Postoperative proliferative vitreoretinopathy development is linked to vitreal CXCL5 concentrations

Souska Zandi1,2*, Isabel B. Pfister1 & Justus G. Garweg1,2

The specific changes linked to de novo development of postoperative PVR have remained elusive and were the object of the underlying study. Vitreous fluid (VF) was obtained at the beginning of vitrectomy from 65 eyes that underwent vitrectomy for primary rhegmatogenous retinal detachment (RRD) without preoperative PVR. Eyes developing postoperative PVR within 6 months after re-attachment surgery were compared to those which did not regarding the preoperative concentrations of 43 cytokines and chemokines in the VF, using multiplex beads analysis. For all comparisons Holm’s correction was applied in order to control for multiple comparisons. Twelve out of 65 eyes (18.5%) developed PVR postoperatively. While 12 of the chemokines and cytokines presented concentration differences on a statistical level of \( p < 0.05 \) (CXCL5, CCL11, CCL24, CCL26, GM-CSF, IFN-γ, CCL8, CCL7, MIF, MIG/CXCL9, CCL19, and CCL25), CXCL5 was the only cytokine with sufficiently robust difference in its VF concentrations to achieve significance in eyes developing postoperative PVR compared to eyes without PVR. CXCL5 may represent a potent biomarker for the de novo development of postoperative PVR. In line with its pathophysiological role in the development of PVR, it might serve as a basis for the development of urgently needed preventive options.

Proliferative vitreoretinopathy (PVR) may develop as a complication of primary rhegmatogenous retinal detachment (primary RRD) in 10% or more of eyes and is a major cause of poor functional outcomes after primarily successful retinal detachment (RD) surgery1,2. The number and size of retinal tears are correlated with the risk of its development. This is linked to an increase of cell-signaling mediators, which are most likely released from the damaged tissue and involved in the regulation of inflammatory processes, breakdown of the blood-retinal barrier, wound healing, and scar formation3–6. Dedifferentiated retinal pigment-epithelial (RPE) cells contribute to the formation of contractile PVR membranes, which form in response to these cell-signaling mediators3,7,8. Clinically, increased levels of a variety of cytokines, chemokines and growth factors have been reported in the vitreous of eyes with RD9–15. Our group revealed differences in vitreal cytokine concentrations between early and advanced primary PVR and reported that CCL19 may represent a biomarker for PVR progression16. Vitreal cytokine levels in eyes developing postoperative PVR after uncomplicated RD repair in the absence of primary PVR, however, have not yet been addressed. Therefore, this study aimed to investigate the cytokine concentrations in the vitreous fluid (VF) of eyes without preoperative but postoperatively developing PVR after vitrectomy for primary RRD and to compare them to those from eyes without the development of PVR.

Patients and methods

Patients. The investigation was designed as a retrospective study involving a consecutive series of eyes undergoing pars plana vitrectomy and gas filling for the treatment of primary RRD. Eyes with any sign of preoperative PVR were excluded. All surgeries were performed by the same surgeon at the Berner Augenklinik am Lindenhospitale, Bern, Switzerland. Patients with any systemic or ocular comorbidities that may potentially influence ocular cytokine levels were excluded (i.e., patients with diabetes mellitus; known rheumatic and autoimmune diseases; systemic treatments involving corticosteroids or immunomodulatory drugs; vitreous hemorrhaging, uveitis, glaucoma, or any concomitant retinal pathology; or who had undergone any intraocular

1Swiss Eye Institute and Clinic for Vitreoretinal Diseases, Berner Augenklinik am Lindenhospitale, Bern, Switzerland. 2Department of Ophthalmology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland. *email: souskasophie.zandi@insel.ch
treatment or surgery within 6 months of the RD diagnosis). If both eyes were affected, only the first operated eye was included.

The study was approved by the Ethics Committee of the University of Bern (KEK no. 152/08) and is fully compliant with the tenets of the Declaration of Helsinki in its latest version. Each participant provided informed written consent to the use of their biological materials and clinical data.

Patient groups. A total of 65 patients were assigned to group 1 (no pre- or postoperative PVR; n = 53) and group 2 (postoperative PVR, n = 12) regarding whether or not they postoperatively developed PVR within 6 months after the first surgery for primary RRD. Part of the samples from group 1 were already included in a previous publication with a different study question16.

Handling of vitreous fluid samples. Approximately 500 µl of undiluted native VF was collected at the beginning of pars plana vitrectomy. After harvesting, VF was immediately stored at – 20 °C and moved to – 80 °C within 2 months, where it remained until the final analysis, which was performed on all samples simultaneously.

Cytokine analyses. The samples were analyzed using a multiplex beads system (Bio-Plex 100 Array Reader with Bio-Plex Manager software version 6.1; Bio-Rad, Hercules, CA, USA). With this highly sensitive technique, multiple analytes can be detected in parallel using a single small volume sample. We quantified the concentrations of 43 cytokines in each vitreous sample as previously published16. All analytic procedures were performed following the manufacturer’s instructions. In short, magnetic microspheres, tagged with a fluorescent label, were coupled to specific capture antibodies and mixed with samples containing unknown cytokine quantities before introducing biotinylated detection antibodies and Streptavidin R-Phycoerythrin. The mixture was then analyzed by flow cytometry. The two lasers of the instrument identify the microsphere type and quantify the amount of bound target. On each test plate, a duplicate concentration standard was run in parallel for each cytokine. The measurements were performed in a blinded manner by a laboratory technician who was experienced in the execution of this technique.

Statistical analyses. According to the standard curve, the lower limit of quantitation (LLOQ) of the assay working range was set by the manufacturer to about 1 pg/ml (http://www.biorad.com). The concentrations of several cytokines ranged below the curve fit of these standards (out of range). To avoid a bias that would have been introduced by excluding these values, they were set at half of the lowest quantified level for the particular cytokine in question17.

The Shapiro–Wilks test was applied to check for the distribution pattern and revealed that data were not normally distributed. The non-parametric Mann–Whitney U test and the Kruskal–Wallis H test were thus employed for the inter-group comparisons. A p value of < 0.05 was considered to be significant. Since multiple comparisons increase the risk of introducing a type I error, we applied the sequentially rejective modification of Bonferroni correction, the Holm correction, to control for type I error, without introducing additional type II error18,19. The Holm correction progressively adapts the threshold for rejecting the null hypotheses. As a first step, all p values are sorted in order of smallest to largest, and k is the number of hypotheses. In a second step, the lowest p value is compared to a/k. If the p value is lower, the null hypothesis is rejected and the result is significant. The same procedure is applied at the remaining k–1 hypotheses, where the threshold of significance is set at a/(k–1). This procedure is repeated sequentially for each p value, until the selected p value is not smaller compared to the sequential threshold. All statistical analyses were performed using R (package FSA, software version 3.4.0).

Results
Sixty-five eyes of 65 consecutive patients admitted to our clinic for primary RRD met the inclusion criteria. Thereof, 34 eyes (52.3%) were phakic. Since we had demonstrated that the lens status does not influence the cytokine profiles in the VF, phakic and pseudophakic eyes were pooled20. The mean age of the patients was 61.3 ± 13.4 years and 38.5% were female.

Postoperative PVR developed in 18.5% of cases: 53 patients did not develop secondary PVR after vitrectomy (group 1), and 12 patients developed PVR within 6 months of primary vitrectomy (group 2). The corresponding PVR stage was CP, type: focal in ten eyes, and only two eyes presented a PVR stage of CA, type circumferential21.

Mean age was similar (group 1: 60.7 ± 14.1 years; group 2: 64.2 ± 9.7, p = 0.46), and no difference was observed regarding gender and lens status between the groups (gender: group 1: 34% females; group 2: 58.3% females, p = 0.19; lens status: group 1 47.2% pseudophakic; group 2 50% pseudophakic, p = 1.0). Both groups were also preoperatively comparable regarding the number of retinal breaks (group 1: 1.6 ± 1.1; group 2: 1.9 ± 1.2, p = 0.30) and the extension of RD (group 1: 4.2 ± 1.9; group 2: 4.8 ± 2.8, p = 0.42). As outlined in Table 1, the extent of the retinal detachment (≥ 6 clock hours or > 6 clock hours), the amount of retinal breaks (≤ 3 retinal breaks or > 3 retinal breaks) and whether the macula was detached (Mac on) or not (Mac off), did not differ in both groups. The concentrations for each of the 43 cytokines in both groups are displayed in Table 2. At a statistical level of p < 0.05, an upregulation of 12 cytokines was found in group 2 (CXCCL5, CCL11, CCL24, CCL26, GM-CSF, IFN-γ, CCL8, CCL7, MIF, MIG/CXCL9, CCL19, and CCL25). After application of the Holm correction (p < 0.00116), the concentration of only one cytokine in the VF, CXCCL5, remained significantly higher in eyes that postoperatively developed PVR (group 2; Table 2, Fig. 1).

When screening the vitreal cytokines of the 10 smallest versus the 10 largest retinal detachments in both groups (n = 65) no significant difference could be observed after Holms correction was applied, indicating that the extent of the retinal detachment is not the key driver for postoperative PVR development (Table 3).
Once PVR has established, the drastic changes to the vitreal environment reduce the relative signal strength of we think is specific to the development of PVR, and, as outlined above, well in line with its biological function.

Without postoperative PVR development has been confirmed independently, this pathway might be used to control this pathway of eyes with active PVR. Interestingly, Schnyder-Candrian et al. found that interferon gamma reduces CXCL5 in human monocyte cultures. Limb et al. demonstrated that interferon gamma is upregulated in eyes with PVR. This well explains why CXCL5 is not increased once PVR has been established.

In line with the findings of our paper, Abu-El Asrar et al. did not find an upregulation of CXCL5 in the VF of eyes with active PVR. Interestingly, Schnyder-Candrian et al. found that interferon gamma reduces CXCL5 in human monocyte cultures. Limb et al. demonstrated that interferon gamma is upregulated in eyes with PVR. This well explains why CXCL5 is not increased once PVR has been established.

The concentrations of almost all tested chemokines and cytokines were elevated in the vitreous of both primary RRD groups, irrespective of the presence or severity of PVR, may indicate the dimension of the tissue trauma associated with RD. While this does not provide specific clues as to the pathophysiology of PVR induction, it is in agreement with previous studies. The direct comparison of the vitreal cytokinome in eyes without postoperative PVR and those newly developing PVR, in contrast, yielded a signal with CXCL5, which we think is specific to the development of PVR, and, as outlined above, well in line with its biological function.

Once PVR has established, the drastic changes to the vitreal environment reduce the relative signal strength of this biomarker compared to several other environmental tissue responses. Once the association of CXCL5 and host defense and chronic disease progression are predominantly expressed on neutrophils and is activated in response to various triggers including tumor necrosis factor alpha. CXCL5 is released from endothelial cells and various inflammatory cells, such as monocytes, and it is involved in recruitment and activation of additional cellular mediators of inflammation, such as macrophages and neutrophils. CXCL5 can bind to CXCR1 and CXCR2 receptors that are predominantly expressed on neutrophils and is activated in response to various triggers including tumor necrosis factor alpha.

In line with the findings of our paper, Abu-El Asrar et al. did not find an upregulation of CXCL5 in the VF of eyes with active PVR. Interestingly, Schnyder-Candrian et al. found that interferon gamma reduces CXCL5 in human monocyte cultures. Limb et al. demonstrated that interferon gamma is upregulated in eyes with PVR. This well explains why CXCL5 is not increased once PVR has been established.

Our finding of CXCL5 as a key regulator in the development of PVR is pathophysiologically well supported by the fact that CXCL5 is implicated in connective tissue remodeling and inflammation. Yet, this chemokine also seems to play a role in various acute and chronic, noninfectious inflammatory processes and is involved in host defense and chronic disease progression. CXCL5 is released from endothelial cells and various inflammatory cells, such as monocytes, and it is involved in recruitment and activation of additional cellular mediators of inflammation, such as macrophages and neutrophils. CXCL5 can bind to CXCR1 and CXCR2 receptors that are predominantly expressed on neutrophils and is activated in response to various triggers including tumor necrosis factor alpha.

The cytokinome comparison of eyes postoperatively developing PVR to those without postoperative PVR revealed no predominant role for the other nine previously identified cytokines (CCL26, CCL1, IL-6, CXCL11, CCL7, CCL13, MIG/CXCL9, CCL19 and TGF-β1). Contrary to our previous publication, where we compared chemo- and cytokines in patients with and without PVR at primary re-attachment surgery, in the current study we focused only on eyes without any detectable PVR and compared those that developed PVR in the 6 months following RD to those, who did not. While our first study demonstrated the presence of active PVR to be linked to elevated CCL19 concentrations in the vitreous, the underlying study confirms that vitreal CCL19 is upregulated along with eight other cytokinome studies.

In the current study, we identified vitreal CXCL5 as the most abundant and thus predictive marker for the de novo development of developing postoperatively PVR. When comparing the cytokine profiles in primary RRD with the ones that underwent vitrectomy for MH and/or ERM, more than 30 abundant chemokines/cytokines in the VF were identified, whereas a ≥ tenfold increase in the concentrations was found for 10 cytokines, including CXCL5. After exclusion of any evident PVR before vitrectomy, the cytokinome comparison of eyes postoperatively developing PVR to those without postoperative PVR showed no predominant role for the other nine previously identified cytokines (CCL26, CCL1, IL-6, CXCL11, CCL7, CCL13, MIG/CXCL9, CCL19 and TGF-β1).

Our finding of CXCL5 as a key regulator in the development of PVR is pathophysiologically well supported by the fact that CXCL5 is implicated in connective tissue remodeling and inflammation. Yet, this chemokine also seems to play a role in various acute and chronic, noninfectious inflammatory processes and is involved in host defense and chronic disease progression. CXCL5 is released from endothelial cells and various inflammatory cells, such as monocytes, and it is involved in recruitment and activation of additional cellular mediators of inflammation, such as macrophages and neutrophils. CXCL5 can bind to CXCR1 and CXCR2 receptors that are predominantly expressed on neutrophils and is activated in response to various triggers including tumor necrosis factor alpha.

In line with the findings of our paper, Abu-El Asrar et al. did not find an upregulation of CXCL5 in the VF of eyes with active PVR. Interestingly, Schnyder-Candrian et al. found that interferon gamma reduces CXCL5 in human monocyte cultures. Limb et al. demonstrated that interferon gamma is upregulated in eyes with PVR. This well explains why CXCL5 is not increased once PVR has been established.

Efforts to reduce the risk of PVR include reduction of surgical trauma, early surgery, pharmaceutical adjuncts, and lower thresholds to use silicone oil or retinotomies, as well as improvements in surgical technique. The identification of a preoperatively present marker of PVR advocates that vitrectomy per se is not a driver of PVR.

The concentrations of almost all tested chemokines and cytokines were elevated in the vitreous of both primary RRD groups, irrespective of the presence or severity of PVR, may indicate the dimension of the tissue trauma associated with RD. While this does not provide specific clues as to the pathophysiology of PVR induction, it is in agreement with previous studies. The direct comparison of the vitreal cytokinome in eyes without postoperative PVR and those newly developing PVR, in contrast, yielded a signal with CXCL5, which we think is specific to the development of PVR, and, as outlined above, well in line with its biological function.

Once PVR has established, the drastic changes to the vitreal environment reduce the relative signal strength of this biomarker compared to several other environmental tissue responses. Once the association of CXCL5 and postoperative PVR development has been confirmed independently, this pathway might be used to control this

|                  | ≤ 3 breaks | > 3 breaks | Chi² test |
|------------------|------------|------------|----------|
| Group 1 n(%)     | 49 (92.5%) | 4 (7.5%)   | p = 1.0  |
| Group 2 n(%)     | 11 (91.7%) | 1 (8.3%)   |          |
| RD ≤ 6 clock hours | 48 (90.6%) | 5 (9.4%)   | p = 0.16 |
| Group 1 n(%)     | 9 (75%)    | 3 (25%)    |          |
| RD > 6 clock hours | 18 (34%)   | 35 (66%)   | p = 0.10 |
| Group 2 n(%)     | 4 (33.3%)  | 8 (66.6%)  |          |

Table 1. Clinical characteristics of RD in group 1 and 2.
Table 2. Mean concentrations (pg/ml) and standard deviations (SDs), as well as medians and interquartile ranges (IQRs) of cytokines in the vitreous of RRD eyes without PVR and without PVR development after surgical intervention (group 1) and eyes with PVR development after surgery (group 2). p Values which remain significant after Holm correction are marked in bold.

| Cytokine | group 1 (n = 53) no postoperative PVR | group 2 (n = 12) postoperative PVR | Mann–Whitney U test (p values) |
|----------|----------------------------------------|------------------------------------|--------------------------------|
|          | Mean ± SD (pg/ml) | Median (IQR) | Mean ± SD (pg/ml) | Median (IQR) |
| CCL21    | 17.19 ± 3.921.4 | 62.8 (400.6–1192.4) | 1678.2 ± 1807.6 | 836.4 (629.0–2454.6) | 0.16 |
| CXCL13   | 1.5 ± 2.7 | 0.9 (0.7–1.4) | 1.6 ± 1.0 | 1.2 (0.9–2.4) | 0.21 |
| CCL27    | 3.6 ± 9.4 | 0.6 (0.5–5.5) | 2.9 ± 3.3 | 1.1 (0–6.4) | 0.53 |
| CCL5     | 123.8 ± 147.4 | 85.7 (81.1–151.1) | 273.7 ± 186.2 | 243.2 (114.3–429.6) | 0.0012 |
| CCL11    | 10.2 ± 12.7 | 5.7 (3.9–10.2) | 17.3 ± 13.2 | 12.8 (7.2–26.6) | 0.015 |
| CCL24    | 18.4 ± 22.4 | 12.8 (8.2–19.3) | 22.0 ± 9.4 | 23.1 (11.9–29.3) | 0.02 |
| CCL26    | 6.7 ± 9.7 | 4.3 (2.7–4.3) | 13.0 ± 12.3 | 6.9 (4.7–21.0) | 0.014 |
| CX3CL1   | 55.7 ± 65.7 | 35.0 (18.7–60.9) | 89.0 ± 80.8 | 53.8 (28.4–168.1) | 0.14 |

...
trigger for the development and progression of PVR. In the absence of supportive results, at the current stage, CXCL5 might be understood as a diagnostic marker for the risk of developing postoperative PVR. However, the cellular source responsible for inducing the increased cytokine concentrations remains to be identified, and their role in the complex pathophysiological process of wound healing in RD has as yet to be determined. RPE and Müller glial cells might be expressing more CXCL5 when injured and when starting the wound healing process, and first attempts to modify the inflammatory environment have already been undertaken. Patients with a higher inflammatory response to RD may be at a higher risk of developing PVR. However, steroids are well capable of controlling inflammation, but after many attempts have not conclusively shown to affect the development of PVR.

The main strength of this study is its well-designed selection process with sufficiently large numbers in each group. This allowed us to apply the Holm correction in order to identify the most relevant cytokines amongst the many screened cyto- and chemokines. This is namely important, since the role of cyto- and chemokines in the pathophysiology of PVR has as yet to be established. Replacing the Holm correction by the more conservative Bonferroni correction revealed almost identical results. While the data are consistent, precise, and reliable, the storage conditions must be regarded as a possible weakness of this study. Samples were not immediately stored at −80 °C due to the distance of our operation room to the lab. Principally, a partial degradation of thermosensitive chemokines and cytokines might have taken place, so that the absolute cytokine concentrations have to be carefully weighed, whereas such cannot explain any of the intergroup differences in their concentrations as all samples were treated the same way. Moreover, the cytokine concentrations in the VF reported here and in our previous studies are well in line with published concentrations in the ocular fluids from independent groups.

In conclusion, we assessed 43 chemokines and cytokines in retinal detachment without active PVR that later developed PVR and those, which did not, and found increased concentrations in 12 of them. Only one of these, CXCL5, was sufficiently abundant to be unequivocally linked to the de novo development of postoperative PVR as compared to eyes without postoperative PVR.

**Figure 1.** Comparison of vitreal cytokine levels of patients who developed secondary PVR and those who did not on a logarithmic scale. Significant differences of \( p < 0.05 \) are marked with °, and significant results after the Holm correction are marked with *. 
Table 3. Comparison of the vitreal cytokine concentrations between the 10 patients with the smallest vs. biggest extent of retinal detachment (RD). After Holm correction, none of the p values remain significant.

| Cytokine | 10 Patients with smallest extent of RD | 10 Patients with biggest extent of RD | p Value Mann-Whitney U test |
|----------|----------------------------------------|----------------------------------------|-----------------------------|
|          | Mean | SD   | Mean | SD   |                                |                            |
| CCL21    | 915.0 | 362.5 | 1893.1 | 2347.6 | 0.85                          |                            |
| CCL13    | 3.2   | 5.7   | 1.5   | 9.0   | 0.97                          |                            |
| CCL27    | 3.5   | 4.8   | 1.8   | 2.5   | 0.68                          |                            |
| CCL5     | 78.2  | 78.6  | 148.1 | 98.0  | 0.11                          |                            |
| CCL11    | 7.5   | 5.0   | 16.1  | 14.0  | 0.19                          |                            |
| CCL24    | 22.4  | 33.2  | 19.0  | 10.6  | 0.32                          |                            |
| CCL26    | 3.5   | 2.8   | 9.2   | 7.6   | 0.08                          |                            |
| CXCL1    | 36.3  | 13.5  | 83.5  | 81.3  | 0.44                          |                            |
| CXCL6    | 0.9   | 1.2   | 3.7   | 4.0   | 0.06                          |                            |
| GM-CSF   | 41.8  | 17.7  | 55.9  | 15.4  | 0.14                          |                            |
| CXCL1    | 39.6  | 17.7  | 82.9  | 90.8  | 0.19                          |                            |
| CXCL2    | 4.4   | 5.8   | 36.8  | 43.0  | 0.06                          |                            |
| CCL1     | 10.4  | 5.5   | 52.5  | 59.2  | 0.052                         |                            |
| IFN-γ    | 5.0   | 6.0   | 15.8  | 14.3  | 0.029                         |                            |
| IL-1β    | 1.1   | 1.0   | 2.2   | 3.8   | 0.91                          |                            |
| IL-2     | 0.9   | 0.8   | 1.8   | 1.8   | 0.28                          |                            |
| IL-4     | 1.8   | 3.8   | 4.1   | 7.1   | 0.44                          |                            |
| IL-6     | 50.9  | 106.1 | 4688.0| 14450.7| 0.32                          |                            |
| IL-8/CXCL8 | 24.0 | 21.3  | 55.8  | 86.1  | 0.63                          |                            |
| IL-10    | 5.3   | 2.5   | 8.6   | 4.5   | 0.17                          |                            |
| IL-16    | 50.8  | 42.2  | 72.6  | 57.8  | 0.63                          |                            |
| CXCL10   | 96.5  | 56.5  | 125.2 | 146.8 | 0.80                          |                            |
| CXCL11   | 1.8   | 1.3   | 5.3   | 6.0   | 0.48                          |                            |
| CCL2     | 959.3 | 608.6 | 2152.5| 1865.9| 0.08                          |                            |
| CCL8     | 5.6   | 3.9   | 8.4   | 8.4   | 0.85                          |                            |
| CCL7     | 7.3   | 7.1   | 34.4  | 24.6  | 0.01                          |                            |
| CCL13    | 1.1   | 0.9   | 2.9   | 2.2   | 0.06                          |                            |
| CCL22    | 13.9  | 7.5   | 10.3  | 8.7   | 0.32                          |                            |
| MIF      | 90084.6| 91024.1| 155658.7| 100572.4| 0.08                          |                            |
| MIG/ CXCL9 | 23.8 | 26.3  | 44.5  | 45.3  | 0.22                          |                            |
| CCL3     | 2.2   | 2.2   | 3.1   | 2.0   | 0.14                          |                            |
| CCL15    | 634.3 | 365.7 | 662.2 | 364.6 | 0.80                          |                            |
| CCL20    | 6.5   | 4.5   | 14.4  | 27.8  | 0.97                          |                            |
| CCL19    | 16.6  | 15.2  | 45.2  | 52.5  | 0.19                          |                            |
| CCL23    | 16.8  | 18.2  | 17.2  | 13.8  | 0.68                          |                            |
| CXCL16   | 774.1 | 199.2 | 853.6 | 365.1 | 0.91                          |                            |
| CXCL12   | 134.2 | 58.7  | 156.1 | 124.2 | 0.74                          |                            |
| CCL17    | 0.4   | 0.1   | 5.5   | 7.9   | 0.22                          |                            |
| CCL25    | 243.6 | 238.4 | 647.3 | 609.0 | 0.08                          |                            |
| TNF-α    | 7.1   | 2.4   | 12.7  | 8.1   | 0.22                          |                            |
| TGF-β1   | 110.3 | 115.2 | 111.3 | 257.0 | 0.25                          |                            |
| TGF-β2   | 1648.8| 868.9 | 1084.9| 769.0 | 0.11                          |                            |
| TGF-β3   | 4.5   | 5.1   | 19.6  | 42.9  | 0.97                          |                            |

Data availability
Data are available here: https://augenklinik-bern.ch/research/Cytokine_Data_Zandi_et_al_2021.xls.

Received: 8 July 2021; Accepted: 30 November 2021
Published online: 14 December 2021
39. Chaudhary, R. et al. Inflammatory and fibrogenic factors in proliferative vitreoretinopathy development. *Transl. Vis. Sci. Technol.* 9(3), 23. https://doi.org/10.1167/tvst.9.3.23 (2020).
40. Dardik, R. et al. The small tellurium-based compound SAS suppresses inflammation in human retinal pigment epithelium. *Mol. Vis.* 22, 548–562 (2016).
41. Koerner, F., Koerner-Stiefbold, U. & Garweg, J. G. Systemic corticosteroids reduce the risk of cellophane membranes after retinal detachment surgery: A prospective randomized placebo-controlled double-blind clinical trial. *Graefes Arch. Clin. Exp. Ophthalmol.* 250(7), 981–987. https://doi.org/10.1007/s00417-011-1919-y (2012).
42. Banerjee, P. J. et al. Slow-release dexamethasone in proliferative vitreoretinopathy: A prospective. *Random. Control. Clin. Trial Ophthalmol.* 124(6), 757–767. https://doi.org/10.1016/j.ophtha.2017.01.021 (2017).
43. Bonfiglio, V. et al. Preoperative, intraoperative and postoperative corticosteroid use as an adjunctive treatment for rhegmatogenous retinal detachment. *J. Clin. Med.* 9(5), 1556. https://doi.org/10.3390/jcm9051556 (2020).
44. Zandi, S. et al. Vitreal cytokine profile differences between eyes with epiretinal membranes or macular holes. *Invest. Ophthalmol. Vis. Sci.* 57(14), 6320–6326. https://doi.org/10.1167/iovs.16-20657 (2016).
45. Garweg, J. G., Zandi, S., Pfister, I. B., Skowronska, M. & Gerhardt, C. Comparison of cytokine profiles in the aqueous humor of eyes with pseudoexfoliation syndrome and glaucoma. *PLoS ONE* 12(8), e0182571. https://doi.org/10.1371/journal.pone.0182571 (2017).
46. Garweg, J. G., Zandi, S., Gerhardt, C. & Pfister, I. B. Isoforms of TGF-β in the aqueous humor of patients with pseudoexfoliation syndrome and a possible association with the long-term stability of the capsular bag after cataract surgery. *Graefes Arch. Clin. Exp. Ophthalmol. Albrecht Von Graefes Arch. Klin Exp. Ophthalmol.* 255(9), 1763–1769. https://doi.org/10.1007/s00417-017-3724-8 (2017).

**Acknowledgements**
Editorial assistance, in the form of language editing and correction, was provided by Proof-Reading-Service.com.

**Author contributions**
S.Z. collected and interpreted the data and was a major contributor in writing the manuscript. I.P. supported the data collection, was responsible for the data analysis and supported in drafting the manuscript. J.G. was responsible for the conception and design of the study, contributed to the data collection, interpretation and drafting of the manuscript.

**Funding**
Supported in part by a Grant from the Scientific Funds of the Lindenhof Foundation. SZ none, IP none, JGG none. JGG acts as an advisor to several pharmaceutical companies (AbbVie, Alcon, Allergan, Bayer, and Novartis) and contributes to several clinical studies. Nevertheless, none of the authors received direct support for this study or have conflicting interests with the data that are presented in this report.

**Competing interests**
The authors declare no competing interests.

**Additional information**
**Correspondence** and requests for materials should be addressed to S.Z.

**Reprints and permissions information** is available at [www.nature.com/reprints](http://www.nature.com/reprints).

**Publisher’s note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit [http://creativecommons.org/licenses/by/4.0/](http://creativecommons.org/licenses/by/4.0/).

© The Author(s) 2021