Comparison of intravitreal ranibizumab and aflibercept for the treatment of diabetic macular edema: a real-world study

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Abstract

Purpose To compare the visual and anatomic outcomes of intravitreal ranibizumab versus aflibercept in patients with diabetic macular edema (DME) in a real-world study.

Methods This is a single-center retrospective comparative study of treatment-naïve patients who received intravitreal ranibizumab or aflibercept administration for DME for at least 12 months on an as needed regimen following three-monthly loading doses. The primary outcomes of the study were the mean change in best-corrected visual acuity (BCVA), central macular thickness (CMT), and central macular volume (CMV). Factors to potentially affect these parameters were also analyzed.

Results A total of 100 eyes (66 patients) were included in the study. Fifty two eyes received ranibizumab and 48 eyes in aflibercept injections. At the end of follow-up, the improvement in mean BCVA was similar in both groups \( (p=0.38) \). While the decrease in mean CMT at the 4th-month visit was significantly higher in the aflibercept-treated group than in the ranibizumab-treated group \( (p=0.02) \), there was no difference between the two groups at the end of the 1-year follow-up \( (p=0.25) \). There was no significant difference between the two groups in terms of change in mean CMV during the follow-up \( (p=0.26, p=0.27 \text{ at 4 and 12 months, respectively}) \). The mean number of injections were also similar between groups \( (4.5 \pm 1 \text{ vs. } 4.6 \pm 1.1 \text{ respectively, } p=0.63) \).

Conclusion In a real-world setting, ranibizumab and aflibercept were both found to be effective in the first-line treatment of DME. Patients with DME who received fewer injections in the real-world could achieve visual and anatomical results comparable to randomized controlled trials participants.

Keywords Ranibizumab · Aflibercept · Central macular thickness · Central macular volume · Diabetic macular edema

Introduction

Diabetic macular edema (DME) is one of the leading causes of visual impairment in diabetic patients [1]. Macular edema can be observed at any stage and in any type of diabetic retinopathy (DR). Vision loss that affects the person’s quality of life due to DME, especially in working-age adults, is also a particular public health problem [2, 3]. The development of vascular endothelial growth factor (VEGF) inhibitors has revolutionized DME treatment with improvement in visual acuity (VA) and reduction of the central macular thickness (CMT) [4–9].

There are three commonly used intravitreal anti-VEGF agents: aflibercept, bevacizumab, and...
ranibizumab. Currently, only two anti-VEGF drugs are approved by health authorities for the treatment of DME. Ranibizumab (Lucentis; Genentech, South San Francisco, CA, USA, 2012) is a recombinant humanized monoclonal antibody fragment that binds to all the isoforms of human VEGF-A. A second commonly used anti-VEGF agent, aflibercept (Eylea; Regeneron, Tarrytown, NY, US, 2014), a soluble decoy receptor fusion protein that inhibits placental growth factor in addition to VEGF-B as well as all isoforms of VEGF-A. Randomized controlled trials (RCT) that lead to the approval of drugs have proven that both ranibizumab and aflibercept are efficient and safe in DME management [4–9]. However, clinical research trials determine the effects of treatments in controlled conditions for a selected group of patients with strict inclusion and exclusion criteria, intensive treatment, and visit schedules. Few studies with a large database have investigated the real-world translatability of controlled trials, showing that patients received fewer injections and had worse visual outcomes compared to participants in RCT [10, 11].

The current study aims to compare the visual and anatomical results of ranibizumab and aflibercept in real-world conditions in treatment-naïve DME patients and to investigate potential predictive factors that could affect the outcome.

Methods

Study design

This retrospective, comparative, single-center study was carried-out in accordance with the tenets of the Declaration of Helsinki. Medical records of treatment-naïve patients who underwent intravitreal ranibizumab or aflibercept injections for DME between June 2015 and January 2019 at Cukurova University Department of Ophthalmology were reviewed. Written informed consent was obtained from each participant. Institutional Review Board approval was obtained from Cukurova University Board of Clinical Research and Ethics (22 January 2021, 107/30).

Participants

The diagnosis of DME was based on fundus examination and spectral domain optic coherence tomography (SD-OCT) (Spectralis, Heidelberg Engineering, Heidelberg, Germany) imaging. Patients with a follow-up of minimum 12 months after the initial treatment were included. Patients with retinal vascular diseases other than DR, refractive errors outside −6.0 D to +4.0 D, chorioretinitis or any other fundus disease associated with morphologic and functional changes, and patients who underwent any intraocular surgery recently and during follow-up were excluded.

Study procedures

Following diagnosis, the patients were treated with 3 consecutive monthly injections of either 0.5 mg/0.05 mL ranibizumab or 2 mg/0.05 mL aflibercept. The drug choice was based on the retinal specialist’s preference. After the loading phase, patients were asked to show up for monthly visits; all follow-up appointments were scheduled one month apart. The treatment regimen was continued with as needed regimen (pro re nata, PRN). All patients were followed-up for at least 12 months. During the follow-up period, the re-treatment was considered on monthly basis if the macular edema persisted or worsened in comparison with the preceding visit. No injection was administered in the absence of the mentioned findings; thus, the next visit was scheduled a month later. During the follow-up period, intravitreal dexamethasone implant was administered in patients with persistent DME who did not show anatomical and visual improvement after 3 consecutive anti-VEGF injections.

All patients underwent OCT imaging with a SD device (Spectralis, Heidelberg Engineering, Germany). The macula was screened by taking 49 sections (512 A-scan) at 120 μm intervals within a 20° × 20° rectangular field. Central macular thickness was defined as the average thickness within the central 1000 μm diameter of the Early Treatment Diabetic Retinopathy Study (ETDRS) grid using the macular thickness map provided by the software. Central macular volume (CMV) was measured in nine subareas of the macula consisting of both fovea and 6-mm circular areas of the perifoveal zones. All OCT images were obtained by the same experienced
technician. The images were examined by two retina specialists (SS & EE) independently, being unaware of the anti-VEGF administered. In case of a discordance the images were evaluated by a third physician (ND).

Diabetic retinopathy was classified as mild, moderate, severe non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) [12]. The diagnosis of PDR was established on clinical examination and fundus fluorescein angiography was performed to confirm the diagnosis. Diabetic macular edema was classified by SD-OCT in three patterns: diffuse macular edema; cystoid macular edema (CME); and cystoid macular degeneration (CMD). This classification was based according to the report by Arf and coworkers [13]. The morphologic findings such as serous macular detachment (SMD), vitreomacular interface abnormalities (VMIA), vitreomacular traction (VMT) and presence of hard exudate (HE) were also recorded. Severe CME with the horizontal diameter of cystoid spaces ≥ 600 μm were graded as CMD [14]. If the posterior surface of the retina was elevated over a non-reflective cavity with minimal shadowing of the underlying tissues, the presence of SMD was accepted. Vitreomacular interface abnormality classifications were based on International Vitreomacular Traction Study Group [15]. Intraretinal or subretinal highly reflective spots were identified as hard exudates [16].

Available data collected from medical records included demographics, best-corrected visual acuity (BCVA), biomicroscopy/ophthalmoscopy findings, intraocular pressure (IOP), lens status types of DR, types and morphological features of DME, CMT and CMV, number of anti-VEGF/ Dexamethasone (Ozurdex, Allergan Inc., Irvine, CA, USA) injections, need of any and focal/panretinal photocoagulation (PRP) laser treatment during the study period.

Outcomes and statistics

Main outcome measures were the changes in BCVA, CMT and CMV in treatment groups at 4 and 12 months. The baseline factors affecting the change in main parameters during the follow-up were also analyzed. Best-corrected visual acuity as examined with a Snellen chart and the values were converted to ETDRS letter scores for statistical analysis, as described previously [17]. Outcomes were also analyzed in eyes stratified by baseline VA into two groups as > 69 letters (20/40) and ≤ 69 letters (20/50) to determine the relationship of initial vision on VA gain.

Categorical variables were expressed as numbers and percentages; whereas, continuous variables were summarized as mean and standard deviation. Chi-square test was used to compare categorical variables between the groups. For comparison of continuous variables between two groups, the Student’s t-test was used. To evaluate the change in the measurements obtained in the time interval (baseline, 4th month and 12th month), the Repeated Measurements Analysis was applied. Linear regression analysis was used to determine the most effective predictors of percentage changes in BCVA, CMT and CMV variables. All analyses were performed using IBM SPSS Statistics Version 20.0 statistical software package. The statistical level of significance for all tests was considered to be 0.05.

Results

The group comprised of 100 eyes of 66 patients. In total, 52 eyes were treated with ranibizumab (group I) and 48 eyes with aflibercept (group II). Baseline characteristics and demographic data are summarized in Table 1. In the 12-months period, the number of injections in group I ranged from 3 to 7 times with an average of 4.5 ± 1; for the eyes in group II, the number of aflibercept injections ranged from 3 to 9 times with an average of 4.6 ± 1.1 (p = 0.63). The mean number of dexamethasone intravitreal implants was similar in both groups during follow-up (p = 0.88).

No significant baseline difference was found between the two groups in terms of BCVA (p = 0.054), age (p = 0.47), gender (p = 0.9), lens status (p = 0.85), IOP (p = 0.63), type of DR (p = 0.93), number of eyes with completed panretinal photocoagulation laser treatment (p = 0.08) (Tables 1, 2).

For the entire group, increase in BCVA and decrease in CMT and CMV were statistically significant after the loading phase and remained significant up to the last visit. The change in BCVA, CMT and CMV in each group was consistent with the change in the whole group during the follow-up (Table 3). At the end of the follow-up period, the mean BCVA in group II improved to 56.0 ± 21.8 letters, and
59.6 ± 19.2 letters in group I; there was no significant difference between the two groups (p=0.39) (Table 4, Fig. 1).

When we grouped the patients according to their initial VA, in patients with equal to and worse than 69 letters (Snellen equivalent 20/50 or worse), the mean improvement of VA was 13.4 ± 17.7 in the ranibizumab group and 17.4 ± 15.9 in the aflibercept group at the end of one year (p=0.10). In patients with good initial VA (> 69 letter score (Snellen equivalent, 20/32 to 20/40) the VA increased by an average of 2.2 ± 7.5 letters in the ranibizumab group and decreased by 6.2 ± 10.9 letters in the aflibercept group at the end of the 12 months follow-up (p=0.08) (Table 5). The VA gain was statistically significantly higher in patients with a baseline letter score of ≤ 69 compared to patients with a baseline letter score > 69 in both treatment groups (for group I; p=0.03, group II; p<0.001). While there was a greater decrease in mean CMT at 4 months in the aflibercept-treated group (p=0.02), no difference was found in both groups at the end of follow-up (p=0.25) (Fig. 1). There was no significant difference between the two groups in terms of mean CMV at the 4th month (p=0.26) and at the end of the first year (p=0.27) (Fig. 1).

Univariate analysis revealed that the BCVA improvement was significantly correlated with focal laser treatment (p=0.04). In univariate analysis,
the decrease in CMT was significantly greater in the presence of mild and moderate NPDR ($p = 0.01$, $p = 0.04$), pseudophakic eyes ($p = 0.02$), completed panretinal photocoagulation ($p = 0.02$) and the presence of CMD and SMD ($p = 0.003$, $p = 0.01$). The greater decrease in CMV was also associated with mild and moderate NPDR ($p = 0.04$, for both), pseudophakia ($p = 0.001$), and the presence of CMD and SMD ($p = 0.013$, $p = 0.002$).

Multivariate analysis showed that young age was the only prognostic factor of better final BCVA.
Factors associated with a greater reduction in CMT in the multivariate regression analysis were the presence of mild to moderate NPDR \((p = 0.001)\), previously completed PRP therapy \((p = 0.03)\) and, the presence of SMD \((p = 0.01)\) and CMD \((p < 0.001)\). The decrease in CMV was significantly greater in the

### Table 6: Univariate regression analysis for influence of various factors on change in BCVA, CMT, and CMV

| Factor                                      | BCVA, logMAR | CMT (µm) | CMV (µm³) |
|---------------------------------------------|--------------|----------|-----------|
| Drug (Ranibizumab/aflibercept)              | –22.6 (–54.6, 9.6) 0.99 | –17.1 (–69.6, 46.2) 0.40 | –8.6 (–34.1, 18.9) 0.24 |
| Gender (Male/female)                        | –22.7 (–52.5, 12.7) | –21.9 (–78.3, 53.5) | –11.8 (–55.7, 25.1) |
| Age, year                                   | –27.5 (–12.5, 29.0) 0.43 | –15.1 (–75.8, 46.2) 0.19 | –8.3 (–55.7, 18.9) 0.25 |
| Grade of DR (mild, moderate, severe NPDR and PDR) | –19.2 (–10.3, 23.1) | –21.8 (–78.2, 53.5) | –11.4 (–45.7, 25.1) |
| Focal laser treatment                       | –28.4 (–48.7, –0.9) 0.04 | –8.2 (–19.9, 3.4) 0.16 | –13.0 (–40.4, 25.1) 0.11 |
| Panretinal laser treatment (no, simultaneously, completed) | –15.3 (–33.4, 2.8) 0.57 | –18.0 (–78.2, 27.4) 0.02 | –8.5 (–40.4, 25.1) 0.13 |
| Lens status (phakic/pseudophakic)           | –23.1 (–55.2, 7.0) 0.37 | –14.4 (–27.0, –1.7) 0.02 | –11.5 (–18.0, –4.9) 0.01 |
| Type of DME (Diffuse ME, CME, CMD)          | –41.3 (–60.9, –16.6) 0.27 | –16.8 (–16.8, –50.1) 0.003 | –9.8 (–28.1, 25.1) 0.01 |
| SMD                                         | –11.0 (–32.7, 10.7) 0.31 | –7.0 (–17.5, 3.4) 0.01 | –8.8 (–14.2, –3.4) 0.002 |
| VMIA                                        | 9.3 (–22.4, 40.8) 0.55 | 5.7 (–9.5, 21) 0.45 | 3.2 (–4.9, 11.4) 0.43 |
| Hard exudate                                | –15.1 (–35.4, 5.1) 0.14 | 2.7 (–7.2, 12.6) 0.58 | 1.4 (–3.9, 6.7) 0.59 |

### Table 7: Multivariate regression analysis to determine the predictor of change in BCVA, CMT, and CMV

| Factors                                      | BCVA, logMAR | CMT (µm) | CMV (µm³) |
|----------------------------------------------|--------------|----------|-----------|
| Drug (Ranibizumab/aflibercept)               | 9.1 (–11.8, 30.1) 0.38 | 3.1 (–6.2, 12.7) 0.49 | 1.0 (–3.7, 5.7) 0.67 |
| Age, year                                    | 1.3 (0.2, 2.3) 0.01 | 0.4 (0.3, 0.9) 0.03 | 0.1 (–0.06, 0.4) 0.14 |
| Grade of DR (mild, moderate NPDR)            | – – – – | –5.4 (–16.0, 5.1) 0.39 | –5.4 (–11.5, 0.68) 0.81 |
| Focal laser treatment                        | –17.3 (–42.4, 7.6) 0.17 | –6.3 (–12.3, 1.3) | –4.1 (–9.3, 1.0) |
| Lens status (phakic/pseudophakic)            | – – – – | –2.1 (–15.3, 10.9) 0.74 | –4.7 (–11.3, 1.8) 0.15 |
| Presence of CMD                              | – – – – | –37.1 (–54.4, –19.8) <0.001 | –18.2 (–27.0, –9.4) <0.001 |
| Presence of SMD                              | – – – – | –12.3 (–22.6, –1.9) 0.02 | –10.7 (–16.0, –5.4) <0.001 |

BCVA, best-corrected visual acuity; NPDR, non-proliferative diabetic retinopathy; DME, diabetic macular edema; CME, cystoid macular edema; CMD, cystoid macular degeneration; SMD, serous macular detachment; CMT, central macular thickness; CMV, central macular volume.
presence of SMD and CMD ($p < 0.001$ for both). The results are summarized in Tables 6 and 7. During the follow-up period, the mean IOP was similar in both groups ($p = 0.74$, $p = 0.54$). No complications except minor subconjunctival hemorrhage, which resolved spontaneously without a potential effect on the outcome, was detected in any patient.

Discussion

In the present study, no significant difference was found in BCVA, CMT, and CMV between aflibercept and ranibizumab groups at the end of the 1-year follow-up. The 12-month VA improvements in this real-world analysis were 8 and 10.9 letters for eyes treated with ranibizumab and aflibercept, respectively. Treatment-naïve patients received an average of 4.5 injections at 1 year, with no significant difference between the two groups (4.5 vs 4.6).

Ranibizumab and aflibercept therapies administered with the PRN regimen were identified as a new standard of DME treatment following the conclusion of randomized controlled RESTORE and DA-VINCI trials [5, 18]. There were similar numbers of injections at 12 months in the RESTORE (ranibizumab, 7 or ranibizumab plus laser, 6.8) and DA-VINCI (aflibercept, 7.2) trials with a mean letter gain, were 6 and 12 letters, respectively. The DRCR.net Protocol T was the first RCT with predominantly treatment-naïve patients that compared the efficacy and safety of ranibizumab (0.3 mg) and aflibercept (2.0 mg) in the treatment of DME [7]. In the study, there was no loading doses, and the treatment was given monthly as needed from the start. At 1 year, the mean number of injections were 9 in the aflibercept group and 10 in the ranibizumab group. Wells and coworkers reported that from baseline to 1 year, the improvement of BCVA was greater with aflibercept than with bevacizumab or ranibizumab (13.3 vs. 9.7 and 11.2 ETDRS letters, respectively) [7]. However, they did not find this result clinically significant because the difference was driven by the eyes with a low baseline BCVA. In current study, while the number of injections was almost half as expected in both groups, the number of letters gained at the end of 1 year was comparable to aforementioned RCT results.

When we performed a comparison between patients in both groups according to baseline BCVA, the initial VA letter score was ≤ 69, the mean improvement from baseline was 13.4 with ranibizumab, 17.4 with aflibercept ($p = 0.10$). When the initial vision loss was mild (VA; > 69 letter score) the improvement was 2.2 with ranibizumab, −6.2 with aflibercept ($p = 0.08$). Our results indicated that patients with worse baseline VA tend to gain higher letters than those with better baseline VA. The more limited potential of patients with higher baseline VA to gain vision (and conversely the greater potential to lose vision) has been termed ‘ceiling effect’ [11, 19, 20]. Other possible factors for vision loss or less visual gain in patients with better baseline VA could be more advanced systemic disease or progression in cataract, as this real-world analysis did not grade the severity of cataract or systemic disease during the follow-up.

In a real-world experience, in cases enrolled from a large database with treatment-naïve patients, the injection rates were 7.7 with ranibizumab, 7.5 with aflibercept, 7.9 with bevacizumab, and they found a similar increase in BCVA at 12-months follow-up (5.5, 4.4 and 5.5 letters, respectively) [11]. When they stratified by baseline VA, the final mean changes in number of letters gained was again similar across each group. The lower letter gain with the higher number of injections in previously untreated patients may be due to the higher mean baseline VA of the study cohort compared to our study (baseline mean VA 57.9 vs 51.6, 45.1).

Recently the treat-and-extend regimen (TAE) has become popular as it decreases treatment burden and number of visits. Shwarzer and coworkers evaluated real-life outcomes of a TAE regimen without a fixed loading dose using ranibizumab or aflibercept in treatment-naïve DME patients in a 12-month follow-up [21]. They reported injection rates of 10.1 with ranibizumab and 9.9 with aflibercept and found a similar increase in BCVA (5.3 vs 6.8 letters, respectively). In a 2-year study comparing the efficacy of aflibercept and ranibizumab with the TAE regimen after initial loading doses, the mean number of injections at the end of the first year was 6.5 and 7, respectively, and the improvement in VA was found similar in both groups (0.15 vs 0.25 logMAR gain) [22]. While the lower number of injections and patient visits seemed to be an advantage of the TAE regimen, our results showed that similar or even slightly better visual improvement could be
achieved with loading doses followed by the PRN regimen with fewer injections at 1-year follow-up.

In current study, both anti-VEGF injections did cause a significant thinning on CMT; however, aflibercept tended to be superior in CMT reduction at 4 months, but this difference disappeared end of the first year. Plaza-Ramos et al. reported that CMT change was greater in the ranibizumab group at the 4-month visit after loading doses [23]. Similar to our results, this difference disappeared at the end of the first year. The study authors explained this by the difference in the number of naïve patients in both groups. In DRCR.net Protocol T, the effects of ranibizumab and aflibercept were also similar but superior to bevacizumab in reducing macular edema at 1 year [7]. Although we should consider the differences in cohorts among the different studies, the greater reduction in CMT after loading doses of aflibercept injection compared to ranibizumab in treatment-naïve patients of this study may be due to aflibercept’s higher affinity for VEGF and longer half-life [24, 25].

Our results indicated that both aflibercept and ranibizumab showed the same degree of CMV decrease at the end of the follow-up time. Despite the few studies evaluating CMV in DME, Plazo-Ramos and colleagues also demonstrated that administration of ranibizumab and aflibercept resulted in a similar reduction in CMV at one year follow-up [23]. The present study revealed the factor that significantly affected the final BCVA was the focal laser treatment. The READ−2, RESTORE, and REVEAL studies have demonstrated that combining focal/grid laser therapy with ranibizumab provides similar improvements in BCVA and anatomical results, despite slightly fewer injections, compared to ranibizumab monotherapy [4, 5, 26]. In this study, we did not investigate the association between the number of injections and laser treatment. However, our results may support that, consistent with previous study results, a synergistic effect, if not superior, can be achieved by combining laser with antiangiogenics [27]. In addition, in this study, focal laser therapy was applied in the presence of leaking microaneurysms around the macula on a fluorescein angiography during follow-up. We consider that the fact that focal laser was applied to more patients in the aflibercept group might be a coincidence, depending on the patient characteristics of both groups (33.3% vs. 13.5%).

When all variables were included in the analysis, younger age became the most important factor for better final VA. This can be explained by the fact that younger age is associated with shorter disease duration and lower grade of DR.

In the current study, SMD and CMD have been shown among the factors associated with a greater reduction in CMT and CMV. According to the results of the study of Shimizu and coworkers, the effectiveness of ranibizumab and aflibercept injections in reducing CMT was significantly better in eyes with SMD than in the absence of SMD at 6-month follow-up [28]. They suggested that anti-VEGF antibodies could be more effective in resolving SMD because of the accumulated VEGF in the subretinal space. Consistent with our results, this may explain the better response of SMD to treatment. Moreover, Koytak and coworkers have shown that the SMD was associated with a more reduction in CMT with a single dose of bevacizumab injection compare with the diffuse retinal thickening type [29].

CMD is more chronic form of macular edema than DME and CME, which is associated with longer symptom duration, worse BCVA, and greater central subfield thickness [13, 14]. Although CMD is associated with poor functional and morphological outcomes, we found it to be associated with better anatomical recovery after treatment. However, due to a low number of eyes with CMD, it is not possible to reach a definite conclusion about the association between the presence of CMD and response to anti-VEGF.

Moreover, our results indicated that in eyes with early stages of DM, completed (PRP) and previous cataract surgery were associated with a significant reduction in CMT and CMV. Given the higher incidence of macular edema associated with simultaneous (PRP), the correlation of previously completed panretinal laser treatment with better anatomical improvement can be explained [30]. As is known, diabetic patients have an increased risk for the development and progression of DME after cataract surgery [31]. However, we can explain the seemingly protective effect of previous cataract surgery on CMV and CMT with the difference in a sample size of pseudophakic eyes.

We believe that the strengths of our study were that only naive patients were included and that the effects of both agents could be compared more
objectively in a homogeneous patient population. There are also limitations relevant to this manuscript like the retrospective nature and the relatively small sample size. It is thought by the study authors that a larger sample size is needed to evaluate the correlation of some parameters with response to treatment. As a last but not least limitation, levels of blood glucose and HbA1c were not included in this study analysis. Due to the retrospective nature, we could not obtain all relevant data. Perhaps, a comparison of a systemic evaluation could yield a more precise comparison. On the other hand, as both groups had similar backgrounds, one could argue that the groups were more or less the similar for levels of blood glucose.

In conclusion, aflibercept and ranibizumab are effective drugs for the first-line treatment of DME with a PRN regimen. The efficacy of both anti-VEGF therapy was more pronounced in patients with worse initial VA. Additionally, although fewer injections may suggest inadequate treatment as well as cost-effectiveness of treatment, this study demonstrated that eyes with DME who received fewer injections in the real-world could achieve visual and anatomical results comparable to RCT participants.

Authors contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Puren Isik, Selcuk Sizmaz, Ebru Esen, Anıl Uysal and Nihal Demircan. The first draft of the manuscript was written by Puren Isik and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Competing interests The authors have no relevant financial or non-financial interests to disclose.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Cukurova University Board of Clinical Research and Ethics (22 January 2021, 107/30). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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