Drugs of the Future 2003, 28(4): 320-322

CCC: 0377-8282/2003

Lerdelimumab

Prevention of Corneal Scarring

Prop INN

CAT-152
Trabio™

Immunoglobulin G_4, anti-(human transforming growth factor β_2) (human monoclonal CAT-152 γ_4-chain), disulfide with human monoclonal CAT-152 λ-chain, dimer

CAS: 285985-06-0

EN: 272599

Abstract

Glaucoma is a sight-threatening ocular condition that involves damage to the optic nerve, mostly due to increased pressure of intraocular fluid. If drug therapy fails to control intraocular pressure (IOP), surgical or laser procedures such as trabeculectomy can be used to improve drainage and thereby lower IOP. However, postoperative scarring can occur as a result of excessive production of transforming growth factor-β (TGF-β) at the wound site. Antiproliferative drugs are widely used to prevent scarring, but they also cause cell death and apoptosis, which may lead to blindness. As TGF-β_2 is the major isoform in the eye, inhibiting its production or activity was proposed as an alternative for reducing postoperative ocular scarring. With this in mind, an engineered recombinant human monoclonal antibody targeting TGF-β_2 – lerdelimumab – was prepared as a potential approach to preventing postoperative scarring in patients undergoing trabeculectomy.

Introduction

Glaucoma is a sight-threatening ocular condition involving damage to the optic nerve, mostly due to increased pressure of intraocular fluid. If drug therapy fails to control intraocular pressure (IOP), surgical or laser procedures are often used to improve drainage and thereby lower IOP, but this is often associated with postoperative scarring due to excessive production of transforming growth factor-β (TGF-β) at the wound site, resulting in failure of glaucoma filtration surgery, or trabeculectomy. Antiproliferative drugs such as mitomycin C and 5-fluorouracil (5-FU) are widely used to prevent scarring, but they also cause cell death and apoptosis, which may lead to blindness. As TGF-β_2 is the major isoform in the eye, inhibiting the production or activity of TGF-β_2 has been proposed as an alternative for reducing postoperative ocular scarring. With this aim, Cambridge Antibody Technology prepared an engineered recombinant human monoclonal antibody targeting TGF-β_2 using phage display technology – lerdelimumab (CAT-152, Trabio™) – as a potential approach to preventing postoperative scarring in patients undergoing trabeculectomy.

Pharmacological Actions

CAT-152 effectively neutralizes active TGF-β_2, binding to this isoform with a K_d of 0.89 nM *versus* 10 nM for TGF-β_3 and no detectable binding to TGF-β_1, and inhibiting its binding to cell-surface receptors. The antibody was found to inhibit TGF-β_2-mediated effects in human ocular fibroblasts and significantly improved the outcome of glaucoma filtration surgery in rabbits by suppressing subconjunctival fibrosis (1). One study compared postoperative subconjunctival injections (7 injections of 100 μl) of CAT-152 (1 mg/ml) to 5-FU (50 mg/ml) and no treatment in rabbits undergoing glaucoma surgery. An improved surgical outcome was seen in the CAT-152-treated animals compared to the other groups, as was a reduced risk of corneal side effects. The CAT-152 group exhibited improved bleb survival (24.6 days *vs.* 19.5 days on 5-FU and 16.8 days in controls) and morphology (2).

The ocular distribution of [^{125}I]-CAT-152 following a single subconjunctival injection was evaluated in pigmented rabbits undergoing glaucoma filtration surgery. Approximately one-third (34.2%) of the dose was detected in external ocular structures, *i.e.*, bulbar and palpebral conjunctiva, nictitating membrane, extraocular muscles and sclera, by 5 min after injection, which decreased to 2.3% at 24 h. Very low penetration of the noninjected eye and of internal ocular structures including the cornea, aqueous humor, iris ciliary body, lens, vitreous, retina,

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Table I: Clinical studies of lerdelimumab (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Glaucoma	Randomized, double-blind, multicenter	Lerdelimumab, 100 μg subconjunctival x 4 [administered before surgery, immediately after surgery and on days 1 and 7] (n=16) Placebo (n=8)	24	Lerdelimumab was safe and well tolerated in patients with glaucoma who had undergone primary trabeculectomy. Compared to placebo, the drug reduced intraocular pressure and the need for postoperative clinical intervention	4-6
Glaucoma	Randomized, double-blind	Lerdelimumab, 100 μg subconjunctival x 4 [administered before surgery, immediately after surgery and on days 1 and 7] (n=36) Placebo (n=20)	56	The subconjunctival injection of lerdelimumab before and after trabeculectomy was well tolerated. Compared to placebo, the drug was associated with a lower intraocular pressure and a reduced requirement for further surgery or topical medication	7

choroid and optic nerve was seen. High systemic absorption and accumulation of radioactivity in the thyroid were also reported (3).

Clinical Studies

The first clinical trial of CAT-152 in patients undergoing glaucoma filtration surgery was a double-blind, randomized phase I/IIa study in 24 patients who recevied CAT-152 (100 μg in 100 μl; n=16) or placebo (n=8) as 4 subconjunctival injections immediately before and after surgery and at 1 day and 1 week after the operation. The incidence of complications was similar in both groups at 1 year and no serious antibody-related adverse events were reported. Unlike antimetabolites, CAT-152 treatment was associated with diffuse, noncystic and nonavascular blebs. Mean IOP, although successfully reduced in both groups, was lower in the CAT-152 group compared to those given placebo at 3, 6 and 12 months (14.9 mmHg *vs.* 17.0 mmHg at 1 year), and those treated with CAT-152 also showed a reduced rate of medical or surgical interventions over 1 year (1, 4-6). The results of these studies and the one that follows are summarized in Table I.

A second clinical trial assessed the safety, tolerability and efficacy of CAT-152 as an adjunct to prevent scarring following trabeculectomy. This study enrolled 56 patients undergoing the intervention for the first time, who were randomized to CAT-152 100 μg or placebo administered as in the initial study. At 6 months, fewer adverse events and ocular adverse events, in particular, were reported in CAT-152-treated patients, and the treatment was not associated with serious adverse events. Although visual acuity was similar in both groups, those on CAT-152 had a lower mean IOP (14.5 mmHg *vs*. 16.6 mmHg) and all of these subjects achieved IOP below 22 mmHg compared to 80% of those on placebo. The CAT-152 group also required fewer medical or surgical interventions (7).

CAT-152 is currently undergoing phase II/III European and phase III international trials for this indication, and it was recently cleared to be tested in the clinic by the FDA (8).

Source

Cambridge Antibody Technology Ltd. (GB).

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