Effects of an Ophthalmic Phospholipid-Based Microemulsion (Lipofilm) on Re-Epithelization Processes in Patients Who Underwent to Photorefractive Keratectomy (PRK). Preliminary Results

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Summary

BACKGROUND: Lipofilm is a recently developed microemulsion for ophthalmic use that contains lipids, phospholipids, triglycerides and unsaturated fatty acids. It is a thermodynamically stable microemulsion of oil in water having a physiological function very close to that of lipid layer present in natural tears. PURPOSE: to demonstrate that the treatment with Lipofilm accelerates the corneal re-epithelization after PRK. METHODS: single masked randomized clinical trial, controlled versus reference drug (0.2% sodium hyaluronate). Nine patients who needed bilateral PRK were enrolled. Difference between the eyes greater than 3 diopters were not accepted. Comparison was carried out within subjects (right eye vs. left eye). The treatment (Lipofilm or Sodium Hyaluronate) was randomly assigned to one of the two eyes, in addition to the standard antibiotic therapy. The follow-up was 5 days. The variables analyzed were: size of the erosions (measured in mm); lid oedema and hyperaemia (assessed by a visual analogic scale), foreign body sensation, tearing, burning/pain, and photophobia (assessed by a semi-quantitative scale).

RESULTS: Lipofilm showed the tendency to be superior than Sodium Hyaluronate in improving all the variable but one (i.e. hyperaemia). In particular, the reduction of foreign body sensation was statistically significant (P=0.03). Both local and systemic tolerability were excellent. CONCLUSIONS: Lipofilm seems to reduce subjective and objective symptomatology in patients who...
underwent to PRK. Also the re-epithelialization rate seems to be increased. Further studies are in progress to confirm these favourable preliminary results.

Introduction

The wound-healing response is an important factor in the outcome of corneal surgical procedure (1). In particular, it mainly contributes to the efficacy and safety of refractive surgical procedures such as photorefractive keratometry (PRK) (2).

PRK is a common procedure used to correct refractive errors (3). The main limit of PRK is the necessity to remove a wide area of corneal epithelium (4). Consequently, the stroma is exposed to possible infections and the patients feel intensive postoperative pain, until the re-epithelialization process is completed. Moreover, the slower is the healing process, the higher is the risk of various complications, such as infectious keratitis, hypercorrection, hypo-correction, and haze (4). It is generally believed that rapid re-epithelialization is the best sign for the most positive outcome of PRK and therefore the use of therapeutic interventions aimed to accelerate the epithelium recovery could be useful in post-operative patient care.

Lipofilm consists in a stabilized microemulsion composed by mean chain triglycerides (MCT) and a mixture of phospholipids. From a physico-chemical point of view, Lipofilm is a thermodynamically stable oil-in-water microemulsion. The mean size of the particles is 200 nm with a very narrow size distribution. It has a physiological pH (about 7.2) and osmolarity (about 300 mOsm) and has a viscosity of 1.25 cps. The physico-chemical properties of Lip film, in particular the very small size and stability of lipid particles, permit a spreading behaviour and a physiological function very close to that of the lipid layer present in the natural tears. Lipofilm is biocompatible, absolutely safe and well tolerated.

In a recent study (5), the topical administration of the microemulsion to patients suffering from non infectious corneal erosions was found to be effective in accelerate the recovery time and in reducing the severity of symptomatology.

According to these previous results, the aim of this study was to evaluate the effect of Lipofilm on corneal re-epithelialization in patient who underwent to photorefractive keratectomy (PRK).

Material and Methods

The study followed the design of single masked randomised clinical trial with intra-subject comparison (i.e. left eye vs. right eye) of the study product Lipofilm (Tubilux Pharma S.p.A., Pomezia, Italy) and of the reference drug 0.2% sodium hyaluronate (Hy-drop, Baush & Lomb). Nine patients entered the study in accordance with the following eligibility criteria:

Main inclusion criteria: myopic patients who needed PRK bilateral procedure.
Main exclusion criteria: refractive difference between the 2 eyes greater than 3 dioptres.

Lipofilm (in one eye) and the reference drug (in the other eye) were administered 4 times/day, in addition to the standard antibiotic therapy. The treatment duration was 5 days. The eyes were assigned to one treatment or to the other according to a randomisation list.

Patients’ visits were scheduled every day for 5 days after PRK was performed. The final visit was scheduled 10 days after PRK was performed.

The main outcomes were the variations of the diseptelization area (intra-operatively delimited by means of a 8.5 mm marker) throughout the follow up. The diseptelization area was assessed by quantitative and semiquantitative method. The former was obtained by measuring in mm the diameter of the erosion, the latter by classifying the fluorescein staining by a 4 point semiquantitative scale (0= no staining; 1=punctate: 2= erosion <1 mm; 3 =erosion >1mm).

Secondary outcomes were:

subjective symptoms (tearing, pain/burning, foreign body sensation, photophobia) reported on a 4 point semi-quantitative scale

objective signs: (conjunctival hyperaemia and oedema, lid oedema) reported on 10 mm visual analogical scale (VAS)

Global efficacy assessment was expressed by the investigator on a VAS. Tolerability was evaluated on the basis of the following variables:

- Burning after instillation reported by the patients on a semiquantitative scale.
- Global tolerability assessment expressed by the investigator on a VAS
- Global tolerability assessment expressed by the patient on a semi-quantitative scale
- Adverse events.

The statistical analysis was carried out on the area under the curve (AUC) applying non parametric tests. A additional multivariate test (Hotelling’s T²) was performed to analyse the overall effect.

Results

Present results refer to the first nine patients enrolled for a phase II clinical trial for which a total of 25 evaluated subjects are foreseen to complete the study. Demographics and baseline values related to this first group of patients are reported in Table I. No statistically significant differences were found between the two treatment groups. Both eyes (that is the eye treated with Lipofilm and the eye treated with sodium hyaluronate) healed on the same day (fig 1). However, in about 30% of the patients there was an early reduction of erosion (< 1mm) in the Lipofilm treated eyes (Fig 1). No significant differences were found between the erosion size in the two eyes (Tab II).

The multivariate analysis indicates that there is no statistically significant difference between the two eyes and hence between the two treatments (Fig 2). However the calculation of the overall effect seems to indicate a better
effect of Lipofilm (Fig 2). In addition, all symptoms and signs, with the exclusion of hyperaemia, appeared to be reduced more consistently by Lipofilm, and, in the case of foreign body sensation, the reduction was statistically significant (P=0.03) (Fig 2). Both local and systemic tolerability were excellent. No adverse events were reported.

Table II: Changes in erosion size. The AUC differences between the two treatments were not statistically significant (P = 0.52).
Figure 1. Changes in corneal erosion size after PRK expressed as percentage of patients presenting different fluorescein staining stage. The erosion was assessed according to a semi-quantitative scale as reported in legend.

Conclusions

This study was designed to provide a within-subject comparison where the only difference was the type of eye drop used postoperatively to facilitate and

Figure 2. Overall results of the study: All variables are expressed as mean and 95% confidence intervals (horizontal lines). If the mean lays on the left-hand side of the vertical line it indicates a favourable effect of Lipofilm, vice versa it indicates a favourable effects of 0.2% sodium hyaluronate. The figure shows that, although the overall effect was not statistically significant, all signs and sympoms, with the exclusion of hyperaemia were improved by Lipofilm. In particular, the improvement of foreign body sensation was statistically significant since both the confidence intervals lay on the left-hand side of the vertical line.
protect the healing process in patients who underwent to PRK. For the efficacy, Lipofilm was compared to 0.2% sodium hyaluronate, that at moment is considered to be the most effective eye drop to be use in post-operative period to protect corneal surface.

The results indicate that the overall efficacy of Lipofilm is not statistically different from that of 0.2% sodium hyaluronate. However, the analysis of the single parameters suggests that Lipofilm is more efficacious than 0.2% sodium hyaluronate in reducing the majority of the subjective and objective symptomatons as well as in increasing the re-epithelization rate.

Concerning the possible mechanism of action of the microemulsion, it is well known that in case of injuries to the superficial layer of the cornea induced by occasional or surgical traumas (such as in refractive surgery), there is the activation of an healing process that mainly consists in the stimulation of epithelial cell replication and eventually in epithelium regeneration. The use of Lipofilm could protect this delicate healing wound process from the microtraumas due to the blinking thus protecting and facilitating the process itself.

The small number of patients does not permit to draw definitive conclusions from these results of this study. Consistent results will be available when the extended study (25 subjects with increased statistical power up to 80% to obtain statistically significant differences) is completed.

However, present data, although preliminary, suggest that the use of a microemulsion formulated for ocular route (6, 7), that is biocompatible with high level of dispersion of the internal phase (mean size 200 nm), could be more efficacious of conventional tear substitutes in assisting the healing process.

References