Research Article

Type 1 Choroidal Neovascularization Evolution by Optical Coherence Tomography Angiography: Long-Term Follow-Up

Marco Rispoli, Maria Cristina Savastano, Bruno Lumbroso, Lisa Toto, and Luca Di Antonio

1Centro Italiano Macula, Rome, Italy
2O.C. Oftalmologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
3Università Cattolica del Sacro Cuore, Rome, Italy
4Ophthalmology Clinic, National High-Tech Center in Ophthalmology, Italian School of Robotics in Ophthalmology, University “G. d’Annunzio” of Chieti-Pescara, Chieti, Italy

Correspondence should be addressed to Maria Cristina Savastano; mariacristina.savastano@gmail.com

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Purpose. To evaluate structural changes in response to antivascular endothelial growth factor (anti-VEGF) treatment in patients with long-term type 1 choroidal neovascularization (CNV) by optical coherence tomography (OCT) and OCT angiography (OCTA).

Method. This is a longitudinal study that involved a total of 51 eyes with type 1 CNV (35 female and 16 male eyes). Structural OCT and OCTA were performed on all the subjects. AngioVue OCTA (XR Avanti, Optovue, Inc., Fremont, CA) was used to obtain qualitative and quantitative information. All eyes were treated with an anti-VEGF ProReNata (PRN) approach and were followed for a mean of 38.9 months (SD ± 7.22). Best-corrected visual acuity (BCVA) was assessed at each follow-up timepoint.

Results. We observed two kinds of possible evolution of type 1 CNV: “positive evolution,” including stabilization in 20% of patients and chronicity in 35%, and “negative evolution,” in which fibrosis was shown in 18% of patients, chorioretinal atrophy in 25%, and hemorrhage or RPE tears in 2%. The mean BCVA at baseline was 33:67 ± 15:85 ETDRS letters; after 1 and 2 years, it was 31:61 ± 18:04 and 31:18 ± 18:58 ETDRS letters, respectively. The mean BCVA at the end of follow-up was 25:27 ± 20 ETDRS letters. The difference between the values at baseline and at the end of follow-up was not statistically significant (P = 0.06, r² = 0.10).

Conclusions. This study describes an in vivo structural long-term evolution of type 1 CNV by OCT and OCTA. Different possible CNV outcomes were observed. This study suggests that new retinal imaging techniques could be useful tools for assessing the potential retinal changes in the evolution of type 1 CNV to develop personalized medicine. Further studies using OCTA in the long term are needed to better understand why similarly treated type 1 CNV cases evolve differently and produce different results.

1. Introduction

Noninvasive dyeless optical coherence tomography angiography (OCTA) is a clinical technique that is spreading rapidly all over the world, as it is safer, easier, and faster than fluorescein angiography (FA) and indocyanine green angiography (ICG) [1, 2]. Structural OCT highlights alterations in the morphology and structure of the retinal layers. OCTA provides images of blood flow in the retina and choroid with a high level of detail. In contrast, FA cannot show the vascular layers of blood vessels as deep as the capillary plexuses, which are well evidenced by OCTA [3]. This allows for several potential options of disease analysis, the research of different disorders, and the evaluation of new treatments [4].

One of the first pathologies studied by OCTA was wet AMD. The dyeless visualization of new vessels was remarkable for a large number of researchers around the world. OCTA enables the understanding, quantification, and tracking of the evolution after new vessel (NV) treatment.

CNV treatment should begin early, shortly after symptoms appear and before the occurrence of extensive structural damage. In the absence of a recognized guideline for
the treatment and evaluation of the timing of eyes with exudative neovascularization, patients should be closely monitored for treatment and retreatment. Antivascular endothelial growth factor (anti-VEGF) treatment is universally recognized as providing positive results in the reduction of CNV activity and in maintaining good vision for patients for years [5-7].

Several trials (ANCHOR, MARINA, VIEW 1, and VIEW 2) have demonstrated visual improvement of approximately 10 letters at 2 years in eyes with neovascular AMD undergoing monthly anti-VEGF therapy [8-10]. Recently, 5-year results from the Comparison of Age-Related Macular Degeneration Treatment Trial (CATT) study showed long-term visual deterioration with chronic anti-VEGF therapy [11].

Although several factors may play a role in causing vision loss in eyes that undergo long-term anti-VEGF therapy, the mechanism of this process remains poorly understood. One possible reason has been postulated by Dansingani and Freund, in which a mature tangled vascular pattern in type 1 lesions was determined to be a resistance factor to macular atrophy [12].

Recently, Christenbury et al. described a high level of macular atrophy development predominantly eccentric to the PED in long-term anti-VEGF therapy for eyes with type 1 NV secondary to AMD [13]. Despite studies reporting results of chorioretinal atrophy and a decrease in BCVA, several other studies have reported a maintained or increased BCVA and OCT morphology improvement [14, 15].

The potential chorioretinal involvement after anti-VEGF treatment led us to investigate the evolution of type 1 CNV in exudative AMD eyes, which we analyzed with structural OCT and OCTA in a long-term follow-up study.

This research project is aimed at studying the particular CNV morphological changes seen on OCTA at the end of the observational period.

2. Methods

This study adhered to the Declaration of Helsinki (52nd WMA General Assembly, Edinburgh, Scotland, October 2000), and written informed consent to participate in this study was routinely obtained from all examined patients. The IRB/ethics committee ruled that ethical approval was not required. In this cross-sectional study, fifty-one wet AMD eyes with type 1 CNV (35 female and 16 male eyes) detected by structural OCT according to a previous study [16] were evaluated. The mean age of the patients was 77.41 years, with a standard deviation (SD) of 12.39 years. All eyes were treated by an anti-VEGF ProReNata (PRN) approach and had follow-up every month. The duration of time followed for the entire cohort ranged from 31 months to 58 months, with a mean of 38.9 months (SD 7.22). The pharmacological agents ranibizumab and aflibercept were randomly chosen for administration. The number of intravitreal injections per eye during the course of treatment ranged from 3 to 29 injections, with a mean of 11.86 injections (SD 6.64). The patient demographics are listed in Table 1.

The exclusion criteria included media opacity and concomitant diseases such as diabetic retinopathy, vein or artery occlusion, glaucoma, any evidence or suspicion of type 2 and/or type 3 CNV, polypoidal choroidal vasculopathy, and any history of photodynamic therapy or macular laser therapy. Patients who presented with cataracts were followed without surgery because they did not have a clinically significant increase over time. All patients underwent a baseline ophthalmic examination, including medical and ocular history, family medical history, measurement of best-corrected visual acuity (BCVA) expressed in Early Treatment of Diabetic Retinopathy Study (ETDRS) letters, slit-lamp examination of the anterior and posterior segments, measurement of intraocular pressure, and dilated fundus examination. All eyes were imaged with an AngioVue OCTA (XR Avanti, Optovue, Inc., Fremont, CA) as the collected CNV assessment. The structural OCT protocol pattern used centered the B-scan line and crossline onto the fovea. The OCTA protocol used centered 3 × 3 mm² and 6 × 6 mm² grids onto the fovea. OCTA software programs automatically analyze retinal layer scans at different depths, providing images that are rich in details. With OCTA technology, the same tissue area is imaged repeatedly, and the differences between the scans are analyzed, thus allowing one to detect zones with high-flow neovascular rates. In cases of segmentation errors, manual editing of the layers was performed if deemed necessary for a correct interpretation. We classified all CNVs as inactive using biomarkers of CNV activity described by AlSheikh et al. [17] The OCTA scans that better represented the CNV features were selected and considered for analysis. We have chosen the images that agreed between CNV features and greater flow in B-scan. If the high flows were observed in the outer retina, the OCTA images in the outer retina were chosen. In case of main flows shown in the sub-RPE area, the OCTA scans were selected at this level. All images were analyzed by two of the authors (B.L. and M.C.S.) on two separate occasions to ensure accuracy of the grading. In cases of disagreement, both readers reanalyzed the images, and a consensus was obtained. The OCTA images analyzed were taken at the last visit. For statistical analysis, one-way ANOVA followed by a Holm-Sidak multiple comparison test was performed using GraphPad Prism (version 6.00 for Windows, GraphPad Software, La Jolla, California, USA: https://www.graphpad.com). Pearson coefficient correlation was used to correlate BCVA and the number of injections. Spearman coefficient correlations were calculated between BCVA and morphological CNV details. \( P < 0.05 \) was considered statistically significant.

3. Results

The enrolled eyes included both naïve eyes and those previously treated with anti-VEGF. The mean BCVA at baseline was 33.67 ± 15.85 ETDRS letters; at the end of the study, it was 25.27 ± 20 ETDRS letters. The difference was not statistically significant \( (P = 0.06, r^2 = 0.10) \).

Almost half of the participants had stable BCVA, although there were some eyes in which BCVA decreased dramatically. Two possible visual acuity patterns can be observed in CNV evolution: increased or stable (positive evolution) or decreased vision (negative evolution) (Table 2).
| Case | Age | Gender | Eye | Baseline BCVA (ETDRS) | Final BCVA (ETDRS) | Total no. of injections | Anti-VEGF agent | Follow-up (months) | CNV evolution | CNV growth pattern |
|------|-----|--------|-----|-----------------------|-------------------|------------------------|----------------|-------------------|--------------|-------------------|
| 1    | 77  | F      | RE  | 45                    | 15                | 27                     | A              | 45                | Atrophy      | Symmetric         |
| 2    | 77  | F      | LE  | 30                    | 45                | 28                     | A              | 36                | Chronicity   | Asymmetric        |
| 3    | 76  | F      | LE  | 35                    | 40                | 29                     | A              | 58                | Chronicity   | Symmetric         |
| 4    | 78  | M      | RE  | 48                    | 48                | 25                     | A              | 34                | Chronicity   | Asymmetric        |
| 5    | 78  | M      | LE  | 35                    | 35                | 24                     | R              | 38                | Fibrosis     | Finger-like projections |
| 6    | 41  | F      | LE  | 55                    | 53                | 22                     | A              | 31                | Chronicity   | Asymmetric        |
| 7    | 90  | F      | LE  | 20                    | 20                | 4                      | A              | 32                | Stabilized   | Asymmetric        |
| 8    | 54  | F      | LE  | 45                    | 53                | 20                     | R              | 55                | Chronicity   | Symmetric         |
| 9    | 73  | F      | LE  | 40                    | 35                | 14                     | R              | 40                | Stabilized   | Finger-like projections |
| 10   | 75  | F      | RE  | 30                    | 35                | 8                      | A              | 56                | Stabilized   | Symmetric         |
| 11   | 93  | F      | LE  | 48                    | 50                | 7                      | A              | 38                | Stabilized   | Asymmetric        |
| 12   | 67  | F      | RE  | 50                    | 55                | 3                      | R              | 36                | Stabilized   | Asymmetric        |
| 13   | 67  | F      | LE  | 20                    | 40                | 8                      | R              | 36                | Chronicity   | Finger-like projections |
| 14   | 60  | M      | RE  | 50                    | 48                | 4                      | R              | 33                | Stabilized   | Asymmetric        |
| 15   | 75  | M      | RE  | 35                    | 20                | 5                      | A              | 37                | Stabilized   | Symmetric         |
| 16   | 68  | M      | LE  | 55                    | 35                | 12                     | A              | 54                | Fibrosis     | Asymmetric        |
| 17   | 74  | F      | RE  | 40                    | 5                 | 7                      | A              | 31                | Atrophy      | Inside fibrous capsule |
| 18   | 85  | M      | RE  | 40                    | 5                 | 5                      | A              | 37                | Atrophy      | Asymmetric        |
| 19   | 75  | F      | RE  | 45                    | 50                | 22                     | A              | 50                | Chronicity   | Asymmetric        |
| 20   | 76  | F      | LE  | 35                    | 40                | 19                     | R              | 46                | Chronicity   | Inside fibrous capsule |
| 21   | 94  | F      | RE  | 20                    | 1                 | 8                      | R              | 35                | Hemorrage    | Symmetric         |
| 22   | 75  | M      | RE  | 1                     | 1                 | 11                     | A              | 37                | Atrophy      | Asymmetric        |
| 23   | 75  | M      | LE  | 1                     | 1                 | 12                     | A              | 39                | Atrophy      | Asymmetric        |
| 24   | 83  | F      | RE  | 35                    | 30                | 14                     | R              | 33                | Chronicity   | Symmetric         |
| 25   | 83  | F      | LE  | 35                    | 20                | 11                     | R              | 33                | Stabilized   | Inside fibrous capsule |
| 26   | 84  | F      | RE  | 45                    | 30                | 12                     | R              | 33                | Atrophy      | Symmetric         |
| 27   | 87  | F      | RE  | 35                    | 5                 | 14                     | R              | 40                | Fibrosis     | Symmetric         |
| 28   | 87  | F      | LE  | 3                     | 3                 | 6                      | R              | 40                | RPE tears    | Finger-like projections |
| 29   | 79  | F      | RE  | 50                    | 45                | 9                      | R              | 38                | Chronicity   | Asymmetric        |
| 30   | 46  | F      | LE  | 20                    | 45                | 11                     | A              | 46                | Chronicity   | Inside fibrous capsule |
| 31   | 91  | M      | LE  | 20                    | 2                 | 14                     | A              | 32                | Fibrosis     | Symmetric         |
| 32   | 81  | F      | RE  | 5                     | 1                 | 13                     | A              | 33                | Fibrosis     | Symmetric         |
| 33   | 81  | F      | LE  | 50                    | 50                | 14                     | R              | 33                | Chronicity   | Asymmetric        |
| 34   | 90  | F      | LE  | 5                     | 20                | 12                     | A              | 39                | Chronicity   | Asymmetric        |
| 35   | 80  | F      | LE  | 48                    | 50                | 14                     | R              | 58                | Stabilized   | Symmetric         |
| 36   | 72  | F      | LE  | 35                    | 2                 | 5                      | A              | 39                | Hemorrage    | Finger-like projections |
| 37   | 88  | M      | RE  | 35                    | 45                | 12                     | R              | 40                | Chronicity   | Asymmetric        |
| 38   | 77  | F      | RE  | 50                    | 50                | 11                     | A              | 35                | Chronicity   | Asymmetric        |
| 39   | 86  | F      | LE  | 40                    | 5                 | 14                     | A              | 46                | Fibrosis     | Asymmetric        |
| 40   | 88  | M      | RE  | 1                     | 1                 | 6                      | A              | 33                | Fibrosis     | Asymmetric        |
3.1. Positive Evolution: Stabilization and Chronicity. We observed positive evolution in 55% of the patients, consisting of CNV stabilization (20%) and CNV chronicity (35%). We considered CNV stabilization as long-term remission and an absence of fluid or hemorrhaging for more than 6 months; the CNV seemed to stop developing, and no activity signals were seen. The clinical appearance showed no exudation or fluid occurrence (Figure 1). Even if there was no CNV exudation, the CNV area was larger at the end of the observation period, growing from 0.68 mm² to 1.68 mm².

CNV chronicity was considered when the neovascularization was consistently responsive to anti-VEGF treatment but required repetitive reinjections. In these cases, acute disease developed into chronic disease. The CNV was often quiescent with consistent and frequent recurrences (Figure 2). The CNV area was consistently larger at the end of the observation period, growing from 0.7 mm² to 1.4 mm².

3.2. Negative Evolution: Fibrosis, Atrophy, Hemorrhage, or RPE Tears. Negative evolution was observed in 45% of the cases, which included fibrosis (18%) (Figure 3), atrophy

| Case | Age | Gender | Eye | Baseline BCVA (ETDRS) | Final BCVA (ETDRS) | Total no. of injections | Anti-VEGF agent | Follow-up (months) | CNV evolution | CNV growth pattern |
|------|-----|--------|-----|-----------------------|---------------------|-------------------------|----------------|-------------------|---------------|-------------------|
| 41   | 95  | M      | LE  | 35                    | 30                  | 13                      | R              | 42                | RPE tears      | Symmetric        |
| 42   | 68  | M      | LE  | 53                    | 53                  | 9                       | R              | 39                | Chronicity     | Asymmetric       |
| 43   | 92  | F      | RE  | 20                    | 5                   | 9                       | R              | 32                | Atrophy        | Asymmetric       |
| 44   | 95  | M      | RE  | 48                    | 30                  | 12                      | A              | 37                | Atrophy        | Asymmetric       |
| 45   | 73  | M      | LE  | 45                    | 45                  | 7                       | A              | 38                | Chronicity     | Asymmetric       |
| 46   | 94  | F      | LE  | 1                     | 1                   | 9                       | R              | 39                | Atrophy        | Asymmetric       |
| 47   | 75  | F      | RE  | 30                    | 30                  | 5                       | R              | 39                | Stabilized     | Asymmetric       |
| 48   | 75  | M      | LE  | 35                    | 20                  | 7                       | A              | 31                | Atrophy        | Symmetric        |
| 49   | 87  | F      | LE  | 30                    | 30                  | 8                       | R              | 34                | Chronicity     | Asymmetric       |
| 50   | 54  | F      | RE  | 45                    | 5                   | 5                       | R              | 34                | Fibrosis       | Symmetric        |
| 51   | 54  | F      | LE  | 35                    | 2                   | 5                       | R              | 34                | Fibrosis       | Symmetric        |

RE: right eye; LE: left eye; A: aflibercept; R: ranibizumab; BCVA: best-corrected visual acuity; F: female; M: male.

| Table 2: Type 1 CNV long-term evolution. |
|-----------------------------------------|
| Evolution of disease | NV Evolution | % | TOT (%) |
| Positive evolution   | Stabilized NV | 20 | 55      |
|                       | Chronic NV   | 35 |         |
| Negative evolution   | Fibrosis     | 18 |         |
|                       | Atrophy      | 25 | 45      |
|                       | Hemorrhage or RPE tears | 2 |         |

NV: neovascularization; RPE: retinal pigment epithelium.

3.1. Positive Evolution: Stabilization and Chronicity. We observed positive evolution in 55% of the patients, consisting of CNV stabilization (20%) and CNV chronicity (35%). We considered CNV stabilization as long-term remission and an absence of fluid or hemorrhaging for more than 6 months; the CNV seemed to stop developing, and no activity signals were seen. The clinical appearance showed no exudation or fluid occurrence (Figure 1). Even if there was no CNV exudation, the CNV area was larger at the end of the observation period, growing from 0.68 mm² to 1.68 mm².

CNV chronicity was considered when the neovascularization was consistently responsive to anti-VEGF treatment but required repetitive reinjections. In these cases, acute disease developed into chronic disease. The CNV was often quiescent with consistent and frequent recurrences (Figure 2). The CNV area was consistently larger at the end of the observation period, growing from 0.7 mm² to 1.4 mm².

3.2. Negative Evolution: Fibrosis, Atrophy, Hemorrhage, or RPE Tears. Negative evolution was observed in 45% of the cases, which included fibrosis (18%) (Figure 3), atrophy
(25%) (Figure 4), and hemorrhage or RPE tears (2%) (Figure 5).

Long-term monitoring of CNV evolution showed that the new vessels become larger, thicker, and straighter. No thin capillaries or fine loops were visible. For any evolution type, the vessel area was larger after treatment than before treatment (Figure 6).

After each treatment, the same main vessels appeared to return with increased flow and decreased branch density. It appeared as though some of the main branches were less affected by the treatment. As previously described by Spaide, the onset of a complex pattern after treatment induced a less complex feature of CNV, arterialization, to become detectable [18]. We defined this morphological pattern as a “maturation pattern” (Figure 7).

Similarly, in agreement with the results of the study by Xu et al., we observed 3 CNV growth patterns: symmetric growth, asymmetric growth, and finger-like projections [19]. Furthermore, we observed a new entity of CNV growth, “inside the fibrous capsule.” This CNV grows in vascular density but not in area. In this specific case, the CNV grew in vascular density inside a fibrous capsule (Figure 8).

Correlation between BCVA and number of injections was not statistically significant (\( P = 0.23, r^2 = 0.02 \)) as well the correlation between CNV evolution (\( P = 0.06, r^2 = -0.23 \)) and CNV growth pattern (\( P = 0.69, r^2 = -0.05 \)).

4. Discussion

Although OCT angiography continues to be developed, it is useful for several visual disorder indications, particularly in the management of AMD. The analysis of neovascular flow without dye injection with OCTA allows detailed monitoring of the different CNV evolutions. Our results show that type 1 CNV has various evolution patterns, which were analyzed over a 4-year observation period.

During long-term type 1 CNV evaluation, recurrence was frequent, and we observed two dissimilar evolutions, positive evolution and negative evolution, occurring independent of the treatment [20].

Type 1 CNV “positive evolution,” manifesting as stabilization or improvement, corresponded to 20% of cases, while that manifesting as chronicity corresponded to 35% of cases. “Negative evolution” included fibrosis, which was observed in 18% of eyes, chorioretinal atrophy, which was observed in 25% of eyes, and hemorrhage or RPE tears, which was observed in 2% of eyes.

In almost all eyes, after the loading phase of the 3 intravitreal anti-VEGF injections, the disappearance of CNV ramifications but not of the main CNV trunk could be observed by OCTA. These findings suggested that it would be very difficult to predict the prognosis from OCTA findings after 3 loading doses.

Most eyes with chronic evolution had periodic reactivation after treatment, with a periodicity of 50 to 60 days after each intravitreal injection. Before the first injection and between recurrences, we observed a dark halo around the CNV of approximately 50 microns in diameter. Although the meaning of the dark halo is still controversial [21–24], in our opinion, it is due to blood sequestering by neovascularization reactivation; an increased dark halo means CNV growth [25].

The cycles seemed to be quite regular. After each treatment, the same main vessels appeared to return with increased flow and decreased branch density. The normal cyclic recurrence was extensive and generally global, although it could be localized to a segment of the CNV. In a few cases, acute nonperiodic reactivation occurred independently from treatment. This type of reactivation could take the shape of a shoot, bud, sprout, or outgrowth and may have had a specific location: terminal, axillary, lateral, fingerlike, or adventitious.

The retinal effect of repeated anti-VEGF treatments is still controversial. However, Christenbury et al. recently described that the multilayered PED aspect after chronic VEGF suppression in type 1 CNV may confer a protective effect on the overlying retinal pigment epithelium and outer retina [13].

The ability of OCTA to assess and quantify CNV may highlight activity biomarkers and guide the evaluation, treatment, and monitoring of neovascularization.

According to our previous study and to a recent observation by Al-Shiekh et al., the morphological evaluation of CNV by OCTA can distinguish nonactive CNV lesions from exudative CNV lesions [17, 20].
Figure 7: Drawing of the CNV evolution after multiple treatments. Before treatment (a), the CNV has a greater proportion of small branching vessels and peripheral arcades, indicating an active lesion. After treatment (b), the same main vessels appear to return with increased flow and decreased branch density (vessels in red). Some main branches are less affected by the treatment (vessels in black). After several anti-VEGF treatments, the CNV shows fewer complex features. This morphological pattern corresponds to the "maturation pattern" of treatment (c).

Figure 8: CNV growth patterns. (a) Asymmetric growth, (b) symmetric growth, (c) finger-like projections. (d) We observed a new type of CNV growth, "inside the fibrous capsule," in which the vascular density increased instead of the vascular area.
In contrast to the results of previous studies [7], in our study, we observed BCVA reduction at the end of follow-up. Although we were unable to determine the real reason for the BCVA decrease, we propose 3 different hypotheses: undertreatment induced by the PRN treatment, the particular aggressiveness of type 1 CNVs, and the lower starting visus compared to that in other studies.

In conclusion, type 1 CNV evolution can progress to different outcomes: stabilization, chronicity, fibrosis, atrophy, hemorrhage, or RPE tears. Approximately half of the eyes in this study followed a positive evolution, while the other half became increasingly worse. We do not know why some CNV cases became stable, with the evolution and activity signals coming to a halt; we also do not know why some CNV cases converted to chronicity. Similarly, it is unknown why some of the CNV cases had important growth, while others led to atrophy or severe fibrosis. In the future, we hope that the use of OCTA will help to better define the morphological details in the development of type 1 CNV and develop personalized medicine.

Data Availability
The data used to support the findings of this study are available from the corresponding author upon request and were included within the supplementary information file(s).

Additional Points
Précis. The long-term evaluation of type 1 choroidal neovascularization (CNV) showed different outcomes for different cases: stabilization, chronicity, fibrosis, atrophy, hemorrhages, or retinal pigment epithelium (RPE) tears. We do not know why some CNV cases became stable, bringing their evolution and activity indicators to a standstill. Similarly, it is unknown why some CNV cases led to significant growth and others to hemorrhage, atrophy, or severe fibrosis. In the future, we hope that the use of optical coherence tomography angiography (OCTA) will better define the details of the development of type 1 CNV.

Conflicts of Interest
No conflicting relationship exists for any of the authors.

Authors’ Contributions
Marco Rispoli and Maria Cristina Savastano contributed equally to this work.

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