The Challenges of Treating Neovascular Age-Related Macular Degeneration

Herausforderungen bei der Behandlung der neovaskulären altersbedingten Makuladegeneration

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ABSTRACT

Age-related macular degeneration (AMD) is one of the main causes of visual impairment and blindness in patients over 60 years in developed countries. Whilst no effective form of therapy is available for the dry form of AMD, intravitreal application of anti-VEGF substances is able to prevent the progression of neovascular AMD (nAMD) in most cases. Aside from the drugs ranibizumab, aflibercept and brolucizumab, other agents such as bevacizumab are often used off-label in order to save expense. The treatment intervals have also been refined, so as to reduce the burden on patients and health care systems. After fixed injection intervals, the pro re nata-regimen has been developed. Each month, it is decided whether the patient receives intravitreal injections based on fixed criteria. In the treat and extend-protocol, patients receive injections on each visit, but the intervals between injections vary due to the clinical outcomes. The observe-and-plan regime allows scheduling of the injection intervals in blocks, for three consecutive injections at a time. However, results of real-world studies were not able to reproduce those obtained in the pivotal studies. A high number of visits and fear of the injection procedure impose a burden on patients, that is mostly accepted due to fear of vision loss. Caregivers also complain of loss of productivity and income from having to provide regular support to patients. Health care systems worldwide are affected by increasing treatment numbers and the costs involved. The treatment of nAMD constitutes an achievement for modern medicine. However, despite the challenges, it must be evaluated and reviewed repeatedly in order to provide the best therapy for patients.

ZUSAMMENFASSUNG

Die altersbedingte Makuladegeneration (AMD) ist eine der Hauptursachen für Visusbeeinträchtigung und Erblindung von Menschen über 60 Jahren in entwickelten Ländern. Während für die trockene Spätform derzeit keine effektiven Therapieoptionen existieren, kann ein Fortschreiten der neovaskulären AMD (nAMD) bei einer regulären Behandlung mittels intravitrealer Applikation von Anti-VEGF-Substanzen zumeist verhindert werden. Neben den zugelassenen Wirkstoffen Ranibizumab, Aflibercept und seit Kurzem Brolucizumab werden andere Wirkstoffe wie Bevacizumab häufig Off-Label angewandt, um Kosten einzusparen. Auch das Behandlungsintervall wurde mehrfach weiterentwickelt, um die Frequenz der Injektionen bei Visuserhalt zu reduzieren und somit Kliniken und Patienten zu entlasten. Nach fix vorgegebenen Injektionsabständen etablierte sich das Pro-re-nata-Regime, bei dem

anhand von festgelegten Kriterien in monatlichen Abständen entschieden wird, ob eine Injektion verabreicht wird. Bei dem Treat-and-extend-Protokoll erhalten Patienten an jedem Termin eine Injektion und die Abstände zwischen den Injektionen werden abhängig von klinischen Ergebnissen verändert. Das Observe-and-plan-Regime erlaubt als Erweiterung des Treat-and-extend-Protokolls eine blockweise Festlegung der Injektionsabstände für jeweils 3 aufeinanderfolgende Injektionen. Leider konnten die Ergebnisse in Real-World-Studien bei keinem der genannten Behandlungsschemata an die der Zulassungsstudien heranreichen. Hohe Terminanzahl und Angst vor dem Injektionsverfahren stellen Belastungen für Patienten dar. Angehörige beklagen Produktivitäts- und Einkommensverluste durch regelmäßige Betreuung der Patienten. Nicht zuletzt sind Gesundheitssysteme weltweit von den steigenden Behandlungszahlen und dem damit verbundenen Aufwand sowie den Kosten betroffen. Die Therapie der nAMD ist eine Errungenschaft der modernen Medizin, die stetig evaluiert und überarbeitet werden muss, um Patienten trotz Herausforderungen bestmöglich zu therapieren.

Introduction

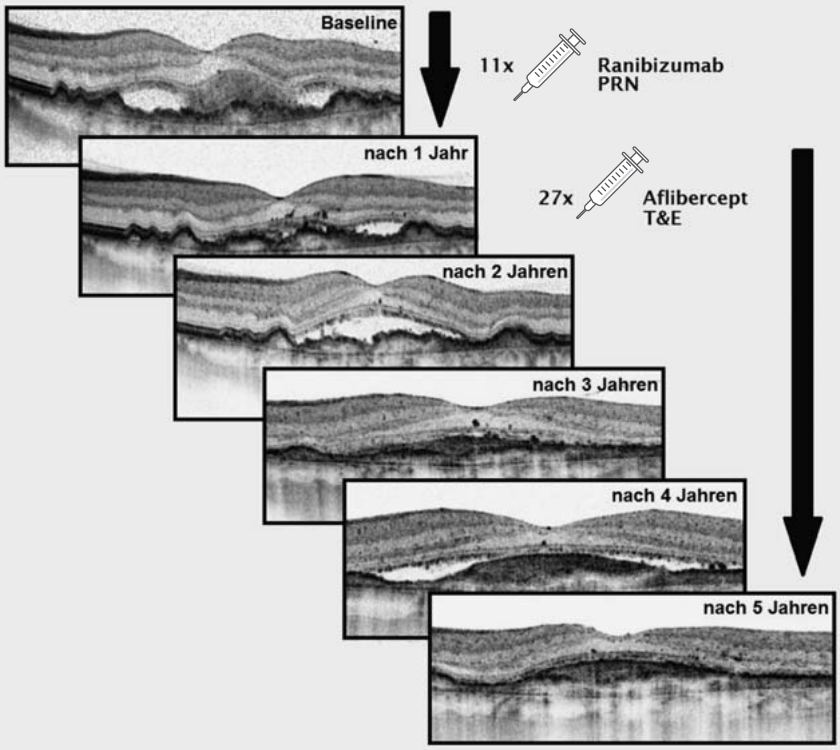
Age-related macular degeneration (AMD) is one of the main causes of visual impairment and blindness in people over 60 years of age in developed countries. This chronic, progressive retinal disease can be divided into early and late forms [1]. The early form is characterised by drusen and pigment changes and has a prevalence of 13.2% in the European population over 70 years of age. The late form of AMD is further subdivided into two classes: the dry form, characterised by geographic atrophy (GA), and the wet form, also called exudative or neovascular AMD (nAMD), characterised by choroidal neovascularisation (CNV). The prevalence of both classes of the late form combined is 3.0% in the European population over 70 years of age [2]. Unlike dry AMD, for which no effective treatment options currently exist, nAMD progression can now be largely prevented or at least delayed. This involves the inhibition of VEGF (vascular endothelial growth factor), which stimulates angiogenesis and vascular leakage from newly formed vascular networks in the choriocapillaris and is thus responsible for the progression of nAMD, by anti-VEGF agents. These are administered by means of intravitreal injection (IVI), which enables visual acuity to be maintained in many cases or even increased (▶ **Fig. 1**) [3]. Anti-VEGF therapy has revolutionised the treatment of nAMD in the last two decades, although rising life expectancy and increasing numbers of treatments present health systems and patients* with new challenges. The regular evaluation of treatment outcomes is therefore important both in order to make treatment efficient and to improve compliance and adherence to treatment among patients [4–6].

Active Substances for treating exudative AMD

Although initial attempts were made to treat nAMD with laser photocoagulation, this form of treatment was replaced with photodynamic therapy in the early 2000s. Treatment with photodynamic therapy showed a stable visual prognosis, but led to recurrences in the medium and long term and thus to a deterioration in the morphological and clinical findings. Use of photodynamic therapy in combination with intravitreal triamcinolone resulted in stabilisation of disease activity but a poorer visual prognosis than for treatment with intravitreal anti-VEGF agents [3, 7]. The authorisation of pegaptanib (Macugen; OSI Pharmaceuticals, Melville, NY, USA, and Pfizer, New York, NY, USA) (▶ **Table 1**) in 2004 in the USA and 2006 in Europe revolutionised the treatment of nAMD: As a result of the administration of 0.3 mg of the anti-VEGF agent at 6-week intervals, 70% (control group 55%) of the patients lost fewer than three lines of visual acuity after one year. Of the patients treated with pegaptanib for another year, 93% (control group 86%) lost fewer than three lines of visual acuity after 2 years [8, 9]. Pegaptanib was relatively quickly superseded by the anti-VEGF agent ranibizumab (Lucentis; Genentech, South San Francisco, California) which was authorised shortly afterwards in 2006 in the USA and 2007 in Europe (▶ **Table 1**). Ranibizumab, administered every 4 weeks in a dose of 0.5 mg, prevented vision loss of more than three lines in 95–96% of study participants, and a visual gain of 7.2 and 11.3 ETDRS (Early Treatment Diabetic Retinopathy Study) letters was also identifiable after one year [10, 11]. Finally, another anti-VEGF product, aflibercept (Eylea; Regeneron, Tarrytown, New York) was authorised in 2011 in the USA and 2012 in Europe. Clinical equivalence to ranibizumab was demonstrated with administration of 2 mg aflibercept in the form of a loading dose of 3 injections at 1-month intervals, followed by injections at 8-week intervals [12].

Besides ranibizumab and aflibercept, bevacizumab (Avastin; Roche, Basel, Switzerland) (▶ **Table 1**) is one of the three most widely used anti-VEGF agents. Unlike ranibizumab and aflibercept, treatment of nAMD with bevacizumab has not yet been authorised for intravitreal therapy and must therefore be used as an off-label therapy. The drug was developed for the treatment of gastrointestinal, lung and breast cancer. Bevacizumab is also demonstrably non-inferior to ranibizumab in terms of its action [13]. Whereas, because ranibizumab and aflibercept are fully reimbursed, bevacizumab use in Switzerland constitutes less than 0.5% of all injections, bevacizumab injections account for around 35% of all injections administered in Germany and 20–60% in Austria, depending on the treatment centre [14]. The cost factor in particular plays a major role in the administration of the different anti-VEGF agents. Worldwide, one dose of ranibizumab costs around $ 240 (India) – $ 1950 (USA), for example, and one dose of aflibercept approximately $ 846 (India) – $ 1950 (USA), whereas one dose of bevacizumab comes to just $ 50 in the USA [15]. Ziv-aflibercept (Zaltrap; Regeneron, Tarrytown, NY and Bayer Healthcare, Leverkusen, Germany) (▶ **Table 1**) is another active substance that is administered off-label. Like bevacizumab, it is

* In the following paper, the masculine form is used exclusively in the interest of better readability. It refers to people of both sexes.



▶ **Fig. 1** Case – A female patient (59 years) presented with a deterioration in vision (visual acuity: 0.8) in her left eye and subretinal fluid on OCT (CRT [central retinal thickness]: 423 µm). Based on the diagnosis of neovascular age-related macular degeneration, injection therapy was initiated. The patient received eleven injections with ranibizumab according to a PRN regimen and was then switched to a treat-and-extend regimen with aflibercept, in which she had received 27 injections at varying intervals to date. Over 5 years and a total of 38 injections, the visual acuity decreased to 0.63, and the patient's eyesight was largely maintained despite recurrent oedema and fibrosis.

▶ **Table 1** Anti-VEGF products used worldwide for the treatment of nAMD.

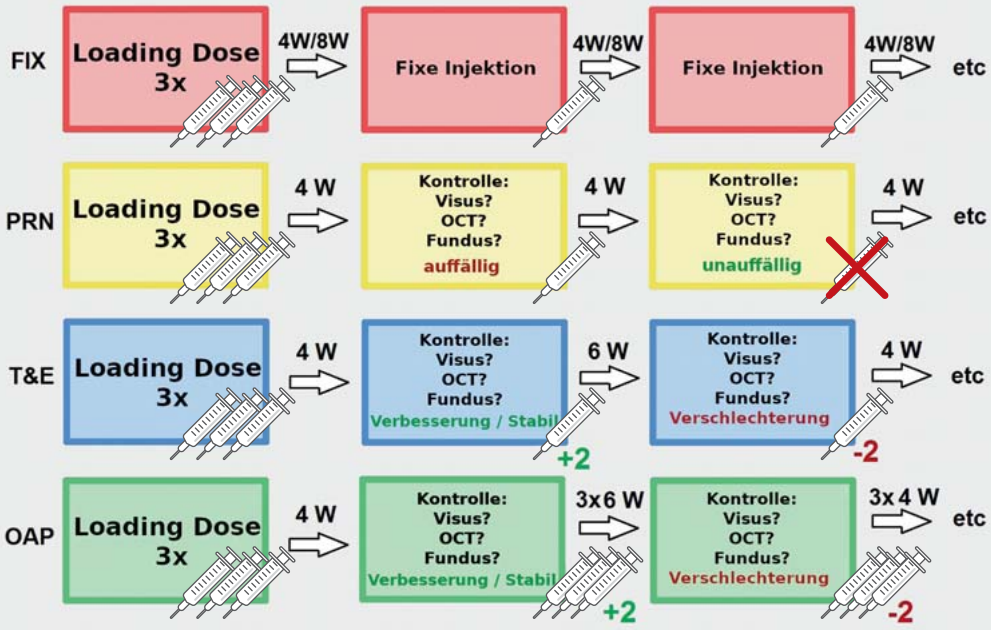
INN	Authorisation in DE	Structure	Mass	Target molecule
Pegaptanib	2006	RNA aptamer	50 kDa	VEGF-A
Ranibizumab	2007	Monoclonal antibody	48.4 kDa	VEGF-A
Aflibercept	2012	Recombinant fusion protein	115 kDa	VEGF-A/B, PlGF
Ziv-aflibercept	Not authorised	Recombinant fusion protein	115 kDa	VEGF-A/B, PlGF
Bevacizumab	Not authorised	Monoclonal antibody	149 kDa	VEGF-A
Brolucizumab	2020	Antibody fragment	26 kDa	VEGF-A

DE = Germany; INN = International non-proprietary name; PlGF = Placental growth factor; VEGF = Vascular endothelial growth factor

authorised for the treatment of metastatic colorectal cancer, but has also shown reliable long-term outcomes in the treatment of nAMD [16]. In addition, ziv-aflibercept is considerably less expensive that the authorised products, with one dose costing approximately $ 30 (USA) [15].

Brolucizumab (Beovu, Novartis, Cambridge, Massachusetts, US) (▶ **Table 1**) has only recently been authorised in the USA (end of 2019) and the EU (start of 2020). The injection interval is 12 weeks, with the option of reducing this to 8 weeks if disease activity increases. The longer interval should reduce the burden on both patients and hospitals [17].

The development of new active substances for treating nAMD has become a real race: Besides the multitude of products that are already authorised and used off-label, numerous active substances that target not only VEGF but also other pathways are currently being studied and research is being carried out into other formulations. Anti-VEGF medications currently in various trial phases include abicipar pegol (Allergan), conbercept (Chengdu



▶ **Fig. 2** Regimens for injection intervals for the treatment of nAMD. FIX = Fixed intervals; OAP = Observe-and-plan regimen; PRN = Pro re nata regimen; T&E = Treat-and-extend protocol; W = Weeks.

Kanghong biotech Co., Ltd., Sichuan, China), faricimab (Roche, Genentech, South San Francisco, California) and KSI-301 (Kodiak Sciences) These promise a longer duration of action than the products available at present and thus reduce the number of injections needed. A new formulation currently being researched is the Port Delivery System. This surgically implanted drug reservoir is filled with anti-VEGF medication at regular intervals, and this is delivered continuously into the eye. Another strategy is offered by gene therapy. This is administered surgically or by means of intravitreal injection and should considerably reduce the number of injections of anti-VEGF medication needed. Gene therapies currently in clinical research include RGX-314 RegenexBio (Rockville, MA, USA) and ADVM-022 (Adverum) [18].

Besides the active substances available at present and used off-label for the treatment of nAMD, research is being carried out into a large number of active substances aimed at prolonging effectiveness and thus reducing the number of injections. The use of these active substances could lead to a considerable reduction in the burden not only on hospitals and physicians but also patients.

Treatment Intervals

In the pivotal studies for the authorisation of ranibizumab in classic and occult nAMD (ANCHOR and MARINA study), a monthly injection regimen was used (▶ **Fig. 2**). Patients who received injections of 0.5 mg ranibizumab every 4 weeks over a period of two years showed a visual gain of 11.3 and 7.2 ETDRS letters respectively after just one year [10, 11]. A regular injection regimen of 3 initial injections at 4-week intervals followed by injections at 8-week intervals was also used in the pivotal studies for the authorisation of aflibercept (VIEW 1 and VIEW 2) to rule out inferiority compared with ranibizumab [12]. Because the effects of the injections within the patient population were very varied, a different treatment regimen was sought in order to be able to provide patients with more individual care and, if possible, to reduce the number of injections while maintaining visual acuity [17]. The PRN (pro re nata) regimen was developed for this: After a loading dose of 3 injections at monthly intervals, monthly assessments take place to decide, on the basis of established criteria, whether the patient will receive an injection at this visit or not. Criteria include, for example, loss of over five lines of visual acuity, identification of sub- and intraretinal fluid on OCT (optical coherence tomography) or retinal bleeding (▶ **Fig. 2**) [17, 19]. Despite very promising results from the first study, the results of regular 4- or 8-weekly administration could not be achieved in the subsequent studies [17]. The T&E (treat-and-extend) protocol represents another treatment regimen: As with the PRN regimen, 3 injections are administered at monthly intervals initially (loading dose), followed by regular monitoring. In contrast to the PRN regimen, however, an injection is administered at each monitoring visit and the interval between the injection visits adjusted. Disease activity is assessed using similar criteria to the PRN regimen, and the treatment interval is extended by two weeks in each case if this has decreased or stabilised, and shortened if it has increased, but never adjusted below 4 weeks or above 12(–16) weeks (▶ **Fig. 2**) [19]. Unlike with the PRN regimen, similar outcomes to the monthly administration regimen were achieved with the T&E protocol [17]. The observe-and-plan regimen described by Mantel et al. represents a variation on the T&E protocol. After three injections at monthly intervals (loading dose), follow-up visits are car-

ried out at monthly intervals which are used to establish the interval for future injections. If disease activity recurs, the interval between the last injection and follow-up visits is decreased by two weeks and set as the new interval for the next three injections. The intervals, which are between 4 and 12 weeks, are re-evaluated after three injections for the next three injections (▶ **Fig. 2**). With a significant improvement in vision within the first year of treatment and a number of injections similar to the other regimens, it was possible to considerably reduce the number of monitoring visits [20].

In most cases, it was not possible to replicate results achieved in randomised controlled studies in routine clinical practice, regardless of the active substance used (ranibizumab, aflibercept, bevacizumab) [21]. Numerous studies investigating anti-VEGF therapy in a real-world setting showed considerably poorer visual outcomes than indicated by the pivotal studies. While the result after one year was predominantly a visual gain, this largely gave way to a decline in visual acuity over longer periods of time. Although maintenance of baseline visual acuity was demonstrated, there were also studies which showed a loss of visual acuity to below the level at baseline [21 – 23].

But what is the reason for this "efficacy gap"? Besides stricter selection criteria for patients who participate in pivotal studies, the injection regimen plays a particularly important role: In routine clinical practice, patients are usually treated according to a PRN regimen and receive fewer injections on average than in controlled studies [17, 21]. Better outcomes have been observed in real-world studies using a T&E regimen [21, 23]. The development or progression of existing macular atrophy and fibrosis also have a negative impact on visual acuity. Changing the anti-VEGF product does not appear to have a negative impact on visual acuity [23].

Subtypes and Complications in the Treatment of nAMD

Although most patients with nAMD respond to treatment, there are cases in which the response to anti-VEGF therapy is poorer. This is often attributable to one of the subtypes of nAMD, in particular polypoidal choroidal vasculopathy (PCV) and retinal angiomatous proliferation (RAP). In a study by Ozkaya et al., it was found that around 1% of patients had a morphologically poor response to treatment with ranibizumab. Of these, only 9.8% were diagnosed as having true nAMD, while the remaining 90,2% had a subtype of nAMD or other macular diseases. In these cases, the correct diagnosis was made by means of indocyanine green angiography. The diagnosis was thus revised to PCV in 56.1% of cases, to chronic central serous chorioretinopathy (CSC) in 26,5% of cases and to RAP and CNV secondary to CSC in 2.3% cases. Additional photodynamic therapy could be given if required. In this study, PCV and RAP are described as subtypes of nAMD, although it is pointed out that other authors consider these two entities as macular diseases to be differentiated from nAMD [24].

Apart from the issue of the response to injection therapy, the associated risks and possible complications must not be overlooked. Minor complications reported by patients in connection with injection therapy include eye irritation, subconjunctival haemorrhage and visual disturbance from the medication or air bubbles [25]. The main serious complications that should be mentioned are increased intraocular pressure after injection, corneal abrasion, retinal detachment, vitreous or retinal haemorrhage and endophthalmitis [25, 26]. Retinal pigment epithelial tears are a complication that deserves special mention in the treatment of nAMD. These can occur spontaneously or in connection with intravitreal therapy. The risk factors for pigment epithelial tears also include pre-existing pigment epithelial detachments, large diameter and vertical height. Better maintenance of visual acuity was achieved in patients who continued to be treated with anti-VEGF medication after pigment epithelial tear [26]. In the case of brolucizumab, in addition to the complications mentioned, the increased incidence of intraocular inflammation, retinal vasculitis and retinal artery occlusion should also be noted [27].

Endophthalmitis is the most feared complication of intravitreal injection therapy. A distinction needs to be made here between infectious endophthalmitis and non-infectious endophthalmitis (also called sterile intraocular inflammation or non-infectious vitritis). The incidence of infectious endophthalmitis is 0.008% to 0.092% per injection, compared with 0.09% to 0.37% per injection for non-infectious endophthalmitis [28]. However, it is important to consider not only the incidence per injection but also per patient, because most patients receive multiple injections. Daien et al. documented the cumulative rate of endophthalmitis after 10, 20, 30, 40, 50 and 60 IVIs. Although an increase in infectious endophthalmitis from 0.055% after 10 injections to 0.843% after 60 injections was identified, the risk of infectious endophthalmitis did not increase significantly with each consecutive injection. The cumulative rate of non-infectious endophthalmitis increased from 0.087% after 10 injections to 0,228% after 20 injections and remained at the same level until after 60 injections. The risk of non-infectious endophthalmitis did not increase significantly with each additional injection administered either [28]. In order to prevent serious complications of endophthalmitis, patients should be advised to return to the treatment centre immediately at the first signs of any acute deterioration in their vision or eye pain, so treatment can be initiated as soon as possible [26].

Importance of nAMD Treatment for Patients

Although patients benefit greatly from nAMD treatment, they also often see it as a burden. Compliance and adherence to treatment are also critical factors for the success of anti-VEGF therapy and thus for maintaining vision. Patients with nAMD usually show a high level of adherence to treatment. Nevertheless, with an average number of 10 injections within a period of two years, a premature dropout rate of approximately 20% has been observed among patients. The main reasons given for missing monitoring and injection appointments included difficulties with transport and getting to the treatment centre, comorbidities preventing attendance and loss of motivation [29]. Most of the patients also showed good adherence to treatment in a study conducted by Boyle et al. examining the experiences of patients during therapy: The participants understood the need for therapy and saw it as a compromise to maintain their visual acuity, mainly out of fear of losing their eyesight, despite the associated inconveniences. Most

therefore said that they would continue with their treatment and continue to recommend it to other patients with newly diagnosed nAMD. Prioritising treatment was described as an additional burden for patients, however, as social and work commitments had to be sacrificed for monitoring visits. Besides the fear of losing eyesight, fear of the injection procedure itself was also noted. In most cases, however, this decreased with the increasing number of injections, duration of treatment and familiarity with the injection procedure [4]. Classical music before and during the treatment also reduced patient anxiety [30]. Besides the fears mentioned, patients stated that the frequency of the visits and waiting time represented a burden for them [5, 29]. Visits at longer intervals and with less waiting time would therefore be preferred and having the assessment at the same visit as the injection would be favoured over separate visits [5].

Overall, the high level of patient compliance is maintained mainly through fear of losing eyesight, although patients wish the treatment was less burdensome.

Role of Relatives

Although many patients rely on help from relatives or caregivers, there has been little research into the impact this has. Because most patients need help in getting to and from home and hospital, it is often relatives or friends who accompany patients [4, 29]. Approximately three quarters of patients have been accompanied on their visits, mainly by spouses or children. Their age was over 60 years on average. Because the hospital visits lasted between one and several hours, working relatives, who accounted for around 35–46% of those surveyed, had to take time off or stated that they suffered a loss of productivity or income as a result of their caregiving. In addition, the relatives spent between one and several hours a day on average helping the patient with everyday activities such as shopping or personal hygiene. Relatives also incurred costs amounting to around € 400 per year for transport, household assistance and purchases or changes. Besides the time and financial burden, relatives reported that caregiving was associated with a subjective burden and reduced quality of life [31, 32].

Impact on Health Systems

The possibility of treating nAMD successfully also has considerable implications for physicians, hospitals and health systems. With approximately 4.1 million injections performed in the USA in 2013, an increase to 5.9 million injections was estimated in 2016 [33]. The number of prescriptions in Germany in 2018 was 294,200 for ranibizumab and 303,600 for aflibercept [34]. These data also include prescriptions of the active substances for other conditions such as diabetic macular oedema, as there has been no separate analysis of data relating to nAMD on its own. In order to incorporate this increase into routine clinical practice and to ensure that the process runs quickly and smoothly, dedicated IVI centres have been set up in many hospitals. However, there is a lack of standardised recommendations regarding assessment and injection frequency [6]. Physicians also feel increasingly overburdened with regard to the management of patients with nAMD. In a survey by Prenner et al., physicians stated that this accounts for around 20% of their weekly workload. On average, one assessment took 90 minutes and involved around 23 members of staff, including receptionists, office managers, account managers, technicians and physicians. More than half of the physicians said that the frequency of assessments and injections as well as billing represented a time and materials burden for personnel and patients. Two thirds would like monitoring visits to be reduced [35]. Besides hospitals and physicians, health systems are also faced with the challenge of increasing costs. In 2015, the American Medicare Part B system spent $ 3 billion on aflibercept and ranibizumab [36]. Aflibercept also proved to be the medicinal product on which the most budget was spent. In England, around 400 thousand injections were administered in the 2014/15 reference period, and in 2015/16 the NHS budget for ranibizumab and aflibercept corresponded to £ 447 million [37]. The net costs of ranibizumab and aflibercept in Germany in 2018, according to the 2019 Drug Prescription Report, were € 349.5 million and € 312.9 million. Together, this accounted for around 57% of the total net costs for ophthalmic agents, which in 2018 were € 1162.5 million. The products were thus the 7th and 9th top medicinal products in Germany in 2018 based on net costs. These costs relate to all prescriptions, as there has been no separate analysis of data relating to nAMD on its own. Unfortunately, data from Austria are not accessible.

Physicians and hospitals are thus increasingly being faced with an rising number of patients in ophthalmology with the associated workload and burgeoning costs, which are also a burden on the health systems of the individual countries.

Telemedicine – the Digitalisation of Medicine

The increasing digitalisation of medicine is opening up new possibilities for early detection, treatment and care outside of the hospital setting for patients with nAMD. Communication and consultation between retina specialists and community-based ophthalmologists using various information technologies make it possible to reduce the burden on treatment centres and retina specialists and at the same time support community-based ophthalmologists in patient care. Patients who travel long distances for injection therapy also benefit from this. Starr et al. described a system whereby community-based specialists cared for patients with nAMD and performed the injections themselves. The assessment, visual acuity and OCT records were then sent to hospital-based retina specialists via eConsult. These specialists reviewed the data submitted and then issued their recommendations for the patient's further care. Patients were thus able to be cared for by their community-based ophthalmologist at the same time as benefiting from the communication between this person and the hospital-based retina specialist [38].

Another study compared diagnostic and treatment decisions by retina specialist relating to patients following a PRN regimen. These decisions were made either in the office or using "remote evaluation" via a server. For the latter, visual acuity, OCT and digital fundus images were stored on a server and downloaded for evaluation. Telemedicine diagnoses showed a sensitivity of 96% and a specificity of 85%, and at 1 minute and 21 seconds on aver-

age, the amount of time spent in the evaluation was a fraction of the time needed for office decision-making, which was around 10 minutes. In this study, telemedicine evaluation also proved to be a useful and time-saving alternative to office evaluation [39].

In addition, telemedicine is used in the everyday home setting. Researchers have developed a device which patients can use to test their eyesight at home for around 3 minutes. The results are then sent to a medical facility and the patient is contacted for a monitoring visit if there are any significant changes. The ForeseeHome device has been tested in a controlled clinical trial, corresponding to level 1 evidence, and has been cleared by the FDA in the USA [40].

As a result of this technical advance, it is now possible to test patients' state of health regularly in their home and, if necessary, to assess them personally as quickly as possible. Communication between hospitals and community-based practices is also simplified and strengthened by the electronic transmission of assessment data. This makes it possible to provide the best possible care for patients with nAMD even outside the hospital setting.

Big Data and artificial Intelligence

The inexorable march towards electronic patient documentation and the development of registries makes it possible to collect and analyse data in large quantities. As a result, it is becoming possible not only to analyse very large patient populations but also to assess wider relationships. For example, a link has also been established between active and previous smoking and development of neovascular AMD [41]. Evaluating data from direct patient care represents another advance. Unlike randomised clinical trials, these real-world data are particularly interesting because they are not limited to a specific patient population. Rather, it is now possible to verify the results of any studies and their application under real conditions of care.

Besides the collection and evaluation of big data, artificial intelligence (AI) also represents a ground-breaking development in ophthalmology. Algorithms are developed which enable patterns and relationships to be identified using datasets. After this automated learning phase, these can also be applied to unknown data [42].

Grassmann et al. created an algorithm which automatically identifies the stage of AMD based on the AREDS classification. Classification by algorithm was even superior to human assessment in terms of accuracy [43]. Another example is an algorithm developed by Schmidt-Erfurth et al. for automated quantification of the fluid volumes in the retina in the presence of nAMD. This capability makes it possible to determine disease activity in a very precise manner and adjust the treatment regimen as a result [44].

Around 40 % of US ophthalmologists already only perform OCT in cases of more prolonged anti-VEGF therapy and no longer carry out a slit-lamp examination at every visit [45]. It is therefore all the more important to establish disease activity in a precise, rapid and standardised manner in future, as would be possible with such an algorithm. The use of artificial intelligence has already gained a foothold in clinical practice in the treatment of nAMD. An algorithm designed to predict the risk of early AMD conversion to nAMD based on imaging and clinical data is currently undergoing clinical testing (NCT04640649). Another algorithm which serves as a decision-making tool for the individual treatment of nAMD based on the automated analysis of sub- and intraretinal fluid is also in clinical trials (Eudra-CT 2019-003133-42). In the future, the use of artificial intelligence in the context of nAMD could lead to rapid and reliable disease stage and activity identification in routine clinical practice. This would make it possible to optimise treatment management and reduce costs.

Discussion

The treatment of nAMD has undergone a transformation in the last two decades. Anti-VEGF agents have made it possible to maintain and even improve visual acuity in the long term. The opportunity of preventing blindness in patients worldwide is also fraught with difficulties, however. Systems needed to be implemented that enable large numbers of patients to be treated every day at the same time as ensuring that the process runs smoothly. Reliable active substances, the setting up of IVI centres, optimised monitoring and injection processes and good patient compliance are important prerequisites for the competent and smooth routine treatment of nAMD. Ever increasing patient numbers and capacity utilisation mean that continuous improvements will also be necessary in the future to avoid overburdening treatment centres, physicians and, not least, patients and their relatives. In view of the high financial burden on health systems, cost-effectiveness studies have been conducted which highlight, inter alia, the possibility of using bevacizumab as an inexpensive alternative to authorised products such as ranibizumab and aflibercept [46]. In 2018, in a lawsuit brought by two pharmaceutical companies in England against several NHS clinical commissioning groups, the High Court ruled in favour of the off-label use of bevacizumab in clinical practice [47]. Another important goal is to find an optimised administration regimen which – despite longer intervals between individual monitoring and injection visits – shows outcomes similar to those of the registration studies. The T&E regimen has asserted itself here: Because monitoring and injection visits are combined and the intervals can be increased if disease activity is absent or decreasing, patients are treated according to their individual needs, visual acuity is kept stable and savings are made in terms of capacities and resources [21, 23]. Attempts are also made to meet the wishes of physicians and patients in the development and manufacture of new anti-VEGF agents. The dosing interval for brolucizumab is already 12 weeks, for example, and only has to be reduced to 8 weeks if disease activity increases [17]. It is important to bear in mind the expanded risk profile for these products, however. In the case of brolucizumab, for example, an increased incidence of intraocular inflammation, retinal vasculitis and retinal artery occlusion has been observed [27]. There are also some very promising active substances and mechanisms in the research pipeline. The more prolonged effectiveness of the products and functional mechanisms could considerably reduce the burden of treatment. New anti-VEGF agents show a longer duration of action than active substances used previously, for example, and thus longer intervals between the administered injections. Gene therapies that are administered on a one-off basis may considerably reduce the number of injections for treat-

ment with anti-VEGF medication. Surgically implanted Port Delivery Systems deliver the active substance continuously and are refilled at regular intervals which are considerably longer than those of the active substances administered at present [18]. Another strategy for increasing capacity is to have intravitreal injections performed by specially trained nurses. This model has already proven reliable, used in parts of the United Kingdom, and also showed high levels of acceptance among patients [48]. It would also be possible to have imaging studies evaluated by a reading centre. In patients treated according to a PRN regimen, the retinal fluid measurement obtained was consistent with the treatment decisions of the treating ophthalmologists for most visits [49]. Imaging could therefore also be assessed by a reading centre for patients treated according to a T&E regimen and the treatment intervals established in a standardised manner according to its recommendation. Finally, the implementation of artificial intelligence could enable disease activity and course to be assessed rapidly and accurately and thus probably enable the burden for patients and health systems to be reduced from both a personal and financial perspective [42–44, 50]. Because the ultimate decision regarding the monitoring intervals and time of treatment remains with treating physicians, this supports medical competence without rendering it obsolete.

Conclusion

Anti-VEGF therapy has helped to make it possible to largely prevent severe loss of vision as a result of nAMD. This achievement of modern medicine is associated with problems, however. Increasing numbers of patients and treatments result in rising costs for health systems. Research into new active substances and administration mechanisms offers one approach to reducing the burden of treatment. In the future, automated algorithms based on artificial intelligence might pave the way for precision medicine at a high level and result in a higher quality of patient care. Hospitals, physicians, patients and relatives are also required to change habits and adapt, and thus make the processes for nAMD injection therapy as efficient as possible. Besides many measures that have already been implemented, it will also continue to be necessary in the future to work on these processes in order to be able to guarantee the best possible treatment for each patient without placing too high a burden on the health system and personnel.

Conflict of Interest

The authors declare that they have no conflict of interests.

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