use were averaged and analyzed with the other variables. Data from the placebo and prednisone therapy periods were analyzed by analysis of variance (ANOVA) for repeated measures using Stratgraphics 4.0 software with treatment and sequence as independent variables (10). If a sequence effect was detected, data were analyzed for therapy period I alone by Student's t-test. Baseline data are presented for comparative purposes. Additional analyses employed the paired t-test or the Wilcoxon signed rank test for ordinal level data. For daily diary data processing, averages for each parameter for selected baseline and therapy periods were used in order to minimize daily fluctuation.

Results

Twenty-two patients gave consent for the study. Three were eliminated because of poor response to induction period I and one patient dropped out for personal reasons. Thus, 18 patients completed the study. The patient population is characterized in Table II.

Table II. *Baseline characteristics of 18 patients completing the study*

Age	60.9 years (38-77) ^a
Disease duration	9.6 years (2-22)
Female male	11/7
Rheumatoid factor positive	18
Functional class	II (all patients)
Concurrent medications	
NSAIDS	16
Remittive	11

^a Mean (range)

Tender joint count improved by an average of 57% from that of the baseline period for the 18 patients (Table III). The patient-determined total pain score improved by an average of 75% from that of the baseline period (Table IV). Further, 17% of the patients received greater than 90% total pain score reduction, 44% greater than 80%, and 67% greater than 75%.

Table III. *Physician and laboratory-derived disease parameters and prednisone use*

	Baseline	Placebo	Prednisone
Tender joint count	13.6 +/- 1.9 ^b	11.5 +/- 2.5	5.9 +/- 1.7 ^a
Swollen joint count	25.3 +/- 1.6	19.1 +/- 1.6	15.3 +/- 1.8 ^a
ESR (Westergren, mm/Hg)	30.1 +/- 5.1	30.9 +/- 5.8	5.9 +/- 6.0
Haemoglobin (g/dl)	12.9 +/- 0.4	12.9 +/- 0.5	13.3 +/- 0.4 ^a
Mean daily drug dose (mg)		3.4 +/- 0.4 ^c	3.0 +/- 0.3

^a Significantly different from the placebo group (p<0.05)

^b Mean +/- standard deviation

^c Calculated as if each placebo tablet contained 5 mg prednisone

Despite a large placebo effect, the prednisone therapy periods are significantly differentiated from those of the placebo therapy periods by six of the nine parameters measured (Tables III and IV). The six parameters are tender joint count, swollen joint count, haemoglobin, total pain score, patient global assessment and painful joint count. The three which did not achieve significance were ESR, fatigue and morning stiffness.

Table IV *Patient-derived disease parameters and flare frequency*

	Baseline	Placebo	Prednisone
Total pain score	90.5 +/- 14.5 ^b	41.0 +/- 9.9	22.2 +/- 5.9 ^a
Global assessment (0-9)	5.8 +/- 0.4	4.1 +/- 0.6	2.7 +/- 0.4 ^a
Morning stiffness (hrs)	2.2 +/- 0.7	3.9 +/- 1.7	1.3 +/- 0.4
Painful joint count	28.1 +/- 3.1	18.7 +/- 2.9	12.2 +/- 2.8 ^a
Flares 30 days		--	3.6 +/- 0.4
3.3 +/- 0.4			

^a Significantly different from placebo (p<0.05)

^b Mean +/- standard deviation

The patients experienced an average of 3.3 flares per 30-day period during the prednisone therapy period and 3.6 during the placebo therapy period. There was no significant difference in the frequency of flares

between the prednisone therapy periods and the placebo therapy ones (Table IV). The frequency of adverse events is recorded in Table V. Of three patients who were assessed by duophoton absorptiometry, none showed worsening of bone density in the six-month interval from beginning to end of the study.

Table V. *Adverse events*

	Induction period	Placebo period	Prednisone period
Weight gain (>2 kg)	2	2	3
Hypertension	1	3	1
Gastrointestinal symptoms	1	2	2
Insomnia	1	0	1
Muscle pain or spasm	1	1	1
Hyperglycaemia	0	0	1
Itching	1	2	0
Other	5	6	3

The patient's improvement during the induction period correlates with the symptom control efficacy during the therapy period, $r = 0.59$, $p < 0.05$. The total pain score of the baseline period does not correlate with either the induction period success nor the therapy period success.

Discussion

Patient control of prednisone medication as used in the present trial increases the efficacy of prednisone threefold while reducing prednisone consumption by 40% from that of the 5 mg prednisone/day clinical trial of Harris and coworkers (11). In the latter trial, the patients were observed to have decreases of 10% in pain, 22% in swelling and 23% in tenderness from that of the baseline and the results were not statistically different from that of the placebo.

The results of the present trial are twofold better for symptom reduction from baseline than that observed with the sales-leading NSAID. Myhal and colleagues (12) reported decreases of 29% in the number of painful or tender joints, 28% in the number of clinically active joints and 29% in morning stiffness from that of baseline using 500-750 mg naproxen/day.

The average per patient consumption of prednisone during the prednisone therapy period was 3.0 mg/day. In accordance with the guidelines for prednisone use proposed by Inannuzzi (13) and consistent with the 9.5-year, 5 mg prednisone/day rheumatoid arthritis study of Hajiroussou and Webley (14), the prednisone regimen employed within the present trial was well tolerated with adverse events no more frequent than those observed with placebo use (Table V). Few if any, of the events were felt to be related to the medication. There was no significant difference in the frequency of flares between the prednisone therapy periods and the placebo therapy periods (Table IV).

The most appropriate analogy to patient control of glucocorticoid timing for rheumatoid arthritis treatment is that of the use of insulin in diabetics, since both hydrocortisone and insulin are hormones. The arbitrary use of the insulin in a fixed dose for all diabetics would be disastrous. Similarly, the observed poor results with fixed daily doses of hydrocortisone or its synthetic analogues in rheumatoid arthritis patients could be related to inappropriate timing. In contrast with the more severe consequences of improper insulin use, too much hydrocortisone would lead to its adverse reactions while too little would result in chronic inflammation when applied to rheumatoid arthritis patients.

Total control of symptoms should be possible for a hormone deficient disease when the hormone therapy is given. In practice, for patients with rheumatoid arthritis who have a history of chronic inflammation, the minimal symptom state rarely is asymptomatic. Residual symptoms are a summation of inflammation from irreversible damage previously done, periodic recurrences of acute inflammation and continuing presence of an inflammatory stimulus.

Patient cooperation and compliance proved to be very good. Fortunately, or unfortunately as one views it, pain is a powerful motivating factor. Only four patients had some difficulty following the instructions for medication use and required reassurance.

The remarkable improvement of rheumatoid arthritis symptoms and signs while on low dose prednisone in the present study can also be related to several factors gleaned from post-study patient interviews. The patients perceived the patient control of prednisone as an additional trust which the physician placed in them. This trust established a sense of partnership with the physician. The patients reported a sense of satisfaction and personal control by being trusted to use their own judgment in starting the flare quenching regimen and welcomed the challenge of quenching each flare as it appeared. Empirically, small flares require less prednisone to quench than do larger ones. When the patient quenched the flare early before it intensified and without waiting for an appointment with a physician, they used less prednisone.

Bone density considerations are of importance in long-term use of corticosteroids. Three of our patients were evaluated using duophoton adsorptiometry. None showed a worsening of bone density in the six month interval from beginning to end of the study. This is consistent with the results of Sambrook and coworkers, in which 8 mg of prednisone given daily for 89 months did not reduce bone density (15). At about 11 mg of prednisone/day, the total cumulative dose has been suggested to be a factor in steroid-induced osteoporosis (16). Thus, our regimen which utilizes a low-dose, flare-response approach at an average of 3 mg prednisone/day should be relatively safe.

Greater use of low dose prednisone may provide a convenient and inexpensive treatment for patients with rheumatoid arthritis. At a time when the traditional use of the pyramid approach to rheumatoid arthritis treatment is being reassessed, we believe that greater consideration should be given to the use of corticosteroids, especially when used in a safe and effective manner. Corticosteroid use as employed herein may be used concurrently with NSAID and DMARD therapies and may spare the patient from exposure to higher doses of NSAIDs or second-line agents, which are potentially dangerous and expensive.

Some potential drawbacks of our approach should be acknowledged. This type of treatment should be limited to reasonably intelligent, motivated and well-trained patients. The use of pain as the main marker of disease activity makes the treatment inappropriate for patients with cool, non-tender synovitis or with significant pain of mechanical origin.

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