Effect of Multiple Intravitreal Injections of Ranibizumab on Corneal Endothelial Cells

DOAA H.M. CHEWAI, MB B.Ch.*; ABDELRAHMAN G. SALMAN, M.D.*; AZZA M.A. SAID, M.D.*; MARWA A. ELFOULY, M.D.** and DOAA M.M. ASHOUR, MD.*

The Department of Ophthalmology, Faculty of Medicine, Ain Shams University* and Research Institute of Ophthalmology**

Abstract

Background: One of the leading causes of legal blindness in adults of working age globally is diabetic retinopathy (DR). One of the main causes of central vision impairment in people with DR is diabetic macular edema (DME). Longer duration of diabetes and higher levels of haemoglobin (HbAlc) that has been glycosylated are linked to a higher risk of developing DME.

Aim of Study: To examine corneal endothelial cells using specular microscopy to determine the impact of repeated intravitreal ranibizumab injections in diabetic patients.

Patients and Methods: This interventional prospective study was conducted on 20 eyes of 20 patients with diabetic macular edema from February 2021 to November 2022 on 20 eyes of 20 recruited from the Ophthalmology department, Ain Shams university hospital and Research institute of ophthalmology. All the study participants were investigated using specular microscopy before intravitreal ranibizumab injections and one month after three IV ranibizumab injections.

Results: According to the current study, there was no significant correlation between (sex, eye side, type of treatment and duration of diabetes) with endothelial cell density either before injection and after ranibizumab injection. Using logistic regression, after adjustment to other variables, it was shown that age was the significant independent factor affecting endothelial cell count (cell density). Cases with higher age have lower CD.

Conclusion: Intravitreal injection of ranibizumab on the corneal endothelium is a safe treatment during a short follow-up period.

Key Words: Multiple intravitreal injections — Ranibizumab — Corneal endothelial cells.

Introduction

DIABETES mellitus (DM) affects almost 400 million people throughout the world; it is considered a global epidemic disease. By 2040, that number is predicted to rise to 640 million [1].

Diabetic retinopathy (DR) involves microaneurysms or worse lesions affecting at least a single eye. It is one of the most pervasive secondary microvascular complication intrinsic in diabetes mellitus (DM), induced by leakage from breakdown of the inner blood-retinal barrier and microvascular occlusion [2].

Diabetic macular edema (DME) is a sight threatening disease causes blindness for people in working age. The pathogenesis is multifactorial and complex. Diabetic macular edema (DME) pharmacotherapy addresses both the inhibition of vascular endothelial growth factor (VEGF) by the intravitreal injection of VEGF inhibitors and inflammatory processes by the intravitreal application of steroids [3].

DME can develop at any stage of DR as a result of chronic hyperglycemia; it is marked by vascular hyperpermeability and fluid buildup at the macular area as a result of the blood-retinal barrier being breached [4], and vascular endothelial growth factor (VEGF) plays a crucial role in the pathogenesis of DME [5].

Anti-VEGF medications have been observed to block VEGF signal by binding to VEGF receptors, hence preventing the creation of aberrant blood vessels and reducing vascular permeability [6].

The corneal epithelium, stroma, and endothelium all contain VEGF and its receptors, so anti-VEGF therapies may have an impact on the cor-
as it has been demonstrated that patients with DM have lower endothelial cell density (ECD) than non-diabetic controls [8]. Therefore, intravitreal injections may further strain the already compromised endothelial cells of DME patients.

In light of the above, the purpose of this study was to evaluate the impact of the intravitreal anti-VEGF injections, ranibizumab, on corneal endothelial cells using specular microscopy.

**Aim of the work:**

The aim of this work is to evaluate the effect of repeated intravitreal ranibizumab injections on corneal endothelial cells using specular microscopy in diabetic patients.

**Patients and Methods**

This study was carried out from February 2021 to November 2022 on 20 eyes of 20 patients attending outpatient clinic, Ophthalmology department, Ain Shams University Hospital and Research Institute of Ophthalmology. The ethical standards stated by the Ethical Committee of Ain Shams Hospital were followed. Informed written consent was obtained from all participating patients after explanation of the study purpose and procedures.

**Inclusion criteria:** Male and female patients aged 40-80 years old with type 2 DM. Clinically significant macular edema, diagnosed clinically and confirmed with OCT with a bestcorrected visual acuity (VA) of 20/30 or worse.

**Exclusion criteria:** Ocular disease that could alter the corneal endothelium morphology, such as Fuchs’ corneal dystrophy or iridocorneal endothelial syndrome. Intraocular surgery within a 6-month period before and after ranibizumab injection. Laser treatment within a 2-month period before and 6-month period after the injection. Anti-VEGF antibody injection within a 6-month period before the injection. Endothelial cell count of <1,500/mm² before the initial ranibizumab injection. Patients experienced systemic or ocular complications after IVI including intraocular inflammation, endophthalmitis, or thromboembolic events. Patients with history of glaucoma or elevated intraocular pressure (TOP) during follow-up. If paracentesis was performed before or after anti-VEGF injection, the case was excluded. History of trauma or ophthalmic surgery. Coexisting retinal or neuro-ophthalmologic diseases. Patients with systemic diseases other than controlled hypertension or DM. Patients with history of contact lens use.

**Methods:**

**Methodology:** This was a prospective interventional study performed on patients presented to the clinic with DME indicated for intravitreal ranibizumab injections.

**Intervention:**

All included patients were subjected to the following:

**Pre-operative assessment:**

**Detailed history taking including:** Demographic data. Medical history and comorbidities (hypertension, hyperlipidaemia) of all participants were recorded. Detailed ocular history (Prior ocular surgeries, laser treatment, ocular surgery or other eye diseases or medications).

**Clinical examination:** Full systemic clinical examination. Standard ophthalmologic assessment including: Best corrected Snellen visual acuity. Intraocular pressure measurement using Goldman applanation tonometer. Slit-lamp examination. Binocular indirect ophthalmoscopy fundus examination. To confirm the diagnosis of DME, spectral domain optical coherence tomography (SDOCT; RTVue XR OCT Avanti; Optovue, Fremont, USA) was conducted. Before the initial injection, endothelial cell examination was done using specular microscopy.

A specular microscope CEM-530 (NIDEK, Gamagori, Japan) was used to quantify corneal endothelial cell density (ECD) in a small area (0.25 x 0.55 mm) while performing noncontact specular microscopy of the central cornea.

The specular microscope automatically calculated the ECD, average cell size (AVG), standard deviation of cell size (SD), coefficient of variation of cell size (CoV), maximum cell size (MAX), minimum cell size (MIN), and percentage of the hexagonal cells (Hex%). The central corneal thickness was assessed and optical pachymetry measures were also provided by specular microscopy. (Fig. 1).

**Operative procedure:**

Treatment with intravitreal ranibizumab 0.5mg (0.05mL of 10mg/mL solution). All patients plan to leading dose three injection.

**Technique of injection:**

Conjunctival anesthesia was 0.4% topically induced by instillation of Benoxinate eye drops. The eyelids and ocular surface were disinfected with iodine.

In an operating room, 0.5mg (0.5mg/0.05mL solution) of ranibizumab was given into the inferotemporal quadrant via the pars plana and into the vitreous cavity 3.5 to 4mm from the limbus using a 30-gauge needle.

The post-injection vision was assessed. A topical 0.5% levofloxacin eye drops was instilled four times daily for 3 days before and after each intravitreal injection.
Postoperative evaluation and follow-up: Endothelial cell analysis was repeated after one month of the last intravitreal ranibizumab injection.

IOP measurement: The IOP in the cases before injection ranged from 13 to 22mmHg, with a mean of 17.85±2.13mmHg. The IOP in the study cases after injection ranged from 12 to 22mmHg, with a mean of 17.40±2.33mmHg

Statistical methods:
Analysis of the collected data was done using the Statistical Package for Social Science (IBM Corp., 2017 release). Paired t-test was used to assess the statistical significance of the difference between two means measured twice for the same study group. The type of data obtained for each parameter was given, and an appropriate analysis was carried out. p-value: Level of significance; p<0.05: Significance (S), p>0.05: Non significant (NS), p<0.001: Highly significant (HS).

Outcome:
Primary outcome: To compare between corneal endothelial cells parameters before and after three intravitreal ranibizumab injections/monthly injection.

Secondary outcome: Complications of IVE on corneal endothelium: Change in BCVA and Change in CME.

Results
A- Demographic data:
I- Age:
The mean age of the study group was 56.55±9.62 years, ranging from 42.0 years to 76.0 years.

II- Sex:
The study included 14 females (70%) and 6 males (30%).

III- Duration of DM:
The mean duration of DM 17.60±5.56 years, ranging from 10.0 to 30.0 years.

IV- Treatment modalities of DM:
Twenty eyes participated in the study, of which thirteen were treated with insulin at a rate of sixty-five percent, and seven cases were treated with OHG at a rate of thirty-five percent.

V- Eye injected:
Twenty eyes participated in the study, thirteen patients were injected in OS while seven of them were injected in OD, the rate of the OS was sixty-five percent and the rate of the OD was thirty-five percent.

B- Specular microscopy data:
I- Mean endothelial cell density before and after injection:
There was no statistically significant difference between males and females (p=0.630), insulin and
OHG treated patients (p=0.495), OD and OS eye (p=0.652), as regard endothelial cell density before injection and there was no statistically significant difference between males and females (p=0.669), insulin and OHG treated patients (p=0.275), OD and OS eye (p=43.402), as regard endothelial cell density after injection (Table 1).

II- Correlation endothelial cell density between the results of specular microscopy with the demographic data before and after injection:

There was no statistically significant Correlation between each of age, diseases duration and Cell count before and after injection (Table 2).

III- Regression to endothelial cell density before injection:

Using logistic regression, after adjustment to other variables, it was shown that Age was the significant independent factor affecting endothelial cell count (cell density). Cases with higher age have lower CD (regression coefficient=-18.19, CI=-34.9 to -1.47, p<0.05) (Table 3).

IV- Comparison between Specular microscopy data before and after injection:

There was no statistically significant difference between before and after injection endothelial cell count (ECD), AVG CV, MAX, MIN, HEX. However, There was a statistically significant difference between CT before and after injection (p=0.027) (Table 4).

V- Regression to endothelial cell density after injection:

Using logistic regression, after adjustment to other variables, it was shown that Endothelial cell count before injection was the significant independent factor affecting endothelial cell count (cell density) after injection (regression coefficient=0.704, CI=0.229 to 1.17, p<0.05) (Table 5).

Table (1): Relation between personal characteristics, endothelial cell density before and after injection.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Treatment</th>
<th>Eye side</th>
<th>ECD before injection (ECD)</th>
<th>ECD after injection (ECD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean ±SD</td>
<td>r</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td>2552.50 ± 311.00</td>
<td>-.359</td>
</tr>
<tr>
<td></td>
<td>Insulin</td>
<td>OHG</td>
<td>2622.50 ± 240.17</td>
<td>.0630</td>
</tr>
<tr>
<td></td>
<td>OD</td>
<td>OS</td>
<td>2532.57 ± 413.70</td>
<td>.652</td>
</tr>
</tbody>
</table>

*Student t-test.

Table (2): Correlations between each of age, diseases duration and endothelial cell density before and after injection.

<table>
<thead>
<tr>
<th>Age</th>
<th>Duration of diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECD before injection</td>
<td>r</td>
</tr>
<tr>
<td>-.359</td>
<td>.120</td>
</tr>
<tr>
<td>-.183</td>
<td>.441</td>
</tr>
</tbody>
</table>

*Pearson Correlation.

Table (3): Multivariate logistic regression to study independent factors affecting endothelial cell density before injection.

<table>
<thead>
<tr>
<th>Regression Coefficients (B)</th>
<th>P</th>
<th>Sig.</th>
<th>%95.0 Confidence Interval for B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-18.191</td>
<td>0.035</td>
<td>S</td>
</tr>
<tr>
<td>Sex</td>
<td>-118.317</td>
<td>0.381</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of diabetic</td>
<td>26.55</td>
<td>0.063</td>
<td>NS</td>
</tr>
<tr>
<td>Medication</td>
<td>-51.037</td>
<td>0.711</td>
<td>NS</td>
</tr>
</tbody>
</table>
Table (4): Comparison between before and after injection specular microscopy parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>±SD</th>
<th>p</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelial cell count before injection</td>
<td>2573.50</td>
<td>287.13</td>
<td>0.706</td>
<td>NS</td>
</tr>
<tr>
<td>Endothelial cell count after injection</td>
<td>2593.40</td>
<td>280.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVG before injection</td>
<td>393.80</td>
<td>49.80</td>
<td>0.761</td>
<td>NS</td>
</tr>
<tr>
<td>AVG after injection</td>
<td>390.45</td>
<td>47.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD before injection</td>
<td>133.10</td>
<td>107.54</td>
<td>0.582</td>
<td>NS</td>
</tr>
<tr>
<td>SD after injection</td>
<td>119.25</td>
<td>36.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV before injection</td>
<td>34.10</td>
<td>17.42</td>
<td>0.592</td>
<td>NS</td>
</tr>
<tr>
<td>CV after injection</td>
<td>31.90</td>
<td>6.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAX before injection</td>
<td>1285.20</td>
<td>732.29</td>
<td>0.158</td>
<td>NS</td>
</tr>
<tr>
<td>MAX after injection</td>
<td>1035.55</td>
<td>222.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIN before injection</td>
<td>137.00</td>
<td>15.59</td>
<td>0.748</td>
<td>NS</td>
</tr>
<tr>
<td>MIN after injection</td>
<td>138.60</td>
<td>13.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEX before injection</td>
<td>68.00</td>
<td>6.42</td>
<td>0.102</td>
<td>NS</td>
</tr>
<tr>
<td>HEX after injection</td>
<td>64.40</td>
<td>7.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT before injection</td>
<td>538.40</td>
<td>43.50</td>
<td>0.027*</td>
<td>S</td>
</tr>
<tr>
<td>CT after injection</td>
<td>528.85</td>
<td>37.08</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Paired t-test.

Table (5): Multivariate logistic regression to study independent factors affecting endothelial cell density after injection.

<table>
<thead>
<tr>
<th>Regression Coefficients (B)</th>
<th>P</th>
<th>Sig.</th>
<th>%95.0 Confidence Interval for B</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>4.96</td>
<td>0.536</td>
<td>NS</td>
<td>-11.849</td>
<td>21.788</td>
</tr>
<tr>
<td>Sex</td>
<td>112.59</td>
<td>0.346</td>
<td>NS</td>
<td>-135.066</td>
<td>360.260</td>
</tr>
<tr>
<td>Duration of diabetic</td>
<td>-1.438</td>
<td>0.912</td>
<td>NS</td>
<td>-28.872</td>
<td>25.996</td>
</tr>
<tr>
<td>Medication</td>
<td>-109.62</td>
<td>0.363</td>
<td>NS</td>
<td>-359.744</td>
<td>140.500</td>
</tr>
<tr>
<td>Endothelial cell density</td>
<td>0.704</td>
<td>0.007</td>
<td>HS</td>
<td>0.229</td>
<td>1.179</td>
</tr>
</tbody>
</table>

Discussion

Therapeutic intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents represent a novel therapy in ophthalmology. Ranibizumab is a (Fab) fragment of a humanized monoclonal anti VEGF-A antibody, also against all VEGF-A isoforms [91].

The aim of this work was to evaluate the effect of repeated intravitreal ranibizumab injections on corneal endothelial cells using specular microscopy.

This interventional prospective study included 20 eyes of 20 DME patients. The mean age of this study patients was 56.5 years, 70% of them were females.

All the study participants were investigated using specular microscopy before IV ranibizumab injections and one month after three IV ranibizumab injections.

Among the present study patients endothelial cell count (ECD) before injection was 2573.5±287.13 cells/mm² and after injection was 2593.4±280.14 cells/mm², the difference was statistically insignificant.

Joshi et al. [10] found no difference in endothelial cell density, central corneal thickness, coefficient of variation, or intraocular pressure before and after a single intravitreal injection over a month of follow-up.

In agreement with the current study, Guzel et al. [11] reported that in patients with DME there was no significant difference between endothelial cell count before and after 3rd intravitreal ranibizumab injection; 2198.9±253.4 cells/mm² and 2231.6±259.8 cells/mm², respectively.

Perez-Rico et al. [12] investigated the effect of intravitreal injection of ranibizumab on the corneal endothelium in patients with choroidal neovascu-
larization in age-related macular degeneration. The results were supporting to this study, where there non-significant difference between Endothelial cell count before and after 3rd intravitreal ranibizumab injection.

Also, Bentez-Herreros et al. [13] used corneal specular microscopy to undertake a morphometric examination of corneal endothelium following 0.5 mg intravitreal ranibizumab injection in AMD patients. There was no significant difference in corneal endothelial cell density at 6 months in their investigation.

Conversely, Urban et al. [14] found that among age-related macular degeneration (AMD) patients the mean ECD before intravitreal ranibizumab injection was 2397.14±459.33 cells/mm², and it was significantly lower after each intravitreal ranibizumab injection. The difference from the current study may be attributed to the mean age difference (72.36 years versus 56.5 years in their study and current study, respectively).

The average corneal cell size (AVG), maximum of cell size (MAX) and also, minimum of cell size (MIN) before and after injection were 393.8pm±49.80 SD and 390.4pm±47.98 SD, respectively. With standard deviation of cell size (SD) before injection 133.1pm±107.54 SD and after injection 119.25pm±36.46 SD. The differences were statistically non-significant. The percentage of hexagonal cell (HEX) before injection was 68.00pm±6.42 SD and after it became 64.40pm±7.04 SD, with insignificant difference.

Perez-Rico et al. [15] conducted a prospective observational case series research on the influence of intravitreal ranibizumab on corneal endothelium in individuals with age-related macular degeneration to support the current study. The study found no significant differences in endothelial cell count, coefficient of variation, % of hexagonal cells, or central corneal thickness after a 6-month follow-up.

On the other hand, Urban et al. [14] looked into changes in the proportion of hexagonal cells (% Hex) in AMD patients receiving injections of ranibizumab. After each intravitreal ranibizumab injection and six months after the initial injection, the percentage of hexagonal cells started to fall. These variations were statistically significant.

The results were different from this study, this can be explained by the different baseline hexagonal cells, where in Urban et al. [14] it was lower (53.7±8.6%) than the present study.

Corneal thickness (CT) before injection in this study was 538.40pm±43.50 SD, and after injection was 528.85pm±37.08 SD. The Corneal thickness (CT) difference after injection was significantly thinner. Although this is a statistically significant result, however, such minor changes (10pm) this difference could be related to the machine reproducibility rather than actual thinning.

In contrast to this result, some studies show no significant difference in the central corneal thickness (CCT) before and after the injection, Urban et al. [14], Perez-Rico et al. [15], Bentez-Herreros et al. [13], Bentez-Herreros et al. [14] and Chiang et al. [16] reported no statistically significant difference in the CCT before injection at one-, three-, and six-months after the injection.

According to the current study, there was no significant correlation between (sex, eye side, type of treatment and duration of diabetes) with endothelial cell density either before injection and after ranibizumab injection. Using logistic regression, after adjustment to other variables, it was shown that age was the significant independent factor affecting endothelial cell count (cell density). Cases with higher age have lower CD. The same was reported in Vila Gonzalez et al. [17] study.

This can be supported by the fact that ECD, CCT and the average size of corneal endothelial cells directly correlated with age [18]. Furthermore, other Egyptian study detected that mean endothelial cell density (MCD) significantly decreased with an increase in age, while mean cell area (MCA) increased with age [19].

In a population-based study age and sex were significantly correlated with ECD [20].

Conclusion:

Intravitreal injection of ranibizumab is a safe treatment during a short follow-up period.

References

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تأثر الحقن المتعدد لمادة الرانبيزوماب بالجسم الزجاجي للعين
على الخلايا المبطنة للقرنئية

الكثير من الأسباب الرئيسية للفقدان في السن المبكر في جميع أنحاء العالم.
مرض ارتفاع ضغط العين السكري سبب رئيسي لضعف مركز الإصابة بمرض السكري نوع 2، ويرتبط خطأ الإصابة
بالإحالة السكرية بpción عمليات مرض السكري وارتفاع مستويات السكر السكرية.

يقدر معدل الانتشار العالمي لمرض السكري بنحو 14% وتزيد على ما يقرب من 21 مليون فرد.

نظرًا لأن معدل ارتفاع مرش السكري يتزايد بسرعة ومن المتوقع أن يرتفع بكثير من 50% على مستوى العالم من عام 2000 إلى عام 2020، حيث يقدر أن يصل عدد حالات الإصابة بمرض السكري إلى 327 مليونًا في جميع أنحاء العالم بحلول عام 2020، وبالتالي فإن نقص ارتفاع ضغط العين السكري سيصبح مشكلة حائلاً على مستوى العالم.

على الرغم من أن السبب في ارتفاع مرش السكري لم يتم توضيحه بالكامل، فمن المعروف أن المستويات المرتفعة لعديل نمو بعذاة الأوعية الدموية في الجسم الإصابة مع زيادة نقاء الأوعية الدموية للذويين في نمط الإصابة في الجسم الإصابة باحتساب السكري في العديد من التجارب الدموية الناجحة واعداد لعلاج الإصابة في مركز الإصابة في العديد من التجارب السكريية الشائعة كبيرة مخا. أصير الحقن داخل الجسم الأوعية الدموية الالم佭ة لعديل نمو بعذاة الأوعية الدموية هو خط العلاج الأول لمرض ارتفاع مرش الإصابة الناجحة للسكري.

وبالتالي، فإن الفرط في هذه الدراسة هو تقييم تأثير حقن رانيبيزوماب داخل الجسم الزجاجي المتكرر على الخلايا الباطنية للقرنئية بإستخدام الفحص المجهري المراوي.

تضمنت هذه الدراسة 20 محلاً من المرضى الذين يعانون من ارتفاع في مركز الإصابة الناجحة من مرض السكري. كان
تزود عمر المرضى في هذه الدراسة 67.5 سنة بين 70% منهم إناث.
تم فحص جميع المشاركين في هذه الدراسة باستخدام الفحص المجهري المراوي قبل حقن رانيبيزوماب وبعد شهر واحد من ثلاث جرعة حقن رانيبيزوماب.

وجد أن عدد الخلايا الباطنية قبل الحقن 0.25 ± 0.16 خلايا / مم² وبعد الحقن كان 0.53 ± 0.37 خلايا / مم²، والفارق
ليس له فلات إحساسية.

وجد أن عدد العين الباطنية في هذه الدراسة 328.4 ± 0.5 ميكرومتر 1.7 و 0.5 ميكرومتر 1.7، على التوالي. مع القياس المجهري لحجم الخلايا قبل الحقن 104 ± 0.10 و 104 ± 0.10
المقدمة في هذه الدراسة كن النسبة النسبية والخلايا. كانت نسب الخلايا الباطنية للخلايا الباطنية قبل الحقن 63.2% ± 0.42 و 63.2% ± 0.42.

وبعدها أجريت لعدة إحساسية.

وجد أن سمك القرنئية قبل الحقن 3.78 ميكرومتر 0.5 و 0.8 ميكرومتر 0.5 و بعد الحقن 3.78 ميكرومتر 0.6. كان
الفرق بين القرنئية قبل الحقن أرق بشكل ملحوظ وكان الفارق ذو دالة إحساسية. و поэтому نحن معتبرون أن هذه النتائج ذات دالة
هذا الباطنية، إلا إذا كنت قياسية ضئيلة بنسب (0 ميكرومتر) وينتظر ذلك إلى إحساسية نكرار القراءة في حياء المجهري المراوي
ما قد يجعل سمك القرنئية أرق.

وفيما يتعلق بال∆يالة الباتنية، لم نجد ارتباطًا بين الجنس وجانب العين ونوع العلاج وعدة مرش السكري مع كنافة الخلايا الباطنية
سواء قبل الحقن أو بعد حقن رانيبيزوماب. باستخدام الإصدار الشريطي في الإصابة، وننند مع التقييمات الأخرى، تبين
أن العسر هو العامل المستلم المهم الذي يؤثر على عدد الخلايا الباطنية (كنافة الخلايا). وبالتالي كنافة الخلايا في الحالات ذات العمر
الأكبر تكون أقل.

في الختام، يعتبر الحقن داخل الجسم الزجاجي من رانيبيزوماب علاجًا طبيعًا خلال فترة متابعة قصيرة.