

## Combined treatment modalities in wet AMD

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### Abstract

**Introduction:** AMD is a disease of social significance and an increasing incidence. The patients with wet AMD need a life-long treatment in order to sustain useful vision. The Anti-VEGF treatment does not ameliorate the dry component of the disease. That's why an alternative treatment is highly needed.

**Aim:** To propose an alternative treatment as an adjunct to the standard of care in an attempt to prolong treatment-free intervals, to ameliorate the degenerative process and to suppress tachyphylaxis.

**Methods:** Nanosecond laser (2RT, Ellex) was used as an adjunct to Anti-VEGF treatment in the first group of patients and Triamcynolon subtenonally and Anti-VEGF in the second group. Patients were followed with visual acuity, FA, FAF, OCT, Angio-OCT.

**Results:** 20 patients were followed in the first group-AntiVEGF+2RT. Improvement of BCVA was achieved in 85% (1 to 3 lines on Snellen). In the follow-up-4 months of treatment-free period was maintained in 6 patient; 2 patients had 12 months of treatment free period; 6 patients had 6 months of treatment-free intervals. Ten patients were followed in the 2nd group. Improvement or stabilization of visual acuity and up to 6 months treatment-free intervals were achieved. Amelioration of degenerative cysts in 2/3 of the patients.

**Conclusion:** The combined treatment of wet AMD with Anti-VEGF and 2RT or Anti-VEGF and Triamcynolone subtenonally can ameliorate the degenerative process by tissue stimulation, and suppression of inflammation. It also shows the potential to elongate treatment-free intervals and diminish tachyphylaxis.

**Keywords:** 2RT, Anti-VEGF, Steroids, Degeneration, Inflammation, Combined Treatment

### Introduction

More than 10 % of the world-wide population has AMD. The projected number by 2020 is expected to be 200 million, increasing to 300 million by 2040 (Wong et al., 2014) and the cost of AMD treatment is predicted to increase to \$60 billion over the next 20 years. The impact of AMD on an individual's quality of life is high. Wet AMD is socially invalidating condition. It turns to be a life-long disease since we just ameliorate the symptoms but do not cure the disease. The affected patients need in most of the cases monthly controls and in most of the cases bi-monthly application of intravitreal AntiVEGF. The therapeutic regimes PRN or Treat and Extend are the preferred practice pattern. The primary aim of the treatment is to maintain useful visual acuity and dry macula at good compliance and minimal side effects of the treatment. We also aim at slowing the disease progression and suppressing the

degeneration. The current standard of treatment for wetAMD is intravitreal application of AntiVEGF medications. The short term (2 years) results, well known by numerous clinical trials (MARINA, ANCHOR, HARBOR, CATT, VIEW1, VIEW2, DRAGON, PrONTO, LUCAS and others), showed promising outcomes. More than 90% of the treated patients demonstrated between 7 and 13 letters improvement on the ETDRS. But when analysing the long term results after Anti-VEGF treatment the perspective looks different. The CATT study published in 2016 in Ophthalmology shows marked decline in visual acuity (more than 5 letters) between the second and fifth year of the treatment. The same results are demonstrated by the SEVEN UP and Chkravarthy's studies. They demonstrate deterioration of 8 letters and more compared to the entry status of the patients treated with PRN regime.

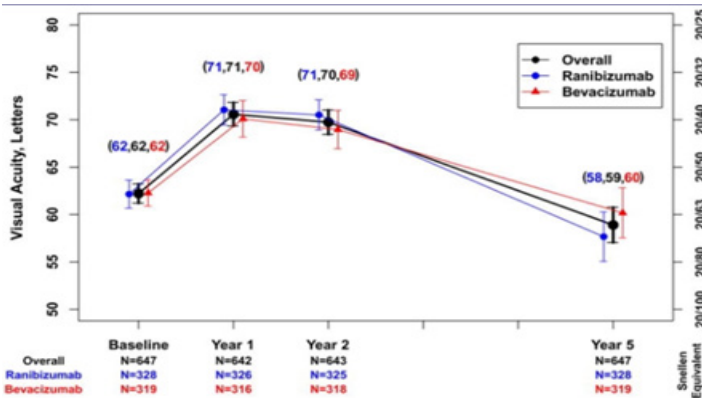


Figure 1: CATT study

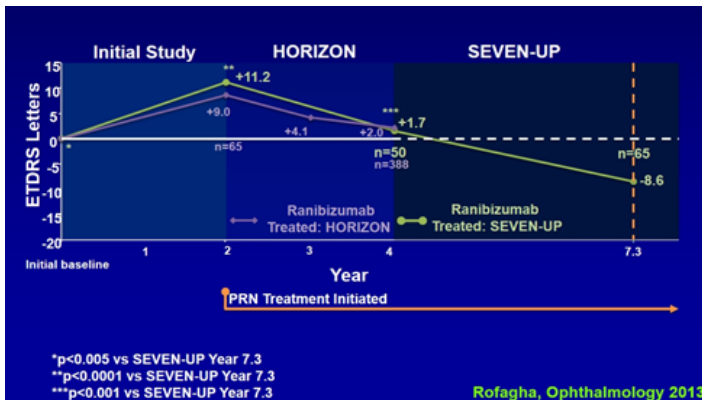


Figure 2: SEVEN-UP study

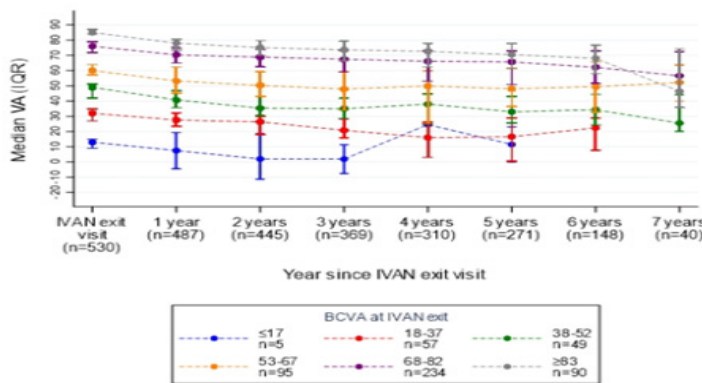


Figure 3: Usha Chkravarthy's study

In summary the long-term results show that 37% to 66% achieve 20/70 or better; 23% -47% achieve 20/40 or better; 22% - 37% achieve 20/200 or worse. Fluorescein angiography (FA) suggests active disease in 48% to 97%, OCT indicates fluid or degenerative cysts in 72% and Fundus auto-fluorescence (FAF) demonstrates macular atrophy in almost all of the patients (98.2%). The conclusions of these results are that the treatment of wet AMD needs life-long maintenance and still a big percentage of the patients lose visual acuity due to drop out or due to degenerative atrophic changes. The treatment of the pathologic vasculature (CNV) with Anti-VEGF does not ameliorate the dry component of the degenerative process. No matter how effective it is we still have RPE

atrophy in almost every patient, degenerative cysts in the inner retina, disruption of ellipsoid zone. This is also supported by some pathomorphological finding revealing photoreceptor and RPE atrophy in CNV lesions and disciform scars. CATT study results also show that geographic atrophy growth rates in treated neovascular AMD are similar to the rates in non-neovascular AMD. Probably one of the key factors for this secondary geographic atrophy is the chronic choroidal hypoxia. Hypoxia or inflammation are the main triggers for CNV. Suppressing the pathological vessels no vascular supply in the macula is left. Progression of atrophy is due to poor perfusion. As CNV grows, there is loss of normal choriocapillaris. As we treat the CNV and initiate its regression we may be eliminating the only remaining blood supply for the outer retina. Therefore Anti-VEGF therapy is supposed to have secondary atrophic effects potentiated by growing ischaemia. VEGF has known neurotrophic effects, and blocking it may also accelerate atrophy.

The purpose of our study is to support the necessity of combined treatment in wet forms of AMD in order to overcome the restrictions of the conventional treatment. To show the ground for this, we have to discuss some of the aspects of the pathogenesis of AMD. Even in non-pathologic conditions certain age-related changes in the tissues are described: thickening of the Bruch's membrane, lipofuscin accumulation due to impaired autophagy, transmembrane transport deterioration, and increase in TIMMP and corresponding decrease in MMP, leading to changes in the extracellular matrix. The key player in AMD is the Outer blood retinal barrier, the RPE- Bruch's membrane complex. The RPE maintains the function of photoreceptors and the choriocapillaris: phagocytosis of photoreceptor outer segments, light absorption, heat exchange, vitamin A metabolism, and secretion of certain cytokines, the most important of which being the VEGF, which is a trophic factor for the choriocapillaris. It is presumed that RPE degeneration precedes all subsequent changes in choriocapillaris and photoreceptor cells. Oxidative stress and inflammation probably are the main triggering events. The Paradigm of AMD molecular pathogenesis discussed in the literature put their accent onto the so called immuno-vascular axis. The RPE reacts to oxidative stress with vascular or immune response. The vascular response is practically an ischaemic response. The activated complement and the oxidative stress, generated by the normal metabolism, inflammation or other insulting factors can stimulate VEGF-A production. On the other hand the activated complement activates the pro-inflammatory macrophages. The pro-inflammatory macrophages alter the surrounding tissues and maintain chronic inflammatory response mediated by intracellular protein signalling complexes, termed inflammasomes. The increase in the number of retinal macrophages is a hallmark of CNV. They are identified in species of CNV membranes. The macrophages also protect against CNV. There are two types of macrophages- pro- and anti-angiogenic. It is the proportion that matters. The proportion of pro-angiogenic macrophages increases after numerous anti-VEGF applications. This is the mechanism that can explain the tachyphylaxis that is developed in some patients. Selective inhibition of pro-angiogenic macrophages would be an appealing adjunct to anti-VEGF therapy. It is known that steroids reduce the pro-angiogenic cytokine secretion by the RPE and also suppress the inflammation. Microglia is another immune cell type that might modulate human CNV pathogenesis. They are dormant macrophages residing in the sub-retinal space. Dysregulation of reparative mechanisms in the aging eye,

particularly the down-regulation of anti-inflammatory cytokines and the up-regulation of pro-inflammatory cytokines by the RPE, in response to stimulation by the deposition of advanced glycation end products (AGEs), might induce and perpetuate a low-grade chronic inflammatory process that contributes to the progression of AMD. Corticosteroids have a number of positive effects in the treatment of neovascular lesions, having a strong anti-inflammatory, antiproliferative and antiangiogenic action.

Another phenomenon implicated in the pathogenesis of AMD is the process of Autophagy. Autophagy is a lysosome-mediated degradation process for damaged cellular constituents. Cell survival is highly dependent on autophagy. Loss of autophagy particularly causes accumulation of ubiquitin-positive inclusion bodies and triggers degeneration processes. Many factors activate autophagy in stress conditions similar to those involved in AMD: inflammation, oxidative stress and hypoxia. There are also several compounds that induce autophagy: *trehalose, metformin, and rapamycin*. It is found that the systemic rapamycin can reduce the number of anti-VEGF-A injections required to treat CNV. Rapamycin is immunosuppressive and anti-proliferative drug. It acts as an inhibitor of mammalian TOR kinase. mTORC1 is promoting cell growth and proliferation, protein, lipid and nucleotide synthesis, energy metabolism and autophagy. Recent evidence indicates that mTORC1 is also an important modulator for aging and age-related diseases.

### Pilot study Purpose

To defy a new treatment alternative for combined treatment of wet AMD. The primary aim is to modify disease progression by suppressing the degenerative process, to prolong treatment-free intervals, to ameliorate side effects of Anti-VEGF treatment and to suppress tachyphylaxis.

### Methods

We used a PRN protocol for CNV treatment with AntiVEGF. All patient were treated with Bevacizumab. The adjunctive therapy in the first group was 2RT. The adjunctive therapy in the second group was Triamcynolon. We apply Triamcynolon subtenonially mixed with sodium hyaluronate. The duration of the effect is between two and four months. Sodium hyaluronate has the ability to potentiate the penetration of the medication through the sclera. Re-treatment is possible after four months. No serious side effects were noticed. No patient with uncontrolled ocular hypertension. Only conjunctival hyperemia and swelling were observed for the first 3-5 days after the application. It is believed that steroids potentiate the Anti-VEGF effect and ameliorate the inflammatory process accompanying AMD. We also believe that it has the potential to suppress the proangiogenic macrophages and the tachyphylaxis. Patients were followed with OCT, Angio-OCT, FA, FAF, visual acuity, changes in the inner and outer retina, RPE, CNV, atrophy progression, frequency of i.v. Anti-VEGF application.

2RT is nanosecond 532 nm, Q-switched, Nd:YAG laser patented by Ellex for treatment of dry AMD and DME. It has complex mechanism of action including certain biochemical and tissue changes. Increase of MMP and extracellular matrix remodelling, thinning of

Bruch's membrane and improvement of transmembrane transport, activation of phagocytes and oligodendrocytes (promoting autophagy), repopulation of RPE are some of the effects [2-9]. The aim of the 2RT laser treatment is to modify the microenvironment sufficiently to the point of altering disease activity. 2RT is applied in one session- 24-30 spots in the paramacular region with sub-threshold intensity (0, 10 mJ power), fixed spot-400 mkr, nanosecond duration.

**Inclusion criteria:** Neovascular AMD with full or partial regression of CNV after Anti-VEGF treatment on PRN basis, presence of drusae or drusenoid RPE detachment, serous detachment of neurosensory retina.

**Exclusion criteria:** sub-retinal cicatricial tissue, extensive sub-retinal haemorrhage, extensive atrophy.

Clinical criteria for CNV recurrence:

- Visual acuity reduction more than 5 letters (more for near)
- Contrast sensitivity deterioration
- OCT criteria (Neurosensory detachment, Cysts in the inner retina, Angio-OCT data)
- Ophthalmoscopic criteria (intra-retinal or sub-retinal haemorrhage).

### Results

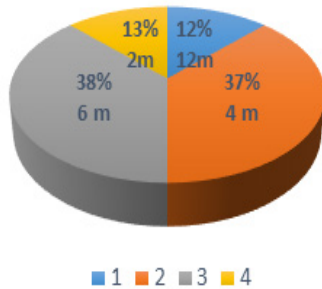
#### 1<sup>st</sup> group

It is a case series of 20 patients treated with Anti-VEGF on PRN regime and 2RT at a single session. Follow-up was done every month. Visual acuity improved in 10 patients (1 to 3 lines on Snellen) and contrast sensitivity improved in nearly all of them (95%). No deterioration of visual acuity was noted. Anatomical improvement was achieved in half of the patients (50%). Analysis was done on case per case basis. In 5 patients there was RPE resolution. And in 6- fluid resorption of neurosensory detachment. Resorption of drusenoid deposits was observed in some of the patients. In the follow-up-4 months of treatment-free period with no recurrence of CNV was observed in 6 patient; 2 patients had 12 months of treatment free period; 6 patients-6 months.

#### 2<sup>nd</sup> group

11 patients were included and followed up. Improvement of visual acuity was detected in 7 patients (ranging from 1 to 3 lines on Snellen) and stabilization in the rest [1-4]. Mean improvement in the visual acuity was from 0,2 (range 0,1-0,4) to 0,35 (range from 0,1 to 0,6). 5 of them had 6 months treatment-free intervals; 4 patients-3 months and two needed extra application of Anti-VEGF after 1 month. Amelioration of degenerative cysts was observed in 80 % of the cases with reduction of CRT (mean reduction 100 mkr +/-30 mkr) [8].

The limitation of the study is the small cohort. The variability of wet forms and their clinical response is also a limitation for statistically significant study results. Flow density in these cases is hard for verification, as an artefact is generated because of RPE disorganization and atrophy and also sub-retinal fibrotic changes due to Anti-VEGF treatment. Visual improvement strongly depends on the amount of RPE atrophy and ellipsoid zone disorganization [10-15].

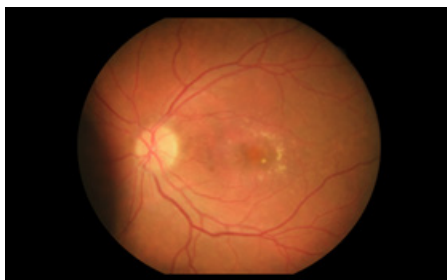


**Graph. 1:** Treatment-free periods in 1st group (Anti-VEGF+2RT)

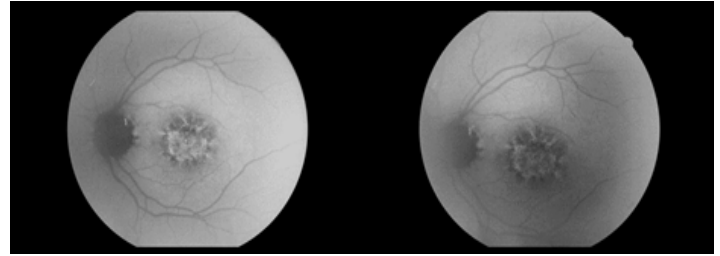
### Conclusions

2RT is a method for prophylaxis of dry forms of AMD. It has the potential to slow the degeneration in the retina and prevent conversion into wet form. We use this form of stimulation in the wet forms of AMD as an adjuvant treatment with Anti-VEGF. The combination of Anti-VEGF+2RT leads to functional (visual acuity, contrast) and anatomical improvement (resorption of deposits; RPE flattening). The effect is due to drying of the macula with Anti-VEGF and changing environment with 2RT through RPE stimulation- autophagy promotion, resorption of deposits, migration and repopulation of RPE cells; extracellular matrix remodelling, slowing the degenerative process, Flow Density improvement. Extension of treatment free periods is additional effect. Probably retreatments are needed every 6 or 12 months to sustain the effect. The combination of Anti-VEGF and Triamcynolon gives better results compared to monotherapy with Anti-VEGF. Amelioration of degenerative cysts is observed and longer-lasting effect of the combination therapy compared to only Anti-VEGF treatment. All this is probably due to the proven effect of the steroids in regard of inflammation (accompanying the AMD degenerative process), suppression of tachyphylaxis and potentiation of the Anti-VEGF effect.

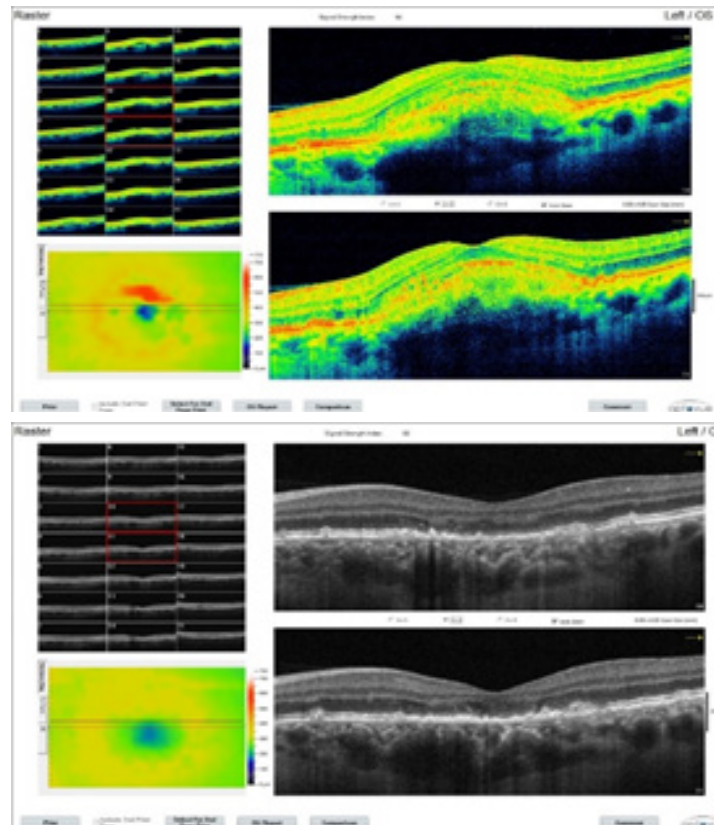
A perspective is the opportunity for expanding the adjunctive treatment: 2RT+Anti-VEGF+TA. It is reasonable to repeat 2RT every 6 to 12 months with a prophylactic Anti-VEGF and Triamcynolon application. Combination therapy has the potential to maintain visual acuity, to improve compliance due to extension of treatment-free intervals, to ameliorate side effects of the treatment, to slow disease progression (degeneration) and may be to regenerate the retinal tissue that is lost or damaged by the pathologic processes.



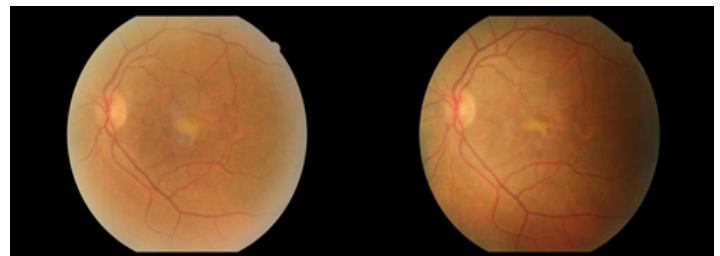
**Figure 4:** Patient N1 Colour photo



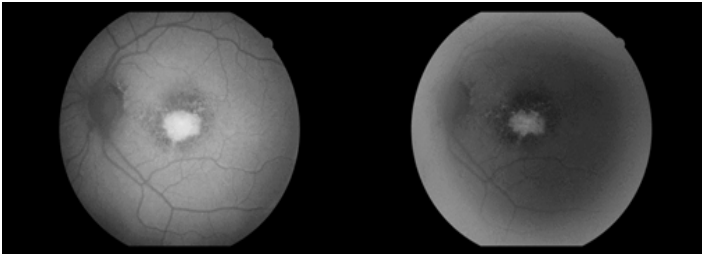
**Figure 5:** FAF before (A) and after (B) treatment



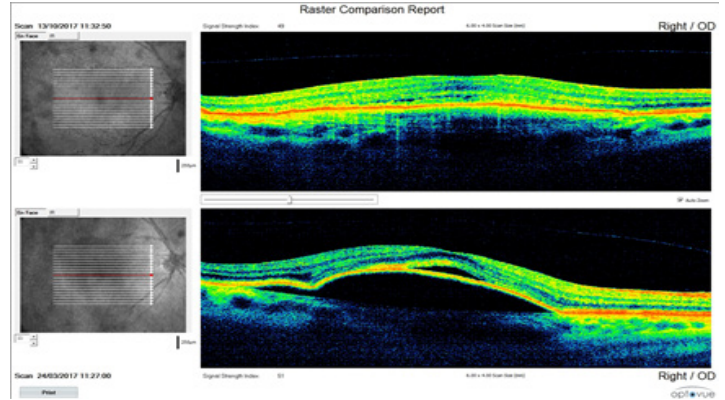
**Figure 6:** OCT before (A) and after (B) 2RT



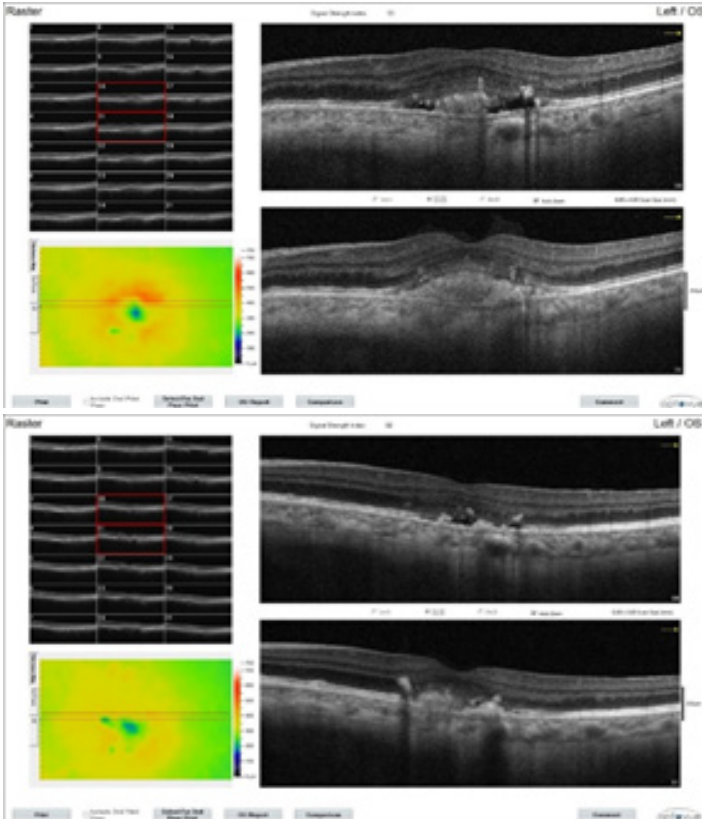
**Figure 7:** Patient N2 Colour photo before (A) and after (B) 2RT



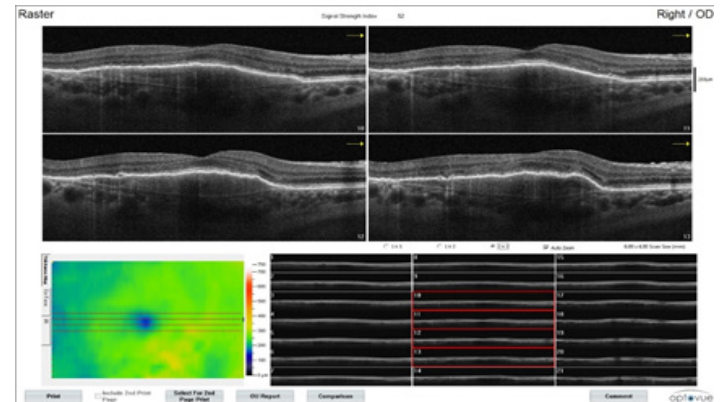
**Figure 8:** Patient 2 FAF before (A) and after (B) 2RT (decrease of deposits)



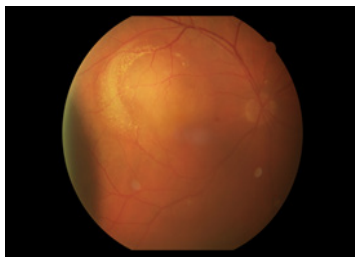
**Figure 11:** Patient N3 before (inferior) and after (above) 2RT



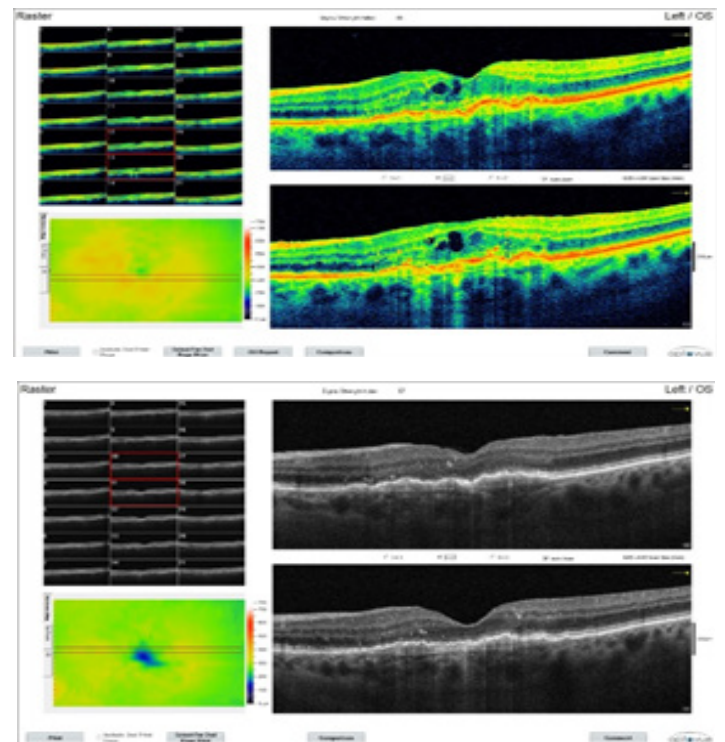
**Figure 9:** Patient N2 OCT before (A) and after (B) 2RT



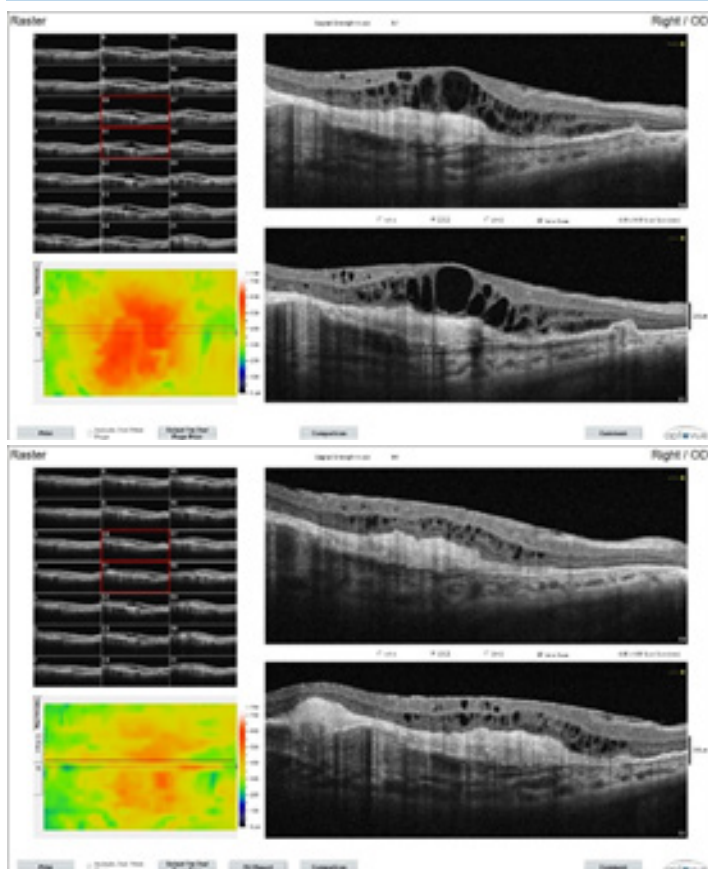
**Figure 12:** Patient N3 OCT after the treatment (raster)



**Figure 10:** Patient N3 Colour photo: PED and SED



**Fig. 13** Patient N4 Combination of Anti-VEGF and Triamcinolone before (A) and after (B) the treatment



**Figure 14:** Patient N5 Fibro-vascular PED detachment and degenerative cysts in the inner retina. Combination of Anti-VEGF and Triamcynolon before (A) and after (B) the treatment

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