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Does megestrol acetate down-regulate interleukin-6 in patients with cancer-associated anorexia and weight loss? A North Central Cancer Treatment Group investigation

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Abstract Megestrol acetate improves appetite and abrogates weight loss in some patients with advanced cancer. Moreover, preliminary studies suggest that progestational agents down-regulate interleukin-6 (IL-6), an inflammatory cytokine widely implicated in cancer-associated anorexia and weight loss. The present investigation examined the effects of megestrol acetate on IL-6 in an attempt to confirm these earlier, preliminary studies. The translational component of a large multi-institutional trial, this investigation examined 85 patients with advanced cancer and weight loss. Patients had been randomly assigned to receive megestrol acetate liquid suspension 800 mg/day + placebo tablets, or oral dronabinol tablets 2.5 mg b.i.d. + liquid placebo, or both agents. Other testing included serial physician-reported weight and patient-reported appetite and global quality of life. We found no significant differences in 1-month changes in serum IL-6 according to whether patients had been treated with megestrol acetate, dronabinol, or the combination: the mean differences ± standard deviation were –1.52±4.7 pg/ml, –0.62±3.5 pg/ml, and –0.2±3.1 pg/ml, respectively (P=0.40, by one-way ANOVA). Among the patients who noted alterations in their appetite over 1 month, we observed no significant changes in IL-6. Finally, changes in serum IL-6 were not associated with shifts in weight or global quality of life. Our investigation provides no evidence that megestrol acetate down-regulates IL-6 in patients with cancer-associated anorexia and weight loss.

Keywords Advanced cancer · Anorexia · Megestrol acetate · Weight loss

Introduction

Several studies have demonstrated that megestrol acetate improves appetite and abrogates weight loss in a small but notable percentage of patients with advanced cancer [2, 6, 9, 13]. Although the mechanisms have not been fully elucidated, there is some evidence to support the hypothesis that progestational agents palliate cancer-associated anorexia and weight loss by means of down-regulation of interleukin-6 (IL-6) [7, 14]. IL-6 is an inflammatory cytokine that has been widely implicated as a cause of cancer-associated anorexia and cachexia [3, 5, 8, 10, 12, 15].

Recent clinical studies suggest that progestational agents may down-regulate IL-6. Mantovani and others evaluated nine head and neck cancer patients, all of whom were treated with megestrol acetate 160–320 mg/day, along with concomitant antineoplastic treatment [7]. After several weeks of treatment, these investigators observed weight gain, an improvement in appetite, and a decline in IL-6 production by peripheral blood mononuclear cells. Similarly, Yamashita and others examined IL-6 concentrations in the serum of medroxyprogesterone-treated patients with advanced breast cancer [14]. Within 4 weeks of initiation of treatment with this progestational agent, serum concen-

trations of IL-6 decreased in all 21 patients. Moreover, patients with a pronounced decline in IL-6, defined as a drop of more than 3 pg/ml from baseline, manifested greater rates of appetite enhancement and weight gain.

In view of such provocative data, we undertook the present study to investigate further whether megestrol acetate lowers serum IL-6 concentrations. To our knowledge, this translational trial represents the largest clinical effort to evaluate the relationship between progestational agents and IL-6 in cancer-associated anorexia and weight loss. This investigation represents a nested translational component within a multicenter North Central Cancer Treatment Group (NCCTG) clinical trial. This clinical trial examined the orexigenic effects of megestrol acetate, the cannabinoid dronabinol, versus the combination of both for the treatment of cancer-associated anorexia and weight loss (work submitted) and found that megestrol acetate was superior to dronabinol in its orexigenic effects in the doses prescribed. It should be noted that a few previous studies have examined the effect of cannabinoids on IL-6 and that overall these studies suggest these agents do not down-regulate this cytokine [4, 11]. The goals of the translational component reported here included the following: (1) to determine whether megestrol acetate was associated with a decline in serum IL-6 concentrations compared to dronabinol or combination therapy; and (2) to determine whether changes in serum IL-6 after 1 month of orexigenic therapy were associated with changes in appetite, weight, and quality of life. Because of the pragmatic constraints imposed by a multi-institutional trial, we chose to measure serum IL-6, as opposed to IL-6 from peripheral blood mononuclear cells.

Methods

Overview

A total of 85 patients were studied. As indicated, these patients were participating in a much larger research effort, in which 469 evaluable cancer patients with anorexia and/or weight loss were randomized to receive megestrol acetate liquid suspension 800 mg/day + placebo tablets versus oral dronabinol tablets 2.5 mg b.i.d. + liquid placebo versus both agents. Costs and logistics dictated that this translational component should include only a subset of the entire patient population, and the subset was chosen on the basis of ability to freeze samples prior to treatment and early recruitment onto the clinical component of the trial in the participating institutions.

A total of 20 institutions within the NCCTG participated in the parent clinical trial, and the Institutional Review Board (IRB) of each of these institutions reviewed and approved the patient study protocol, which included this translational component, prior to patient enrollment.

Eligibility criteria

All patients included in the translational component of this trial had blood taken for serum IL-6 at baseline and at 1 month. As required by the parent trial, adult patients (≥18 years of age) with histological evidence of an incurable malignancy (other than brain, breast, ovarian, or endometrial cancer) were eligible. Patients had an estimated life expectancy of ≥3 months and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, as judged by their oncologist. Patients also had a self-reported weight loss of at least 5 lb (2.3 kg) over the preceding 2 months and/or a physician-estimated caloric intake of <20 calories per kg of body weight per day. Eligible patients indicated that loss of appetite or weight was an ongoing problem. Antineoplastic treatment was permitted.

Exclusion criteria

Exclusion criteria included: (1) ongoing use of tube feeding or parenteral nutrition; (2) ascites; (3) treatment with adrenal steroids (except for short-term dexamethasone around the time of chemotherapy), androgens, progestational agents, or other appetite stimulants within the past month; (4) brain metastases; (5) insulin-dependent diabetes; (6) pregnancy or an unwillingness to use oral contraceptives (for premenopausal women); (7) anticipated alcohol or barbiturate use during the study period; (8) poorly controlled hypertension or congestive heart failure; and (9) a history of thromboembolic disease.

Baseline testing

In addition to the blood sampling at baseline and at 1 month, patients were asked to complete a previously validated appetite questionnaire [6] and a single-item uniscale for assessment of global quality of life. Our validated appetite questionnaire included the question, “How would you rate/describe your appetite?” Patients were allowed to answer with “very good,” “good,” “fair,” “poor,” and “very poor,” and appetite was assessed on the basis on patients’ responses. Repeat assessments occurred at 1 month. Baseline and 1-month weights were obtained in physicians’ offices.

Laboratory analysis

All serum samples were frozen at –70°C immediately after collection and were shipped to the Mayo Clinic in Rochester, Minnesota on dry ice. Samples were later shipped, again on dry ice, to the laboratory of Dr. Jun-ichi Yamashita at the Kumamoto University Medical School, Kumamoto, Japan for IL-6 measurement.

Serum IL-6 was measured with a commercially available enzyme-immunoassay kit (Cytoscreen, Biosource International, Camarillo, Calif.). This assay carries with it a sensitivity of <2 pg/ml, according to the manufacturer of the kit. When sample concentrations exceeded the upper limit of the standard curve (>10 pg/ml), samples were diluted and assays re-run to allow for total, accurate quantitation of IL-6 in each serum sample.

Statistical analyses

Data were analyzed with the SPSS 7.0 statistical package (SPSS, Incorporated; Chicago, Ill.). Descriptive statistics (including means, medians, standard deviations, and ranges) are reported. A one-way analysis of variance (ANOVA), Kruskall-Wallis test, or Chi-square analysis was used to compare differences between patients in the three study arms and between patients with no change in appetite, worsening appetite, or improvement in appetite. Correlations between 1-month changes in anorexia and serum IL-6 concentrations were determined with a Pearson’s correlation coefficient. A similar analysis was performed with 1-month weight changes (weights were censored if there was evidence of ascites or edema) and serum IL-6 changes. A comparison-wise *P*-value of <0.05 was con-

sidered statistically significant, and all statistical tests were two-tailed.

Results

Between December 1996 and December 1999, 85 patients underwent blood sampling both at baseline and after 1 month. Baseline characteristics are illustrated in Table 1. Of these 85 patients, 15 (18%) had missing data on appetite, 17 (20%) on global quality of life, and 5 (6%) on physician-reported weight at the end of the 1-month evaluation period.

Serum IL-6 concentrations at baseline and after 1 month of treatment for this study population as a whole were as follows (mean ± SD): 4.8±4.1 pg/ml versus 4.0±3.9 pg/ml, respectively (see Fig. 1). Data on changes in IL-6 were normally distributed. We found no significant differences in changes in serum IL-6 after 1 month according to whether patients had been treated with megestrol acetate alone, dronabinol, or a combination of both: the mean differences ± SD from baseline to after 1 month of treatment were –1.52±4.7 pg/ml, –0.62±3.5 pg/ml, and –0.2±3.1 pg/ml, respectively (P=0.40, by one-way ANOVA) (see Fig. 2). Similarly, actual IL-6 values assessed after 1 month showed no significant differences between treatment groups.

Among the patients who did note changes in their appetite, we observed no significant 1-month changes in IL-6 according to whether patients reported their appetite

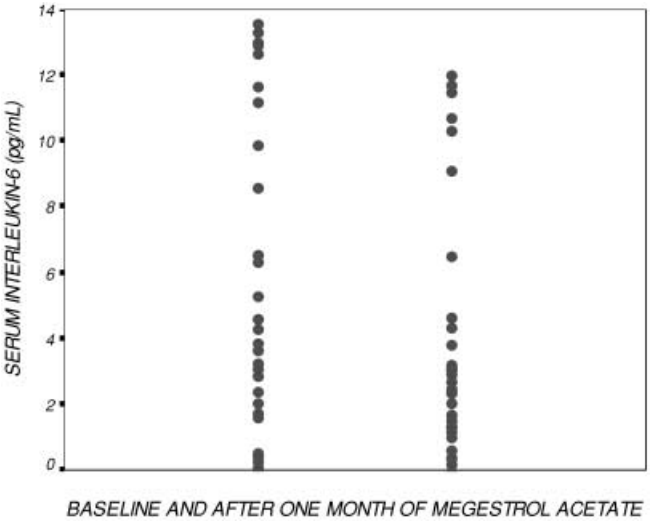

Fig. 1 Serum IL-6 concentrations at baseline and at 1 month were evaluated for all three study groups. Shown here are values from the megestrol acetate-treated group

was the same (n=15), improved (n=50), or worse (n=5): the changes (mean±SD) were: –2.03±3.2 pg/ml, –0.43±4.4 pg/ml, and –1.32±2.9 pg/ml, respectively (P=0.42, by one-way ANOVA).

Finally, we examined whether 1-month changes in serum IL-6 concentrations were associated with changes in weight or with changes in global quality of life and found no statistically significant associations. Scatter-

Table 1 Baseline characteristics[a]

	Megestrol acetate (n=33)	Dronabinol (n=22)	Megestrol acetate + dronabinol (n=30)	P-Value[b]
Age [years: median (range)]	69 (49–82)	65 (40–86)	64 (37–94)	0.72
Sex (M/F)	18/15	14/8	20/10	
Malignancy				
Lung (%)	30	45	30	–
Gastrointestinal (%)	39	27	30	–
Other (%)	30	27	40	–
Weight loss in preceding 2 months				
<10 lb (%)	36	59	43	0.25
≥10 lb (%)	63	41	57	
Planned concurrent chemotherapy				
No (%)	15	41	0	–
Yes (%)	85	59	100	–
Physician-reported weight (kg: mean±SD)	64±12	69±15	66±13	0.39
Quality of life (uniscale: mean±SD)	49±24	58±24	47±25	0.30
Serum IL-6 [pg/ml: median (range)]	3.7 (0–14)	4.1 (0.58–13)	2.9 (0–11)	0.26
Severity of anorexia: “fair” + “poor” + “very poor” (cumulative %)	96	91	90	–

[a] Percentages do not always add up to 100%, because of rounding
[b] ANOVA, Kruskall-Wallis, or Chi-square, as appropriate

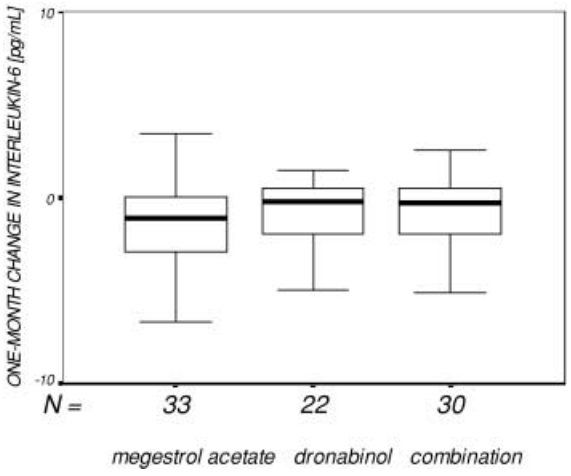

Fig. 2 There were no significant differences in serum IL-6 changes at 1 month according to whether patients had been treated with megestrol acetate, dronabinol, or a combination of both: mean difference ± standard deviation: –1.52±4.7 pg/ml, –0.62±3.5 pg/ml, –0.2±3.1 pg/ml, respectively (P=0.40), by one-way ANOVA). Nine outliers were included in the analysis but are not shown in the graph

plots were used to verify the lack of correlative findings (not shown).

Discussion

Our study provides no evidence that megestrol acetate down-regulates IL-6 in patients with cancer-associated anorexia and weight loss. Furthermore, our data do not suggest that changes in IL-6 are associated with 1-month alterations in appetite, weight, or quality of life. Our findings differ from those of earlier studies [7, 14], which have implicated this cytokine in the palliation of cancer-associated anorexia and weight loss with progestational agents.

Several aspects of our study design are worth emphasizing. First, our sample was relatively large: 85 patients, as opposed to 21 in one of the larger trials alluded to earlier, with 33 of our patients receiving megestrol acetate alone [14]. We acknowledge that in our study data on secondary endpoints such as physician-reported weight, anorexia, and quality of life were missing. It is important to point out, however, that these rates of missing data are typical of studies examining anorexia and weight loss in advanced cancer patients, in whom multiple end-of-life issues arise and preclude patients' participation in all aspects of the study protocol [1, 15]. In addition, we acknowledge that our study did not capture and adjust for other variables that might have altered cytokine measurements, such as type of chemotherapy, timing of chemotherapy, and other comorbidities, such as infection. Nonetheless, compared with other previously published studies, our investigation remained robust with regard to serum IL-6 measurements. Thus, our data are worth taking seriously, despite their divergent, negative conclusions.

A second aspect of our study design that is worth emphasizing is the fact that we included a control group (the dronabinol-treated group), which consisted of cancer patients who were not receiving progestational agents. As noted earlier, the effects of cannabinoids on IL-6 have not been well studied, but there are several reports that do not suggest they down-regulate this cytokine [4, 11]. The other two studies cited earlier included either a baseline comparison or a comparison with a control group of non-cancer patients. By comparing IL-6 levels between three groups of cancer patients, we sidestepped problematic issues that might arise from paired measurements or from healthy control group comparisons that would not account for confounding cancer effects.

Thirdly, another important aspect of our trial is that we analyzed serum IL-6 as a continuous variable. While the earlier study by Yamashita and others had defined groups based on IL-6 cut-off points (>3 pg/ml versus ≤3 pg/ml), some might argue these cut-off points are arbitrarily chosen [14]. In contrast, we examined group differences without including subgroup analyses based on such cut-off points. In all, despite the divergence of our conclusions from earlier studies, the large sample size, choice of control subjects, and analysis of IL-6 as a continuous variable make our negative results worth reporting.

Finally, it is important to point out that although our study investigated the role of progestational agents in modulating appetite by means of IL-6 modulation, it did not address the direct role of IL-6 in mediating cancer-associated anorexia and weight loss. Several earlier studies have already strongly implicated this cytokine in cancer-associated anorexia and weight loss. IL-6 has been associated with weight loss in tumor-bearing animals, and the administration of antibodies against this cytokine has led to weight gain [12]. Similarly, earlier clinical studies have demonstrated that serum IL-6 is higher in malnourished cancer patients than in non-cancer patients [5, 8, 10, 15]. Because our study population consisted of advanced cancer patients who were well enough to attend for both baseline and 1-month blood sampling, these patients represent a select group who were presumably in better health than those who did not and probably could not return for a second blood sample to be taken. (Roughly half the patients from our original translational cohort did not return to have a second blood sample taken, because of intercurrent morbidity or mortality.) The present investigation was not designed to address whether IL-6 is a direct mediator of cancer-associated anorexia and weight loss, because of this potential for selection bias. Instead, we accepted IL-6 as a well-

established mediator of anorexia and weight loss and set about testing the hypothesis that progestational agents might exert their well-established orexigenic effects by means of IL-6 modulation.

In conclusion, our study suggests that other mechanisms, perhaps involving other cytokines, should be invoked to explain megestrol acetate's favorable effects on cancer-associated anorexia and weight loss. Future investigations might be aimed at exploring what these mechanisms might be.

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