A DOUBLE-BLIND, VEHICLE-CONTROLLED CLINICAL STUDY TO EVALUATE THE EFFICACY OF MAS065D (XCLAIR^{TM}), A HYALURONIC ACID-BASED FORMULATION, IN THE MANAGEMENT OF RADIATION-INDUCED DERMATITIS

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A DOUBLE-BLIND, VEHICLE-CONTROLLED CLINICAL STUDY TO EVALUATE THE EFFICACY OF MAS065D (XCLAIR™), A HYALURONIC ACID-BASED FORMULATION, IN THE MANAGEMENT OF RADIATION-INDUCED DERMATITIS

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This study was designed to assess the efficacy and tolerability of MAS065D (Xclair™) compared to a vehicle control in the management of radiation dermatitis in patients receiving radiotherapy for breast cancer. Twenty patients were randomized blindly to use the two study substances, three times daily, on separate sections of irradiated skin throughout the duration of radiotherapy and for two weeks afterwards. Patients were monitored before therapy, weekly during therapy, and for 2 weeks after radiotherapy was completed. Skin appearance according to National Cancer Institute (NCI) toxicity criteria, erythema rating, transepidermal water loss (TEWL), skin hydration, patients' view of itch, pain, acceptance, and view of each cream and adverse events, were monitored; at the final visit patients and investigators expressed their preference for one of the creams. MAS065D showed statistically significant superiority in the outcomes of NCI grading for radiation dermatitis and erythema. Patients' and investigators' preferences for one of the study substances were statistically in favor of MAS065D. Very few patients recorded nonzero itch and pain scales, so no significant differences emerged between the two groups. It was concluded that MAS065D can provide an effective option for managing radiation dermatitis although further studies are needed to assess its effect on pain and itch.

Keywords: Breast cancer; Dermatitis; MAS065D; Radiotherapy; Xclair™

INTRODUCTION

Radiotherapy is a major approach to the treatment of cancer. However, up to 95% of patients receiving chest wall radiotherapy experience some dose-dependent degree of cutaneous reactions (1). These can range from mild erythema, through dry desquamation (dry, flaky or scaly skin), to confluent moist desquamation, where blistering, peeling, and sloughing of the skin occur. Fibrosis and atrophy of

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connective tissue have also been observed (2,3). Functional damage to the epidermis generally appears within a mean period of 11 days (4). Although relatively short-lived, these reactions can be painful and irritating, and often dose-limiting (5). These side effects induce discomfort ranging from mild irritation to severe pain, and may require temporary or permanent cessation of the therapy (6). Currently, therapy management is focused on trying to prevent the skin from deteriorating to higher grades of dermatitis, on relieving the pain and itch, and on addressing any infections (7). This is done by advising patients to keep the skin clean and moist throughout their radiotherapy treatment and in the period afterwards (8).

MAS065D contains hyaluronic acid, vitis vinifera, shea butter, telmestine, glycyrrhetinic acid, and bisabolol in a hydro-lipidic base; it is designed to reduce inflammatory reactions and maintain a moist skin environment. Hyaluronic acid (HA) is a major constituent of the extracellular matrix of the skin. It has demonstrated remarkable rheological, viscoelastic, and hygroscopic properties that are relevant to wound healing (9). Topical applications of HA have been shown to improve wound healing, particularly in radioepithelitis (10). Vitis vinifera and telmestine exhibit antiproteasic and antioxidant activities, inhibiting harmful enzymes that are exuded by damaged skin, and protecting the skin from damage by free radicals (11–13). Another key ingredient in MAS065D is glycyrrhetinic acid (licorice extract), which is reputed to have anti-inflammatory properties (14–16). Shea butter, which is derived from butyrospermum parkii, is employed for its emollient action.

METHODS AND MATERIALS

Study Population

Patients were eligible for the study if they were being treated with radiotherapy for breast cancer, were 18 years or over, and had signed an Institutional Review Board (IRB) – approved informed consent form. The baseline visit was on the first day of planned radiotherapy. The planned radiotherapy volume was directed at the breast or underlying chest wall, with a field size of 15×25 cm. Patients received a total of 50–70 Gy over a period of 4–6 weeks in daily fractions Monday to Friday (linear accelerator VARIAN CLINAC L 2100). The use of other topical products on test areas was prohibited throughout the study period. Exclusion criteria comprised history of previous radiotherapy to the area, concomitant chemotherapy, and other skin conditions that might affect the outcome of the study. Patients with known hypersensitivity or previous allergic reaction to any of the components of MAS065D, or the vehicle cream, as well as pregnant or nursing women, were also excluded. The study was carried out in accordance with the Declaration of Helsinki (as amended in October 2000) and with the approval of the San Gallicano's Dermatological Institute's Ethics Committee/IRB.

Study Design

This was a double-blind, randomized, vehicle-controlled study. A washout period of 7 days for other topical medications including topical corticosteroids was observed. Each patient's field of treatment was divided into two sections (section 1

and section 2), one towards the center of the body and one away from the center of the body. Patients were randomized into two groups: one received MAS065D on section 1 and vehicle on section 2, and the other group the reverse. This was a preliminary study, therefore the sample size was chosen on empirical basis. Twenty patients were expected to be sufficient to gain an initial impression of the differences between the two groups and to provide data needed for the planning of future studies.

Treatments

MAS065D and the vehicle were presented blindly in identical prerandomized white tubes. Patients were instructed to apply the study substance three times daily, or more if required, throughout the duration of radiotherapy and for two weeks afterwards. The vehicle was an emollient base cream, similar to MAS065D but without the key ingredients.

Study Assessments

Patients were assessed before the first dose of radiotherapy (baseline assessment), weekly at radiotherapy visits during therapy, and weekly for two weeks after radiotherapy was completed. During the control visits, the appearance of the skin and the patient's view of the symptoms were assessed by the following measurements: appearance of skin according to the National Cancer Institute skin radiation toxicity criteria (grade 0–4) (17); erythema rating (18), using the Mexameter^{TM} MX16 (Courage and Khazaka electronic GmbH Koln, Germany); transepidermal water loss (TEWL), using the Tewameter^{TM} (Courage and Khazhaka, electronic GmbH Koln, Germany); skin hydration, using the Corneometer^{TM} CM 825 (Courage and Khazhaka, electronic GmbH Koln, Germany); patient's view of itch and pain on a Visual Numerical Scale (0–10); and adverse events. At the final visit both the Investigator and the patients were asked for their preference between the two creams.

Statistical Methods

Demographic data and efficacy data, both as observed values and as changes from baseline (Visit 1), were summarized using sample counts, means, standard deviations, and quartiles. The Wilcoxon Matched-Pairs Signed Rank Test with exact two-sided p-values was used for NCI grading, erythema, TEWL, and skin hydration, to compare the treatment differences within patient for each visit, and the difference between maximum in-study value and baseline. The patient and investigator preferences were compared using the binomial test with exact two-sided p-values, ignoring the no-preference categories. No adjustments to significance levels were made because of multiple testing.

RESULTS

Patients

Twenty female patients with a mean age of 57.6 years (median 57 years) entered and completed the study between May 2003 and May 2004. Six (30%)

patients were smokers, and 16 (80%) stated that they did not consume alcohol. All patients concluded the planned treatment with a total dose ranging from 20 to 70 Gy (mean ± SD : 65.5 ± 13.9), over a mean period ranging from 1 to 6 weeks (5.6 ± 1.4). No interruptions in radiotherapy occurred.

Efficacy

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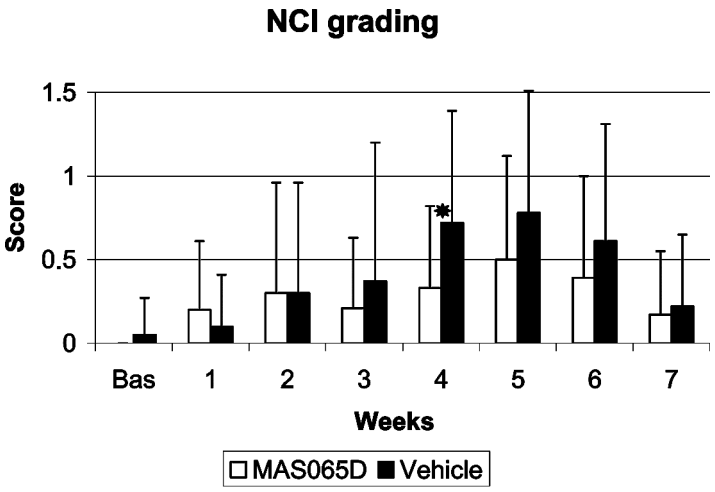
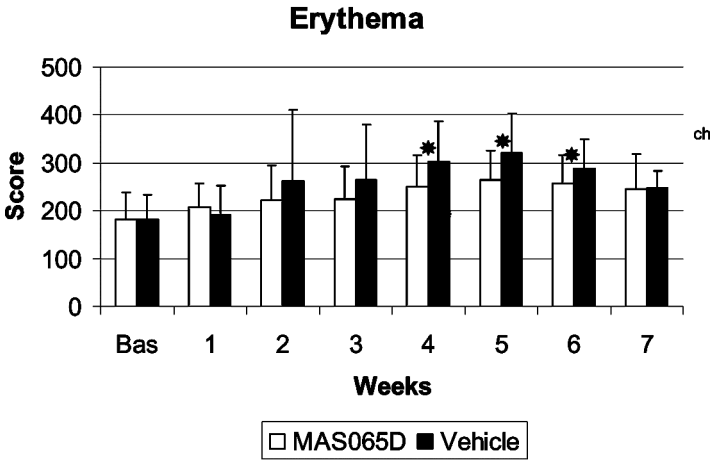
NCI grading (National Cancer Institute toxicity scale). The mean scores for both treatments increased from Visit 1 to Visit 6 and then declined (Fig. 1a). There were few nonzero differences in the NCI grades from patients, and the skin



(a)



(b)

Figure 1 Key outcomes.

reaction scores observed were the following: NCI Grade 1, 35% of patients (7/20); Grade 2, 35% (7/20); Grade 3, 5% (1/20); while 25% (5/20) did not show any reaction to radiotherapy. The mean score of the MAS065D treatment group was found to be significantly better than that of vehicle ($p = 0.031$) only at Visit 5, when all the nonzero differences were in the same direction.

Erythema. Similarly, the erythema mean score increased from Visit 1 to Visit 6 and then decreased for both treatments (Fig. 1b). The mean scores for breast sections treated with MAS065D were significantly lower than those treated with the vehicle at Visits 5, 6, and 7 ($p = 0.01$, 0.005, 0.03 respectively). A significant difference between treatments ($p = 0.004$) was also observed for the maximum score achieved in each section (438 for MAS065D and 856 for the vehicle).

Trans Epidermal Water Loss (TEWL). The TEWL mean scores observed for breast sections treated with MAS065D were lower than those treated with vehicle from Visit 3 onward, but no statistically significant difference between treatments was found.

Other end points. No significant treatment difference was found for skin hydration in any of the analyses performed; for pain and itch the scores (VAS 0–10 cm) for the MAS065D group were all zero, and only few scores in the vehicle group were greater than zero, with no significant difference between treatments.

Treatment preference. Concerning treatment preference as noted by patients and investigators, 65% (13/20) of patients preferred MAS065D against 10% (2/20) who preferred vehicle. Similarly the Investigator preferred MAS065D in 60% of the cases (12/20). For both assessments, the difference between treatments was statistically significant ($p = 0.007$ and $p = 0.035$, for patients and Investigator's preference, respectively) in favor of MAS065D.

Adverse events. No adverse events were reported during the study in either group.

DISCUSSION

This study was designed to evaluate the efficacy of MAS065D in radiation dermatitis, a commonly observed side effect of radiotherapy. MAS065D demonstrated significant benefits over the vehicle, for overall NCI grading at Visit 5, and for erythema at Visits 5, 6, and 7. These visits correspond with the period at which radiation dermatitis is expected to be at its most severe. The observed trends in TEWL and skin hydration did not reach a statistically significant difference between groups. The treatment mean differences were not large relative to the general variability in the results. Pain and itch scores were mainly zero throughout the study, and no significant differences between the groups could be observed. The control substance was a vehicle emollient and was anticipated to have some beneficial moisturizing effect. This should be taken into consideration when noting the significant differences between the two treatment groups. The lack of observed or reported adverse events in both groups indicates that MAS065D and the emollient alone are well-tolerated.

These results show an overall reduction in radiation skin reactions as well as a delay in appearance of the reactions. It can be concluded that MAS065D provides an effective option for managing radiation dermatitis. Further studies should be considered to assess the efficacy on pain and itch in an appropriate patient group, for example in patients with specific high risk factors for radiation dermatitis.

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