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Real-Life Experience with Aflibercept and Ranibizumab in the Treatment of Newly Diagnosed Neovascular Age-Related Macular Degeneration over 24 Months

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Abstract

Purpose: Comparative data appertaining to the long-term effects of Aflibercept or Ranibizumab in newly diagnosed cases of neovascular age-related macular degeneration (nAMD) over follow-up periods exceeding 12 months in clinical routine are scarce.
Methods: In this retrospective comparative analysis, a case series of patients with treatment-naïve nAMD and requiring anti-vascular endothelial growth factor (VEGF) therapy in a routine clinical setting were treated with either Aflibercept [Afl ($n=106$)] or Ranibizumab [Ran ($n=47$)]. During the drug-loading phase, 3 monthly injections were administered. Thereafter, a treat-and-extend protocol was pursued for a maximum of 24 months. Ran was administered predominantly in eyes with classical lesions; Afl was administered in all others. The primary outcome parameters included anatomical and functional stability after 24 months.
Results: Patients were comparable regarding age, gender distribution, and lens status. Fewer patients presented with intraretinal fluid in the Afl- than in the Ran group at diagnosis (46.2% vs. 67.4%; $P=0.02$), but not after the drug-loading phase. After the drug-loading phase, visual acuity [–4.2 letters (Afl) vs. –4.5 letters (Ran); $P=0.78$] and the central foveal thickness remained stable. Linked to the lesion type, the number of scheduled clinical visits during the course of 24 months was higher for the Ran- than for the Afl group [11.9 ± 4.7 visits (Ran) vs. 8.4 ± 3.1 visits (Afl); $P=0.0005$]. However, the total number of injections was similar [10.5 ± 2.8 (Ran) vs. 11.7 ± 3.6 (Afl); $P=0.06$].
Conclusions: Based on tailoring according to the lesion type in cases of nAMD, the anatomical and the functional outcomes of treatment with either Afl or Ran were comparable for a maximum of 2 years.

Keywords: neovascular age-related macular degeneration, anti-VEGF drugs, intravitreal injections, Ranibizumab, Aflibercept, treat-and-extend protocol

Introduction

AFLIBERCEPT (AFL) WAS APPROVED for the treatment of neovascular age-related macular degeneration (nAMD) in Western countries late in 2012. Since then, speculations have been rife that it might be at least as effective as Ranibizumab (Ran) in the handling of this disease, but with a lower therapeutic burden.[1,2] This prognosis was based on the findings of the VIEW studies, in which the effects of treatment with Afl and Ran at a fixed monthly or bimonthly dosage of 2 mg in the former case and of a monthly one of 0.5 mg in the latter were compared after a follow-up period of 96 weeks.[3] Since the functional status of patients who had been administered Afl every second month after receiving 3 monthly injections during the drug-loading phase was comparable to that in individuals who had been administered Ran on a monthly basis, many centers switched from the latter to the former drug as a first-line strategy in the treatment of nAMD. Several publications that have appeared during the past few years have reported a good anatomical response in the absence of an additional functional gain 6–12 months after switching from Ran to Afl.[4–13]

Cumulative evidence supports the notion that pigmented epithelial detachments (PED) respond less well to anti-vascular endothelial growth factor (VEGF) therapy than do accumulations of intra- and subretinal fluid.[14] And there are indications that the outcome may be less favorable under Ran- than under Afl therapy.[10,15–17] However, this finding

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has not been confirmed in more recent sub-group analyses.[18,19] Both the ANCHOR study of patients with predominantly classic choroidal neovascular (CNV) lesions and the MARINA study of patients with minimally classic or occult lesions report a good response to intravitreal Ranibizumab.[20–22] Since the visual gain was greater in classical than in occult lesions (roughly 11 letters vs. 8 letters), we decided to treat eyes with newly diagnosed, predominantly classic lesions with Ran and those with less typical or occult ones with Afl. A standard therapeutic approach, involving 3 monthly loading injections, was implemented. The anatomical and the functional outcomes of treatment with the 2 drugs were retrospectively compared after follow-up periods of 12–24 months.

Methods

In this retrospective study, patients with nAMD, who had undergone treatment in the macula clinic of the Berner Augenklinik am Lindenhofspital since late 2012, were included if they fulfilled the following criteria: (1) newly diagnosed nAMD with a need for intravitreal intervention against CNV activity, as indicated by the presence of intra- and subretinal fluid in optical coherence tomography (OCT); (2) initial treatment with at least 3 intravitreal injections (loading phase); and (3) a follow-up period of minimally 11 months after the primary therapeutic intervention. Patients who had not complied with the treatment regime that had been indicated by the consultant were secondarily excluded. Eyes that conformed with the inclusion criteria were subdivided according to treatment with either Afl or Ran.

The study fully complied with the tenets of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of the University of Bern (Reference No.: KEK 099/15). Before inclusion in the study, all patients had given their informed consent for the use of their coded data.

Exclusion criteria

Patients with underlying diseases that interfered with the clinical outcome, namely, those with either an active vascular or ocular affection (viz., any stage of active diabetic retinopathy) or an inflammatory one (viz., uveitis), as well as individuals with other possible CNV etiologies and those who had not adhered to the scheduled visits, were excluded from the study; so, too, were patients whose treatment regime had been changed during the course of the study period.

Data acquisition

All data related to the patients were extracted from their electronic records and from OCT database entries that were linked to the corresponding consultations. From these data, we extracted the Snellen best-corrected visual acuities—which, for the purpose of the present study, were later transformed into the corresponding ETDRS-letter scores, as well as functionally relevant findings and changes appertaining to the anatomical situation of the anterior (slit lamp) and the posterior segment [stereo-fundoscopy aided by a 78-dioptre lens (Volk Optical, Inc., Mentor, Ohio)], at prespecified points in time. At the time of the diagnosis, and thereafter if needed, macular color and autofluorescence imaging, as well as fluorescein angiography, had been performed to direct treatment decisions.

If the patients had undergone bilateral therapy, then both eyes were included in the study and were treated with the same drug (Afl: 7 patients; Ran: 4 patients). Since misalignment in the automated mode of OCT is likely in the exudative stages of advanced nAMD, namely, in the presence of either a large fibrovascular mass that involves Bruch's membrane or subretinal hemorrhaging, we decided to measure the central retinal thickness manually, on a micrometer scale, from the inner retinal surface to Bruch's membrane, when this was visible, or where it was estimated to be if it was masked by the hyper-reflective fibrovascular mass. The OCTs were also used to ascertain whether the macula was dry (absence of any fluid) or not dry [any fluid in the central zone with a diameter of 1 mm, as determined by using a horizontal-line algorithm with a length of 6 mm (Spectralis™; Heidelberg Instruments, Heidelberg, Germany)]. All measurements were performed by a trained independent specialist (H.M.R.), who was blinded to the group affiliations of the patients.

The data appertaining to all of the patients were collected from the time of the diagnosis until the end of the follow-up period, which preceded the data-lock on October 1, 2016. The findings were recorded at the time of the diagnosis, before the onset of treatment initiation (T0), 1 month after the drug-loading phase, which consisted of 3 consecutive intravitreal injections of Ran or Afl (T1), and after 12 (T2) and after 24 months (T3). Both of the agents were administered according to the same treat-and-extend (T&E) protocol. Initially, this involved the administration of minimally 3 monthly injections of the drug until such a time as the lesion was observed to have stabilized [absence of intraretinal fluid and absence or stability of subretinal fluid and/or of PED]. Thereafter, the therapy was either interrupted or the interval between the injections was extended by 2 weeks up to the 14th week until such a time as a fresh accumulation of intraretinal fluid was observed or the situation respecting the persisting level of subretinal fluid or the state of the PED had worsened.

Statistical analysis of data

On the basis of the assumption that the 2 groups were independent and behaved differently in their temporal response to therapy, and that the data were not normally distributed, a series of nonparametric tests were performed. To estimate the significance of the changes in the ETDRS-letter scores, Wilcoxon's signed-rank test was run for each group separately. To ascertain whether the ETDRS-letter scores, the annual number of intravitreal injections, and the inter-treatment interval differed between the 2 groups, the Mann–Whitney *U*-test was applied.

Qualitative data appertaining to the patients with dry AMD were analyzed by implementing separate Pearson χ^2-tests for each group at each time-point. The statistical analyses were performed by using the SPSS software package V.23 (SPSS, Inc., Chicago, IL), with the level of significance being set at $P < 0.05$. Unless otherwise indicated, the data are represented as mean values together with the standard deviation.

Results

One hundred fifty-three eyes (142 patients) satisfied the inclusion criteria: 106 (99 patients) having been treated with Afl and 47 (43 patients) with Ran. Another 23 patients had

to be secondarily excluded due to noncompliance with the protocol (17 in the Afl- and 6 in the Ran group). At the time of the diagnosis, the patients in the 2 groups were of comparable age [Afl: 79.0 ± 8.1 (59.8–101.2) years; Ran: 81.8 ± 6.8 (59.1–81.8) years] and gender [70% women (Afl) vs. 66% women (Ran)], and the lenticular status of the afflicted eye was similar in each category [45.3% pseudophakic (Afl) vs. 40.4% pseudophakic (Ran); $P = 0.29$]. To our surprise, the number of examinations that were performed differed between the groups [Afl: 8.4 ± 3.1 (4–23) visits; Ran: 11.9 ± 4.7 (3–20) visits; $P = 0.0005$], whereas the total number of injections that were administered did not [Afl ($n = 106$): 11.7 ± 3.6 (3–20); Ran ($n = 47$): 10.5 ± 2.8 (6–17); $P = 0.06$]. The number of injections that were administered during the first 12 months [Afl ($n = 106$): 7.5 ± 1.8 (3–11); Ran ($n = 47$); 6.9 ± 2.2 (3–12); $P = 0.07$] and during the second 12 months [Afl ($n = 65$): 4.3 ± 2.4 (0–10); Ran ($n = 31$): 3.4 ± 2.5 (0–9); $P = 0.11$] were likewise comparable.

With respect to the presence of any fluid *per se*, no differences between the 2 groups were observed at any point in time. However, the proportion of eyes that harbored intraretinal fluid tended to be lower in the Afl- than in the Ran group at the time of the diagnosis (46.2% vs. 67.4%, respectively; $P = 0.02$) but not thereafter (Fig. 1A, B). The best-corrected visual acuity (Fig. 2A) and the central retinal thickness (Fig. 3) remained stable after the drug-loading phase until the end of the follow-up period in both groups [change in visual acuity: –4.2 letters (Afl) vs. –4.5 letters (Ran); $P = 0.78$; Fig. 2B].

Discussion

Differences in the effects of Afl and Ran on the anatomical and the functional stability of treatment-naïve nAMD eyes after a follow-up period of 24 months may be negligible in a routine clinical setting if they are based on therapeutic tailoring according to the lesion type. Both of the drugs maintained the initial visual gain and the anatomical stability with comparable treatment demands over the same period. Similar results have recently been reported by another group for the first 12 months of treatment.[23] The circumstance that more clinical visits were scheduled for Ran-treated eyes may reflect the expectation of a longer-lasting effect for Afl or a lower predictability of therapeutic success under Ran. However, owing to the retrospective nature of the study, such an interpretation is made reservedly. It remains open to speculation whether the presented outcomes are related to or independent of the therapeutic tailoring that was influenced by the lesion type (predominantly classical ones being treated with Ran and all others with Afl). However, with respect to the inter-treatment interval in treatment-naïve eyes and the proportion of patients who required re-treatment, similar outcomes have been recently reported for the 2 drugs without tailoring according to the lesion type.[24] Furthermore, in a sub-group of ANCHOR- and MARINA patients, a lower baseline visual acuity, a smaller baseline CNV lesion size, and a younger baseline age were associated with a greater visual gain but not with a distinct lesion type.[21,22]

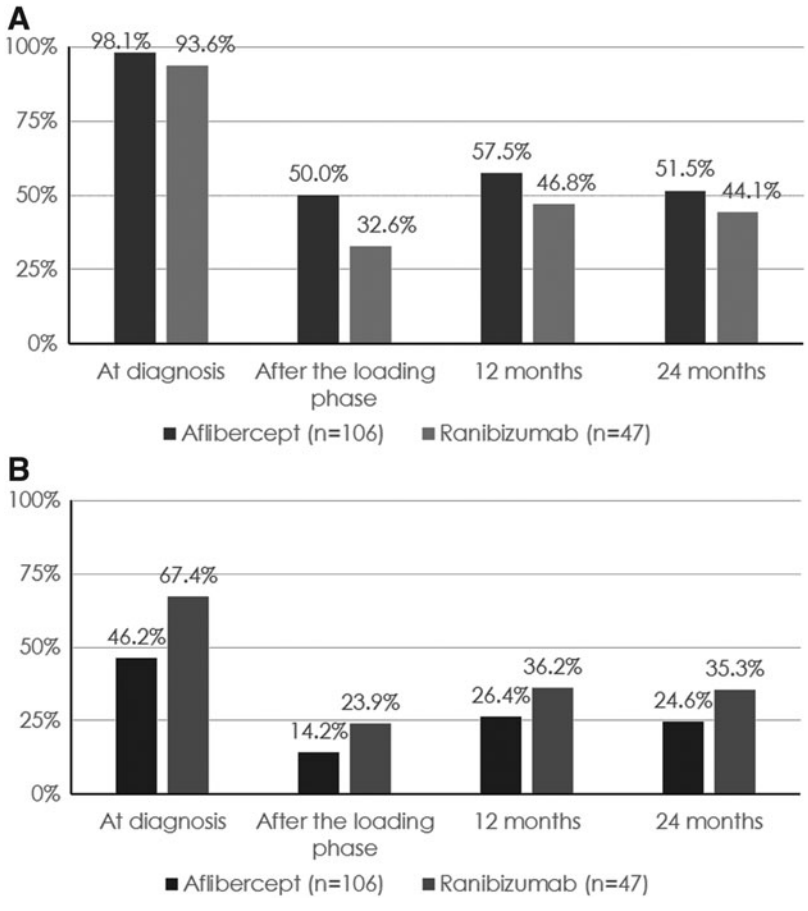

FIG. 1. Disease activity. **(A)** Any fluid, *per se*, that was evident in ocular coherence tomographs. **(B)** Intraretinal fluid [At diagnosis, Ran group showed significantly more intraretinal fluid than Afl group ($P = 0.02$) (χ^2-test)].

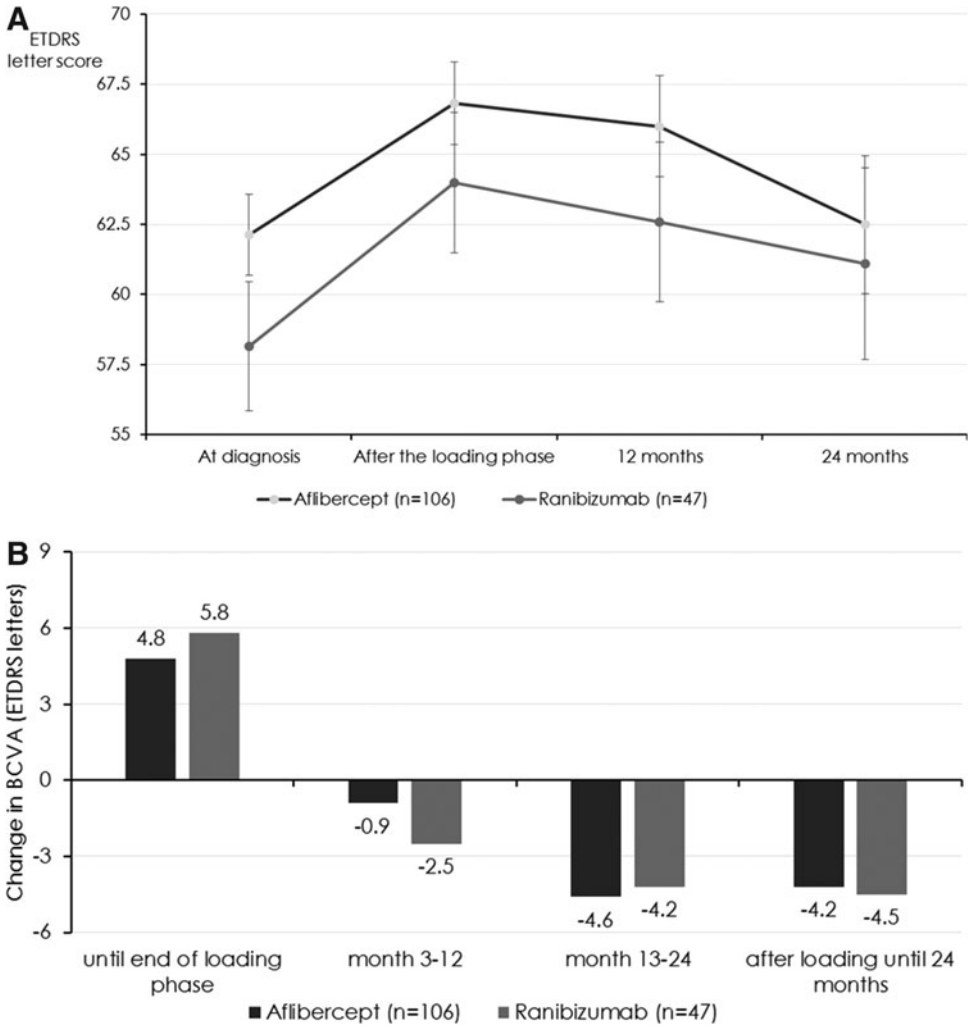

FIG. 2. Functional outcome. **(A)** Best-corrected visual acuity (BCVA in ETDRS-letter scores). **(B)** Change in best-corrected visual acuity (ETDRS-letter scores).

It is also conceivable that a switch from one to the other drug during the course of treatment might have a bearing on the outcome. Since patients in this category were excluded from our study, we cannot ourselves throw any light on this issue. However, in a recent publication, a switch from Ran to Afl was reported to yield comparable anatomical and functional outcomes after a follow-up period of 12 months to those that were achieved in eyes that had been treated throughout with the former drug alone and with a comparable number of injections.[25] These findings are supported by those of a recent meta-analysis.[26] Furthermore, eyes in which a switch from Ran to Afl was made due to nonresponsiveness

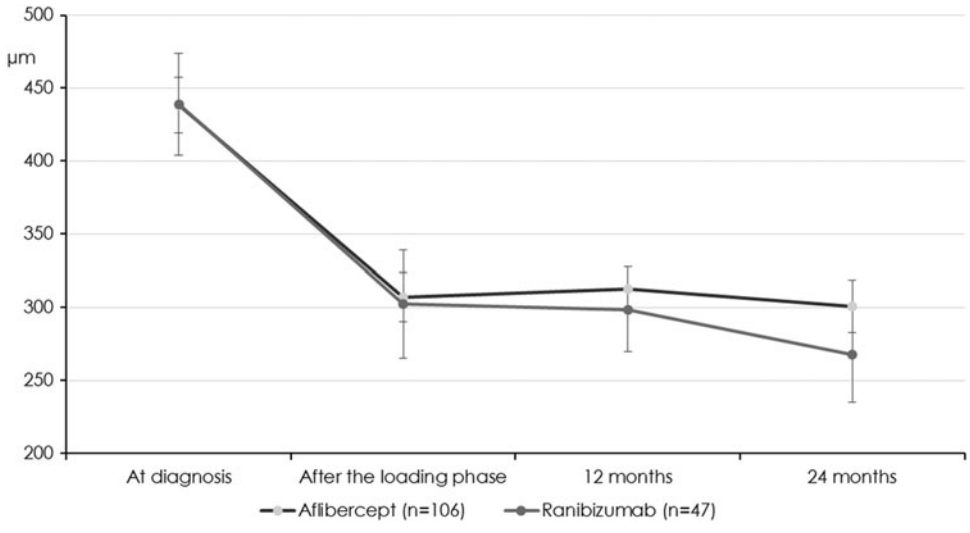

FIG. 3. Central foveal thickness.

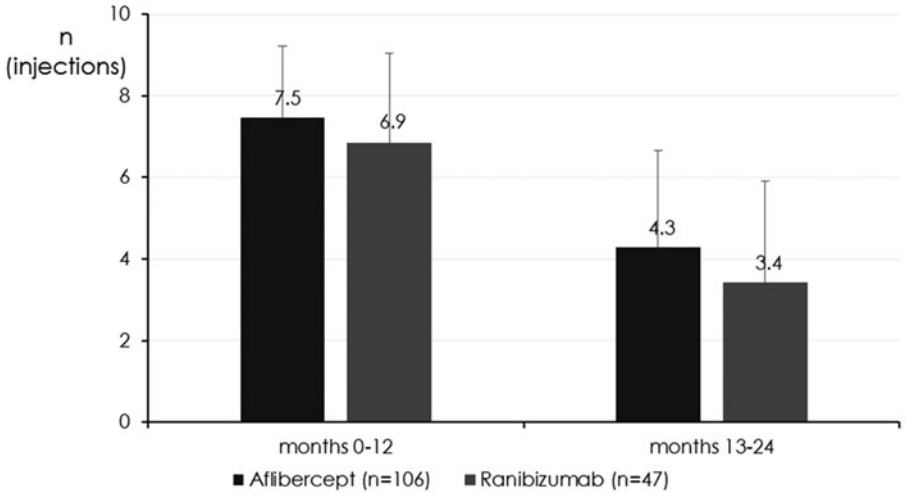

FIG. 4. Treatment demand over 24 months.

or other reasons have been reported to improve anatomically, with reductions in intra- and subretinal fluid, but not functionally. These findings have been generally interpreted as a stabilization of the disease during the follow-up period, which was limited to maximally 12 months.[4–13] Data appertaining to longer follow-up periods are scarce. However, our own analysis has revealed no differences between responders and nonresponders over 2 years.[27]

It could be argued that in patients with (persisting) subretinal fluid and/or PED, the functional outcomes may differ only in the long term, after 24 months.[28,29] In our series of patients, the proportion of eyes with persisting fluid was tendentially, but not significantly higher under Ran- than under Afl treatment. Moreover, the existence of persisting intraretinal fluid may be indicative of lesion activity and growth; consequently, it could have a negative impact on the functional outcome after 2 years. But also in this respect, no differences were observed between the 2 groups. On the basis of OCT observations, the proportion of eyes that harbored fluid at the 2-year juncture was high in both groups. We interpret this finding as a real-life phenomenon, which was accounted for by an extension of the inter-treatment interval. Such was also the case in situations in which the levels of subretinal and sub-pigmented epithelial fluid had stabilized. Additional contributory factors may have been the decision of patients to postpone a scheduled visit due to ill health or to a stabilization of the visual function, which was felt by the physician to justify an extension of the inter-treatment interval. Our finding that the number of administered injections did not differ between the 2 groups is generally in accord with recently published, real-world data,[23,28] with the exception that we did not observe the expected higher therapeutic demand for Ran-treated eyes (Fig. 4).

In conclusion, given that the treatment was tailored to the lesion type, the data appertaining to the 2 groups are not directly comparable. But on this basis, the anatomical and the functional outcomes that were achieved in treatment-naïve eyes that had undergone therapy with either Afl or Ran over a course of 24 months were similar. With a view to guiding therapeutic decisions and to weighing the advantages and the disadvantages of the 2 drugs in a given case of treatment-naïve nAMD, our data deserve prospective reconfirmation.

Author Disclosure Statement

J.G.G. advises several pharmaceutical companies (Alcon, Allergan, Bayer, Novartis) and participates in a number of industry-sponsored (Novartis, Bayer) and independent international multicenter clinical studies in the fields of AMD and diabetic retinopathy. These activities had no bearing on the study that gave rise to the submitted article, for which J.G.G. received neither direct nor indirect financial support. None of the authors have conflicts of interest with any of the presented data.

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