Four-Year Treatment Results of Neovascular Age-Related Macular Degeneration With Ranibizumab and Causes for Discontinuation of Treatment

MADS KRÜGER FALK, HENRIK KEMP, AND TORBEN LYKKE SØRENSEN

• PURPOSE: **To evaluate 4-year treatment results of neovascular age-related macular degeneration with ranibizumab using a variable dosing regimen.**
• DESIGN: **Retrospective, single-center chart review.**
• METHODS: **This was a retrospective single-center study that included 855 patients with neovascular age-related macular degeneration receiving treatment with ranibizumab during a 4-year period. Included in the study were patients with a minimum follow-up of 15 months and all patients who terminated treatment regardless of follow-up.**
• RESULTS: **A total of 1321 patients were treated over the 4-year period, and 855 patients were eligible for inclusion. Of those, 456 patients were still receiving active treatment, whereas 399 patients had discontinued treatment. Overall treatment results showed a significant decrease in vision from 53.2 Early Treatment Diabetic Retinopathy Study letters (range, 1 to 85 letters) to 50.5 letters (range, 1 to 87 letters; $P < .001$). Mean follow-up was 23.3 months (range, 4 to 48 months). The reason for discontinuing treatment in 181 patients was no signs of activity, whereas 113 patients were judged to be nontreatable. Thirty-six patients declined further treatment for various reasons.**
• CONCLUSIONS: **This report shows that when follow-up extends beyond 2 to 3 years, visual acuity does seem to decrease. Our data show that different responder groups can be identified: bad or nonresponders (approximately 15% of all patients) and good responders (approximately 21% of all patients). These 2 groups in general can be identified within the first 2 years of treatment, whereas the third group of regular responders (approximately 64% of all patients) require continuous monitoring and treatment for years. (Am J Ophthalmol 2013;155:89–95. © 2013 by Elsevier Inc. All rights reserved.)**

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From the Department of Ophthalmology, Copenhagen University Hospital Roskilde, Roskilde, Denmark (M.K.F., H.K., T.L.S.); and the University of Copenhagen, The Faculty of Health and Medical Sciences, Copenhagen, Denmark (M.K.F., T.L.S.).

Inquiries to Mads Krüger Falk, Department of Ophthalmology, Copenhagen University Hospital Roskilde, Køgevej 7-13, DK-4000 Roskilde, Denmark; e-mail: mfal@regionsjaelland.dk

AGE-RELATED MACULA DEGENERATION (AMD) IS THE most common cause of blindness in the Western world. The prognosis for neovascular AMD has changed dramatically since the introduction of anti–vascular endothelial growth factor treatment. Hallmark randomized clinical trials have shown a marked effect of monthly injections with ranibizumab (Lucentis; Genetech, South San Francisco, California, USA) compared with placebo, and when the trials were extended to 24 months, there was a sustained treatment effect.[1,2] However, because other studies have reported that pro re nata (PRN) treatment can obtain comparable treatment results and because monthly injections are not feasible, many retinal clinics, including ours, have adhered to a clinician-determined retreatment strategy, in which treatment is administered when there are signs of activity indicating choroidal neovascularization (CNV) on clinical follow-up.[3,4]

Numerous reports have shown that anti–vascular endothelial growth factor treatment is effective in maintaining or improving visual acuity (VA) in real-world clinical practice using the PRN treatment strategy, but very few of those reports, and none with a long follow-up period, have given a detailed account of the cause of termination of treatment and how many patients obtain complete inactivation of the CNV. This information is highly relevant to the clinician when discussing treatment prognosis with the patient.

One recent study reported the causes of discontinuing treatment after 1 year among 101 (21.4%) of a total of 471 patients. Of the 471 patients included in the study, 1.2% declined further treatment, and in 7.2% of cases, the physician decided that no further follow-up was necessary, although it is unclear whether this was because of inactivation of the lesion or because the lesion was judged to be untreatable. In 13% of cases, the cause was ascribed to "other reasons."[5]

Treatment of neovascular AMD with ranibizumab has been performed at our department since 2007. In Denmark, treatment with Lucentis is covered by the Public National Health Insurance, which is a privilege extended to all citizens and is financed from general taxation. Herein, we present the results from a 4-year period, including a detailed account of the patients who stopped treatment. Our findings suggest that relatively few patients stop treatment because of inactivation, and that most patients should be considered as having chronically active disease.

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TABLE 1. Demographic and Clinical Characteristics of Patients with Neovascular Age-Related Macular Degeneration Treated with Ranibizumab Included in the Review

	No. of Patients	Gender (Female/Male)	Mean Age (Range), y	Mean Starting Visual Acuity (Range), ETDRS Letters	Mean Visual Acuity at Latest Follow-up (Range), ETDRS Letters	Mean Follow-up (Range), mos	Mean No. of Injections with Ranibizumab (Range)
All patients included	855	537/318	77.3 (54 to 98)	53.2 (1 to 85)	50.5 (1 to 87)	23.3 (4 to 48)	8.7 (1 to 35)
Patients in active treatment	456	291/165	76.0 (55 to 98)	56.9 (1 to 85)	57.8 (1 to 87)	29.5 (15 to 48)	11.3 (2 to 35)
Patients stopped treatment (total)[a]	399	246/153	78.7 (54 to 96)	48.9 (1 to 85)	42.3 (1 to 87)	16.1 (4 to 47)	5.6 (1 to 22)
No signs of activity	181	116/65	77.7 (54 to 95)	50.8 (1 to 85)	52.4 (5 to 87)	18.6 (5 to 47)	5.2 (1 to 17)
Did not want to receive further injections	36	24/12	79.7 (61 to 96)	50.3 (20 to 72)	43.3 (8 to 75)	11.7 (4 to 38)	5.1 (2 to 18)
Judged nontreatable	113	70/43	79.1 (60 to 95)	43.8 (1 to 80)	21.8 (1 to 69)	15.1 (4 to 41)	6.8 (2 to 22)
Other reasons	69	36/33	80.3 (60 to 92)	52 (5 to 82)	48 (1 to 82)	13.8 (4 to 45)	6.1 (2 to 19)

ETDRS = Early Treatment Diabetic Retinopathy Study.

[a]The patients who terminated treatment are divided into the following subgroups: no signs of activity, did not want to receive further treatment, and judged nontreatable, and other reasons comprising death and the patient moving to another region.

METHODS

THIS WAS A SINGLE-CENTER STUDY OF 1321 PATIENTS WITH neovascular AMD who received treatment with ranibizumab in the 4-year period from April 2007 to April 2011. Included in the review of treatment results are patients with a minimum of 12 months of follow-up from the assessment visit after the third injection (minimum of 15 months of follow-up from initiation of treatment). All patients who terminated treatment in the 4-year period were included in the study, regardless of length of follow-up. Of the 1321 eyes, a total of 855 met the inclusion criteria (Table 1).

Patients suspicious of neovascular AMD were examined with funduscopy, spectral-domain optical coherence tomography (Spectralis HRA-OCT; Heidelberg Engineering, Heidelberg, Germany), and fundus autofluorescence. Best-corrected visual acuity (BCVA) was determined using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. All patients underwent fluorescein angiography (FA), indocyanine green angiography (ICGA), or both. All patients with clinical signs of active neovascular AMD and a BCVA of more than 20 letters were offered treatment with ranibizumab. In some cases, treatment was offered although BCVA was fewer than 20 letters. Findings considered signs of activity were retinal hemorrhages, leakage on FA, and presence of subretinal or intraretinal fluid, or both, on OCT. Definite signs of active CNV under a pigment epithelial detachment (PED) was detected using ICGA and also was considered an indication for treatment, whereas only serous PEDs were monitored. All initial data including clinical findings were recorded in a database for treatment follow-up. The treatment initially was given as a loading dose using a series of 3 monthly injections. Very few patients received fewer injections initially. The first clinical follow-up took place 4 to 6 weeks after the third injection. At the follow-up, consultation measurement of BCVA using the ETDRS chart, funduscopy, and OCT was performed. At follow-up visits, FA and ICGA were not performed routinely and generally were reserved to cases with unusual treatment responses or unexpected morphologic changes. All the findings were recorded in the database. If there were signs of activity, the examining physician assessed the number of injections needed (1 to 3 injections). Minimal signs of activity (limited amount of fluid) could have indicated the need for only 1 additional injection, whereas extensive signs of activity resulted in 3 injections. If no signs of activity were detected, the patient was invited to a follow-up visit after 4 to 6 weeks. We terminated treatment if there were no signs of activity after 6 months after the last injection or if BCVA had deteriorated after 3 to 6 injections. No distinct BCVA threshold was defined, and the decision to terminate treatment always was individualized. All patients discontinuing treatment were recommended to attend regular follow-up visits at the referring clinic every 3 to 6 months from termination of treatment. Facilities at referring clinics vary, but many have the capacity to perform OCT. It is easy for the referring clinics to obtain a second opinion at the treating clinic, despite limited suspicion of reactivation. If reactivation occurred, the patients were included in the group of patients receiving active treatment, and registration in the database was continued. Treatment, monitoring and decisions regarding retreatment or discontinuation of treatment followed the Danish National guidelines set forward by the Danish Ophthalmological Society. All doctors involved in treating patients with AMD were instructed to follow these guidelines under the supervision of the retinal specialists and chief physicians (T.L.S. and H.K.) at the department. There has been no formal quality control of this or control of

reproducibility regarding interpretation of OCT, FA, or ICGA results.

• **STATISTICAL ANALYSIS:** Because the data were normally distributed, the data are reported as means and ranges. Differences among groups were calculated using a 1-way analysis of variance, differences between 2 groups were calculated using the independent samples *t* test, and the paired-sample *t* test was used to calculate changes over time. SPSS software for Windows version 19 (SPSS Inc, Chicago, Illinois, USA) was used, and a *P* level of less than .05 was considered significant.

RESULTS

• **PATIENTS:** The 855 eyes included in the review were divided into 2 groups, one with 456 patients currently in active treatment and another with 399 patients who have discontinued treatment (Table 1). Overall treatment results show a significant decrease in vision from 53.2 letters (range, 1 to 85 letters) to 50.5 letters (range, 1 to 87 letters; $P < .001$, paired-sample *t* test). The mean number of injections was 8.7 (range, 1 to 35). Mean duration of follow-up was 23.3 months (range, 4 to 48 months).

• **PATIENTS CURRENTLY IN ACTIVE TREATMENT:** The clinical characteristics and treatment results for patients currently in active treatment are given in Table 1. In total, 291 women and 165 men had a follow-up longer than 15 months from initiation of treatment. Thirty-four patients were referred again during the 4-year period because of reactivation. The mean length of follow-up was 29.5 months (range, 15 to 48 months). The mean age was 76 years, the youngest patient being 55 years of age and the oldest patient being 98 years of age. The mean BCVA before treatment was 56.9 letters (range, 1 to 85 letters), and at the latest follow up consultation, the mean visual acuity was 57.8 letters (range, 1 to 87 letters), a small and nonsignificant increase in vision ($P = .232$, paired-sample *t* test; Table 1 and Figure). The mean number of injections was 11.3 (range, 2 to 35). Treatment results are given in more detail in Tables 2 and 3. Eighty-one (18%) of 456 patients currently in active treatment gained a minimum of 15 letters, whereas 66 (14%) of 456 patients experienced a loss of a minimum 15 letters. At baseline, 6 (1%) of 456 patients had a BCVA of fewer than 20 letters, whereas 51 (11%) of 456 patients of had a BCVA of more than 70 letters. At the latest follow-up, 10 (2%) of 456 patients in this group had a BCVA of fewer than 20 letters, whereas 116 (25%) of 456 patients had a BCVA of more than 70 letters (Table 3). Seven patients in active treatment had a total follow-up of 48 months, whereas 122 patients in active treatment had a follow-up of between 36 and 48 months.

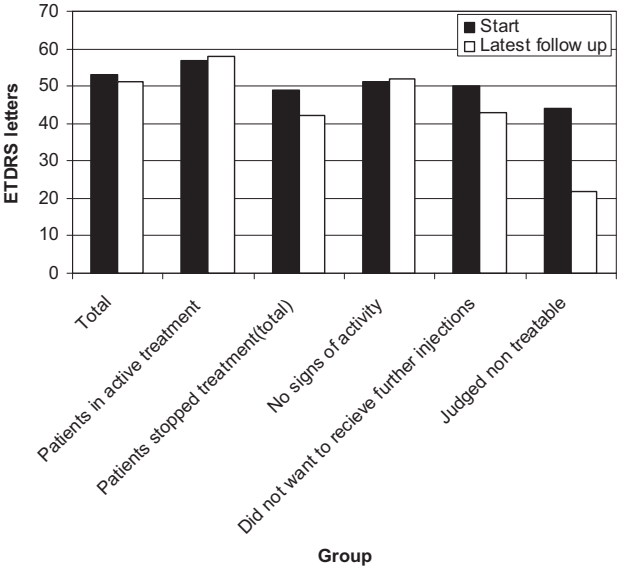

FIGURE. Bar graph showing best-corrected visual acuity for the different groups of patients with neovascular age-related macular degeneration included in the study before treatment with ranibizumab and at the latest follow-up. ETDRS = Early Treatment Diabetic Retinopathy Study.

• **PATIENTS DISCONTINUING TREATMENT:** Clinical characteristics and the cause of discontinuation of treatment of the patients who stopped treatment are summarized in Table 1. A total of 399 patients (246 women and 153 men) with a mean age of 78.7 years (range, 54 to 96 years) discontinued treatment in the 4-year period. In 181 (45%) of 399 patients discontinuing treatment, there were no signs of activity (denoted as having no signs of activity), 36 (9%) of 399 patients did not want to receive further treatment, and 113 (28%) of 399 patients were judged nontreatable by the treating physician (denoted as being judged nontreatable). Of 399 patients discontinuing treatment, 69 (17%) could not complete follow-up primarily because of death (n = 56) or because they moved to another region of the country (n = 13). There was a significant difference among the 3 groups regarding the BCVA at baseline ($P = .003$, analysis of variance). The mean visual acuity at the initiation of treatment was 50.8 letters (range, 1 to 85 letters) in the group showing no signs of activity and was 50.3 letters (range, 20 to 72 letters) in the group of patients who did not want further treatment, whereas the mean visual acuity was only 43.8 letters (range, 1 to 80 letters) in the group judged nontreatable (significantly lower compared with the group with no signs of activity ($P = .001$, *t* test) and almost significantly lower than the group of patients who did not want further treatment ($P = .06$, *t* test). At the end of follow-up, the BCVA was 52.4 letters (range, 5 to 87 letters) in the group showing no signs of activity, a nonsignificant change from baseline ($P = .295$, paired-sample *t* test), 43.3 letters (range, 8 to 75

TABLE 2. Gain and Loss of Minimum of 15 Letters in the Different Groups of Patients with Neovascular Age-Related Macular Degeneration Treated with Ranibizumab during the 4-Year Period

	Minimum 15-Letter Gain	Minimum 15-Letter Loss
All patients included (n = 855)		
No. of patients	142 (17%)	198 (23%)
Mean no. of injections	8.2	8.1
Patients in active treatment (n = 456)		
No. of patients	81 (18%)	66 (14%)
Mean no. of injections	11.0	11.4
Total patients stopping treatment[a] (n = 399)		
No. of patients	61 (15%)	132 (33%)
Mean no. of injections	4.4	6.4
No signs of activity (n = 181)		
No. of patients	43 (24%)	36 (20%)
Mean no. of injections	4.4	5.9
Did not want to receive further injections (n = 36)		
No. of patients	4 (11%)	13 (36%)
Mean no. of injections	5.3	5.4
Judged nontreatable (n = 113)		
No. of patients	3 (3%)	67 (59%)
Mean no. of injections	4.0	7.1
Other reasons (n = 69)		
No. of patients	11 (16%)	16 (23%)
Mean	6.0	6.2

[a]The patients who terminated treatment were divided into the following subgroups: no signs of activity, did not want to receive further treatment, and judged nontreatable, and other reasons comprising death and the patient moving to another region.

letters) in the group who did not want further treatment, an almost significant decrease from baseline ($P = .092$, paired-sample t test), and 21.8 letters (range, 1 to 69 letters) in the group judged nontreatable, a significant decrease compared with baseline ($P < .0001$, paired-sample t test; Table 1 and Figure).

Tables 2 and 3 show in more detail the treatment results of the different groups. In the group with no signs of activity, 43 (24%) of 181 patients experienced a gain of 15 letters or more, whereas 36 (20%) of 181 patients experienced a loss of 15 letters or more. In the group of patients who did not want to received further treatment, 4 (11%) of 36 patients experienced an increase of minimum 15 letters, whereas 13 (36%) of 36 patients lost a minimum of 15 letters after treatment.

In the group of patients who did not want to receive any further treatment, none of the patients started of treatment with a BCVA of fewer than 20 letters and only 2 (6%) of 36 patients identified fewer than 20 letters on the ETDRS chart at the last follow-up. One patient (3%) of 36 patients had a BCVA of more than 70 letters at initiation of therapy, whereas 5 (14%) of 36 patients had a BCVA of more than 70 letters at the end of follow-up. In the group judged nontreatable, 11 (10%) of 113 patients had a BCVA of fewer than 20 letters at initiation of therapy, increasing to 54 (48%) of 113 patients after treatment. Three (3%) of 113 patients in this group had a BCVA of more than 70 letters at inclusion, whereas no patient in this group could identify more than 70 letters on the ETDRS chart at the last follow-up consultation.

Only 3 (3%) of 113 patients in the group judged nontreatable gained 15 letters or more, whereas 67 (59%) of 113 patients in this group had lost 15 letters or more at the end of follow-up. Four (2%) and 17 (9%) of the 181 patients in the group with no signs of activity had a BCVA of fewer than 20 letters at the initiation of therapy and at the last clinical follow-up, respectively. However, 7 (4%) and 42 (23%) of the 181 patients had a BCVA of more than 70 letters at inclusion and at the last follow-up, respectively.

The reasons that the patients gave for not wanting to receive further treatment and the BCVA of the individual patients are summarized in the Supplemental Table (available at AJO.com). Of the 36 patients who did not want to receive further treatment, 23 patients (64%) did not give a specific reason for their decision, although they were asked to offer one. Three (8%) of the 36 patients explained that they were generally too tired and could not report to the department so often, and 2 (6%) other patients stopped treatment because of other diseases. Three (8%) of the 36 patients did not show up 3 times consecutively and did not respond to the department attempts to contact them, and 2 (6%) of 36 patients patients believed that the treatment had no effect. One patient (3%) thought that the treatment had made the visual acuity even worse. One patient (3%) stopped because he had experienced corneal abrasions in connection with the last 3 injections, and 1 patient (3%) did not want further treatment because he did not like the treating physician. During the 4-year period, 157 (18%) of the 855 patients included in the study discontinued treatment within the first year of treatment and 174 (20%) patients discontinued treatment during the second year of treatment, whereas 55 (6%) and 13 (2%) patients discontinued treatment during the third and fourth year of treatment, respectively.

DISCUSSION

IN THIS STUDY, WE ANALYZED 4-YEAR SINGLE-CENTER DATA on ranibizumab treatment for neovascular AMD, including a more detailed study of the patients who discontinued the treatment.

• **OVERALL TREATMENT RESULTS:** The pivotal clinical trials showed an overall improvement of vision. In the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related

TABLE 3. Number of Patients with Best-Corrected Visual Acuity of Less than 20 Letters or More than 70 Letters before Treatment and at the Latest Follow-up among Patients with Neovascular Age-Related Macular Degeneration Treated with Ranibizumab

	BCVA < 20 Letters		BCVA > 70 Letters	
	Start	Latest Follow-up	Start	Latest Follow-up
All patients (n = 855)				
No. of patients	23 (3%)	90 (11%)	68 (8%)	171 (20%)
Patients in active treatment (n = 456)				
No. of patients	6 (1%)	10 (2%)	51 (11%)	116 (25%)
Total patients stopping treatment[a] (n = 399)				
No. of patients	17 (4%)	80 (20%)	17 (4%)	55 (14%)
No signs of activity (n = 181)				
No. of patients	4 (2%)	17 (9%)	7 (4%)	42 (23%)
Did not want to receive further injections (n = 36)				
No. of patients	0 (0%)	2 (6%)	1 (3%)	5 (14%)
Judged nontreatable (n = 113)				
No. of patients	11 (10%)	54 (48%)	3 (3%)	0 (0%)
Other reasons (n = 69)				
No. of patients	2 (3%)	7 (10%)	6 (9%)	8 (9%)

BCVA = best-corrected visual acuity.

[a]The patients who terminated treatment were divided into the following subgroups: no signs of activity, did not want to receive further treatment, and judged nontreatable, and other reasons comprising death and the patient moving to another region.

Macular Degeneration (MARINA) trial, in which patients with minimally classic or occult lesions received monthly injections of ranibizumab for 24 months, there was an increase of 6.6 letters in the treated group and a loss of 14.9 letters in the sham group.[1] In the *Anti*-vascular endothelial growth factor (VEGF) Antibody for the Treatment of Predominantly Classic *Cho*roidal Neovascularization (CNV) in Age-related Macular Degeneration (ANCHOR) trial, patients with predominantly classic lesions were included, and that study reported an increase of 10.7 letters in the treatment group after 24 months.[2] In the recent Comparison of Age-Related Macular Degeneration Treatments Trials (CATT), there was an increase of 8.5 and 6.8 letters, respectively, as a result of monthly administered ranibizumab and ranibizumab administered as needed, respectively.[6] Our data showed that over a period of up to 4 years, vision deteriorated moderately (approximately 3 letters) when treating neovascular AMD with ranibizumab using a clinician determined retreatment strategy. This is including all patients in the analysis with a minimum follow-up of 15 months from first treatment and all patients who discontinued treatment during the 4-year period. Our report shows that when follow-up extends beyond 2 to 3 years and includes all patients with a negative response despite shorter duration of follow-up, vision does seem to decrease. Omitting patients who responded negatively to treatment with short follow-up from the analysis would cause a bias toward a more favorable response. The results still are much better than those of the sham group in the MARINA trial and the verteporfin group in the ANCHOR trial, where losses of 14.9 and 9.8 letters, respectively, were found.[1,2] However, when looking at the patients currently receiving treatment, ranibizumab does provide stabilization or even a small (approximately 1-letter) improvement in BCVA from baseline when using a clinician determined retreatment strategy in normal clinical practice. This increase is smaller than those reported in the randomized clinical trials, but one should also take into account that patients in our cohort were treated even though they had better or worse visual acuity than the patients in the trials and regardless of lesion size and morphologic features. Furthermore, it is difficult to follow a stringent treatment and follow-up regimen in daily clinical practice.

Our treatment results are somewhat comparable with those of most other studies using the PRN treatment strategy. Some studies have shown an overall decrease in visual acuity,[7,8] whereas others have reported a slight improvement.[4,5,9–13] However, no study has been as large as ours with up to 4 years of follow-up, making direct comparisons difficult. When evaluating the PRN treatment strategy, the HORIZON study showed that a gain of 2 letters could be obtained.[9] A 24-month outcome study reported the results for 96 eyes in which an increase of 6.5 letters was obtained,[10] whereas a Swedish study of 471 patients using the PRN treatment strategy observed an increase of 1 letter after 12 months.[5] Kumar and associates presented a mean VA before treatment of 49.5 letters and a mean VA of 52.6 letters after 12 months in 81 patients, a study from Spain showed an increase of 1.3 letters after 12 months, and a German study reported a stabilization of vision after 24 months in 152 eyes.[4,11,12]

• **GAIN OF 15 LETTERS:** In the MARINA trial, 33.8% gained a minimum of 15 letters after the first year, and

this result was sustained 24 months after initiating treatment. In the sham group, these figures were 5.0% and 3.8%, respectively.[1] In the ANCHOR study, 40.3% gained a minimum of 15 letters at 12 months from baseline, whereas this figure was 5.6% for the verteporfin group at 12 months from baseline.[2] Our data showed that 142 (17%) of 855 patients included in our study had an increase of 15 letters or more after treatment (mean follow-up, 23.3 months), whereas 81 (18%) of 456 patients currently in treatment gained 15 letters or more. Again, our results are based on a clinician-determined retreatment strategy in an everyday clinical setting and therefore are not directly comparable with those of randomized clinical trials. However, our data are somewhat comparable with other studies using the PRN treatment strategy. Kumar and associates reported that 17.1% of patients gained a minimum of 15 letters, and Hjelmqvist and associates reported that 14.7% had improved by 15 letters or more.[4,5] Querques and associates reported in a study of 24-month outcomes of ranibizumab treatment for exudative AMD that 25% of patients gained at least 15 letters using a variable dosing regimen treatment strategy.[10] In contrast, the Prospective Optical coherence tomography imaging of patients with Neovascular AMD Treated with intra-Ocular ranibizumab (PrONTO) study revealed that 35% of patients receiving PRN treatment gained a minimum of 15 letters at 12 months from baseline, whereas a Swiss study including 138 patients receiving PRN treatment reported that 31% and 30% of study patients gained a minimum of 15 letters at 12 and 24 months from baseline, respectively.[3,14]

• **NUMBER WITH MORE THAN 70 LETTERS:** We found that the number of patients identifying more than 70 letters increased from 68 (8%) of 855 patients at baseline to 171 (20%) of 855 patients at the last follow-up visit. In the group of patients in active treatment or follow-up, these figures were 51 (11 %) of 399 patients at baseline, increasing to 116 (25%) of 399 patients at the latest follow-up visit. In contrast, 4.3% of patients receiving ranibizumab in the ANCHOR study identified more than 70 letters at baseline, whereas 38.6% of patients were able to identify a minimum of 70 letters at 12 months from baseline.[15] In the MARINA study, these figures were 15% and 40%, respectively, and at months 24, there was a further increase to 42%.[1]

A change in BCVA of fewer than 15 letters is considered to be a stabilization of vision. Hjelmqvist and associates showed in a multicenter study on 1-year outcomes of ranibizumab treatment in 471 patients that 74.4% of the patients showed a stable VA over the 12-month period (change in BCVA, < 15 letters).[5] This is quite similar to our results, because we found 77% of all patients included in our study had a change in BCVA of fewer than 15 letters.

• **PATIENTS DISCONTINUING TREATMENT:** The duration of disease activity and the cause of termination of treatment was not described extensively. This information is highly relevant to the patient, but also to the physician monitoring and evaluating treatment. In Denmark, patients receive treatment with ranibizumab free of charge because the cost of treatment is covered by the Danish National Health Insurance, which is financed by general taxes. Therefore, no patient or physician terminated treatment for economic reasons. In our study, 181 (45%) of 399 patients discontinued treatment because the physician assessed that there were no signs of activity and that no further treatment was required. Of these, 113 patients (28%) were judged nontreatable and 34 patients (9%) decided that they did not want further treatment. Finally, 69 (17%) patients stopped for other reasons (56 died and 13 moved out of the region). We found a significant difference in BCVA at baseline when comparing the group of patients who were judged nontreatable with the group of patients with no signs of activity. Furthermore, we found that the patients who were judged nontreatable had a worse BCVA compared with any of the other groups at baseline. Thus, 11 (10%) of 113 patients in this group were able to recognize fewer than 20 letters at baseline. After treatment, the number of patients recognizing fewer than 20 letters had increased to 54 (48%) of 133 patients. In a recent Danish study of 279 patients with CNV in AMD, Bloch and associates found that a BCVA of fewer than 35 letters at baseline and after 3 months was associated with a BCVA of 35 letters or fewer after 12 months.[16] We found a significant decrease in BCVA in the group judged nontreatable from 43.8 letters (range, 1 to 80 letters) at initiation of treatment to 21.8 letters (range, 1 to 69 letters) at the last follow-up, further suggesting that low vision at the initiation of therapy does hold a less favorable prognosis. In the group with no signs of activity, there was an increase in BCVA of 2 letters, which was found to be a nonsignificant change.

Of the 399 patients discontinuing treatment in the 4-year period, 157 (39%) terminated treatment within the first year and 174 (44%) terminated treatment within the second year. Thus, 331 (83%) of 399 patients terminating treatment did so within the first 2 years. Of last 68 (17%) patients who discontinued treatment in the third and fourth year, 55 patients (14%) did so in the third year and 13 (3%) patients did so in the fourth year. In comparison, 122 (27%) patients in the active treatment group were still receiving treatment or being followed up in the fourth year from baseline. Our results give an indication that the patients receiving ranibizumab can be divided into 3 overall groups. The first 2 groups are the bad or nonresponder group, consisting of approximately 15% of all patients, and the good responders, consisting of approximately 21% of all patients. These 2 groups generally can be identified within the first 2 years of treatment, whereas the third group, the regular responders consisting of approximately 64% of all patients, require continuous monitoring and treatment for years.

The patients who decided to discontinue treatment ($n = 36$) did so for various reasons. In general, these

reasons had to do with general health problems and difficulty in overcoming the many visits to the department.

With the current treatment regimen, we were able to maintain a longer period with stable vision, and in this report, we showed that most patients require treatment for a period of months or even years. In our group of patients, only 181 (21%) of 855 patients have discontinued treatment because of complete inactivation of the CNV. Another 131 (15%) did not respond to treatment, leaving almost 60% to 70% of patients in need of continuous treatment for up to 4 years, and possibly even longer. This is important information that should be given to the patients at the initiation of the treatment; the psychological aspects of having an uncertain social situation regarding one's visual abilities may affect the patient's quality of life negatively. In our experience, many patients prefer to know their prognosis—even though it may be grim—so that they can plan ahead, and therefore the patients should be informed of the very protracted nature of the treatment and that there is a certain level of unpredictability.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and the following were reported. Torben Lykke Sørensen is on the advisory board of Bayer and Allergan. Involved in design and conduct of study (M.K.F., T.L.S., H.K.); Data collection (M.K.F., T.L.S., H.K.); Management, analysis, and interpretation of data (M.K.F., T.L.S., H.K.); and preparation, review, or approval of the manuscript (M.K.F., T.L.S., H.K.). The study adhered to the Declaration of Helsinki and all state laws in Denmark. According to national law and local hospital research guidelines, a retrospective study of treatment results, when the treatment is administered as part of routine clinical practice, does not require institutional review board approval.

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Biosketch

Mads Falk, MD, is currently a PhD fellow at the Department of Ophthalmology, Copenhagen University Hospital Roskilde in Denmark. He graduated from the University of Copenhagen in 2007. He is interested in the immunological changes in age-related macular degeneration.

Biosketch

Torben Lykke Sørensen is a Clinical Associate Research Professor at the University of Copenhagen, Denmark. He completed his MD from the University of Copenhagen and received his Doctor of Medical Sciences Degree (DMSc) from the University of Copenhagen in 2004. He is a board-certified ophthalmologist, chief physician and Director of Research at the Department of Ophthalmology, Copenhagen University Hospital Roskilde. He holds a Hirsch-index of 16 and is currently supervising 2 PhD students.

SUPPLEMENTAL TABLE. Demographic and Clinical Characteristics of Patients with Age-Related Macular Degeneration in Active Treatment with Ranibizumab Rejecting Treatment and Causes for Rejecting Treatment

Gender	Age (y)	Starting Visual Acuity (ETDRS Letters)	Visual Acuity at Latest Follow-up (ETDRS Letters)	Difference in Visual Acuity from Start to Latest Follow-up (ETDRS Letters)	No. of Injections	Follow-up (mos)	Cause
Female	66	72	75	3	18	38	No reason given
Male	67	35	45	10	11	23	No reason given
Male	81	60	50	−10	7	18	No reason given
Male	82	65	20	−45	5	15	No reason given
Female	84	60	50	−10	6	22	No reason given
Female	96	50	50	0	5	11	No reason given
Female	66	70	50	−20	6	10	No reason given
Female	93	65	20	−45	2	10	No reason given
Male	75	60	30	−30	4	10	No reason given
Female	84	50	35	−15	3	9	No reason given
Female	73	35	70	35	6	8	No reason given
Male	75	60	50	−10	4	9	No reason given
Male	80	60	72	12	3	8	No reason given
Female	81	35	35	0	3	7	No reason given
Female	92	35	35	0	3	6	No reason given
Female	94	65	35	−30	3	6	No reason given
Male	81	60	74	14	3	5	No reason given
Female	75	35	35	0	3	4	No reason given
Female	75	35	55	20	3	4	No reason given
Female	72	35	30	−5	6	11	No reason given
Male	85	35	20	−15	4	13	No reason given
Male	75	35	50	15	5	9	No reason given
Female	61	50	35	−15	7	22	No reason given
Male	87	20	50	30	3	6	Tired, does not have the energy to attend the many visits in the clinic.
Female	84	50	25	−25	11	31	Does not have the energy to attend the many visits in the clinic
Female	84	50	18	−32	6	21	Does not have the energy to attend the many visits in the clinic
Female	79	65	47	−18	4	11	Did not attend follow-up
Male	89	65	72	7	3	8	Did not attend follow-up
Female	93	35	35	0	3	4	Did not attend follow-up
Female	80	32	45	13	3	7	Generally ill
Female	86	35	35	0	3	6	Generally ill
Female	74	35	35	0	3	12	Doesn't think the treatment has had any effect
Female	82	65	35	−30	12	15	Doesn't think the treatment has had any effect
Male	77	70	8	−62	3	9	Believes the injections have worsened the visual acuity
Female	61	60	72	12	6	9	Experienced corneal abrasions 3 times in connection with injections
Female	81	65	60	−5	4	4	Did not like the treating physician

ETDRS = Early Treatment Diabetic Retinopathy Study.