

# MEGESTROL ACETATE FOR THE TREATMENT OF ANOREXIA-CACHEXIA SYNDROME (Protocol)

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## **BACKGROUND**

Anorexia cachexia syndrome is a common clinical problem that substantially impacts upon the quality of life and survival of affected patients. It is characterized by loss of appetite, weight loss and tissue wasting, accompanied by a decrease in muscle mass and adipose tissue, impoverishing the quality of life, and often preceding the patient's death ([Nelson 1994](#); [Splinter 1992](#)).

More than two-thirds of patients dying with advanced cancer suffer from anorexia cachexia syndrome ([Argilés 2001](#)). Anorexia cachexia syndrome is also described in other pathologies such as Acquired Immune Deficiency Syndrome (AIDS); anorexia nervosa; in degenerative illnesses of the central nervous system; and in the terminally ill patient ([Von Roenn 1996](#)). Incidence is variable and difficult to determine but in general the syndrome may occur in 15% to 40% of patients with cancer, and in more than 80% of patients with advanced illness ([Bruera 1992](#)).

Cachexia in the cancer patient is thought to occur as a result of metabolic changes brought about by substances secreted by the tumour and the host ([Alexander 1993](#)). Substances have been identified that cause severe anorexia and weight loss. Tumour necrosis factor, synthesized by the host's macrophages (important cells in the immune system), and inflammatory cytokines (including interleukin 1 (I 1) and 6 (I 6)) are considered responsible for some of the clinical manifestations ([Mantovani 1998](#)).

Early intervention and attention to nutritional status are essential in patients with anorexia cachexia syndrome. Pharmacological interventions for neoplastic cachexia include drugs that stimulate the appetite (megestrol acetate and dronabinol); cytokine inhibitors (such as cyproheptadine, thalidomide and pentoxifylline); and anabolic agents such as nandrolone decanoate, oxandrolone and corticosteroids ([Balog 1998](#)). Megestrol acetate is a synthetic progestogen agent. The biological mechanism of the anti-tumoral activity of megestrol acetate is not well understood but it probably acts on hormone-dependent tumoral cells. The inhibitor effects of growth in the cellular cycle are not phase-specific, but their activity seems to be maximized in phase G1 of cellular division ([Tchekmedyian 1986](#)).

Megestrol acetate was first synthesized in England in 1963. Developed as an oral contraceptive, the agent was first tested in the treatment of breast cancer in 1967 and later on for the treatment of endometrial cancer. Megestrol acetate is currently used to improve appetite and to increase weight in cancer-associated anorexia. From September 1993 megestrol acetate was approved by the Federal Drug Administration (FDA) in the USA for the treatment of anorexia, cachexia, or unexplained weight loss in patients with AIDS. In addition, there are recent reports of the drug being used to improve the quality of life of elderly patients with cachexia. A possible role in anorexia nervosa has also been proposed ([Yeh 2000](#)).

Megestrol acetate is usually available in tablet or liquid form. Usual dosage for the tablet is 80 mg four times per day. The liquid form is usually dosed at 20 ml per day. Although the therapeutic dose is 800 mg per day, great variability in doses are observed in the scientific literature, ranging from 320 mg to 1600 mg per day. The recommended duration of treatment is more than six weeks.

Megestrol acetate is considered a relatively non toxic drug with a low incidence of adverse effects such as fluid retention, venous thrombosis, diarrhea, rash, impotence, pruritus, increased sugar level in the blood, and headache.

Although the mechanism by which megestrol acetate increases appetite is unknown, most hypotheses point to action on cytokines, which inhibit the action of tumour necrosis factor on fatty tissue and its products. Currently, interest is focused especially on its effectiveness in the treatment of anorexia and cachexia in neoplastic and AIDS patients. Studies at the Mayo Clinic and The North Central Cancer Treatment Group Study have reported and reviewed multiple placebo-controlled, randomized, double blind, clinical trials of megestrol acetate and other drugs for the improvement of anorexia cachexia syndrome in all types of cancer ([Loprinzi 1990](#)).

Two systematic reviews have been undertaken recently. A systematic review by Maltoni et al ([Maltoni 2001](#)) assesses the efficacy of high dose progestins for the treatment of anorexia cachexia syndrome in patients with hormone-independent tumours. This review included 15 randomized clinical trials and more than 2000 patients. The authors concluded that high-dose progestins improve appetite and weight, but could not define optimal dose: duration of treatment; impact on quality of life ([Maltoni 2001](#)). The review by [Ruiz-Garcia 2002](#) evaluated the efficacy of megestrol acetate versus placebo in patients with cancer and anorexia cachexia syndrome. Eight trials (719 patients) were included in the review and found that megestrol acetate was associated with a slight weight gain at doses of 240 mg per day or less. No statistically significant effect was observed with higher doses. However, there is a need for a further systematic review incorporating an extensive search for studies of high quality to assess the effectiveness and safety of megestrol acetate in cancer and AIDS patients.

### **OBJECTIVES**

- 1) To evaluate the efficacy, effectiveness and safety of megestrol acetate in palliating anorexia-cachexia syndrome (with subgroups of cancer and AIDS patients)
- 2) To determine the optimal dose regimen for megestrol acetate in palliating the anorexia-cachexia syndrome

### **CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW**

#### **Types of studies**

Randomized controlled trials (RCTs) which may be double blind, single blind or unblinded. Cross-over studies will be included if they report the results of the first phase of the study. Both inpatient and outpatient study settings will be included.

#### **Types of participants**

Patients with a clinical diagnosis of anorexia-cachexia related to cancer, AIDS or another underlying pathology, independent of gender, age or race.

#### **Types of intervention**

This review will focus on the following treatment comparisons:

- a) Megestrol acetate at any dose versus placebo
- b) Megestrol acetate at any dose versus other active treatments
- c) Megestrol acetate at different doses

#### **Types of outcome measures**

The following outcome measures will be assessed:

- Appetite increase, expressed as a dichotomous variable (number of patients who experience appetite increase) or a continuous variable (calorific intake expressed as calories/day).
- Weight gain, measured as a continuous variable in kg/day at the end of the treatment compared with the baseline.

- Measurements of the mid-arm circumference and triceps skin fold thickness by anthropometry, as a percentage of the differences in the total body muscle and fat mass.
- Improvement in quality of life (QoL), by means of a validated instrument, or with scales of functional scores (eg, Index of Karnofsky and performance status) that measure the well-being status of the patient. The QoL measures will depend of the instrument used, eg, patient assessments using a Likert-type scale based on patients' statements and self-report questionnaires; or as the Spitzer QL-Index of quality of life, completed by the clinician. Study withdrawals and dropouts will be analyzed as:
  - a) Total number of dropouts and withdrawals
  - b) Number of withdrawals due to lack of effectiveness of treatment
  - c) Number of withdrawals due to adverse effects

Adverse effects: These will be analyzed as the number of patients who suffer each of the side effects described, or by means of toxicity scores reported on a symptom list according to WHO toxicity classification.

## ***SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES***

### **ELECTRONIC SEARCHES**

The following electronic databases will be searched to identify relevant studies:

- i) MEDLINE from 1966 to 2002
- ii) EMBASE from 1986 to 2002
- iii) The Cochrane Central Register of Controlled Trials (CENTRAL), The Cochrane Library Issue 3, 2002.

For the identification of studies included or considered for this review, detailed search strategies will be developed for each database searched. These will be based on the search strategy developed for MEDLINE but revised appropriately for each database.

The general strategy for identifying randomized clinical trials in MEDLINE will be combined with the following specific strategy designed to retrieve trials of megestrol acetate for cachexia:

- (Acquired Immunodeficiency Syndrome"[All Fields] OR (acquired immunodeficiency syndrome"[MeSH Terms] OR AIDS [Text Word]))
- ((neoplasms"[MeSH Terms] OR Neoplasm [Text Word]) OR cancer [Text Word]))
- ((end of life"[All Fields] OR (terminally ill" [MeSH Terms] OR Terminally ill [Text Word])) OR (terminal care"[MeSH Terms] OR Terminal care[Text Word]))
- (cachexia"[MeSH Terms] OR cachexia [Text Word])
- (megestrol acetate" [MeSH Terms] OR megestrol acetate [Text Word])

List of references of the included studies will be checked to identify further trials.

We will attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress). If necessary, additional data from published trials will be sought by contacting authors. All appropriate pharmaceutical companies will be asked to comment on the list of identified trials.

## ***METHODS OF THE REVIEW***

### ***STUDY SELECTION***

The results of the search strategy will be independently screened by two authors (EGB, ZO) and assessed for inclusion in the review. Disagreement will be resolved by discussion. Reasons for excluding trials will be reported.

### ***DATA EXTRACTION***

Data on patients, methods, interventions, outcomes and results will be extracted by two reviewers using a data extraction form (EGB, ZO). Differences will be resolved by consensus, and when necessary, in consultation with a third reviewer. Where there is uncertainty, authors will be contacted to clarify details.

### ***QUALITY OF STUDIES***

The methodological quality of the studies will be evaluated using a validated scale published by Jadad ([Jadad 1996](#)). This scale includes an evaluation of the randomisation, blinding and patient attrition. The scale produces a composite score ranging from 1 (low quality) to 5 (high quality). Allocation concealment will also be evaluated as a parameter of quality of the design of the studies.

### ***DATA ANALYSIS***

Studies with more than 50% of patients lost to follow up will not be included in the analysis. For any crossover study included in the review, the results of the first treatment period only will be analysed to avoid carry-over effects.

For dichotomous variables, treatment effects will be computed as relative risk (RR) with 95% confidence intervals. For continuous variables (including scales), differences in means and their 95% confidence interval will be calculated (WMD). To be included in the analysis, scales should fulfil two requirements: the scale should be validated and the data should have a normal distribution. Validity of the scale will be determined by the psychometric properties of the instrument described in the trial by the reviewers. Specific instruments of quality of life should have been completed by the patient themselves or by a relative.

Heterogeneity between studies will be analysed with a Chi-square test, using  $p < 0.1$  as a cut-off value to consider that significant heterogeneity exists. If worrying heterogeneity is detected, further analysis will be performed to try to identify the sources of heterogeneity. Meta-analysis will be performed using a random effects model.

### ***SUBGROUP ANALYSIS***

Analysis of subgroups will be undertaken according to the underlying pathology of the patients. Three subgroups of studies will be defined:

- a) patients with AIDS;
- b) patients with cancer;
- c) patients with other underlying disease.

### ***SENSITIVITY ANALYSES***

In order to explore the impact of specific factors on the meta-analysis results, sensitivity analyses will be undertaken with:

- parallel studies
- studies of high methodological quality (defined as studies with appropriate concealment of allocation, appropriate blinding, and analysis by intention to treat).
- studies where patients received more than four weeks of treatment.

The statistical analyses will be carried out using the statistical package Rev Man 4.1.

### ***POTENTIAL CONFLICT OF INTEREST***

The authors of this review wrote an internal report on this topic for a pharmaceutical company that produces megestrol acetate. The current protocol and proposed review are independent from that report and will follow the requirements of the editorial team of the Pain, Palliative and Supportive

Care CRG, even if following those guidelines produces results that are different from the original report. Aside from the above project, the reviewers certify that they have no affiliations with any organisation or entity with a direct financial interest in the subject matter of the review.

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#### **COVER SHEET**

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### ***SOURCES OF SUPPORT***

#### **External sources of support**

- No sources of support supplied

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### **ADDITIONAL TABLES**

Additional tables are not available for this protocol