Clinical Trials for the Treatment of Secondary Wasting and Cachexia

Approved Pharmacologic Interventions for Wasting: An Overview and Lessons Learned

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There are currently four approved drug products for the treatment of wasting: oxandrolone, dronabinol, megestrol acetate, and growth hormone. We have learned some important lessons with the reviews of each of these products. This review will summarize the pivotal trials performed for each of these drug products, and will provide some commentary on the design of clinical trials for wasting, in general.

Oxandrolone, approved in 1964, was the first drug approved for the treatment of wasting. Oxandrolone is an anabolic steroid being a synthetic derivative of testosterone. The indications for oxandrolone include use as an adjunctive therapy to promote weight gain following weight loss after extensive surgery, chronic infections, or severe trauma; for patients with unexplained weight loss; and to offset protein catabolism associated with prolonged corticosteroid use. An additional non-wasting use for Oxandrolone is for the relief of bone pain associated with osteoporosis. The evidence used to support the oxandrolone application for wasting was data from a six-week crossover, placebo-controlled study performed in 224 patients. Of the 224 patients enrolled, data from 220 were used to evaluate efficacy. The primary endpoint examined was weight gain which was divided into three categories: 0 to 3 pounds, 3 to 6 pounds, and more than 6 pounds.

Subjects were divided into two groups differing in order of treatment. One group received placebo first followed by Oxandrolone (P-O; n = 119) while the second group (O-P; n = 101) received Oxandrolone first, followed by placebo. In the P-O group, the percentage of patients who gained weight was greater during the oxandrolone phase of therapy than during placebo. Approximately one-third of patients lost weight during the placebo phase compared with only 12% of patients who lost weight during the oxandrolone phase. The results for the O-P group were similar. In the O-P group, more patients gained weight during the oxandrolone phase of therapy than placebo, and while 12% to 13% of patients lost weight during oxandrolone therapy, approximately one-half of the patients lost weight during the placebo phase of treatment.

There are several concerns about the oxandrolone data that can be raised in retrospect. First, the clinical relevance of the weight gain is not clear. Conceivably, the weight gain might have represented primarily edema. Second, the study population represented a very wide variety of clinical backgrounds. For example, some patients had psychiatric diseases, some were post-surgery, and some had gastrointestinal diseases. Given the knowledge we now have about the complex pathophysiology of wasting and how it varies in patients with different underlying diseases, the heterogeneity of the oxandrolone patient population might be considered problematic. Third, the cross-over study design is a concern, because weight does not return to a stable baseline prior to crossover. The most meaningful comparison from the data available from the oxandrolone trial would have been the parallel comparison of the patients randomized to the initial three weeks of either placebo or oxandrolone, but this analysis was not provided. Finally, the duration of the trial was only six weeks; therefore, it is difficult to judge the efficacy and safety of more chronic therapy, which many patients with wasting would require.

In the ensuing years between 1964 and 1992, no drugs were approved for wasting. The increasing importance and prevalence of AIDS-related wasting served to stimulate activity in this area of drug development. For example, the indications for the use of Dronabinol, an orally active canniboid first approved for the treatment of nausea and vomiting, were extended in 1992 to the treatment of anorexia associated with AIDS. This extension was based on data from two trials. The first trial was a six-week randomized, double-blind, placebo-controlled trial performed in 139 AIDS patients. Of the 139 enrolled subjects, data from 112 were used to evaluate efficacy. The endpoints examined were mood, weight, and appetite (reflected by scores from using a 100 mm visual analog scale). Although there was no effect on mood or weight, the dronabinol treatment was associated with improved appetite on the visual analog scale.

In the second trial, a 12-week crossover trial performed in 12 AIDS patients, study participants spent five weeks on either dronabinol or placebo, had a two-week washout periods, and then were crossed over for five weeks on the alternative treatment. The dependent measures were appetite and weight gain. Again, dronabinol had no effect on weight, but the beneficial impact on appetite (in this case a 61% improvement...
compared with 9% on placebo) was confirmed. Thus, dronabinol was approved specifically for the indication of anorexia associated with AIDS.

Several points of interest can be noted about the dronabinol trials. The pivotal trial was a randomized, placebo-controlled, double-blind study with a 12-week treatment period, an improvement over the previous 6-week crossover studies performed with oxandrolone. Although 139 patients were enrolled, the attrition rate for the sample of AIDS patients was high resulting in data from only 112 subjects being available to evaluate efficacy. It was notable that a placebo effect on appetite was reported in both of the dronabinol trials. Concern is also raised by the lack of impact on mood and weight in light of the positive effect of dronabinol on appetite. The absence of a positive impact on mood may be a reflection of the adverse CNS effects of dronabinol reported in one-third of patients. In summary, although the change in the visual analogue appetite scale with dronabinol was statistically significant, the clinical relevance of this finding remains unclear. The previous clinical experience with dronabinol in the treatment of nausea and vomiting related to chemotherapy (a somewhat related indication), may be the most likely explanation of the perception of improved appetite.

The third drug approved for a wasting related indication was megestrol acetate. Megestrol acetate is a synthetic progesterone derivative, and is available as an oral solution for the treatment anorexia, cachexia, or unexplained weight loss in patients with AIDS. Megestrol had previously been approved in a tablet form using a much lower dose for the management of hormone-sensitive malignancies. Two pivotal trials were performed to support the megestrol application. The first was a 12-week randomized, double-blind, dose-response trial in 270 AIDS patients suffering from cachexia and wasting. Data from 195 of these patients were evaluated for efficacy. Three doses of megestrol (100 mg, 400 mg, and 800 mg per day) were compared with placebo. The prespecified primary endpoint was the percentage of patients with a body weight gain of at least five pounds at the time of last evaluation in the study. Both the 400 mg and 800 mg doses of megestrol were superior to placebo. For the 800 mg arm, approximately 64% of patients met the criteria of five pounds or more weight gain compared with 21% of placebo subjects. In addition, a dose-response relationship was noted between the 100 mg, 400 mg, and 800 mg arms of megestrol acetate. Importantly, 21% of the placebo patients in this study gained at least five pounds of weight or more, which again established that there can be a considerable placebo response in wasting trials.

Evaluations of body composition using bioelectrical impedance were included as secondary endpoints in the megestrol trial. An analysis of these data revealed little change in the placebo arm: fat changed hardly at all, lean body mass decreased by approximately 1 kg, and about 1.5 kg of total body water was lost. However, for each of the megestrol treatment arms, the primary body component which increased was fat, and, again, there was a dose-response noted. Changes in lean body mass were nominal. Although concern was raised that the overall weight gained could be due to edema, the bioelectric impedance data showed no significant change in total body water. Additional endpoints included appetite, caloric intake, and an overall sense of well-being. Appetite, caloric intake, and sense of well-being were all significantly better in the 800 mg treatment arm compared with placebo.

The second trial supporting the approval of megestrol acetate was also a 12-week trial in which 100 patients with AIDS wasting were enrolled. Again a high attrition rate was reported with data for 65 patients available for evaluation of efficacy. The primary endpoint in this trial was the percentage of subjects with five pounds or more overall weight gain. As in the previous trial, a relatively high placebo effect was reported with 28% of placebo patients gaining at least five pounds or more compared with 47% of those receiving megestrol. While not reaching statistical significance, this trial was nonetheless supportive of the larger dose-finding trial described previously. Analysis of body composition again revealed that fat was the major component being affected by megestrol acetate.

Among the strengths of the megestrol trials were the inclusion of an assessment of body composition to address the possibility that the body weight changes were simply the result of edema. In addition, the two trials submitted were both randomized and placebo-controlled with a relatively large number of subjects. The dose-response noted in the larger trial, and the high frequency of meeting multiple primary and secondary endpoints criteria in both trials were also encouraging. However, several weaknesses were also noted. First, the dropout rates were considerable. Because the final results only reflected the data available from the patients completing the trials, an intent-to-treat analyses might arguably have provided a more realistic assessment of efficacy. The placebo effect was considerable and warrants further study. The long-term duration of the effect of megestrol on AIDS wasting was unclear. Finally, in the absence of any evidence other than the change in body weight, it was difficult to determine the actual clinical relevance, i.e., impact on morbidity, mortality, or quality of life, of a five-pound gain in body weight.

Growth hormone was the final product to be approved for the treatment of AIDS wasting and cachexia. This drug received accelerated approval for wasting based on a positive change in lean body mass. The reviewers concluded that a follow-up study to confirm the clinical benefits of a change in lean body mass was necessary. Consequently, accelerated approval was contingent on the performance of a follow-up study designed to confirm the positive change in lean body mass, and its clinical relevance.

The first trial performed with growth hormone was a 12-week randomized, double-blind, placebo-controlled trial involving 178 patients with AIDS-related wasting. Of the 178 subjects enrolled, data from 140 subjects were evaluated. Growth hormone (0.1 mg/kg/day) or placebo were administered subcutaneously by injection. Weight and body composition were the primary endpoints of interest. A significant increase in body weight was reported with a mean weight gain of 1.6 kg in patients receiving growth hormone, compared with 1 kg in patients receiving placebo. More importantly, however, the patients receiving growth hormone had a 3 kg gain in lean body mass which was offset by a mean 1.7 kg loss of body fat. The relative change in lean body mass in the placebo group was negligible. Functional performance, as reflected by treadmill workout, was assessed as a secondary endpoint in this trial. Treadmill work output increased in the growth hormone arm by 13% compared with a 2.5% increase in the placebo arm. Grip strength was also assessed, with no differences noted. In addition, a number of quality-of-life surveys were performed, with no differences noted.

The second growth hormone trial involved an initial enrollment of 177 patients with AIDS, studied for 12 weeks. Data from 129 were available for evaluation of efficacy. Growth hormone was administered at a fixed dose of 6 mg/day instead of being adjusted for patient weight. The only endpoint examined were those of weight and quality of life. Although the average gain in weight in the growth hormone arm was 1.6 kg compared with a 0.4 kg weight gain in the placebo arm, the difference was not statistically significant. It
was supportive, however, that the weight gain of 1.6 kg was identical to that noted in the previous trial. No significant difference were noted in the quality of life measures between treatment arms.

The growth hormone trials increased our understanding about the conduct of wasting trials. The performance of two separate randomized controlled clinical trials and the attempt to confirm that the weight being gained was not edema was supportive of the application. The finding of a positive lean body mass change was perhaps the most notable, but was only tested in one of the two pivotal trials. Extending beyond the lean body mass changes to attempt to determine a more clinically relevant change in overall body strength by treadmill testing and grip strength was also noteworthy of this trial.

In conclusion, we have evolved in our approach to wasting trials over the past 30 years. The finding of significance on a prespecified primary endpoint in a well-designed randomized trial is critical. In addition, the inclusion of other more descriptive endpoints such as body composition, functional endpoints of strength and quality of life clearly increase our ability to understand the clinical significance of these treatments. In the future, we hope to continue to learn additional important lessons to improve the design of wasting trials.