Transient postoperative vascular endothelial growth factor (VEGF)-neutralisation improves graft survival in corneas with partly regressed inflammatory neovascularisation

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ABSTRACT

Background: High-risk keratoplasties are usually performed after an uninflamed and quiescent interval in corneas with partly regressed blood and lymphatic vessels. We analysed whether the inhibition of post-keratoplasty revascularisation in mice with partly regressed corneal vessels (“intermediate-risk”) improves graft survival.

Methods: Three interrupted stromal sutures (11-0) in corneas of Balb/c mice (6–8 weeks old) were placed for 6 weeks. Six months after suture removal, penetrating keratoplasty was performed with C57BL/6 donors. The treatment group received a vascular endothelial growth factor-A specific cytokine trap (VEGF Trap) intraperitoneally at days 0, 4, 7 and 14 after keratoplasty (25 mg/kg per mouse; controls received equal amounts of Fc protein). Pathological haemangiogenesis and lymphangiogenesis prior to as well as 3 days or 8 weeks after keratoplasty and graft survival were analysed.

Results: Three days after keratoplasty corneal revascularisation was sufficiently reduced by VEGF Trap (haem-vascularised areas 42.7% reduction; lymph-vascularised areas 54.7% reduction). Survival proportions 8 weeks after keratoplasty were 36% in the treatment group compared with 9% in the control group (n = 11; p < 0.05). At that time no differences in haemangiogenesis or lymphangiogenesis were observed between the two groups.

Conclusion: Early transient postoperative induction of haemangiogenesis and lymphangiogenesis and reformation of regressed corneal blood and lymphatic vessels are important for transplant rejections after “intermediate-risk” corneal transplantation.

Corneal neovascularisation (CNV) occurs in many pathological conditions, including chemical burns, infections and many ocular surface disorders.1,2 Although CNV is beneficial in some instances (eliminating inflammation, promoting wound healing and inhibiting corneal melting), CNV has become one of the major reasons for corneal blindness.3 Once stable CNV has become established, often the only possible treatment option for achieving a clear cornea is perforating keratoplasty. The role of pre-existing CNV has long been established as a strong risk factor for immune rejections following keratoplasty. However, the role of CNV occurring after keratoplasty and its strong influence on inducing transplant rejection has recently been elucidated in a mouse model of low-risk keratoplasty, and more recently also in a high-risk model.4,5

The time course of CNV occurring after keratoplasty might be important for the development of strategies against corneal graft rejection. The early growth of vessels after keratoplasty might interfere with tolerogenesis and ultimately graft survival. We hypothesise that an initial transient inhibition rather than an ongoing inhibition of haemangiogenesis and lymphangiogenesis following high-risk keratoplasty is important for the prolongation of graft survival.

We recently demonstrated that murine corneal neovascularisation after a transient inflammatory stimulus started to regress after a few weeks; after 6 months there was no evidence of lymphatics and only a few blood vessels still remained.6 In human corneas with a history of CNV of less than 3 months, lymphatic vessels were detectable, whereas none were present in corneas with a history of CNV of more than 6 months.7 In addition, there was a significant positive correlation between the degree of human corneal haemangiogenesis and lymphangiogenesis.

Since in the clinical setting keratoplasties are not usually performed in freshly vascularised and inflamed eyes, but rather later after a quiescent and uninflamed interval with at least partly regressed CNV, we wanted to test the ability of VEGF-A blockade to inhibit postoperative revascularisation and to improve graft survival after keratoplasty in corneas with partly regressed blood and lymphatic vessels. Therefore, we developed a new mouse model of intermediate-risk keratoplasty that more closely resembles the human situation than the standard mouse model.

Here we show that inhibition of post-keratoplasty reconstitution of regressed corneal blood and lymphatic vessels by VEGF-A blockade can significantly prolong graft survival. This supports the concept of an important role for early postoperative induction of haemangiogenesis and lymphangiogenesis for immune responses after corneal transplantation.

METHODS

Mice and anaesthesia
Six- to 8-week-old female Balb/c mice (Charles River Germany, Sulzfeld, Germany) were used for vessel-inducing suturing of the corneal stroma and further served as recipients for corneal transplantations.
Corneal flatmounts and morphological determination of haemangiogenesis and lymphangiogenesis

To measure the influence of VEGF deprivation on the amount of CNV corneas were excised either prior to or 3 days after keratoplasty for investigation of the immediate influence of VEGF Trap or 8 weeks after keratoplasty for the long-term effect. The corneas were processed for morphometric analysis of both haemangiogenesis and lymphangiogenesis in corneal flatmounts as described previously.11 12 The corneas were rinsed in PBS and fixed in aceton for 30 min. After three additional washing steps in PBS and blocking with 2% BSA in PBS for 2 h the corneas were stained overnight at 4°C with rabbit anti-mouse lymphatic vessel hyaluronan receptor-1 (LYVE-1) (1:500; AngioBio, Del Mar, California, USA). On day 2 the tissue was washed, blocked and stained with fluorescein isothiocyanate (FITC)-conjugated rat anti-CD31 (Acris Antibodies GmbH, Hiddtenhausen, Germany) antibody overnight at 4°C. After a last washing and blocking step on day 3, LYVE-1 was detected with a Cy3-conjugated secondary antibody (goat anti rabbit, 1:100, Dianova, Hamburg, Germany).

RESULTS

Regressed corneal blood and lymphatic vessels in older mice have a capability for vascular reformation after keratoplasty

To evaluate whether a keratoplasty causes an additional in-growth of blood and lymphatic vessels in a cornea with almost completely regressed prevascularisation (6 months after suture removal after 6 weeks of stromal stumps in place), we compared the density of vascularisation immediately prior to transplantation with that observed 3 days after allografting (n = 4). Preoperatively, vital microscopy revealed a calm cornea with little vascularised area and without any sign of an ongoing inflammation. Immunohistochemical staining using LYVE-1 as a lymphatic vessel endothelial specific marker confirmed that blood vessels (CD31+/−/LYVE-1−) were present in small numbers and only very few lymphatic vessels (CD31+/LYVE-1++) appeared adjacent to physiologically vascularised limbal arcade.

Three days after corneal transplantation a considerable increase in blood vessel density and a small additional in-growth of lymphatic vessels was observed. Quantitative analyses revealed that immediately pre-operatively 6.95 (SD 5.44)% of the corneal surface was covered by pathological blood vessels and only 0.43 (SD 0.76)% of the cornea was covered by lymphatic vessels. Three days after corneal transplantation, there was a significant increase in both blood vessel density, covering 14.10 (SD 1.37)% (p<0.001) and lymphatic vessel density, covering 1.72 (SD 1.07)% (p<0.05) of the cornea (fig 1A, B; fig 2A, B, D, E).

Additional vascularisation can be blocked by initial VEGF deprivation after keratoplasty in corneas with regressed blood and lymphatic vessels

Blocking of VEGF-A using VEGF Trap has been proven to inhibit corneal haemangiogenesis and lymphangiogenesis following a corneal inflammatory stimulus as well as after low-risk and “classic” high-risk keratoplasty. VEGF Trap binds and neutralises all isoforms of VEGF-A, as well as placental growth factor (PLGF), but does not directly block VEGF-C or -D. In a prior study we demonstrated a positive effect of VEGF blocking on transplantant survival in high-risk corneas with only minimally regressed vascularisation when keratoplasty was performed 3 weeks after removal of neovascularisation-inducing sutures.4 To obtain donor mice with a more pronounced regression of corneal blood and lymphatic vessels more closely mimicking the human setting, corneal stromas of 6–8-week-old Balb/c mice were sutured with three interrupted 11-0 sutures (nylon; Serag Wiessner, Nails, Germany). The sutures were left in place for 6 weeks. Penetrating corneal transplantation was performed 6 months after suture removal. According to previous studies from our group almost no lymphatic vessels and only a few blood vessels are detectable at this time point (corneal sutures in that study remained for only 2 weeks).9 Keratoplasty was performed as described previously.9 10 Briefly, donor corneas were excised by trephination using a 2.0 mm bore, and cut with curved Vannas scissors. Until grafting, corneal tissue was placed in chilled phosphate-buffered saline (PBS). Recipients were anaesthetised, and the graft bed was prepared by trephining a 1.5 mm site in the central cornea of the right eye and discarding the excised cornea. The donor cornea was immediately applied to the bed and secured in place with eight interrupted 11-0 sutures. Antibiotic ointment (Refobacin; Merck KGaA, Darmstadt, Germany) was placed on the corneal surface and the eyelids were closed with 8-0 suture (Serag Wiessner, Nails, Germany). The sutures were left in place for 6 weeks. Penetrating corneal transplantation was performed 6 months after suture removal. According to previous studies from our group almost no lymphatic vessels and only a few blood vessels are detectable at this time point (corneal sutures in that study remained for only 2 weeks).9 Keratoplasty was performed as described previously.9 10 Briefly, donor corneas were excised by trephination using a 2.0 mm bore, and cut with curved Vannas scissors. Until grafting, corneal tissue was placed in chilled phosphate-buffered saline (PBS). Recipients were anaesthetised, and the graft bed was prepared by trephining a 1.5 mm site in the central cornea of the right eye and discarding the excised cornea. The donor cornea was immediately applied to the bed and secured in place with eight interrupted 11-0 sutures. Antibiotic ointment (Refobacin; Merck KGaA, Darmstadt, Germany) was placed on the corneal surface and the eyelids were closed with 8-0 suture (Serag Wiessner, Nails, Germany).

To study graft survival proportions, tarsorrhapy and corneal survivals were removed after 7 days; grafts with technical difficulties (hyphaema, cataract, infection, loss of anterior chamber) were excluded from further consideration. Grafts were then examined at least twice a week until week 8 after transplantation by slit lamp microscopy and scored for opacity (score 0 = clear cornea, 1 = minimal superficial opacity, 2 = minimal, deep (stromal) opacity (pupil margin and iris vessels visible, 3 = moderate stromal opacity (only pupil margin visible), 4 = intense stromal opacity (only a portion of pupil margin visible), 5 = maximum stromal opacity, anterior chamber not visible) as described previously.9 10 Grafts with opacity scores ≥2 after 2 weeks were considered to have been rejected.

Vascular regression in high-risk corneas

In a prior study we demonstrated a positive effect of VEGF blocking on transplantant survival in high-risk corneas with only minimally regressed vascularisation when keratoplasty was performed 3 weeks after removal of neovascularisation-inducing sutures.4 To obtain donor mice with a more pronounced regression of corneal blood and lymphatic vessels more closely mimicking the human setting, corneal stromas of 6–8-week-old Balb/c mice were sutured with three interrupted 11-0 sutures (nylon; Serag Wiessner, Nails, Germany). The sutures were left in place for 6 weeks. Penetrating corneal transplantation was performed 6 months after suture removal. According to previous studies from our group almost no lymphatic vessels and only a few blood vessels are detectable at this time point (corneal sutures in that study remained for only 2 weeks). Keratoplasty was performed as described previously.9 10 Briefly, donor corneas were excised by trephination using a 2.0 mm bore, and cut with curved Vannas scissors. Until grafting, corneal tissue was placed in chilled phosphate-buffered saline (PBS). Recipients were anaesthetised, and the graft bed was prepared by trephining a 1.5 mm site in the central cornea of the right eye and discarding the excised cornea. The donor cornea was immediately applied to the bed and secured in place with eight interrupted 11-0 sutures. Antibiotic ointment (Refobacin; Merck KGaA, Darmstadt, Germany) was placed on the corneal surface and the eyelids were closed with 8-0 suture (Serag Wiessner, Nails, Germany).

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Donor buttons were generated by trephination of corneas from 6- to 8-week-old female C57Bl/6 mice. No animal showed any symptoms suggesting of systemic disease due to the experiment. For surgical procedures, mice were anaesthetised using a mixture of ketamine and xylazine (120 mg/kg and 20 mg/kg body weight, respectively).

Functional and statistical analysis

Double-stained wholemounts were analysed with a fluorescence microscope (BX51; Olympus Optical Co., Hamburg, Germany) and digital pictures were taken with a 12-bit monochrome CCD camera (F-View II; Soft Imaging System, Münster, Germany). The areas covered with blood or lymphatic vessels were detected with an algorithm established in the image analysing program cell F (Olympus, Hamburg, Germany) as described previously11: prior to analysis grey value images of the wholemount pictures were modified by several filters. Blood and lymphatic vessels were detected by threshold setting including the bright vessels and excluding the dark background. Quantitative analysis was performed using rectangles of a standardised size (1.11 mm²) aligned along the limbus. Blood or lymphatic vessels in each rectangle were measured and correlated with the rectangle area (vessel ratio).

Statistical differences were analysed using the Mann–Whitney U test and Kaplan–Meier survival curves. Graphs were drawn using Excel (Microsoft Corporation).

Additional vascularisation can be blocked by initial VEGF deprivation after keratoplasty in corneas with regressed blood and lymphatic vessels

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the context of pathological angiogenesis, PLGF mainly acts as an enhancer of the stimulation of VEGFR-2 by VEGF-A. Therefore, we utilised VEGF Trap to evaluate the extent to which combined haemangiogenesis and lymphangiogenesis occurring after intermediate-risk corneal transplantation also depend on VEGF-A. Three days after corneal transplantation, vital microscopy revealed that a single injection of VEGF Trap (25 mg/kg) on the day of surgery effectively suppressed additional corneal blood vessel ingrowth, compared with control mice treated with equal amounts of Fc protein. Quantitative, immunohistochemical and morphometrical analyses showed that 3 days following high-risk corneal transplantation, the density of blood vessels was statistically reduced. Although even the additional in-growth of lymphatic vessels in corneas of VEGF Trap treated mice was markedly reduced it did not reach the level of significance (haem-vascularised areas 6.02 (SD 2.46)% versus 14.10 (SD 1.37)% in Fc controls, p < 0.0001 and lymph-vascularised area in the treatment group: 0.94 (SD 0.91)% versus 1.72 (SD 1.07)% Fc treated, p = 0.15) (fig 2B, C, E, F; fig 3A, B).

Early blocking of VEGF leads to prolonged graft survival after keratoplasty in corneas with regressed blood and lymphatic vessels

To test whether a decrease of additional in-growth of blood and lymphatic vessels after intermediate-risk corneal transplantation by VEGF-A blocking leads to a reduced transplant rejection rate, VEGF Trap was used immediately for 2 weeks after keratoplasty. Six months after temporary suture-induced corneal inflammation, keratoplasty was performed and mice were treated with VEGF Trap (n = 11) on the day of surgery, and 3, 7 and 14 days thereafter. The animals showed significantly prolonged long-term graft survival (p < 0.05) relative to control mice injected with Fc. Notably, in the VEGF Trap-treated group, 56% of the grafts survived to the end of the 8-week observation period. In marked contrast, 91% of the grafts were rejected within 2 weeks of transplantation in the Fc control group (fig 4).

Initial transient blocking of VEGF after keratoplasty has no effect on final corneal revascularisation

To investigate whether temporary inhibition of VEGF-A influences the long-term degree of corneal revascularisation, we quantified the amount of revascularisation 8 weeks after keratoplasty in corneas with regressed blood and lymphatic vessels (Fig 5A, B). Mice who received an initial treatment with VEGF-Trap or Fc protein the first 2 weeks after keratoplasty had the same amount of corneal blood (36.0 (SD 5.8)% VEGF-Trap-treated vs 37.0 (SD 8.9)% Fc protein-treated, p = 0.76) and
lymphatic vessels (15.1 (SD 4.3)% VEGF-Trap-treated vs 13.9 (SD 2.3)% Fc protein-treated, p = 0.42).

DISCUSSION

Allogenic graft rejection strongly depends on the initiation of an immune response by contact of antigen-presenting cells with T lymphocytes in the corresponding lymph nodes. In rodent low-risk keratoplasties, allosensitisation occurs 2–4 weeks after corneal transplantation, presumably through lymphatic drainage pathways. In contrast, after high-risk corneal transplantation in mice, the graft comes into direct contact with blood and lymphatic vessels almost immediately, leading to rapid donor-specific sensitisation and a 100% rejection rate in as little as 1 week. The physiological blood and lymphatic vessel-free cornea does not offer an immediate pathway for allogenic material to the draining lymph nodes after keratoplasty, leading to a very low transplant rejection rate of less than 10% in humans. Draining cervical lymph nodes play a critical role in allosensitisation and subsequent rejection, but seems not to be responsible for tolerance induction after keratoplasty. This suggests that the initiation of tolerogenic mechanisms leading to long-term acceptance of the graft may be achieved when the graft remains concealed for the local lymph nodes for a certain time. In addition, although many other factors besides avascularity are important for the corneal “immune privilege”, the graft rejection rate increases dramatically when the transplantation is performed in a freshly

![Figure 3](image_url) Blood and lymphatic vessels 3 days after keratoplasty in corneas 6 months after a 6-week inflammatory stimulus (“sutures”) treated either with vascular endothelial growth factor-A specific cytokine trap (VEGF Trap) or with Fc control protein.

![Figure 4](image_url) Temporary, early postoperative neutralisation of VEGF-A improves long-term graft survival when performed in corneas with regressed blood and lymphatic vessels 6 months after temporary suture-induced inflammation.

![Figure 5](image_url) Despite early transient blockade of VEGF leads to reduced initial corneal neovascularisation, no effect on long-term in-growth of both blood (A) and lymphatic (B) vessels was detectable 8 weeks after keratoplasty.
prevascularised cornea. The grafted material gets instantaneous connection to the draining lymphatic system, leading to a transplant rejection rate of more than 50%.24

The beneficial effect of an early transient anti-angiogenic treatment after keratoplasty on long-term graft survival has been shown in only two publications so far.6,7 In a low-risk as well as in a classic high-risk set-up of murine corneal transplantation, a beneficial effect for the reduction of post-keratoplasty in-growth of blood and lymphatic vessels by postoperative blocking of VEGF was observed. In addition, in both models VEGF deprivation led to an improved graft survival in comparison with their respective control group. The model of the current work utilises hosts where the corneal prevascularisation ranks between the two extremities of the traditional murine model of low-risk and high-risk keratoplasty. We were able to prove that even in this set-up, which more closely mimics the human high-risk situation, decreased influence of VEGF reduces postoperative neovascularisation and promotes graft survival. In addition, whether transient early anti-angiogenic treatment leads to a long-standing diminished corneal vascularisation has been unclear to date. We have shown for the first time that transient early deprivation of VEGF following keratoplasty leads to impaired early vascularisation, whereas long-term vascularisation is not altered. Moreover, this reduced early vascularisation is coincidental with an improved long-standing graft survival. Our findings underscore that early transient and not necessarily the long-term avoidance of contact of antigen-presenting cells to the draining lymphatic vessel system leads to long-standing graft tolerance.

Earlier work demonstrated that temporary placement of sutures in the corneal stroma induced an inflammatory response with pathological corneal haemangiogenesis and lymphangiogenesis, but that the vessels regressed over time.8 In that study, the sutures were left for 2 weeks only before being removed. The results showed that lymphatic vessels regressed earlier and to a greater extent than blood vessels. By 6 months after suture removal, no lymphatic vessels were observed, while there were only some partially perfused and non-perfused ("ghost") blood vessels. Similar results indicate that the regression of blood and lymphatic vessels after a CNV-inducing stimulus also appears in human corneas.9 This bears analogy with our modified intermediate-risk model. When corneal stromal sutures were left for 6 weeks only, few blood and almost no lymphatic vessels were visible after 6 months. This model with regressed blood and lymphatic vessels is closer to the clinical situation where—whenever possible—one would wait a certain time after an angiogenic stimulus before performing the corneal transplantation. Graft survival in this model of intermediate-risk keratoplasty was slightly better in both the treatment and the control group compared with our recent experiment, where the keratoplasty was performed 3 weeks after suture removal.1 This better graft survival indicates that, if possible, one should always wait a certain inflammatory-free interval before performing a keratoplasty.

One would still expect a higher capacity for the reformation of regressed blood or lymphatic vessels than seen in our model. In addition to the assimilation of corneas with regressed vascularisation to corneas without pathological vascularisation, there might be a further factor contributing to the very low observed additional in-growth of blood and lymphatic vessels after keratoplasty: recent findings suggest that corneas of young mice have an increased capacity for neovascularisation after stromal suturing compared with older mice.20 Older mice thereby have a reduced angiogenic response to an inflammatory corneal stimulus.

In conclusion, our findings indicate that early transient anti-VEGF treatment after keratoplasty has a benefit for limiting the early and not the long-term in-growth of vessels. Early VEGF deprivation improves long-term graft survival in the "intermediate-risk" murine model of corneal transplantation, which more closely mimics the human scenario.

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Competing interests: VEGF Trap was provided by Regeneron Pharmaceuticals Inc, Tarrytown, New York, USA.

Ethics approval: All animals were treated in accordance with the Association for Research in Vision and Ophthalmology (ARVO) Statement for the Use of Animals in Ophthalmic and Vision Research.

REFERENCES


Education

ANSWERS

From questions on page 1073

1. Discuss the imaging findings

This is stratus OCT of the right macula (fig 1A) showing separation of the sensory retina from the retinal pigment epithelium (RPE). Foveal height measured 833 μm. On subsequent visits, serial OCT images demonstrate a progressive decrease in foveal height. At 1-month follow-up, the OCT shows complete resolution of subretinal fluid with restoration of the normal foveal architecture (fig 1B–D).

The FFA in fig 2A–D shows normal segmental filling of the choriocapillaries in the early frames. There are no signs of focal leakage seen in the late phases, thereby excluding CSR, Harada syndrome, choroidal neovascularisation and APMPPE.

2. What is your diagnosis?

The FFA excluded central serous retinopathy, Harada syndrome, choroidal neovascularisation and APMPPE. We therefore made a diagnosis of unilateral acute idiopathic maculopathy (UAIM).

3. How would you manage this patient?

We decided on a conservative approach to his management and observed him on a weekly basis. There was a considerable improvement in his visual acuity on each visit with reduction in the subretinal fluid, which was confirmed with serial OCT scans. After 4 weeks, the visual acuity in the right eye had improved to 6/6, with restoration of the normal foveal anatomy on OCT scanning.

DISCUSSION

UAIM presents as an acute onset of unilateral visual loss following symptoms simulating the common cold.1 It was first described as a syndrome by Yannuzzi et al in 1991. Patients develop a characteristic exudative macular detachment that resolves spontaneously with near-complete recovery of vision.2 In some patients, tiny haemorrhages have also been noted at the macula.

A possible relationship between UAIM and APMPPE has been suggested due to the overlap of many common features including the rapid onset and resolution of symptoms and the following of a prodromal flu-like illness.1 We also considered a possibility of central serous retinopathy and Harada syndrome in this young man. FFA did not show any signs of focal leakage and was essentially normal, which excluded all these conditions.

In the acute phase, Stratus OCT showed an exudative process causing separation of the sensory retina from the RPE. In our patient, a significant amount of subretinal fluid was seen on OCT compared with a previously reported atypical case where a lack of subretinal fluid was noted. Our clinical and diagnostic findings are more consistent with previously reported cases of UAIM.1,2 As suggested by Aggio et al,4 we also confirm that Stratus OCT is an important tool in the diagnosis of UAIM. It is essential to perform OCT at presentation and at each follow-up visit. In our case, OCT showed a dramatic resolution of fluid within 2 weeks with total restoration of the normal foveal anatomy within a month, stressing the benefit of an OCT scan at presentation and at subsequent visits to closely monitor the disease course.

UAIM has been misdiagnosed in the past, and cases have been reported where interventions such as photodynamic therapy,3 systemic corticosteroids2 and intravitreal triamcinolone have been prescribed. The recommended approach to the management of UAIM is conservative, and the disease is known to resolve almost always spontaneously.

The occurrence of UAIM has been noted with pregnancy and human immunodeficiency virus.2 Coxsackie virus has also been suggested as a cause,3 but aetiology still remains unclear. In our patient, we were unable to determine any specific cause.

After a 3-month follow-up, the foveal reflex returned to normal, which is unlike the natural history of UAIM where it leaves behind a characteristic bull’s eye appearance in the macula.1 UAIM may also be renamed as AIM, as there are cases that have been reported to be bilateral,7 cautioning us to not be misled by the title.


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