Intravitreal panitumumab and myopic macular degeneration

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Received 8 February 2023
Accepted 26 June 2023

To cite: Bikbov MM, Kazakbaeva GM, Holz FG, *et al*. *Br J Ophthalmol* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/bjo-2023-323383

ABSTRACT

Background In experimental studies, intravitreally applied antibodies against epidermal growth factor (EGF), EGF family members (amphiregulin, neuregulin-1, betacellulin, epigen, epiregulin) and against the EGF receptor (EGFR) were associated with a reduction in lens-induced axial elongation and decrease in physiological eye elongation in guinea pigs and in non-human primates. Here, we investigated the intraocular tolerability and safety of a fully human monoclonal IgG2-antibody against EGFR, already in clinical use in oncology, as a potential future therapeutic approach for axial elongation in adult eyes with pathological myopia.

Methods The clinical, monocentre, open-label, multiple-dose, phase-1 study included patients with myopic macular degeneration of stage 4, who received intravitreal injections of panitumumab in various doses and in intervals ranging between 2.1 months and 6.3 months.

Results The study included 11 patients (age:66.8±6.3 years), receiving panitumumab injections in doses of 0.6 mg (4 eyes; 1×1 injection, 3×2 injections), 1.2 mg (4 eyes; 1×1 injection, 2×2 injections, 1×3 injections) and 1.8 mg (3 eyes; 1×1 injection, 2×2 injections), respectively. None of the participants showed treatment-emergent systemic adverse events or intraocular inflammatory reactions. Best-corrected visual acuity (1.62±0.47 logarithm of the minimal angle of resolution (logMAR) vs 1.28±0.59 logMAR; p=0.08) and intraocular pressure (13.8±2.4 mm Hg vs 14.3±2.6 mm Hg; p=0.20) remained unchanged. In nine patients with a follow-up of >3 months (mean:6.7±2.7 months), axial length did not change significantly (30.73±1.03 mm vs 30.77±1.19 mm; p=0.56).

Conclusions In this open-labelled, phase-1 study with a mean follow-up of 6.7 months, panitumumab repeatedly administered intravitreally up to a dose of 1.8 mg was not associated with intraocular or systemic adverse effects. During the study period, axial length remained unchanged.

Trial registration number DRKS00027302.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Experimental and clinical studies have suggested that myopic axial elongation is associated with epidermal growth factor (EGF).

WHAT THIS STUDY ADDS

⇒ Panitumumab as an EGF receptor blocker already in clinical use in oncology was well tolerated when intravitreally applied in patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Future clinical studies may address the efficacy of intravitreally applied panitumumab to prevent axial elongation in adult patients with pathological myopia.

INTRODUCTION

With the prevalence of axial myopia markedly increasing worldwide, pathological myopia has become one of the most common causes for irreversible visual impairment and blindness worldwide.[1–5] A recent meta-analysis of the prevalence of myopia and high myopia estimated that in the year 2000, 1.4 billion people were myopic and that 163 million people were highly myopic (myopic refractive error ≥−5 dioptres) (2.7% of the world population).[1] For 2050, figures of 4.8 billion people with myopia and 938 million highly myopic people (9.8% of the world population) have been predicted. High myopia is the main risk factor for the development of pathological myopia, including myopic macular degeneration and high myopia-associated optic nerve damage.[6–10] Clinical longitudinal studies have shown that highly myopic eyes can undergo further axial elongation during adulthood, and that this axial elongation is a main risk factor for the development and progression of myopic macular degeneration.[11–14]

Recent investigations suggested that the mechanism leading to axial elongation may be associated with an enlargement or growth of Bruch's membrane (BM) in the midperiphery of the ocular fundus.[15 16] BM is produced by the retinal pigment epithelium (RPE) containing receptors for epidermal growth factor (EGF).[17 18] In experimental studies in young guinea pigs and non-human primates, the intravitreal application of antibodies to EGF, EGF family members (such as amphiregulin, betacellulin, epigen and epiregulin) and to the EGF receptor (EGFR) resulted in a reduction of axial elongation, while the intravitreal injection of amphiregulin was associated with an increase in axial elongation.[19–23] Fitting with the observations made in guinea pigs and non-human primates, eyes of highly myopic patients, in particular in combination with a myopic macular degeneration, showed a significantly higher axial length (AL)-adjusted

intraocular concentration of EGF in their aqueous humour as compared with eyes of non-highly myopic patients.[24]

Since EGFR antibodies have been in clinical use for the systemic therapy of colorectal cancer and other malignancies for almost 20 years, and since there has been no therapeutic possibility to prevent progressive axial elongation in highly myopic adult patients so far, we here examined in a clinical phase-1 study whether intravitreally applied panitumumab, a clinically used EGFR antibody, is well tolerated intraocularly.[25] If proven safe and tolerable for intraocular use, future studies are planned to evaluate the efficacy of intravitreally administered panitumumab to prevent further axial elongation in highly myopic adult eyes with myopic macular degeneration.

Panitumumab is a fully human monoclonal IgG2-antibody which is produced by recombinant DNA-technology in a mammal cell line.[26] In contrast to other chimeric antibodies (eg, cetuximab as another example of an EGFR antibody) and humanised antibodies, panitumumab does not contain foreign protein parts which could be detected and recognised as foreign protein by the human immune system. Panitumumab works by binding to the extracellular domain of the EGFR, which is a transmembrane protein. By preventing the receptor's activation, it halts the cascade of intracellular signalling dependent on the EGFR. The main goal of the study was the evaluation of the safety of intravitreally applied panitumumab at various doses.

METHODS

This study was designed as a monocentre phase-1 examination in an open-label, multiple-dose study on safety and tolerability of intravitreally applied panitumumab in adult highly myopic patients with myopic macular degeneration. Recruitment began in November 2021. Inclusion criteria were an age of 50+ years, an AL of ≥26.5 mm, myopic macular degeneration stage 4 with foveal patchy atrophies as defined by the META-analysis for Pathologic Myopia Study Group, best-corrected visual acuity (BCVA)≥1.0 logMAR (logarithm of the minimal angle of resolution) (20/200 Snellen equivalent), and clear optic media to allow imaging of the macula and optic nerve head.[27] Exclusion criteria were previous vitreoretinal or retinal surgeries (except for peripheral retinal laser coagulation), previous intravitreal medical therapy with vascular endothelial growth factor (VEGF) inhibitors during the last 3 months before inclusion into the study, active choroidal neovascularisation, subretinal or intraretinal oedema in the macular region, pregnancy, lack of reliable contraception unless menopause had occurred, known intolerance or hypersensitivity against panitumumab (Vectibix; Amgen Co., Thousand Oaks, California, USA) or its ingredients, participation in another clinical trial (parallel or within a cooling off period of a previous trial), and missing ability to understand and sign a written informed consent. In addition, patients with myopic traction maculopathy and dome-shaped macula were excluded.

The study population consisted of three dose cohorts with increasing doses of panitumumab (0.6 mg, 1.2 mg or 1.8 mg). Each dose-step was separated by a comprehensive review of safety and tolerability of the injections considering adverse events and the results of detailed ophthalmological examinations including the sclera and cornea, the conjunctiva with the injection site, the lens and the ocular fundus in the period after the injections. The inclusion of 11 patients into the study was assessed to be sufficient since no formal statistical comparisons were planned, and the minimum of 3 participants per cohort was regarded sufficient to proceed to a higher dose level as long as no dose-limiting findings were noted. According to the original plan, each participant should have received three injections of panitumumab of the same dose, given in intervals of 2.5 months. Due to problems associated with the COVID-19 pandemic and other local logistic parameters, the participants were not able to fully comply with the prearranged schedule.

At baseline, the patients underwent a detailed ophthalmological examination including automated and subjective refractometry (performed three times at different time points, which could be during the same day), measurement of BCVA (using the standard Early Treatment of Diabetic Retinopathy Study testing protocol), perimetry (PTS-1000, Optopol Technology, Zawiercie, Poland), laser interferometric biometry for measurement of AL (Nidek, Gamagori, Japan), slit lamp-based examination of the anterior and posterior segment with special attention on intraocular inflammatory signs, tonometry (Tonoref III, Nidek, Japan), photography of the fundus, optical coherence tomography (OCT) of the macula and optic nerve head, OCT-based angiography (OCTA) of the macular region, assessment of the fundus autofluorescence (SS-OCT (DRI-OCT, Triton; Topcon, Tokyo, Japan)), and electroretinography ('Neiro-ERG' Neirosoft, Russia). OCT imaging included serial sectioning of the macula in horizontal and vertical direction, circular scanning of the peripapillary region including the peripapillary retinal nerve fibre layer, and scanning of the optic nerve head. OCTA imaging assessed the macular region. The Ganzfeld-ERG examinations were conducted under scotopic and photopic conditions according to the guidelines published by the International Society for Clinical Electrophysiology of Vision.[28] This whole series of examinations were repeated at the time of every re-injection and at the end of the observation period.

The intravitreal panitumumab injections were performed in the operation theatre under sterile conditions in topical anaesthesia, similar to conventional intravitreal injections of anti-VEGF drugs. In a first step, a paracentesis was performed to release about 0.1–0.2 mL of aqueous humour to reduce the intraocular volume and to create space for the following intravitreal injection of panitumumab (Vectibix). A paracentesis performed prior to an intravitreal injection has been shown to be a safe procedure and can prevent intraocular pressure (IOP) spikes after injections.[29]

The sampled aqueous humour samples were collected and deeply frozen for later biochemical analyses. The intravitreal injection was performed transconjunctivally in the temporal inferior quadrant in a distance of 3.0–3.5 mm from the limbus. Care was taken that before the injection, the conjunctiva was slightly shifted so that the conjunctival perforation site was not identical with the scleral perforation site. The injections in volumes of 60 µL (0.6 mg panitumumab), 120 µL (1.2 mg panitumumab) and 180 µL (1.8 mg panitumumab) were directed into the centre of the vitreous cavity. Depending on the IOP at the end of the injection and of the alignment of the scleral perforation site, some fluid from the vitreous cavity spilled back under the conjunctiva. Testing of the visibility of hand movements followed the intravitreal injections. An ointment containing a topical antibiotic and a topical steroid (levofloxacini 0.5%, Lekko, Russia dexamethasone 0.1%. «Belmedpreparaty», Republic of Belarus) was applied.

Dose considerations

In animal studies, a dose of 20 µg EGFR antibody (molecular weight: 175 kDa; #2232, Cell Signaling Technology, Danvers, Massachusetts, USA) was used in guinea pig eyes with a diameter

of about 8 mm, corresponding to an ocular volume of about 268 mm^3.[19–22] It related to an intraocular concentration 0.07 µg EGFR antibody/mm^3). It corresponded to a dose of 0.72 mg EGFR antibody in a highly myopic adult human eyes with an AL of 27 mm or an intraocular volume of approximately 10.306 mm^3, assuming a spherical eye shape. Taking into account the molecular weight of panitumumab (144.3 kDa) compared with the molecular weight of the antibody used in the guinea pig study (175 kDa), the equimolar dose of panitumumab is 0.59 mg. This dose of 0.6 mg panitumumab is approximately 1/700 of the systemically applied dose of panitumumab (Vectibix) administered intravenously every 2 weeks for oncological indications according to the SmPC (summary of product characteristics) (6 mg panitumumab/kg body weight or about 420 mg panitumumab for a patient with a body weight of 70 kg).[25] Panitumumab (Vectibix) is delivered by the pharmaceutical company in a concentration of 100 mg/5 mL (or 20 mg/mL) and has to be diluted to a concentration of 10 mg/mL. The doses of 0.6 mg, 1.2 mg and 1.8 mg panitumumab for intravitreal application thus led to an injection volume of 60 µL, 120 µL and 180 µL, respectively.

Based on the experiences gathered worldwide with the intravitreal application of bevacizumab (Avastin) used for the treatment of neovascular macular degeneration and other retinal diseases, an intravitreally injected dose of 1.25 mg bevacizumab (molecular weight: 149 kDa), corresponding to a molecular dose of 0.000, 000, 008 mol bevacizumab, is intraocularly and systemically well tolerated.[30] In a similar manner, the intravitreal application of ranibizumab (Lucentis) (also for the therapy of exudative macular degeneration) in a dose of 0.50 mg ranibizumab (molecular weight: 48 kDa) (corresponding to a molecular dose of 0.000, 000, 01 mol ranibizumab) is intraocularly and systemically well tolerated.[30] A dose of 0.6 mg panitumumab (molecular weight: 144.3 kDa) corresponds to 0.000, 000, 004 mol panitumumab, which is about half of the molar dose of ranibizumab injected intravitreally. In oncology, Avastin (bevacizumab) is given intravenously every 3 weeks at a dose of 15 mg/kg body weight (or 1.2 g bevacizumab at a body weight of 80 kg).[31] The routinely and intravitreally applied dose of bevacizumab of 1.25 mg is thus about 1/1000 of the intravenously applied dose of bevacizumab in oncology. A roughly similar ratio is obtained when the systemically routinely applied dose of 420 mg panitumumab is compared with an intravitreally applied dose of 0.6 mg panitumumab.

RESULTS

A total of 11 patients (2 men, 9 women) with a mean age of 66.8±6.3 years (median: 65.7 years; range: 57.6–80.2 years) were included. Mean BCVA was 1.62±0.47 logMAR (median: 1.52 logMAR; range: 1.00–2.30). All participants treated in the study self-identified as Russian (n=6), Tartar (n=3) or of other ethnicity (n=2). The mean body height was 1.67±0.10 m (median: 1.70 m; range: 1.46–1.80 m), mean body weight was 66.6±8.2 kg (median: 65.0 kg; range: 53–80 kg), and mean body mass index was 24.0±2.4 kg/m^2 (median: 24.7 kg/m^2; range: 20.1–27.6 kg/m^2). The follow-up ranged between 1 week and 11.9 months (mean: 5.6±3.4 months; median: 6.6 months).

All patients received at least one intravitreal injection of panitumumab. The patients received the panitumumab injections in doses of 0.6 mg (4 eyes; 1×1 injection, 3×2 Injections), 1.2 mg (4 eyes; 1×1 injection, 2×2 injections; 1×3 injections) and 1.8 mg (3 eyes; 1×1 injection, 2×2 injections), respectively (table 1). The mean interval between the first injection and second injection was 3.6±1.8 months (medium: 2.6 months; range: 2.1–6.3 months), and the interval between the second injection and third injection was 4.7 months. Reasons for the unequal intervals between the injections and the differences in the number of injections applied were problems associated with the COVID-19 pandemic and other local logistic parameters, so that the study participants could not fully comply with the prearranged schedule.

None of the participants had treatment-emergent systemic adverse events, while subconjunctival haemorrhages commonly occurred as side effects of the intravitreal injection procedure. All conjunctival haemorrhages resolved on their own. One patient reported floaters and a subjective decrease in quality of vision 1 month after the second injection, without a measurable

Table 1 Demographic data (mean±SD) and measurements in highly myopic adult patients with myopic macular degeneration and receiving intraocular injections of panitumumab in various doses

Patient	Age	Sex	Study duration (follow-up) (months)	No of injections	Visual acuity, baseline (logMAR)	Visual acuity, study end (logMAR)	Axial length (mm), baseline	Axial length (mm), study end	Axial length change (mm)	Intraocular pressure (IOP) baseline (mm Hg)	IOP, study end (mm Hg)
Dose: 0.6 mg panitumumab											
1	58.9	Male	1.10	1	1.30	1.30	28.64	29.15	0.51	12	14
2	68.7	Female	11.9	2	1.30	1.00	31.17	31.24	0.07	17	20
3	65.7	Female	3.30	2	2.30	2.30	31.78	31.97	0.19	13	14
4	57.6	Female	8.87	2	1.30	1.10	31.12	31.13	0.18	17	17
Dose: 1.2 mg panitumumab											
5	69.6	Female	7.20	3	2.00	2.00	30.40	30.40	0.00	12	11
6	64.1	Female	6.57	2	1.00	1.00	30.86	31.16	0.30	14	14
7	69.1	Female	3.10	2	1.52	1.52	29.60	29.27	−0.33	10	12
8	64.3	Female	6.57	1	2.30	1.70	32.67	32.72	0.18	13	13
Dose: 1.8 mg panitumumab											
9	72.4	Female	5.57	2	1.10	1.10	29.67	29.53	−0.24	12	12
10	64.2	Female	7.17	2	2.00	1.52	29.48	29.51	0.03	17	16
11	80.2	Female	0.27	1	1.70	1.00	29.64	28.81	−0.83	15	18

LogMAR, logarithm of the minimal angle of resolution.

decrease in vision. The subjective symptoms subsided within 4 weeks. None of the eyes showed an intraocular inflammatory reaction such as vitritis or retinal vasculitis during the postoperative period. There was no case of endophthalmitis or development of a choroidal neovascularisation. In particular, there were no abnormalities detected in the region of the external eye including the cornea and conjunctiva, except for the hyposphagmata mentioned above. The IOP as assessed about 15 min after the injections was less than 25 mm Hg. The assessment of the OCT images of the macula and optic nerve head did not reveal changes when the baseline images were compared with the images obtained at study end. In particular, there were no changes observed with respect to macular choroidal and retinal thickness, prevalence, length and area of macular Bruch's membrane defects, size of parapapillary beta zone, gamma zone and delta zone, and size and shape of the optic disc. In a similar manner, the OCTA images did not show any show during the study period.

BCVA remained unchanged (p=0.08) during the study period with a mean BCVA of 1.62±0.47 logMAR at baseline and of 1.28±0.59 logMAR at study end (median: 1.10; range: 0.10–2.30). In a similar manner, IOP at baseline and IOP at study end did not differ significantly (13.8±2.4 mm Hg vs 14.3±2.6 mm Hg; p=0.20) (table 1). None of the eyes showed an IOP higher than 21 mm Hg during the study period.

Nine of the 11 patients had a follow-up of at least 3 months (mean: 6.7±2.7 months; median: 6.6 months; range: 3.1–11.9 months). The nine patients received the panitumumab injections in doses of 0.6 mg (3 eyes; 3×2 Injections), 1.2 mg (4 eyes; 1×1 injection, 2×2 injections; 1×3 injections) and 1.8 mg (2 eyes; 2×2 injections), respectively (table 1).

Including only the nine patients with a minimal follow-up of 3 months into the analysis, BCVA remained unchanged (p=0.15) during the study period with a mean BCVA of 1.65±0.51 logMAR at baseline (median: 1.52; range: 1.00–2.30) and of 1.31±0.65 at study end (median: 1.10; range: 0.10–2.30). In a similar manner, IOP at baseline and IOP at study end did not differ significantly (13.9±2.6 mm Hg vs 14.3±2.8 mm Hg; p=0.37) (table 1). In a similar manner, the amplitude of the b-wave of the ERG did not differ significantly (p=0.59) between baseline and study end.

In these nine eyes with a follow-up >3 months, AL measured at baseline did not differ significantly from AL measured at study end (30.73±1.03 mm vs 30.77±1.19 mm; p=0.56). The mean change in AL during the study period was 0.04±0.21 mm (median: 0.07 mm; range: −0.33 to +0.30 mm) (table 1). In univariate analysis, the change in AL increased with longer AL at baseline (standardised regression coefficient beta: 0.70; p=0.04) and younger age (beta: −0.68; p=0.04), while it was statistically independent of the follow-up duration (beta: 0.34; p=0.37) (figures 1 and 2).

DISCUSSION

In this phase-1 study, panitumumab intravitreally and repeatedly applied was well tolerated in highly myopic eyes in patients with myopic macular degeneration. In addition, the eyes did not show a further axial elongation during the study period with a mean of 6.7 months.

The findings obtained in our study cannot directly be compared with results of previous investigations since the intraocular tolerability of intravitreally applied panitumumab has not been examined yet. It is in accordance with previous observations from studies on the safety of intravenously applied panitumumab for the therapy of colorectal cancer. In these studies, intraocular ocular side effects were not noted, however, corneal lesions including keratitis and ulcerative keratitis, meibomian gland dysfunction, periorbital and lid dermatitis, blepharitis and conjunctivitis were observed in the region of the external eye.[26] While the observations may suggest that the patients included

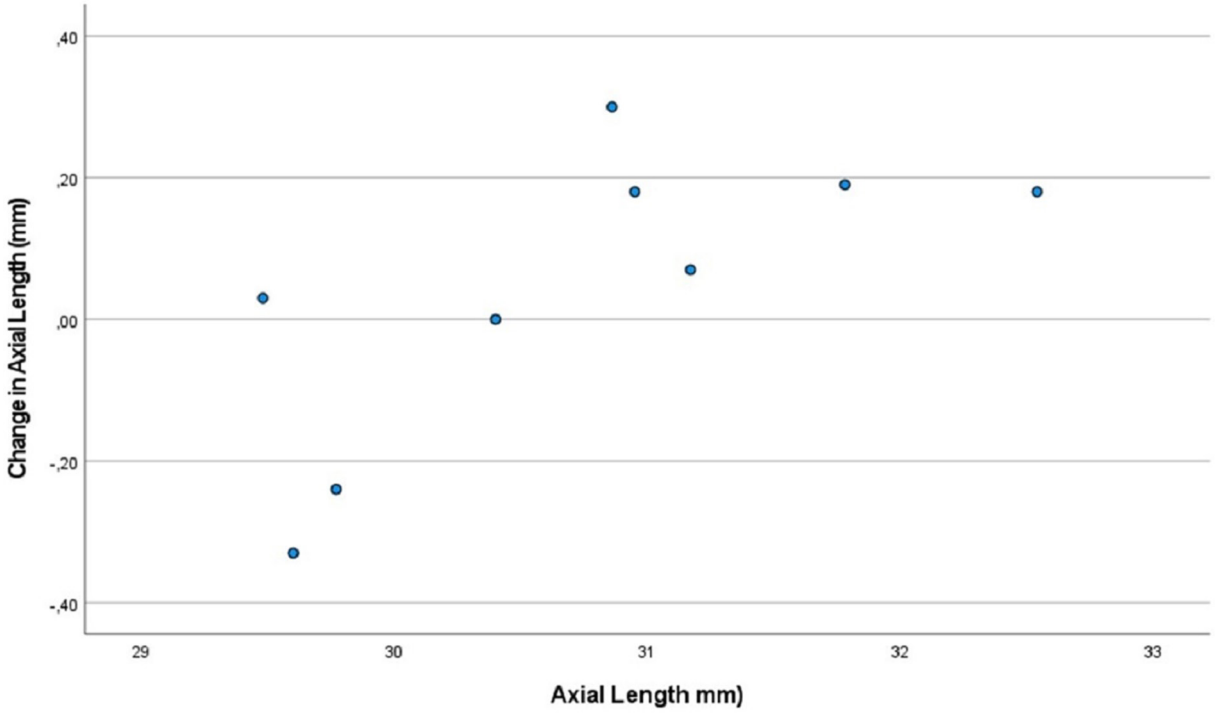

Figure 1 Distribution of the change in axial length versus axial length at baseline in highly myopic adult eyes with myopic macular degeneration after receiving intravitreal injections of panitumumab.

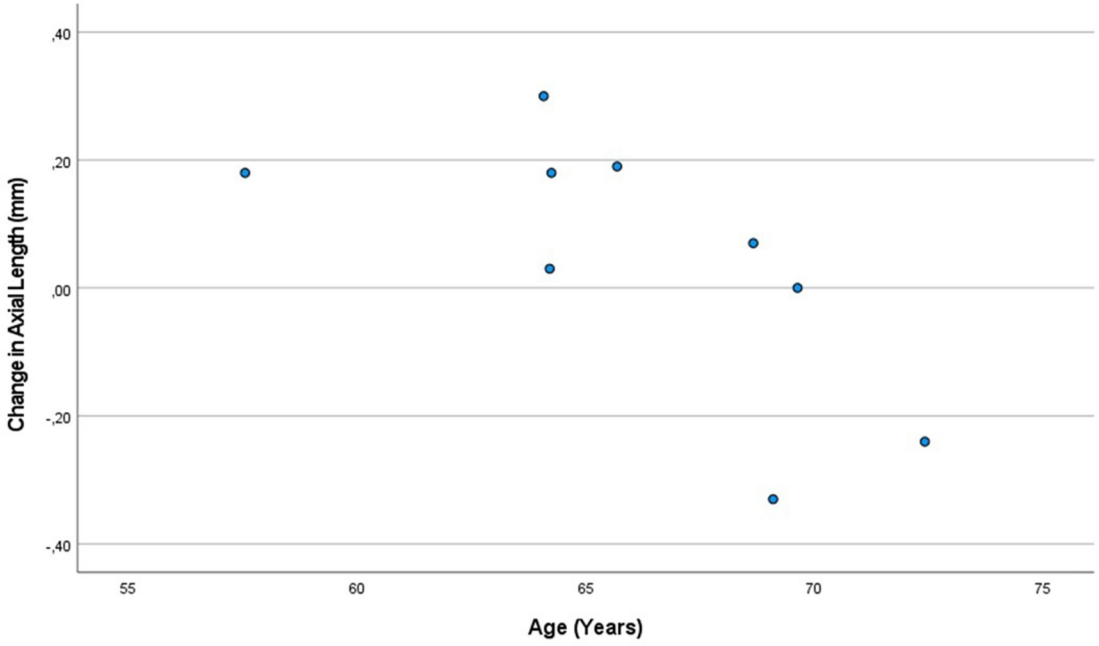

Figure 2 Distribution of the change in axial length versus age in highly myopic adult eyes with myopic macular degeneration after receiving intravitreal injections of panitumumab.

into our study did not experience relevant intraocular side effects following to the intravitreally applied panitumumab, the small study sample size does not allow to make broad conclusions. It may be taken into account, that for intravitreally injected brolucizumab (an anti-VEGF antibody) the results of phase-3 clinical trials were quite promising, while the association between intravitreally applied brolucizumab and intraocular inflammation was reported later.[32]

After a mean and median follow-up of 6.7 months and 6.6 months, respectively, AL did not change significantly in the eyes with a minimal follow-up of >3 months (table 1). Since the follow-up was relatively short and the study sample was small, the data obtained in our study cannot directly be compared with findings of longitudinal studies, such as the population-based Beijing Eye Study with a follow-up of 10 years. In the latter investigation, seven out seven eyes with extrafoveal or foveal patchy atrophies showed a progression during the observation period.[9] In a similar manner, in an 18-year long, large-scaled, hospital-based follow-up study, 60 out of 63 (95%) eyes with patchy atrophies showed a progression.[8] With respect to axial elongation, a recent retrospective cohort study on 1877 patients with a mean age of 62.10 years, a mean AL of 29.66 mm showed a significant mean elongation of 0.05±0.24 mm/year.[9] The number of study participants in this study was too low to allow a statement whether the intravitreally applied panitumumab resulted in a decrease in axial elongation.

Limitations of our study should be discussed. First, we did not assess the immunogenicity with respect to the formation of anti-drug antibodies (ADAs) against panitumumab in the serum of the patients included into the study. Since, however, systemically applied panitumumab has been in clinical use for more than 20 years for the treatment of colorectal cancer, and since the dose injected intravitreally was approximately 1/700 or 0.1% of the dose applied intravenously for the cancer therapy, the data obtained in previous large-scaled clinical studies on the therapy of cancers by panitumumab may be taken as basis for the question whether the relatively small amount of 1.8 mg of panitumumab injected intraocularly could lead to the formation of ADAs against panitumumab. In that context, one may also take into account that the intraocular compartment has a certain immune privilege.[33] Second, we did not assess the pharmacokinetics by taking blood samples in regular intervals after the intraocular application. Since, however, data were available on the pharmacokinetics when panitumumab was applied systemically, it might predominantly have been interesting to assess the intraocular pharmacokinetics. That, however, would have been possible only by repeated vitreous aspirations which would not have been acceptable with respect to their invasiveness and associated risks. Third, we did not examine the pharmacodynamics with respect to the potential impact of intravitreally administered panitumumab on the systemic complement activity. Since data had already been available based on the systemic application of panitumumab, the additional examination of the pharmacodynamics of intraocularly applied panitumumab might not have been additionally informative. Fourth, as also pointed out above, the study sample was too small to allow firm statements about the efficacy of the therapy for the reduction of axial elongation and decrease in the risk of progression of myopic maculopathy.

In conclusion, intravitreally and repeatedly applied panitumumab in doses escalating from 0.6 mg to 1.8 mg was not associated with intraocular adverse effects except transient floaters nor corneal or conjunctival problems except for procedure-related conjunctival haemorrhages. In addition, the highly myopic eyes did not show a statistically significant further axial elongation in the study period with a mean of 6.7 months. The results may represent the basis for a clinical phase-2/3 trial examining the efficacy and safety of intravitreally administered panitumumab with the aim to prevent further axial elongation in highly myopic eyes.

Contributors Design of the study: MMB, GMK, FGH and JBJ; Funding: MMB; Examination of study participants and clinical images: MMB, GMK, SP-J, LIG, DAK and JBJ; Supervision: MMB, GMK; Writing the first manuscript draft: SP-J and JBJ;

Revision and final approval of the manuscript: MMB, GMK, FGH, SP-J, LIG, DAK and JBJ. Guarantors are MMB and JBJ.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests JBJ and SP-J: Patent holder with Biocompatibles UK (Franham, Surrey, UK) (Jonas JB, Wallrapp C, Geigle P, Panda-Jonas S, Thoemes E): (Title: Treatment of eye diseases using encapsulated cells encoding and secreting neuroprotective factor and / or anti-angiogenic factor; Patent number: 20120263794), and European patent EP 3 271 392, JP 2021-119187, and US 2021 0340237 A1: Agents for use in the therapeutic or prophylactic treatment of myopia or hyperopia; Patent application: European patent application: WO 2021/198369 A1; PCT/EP2021/058500: Agents for the use in the therapeutic or prophylactic treatment of retinal pigment epithelium associated diseases.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the Ethics Committee of the Academic Council of the Ufa Eye Research Institute approved the study (date: 2 November 2021) and confirmed that the study adhered to the tenets of the Declaration of Helsinki. Informed written consent was obtained from all study participants. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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