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Original Research Article

Efficacy and safety of the medical devices Fitostimoline Mucodefend® Gel And Fitostimoline Mucodefend® Mouthwash for the treatment of patients affected by oral mucositis

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Abstract: Thirty both gender outpatients suffering from oral mucositis were treated with the Triticum vulgare-containing medical devices Fitostimoline Mucodefend® oral gel (n=15) or Fitostimoline Mucodefend® mouthwash (n=15) applied bid or tid for 7-14 days. Before and after one-two weeks treatment patients were checked for clinical signs/symptoms, mucositis degree and safety. After 7 days treatment, 14 patients (93.3%) were healed or almost healed; at the final visit all patients were healed. The results of the study show the efficacy and the safety Fitostimoline Mucodefend oral gel and of Fitostimoline Mucodefend mouthwash in the treatment of oral mucositis.
Keywords: Medical devices; oral mucositis treatment; Triticum vulgare

INTRODUCTION

Phlogistic-dystrophic surface alterations of the oral mucosa due to physical, chemical, traumatic or infective cause are common [1]. In most of cases, they consist in mild diseases that spontaneously resolve, however causing pain and functional impairment (as an example difficulty in chewing and swallowing). In some cases, the disease may have a more serious clinical relevance, such as in case of mucositis due to auto-immunity [2] or to antiblastic therapy [3]. The use of measures that protect the mucosa and favour the "restitution ad integrum" process allow reducing the time of healing and hence limiting over time the symptomatic manifestations [4]. The medical device Fitostimoline Mucodefend® gel, due to its physical formulation and of its composition (1) forms a protective lining of the gingival and oral mucosa in the site of application, thus exerting a refreshing and lenitive action that promote the tissutal reparation and the restoring of the cellular microenvironment. Due to these characteristics, the product may be used for the treatment and the prevention of alterations of phlogistic-dystrophic nature of the oral mucosa (oral mucositis). The medical device Fitostimoline Mucodefend® mouthwash has similar characteristics to those of the gel, but, as a consequence of its formulation, is indicated in those cases in which phlogistic-dystrophic phenomena have a diffuse distribution (rather than local) and spread to large areas of the oral-pharyngeal cavity. A recent clinical trial conducted with devices that have a similar composition, and used in the same [5] and other indications has confirmed the protective effects and the tolerability. Finally, there are evidences that support the efficacy of the extract of Triticum vulgare – contained in the Fitostimoline Mucodefend - in reducing the clinical symptomatology of the oral mucositis caused by antineoplastic agents [7].

The objective of this clinical study was to confirm the activity of the medical device Fitostimoline Mucodefend (Damor Farmaceutici S.p.A., Napoli , Italia), in the two different formulations on the process of healing of mucositis of the oral cavity, while evaluating its tolerability.

PATIENTS AND METHODS

Overall study design

The study was conducted according to a non-controlled design and included 30 outpatients of either sex, 15 of which treated with the gel and 15 treated with the solution. The treatment period was maximum two weeks with both products, and the study plan included an initial visit, and intermediate visit (after 7 ± 1 days of treatment) and a final visit (after 14 ± 2 days of treatment). The intermediate visit could coincide with the final visit in case of healing or complete resolution of symptoms. At each visit the subjective and objective

clinical state was evaluated, together with the tolerability of the devices. In case of necessity, an evaluation of patients could take place at any time, even outside the scheduled visits.

Patients

The demographic and baseline characteristics of patients are show in Table 1.

The diagnosis of the oral pathology at screening is summarised in Table 2.

Table-1: Patients

		Fitostimoline Mucodefend gel	Fitostimoline Mucodefend mouthwash
Age (yrs)	mean±SD	53.1±15.0	58.3±13.5
	min-max	25-77	22-71
Gender [n (%)]	M	3 (20)	7 (46.7)
	F	12 (80)	8 (53.3)
Race [n (%)]	caucasic	15 (100)	13 (92.9)
	other	0	2 (4.1)
Wright (Kg)	mean±SD	62±13	73±10
	min-max	45-90	58-87
Height (cm)	mean±SD	164±8	167±9
	min-max	155-183	150-87

Table-2: Diagnosis [n (%)]

	Fitostimoline Mucodefend gel	Fitostimoline Mucodefend mouthwash
Surgical/traumatic wound	6 (40.0)	6 (40.0)
Mucositis due to chemo and/or radiotherapy	2 (13.3)	8 (53.3)
Infectious mucositis	4 (26.7)	1 (6.7)
Decubitus ulcer	3 (20.0)	0

Ten patients (i.e. one third of the total sample) had mucositis caused by antineoplastic agents.

METHODS

To be eligible for study participation, patients were required to satisfy all the following inclusion criteria: availability in taking part in the study and in adhering to study procedures, documented by informed consent signature; age $\geq$ 18 years and $\leq$ 75 years; presence of phlogistic and/or dystrophic lesions of the oral and/or gingival mucosa, such as irritative states and/or pressures by prosthesis and/or orthodontic devices, post-extractive sequel, mucosal lesions due to detartrage procedures, district disepithelializations, mucositis secondary to oncologic and/or immunosuppressant therapies; availability to cooperate and ability to understand the study procedures and objectives. Exclusion criteria were: pregnancy or breastfeeding; inadequate contraception in childbearing potential women; presence of metabolic or endocrine diseases (e.g. uncontrolled diabetes mellitus) or of any other local disease to disease under study and/or any systemic disease that could potentially interfere with the study parameters; concomitant treatment with antibiotics/antiseptic agents, steroidal and non-steroidal anti-inflammatory drugs, analgesics (except paracetamol as pain killer); non-therapeutic use of psychotropic substances; alcohol and/or drugs abuse; neurological and/or psychiatric diseases that could compromise the validity of the consent and/or the patient's adherence to study procedures; known allergy, hypersensitivity or intolerance to ingredients of study products; any medical or non-medical condition that could significantly reduce the possibility of obtaining reliable data, achieving the study objectives, completing the study; presumed poor patient's cooperation; treatment with any investigational product in the 30 days preceding the study initiation.

The investigational products were used for local application 2-3 times daily, for one week or two weeks (in case of persistency of significant symptoms at visit 2). At any follow-up visit (study entry, after 7 and eventually 14 days of treatment), the following parameters were evaluated: presence and intensity of pain, burning, dysphagia, difficult chewing, bleeding, redness, oedema, disepithelialization, ulcers. Signs and symptoms were quantified according to the scale absent=0, mild=1, moderate=2 and severe=3 (scale was used for the assessments of ulcers: mild = single ulcer of small size (diameter $\leq$ 3 mm); moderate = single ulcer of diameter > 3 mm; severe = multiple ulcers). The overall symptoms were summarised by means of the Total Symptoms Score (TSS), defined as the sum of scores of all signs and symptom. At any visit, the degree of mucositis was evaluated by using the WHO Scale for oral mucositis [6], and the local tolerability was evaluated in any post-baseline visit. Considering that the epithelium of the oral mucosa has a physiological turnover of approximately 14 days if nor exposed to pathogen triggers, the percentage of responder patients

at visit 2, defined as a patients presenting a decrease in TSS ≥ 50% from baseline, was considered as the primary efficacy endpoint. The primary and secondary efficacy endpoints were analysed separately in the two groups of treatment. Secondary efficacy endpoints were the changes from baseline in any signs and symptoms, and the change from baseline in total score of the degree of mucositis. The tolerability was evaluated by collecting adverse events.

STATISTICS

The following populations were defined: intention-to-treat (ITT), which included all treated patients with at least one post-baseline follow-up; per-protocol (PP), which included all patients of the ITT population without major protocol violations (i.e. those violations potentially interfering with the results of efficacy and safety, such as violation of eligibility criteria, incorrect application of the devices, etc...); safety population, which included all patients that took part in the study with evidence of at least one application of the study devices. As there were no major protocol violations, the analysis of all efficacy parameters was performed in the ITT population. The semi quantitative scores of the intensity of signs and symptoms were presented as frequency at any visit, and missing data at visit 3 were replaced with those of visit 2, according to the last observation carried forward (LOCF) approach. Values of TTS at the post-baseline visits (expressed as fraction of baseline and changes from baseline) were analysed with non-parametric tests, using the 95% confidence interval (CI) of the median values and the Wilcoxon paired test, whereas the mean values were presented as descriptive statistics. The results of therapeutic success were presented by analysing the proportions, with their 95% CI, of responder patients at visit 2 and at the end of the study. The minimum level of statistical significance was set at a p value < 0.05 (95% CI, i.e. with alpha = 0.05). All p values and CIs were two-tailed.

Ethic and regulatory issues

The study protocol, the patient information sheet, the informed consent form, the letter to general practitioner and the "information on the privacy" were submitted to the approval of the reference Ethic Committee of the investigational study site prior to any study-related procedure was commenced. The study initiation was notified to the Italian Minister of Health. The study was conducted according to the principles defined in the Declaration of Helsinki and in the following amendments, and to the procedures of Good Clinical Practice, expressed in the guideline set out by the International Conference on Harmonization.

Patients received detailed verbal and written information, by means of a specific information sheet, on all issues related to study participation, in terms of study objectives and procedures, possible benefits and potential risks. Both the investigator and the patient signed a double copy of the informed consent form before the patient took part in the study. The patient received one of the two copies, and the other one was archived in the investigational study site together with the study documentation. The decision on study participation was freely taken by the patient, and it was clarified that the consent could have been withdrawn at any time, without penalty or loss of patient' rights of benefits.

RESULTS

Therapeutic success; percentage of responder patients

Response to treatment after 7 days of application has been observed in 14 patients in both groups (Fitostimoline Mucodefend gel and Fitostimoline Mucodefend mouthwash), i.e. in 93.3% of cases (95% CI: 68.0-99.8% in both groups). At the final visit all patients achieved therapeutic success (95% CI: 78.2-100.0% in both groups). In the Fitostimoline Mucodefend gel group one patient, who was carrying a total prosthesis due to gingival decubitus, had a decrease of TTS < 50% (from 7 to 6, 14.3%) at visit 2 and thus continued treatment up to visit 3, where a complete symptoms regression was observed. In the Fitostimoline Mucodefend mouthwash group, one patient with grade 3 mucositis due to radiotherapy for the treatment of squamous cell carcinoma of the oral floor showed a decrease of TTS < 50% (from 11 to 8, 37.3%) at visit 2 and thus continued treatment up to visit 3, where a complete symptoms regression was observed. Of the other 28 patients who completed the study at visit 2 due to complete healing, 3 in each group presented a minimal residual symptomatology (TTS between 1 and 3), while symptoms totally disappeared in the other 11 patients in each group.

Evolution of individual signs and symptoms:

Figure 1 summarizes the intensity of signs and symptoms from baseline to the end of study. Pain was always present at the baseline visit, while only 5 patients presented oedema. At visit 2, only one patient with post-radiotherapy mucositis on treatment with Fitostimoline Mucodefend mouthwash still presented grade 2 symptoms (moderate burning and dysphagia), which completely disappeared at visit 3. Mild signs and symptoms, mainly pain and redness, could be still present in patient clinically judged as healed that therefore did not continue treatment.

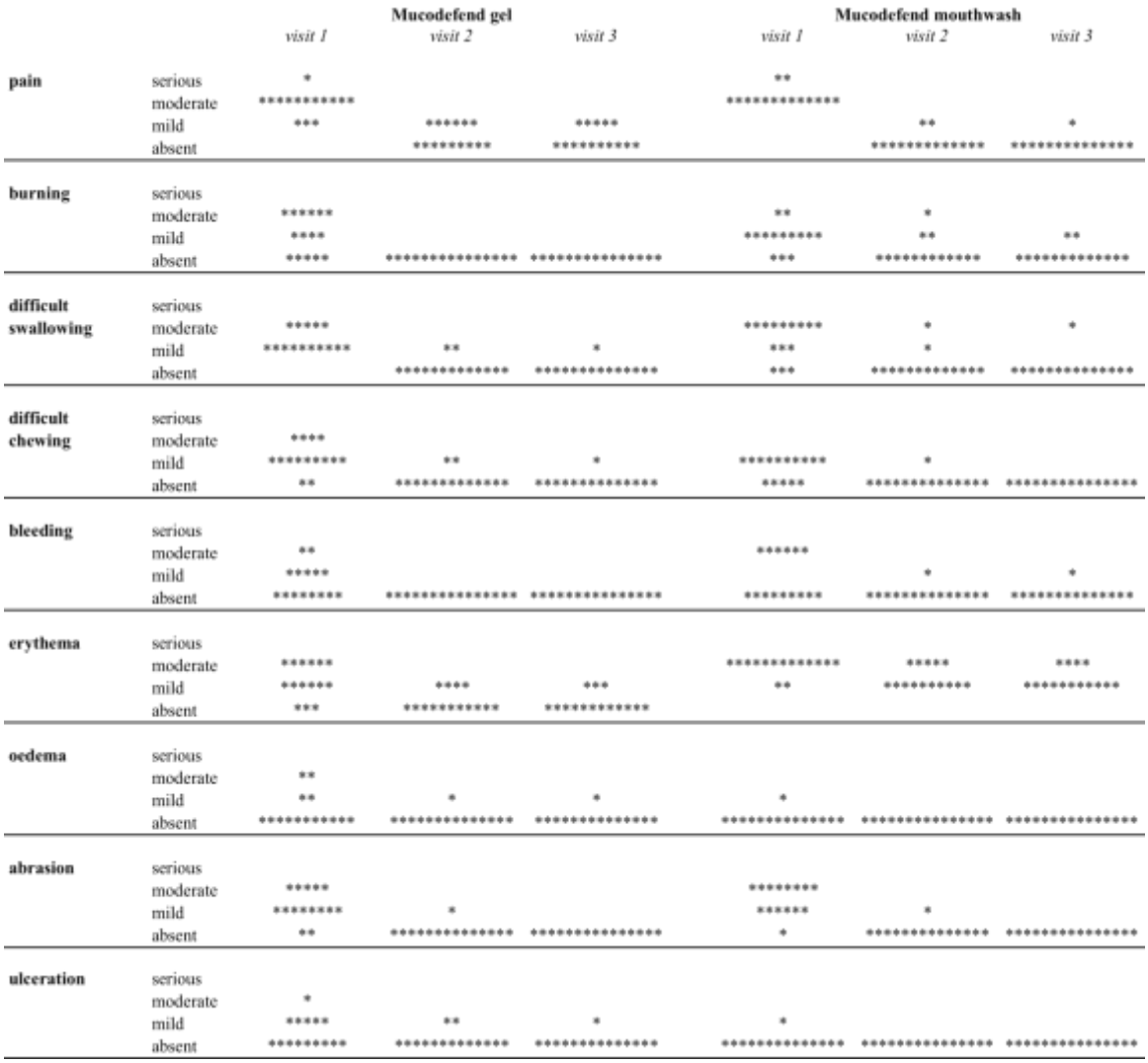

Fig 1: Symptoms score at the time points (n° of patients)

Total Symptoms Score (TSS):

TSS decreased as a result of decrease in individual signs and symptoms, with a statistically significant change ($p < 0.0001$) already at visit 2 in both treatment groups (Figure 2).

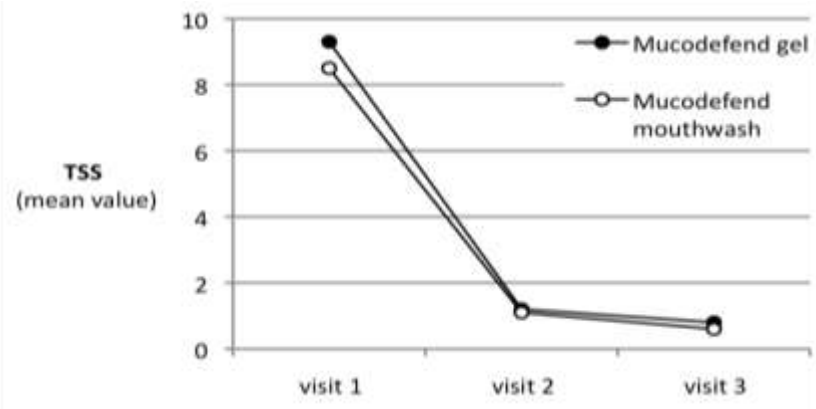

Fig 2: Mean Total Symptoms Score (TSS) through the study

Degree of mucositis

Mucositis at baseline was judged as mild in most of cases. At visit 2 mucositis was still present only in 3 cases, all of grade 1: one patient with necrotic ulcer of the geniena mucosa and grade 2 mucositis at baseline treated with Fitostimoline Mucodefend gel; one patient with gingival decubitus sore and grade 2 mucositis at baseline treated with Fitostimoline Mucodefend gel;

and one patient with grade post-radiotherapy mucositis at baseline treated with Fitostimoline Mucodefend mouthwash. In the latter two patients mucositis disappeared at visit 3, whereas the first one was judged as healed at visit 2 (thus resulting the only patients with residual mucositis, according with the LOCF approach) (Table III).

Table 3: Mucositis score through the study

	mucositis score	Fitostimoline Mucodefend gel n (%)	Fitostimoline Mucodefend mouthwash n (%)
Visit 1	1	10 (66.7)	14 (93.3)
	2	5 (33.3)	0
	3	0	1 (6.7)
Visit 2	0	13 (86.7)	14 (93.3)
	1	2 (13.3)	1 (6.7)
Visit 3	0	14 (93.3)	15 (100)
(LOCF)	1	1 (6.7)	0

None of patients took paracetamol as rescue analgesic. None of patients reported adverse events.

DISCUSSION AND CONCLUSIONS

Oro-gingival mucosa is frequently the site of phlogistic-dystrophic diseases of infective (e.g. aphthosis), traumatic (e.g. dental extractions, detartrage, prosthesis decubitus) or toxic (smoking habit, pharmacological treatments) origin. In most of cases such manifestations are not significant from a physio-pathological perspective and are generally auto-limiting, however leading to pain, discomfort and often difficultly in chewing. Except for the lesions caused by specific infective agents, systemic diseases or pre-neoplastic/neoplastic processes, the phlogistic/dystrophic manifestations of odontoid origin do not require specific therapies. However, the local protection of the involved mucosa and a lenitive action may accelerate the healing process and limit the patient's discomfort. The medical device Fitostimoline Mucodefend gel, due to its physical formulation and composition, forms a protective layer on the gingival and oral mucosa on which it is applied. When used in tissutal wounds, it contributes to re-epithelialisation processes and to the restoring of the normal micro-environment, other than exerting a lenitive and refreshing effect. Due to these characteristics, the product may be used for the prevention or to resolve mild phlogistic-dystrophic alterations of the oral cavity mucosa, such as gingival irritations, effects of detartrage or otherwise oral hygiene, use of prosthesis or orthodontic devices, small burnings, apthtae etc...

The medical device Fitostimoline Mucodefend mouthwash has similar characteristics to those of the gel formulation, but, due to its different formulation, it is ideally used in those cases in which the phlogistic-dystrophic phenomena have a diffuse rather than local distribution, and extend to wide areas of the oro-pharyngeal cavity.

In this study the local application of the medical devices Fitostimoline Mucodefend gel and Fitostimoline Mucodefend mouthwash was associated with a rapid regression of the mucositis manifestations within the first week of application in most of cases, without the occurrence of any adverse effect. Therefore, the studied devices may be indicated in several different irritative diseases of the oro-pharyngeal cavity with phlogistic-dystrophic origin, including those caused by oncologic therapies.

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