**TECHNICAL REPORT**

# The Effect of Intravitreal Ocriplasmin on Hue Discrimination

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**ABSTRACT**

**Significance.** We report 13 patients who received ocriplasmin for symptomatic vitreomacular adhesion. Farnsworth-Munsell 100 (FM 100) hue test total error score increased from baseline to month one, before recovering at year one. Ocriplasmin may alter hue discrimination.

**Purpose.** To determine whether intravitreal ocriplasmin affects hue discrimination. **Methods.** Thirteen patients with symptomatic vitreomacular adhesion received intravitreal ocriplasmin 125 µg. Patients underwent full ocular examination, optical coherence tomography and FM 100 hue test at baseline, one week, one month and one year. **Results.** Mean age was 74.8 years. The median baseline FM 100 total error score (TES) was similar in the injected and fellow eyes (272 vs 252, respectively). Median TES in the injected eye increased from 272 to 348 at one week (median difference compared to baseline +52.0, 98.8% CI of difference -64.0 to 184.0, $P = .29$), decreased to 324 at one month (median difference compared to baseline -4.0, 98.8% CI of difference -44.0 to 256.0, $P = .40$) and decreased to 268 at one year (median difference compared to baseline -108.0, 93.8% CI of difference -200.0 to 52.0, $P = .19$). Two patients (15.4%) had anatomic release of VMA, occurring within one month of injection.

**Conclusions.** Ocriplasmin may alter hue discrimination, but larger studies are required to provide sufficient power to detect or exclude a statistically significant effect. Longer follow-up is needed to determine the duration of any effect.

Ocriplasmin is a recombinant protease protein designed to treat symptomatic vitreomacular adhesion. It has marketing authorization for the treatment of vitreomacular traction, including when vitreomacular traction is associated with a macular hole of diameter of 400 μm or less.[1] It is delivered via a single intravitreal injection. A Cochrane collaboration meta-analysis of ocriplasmin, combining evidence from four randomised controlled trials, showed an improved likelihood of vitreomacular adhesion release within 28 days with ocriplasmin, compared to sham or placebo treatment (risk ratio (RR) 3.46, 95% confidence interval (CI) 2.00 to 6.00).[2-6] Furthermore, treatment with ocriplasmin was found to be more likely to result in macular hole closure (RR 2.87, 95% CI 1.50 to 5.51), and more likely to result in complete posterior vitreous detachment (RR 2.94, 95% CI 1.39 to 6.24).[2-6]

Untreated, symptomatic vitreomacular adhesion, can be associated with variable loss of visual function.[7,8] Treatment options include observation, pars plana vitrectomy, pharmacologic vitreolysis with ocriplasmin and pneumatic vitreolysis.[9-11] As well as visual acuity improvement, ocriplasmin treatment has been shown to result in better visual quality of life, when measured with standardized questionnaires.[6,12,13] There have been multiple reports of safety issues with ocriplasmin, often attributed to its non-selective targeting of fibronectin and laminin. Reassuringly, most adverse events have tended to be transient. In terms of visual function, there have been reports of reduced contrast sensitivity and sudden severe sight loss which has usually been reversible.[14,15] Subjective dyschromatopsia (abnormal color vision) has been documented following ocriplasmin, as well as retinal abnormalities such as acute neuroretinopathy, electroretinogram abnormalities and ellipsoid zone changes on optical coherence tomography, most of which occur in patients where ocriplasmin has successfully

released vitreomacular adhesion.[16-19] There have also been reports of zonular instability during subsequent cataract surgery.[20]

Patients who have described dyschromatopsia following ocriplasmin tend to find it is transient and self-limiting.[19,21] Data from the Microplasmin for Intravitreous Injection – Traction Release without Surgical Treatment trials and post-marketing surveillance studies estimated the risk of dyschromatopsia at 0.5-9.1 %, although these are potentially at risk of recall bias and underreporting.[4,19,22,23] A retrospective case series of 19 patients described subjective complaints of color abnormalities or brightness reduction in 36.8 %, all of whom had increased subretinal fluid and ellipsoid zone attenuation on optical coherence tomography, which tended to settle at 3 months post-injection.[24] The dyschromatopsia can occur rapidly after ocriplasmin, within 4 hours.[25] Dyschromatopsia is a highly subjective symptom, and objective measurement of color vision is largely lacking from the literature.

Given these concerns about color vision abnormalities we incorporated hue discrimination testing as part of the routine care pathway for patients receiving intravitreal ocriplasmin at our institution. Herein we report our findings using the Farnsworth Munsell 100 (FM 100) hue test, undertaken before and after ocriplasmin injection.

## METHODS

### Design, Setting and Eligibility

This retrospective consecutive case series included all patients who elected to receive an intravitreal injection of ocriplasmin 125 µg for the treatment of symptomatic vitreomacular

adhesion at King's College Hospital, a large London teaching hospital. The assessment of hue discrimination was performed to objectively measure and detect any change in color vision as part of routine clinical care and therefore did not require ethical review. This was formally confirmed by the local Research and Development team at King's College Hospital NHS Foundation Trust, London, who determined that this work was exempt from review by a Research Ethics Committee. The work adheres to the tenets of the Declaration of Helsinki.[26]

All patients had a diagnosis of symptomatic vitreomacular adhesion made by clinical examination and spectral domain optical coherence tomography (Spectralis, Heidelberg Engineering, Heidelberg, Germany). Patient eligibility was in accordance with technology appraisal TA297 issued by the UK's National Institute of Health and Care Excellence. This states that ocriplasmin is suitable for patients with vitreomacular traction causing either severe sight problems or a macula hole up to 400 μm, in the absence of epiretinal membrane.[27]

**Intervention**

Ocriplasmin treatment was given in accordance with its marketing authorisation via a pars plana injection at 3.5 to 4.0 mm from the limbus, using a standard 30-gauge needle aimed towards the optic nerve and inserted up to the hub.[28]

**Follow-up, Outcomes and Analysis**

Clinical examination and all tests were performed on both the injected eye and the fellow uninjected eye at baseline, one week, one month and one year after ocriplasmin injection. Each visit included assessment of best-corrected visual acuity using a standard Early

Treatment Diabetic Retinopathy visual acuity chart at 4m, color vision testing, full ocular examination including dilated fundoscopy, and optical coherence tomography. Patients used their regular method of refractive correction (e.g. spectacles). Specifically, best-corrected visual acuity assessment was performed using their distance refractive correction and FM 100 hue testing was performed using their near refractive correction.

Color vision was assessed using the FM 100 hue test according to the manufacturers' instructions under standard overhead fluorescent lighting conditions.[29,30] This consists of 85 removable colored caps each of a different hue, which subtend 1.5° at 50 cm, divided across 4 rows. The caps are pre-scrambled by the assessor, and the patient is instructed to rearrange them in a gradual orderly progression of color between two fixed caps. Once the patient is content with their arrangement, the results are analyzed by the computer program developed by the manufacturer. This generates a total error score, with a higher total error score signifying worse color discrimination.[29] The normal range of competence for color discrimination is between 16 and 100; a total error score less than 16 indicates superior color discrimination, while a total error score greater than 100 indicates poor color discrimination.[30]

While the primary outcome measure was FM 100 total error score, secondary outcomes included best-corrected visual acuity and anatomic success, defined as complete release of vitreomacular adhesion using optical coherence tomography, in the absence of macular hole. We also evaluated potential relationships between FM 100 total error score and other outcomes including best-corrected visual acuity and optical coherence tomography parameters.

Due to the small sample size and pilot nature of this retrospective analysis, non-parametric Wilcoxon matched-pairs signed ranks tests were used to compare FM 100 and visual acuity scores at various time points in both the treated eye and fellow eye. Two-tailed p-values < .05 were considered statistically significant.

**RESULTS**

Thirteen patients received an intravitreal injection of ocriplasmin 125 µg, with a mean age of 74.8 years (range: 48 to 89 years). Five patients received the ocriplasmin injection in their right eye, and eight patients received the injection in their left eye. There were no intraoperative complications. None had anatomic success at one week, but two patients (2/13, 15.4 %) had anatomic success at one month. Subsequently, 6 out of 11 patients chose to undergo pars plana vitrectomy for surgical release of vitreomacular traction, after ocriplasmin had been unsuccessful.

The median best-corrected visual acuity in the entire cohort of injected eyes decreased from 65 letters (Snellen equivalent 20/50) at baseline (n=13) to 60 letters (Snellen equivalent 20/63) at one week (median difference compared to baseline -3.0 letters, 97.5% CI of difference -10.0 to 1.0 letters, P = .11) and to 54 letters (Snellen equivalent 20/80) at one month (n=13, median difference compared to baseline -5.0 letters, 97.5% CI of difference -9.0 to 4.0, P = .24). However, median best-corrected visual acuity increased to 71 letters (Snellen equivalent 20/40) at one year (n=10, median difference compared to baseline +3.5 letters, 98.5% CI of difference -10.0 to 16.0, P = .32). In fellow eyes, median best-corrected visual acuity remained stable at 20/40 Snellen equivalent during the follow-up period - 69 letters at

baseline (n=13), 71 letters at one week (n=13), 69 letters at one month (n=13) and 71 letters at one year (n=10).

Table 1 shows the results of FM 100 hue testing on both the injected and fellow eyes. Two patients did not undergo FM 100 hue testing at week one or month one, while one-year data was only available on five patients. The median total error score at baseline was similar in the injected eye and fellow eye (272 vs 252). In injected eyes, median total error score increased from 272 at baseline (n=13) to 348 at one week (n=11) following ocriplasmin, but this did not reach significance (median difference compared to baseline +52.0, 98.8% CI of difference -64.0 to 184.0, P = .29). The median total error score at one month (n=11) decreased to 324 (median difference compared to baseline -4.0, 98.8% CI of difference -44.0 to 256.0, P = .40) and continued to decrease to 268 at one year (n=5, median difference compared to baseline -108.0, 93.8% CI of difference -200.0 to 52.0, P = .19) (Fig. 1). In fellow eyes, the median total error score was similar comparing baseline (252, n=13) to one week (264, n = 11, median difference compared to baseline -20.0, 98.8% CI of difference -100.0 to 80.0, P = .29), one month (264, n=11, median difference compared to baseline -28.0, 98.8% CI of difference -112.0 to 64.0, P = .38) and one year (224, n=5, median difference compared to baseline -50.0, 93.8% CI of difference -204.0 to 336.0; P = .81) (Fig. 2).

Cases 1 and 2 achieved successful release of vitreomacular traction by month one. In Case 1, total error score was not recorded at one week or one month, but at one year had decreased to 100 from 208 at baseline, while best-corrected visual acuity improved from 71 to 86 letters (Snellen equivalent 20/40 to 20/20). In Case 2, total error score decreased from 228 at

baseline to 164 at one week, but then increased to 300 at one month. Best-corrected visual acuity was 70 letters at baseline (Snellen equivalent 20/40), and remained relatively stable at one week (69 letters; Snellen equivalent 20/40) and one month (70 letters; Snellen equivalent 20/40) but decreased to 60 letters (Snellen equivalent 20/60) at one year.

One patient (case 9) developed new sub-retinal fluid after ocriplasmin which persisted at the 1 month visit, but had resolved by one year. In association with the optical coherence tomography changes, the total error score increased from 172 at baseline to 512 and 432 at week one and month one, respectively and the best-corrected visual acuity similarly decreased from 56 letters (Snellen equivalent 20/70) at baseline to 49 letters (Snellen equivalent 20/100) and 47 letters (Snellen equivalent 20/100) at week one and month one, respectively.

The only subjective report of color vision change was case 8, who reported a mild color vision abnormality at one year post-ocriplasmin. Paradoxically, his total error score decreased to 264, from 464 at baseline.

Of the patients that underwent vitrectomy for surgical release of vitreomacular traction, five had this intervention between one and six months after ocriplasmin injection, while one underwent vitrectomy at 13 months post-injection. Seven patients did not undergo any vitreoretinal surgery.

## DISCUSSION/CONCLUSIONS

Color vision is a highly complex neurological process that relies on various mechanisms such as healthy photoreceptors, retinal transmission and cortical processing. Differences in wavelengths of light result in different perceived hues, and in humans this gives rise to a very high number of distinguishable hues. Various tests can be performed to assess color vision, including anomaloscopes, plate tests (e.g. Ishihara) and arrangement tests (e.g. FM 100 hue test).[31] In the general ophthalmology clinic, Ishihara plate testing is a quick and easy method to screen for color vision defects, whereas FM 100 hue test is a more involved time consuming test that can more accurately assess exacting hue discrimination. Farnsworth Munsell 100 hue test also can detect color defects at early stages and quantify them in order to assess whether they fall within the normal range. Sequential FM 100 hue testing can be used to determine whether a defect is progressing or resolving.[32]

Dyschromatopsia was reported in 1.6 % (16/999) of patients during the main ocriplasmin clinical trials, and in general the vision was subjectively described as being 'yellowish'.[22] More specifically, symptoms tended to occur early (usually within 24 hours of injection), were reversible, and were related to cases in which successful vitreomacular traction release had occurred. Post-market surveillance reporting has found a wide rate of dyschromatopsia (0.5-9.1 %) and found similar onset and reversibility.[22,23]

Our study assessing hue discrimination did not find a statistically significant reduction following ocriplasmin at one year, but there was a trend for worsening color vision at both one week and one month. Fellow eyes showed relatively stable color vision. Farnsworth

Munsell 100 hue testing can identify different types of defects such as protanomaly and deuteranomaly, but our work did not identify any specific color defect.

The therapeutic target site for ocriplasmin is the vitreomacular interface, and it has been suggested that the drug may also penetrate the adjacent retina and affect structural laminins in the interphotoreceptor matrix.[33,34] An animal model has shown laminin in this region is potentially susceptible to ocriplasmin degradation.[35] Adverse events of subretinal fluid accumulation after ocriplasmin are well described, which are thought to be due to structural disruption of the retina following a powerful enzymatic response.[20,24] Sub-retinal fluid and associated photoreceptor misalignment may potentially be the cause of dyschromatopsia after ocriplasmin, particularly as this has been described as the mechanism for pseudoprotanomaly sometimes seen in central serous retinopathy.[36] One case in our study (case 9) developed sub-retinal fluid and reduced best-corrected visual acuity after ocriplasmin, which was accompanied by an increasing of the FM 100 total error score from 176 at baseline to 512 and 432 at one week and one month, respectively.

Analysis of optical coherence tomography scans at baseline, one week and one month showed some changes after ocriplasmin including new intra-retinal cysts and sub-retinal fluid. It is not possible to determine whether these structural alterations were due to ocriplasmin or the natural disease processes. In five cases, a deterioration of the macular architecture was associated with an increase in FM 100 total error score, although others had total error score variation which did not correlate with optical coherence tomography appearance. Interestingly, all but one patient reported no change in their color vision at any of the study

visits, which raises the possibility that subclinical dyschromatopsia may be more common that previously reported.

In terms of vision, the mean best-corrected visual acuity showed a trend for worsening vision following injection, but this did not reach statistical significance. Given the small numbers, this is perhaps unsurprising, although it was reassuring to see there were no cases of sudden loss of vision, as has been reported previously.[6,20] In the two patients who had successful release of vitreomacular adhesion, concurrent best-corrected visual acuity was stable, but it well known that visual quality of life measures often improve independent of best-corrected visual acuity when symptomatic vitreomacular adhesion resolves.[12] It is also important to note that 6 patients underwent vitrectomy, all at least one month following ocriplasmin, which may have influenced the one year visual acuity results. Another limitation of this study was the use of fluorescent lighting conditions for FM 100 testing which is a potential source of variability.

A limitation of our case series is the low number of cases. The trend for increasing of the FM 100 total error score may have been significant with a larger cohort, but conversely the apparent trend may be due to chance. A larger cohort may also be able to determine if any changes in color vision relate to anatomic success. Our low success rate makes this impossible to determine. Further studies of color vision appear warranted, with larger patient numbers using multiple measuring tools such as Farnsworth D15, Hardy Rand and Rittler plates, and computer-based tests of color vision. Imaging modalities such as optical coherence tomography angiography and longer follow-up would further help to identify whether ocriplasmin affects vision.

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**Table 1.** Farnsworth Munsell 100 total error score following intravitreal ocriplasmin injection in injected and fellow eyes.

| Case | Diagnosis | Injected Eye | | | | Fellow Eye | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | B/L | W1 | M1 | Y1 | B/L | W1 | M1 | Y1 |
| 1 | VMT | 208 | - | - | 100 | 244 | - | - | 92 |
| 2 | VMT | 228 | 164 | 300 | - | 200 | 196 | 264 | - |
| 3 | VMT | 128 | 192 | 104 | - | 172 | 152 | 108 | - |
| 4 | VMT | 296 | 240 | 292 | 268 | 274 | 264 | 260 | 224 |
| 5 | VMT | 656 | 740 | 1124 | - | 872 | 840 | 844 | - |
| 6 | VMT | 596 | - | - | 424 | 320 | - | - | 656 |
| 7 | MH | 284 | 336 | 272 | - | 148 | 64 | 104 | - |
| 8 | VMT | 464 | 348 | 356 | 264 | 400 | 276 | 272 | 196 |
| 9 | VMT | 176 | 512 | 432 | - | 220 | 380 | 268 | - |
| 10 | VMT | 272 | 428 | 324 | - | 616 | 516 | 504 | - |
| 11 | MH | 192 | 376 | 404 | - | 160 | 180 | 140 | - |
| 12 | MH | 168 | 156 | 164 | - | 252 | 156 | 168 | - |
| 13 | VMT | 640 | 596 | 596 | 692 | 500 | 580 | 644 | 548 |
| Median | | 272 | 348 | 324 | 268 | 252 | 264 | 264 | 224 |

B/L, baseline; M1, Month 1; MH, Macular Hole; VMT, Vitreomacular Traction; W1, Week 1; Y1, Year 1. Missing data denoted with hyphens.

## FIGURE LEGENDS

**Figure 1.** Farnsworth Munsell 100 total error score over 12 months in ocriplasmin injected eyes. Column scatter plot of Farnsworth Munsell 100 total error scores (FM 100 TES) in injected eyes, at baseline, one week, one month and one year post-injection. The median is shown as a wide band and the smaller bands represent the $75^{th}$ and $25^{th}$ quartiles.

**Figure 2.** Farnsworth Munsell 100 total error score over 12 months in fellow eyes. Column scatter plot of Farnsworth Munsell 100 total error scores (FM 100 TES) in fellow eyes, at baseline, one week, one month and one year. The figure conventions are the same as those described for Fig. 1.

Figure 1 RGB finalKAZ

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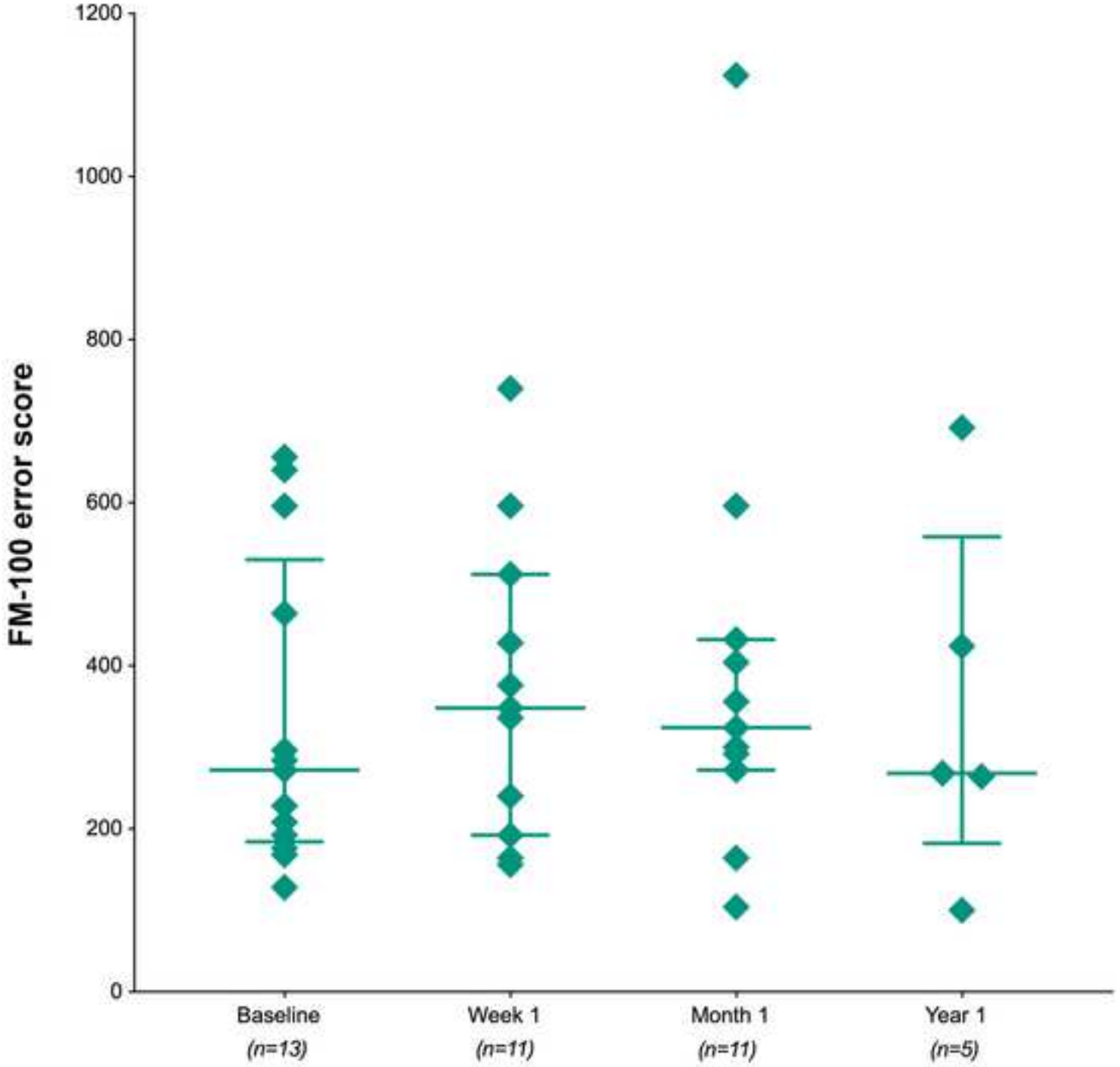

Figure 2 RGB finalKAZ

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