Diquafosol Ophthalmic Solution for Dry Eye Treatment

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ABSTRACT

Introduction: There has been rapid progress in our understanding of dry eye pathogenesis, as well as the development of improved diagnostic clinical tests. Various types of dry eye treatment drugs have been developed. This review summarizes the basic and clinical research carried out in the development of diquafosol for ophthalmic use.

Results: Diquafosol is a dinucleotide, purinoreceptor P2Y₂ receptor agonist. Basic pharmacological studies have shown that it acts on P2Y₂ receptors at the ocular surface, to promote tear and mucin secretion via elevated intracellular Ca²⁺ concentrations. Diquafosol also improves tear and mucin secretion in experimental dry eye models. Based on the results of laboratory experiments, the authors conducted a series of clinical studies in patients with dry eye disease. Diquafosol was effective in the treatment of dry eye disease at an optimal dose of 3% six times a day. In comparison to commercially available 0.1% sodium hyaluronate ophthalmic solution, 3% diquafosol ophthalmic solution showed non-inferiority in improving corneal fluorescein staining scores and superiority in improving keratoconjunctival Rose Bengal staining scores.

Conclusions: Diquafosol ophthalmic solution has a novel mechanism of action that is characterized by its stimulatory effects on tear and mucin secretion. This drug has the potential to be effective in patients with tear film instability and short break-up time type of dry eye, which are essential factors in dry eye pathogenesis.

Keywords: Diquafosol; Dry eye; Mucin secretion; Ocular surface; P2Y₂ receptor agonist; Short break-up time; Tear film instability; Water secretion
INTRODUCTION

Since the 1990s, the number of reports on active basic research on dry eye disease (e.g., pathological analysis) and its clinical manifestations (e.g., diagnostic and testing methods) have increased [1]. During 1994–1995, the National Eye Institute collaborated with pharmaceutical companies to hold a joint workshop, where dry eye specialists from around the world discussed the diagnosis, categories, pathogenesis, and testing methods for dry eye disease [1]. In Japan, the Dry Eye Research Group proposed a definition and diagnostic criteria for dry eye disease in 1995 [2]. Dry eye research has changed drastically and there has been rapid progress in the understanding of dry eye pathogenesis as well as development and improvement of diagnostic technology.

In 2004, dry eye specialists from around the world met once more for an extensive discussion and organized the International Dry Eye Workshop (DEWS). In 2007, these discussions were documented in the “2007 Report of the International Dry Eye Workshop” [3]. The DEWS Report defined dry eye disease as follows: “Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.” The definition and diagnostic criteria proposed by the Japanese Dry Eye Research Group were fundamentally revised after DEWS [4]. Dry eye disease is now widely recognized to include many types of chronic ocular surface diseases. The ocular surface is covered by continuously renewing precorneal tear film, which is composed of two layers, aqueous-mucin and lipid layers. The water is produced by the lacrimal gland as the major source and the conjunctiva as a minor source. The gel-forming mucin is secreted by the conjunctival goblet cells and the membrane-bound mucin is formed from the glycocalyx, which are attached to the microvilli and microplae of the epithelial cells. Based on these new insights into dry eye pathogenesis, a number of drugs are now being developed to target individual factors in this multifactorial disease [5].

This review presents a summary of basic research leading to the clinical development of 3% diquafosol ophthalmic solution (DIQUAS® ophthalmic solution 3%; Santen Pharmaceutical Co. Ltd., Osaka, Japan). DIQUAS ophthalmic solution 3% was launched at the end of 2010 as a drug for the treatment of dry eye with a novel mechanism of action involving the stimulation of tear and mucin secretion; this was 15 years after the launch of purified sodium hyaluronate (HA, Hyalein® ophthalmic solution; Santen Pharmaceutical Co. Ltd., Osaka, Japan).

METHODS

The basic researches of diquafosol in this review are summarized, and all results were based on the authors’ laboratory experiments to understand the action mechanisms of diquafosol for the treatment of the dry eye. All results of clinical studies are derived from the results of clinical trials of 3% diquafosol ophthalmic solution in Japan. All studies were conducted for a new drug application in Japan, conformed to the Tenets of the Declaration of Helsinki, and were approved by the Ethical Review Board of each institution. All patients who agreed to participate in these studies provided written informed consent.

DIQUAFOSOL

Diquafosol is a dinucleotide derivative with a molecular weight of 878 g/mol and exhibits purinoreceptor P2Y2 receptor agonist activity [6]. It was developed by Inspire Pharmaceuticals