

Mineralocorticoid Antagonists as Adjuncts in Neovascular Age-Related Macular Degeneration

Kapil G. Kapoor · Niket Todi · Alan L. Wagner

Received: October 24, 2016 / Published online: November 29, 2016
© The Author(s) 2016. This article is published with open access at Springerlink.com

ABSTRACT

Introduction: The purpose of this project was to evaluate the role of MR antagonists as an adjunct in patients with neovascular age-related macular degeneration (AMD) who have chronic subretinal fluid.

Methods: Inclusion criteria were patients with a diagnosis of neovascular AMD, who had completed at least six anti-VEGF injections, and had persistent subretinal fluid (SRF) on optical coherence tomography (OCT). Treatment with oral eplerenone was initiated and dose titrated according to protocol.

Results: 23 patients were included in the study (mean age = 54.6, 52.2% female, 47.8% male). 13 of the 23 patients had predominantly chronic subretinal fluid without large PEDs. In this subgroup, mean initial central macular thickness (CMT) prior to starting oral eplerenone was 305.3 μm , and mean injection

interval was 40.25 days. Mean final CMT after at least 3 months of adjunctive eplerenone treatment was 240.6 μm and mean injection interval with adjunctive treatment was 54.61 days. Mean extension of the injection interval after commencing oral eplerenone was 14.36 days.

Conclusions: These findings suggest oral MR antagonists may have a role as an adjunctive treatment in neovascular AMD, and may be particularly useful in dehydration of the subretinal space in the setting of chronic subretinal fluid. Further research is needed in randomized controlled trials to elucidate the precise role of oral MR antagonists in neovascular AMD.

Keywords: Central serous retinopathy; Mineralocorticoid antagonists; Neovascular AMD; Subretinal fluid; Wet AMD

Enhanced content To view enhanced content for this article go to <http://www.medengine.com/Redeem/5137F0603E01499A>.

K. G. Kapoor (✉) · N. Todi · A. L. Wagner
Wagner Macula and Retina Center, Eastern Virginia
Medical School, Virginia Beach, VA, USA
e-mail: Kaps2003@gmail.com

INTRODUCTION

Overactivation of mineralocorticoid receptor pathways in choroidal vessels have been noted in experimental models of central serous chorioretinopathy (CSCR) [1].

Mineralocorticoid antagonism through oral agents (eplerenone and spironolactone) have subsequently demonstrated success in treatment of persistent CSCR [2, 3]. CSCR can have a relapsing or persistent course that is marked by chronic subretinal fluid and can lead to significant visual morbidity [4].

Chronic subretinal fluid is also encountered in select cases of persistent neovascular age-related macular degeneration (AMD) that is refractory to anti-VEGF treatment. There are multiple treatment options that have been explored in this setting; these have demonstrated varying levels of success. Alternating one's choice of anti-VEGF treatment can lead to an improved treatment response in selected cases [5]. A subset of patients appear to have persistent subretinal fluid in the absence of persistent intraretinal fluid, and this has been described as a "secondary sick RPE syndrome" [6]. Photodynamic therapy (PDT) has been described as successful in some of these cases, even in the absence of any identification of polypoidal choroidal vasculopathy or true CSCR [6].

No satisfactory treatment modality has been described for these cases of neovascular AMD refractory to anti-VEGF treatment [7]. The purpose of this study was to evaluate the efficacy of eplerenone as an adjunctive treatment in cases of neovascular AMD with refractory subretinal fluid.

METHODS

This was a retrospective study conducted at a single center with two retinal surgeons with IRB approval. Patients were included in the study if they had a previous diagnosis of neovascular AMD, had completed at least six anti-VEGF injections (bevacizumab, ranibizumab, and/or

aflibercept), and had persistent subretinal fluid in the absence of intraretinal fluid on optical coherence tomography (OCT) imaging. All patients underwent repeat imaging with fluorescein angiography and indocyanine green angiography to rule out polypoidal choroidal vasculopathy, classic central serous retinopathy, or other pathology as causes of persistent subretinal fluid. Patients were then started on oral eplerenone 25 mg PO BID, initially maintaining their same injection interval. If subretinal fluid persisted, the medication dose was increased based on the following incremental doses: 25 mg PO TID, 50 mg PO BID, 50 mg PO TID. Dose increments were communicated with the primary care physician, and the highest dose of 50 mg PO TID was only used if explicitly approved by the patient's primary care physician. All patients were maintained on the medication for at least three months, and electrolytes were evaluated every 3 months.

If subretinal fluid resolved, the injection interval was extended. At each visit, patients had a complete eye exam, OCT with enhanced depth imaging, and an evaluation of side effects and tolerance of the medication.

Data analysis included a review of demographic data and detailed analysis of OCT images, including documentation of subretinal fluid, central macular thickness, pigment epithelial detachment height, presence of a pachychoroid, and presence of shaginess of the photoreceptor outer layer. Pachychoroid was defined as increased choroidal thickness, as would be expected for modifications of age and myopia based on SD-OCT images. Shaggy photoreceptors were defined as elongated with a slightly stippled edge, and were clearly distinct from the normal photoreceptor junction. In data analysis, patients were divided into groups with (group

A) and without (group B) moderate-large pigment epithelial detachments (PEDs), defined as greater than 350 μm in height by SD-OCT imaging. The *T* test was used to determine statistical significance.

Compliance with Ethics Guidelines

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent to be included in the study was obtained from all patients.

RESULTS

Twenty-three patients were included in the study. Mean age was 64.6 years, and 12 patients were female (52.2%), 11 were male (47.8%). 10 of the 23 patients were in group A (large PEDs), and this group did not show a significant reduction in SRF or an extension of the injection interval. 13 of the 23 patients were in group B and had predominantly chronic subretinal fluid with an absence of medium-large pigment epithelial detachments. In group B, mean initial CMT was 305.3 μm and mean final CMT was 240.6 μm ($p < 0.05$). Mean initial injection interval was 40.25 days and mean final injection interval was 54.61 days ($p < 0.05$). The mean extension of the injection interval in this group was 14.36 days.

An overall optimal response was noted in patients that had a shaggy photoreceptor outer layer, were pachychoroid for age, and had an absence of moderate-large pigment epithelial detachments. 8 of the 13 patients in group B had all these characteristics. In this subgroup, mean initial CMT was 319.4 μm and mean final CMT was 236.1 μm . The mean initial injection

interval was 39.5 days and the mean final injection interval was 60.7 days ($p < 0.05$), for a mean extension of the injection interval in this group of 21.2 days.

Two cases are presented of patients from group B. Case 1 (Fig. 1a–e) was a 72-year-old female who presented with 20/200 vision and typical findings of neovascular wet AMD with minimal subretinal fluid and significant cystoid macular edema due to evident choroidal neovascularization on FA. After three months of serial intravitreal bevacizumab, her vision improved to 20/60 and her significant CME had largely resolved, with some persistence of trace subretinal fluid. At month 6, all of her CME had resolved, the subretinal fluid had slightly increased, some shagging of the photoreceptor

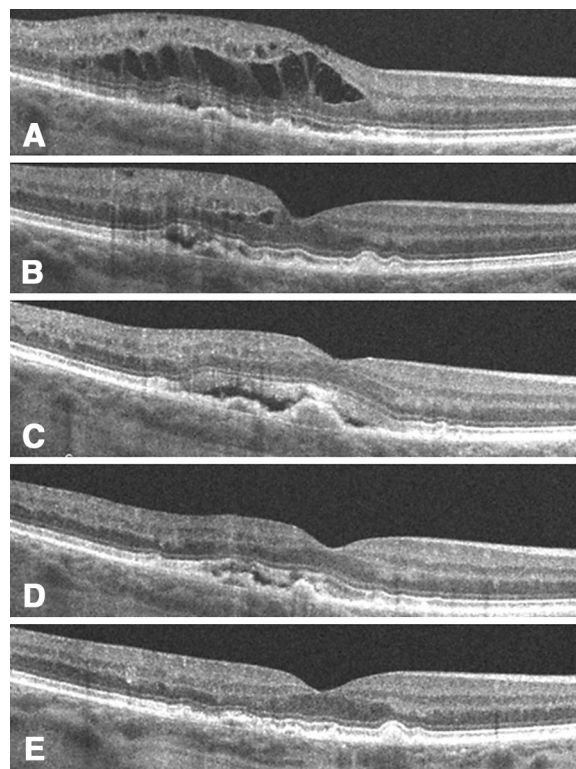


Fig. 1 **a** Month 0: VA: 20/200. **b** Month 3: after 3 months bevacizumab, VA: 20/60. **c** Month 6: after 6 months bevacizumab, VA: 20/70. **d** Month 9: after 6 months bevacizumab, 3 months aflibercept, VA: 20/70. **e** Month 11: after 2 months eplerenone, VA: 20/50

outer layer had become evident, and vision had decreased to 20/70. At this point, the patient was switched to aflibercept, and after three months of serial aflibercept, the patient presented a further increase in subretinal fluid and shaginess of the photoreceptor outer layer, with vision remaining at 20/70. At this point, the patient was started on oral eplerenone 25 mg PO BID, and two months later all the subretinal fluid had resolved, and vision had improved to 20/50.

Case 2 (Fig. 2a–e) was an 80-year-old female. She initially presented with significant CME and SRF with a BCVA of 20/150. After three months of bevacizumab, all the CME had resolved, and vision had improved to 20/80, but she had persistent subretinal fluid and a shaggy photoreceptor outer layer, so she was switched to aflibercept. After 6 months of

aflibercept, there was only a very slight reduction in pigment epithelial detachment subretinal fluid height, and oral eplerenone was initiated. After 2 months of oral eplerenone, most of the subretinal fluid had resolved, pigment epithelial detachment height had decreased further, and vision had improved to 20/40. One month later (3 months after starting oral eplerenone), all subretinal fluid had resolved, and vision remained at 20/40.

DISCUSSION

Intravitreal anti-VEGF agents have become the standard of care for wet AMD. There is a small percentage of patients that have refractory subretinal fluid despite serial anti-VEGF treatments. While some of these patients respond to switching anti-VEGF agents, in some cases chronic SRF can persist [1, 2]. Photodynamic therapy (PDT) has been described as successful in some of these cases, even in the absence of any identification of polypoidal choroidal vasculopathy or true CSR, and the etiology has been proposed as a “secondary sick RPE syndrome” [2, 3].

In this series, oral eplerenone demonstrated efficacy as an adjunct to intravitreal anti-VEGF in cases of presumed neovascular AMD with chronic subretinal fluid. The optimal response to eplerenone was evident in patients with an absence of moderate-large pigment epithelial detachments and with pachychoroid and a shaggy photoreceptor outerlayer present. In this subset of patients, SRF resolved completely, and they experienced an extension of their injection interval of approximately 3 weeks. Given recent data suggesting that serial anti-VEGF may contribute to geographic atrophy progression in some cases, this data is noteworthy [8].

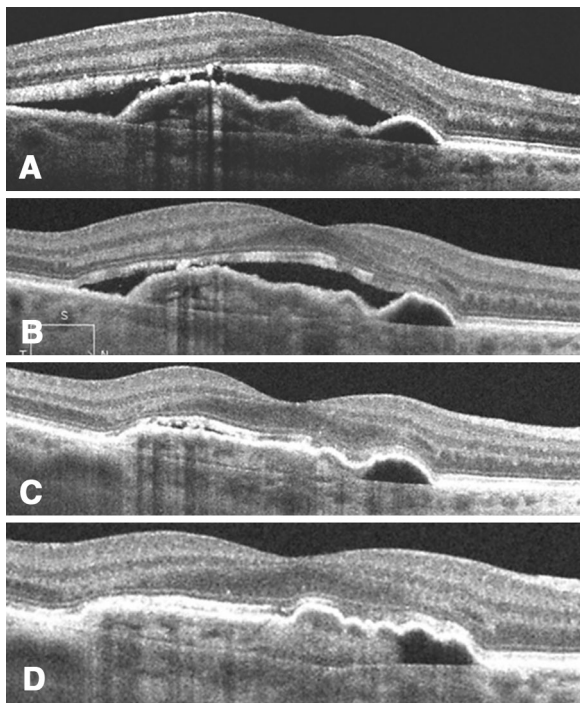


Fig. 2 **a** Month 3: after 3 months bevacizumab, VA: 20/80. **b** Month 9: after 3 months bevacizumab and 6 months aflibercept, VA: 20/70. **c** Month 11: after 2 months eplerenone, VA: 20/40. **d** Month 12, after 3 months eplerenone, VA: 20/40

It is interesting that patients with these characteristics responded optimally to the medication in this study, as each of these findings have been independently correlated as anatomic findings in CSCR. Patients with CSCR tend to have single or multiple discrete low-lying PEDs, if they are present [9]. A pachychoroid, clearly identifiable as an abnormal increase in choroidal thickness on enhanced-depth OCT imaging, has been described as a consistent feature of CSCR [10]. “Shaggy” photoreceptor outer layer segments have also been described as a key anatomic feature of CSCR [11].

This anatomic overlay begs the question of whether a deeper overlap of wet AMD and CSCR exists in some patients than previously realized. The demographic breakdown in the present study does not classically point to one typical of patients with CSCR, given a relatively equivalent breakdown of sex and a mean age that is much higher than average for CSCR. We also did not find evidence of a true sick RPE syndrome in these patients, as initial or repeat ICG did not show evidence of a true diffusely abnormal choroidal circulation. It is possible that these patients develop a secondary focal reactive RPE dysfunction that leads to a CSCR-type response.

Limitations of this study include its retrospective nature and the limitation of our ability to make inferences until a randomized controlled trial is completed.

CONCLUSION

In this study, oral eplerenone treatment demonstrated efficacy as an adjunct to the treatment of neovascular AMD, as demonstrated by statistically significant decreases in subretinal fluid and central

macular thickness and the extension of the anti-VEGF injection interval in select patients. Further research is needed to better elucidate the precise role of mineralocorticoid antagonists in neovascular AMD.

ACKNOWLEDGEMENTS

No funding or sponsorship was received for this study or the publication of this article. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published. Presented at The Retina Society, Paris, France, 10/11/15.

Disclosures. K.G. Kapoor, N. Todi and A.L. Wagner have nothing to disclose.

Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent to be included in the study was obtained from all patients.

Open Access. This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits any non-commercial use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

REFERENCES

1. Zhao M, Celerier I, Bousquet E, Jeanny JC, Jonet L, et al. Mineralocorticoid receptor is involved in rat and human ocular chorioretinopathy. *J Clin Invest*. 2012;122(7):2672–9.
2. Bousquet E, Beydoun T, Zhao M, Hassan L, Offret O, et al. Mineralocorticoid receptor antagonism in the treatment of chronic central serous chorioretinopathy; a pilot study. *Retina*. 2013;33(10):2096–102.
3. Herold TR, Prause K, Wolf A, Mayer WJ, Ulbig MW. Spironolactone in the treatment of central serous chorioretinopathy—case series. *Graefes Arch Clin Exp Ophthalmol*. 2014;252(12):1985–91.
4. Hasegawa T, Okamoto M, Masuda N, Ueda T, Ogata N. Relationship between foveal microstructures and visual outcomes in eyes with resolved central serous chorioretinopathy. *Graefes Arch Clin Exp Ophthalmol*. 2015;253(3):343–50.
5. Shing JY, Woo SJ, Ahn J, Park KH. Anti-VEGF refractory exudative age-related macular degeneration; differential response according to features on optical coherence tomography. *Korean J Ophthalmol*. 2013;27(6):425–32.
6. Kloos P, Niederberger H, Valmaggia C. Photodynamic therapy in “secondary sick RPE syndrome” after repeated intravitreal injections of VEGF inhibitors in patients with wet age-related macular degeneration. *Klin Monbl Augenheilkd*. 2011;228(4):340–4.
7. Broadhead GK, Hong T, Chang AA. Treating the untreatable patient: current options for the management of treatment-resistant neovascular age-related macular degeneration. *Acta Ophthalmol*. 2014;92(8):713–23.
8. Xu L, Mrejen S, Jung JJ, et al. Geographic atrophy in patients receiving anti-vascular endothelial growth factor for neovascular age-related macular degeneration. *Retina*. 2015;35:176–86.
9. Nair U, Ganekal S, Soman M, Nair K. Correlation of spectral domain optical coherence tomography findings in acute central serous chorioretinopathy with visual acuity. *Clin Ophthalmol*. 2013;6:1949–54.
10. Gallego-Pinazo R, Dolz-Marco R, Gomez-Ulla F, Mrejen S, Freund KB. Pachychoroid disease of the macula. *Med Hypothesis Discov Innov Ophthalmol*. 2014;3(4):111–5.
11. Matsumoto H, Kishi S, Otani T, Sato T. Elongation of photoreceptor outer segment in central serous chorioretinopathy. *Am J Ophthalmol*. 2008;145(1):162–8.