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Original Article

Direct Treatment Costs of Neovascular Age-related Macular Degeneration and Comparison of Gained and/or Preserved Vision with Expenditure

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Abstract

Objectives: The aim was to quantify the direct medical cost of neovascular age-related macular degeneration (AMD) versus gained or preserved vision.

Materials and Methods: Data of patients treated for neovascular AMD between January 2009 to January 2014 were reviewed. Patients with complete follow-up for two years, treated with only intravitreal ranibizumab injections and with no intraocular surgery were included. Demographics, diagnostic investigations, the number of visits and injections, changes in visual acuity (VA) at one year and two years from baseline were noted. Total cost was calculated for the first and second years, and the cost of improving or preserving initial vision level was determined with subgroup analysis.

Results: Two-hundred eyes of 175 patients (86 male and 89 female) with a mean age of 72.3±7.8 years were included. Mean VA was 0.67 logMAR at baseline, 0.60 logMAR at the end of the first year, and 0.67 logMAR at the end of the second year. At the end of the 2 years, VA increased in 82 eyes (41%), remained the same in 42 eyes (21%), and decreased in 76 eyes (38%). The mean number of visits in the first and second years were 6.56 (3-12) and 5.74 (3-10), respectively. An average of 4.42 (1-8) injections were performed in the first year and 2.25 (0-7) in the second. The total direct medical cost for AMD was 9,628 TL (Turkish Lira) per patient for 2 years, which consisted of 529 TL in visit costs, 115 TL in fluorescein and indocyanine angiography costs, 611 TL in injection procedure costs, and 8,371 TL in drug costs. The cost of one line of VA gain was 11,911 TL in the first year.

Conclusion: This study showed that treatment increased or stabilized vision in a reasonable proportion of patients, that cost of management decreases in the second year, and that drug expenses are the leading item in reimbursement.

Keywords: Age-related macular degeneration, direct medical cost, ranibizumab

Introduction

Age-related macular degeneration (AMD) is a chronic progressive disease of the macula which is usually bilateral and seen in individuals over 50 years of age. It is among the main causes of blindness in populations aged 65 years and older in developed countries.[1] There are two types of AMD, dry and wet (exudative), with the exudative type responsible for 90% of blindness associated with AMD.[2] Without treatment, the visual prognosis of exudative AMD is poor, and quality of life is severely impaired.[3]

Many treatment alternatives have been developed for the treatment of AMD and were shown in numerous studies to significantly improve visual acuity (VA). However, there are insufficient data regarding the costs of treatment and the economic burden AMD imposes on patients and society.[4]

Health-related costs are classified into three main categories with respect to expenditures made to treat disease and to solve the problems patients experience in their daily life due to disease. These are medical, non-medical, and indirect expenditures.[5] Medical expenditures include medical consumables, drugs, and staff expenses which arise during the treatment process and are paid by the patient or through reimbursement systems. Non-medical expenditures are those made personally by the

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patient due to disease (such as travel and food costs). Indirect expenditures are defined as the collective cost of labor loss due to illness, disability, or premature death. The monetary value of these costs is difficult to measure.[6]

The aim of this study was to calculate the medical expenses incurred during the first two years of treatment with ranibizumab, an anti-vascular endothelial growth factor (anti-VEGF) agent commonly used to manage exudative AMD, and to compare restored/preserved vision with treatment cost.

Materials and Methods

After receiving approval from the Ege University Ethics Committee (15-9.1/14), 200 eyes of 175 patients aged 50 years and older (mean age 72.3±7.8 years; 89 female and 86 male) who started intravitreal ranibizumab therapy for exudative AMD at the Ege University Medical Faculty Retina Unit between January 2009 and January 2014 were included in the study. The patients were all followed regularly and data from their first two years of treatment were retrospectively analyzed. Treatment was administered based on a PRN (pro re nata) regimen in most of the patients; intravitreal injections were given monthly for the first three months, followed by injections as needed. The study population also included a small number of patients who were not given the three-month loading dose based on individual evaluation.

In order to derive a standard cost of treatment, we excluded patients who underwent any treatment other than intravitreal ranibizumab injection (laser photocoagulation, photodynamic therapy, or other anti-VEGF agent injections), patients who underwent cataract surgery or any other similar ocular surgery during the period in which they were included in the study (due to possible effects on VA), and patients with ocular diseases other than AMD. Furthermore, in order to be able to express degree of VA change during follow-up in the form of rows on a decimal system scale, patients with VA less than 0.05 were also excluded.

From the patients' medical records we recorded their sex, age at start of treatment, VA at 1 and 2 years after start of treatment (decimal), and the number of examinations, fundus fluorescein angiographies (FFA), indocyanine green angiographies (ICGA), and intravitreal ranibizumab injections performed during 2 years of follow-up. The VA values measured on a decimal scale were converted to logMAR and Early Treatment Diabetic Retinopathy Study (ETDRS) as corresponding letters.

To calculate medical expenditures, the annual number of examinations, FFA, ICGA, and intravitreal injection services were determined for each patient. These numbers were then multiplied by the current prices pertaining to the relevant health service (based on the Health Practices Statement [HPS] updated 18 January 2016) and the results were summed to yield annual service expense per eye in Turkish liras (TL). In order to rule out factors such as inflation and price changes, current service fees and drug prices were used as the basis for calculating medical treatment expenses.

According to HPS Appendix 2A (Outpatient Treatment Payment List) published on 18 January 2016, payments of 43 TL for an examination, 89.20 TL for FFA, 161.20 TL for ICGA+FFA, and 91.80 TL for an intravitreal injection are made to the Social Security Institution (SSI). Optical coherence tomography (OCT) is included in the examination package by the SSI and there is no reimbursement fee for OCT in addition to the examination fee.

The public price of a dose of injectable ranibizumab (Lucentis; Genentech, South San Francisco, California, CA, USA) was derived by applying the public discount stated in the HPS to the retail price determined by the Turkish Pharmaceuticals and Medical Devices Agency. We used the most recent (updated on 22 February 2016) public price for Lucentis of 1,256.09 TL in our study.

The eyes included in the study were grouped in two different ways: Firstly, we grouped the eyes based on change in VA from baseline to the end of the second year of treatment as eyes with increased VA, preserved VA, and decreased VA. Secondly, the eyes were divided into those with VA of ≥0.5 and those with VA <0.5 at the start of treatment.

Based on the recorded data, we calculated the exudative AMD-related costs for the SSI per eye in the first and second years of treatment and compared these costs to amount of change in VA for all eyes and the subgroups described above.

Results

The study included 200 eyes of 175 patients (89 female, 86 male) with a mean age of 72.3±7.8 years.

The average numbers of examinations, FFA and ICGA procedures, and intravitreal ranibizumab injections during the first and second years of treatment are presented in Table 1. Over the 2 years of treatment, the patients were examined approximately 12 times on average and had received an average of 7 intravitreal ranibizumab injections. When the costs of examinations, testing, drugs, and drug administration were added, it was found that the total average medical expenditure per eye at the end of 2 years was about 9,600 TL, with an average of 6,312 TL in the first year and 3,315 TL in the second year. Table 2 shows the average annual expenses for each expenditure item and the total annual expenditure. We determined that the cost of the drug accounted for 88% of the total expenditure in

Table 1. Mean annual number of medical health expenditure items

	Number in year 1 ± SD (range)	Number in year 2 ± SD (range)
Examinations	6.56±1.45 (3-12)	5.74±1.64 (3-10)
FFA	0.71±0.51 (0-2)	0.09±0.31 (0-2)
ICGA	0.06±0.25 (0-2)	0.21±0.42 (0-2)
Intravitreal injections	4.42±1.51 (1-8)	2.25±1.92 (0-7)

SD: Standard deviation, FFA: Fundus fluorescein angiography, ICGA: Indocyanine green angiography

the first year and 85% in the second year. In contrast, the cost of the surgical procedure of intraocular administration of this costly drug represented only 6% of the total medical expenditure (Table 2).

The annual number of injections (Table 3) and the total annual cost (Table 4) were similar among the subgroups based on VA change (increased/preserved/decreased) and initial VA (<0.5 and ≥0.5).

Mean VA (decimal) was 0.292±0.21 at the start of treatment, 0.338±0.23 at the end of the first year, and 0.299±0.23 at the end of the second year. Based on these values, VA increased by a mean of 0.53±2.33 lines in the first year of treatment and decreased by 0.45±1.88 lines in the second year. Therefore, there was a net increase of 0.08±2.67 lines after 2 years of treatment; essentially, mean VA was preserved. When the eyes were grouped based on change from initial VA, final VA was increased in 82 eyes (41%), preserved in 42 eyes (21%), and decreased in 76 eyes (38%) at the end of 2 years. When VA change was analyzed by year, we noted that the mean VA had increased during both the first and second year in the group with increased VA (n=82). VA had increased in the first year but decreased in the second year in the group with preserved VA (n=42), thus returning to the initial level. In the group with decreased VA (n=76), VA had continued to decrease during both years. At the start of treatment, VA was <0.5 in 157 eyes and ≥0.5 in 43 eyes. In the group with initial VA <0.5, VA increased in the first year and decreased slightly in the second year, for an overall increase in VA. In the group with initial VA ≥0.5, VA decreased in both years. The changes in VA in all eyes and subgroups during the first 2 years of treatment are presented in Table 5.

In this study, we calculated the cost of 1 line of VA gain by dividing the total cost by increase in lines. Based on this, the average cost of one line of VA gain for all eyes during the first year was 11,911 TL. Because the mean VA of all eyes did not increase in the second year, this figure could not be calculated. In the subgroup with increased VA at the end of 2 years, the average cost of one line of VA gain was calculated as 2,999 TL for the first year and 3,636 TL for the second year. The total average cost of preserving VA for 2 years was 9,337 TL in the subgroup of eyes with preserved VA. In this group, VA increased in the first year and the average cost of 1 line VA gain was 8,477 TL. However, as there was no improvement in VA in the second year, this figure could not be calculated for the second year. Despite an average expenditure of 10,092 TL over 2 years, VA decreased in both years in the group with decreased VA. Therefore, the cost of 1 line of VA gain could not be calculated. In the group with initial VA <0.5, the cost of one line of VA gain was 6,692TL for the first

Table 2. Mean annual cost of medical health expenditure items

	Year 1, TL ± SD (%)	Year 2, TL ± SD (%)
Drug	5,552±1,903 (88)	2,820±2,414 (85.1)
Surgical procedure	405±139 (6.4)	206±176 (6.2)
Examination	282±62 (4.5)	247±70 (7.4)
FFA+ICGA	73±53 (1.1)	42±73 (1.3)
Total cost	6,313±2,061 (100)	3,315±2,634 (100)

TL: Turkish lira, SD: Standard deviation, FFA: Fundus fluorescein angiography, ICGA: Indocyanine green angiography

Table 3. Mean annual number of injections in the patient subgroups

	Year 1, number ± SD	Year 2, number ± SD
All eyes (n=200)	4.42±1.51	2.25±1.92
VA increased (n=82)	4.41±1.65	2.06±2.02
VA preserved (n=42)	4.33±1.52	2.11±1.78
VA decreased (n=76)	4.47±1.36	2.51±1.87
Initial VA <0.5 (n=157)	4.40±1.50	2.15±1.90
Initial VA ≥0.5 (n=43)	4.46±1.57	2.58±1.95

SD: Standard deviation, VA: Visual acuity

Table 4. Mean annual cost of medical health expenditure items in the patient subgroups

	Year 1, TL ± SD	Year 2, TL ± SD
All eyes (n=200)	6,313±2,061	3,315±2,634
VA Increased (n=82)	6,298±2,257	3,047±2,761
VA Preserved (n=42)	6,188±2,071	3,149±2,435
VA Decreased (n=76)	6,397±1,846	3,695±2,587
Initial VA <0.5 (n=157)	6,290±2,040	3,186±2,610
Initial VA ≥0.5 (n=43)	6,393±2,159	3,786±2,697

TL: Turkish lira, SD: Standard deviation, VA: Visual acuity

Table 5. Visual acuity at baseline, 1 year, and 2 years

		Initial VA	VA at 1 year	VA at 2 years
All eyes (n=200)	Decimal	0.29	0.34	0.29
	logMAR	0.67	0.60	0.67
	ETDRS	51.5	54.9	51.7
VA increased (n=82)	Decimal	0.21	0.39	0.42
	logMAR	0.81	0.52	0.45
	ETDRS	44.64	58.8	65.5
VA preserved (n=42)	Decimal	0.21	0.28	0.21
	logMAR	0.81	0.71	0.81
	ETDRS	44.3	49.5	44.3
VA decreased (n=76)	Decimal	0.41	0.31	0.21
	logMAR	0.44	0.62	0.82
	ETDRS	62.8	53.7	44.1
Initial VA <0.5 (n=157)	Decimal	0.20	0.28	0.25
	logMAR	0.79	0.66	0.71
	ETDRS	45.4	51.6	49.0
Initial VA ≥0.5 (n=43)	Decimal	0.61	0.52	0.45
	logMAR	0.22	0.35	0.46
	ETDRS	73.6	67.2	61.5

VA: Visual acuity, ETDRS: Early Treatment Diabetic Retinopathy Study

Table 6. Visual acuity change from year 1 to year 2 (lines), annual cost. and cost per 1 line of visual gain				
	VA change(Lines)	**Total cost (TL)**	**Cost of 1 line visual gain (TL)**	
All eyes n=200	+0.53	6,312	11,911	Year 1
	-0.45	3,315	-	Year 2
VA Increased (n=82)	+2.10	6,298	2,999	Year 1
	+0.46	3,047	6,625	Year 2
VA Preserved (n=42)	+0.73	6,188	8,477	Year 1
	-0.73	3,149	-	Year 2
VA Decreased (n=76)	-1.28	6,397	-	Year 1
	-1.27	3,695	-	Year 2
VA <0.5 (n=157)	+0.94	6,290	6,692	Year 1
	-0.34	3,186	-	Year 2
VA ≥0.5 (n=43)	-0.97	6,393	-	Year 1
	-0.83	3,786	-	Year 2
VA: Visual acuity, TL: Turkish lira				

Table 7. Total visual acuity change after 2 years. total cost. and total cost of 1 line gain in visual acuity			
	VA (lines)	**Total cost (TL)**	**Cost of 1 line VA gain (TL)**
All eyes (n=200)	+0.08	9,628	-
VA Increased (n=82)	+2.57	9,346	3,636
VA Preserved (n=42)	0	9,337	-
VA Decreased (n=76)	-2.56	10,092	-
Initial VA <0.5 (n=157)	+0.59	9,477	16,062
Initial VA ≥0.5 (n=43)	-1.81	10,179	-
VA: Visual acuity, TL: Turkish lira			

year, but could not be calculated for the second year due to an overall decrease in VA. In the group with initial VA ≥0.5, there was a decrease in VA in both years despite a total expenditure of 10,179 TL over 2 years. The average change in VA (lines) in the first and second years of treatment, total average medical expenses, and the cost of 1 line of VA gain (when applicable) for all eyes and subgroups are shown in Table 6. Table 7 shows the total change in VA at the end of 2 years and the total cost, together with the cost of increasing VA by one line.

Discussion

The clinical efficacy and reliability of ranibizumab in various retinal diseases including AMD has been demonstrated in randomized, controlled clinical trials involving over 1.7 million patient-years and including over 12,500 patients.[7,8] However, relatively few studies address the financial aspect of treatment, and the cost of treating AMD with intravitreal anti-VEGF agents is quite high. Moreover, as the population aged 65 years and older continues to grow, health spending related to AMD has also increased and the economic burden is expected to increase further in the coming years.[9]

Currently, intravitreal anti-VEGF agents are mainly used to treat exudative AMD, but they are an extremely costly option. In the present study, we determined based on real-life data that a patient with AMD receives an average of about 4.4 injections within the first year and about 2.2 in the second year. We also found that in Turkey, the cost of the drug used for these injections accounted for nearly 90% of the related health expenditures. This cost is an average of 9,628 TL for 2 years, with VA being preserved, though not significantly improved, at the end of this period. The average cost of one line of VA gain for one AMD patient was calculated to be 11,911 TL for the first year, but because VA returned to initial levels at the end of the second year, this calculation could only be done for the subgroup with increased VA.

The issue of concern is how to provide uninterrupted treatment with intravitreal anti-VEGF therapy, which is necessary for AMD, a disease with high prevalence in advanced age, but is also costly. The question of how to provide the best healthcare within a limited budget has increased the importance of health economics research. In the ANCHOR and MARINA trials, which were the first studies to investigate the clinical efficacy of intravitreal ranibizumab therapy for the treatment of neovascular AMD, injections were administered monthly.[10,11] Although favorable clinical outcomes were achieved in these studies, such a treatment scheme does not seem feasible considering the limited human, technical, and financial resources in real-life clinical practice. For this reason, attempts have been made to develop alternative treatment schemes for intravitreal therapeutic applications in order to reduce follow-ups, testing, and costs.

In the LUMINOUS study, which examined the outcomes of ranibizumab therapy applied in routine clinical practice, the one-year data of a total of 4,444 patients with wet AMD who received ranibizumab injections in Germany, the Netherlands, Belgium, and Sweden were evaluated.[12] According to the results

of the LUMINOUS study, the number of injections done in the first year varies between 4.3 and 5.7 in different countries. Similarly, we determined that the average number of injections during the first year of treatment in our study was within this range (4.4 on average).

In terms of visual improvement, mean letter gains at the end of 1 year of treatment in the countries in the LUMINOUS study were as follows: -0.8 letters in Germany, +5.6 letters in the Netherlands, +2.5 letters in Belgium, and +1 letter in Sweden. In the present study, there was an average gain of 3.4 letters at the end of the first year. However, this was offset by an average loss of 3.2 letters in the second year, resulting in an overall gain of 0.2 letters at the end of 2 years compared to the start of treatment. Therefore, initial VA was more or less preserved. These results are similar to the LUMINOUS study, which was based on real-life data, but lagged behind the gains reported in the ANCHOR (10.7 letters in 2 years) and MARINA (6.6 letters in 2 years), in which injections were given monthly.[10,11] This difference may be attributable to the lower average number of injections in the clinical setting, especially in the second year of treatment.

In their study assessing the results of the CATT study, Ying et al.[13] reported that initial VA of 0.5 or greater is a poor prognostic marker for VA improvement. We also observed in our study that treatment was less effective in patients with an initial VA of 0.5 or higher. This group had a mean loss of 12.0±17.8 letters at the end of 2 years, whereas the group with an initial VA below 0.5 had a mean gain of 3.5±18.6 letters in 2 years. Moreover, the two groups had similar numbers of intravitreal injections and total treatment costs, meaning that a more successful clinical result was obtained at the same cost in the group with low VA. However, explaining why the subgroups showed different responses is beyond the scope of this study.

Comparing studies conducted in different countries in terms of cost is problematic. This can be partially attributed to international variations in currencies and unit prices for health procedures and services, treatment regimens applied, and reimbursement agency tariffs. The fact that the analyses were done in different years is another factor that precludes comparison.

Although the present study focused on the treatment costs of wet AMD, it is important to remember that treatment of AMD is not limited to the wet type. Approximately 90% of AMD patients have the non-exudative form, and the cost of supportive treatment for these patients should also not be underestimated. Patients with dry AMD also require regular ophthalmology visits. For treatment, nutritional supplements are recommended to prevent the dry form from progressing to the wet form. These supplements are not covered by the reimbursement system in our country and the expense is directly paid for by the patient. In addition to available nutritional supplements, studies are ongoing into new intravitreal drugs that reduce the growth of geographic atrophy, targeting inflammasomes, developing drugs that affect the photoreceptor pigment cycle, neuron protection, and stem cell transplantation.[14,15,16,17,18] With newly developed drugs, cost will also become an important issue in the treatment of dry AMD in the coming years.

In addition to assessing the clinical effectiveness of AMD treatment, our study also examines its cost and compares patient expenditures with clinical outcomes. This makes it a pioneering study in Turkey. However, another issue that needs to be emphasized is the importance of investigating how treatments affect patients' quality of life, aside from their clinical efficacy. Assessing the benefit of treatment based solely on VA is inadequate, and the quality of health services cannot be improved without knowing about objective patient satisfaction. Patients with AMD can face serious problems with activities of daily living, such as driving, reading, face recognition, shopping, cleaning, home repairs, taking medication, cooking, paying bills, and maintaining personal hygiene, and these problems increase in proportion to reduction in VA.[19] Investigating the adverse effects of AMD on quality of life will help to better understand the value of treatment.

A limitation of this study is the fact that we calculated expenditures associated with the medical treatment only. Total cost, which includes myriad expenses such as personal nonmedical AMD-related expenditures made by the patient, staffing costs, hospital stationary expenses, and expenses associated with providing the physical environment where devices are located, could not be ascertained. These costs are difficult to quantify monetarily, which in turn makes it difficult to determine the necessary amount of reimbursement from the state. Another limitation is that VA levels were recorded according to a decimal system, which required these values to be converted to Snellen and ETDRS letter equivalents in order to compare our data with the international literature. Although the literature was taken as an example, small changes in the data during these conversions are unavoidable. Finally, this research was conducted in a single center with data from a limited number of patients, which limits the generalization of our results. However, it allows us to shed some light on the situation in Turkey. Multicenter studies with large patient numbers are needed to enable the calculation of national medical expenditures associated with the treatment of exudative AMD.

Conclusion

This study revealed that individuals incurred an average of 9,628 TL of medical expenses for 2 years of AMD treatment, that VA was preserved at the end of 2 years compared to initial levels, and that patients who improved with treatment in the first year spent less in the second year. In particular, we noted that the number of injections in the second year and the amount of VA gain with 2 years of treatment were lower in our study compared to the literature. Increasing the frequency of treatment applications may result in better visual outcomes. We believe that our study offers potentially useful information regarding treatment costs in AMD, especially for our country.

Ethics

Ethics Committee Approval: Ege University Faculty of Medicine Clinical Research Ethics Committee (15-9.1/14).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Şeyda Yıldırım, Cezmi Akkın, Zafer Öztaş, Serhad Nalçacı, Filiz Afrashi, Jale Menteş, Concept: Şeyda Yıldırım, Cezmi Akkın, Filiz Afrashi, Jale Menteş, Design: Şeyda Yıldırım, Cezmi Akkın, Filiz Afrashi, Jale Menteş, Data Collection or Processing: Şeyda Yıldırım, Analysis or Interpretation: Şeyda Yıldırım, Cezmi Akkın, Zafer Öztaş, Serhad Nalçacı, Literature Search: Şeyda Yıldırım, Zafer Öztaş, Cezmi Akkın, Serhad Nalçacı, Writing: Şeyda Yıldırım, Zafer Öztaş, Cezmi Akkın, Serhad Nalçacı.

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