Protection from Radiation-Induced Oral Mucositis by MuGard™ Oral Rinse
A Clinical Study and *in silico* Analysis

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Abstract

Mucositis is a common debilitating side effect of several types of cancer therapy for which there is no established treatment. MuGard™ is a viscous, mucoadhesive polymer-based oral rinse developed for the prevention and treatment of mucositis. MuGard™ is formulated to provide a long-lasting yet unobtrusive protective coating of the oral mucosa. We have conducted a 56-patient multi-center, randomized, double-blind clinical study in patients undergoing radiation therapy for head and neck cancer, in which MuGard™ Oral Rinse was compared to MuGard™ containing amlexanox, an anti-allergic and anti-inflammatory compound. Mucositis was scored daily using the oral mucositis assessment scale (OMAS). OMAS scores were slightly better in the patients receiving MuGard™ Oral Rinse alone indicating no benefit for the addition of amlexanox. As part of the analysis, the scores for patients receiving MuGard™ alone were compared with those observed in two prior trials of best available care scored in the same manner. Subjects treated with the MuGard™ Oral Rinse had less severe mucositis when compared to 44 patients who received no specific therapy for the prevention of mucositis (Sonis et al, Cancer, 2000, 89: 2103). Only 7% of patients in the control group had zero or 'mild' mucositis (no individual OMAS score greater than 0.5) compared with 42% in the MuGard™ group. The beneficial effects of MuGard™ Oral Rinse were further confirmed when they were compared to another previously published set of 18 historical controls (Epstein et al, Cancer, 2000, 89: 2258). We conclude that MuGard™ Oral Rinse shows substantial promise for reducing the severity of radiation-induced mucositis.

Introduction

Oral mucositis is a frequent complication of cancer chemotherapy or radiation therapy to the head and neck region. Currently available therapy is usually inadequate, and a more effective treatment to minimize the extent and duration of mucositis is clearly needed. Historically, treatment of mucositis has been palliative and aimed at minimizing mucosal trauma. Mucositis and infection of the mouth have remained major complications despite the usual oral care provided for patients with cancer such as frequent mouth cleansing, rinsing with buffered saline and fluoride solutions, and administration of topical and systemic antimicrobial agents. We set out to examine the potential of amlexanox in the prevention and treatment of mucositis. Amlexanox is an anti-allergic, anti-inflammatory compound that has been approved for marketing by the FDA for the acceleration of healing of aphthous ulcers. Six vehicle-controlled, double-blind, randomized clinical studies were conducted to assess the safety and efficacy of paste and erodible patch formulations of amlexanox in the treatment of minor aphthous ulcers. Over 2,000 subjects participated in clinical studies of amlexanox for this indication. The results of these studies demonstrated that the 5% amlexanox paste and the buccal patch formulation of amlexanox accelerated the healing of minor aphthous ulcers and reduced the duration of pain, as compared to patients receiving either vehicle alone or no specific treatment. Amlexanox was therefore considered to offer potential in treating other ulcerative conditions of the oral cavity.

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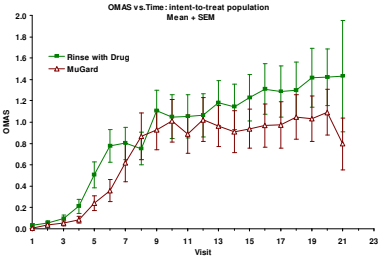
Methods

The comparison of amlexanox rinse versus MuGard™ was a phase II double-blind, randomized clinical study conducted at 11 centers. The 56 patients that entered the study had documented diagnosis of head and neck cancer and were about to receive a course of radiation therapy (with or without concomitant chemotherapy) with a planned dose of at least 60 Gy over 6-7 weeks, and with planned fields to involve at least 50% of the oral mucosa. Patients were assessed using oral mucositis assessment scale (OMAS) three times per week for seven weeks. The extent of ulceration and erythema was recorded at 9 sites throughout the oral cavity: upper lip, lower lip, right cheek, left cheek, right ventral and lateral tongue, left ventral and lateral tongue, floor of the mouth, soft palate/fauces, hard palate. At each anatomical site, ulceration was graded on a scale of 0 to 3 and erythema on a scale of 0 to 2. The OMAS was computed as the sum of all the individual erythema and ulceration scores, divided by the number of anatomical sites graded. Patients with "no significant mucositis" are defined as those with no daily OMAS score above 0.5. OMAS scores were summarized by treatment group and visit by presenting number, mean and standard deviation. Missing data points were imputed by using the last available data point prior to the missing value (for up to three consecutive data points).

For the comparison of MuGard™ data with data from two sets of patients receiving standard care, plots were developed of the mean daily OMAS score versus treatment visit day for the MuGard™ group to each of the two untreated groups. The mean maximum OMAS score was computed for each patient as the mean of the three highest OMAS scores during treatment. Statistical analysis comparing the mean maximum OMAS score of the MuGard™ group to each of the untreated groups was performed using two-sided tests at the 0.05 level of significance.

Results – Clinical Study

Patients treated with the amlexanox rinse showed slightly higher OMAS scores over time in both the intent-to-treat population and efficacy-evaluable population as compared to the vehicle group. This difference was also noted in the mean of 3 highest daily scores, AUC and weighted AUC. However, this difference did not reach statistical significance. Results of the categorical analysis comparing. the number of patients with any daily OMAS score > 2 showed no differences between the treatment groups, in either the intent-to-treat or the efficacy-evaluable population. No difference was observed in the time to objective signs of mucositis and to peak mucositis score for the amlexanox as compared to the MuGard™ group. The most commonly reported adverse events for both treatment groups were nausea, vomiting, sore throat, dry mouth, dysphagia and oral candidiasis. There were no SAEs that were deemed related to study medication.



Results – *In Silico* Analysis

There were numerous favorable comments from clinical centers regarding the benefit to patients from study medication, yet the study results indicated that the drug amlexanox had no beneficial effect. It was apparent, therefore, that the vehicle, MuGard™, might be providing a benefit. As a result, the OMAS scores of patients treated with the MuGard™ in this study were compared with historical data obtained from two different sources:

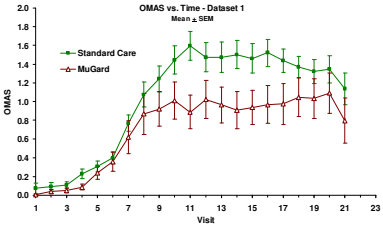
1. The first dataset was provided by Dr. Stephen Sonis from the Brigham and Women Hospital in Boston and served as the basis of the results published in: Sonis ST, Eilers JP, Epstein JB, LeVeque FG, Liggett WH, Mulagha MT, Peterson DE, Rose AH, Schubert MM, Spijkervet FK, Wittes JP. Validation of a New Scoring System for the Assessment of Clinical Trial Research of Oral Mucositis Induced by Radiation or Chemotherapy (1999) Cancer; 85 (10): 2103-2113.

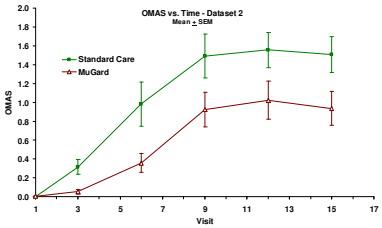
2. The second dataset was taken directly from the published article: Epstein, Gorsky, Guglietta, Le and Sonis. The Correlation between Epidermal Growth Factor Levels in Saliva and the Severity of Oral Mucositis during Oropharyngeal Radiation Therapy. (2000) Cancer; 89 (11): 2258-2265.

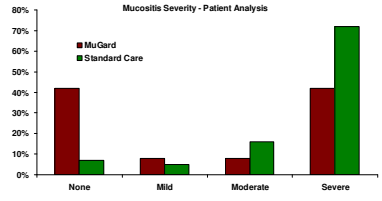
The first set of patients (Sonis et al., 1999) included data from a total of 52 patients. Patients were evaluated 3 times a week. For the comparison described below, 8 patients with parotid tumors were removed from the dataset, because it is known that this type of tumor is infrequently bilateral and does not require an extended radiation field. Thus the dataset for comparison included 44 patients.

The second set of data includes data from 18 patients as reported in the published article. Patients were evaluated once a week only. Five patients with parotid tumors were removed from the dataset.

The results from the comparison are illustrated in the graphs to the right. The two historical control data sets were very similar in term of mucositis severity, although they have been obtained at different times in different study centers. The comparison also showed that patients treated with MuGard™ had significantly improved OMAS scores when compared to the 2 historical controls. When analyzed for mucositis severity, only 7% of patients never exceeded an OMAS score of 0.5 in the control groups, compared with 42% in the MuGard™ group (p = .0001).







Conclusions

The anti-allergic, anti-inflammatory drug amlexanox, appears to be ineffective in either preventing, reducing the severity, or accelerating the healing of mucositis. Recognizing the limitations of a retrospective analysis of historical databases, it appears that significant patient benefit is achieved when patients utilize the viscous, mucoadhesive rinse, MuGard™. Compared with patients on standard care (historical controls), patients using MuGard™ had delayed onset of mucositis and reduced severity, as assessed by the OMAS scoring system. Of particular note was that 43% of patients on MuGard™ experienced no mucositis (OMAS score never exceeded 0.5) compared with only 7% in the control group. These results indicate that MuGard™ could be highly effective in the prevention and treatment of mucositis.