Editorial

New therapies for neurotrophic keratitis

Nuevas terapias para el tratamiento de la queratitis neurotrófica

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The complex therapeutic approach of corneal diseases such as in neurotrophic keratitis (NK) or persistent epithelial defects (PED) secondary to numerous etiologies has opened up a large and interesting field of research. The lack of specific treatments for these entities has given rise to new drugs acting on different stages of the altered cicatrization process.\textsuperscript{1}

The various treatments utilized at present as well as the multiple research lines which have been opened are summarized below.

The use of autologous serum eyedrops and platelet-rich plasma or growth factor-rich plasma is broadly extended in clinical practice. The content of growth factors (EGF, TGF-\(\beta\), PDGF, NGF, IGF-1), cytokins, fibronectin, vitamin A and antimicrobial factors (lysozime, IgG, complement factors) enhance cicatrization, inhibit infections and have a lubricant effect which has demonstrated to be beneficial in keratopathies associated to the dry eye syndrome, in recurrent corneal erosions as well as in the closure of ulcers and epithelial defects of various origins.\textsuperscript{2-5}

Thymosin beta-4 (T\(\beta\)4), a peptide with 43 aminoacids having main function of bonding to G-actin, has demonstrated a stimulating effect for corneal cicatrization through the regulation of metalloproteinase-1 and laminine-5, as well as of other epithelial cell pro-migratory factors. Even though this seems to enhance synaptogenesis, axonal growth, cellular migration and plasticity at the spinal level, its action at the level of the corneal nerves is yet to be confirmed. Its clinic efficacy when applied in the form of eyedrops for postherpetic neurotrophic ulcers has been tested with pilot trials in a small number of patients, obtaining positive results for cicatrization.\textsuperscript{6}

Experimentally, netrin-1 has been used in lab animals. This is a protein that is present in several systems in physiological condition, mainly the nervous system, and is also related to several neoplasias. After inducing corneal ulcers with alkali, the application of this molecule enhanced cicatrization and reduced corneal neovascularization through different mechanisms related to growth factors such as the epithelial growth factor (EGF) and the vascular endothelial growth factor (VEFG).\textsuperscript{7}

The CODA001 molecule (Nexagon\textsuperscript{\textregistered}, Co Da Therapeutics) is an oligonucleotide that inhibits the gap-joining connexin 43 protein, involved in cell–cell communication and playing an important role in cicatrization processes. Even though phase 1 studies have already been carried out in diabetic skin ulcers and phase 2 studies in post-vitrectomy diabetic PED patients, the results have not yet been published.\textsuperscript{8,9}

Combining in eyedrops 2 peptides derived from the P substance, of a neurotransmitter of corneal sensory nerves...
FGML-amide) and of the insulin-like growth factor-1 (ILGF-1) (SSSR) promotes the regularization of corneal nerves and epithelium proliferation without the side effects caused by the complete molecule (miosis, neovascularization, etc.). Accordingly, several clinical trials have observed that this had a healing efficacy of 75–89% of PED cases with neurotrophic origin, with complete epithelization and improvement of corneal sensitivity, mainly in cases without limbal insufficiency.\textsuperscript{10,11}

In addition, different growth factors involved in the cicatriztion process have been utilized. Several studies described the efficacy of EGF in neurotrophic ulcer case series as well as keratoconjunctivitis sicca, although these data were not confirmed in larger clinical trials.\textsuperscript{12,13} The nerve growth factor (NGF) is a polypeptide of the neurotrophin family that is present in the nervous, endocrine, immune and visual systems. At the corneal level, NGF has evidenced stimulation of epithelial cells, keratocytes, stem cells, interaction with immune system cells, indirect stimulation for releasing various neuropeptides and growth factors as well as their re-modulation of the extracellular matrix through the activation of metalloproteinases. Several case series of NK resistant to conventional treatment treated with murine NGF confirmed its efficacy (closure in 100% of cases, with improved vision and sensitivity), as well as excellent tolerability. Also, case reports of immune and neurotrophic ulcers due to congenital anesthesia have been reported with good results. A new multi-center study with human recombinant NGF (rhNGF) (Dompé, Italy) is being developed in Europe (the REPARO study) to assess the efficacy and safety of 2 rhNGF doses (10 μg/ml and 20 μg/ml) against a vehicle in patients with stage II and 3 neurotrophic keratitis. The preliminary results indicate excellent tolerance and improvement of all symptoms.\textsuperscript{14–18}

Finally, it is worth pointing out that extracellular matrix regenerators (RGTA\textsuperscript{®}, Caccio\textsuperscript{©}, Thea, France) are becoming an efficient and accessible therapy for NK and PED. These are heparan sulfate analogs that protect and stabilize the action of growth factors (FGF-1, FGF-2, TGF-beta-1, VEGF, etc.), stimulate the synthesis of collagen and glycosaminoglycans and inhibit the action of enzymes such as elastase, hapananal as or plasmin, all of which enhances the process of extracellular matrix remodeling and regeneration. A number of case series articles with NK resistant to conventional treatment (lubricants without preservatives, anticollagenolytics, topical antibiotics or therapeutic contact lenses) reported positive response to treatment with Caccio\textsuperscript{©}.

At present, a phase 3 multicenter clinical trial is being carried out in Europe to evaluate the efficacy and tolerability of Caccio\textsuperscript{©} versus vehicle in chronic NK. This new drug is already marketed in Spain and is becoming a new option to be taken into account for treatment of NK and noninfectious PED due to the efficacy and good tolerance it is demonstrating, as well as to avoid surgical treatment whenever possible. We are awaiting the results of the ongoing clinical trial as well as of new trials comparing it with other treatments such as autologous serum or platelet-rich plasma.\textsuperscript{19–22}

By way of conclusion, the development of new drugs showing promising preliminary results will enable progress in the approach of neurotrophic corneal diseases, thus improving the quality of life of our patients as well as obtaining savings related to surgical interventions.

REFERENCES


