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# Treatment of retinal pigment epithelial detachment secondary to exudative age-related macular degeneration

Andres Gonzalez*,[1], Gibran Khurshid[1]

*Department of Ophthalmology, University of Florida, Gainesville, FL, United States*

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ABSTRACT

*Purpose:* This pilot study evaluated the combination of photodynamic therapy (PDT) and anti-vascular endothelial growth factor (anti-VEGF) as a treatment in patients with a pigment epithelial detachment (PED) due to exudative age-related degeneration (AMD).

*Methods:* We analyzed seven consecutive patients between September 1, 2015 and September 1, 2017 with a PED secondary to exudative AMD who were treated with full fluence standard PDT and a series of monthly intravitreal anti-VEGF injections. Follow-up ranged between 3 and 24 months. Variables collected for the purpose of this study included baseline best-corrected visual acuity converted to logMAR (logarithm of minimum angle of resolution), central macular thickness, and maximum PED height. This information was then reviewed at subsequent follow-ups.

*Results:* The PED completely resolved in 4/7 eyes while three patients had a significant improvement in PED size with a corresponding improvement in visual acuity. Initial PED heights ranged from 147 to 423 μm and was reduced by an average of 255.7 μm (83.2% average reduction, range −143 to - 405 μm). Initial CMT ranged from 223 to 719 μm and was reduced by an average of 225.7 μm (54.4% average reduction, range −88 to - 529 μm). Mean logMAR VA improved from 0.669 (Snellen equivalent 20/93, [20/40 to 20/200]) to 0.269 (Snellen equivalent 20/37, [20/25 to 20/80]) at last follow-up. No complications were observed in our patients.

*Conclusions and Importance:* PED in the setting of exudative AMD showed an excellent response to a combined multimodal approach that includes PDT with intravitreal anti-VEGF injection followed by a monthly anti-VEGF schedule. Most importantly, visual acuity showed a significant improvement from baseline. If confirmed by future studies, this would offer another treatment avenue for this difficult-to-treat consequence of exudative AMD.

## 1. Introduction

Pigment epithelial detachment (PED) is a condition where the retinal pigment epithelium (RPE) detaches from Bruch's membrane[1] due to the buildup of fluid or blood between these layers from leakage or hemorrhage from an occult neovascular lesion related to exudative age-related macular degeneration (AMD). PED can occur in up to 62% of eyes with exudative AMD.[2]

The treatment for PED is unpredictable and results in unsatisfactory outcomes despite multiple anti-vascular endothelial growth factor (anti-VEGF) agents available. Whereas one study[3] found a weak correlation with intravitreal aflibercept and improvement in PED height corresponding to an improvement in visual outcome, other studies with bevacizumab have shown little effect on PED size.[4,5] Previous studies that have evaluated the use of photodynamic therapy (PDT) for AMD patients with PED have reported minimal improvement in terms of visual outcomes.[6–8] The large clinical trials that used laser to treat choroidal neovascularization (CNV) associated with exudative AMD (TAP, VIP, MPS) excluded those with serous PEDs while the TAP trial did not show benefit with occult lesions which could include fibrovascular PEDs given that fibrovascular PEDs are one of the two forms of occult neovascularization as defined by the MPS trial.[9–11]

The purpose of this pilot case series is to evaluate the combination of photodynamic therapy and anti-VEGF therapy in patients with PED due to exudative AMD.

## 2. Methods

We analyzed seven consecutive patients between September 1, 2015 and September 1, 2017 with a PED secondary to exudative AMD treated

* Corresponding author. Department of Ophthalmology, University of Florida, P.O. Box 100284, Gainesville, FL 32610-0284, United States.
*E-mail address:* andres.gonzalez@ufl.edu (A. Gonzalez).
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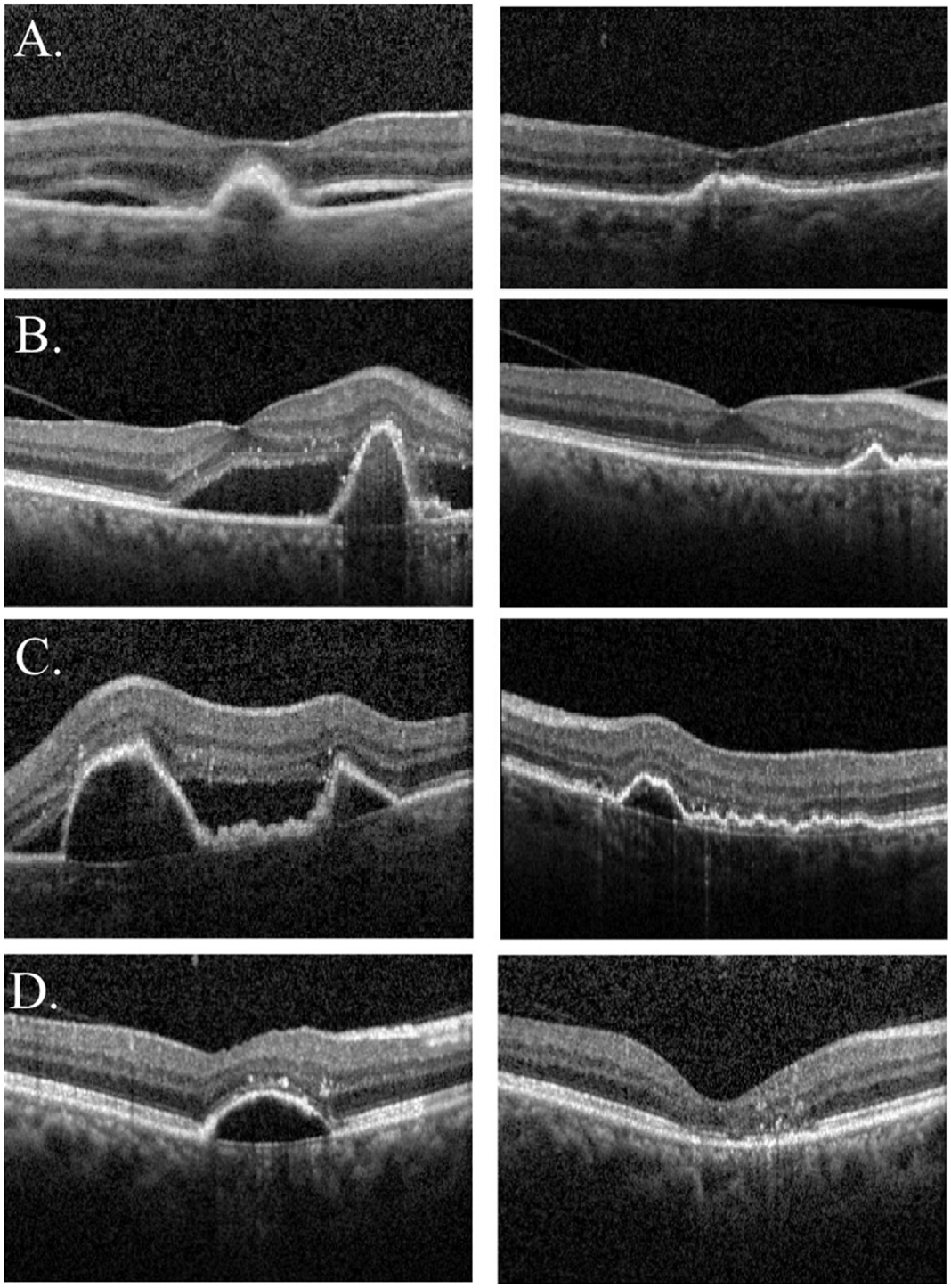


**Fig. 1.** Optical coherence tomography images of Patients 1–4 (A-D) prior to combination therapy (left) and OCT images at last follow-up (right).

with full fluence standard PDT and an anti-VEGF injection on the same day (ranibizumab, aflibercept, or bevacizumab 5 units) followed by a regular anti-VEGF schedule afterwards. The study and accumulation of data was carried out with approval from our Institutional Review Board (IRB). Informed consent for the research was obtained from the patients and is in accordance with HIPAA regulations.

All patients received full-fluence PDT with verteporfin following the standard protocol of treatment. Verteporfin (6 mg/$m^2$ body surface area) was administered via intravenous infusion of 30 ml over 10 min. Fifteen minutes after the start of the infusion, a diode laser light at 689 nm delivered 50 J/$cm^2$ at an intensity of 600 mW/$cm^2$ over 83 s using a spot size with a diameter 1000 μm larger than the greatest linear dimension (GLD) of the PED measured on OCT. Follow-up ranged between 3 and 24 months. The patient's ages ranged from 63 to 92 years (mean 74.9), 4 males and 3 females.

Variables collected included baseline best-corrected visual acuity (BCVA) converted to logMAR (logarithm of minimum angle of resolution), central macular thickness (CMT), and PED height. This information was then reviewed at subsequent follow-ups.

Optical coherence tomography (OCT) images were obtained with the Heidelberg Spectralis (Heidelberg Engineering, Carlsbad, California). Measurements were obtained using the caliper function on

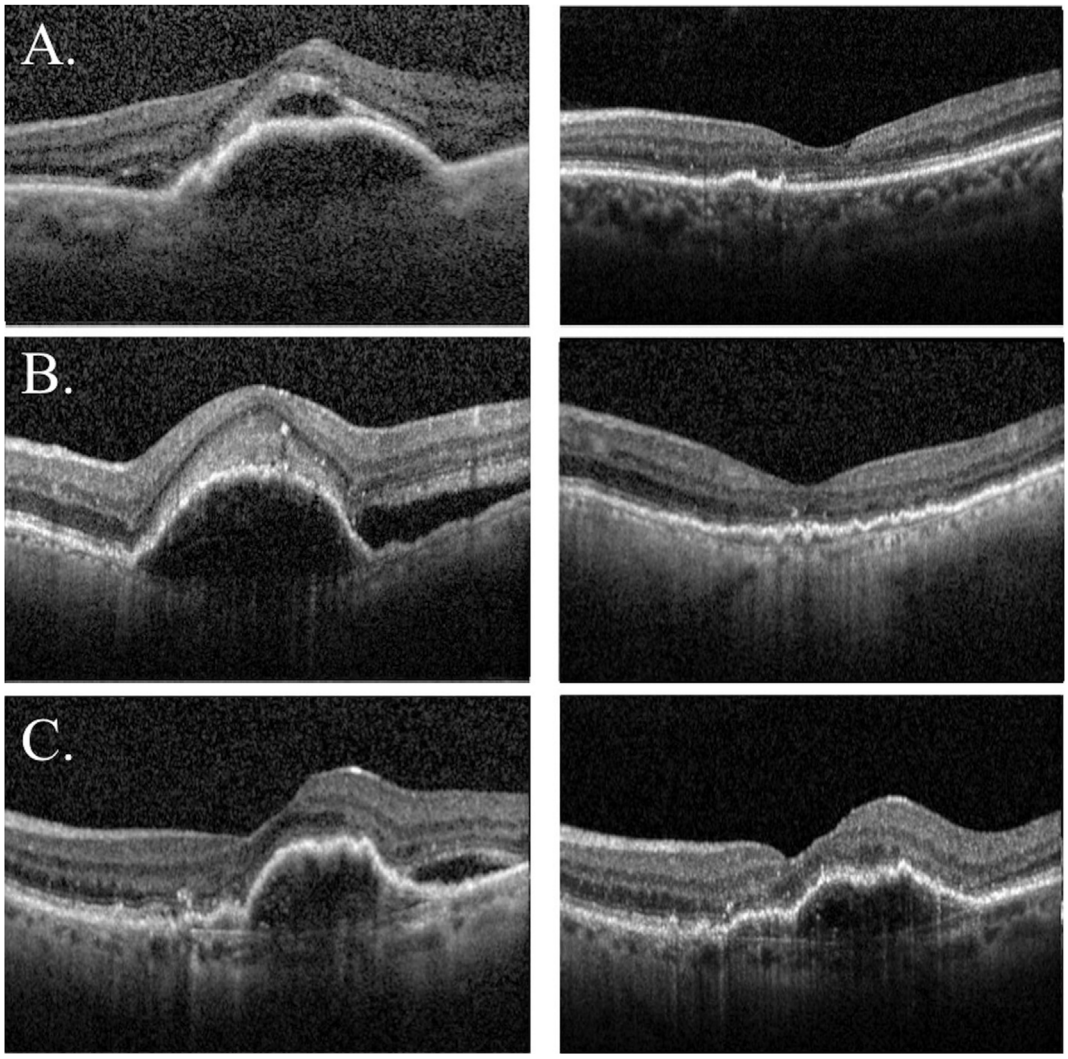


**Fig. 2.** Optical coherence tomography images of Patients 5–7 (A-C) prior to combination therapy (left) and OCT images at last follow-up (right).

Heidelburg Spectralis OCT in-built software. CMT was obtained by measuring the distance between the foveal depression (if significant IRF, the expected area of depression) and Bruch's membrane. Maximum PED height was defined as the maximum distance between Bruch membrane's internal border and RPE's external border.

## 3. Results

Follow-up ranged between 3 and 24 months. Average age ranged from 63 to 92 years (mean 74.9), 4 males and 3 females. Four patients were classified as having a fibrovascular PED, while three were classified as having a serous PED. Four patients were treatment naïve prior to combination therapy. Patient 2 had one prior bevacizumab injection without improvement while Patient 5 had four aflibercept injections and one ranibizumab injection without improvement. Patient 5 also underwent half-fluence PDT with significant improvement in PED size along with visual improvement to 20/30 from 20/200. However, the PED recurred and vision worsened to 20/100 four months later, prompting combination therapy. Patient 7 underwent many intravitreal injections prior to combination therapy.

The PED completely resolved in 4/7 eyes within 7 months of combination therapy, and decreased significantly in Patient 2 after only three months of follow-up, see Figs. 1 and 2. Patients 3 and 7 experienced a reduction in PED size and improvement in visual acuity after combination therapy. Initial PED heights ranged from 147 to 423 μm and was reduced by an average of 255.7.0 μm (83.2% average reduction, range −143 to - 405 μm). Initial CMT ranged from 223 to 719 μm and was reduced by an average of 225.7 μm (54.4% average reduction, range −88 to - 529 μm). Mean logMAR VA improved from 0.669 (Snellen equivalent 20/93, [20/40 to 20/200]) to 0.269 (Snellen equivalent 20/37, [20/25 to 20/80]) at last follow-up. No complications were observed in our patients. See Table 1.

All patients were continued on monthly anti-VEGF after combination therapy. After 11 monthly ranibizumab injections after combination therapy, Patient 1 was switched to monthly bevacizumab as a maintenance dose. Patient 2 continues on monthly bevacizumab, while Patient 3 received three aflibercept injections after combination therapy prior to switching to bevacizumab as a maintenance dose. Patients 4 and 5 continue to be on monthly aflibercept and ranibizumab, respectively. Patient 6 had a significant improvement in PED height after combination therapy, although did not improve further after 3 monthly bevacizumab injections. He was switched to aflibercept, upon which his PED completely resolved. Patient 7 is doing well with a reduced PED and is being monitored off injections after receiving 6 post-combination therapy monthly injections.

At last follow-up, OCT showed a shrunken CNVM without fluid for Patient 1, a significantly reduced PED for Patients 2 and 3, minimal subretinal fluid without PED for Patient 4, minimal intra-retinal fluid without PED for Patient 5, shrunken CNVM without fluid for Patient 6, and a significantly reduced PED in Patient 7.

**Table 1**
Patient characteristics.

| Patient | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| Age (Gender) | 92 (Male) | 78 (Female) | 63 (Female) | 65 (Male) | 69 (Male) | 77 (Male) | 80 (Female) |
| PED type | Fibrovascular | Serous | Fibrovascular | Serous | Serous | Fibrovascular | Fibrovascular |
| Prior treatment | None | IVA x 1 | None | None | IVE x 4, IVL x 1 and half-fluence PDT | None | IVA x 6, IVL x 1 |
| Anti-VEGF given with PDT | IVL | IVA | IVE | IVE | IVL | IVA | IVA |
| Pre-PDT CMT (μm) | 330 | 349 | 406 | 223 | 605 | 719 | 271 |
| Post-PDT CMT (μm) | 210 | 207 | 238 | 135 | 149 | 190 | 194 |
| Pre-PDT PED height (μm) | 147 | 364 | 423 | 163 | 405 | 363 | 285 |
| Post-PDT PED height (μm) | 0 | 83 | 135 | 0 | 0 | 0 | 142 |
| Months until PED resolution | 1 | N/A | 5 | 1 | 3 | 7 | N/A |
| Pre-Treatment Snellen VA (logMAR) | 20/80 cc (0.602) | 20/60-2 sc (0.48) | 20/200 cc(1) | 20/200 sc (1) | 20/100 sc (0.70) | 20/80 sc (0.60) | 20/40 sc (0.30) |
| 1 month Snellen VA (logMAR) | 20/40-2 cc (0.30) | 20/60 sc (0.48) | 20/100-1 sc (0.70) | 20/70 + sc (0.54) | 20/100 sc (0.70) | 20/50-2 sc (0.40) | 20/40-2 sc (0.30) |
| 3 month Snellen VA (logMAR) | 20/50-1 sc (0.40) | 20/25 sc(0.10) | 20/60 + 1 sc (0.48) | 20/70 sc (0.54) | 20/30-2 cc (0.18) | 20/50 + sc (0.40) | 20/40 + 2 sc (0.30) |
| Best VA (logMAR) | 20/50 cc (0.40) | 20/25 sc(0.10) | 20/50-1 sc (0.40) | 20/50 sc (0.40) | 20/25 + 1 cc (0.10) | 20/25 cc (0.10) | 20/30 sc (0.18) |
| Months after PDT for Best VA | 13 | 2 | 9 | 5 | 6 | 19 | 24 |
| Snellen VA at last follow-up (logMAR) | 20/50 cc (0.40) | 20/25 sc(0.10) | 20/50-1 sc (0.40) | 20/80 sc (0.60) | 20/25-2 cc (0.10) | 20/25 cc (0.10) | 20/30 sc (0.18) |
| Follow-up after PDT (months) | 13 | 3 | 10 | 15 | 9 | 19 | 24 |

*IVE: intravitreal aflibercept.
*IVL: intravitreal ranibizumab.
*IVA: intravitreal bevacizumab.
*cc: with correction.
*sc: without correction.

## 4. Discussion

PEDs associated with exudative AMD include those of the serous, fibrovascular, and hemorrhagic type. All of these PEDs can lead to significant morbidity, with one study reporting an average visual loss of more than three lines over 1 year in 50% of those with a newly diagnosed serous PED.[12] Until now, treatment of PEDs has remained challenging.

The large clinical trials that treated CNV associated with exudative AMD with laser (TAP, VIP, MPS) excluded those with serous PEDs.[9–11] The MPS trial recognized fibrovascular PEDs as one one type of occult neovascularization.[11] Using this definition, the TAP study did not show any visual benefit when assessing PDT in those with an occult CNV component (which could include fibrovascular PEDs).[10]

Direct thermal laser photocoagulation to the PED, ICG-guided photocoagulation of CNV feeder vessels, selective photocoagulation of a CNV associated with a PED have been attempted although most patients did not improve or stabilize after such treatment.[13–17] Results with photodynamic therapy have been unsatisfactory,[6–8] even when combined with triamcinolone acetonide.[18]

With the era of anti-VEGF treatments, attempts have been made to treat with intravitreal bevacizumab, ranibizumab, and aflibercept. Studies evaluating intravitreal bevacizumab have shown minimal effect on PED size.[4,5] In the RECOVER trial, 40 patients with either a serous or a fibrovascular PED were treated with monthly 0.5 mg ranibizumab. After excluding those with an RPE tear, there was an increase in mean BCVA from 56.1 ± 10.3 letters at baseline to 62.4 ± 10.2 at the 12-month follow-up mark in those with a serous PED, compared to a slight decrease in those with a fibrovascular PED.[19] Major et al. found a weak correlation between improvement in PED height and final visual outcome using 2.0 mg of intravitreal aflibercept for cases resistant to prior bevacizumab and ranibizumab.[3] Patel et al. reported on three patients who failed initial bevacizumab and/or ranibizumab and after the first injection with aflibercept, there was near-complete resolution of the PED with improved visual acuity. However, six other patients had unchanged PED size with variable effects on visual acuity.[20]

This case series assessed the efficacy of combining full-fluence PDT with anti-VEGF therapy in patients with a PED from exudative AMD. This combined treatment has been attempted in those with CNV from AMD, with promising results with respect to visual acuity[21] and reduction of treatments.[22] However, this is the first study to assess this treatment for PEDs. One of the reasons we decided to combine these two treatment regimens was that we believe an occult lesion causes the PED resistance to anti-VEGF.[23] We hypothesize that PDT may aid an exudative occult lesion to thrombose, causing an increased angiogenic drive that anti-VEGF treatment would help mitigate. Due to this angiogenic drive, we believe both treatments must be done on the same day. We are unsure of the efficacy of this therapy if anti-VEGF is provided a day or two after PDT due to the pilot nature of this study. Using this multimodal treatment approach, all patients experienced a significant improvement in vision along with complete resolution of the PED in 4/7 cases. Four patients were treatment-naïve prior to combination therapy, and at this stage it is difficult to comment conclusively on the efficacy of this therapy on treatment-naïve and treatment-resistant patients, although our observation supports the efficacy in both groups. This study was conducted as a pilot project, and we aim to conduct a randomized trial on this subject.

Potential complications of PDT include RPE atrophy, RPE rip, choroidal ischemia, and development of secondary choroidal neovascularization.[24] Half-fluence PDT continues to be favored for non-AMD conditions such as chronic central serous retinopathy.[25] The recent RADICAL study evaluated AMD patients that received either quarter-fluence PDT, half-fluence PDT in combination with ranibizumab/dexamethasone, half-fluence PDT with ranibizumab, and ranibizumab monotherapy. Visual acuities appeared similar among the groups although the confidence intervals were too wide to preclude conclusions. Half-fluence PDT required the fewest retreatments, although this was not statistically significant.[26] Patient 5 in our case series failed multiple intravitreal injections before half-fluence PDT was performed, which led to incomplete resolution of PED. He developed a recurrence 4 months later and underwent full-fluence PDT in combination with ranibizumab, which led to complete resolution of the PED.

Besides this study suggesting the benefit of full-fluence PDT, we theorized that full-fluence PDT would provide better penetration of the laser. However, more studies are needed to assess the efficacy of half-fluence PDT to decrease PDT-related complications.

Limitations of this study included a small sample size, non-randomization, retrospective nature, and a short follow-up period. Visual acuities were also not consistently obtained with/without correction with respect to each patient throughout the follow-up period. However, pretreatment and last follow-up visual acuities were obtained in the same manner, with the exception of Patient 5 (although it was noted that there was no improvement with pinhole for this patient's pretreatment visual acuity).

In conclusion, a PED in the setting of exudative AMD showed an excellent response to a combined multimodal approach that includes full fluence PDT combined with an anti-VEGF injection followed by a monthly anti-VEGF schedule. Most importantly, visual acuity showed a significant improvement from baseline. If confirmed by future studies, this would offer another treatment avenue for this difficult-to-treat consequence of exudative AMD. Perhaps larger studies are needed to evaluate the role of different anti-VEGF treatments.

## Patient consent

The study and accumulation of data was carried out with approval from our Institutional Review Board (IRB). Informed consent for the research was obtained from the patients and is in accordance with HIPAA regulations.

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### *Conflicts of interest*

The following authors have no financial disclosures: A Gonzalez, G Khurshid.

### *Authorship*

All authors attest that they meet the current ICMJE criteria for Authorship.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ajoc.2017.12.004.

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