ActiMaris® Clinical ENT Study for Inflammatory Skin and Mucosal Processes

Mechanisms of action, indications and therapeutic results

Dr. med. D. Marincic, St. Gallen, SWITZERLAND

Introduction

Skin and mucosal diseases of different etiopathogenesis such as inflammatory, allergic, pseudo-allergic, infectious and others often occur in the ENT area. In the context of an open, prospective, partially randomized clinical study, we investigated the effectiveness of a newly conceptualized medical product, Class II b, ActiMaris®[1] in gel form, regarding the various mucosal and skin processes/changes, especially in the case of acute and chronic inflammation in 417 ENT patients.

Many "standardized" treatment regimens are not without side effects, are too long in duration and are associated with unfavorable cost-benefit effects. Treatment of bacterial infections with antibiotics often results in undesirable side effects and through various mechanisms the bacteria develop resistant mutations to many antibiotics, which weakens the efficiency of the therapy even more. On the other hand, we still generally do not have efficient therapeutic weapons against viruses. ActiMaris® was developed with the objective of closing these therapeutic gaps. The mechanisms of action for this medicinal product were chosen, conceptualized and "packaged" in a complex in such a way that they do not differ from processes in nature and do not require additives, preservatives and/or coloring agents. As such, the product does not cause irritation or has any toxicity with a multimodal broad spectrum of action on inflammatory processes and infections in the area of mucous membranes and the skin, as well as acute and chronic wounds that are difficult to heal.

The absence of irritation and toxicity of ActiMaris® on the tissue of the mucous membranes and the skin was proven and confirmed in various laboratory tests (also on living animals) and now also in this clinical study, as well as the broadest spectrum of action/potential in the treatment of etiologically different infectious and inflammatory processes in mucous membranes and the skin.

The natural mechanisms of action are basically very simple, but at the same time very efficient, and very importantly, have no side effects either locally on the areas of application nor any systemic side effects. The cost-effective aspect of the treatment can thereby not be overlooked.

---

[1] * ActiMaris® = hypertonic (3%) alkaline ionized (pH 9.8) sea water solution/gel with active singlet oxygen

Mechanisms of action

Through the specially modified electrolysis process of sea water, active singlet oxygen (energy-rich) is bound to NaCl in the form of NaOCI (sodium oxychloride 0.2%) and is actually very stable, which was not possible to this extent before. This stability is therapeutically very important and is achieved through the very high concentration of NaCI of 3% (as in the sea) and the high pH value of 9.8. The oxygen, NaOCl and pH stability in the unopened packaging (tube, bottle) is 2.5 years and after opening the packaging it is 6 months.

Sea water has a NaCI concentration of 3.0 – 3.5% and a very low concentration of other sea salts, in addition to about 80 minerals and trace elements. The composition of sea water with 1.0 – 1.2% NaCI is serum-like and the bioavailability of the sea salts, minerals and trace elements in the size of 0.0001 g, as in the case of ActiMaris®, is optimal.

Through the ionization of sea water, much smaller water clusters (5-6 instead of 12-15 as in tap water) are formed, which makes better penetration and a more efficient action in the tissue possible. Upon making contact with the tissue of the mucous membrane and skin, the active, energy-rich singlet oxygen ($^1O_2$) and OCI-anion (oxychlorite) free themselves from the complex, not explosively as with H_2O_2, but slowly, and can develop its full effect. In terms of time, there are two mechanisms of action of ROS substances: a superficial one, which occurs within seconds and minutes, and a deeper submucosal / subepithelial one, which occurs within 10 to 15 minutes.

With the energy releasing from the active singlet oxygen (158 kJ/mol) into the tissue (which is also benefitted by the smaller clusters of sea water), and concentration of physical dissolved triplet oxygen the partial oxygen pressure in the tissue is increased, which additionally increases the therapeutic effect against infections. It has been found that the increased pressure of partial oxygen in the issue from 40% to 80% brings about a 50% infection reduction. At the same time, oxygen is used by the healthy cells for the processes of oxidative phosphorylation and synthesis of ATP in the mitochondria, and by immune cells for “respiratory burst” processes which additionally supports the physiological metabolism and regeneration process.

Active singlet oxygen and sodium hypochlorite belongs to the group of Reactive Oxygen Species / ROS, which are also produced in mitochondria (which bacteria do not possess) and in epithelial cells and in neutrophils and macrophages. In the concentration as in ActiMaris®, however, it does not lead to so-called oxidative stress and apoptosis in normal functioning cells but has a positive stimulating effect on the many cells and growths factors as a signaling molecule as well as on cell migration, dilates the peripheral vessels, promotes angiogenesis and improves local circulation, which also has a positive effect on inflammatory processes.

In addition, the basic reaction of ActiMaris® (pH 9.8) counteracts an increased concentration of more aggressive free radicals (such as hydroxyl radical, superoxide anion), similarly to the catalases, and superoxide dismutases. An acidic milieu exists in inflammatory infected tissue and the alkaline hypertonic reaction of ActiMaris® positively counteracts this. Also, half of the proteolytic enzymes (MMP) active in chronic wounds tend to have an optimal effect in an acid/neutral environment. For example, a shift in pH to alkaline shows a 40-90% decrease in protease enzyme activity in the wound. Ionized alkaline reduced seawater (water molecule) can provide additional oxygen and several additional electrons. The basic pH value of 9.8 has approx. 100 times more free OH ions (oxygen pool) than normal water, which improves the transport of electrons (energy quanta) and increases

the electrochemical potential. The basic pH value and ROS substances make ActiMaris® complex an efficient and local REDOX modulation/control system. All life on earth is based on ROS regulation and REDOX metabolism. The cell biologist Gabi Nindl from Indiana University summarized the results of her research as follows: "Understanding the regulation of cellular ROS and REDOX metabolism will aid in developing novel therapeutic tools." Based on these scientific findings, the mechanisms of action of the ROS and REDOX complex with active singlet oxygen and physically dissolved oxygen in ActiMaris® products were developed.

The hypertonic/hyperosmolar concentration of sea water with 3% NaCl has an additional decongestant effect on the inflammatory, edematous tissue and in disrupting biofilms.

Since bacteria and viruses do not have efficient defense mechanisms against ROS and active singlet oxygen, the cell membranes (murein, peptidoglycans) and cell structures (DNA) are destroyed, and no resistant mutations (as with antibiotics) can be formed. The other defense mechanisms of prokaryotic cells such as quorum sensing in biofilms are also inefficient against active, energy-rich singlet oxygen and alkaline pH. All these positive mechanisms of action, which have been proven by various laboratory tests, were also confirmed in the clinical ENT study that was conducted.

Tested indications for the treatment (monotherapy) with ActiMaris®

- Acute and chronic rhinitis and rhinosinusitis
- Postoperative endonasal local therapy after nasal/sinus surgeries
- Petechial nasal hemorrhages
- Diffuse otitis externa and myringitis
- Cavum oris mucositis, gingivitis and glossitis
- Cheilitis, angulus infectiosus oris, herpes simplex labialis
- Bruises, hematomas, abrasions and lacerations
- Dermatitides, acne, erysipelas

Treatment results

In each of the 5 treatment groups of ENT regions, the treatment results, both in terms of diagnosis (16) and study variables or evaluation parameters, were compared between the two treatment regimens of local treatment, and differences were qualitatively and quantitatively weighted and statistically evaluated.

In doing this, the "standard" treatment from the historical control group was compared with the local treatment with ActiMaris®.

In order to increase the validity of the therapeutic comparison, a real time comparison of the two treatment regimens was made in 61 "subjects" (14.5%) through right/left randomization ("facesplit" study design). When compared with the standard treatment, the ActiMaris® side showed better,

faster and more lasting decongestion of the mucous membrane in the “rhino” group (also rhinometrically), faster resolving of the signs of inflammation and faster resolution of the symptoms. Within the post-operative “rhino” group, softer crusts were formed that also persisted for a shorter time. Faster epithelization of the mucous membrane was also observed in the area of the inferior nasal concha along with less bloody secretion. With the “randomized” otitis group, a faster reduction of pain was shown, faster decongestion of the skin in the ear canal as well as faster resolution of the signs of inflammation on the side that was treated with ActiMaris® gel. In the ActiMaris® group, the duration of therapy was reduced by three days. Systemic therapy had no significant effect on the two local therapeutic outcomes in 8 of 18 patients in this group. The standards of treatment (historical controls) are defined in guidelines of the ENT societies based on region and diagnosis.

To keep the probability of error of the comparison in the statistical evaluation between two study groups as low as approx. 0.05 (probability of 95%), the evaluation parameters (variables) were reduced to two or three so that it was not necessary to increase the number of patients in each group. The first evaluation parameter was the signs of inflammation (calor, rubor, dolor, tumor), the second parameter was the time (in days) it took for the swelling to reduce and the third parameter was the time it took for the decrease of symptoms.

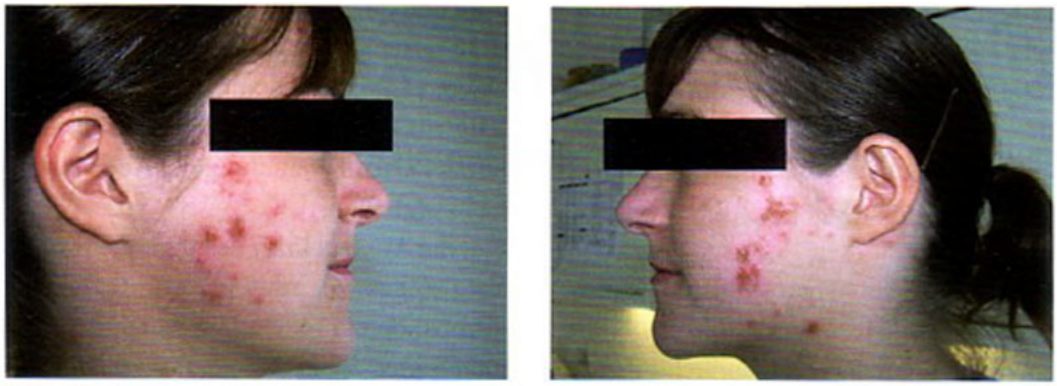

Figure 1: Acne vulgaris before treatment

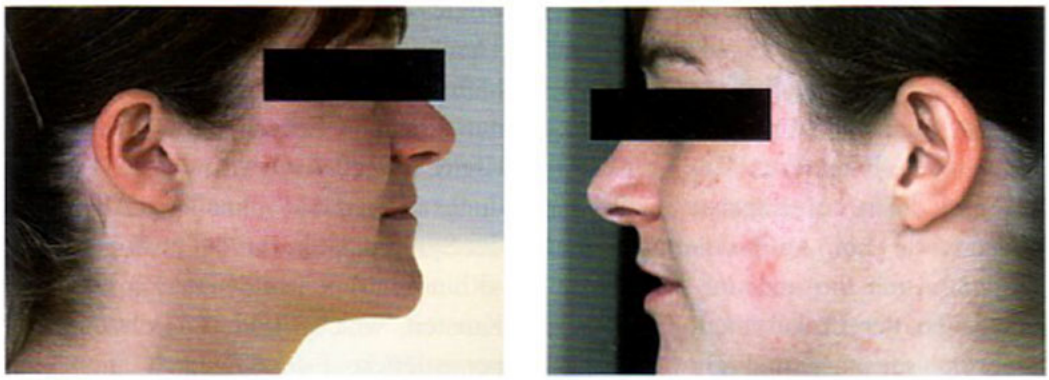

Figure 2: Acne vulgaris four weeks after treatment with ActiMaris® gel and cleansing with ActiMaris®-forte liquid

Only the respiratory volume (respiratory area) before, after 15 minutes and after 30 minutes of endonasal application of ActiMaris® gel could be determined quantitatively in an exact way by acoustic rhinometry and compared with the decongestant effect of sea salt spray (0.9%) and cortisone spray. Here, a significantly better decongestant effect could be observed 30 minutes after

ActiMaris® gel was applied compared to the physiological sea salt solution (0.9%) and the cortisone spray (see illustration).

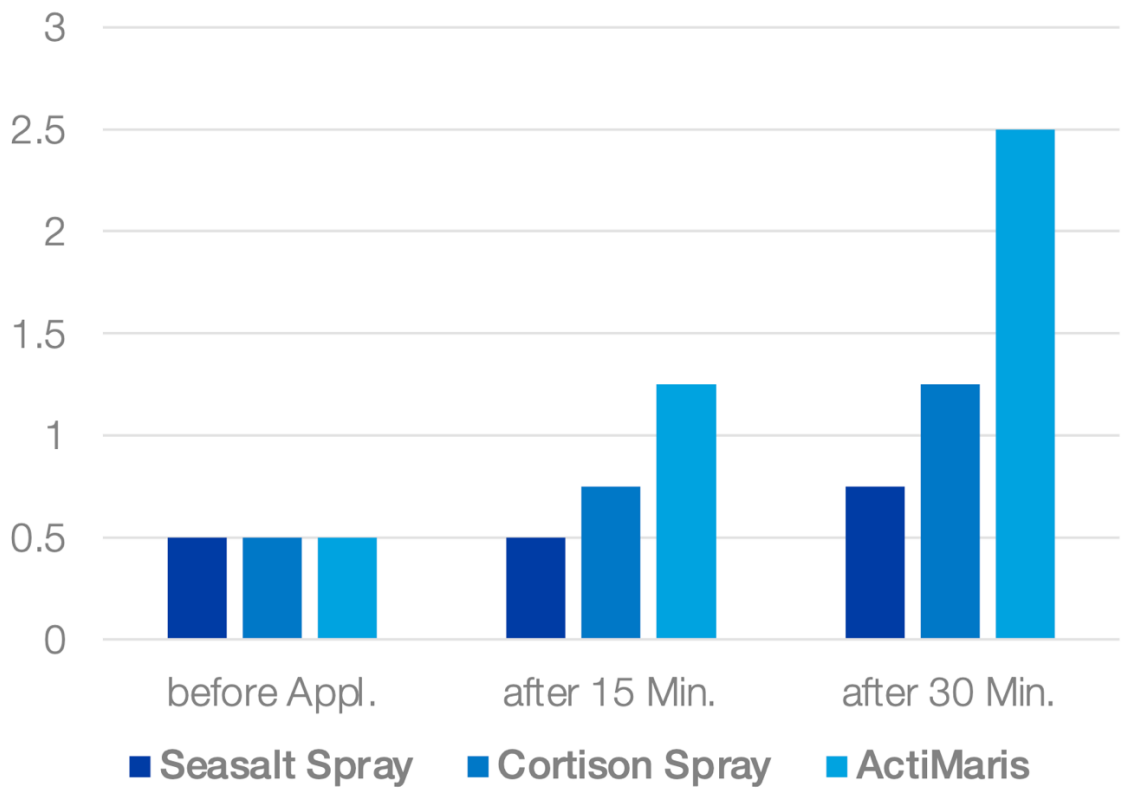

Figure 3: Acoustic rhinometry: Degongestant effect of ActiMaris® gel after 15 and after 30 minutes compared to a physiological sea salt solution 0.9% and cortisone spray

Summary

A simple statistical F-test according to the “likelihood ratio” test was used for null hypothesis testing. A positive test result of the F-test meant that the null hypothesis could be ruled out or refuted, and the assumption of interest in the sense of the "alternative hypothesis" could be confirmed, and the questions raised in the context of the study’s objective can be answered as follows:

- ActiMaris® is superior to the standardized local medicinal treatment of inflammatory processes/diseases of the mucous membrane and of the skin in the ENT area.
- Through local treatment with ActiMaris®, a relevant reduction of the clinical signs of inflammation can be achieved after a relatively short time and clinical complaints (such as pain) can be reduced significantly.
- Through local treatment with ActiMaris® gel, a faster and more significant decongestant effect in the area of the mucous membrane and the skin can be achieved.
- Local therapy with ActiMaris® gel alone can also shorten the treatment time when compared to standard local therapy.

- The granulation and epithelialization processes in the mucous membrane and skin occur at a faster rate than known from conventional preparations.
- Even after prolonged local therapy with ActiMaris® gel, no side effects and / or irritations of the mucous membrane and skin were observed. A slight burning sensation when sneezing was observed and only in the case of acute rhinitis, which, however, does not compromise the continuation of the therapy and which subsides in due course.
- ActiMaris® in gel form is accepted equally well by patients as the usual local sprays and ointments.
- The cost-benefit effect of local therapy with ActiMaris® gel is superior to those of standardized treatment regimens.

In 98% of the 417 patients that were treated, monotherapy with ActiMaris® was sufficient to return inflammatory processes to normal and to soothe clinical symptoms (discomfort) without needing adjuvant and/or systemic therapy.

Note - conflict of interests

After studying the final report of the company Confarma France SARL Hombourg, which undertook microbiological testing and laboratory studies with ActiMaris® gel and liquid on animal models, the scientific curiosity of the author of this study was awakened to research and to find out the new therapeutic ways and concepts (innovations) regarding the treatment of inflammatory diseases of the mucous membrane and of the skin in the ENT area. This study was undertaken free of charge and 1,500 ActiMaris® gel tubes of 20g each were made available by the firm QuantumMedis, Vaduz in Liechtenstein.

Dr. Med. D. Marincic

Member of the Swiss Medical Association (FMH),
Specialist in Otorhinolaryngology,
Neck and Facial Surgery
QuorumMedis
Marktplatz 25
9000 St Gallen