EJO
ISSN 1120-6721

Eur J Ophthalmol 2015; 25 (6): 529-534
DOI: 10.5301/ejo.5000629

ORIGINAL ARTICLE

Ranibizumab prefilled syringes: benefits of reduced syringe preparation times and less complex preparation procedures

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ABSTRACT

Purpose: A recently developed ranibizumab prefilled syringe (PFS) eliminates several preparatory steps versus the standard vial-based method, and is expected to reduce syringe preparation time (SPT) and enhance procedural simplicity for intravitreal injections.

Methods: Syringe preparation times for the ranibizumab PFS and vial were recorded during standard treatment sessions at 2 centers, without randomization. The duration of each step in preparing the syringe was recorded. At each center, total SPT (mean total duration of all syringe preparation steps) for each method was compared using a 2-tailed *t* test.

Results: In total, 97 SPTs were analyzed across both centers. Center 1 SPTs were 46 seconds (PFS) versus 75 seconds (vial; difference, 29 seconds; p<0.001). Center 2 SPTs were 46 seconds (PFS) versus 63 seconds (vial; difference, 17 seconds; p<0.001). This equates to a 27%-39% reduction in SPT when using the PFS rather than the vial, resulting mostly from the reduced number of syringe preparation steps associated with the PFS.

Conclusions: Syringe preparation times for ranibizumab intravitreal injections are significantly shorter with the PFS than with the vial. The time saved by using the PFS may benefit physicians and nurses, and the simplicity of the injection preparation process with the PFS is advantageous.

Keywords: Anti-VEGF therapy, Intravitreal injections, Prefilled syringe, Ranibizumab, Syringe preparation time, Vial-based syringe preparation

Introduction

In recent years, there has been a significant increase in the number of patients who require and are eligible for treatment of retinal conditions (1), including visual impairment due to neovascular age-related macular degeneration (AMD), visual impairment due to diabetic macular edema (DME), visual impairment due to macular edema following retinal vein occlusion (RVO), and visual impairment due to choroidal neovascularization secondary to pathologic myopia (myopic CNV). Neovascular AMD and DME are responsible for over 50% of patient registrations for severe sight impairment worldwide (2-4). This increase has been driven by a combination of an aging global population and the introduction of new treatment modalities, including anti–vascular endothelial growth factor (anti-VEGF) therapies such as ranibizumab, bevacizumab, and aflibercept (5, 6).

In patients with myopic CNV, neovascular AMD, and DME, ranibizumab treatment results in superior outcomes, such as improved visual acuity, relative to earlier interventions (e.g., photodynamic therapy or laser photocoagulation) (7-10). However, anti-VEGF therapies have increased the clinical workload, because more patients meet the eligibility criteria for these therapies than for the earlier interventions; anti-VEGF therapies also require more frequent administration and follow-up (5-11). As with most invasive treatments, there are safety risks associated with intravitreal injections of anti-VEGF agents, such as endophthalmitis (12).

Many clinicians report that the preparation of ranibizumab intravitreal injections is time-consuming (data on file); the

Accepted: April 27, 2015
Published online: May 18, 2015

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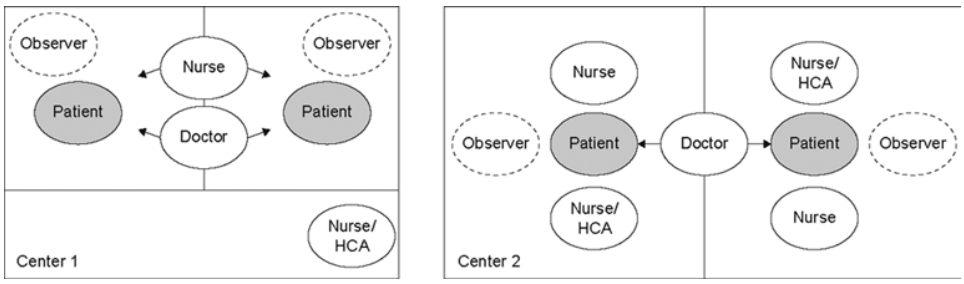

Fig. 1 - Schematic representation of treatment centers 1 and 2. HCA = health care assistant.

ranibizumab prefilled syringe (PFS) may reduce the injection preparation time and improve convenience. Ranibizumab solution for injection from the PFS was approved in the European Union in 2013 for the treatment of visual impairment due to neovascular (wet) AMD, visual impairment due to DME, visual impairment due to macular edema secondary to RVO (branch RVO or central RVO), and visual impairment due to CNV secondary to pathologic myopia. The solutions in the PFS and in the vial have the same formulation (0.5 mg given as a single intravitreal injection, with an injection volume of 0.05 mL).

This study compared syringe preparation time for injection with the ranibizumab PFS versus the vial, with the hypothesis that the PFS would offer significant time savings owing to the elimination of several preparation steps. The study was conducted in patients with a range of retinal disorders in a real-world clinical setting. Health care professionals also provided their views on what benefits the PFS procedure offers, and to whom.

Methods

Study design

A cross-sectional time-and-motion study was conducted to collect data on ranibizumab injection preparation times in routine clinical practice at 2 treatment centers in France. Data were collected in June 2014 at both centers. It was planned to include at least 12 sets of preparation data for both the PFS and the vial per site, providing a minimum of 48 syringe preparation time measurements. Data were collected during standard treatment sessions following the center's usual procedure.

All ranibizumab intravitreal injections performed during a total of 6 treatment sessions at the 2 treatment centers were potentially eligible for time measurement. Injections were excluded if the patient objected to having an independent observer present during the treatment. Injections of other agents during the sessions were also excluded, as were ranibizumab injections that involved disruptions during the drug administration process that were due to external factors, or if there were other causes of error in measuring the preparation time. A signed consent form was not required for participation because the study involved only observation of clinical practice, and no identifying patient data were collected.

Center 1 was a private retina clinic. It comprised 2 treatment rooms and a patient preparation room; the treatment rooms were staffed by a single physician and single nurse working across both rooms, and the patient preparation room was staffed by a nurse or health care assistant. Center 2 was at a public hospital and comprised 2 treatment rooms, with 2 nurses or a nurse and a health care assistant present in each. Injections were administered by a single physician working across both rooms. These setups conformed to regulations in France, which require intravitreal injections to be performed in specially equipped rooms, in contrast to countries such as the United States, where injections may be performed in, for example, a physician's office. The setups are illustrated schematically in Figure 1.

Ranibizumab PFS

The ranibizumab PFS has a Luer lock system to grip the needle tightly. The syringe barrel is made of unreactive borosilicate glass, which is therefore stable during storage; the baked siliconization manufacturing process minimizes the risk of transfer of silicone oil into the ranibizumab solution. The small syringe barrel (0.5 mL) may reduce the dose variability associated with larger barrels. The latex-free plunger prevents contact reactions from latex sensitivities or allergies, and is nonretractable, preventing nonsterile air from entering the barrel.

Data collection

Preparation steps for injections were observed and timed by external researchers from Q_PERIOR AG (Zurich, Switzerland) who were familiar with the procedures, with one observer present in each treatment room. Times were directly entered on time-stamped, hard-copy data collection sheets. No identifying patient data (such as date of birth, name, or sex) were collected. Physicians and nurses involved in the study completed a 6-item questionnaire regarding the use of the PFS and their opinions of it, including whether they preferred the PFS or the vial, and reasons why, immediately after the last data collection.

A specific therapy protocol, diagnostic or therapeutic procedure, or visit schedule was not required as part of the study. Procedures were carried out in accordance with local prescribing information and routine medical practice. Only time data were collected during this study. Data for the ranibizumab vial were collected during 2 half-days at center 1 and 1 half-day at center 2. Data for the PFS were collected subsequently, for 2 half-days at center 1 and 1 half-day at center 2. The same medical staff and external

TABLE I - Injection preparation steps when using the ranibizumab prefilled syringe and vial

Step number	Step description	Processes involved in ranibizumab vial preparation	Processes involved in ranibizumab prefilled syringe preparation
1	Remove contents from box and internal packaging	a) Open and empty box b) Open every blister package (injection, filter needle, and syringe) and drop contents onto sterile table c) Throw empty box and blister packages into bin	a) Open and empty box b) Open sterile plastic package and take out syringe c) Throw empty box and blister package into bin
2	Put gloves on	Open package, take out gloves, and put them on	Open package, take out gloves, and put them on
3	Attach filter needle	Take syringe, attach filter needle, then replace onto sterile table	Step not needed
4	Disinfect vial lid	Take off vial cap and disinfect vial with iodine and a compress	Step not needed
5	Draw solution from vial using filter needle	Lance the syringe with the filter needle into vial and draw ranibizumab into syringe, remove syringe (with or without filter needle)	Step not needed
6	Remove filter needle and attach injection needle	a) Remove filter needle from syringe, discard into bin b) Take injection needle and attach it to syringe	a) Step not needed b) Take syringe, open Luer Lock, and attach injection needle
7	Adjust dose	Adjust dose to 0.05 mL by depressing plunger	Adjust dose to 0.05 mL by depressing plunger

observers were present during each session to avoid variation in measurements arising from the involvement of different personnel.

Seven steps in the preparation of the syringe when using the vial and 4 steps when using the PFS were identified during pre visits to each center; these steps are described in Table I. The 4 steps for the PFS were the same as steps 1, 2, 6(b), and 7 for the vial; steps 3-5 and 6(a) were not necessary with the PFS (Tab. I).

The timing of each step started at the point when the health care professional touched the relevant item (e.g., the ranibizumab box in step 1, or the glove package in step 2) and ended when the task was completed (e.g., the contents of the ranibizumab box were unpacked and the box discarded, or the gloves were fully on).

Statistical analysis

It was predicted that there would be 24 evaluable injection procedures per site, factoring in a dropout rate of approximately 20%. A mean difference of 22 seconds (standard deviation 15 seconds) in preparation time between treatment groups was expected based on data from a laboratory simulation. Power analysis indicated that the study design had least 90% power to demonstrate a statistically significant difference in syringe preparation time between the PFS and the vial using a 2-sided *t* test and an α value of 5%. Owing to slight differences in setup and processes between the 2 centers, treatment comparisons were conducted within each center. Sample size calculations were performed using nQuery Advisor®, 7.0 (Statistical Solutions Ltd., Cork, Ireland).

Results

In total, 122 timings of syringe preparation were collected across both centers; this was a considerably larger sample size than was originally planned, owing to the fact that more values could be obtained during the scheduled observation periods and there were less exclusions than had been expected. Data from 25 injections were excluded owing to an inability to determine when the start or end of a step had occurred (13 data recordings); a recording point being missed while health care professionals were conducting other activities (5 recordings); or the external observer being unable to determine a timing precisely enough (7 recordings). After these exclusions, 97 valid syringe preparation timings were collected across both sites (Tab. II). No patients objected to being observed for the study.

At center 1, using the ranibizumab PFS saved a mean of 29.3 seconds (39%) in syringe preparation time per patient versus the vial (PFS 46.0 ± 7.3 seconds [mean ± standard devi-

TABLE II - Sample numbers and breakdown of included and excluded data

	Center 1		Center 2	
	Vial	PFS	Vial	PFS
Valid	24	39	16	18
Excluded	21	1	1	2
All samples	45	40	17	20

PFS = prefilled syringe.

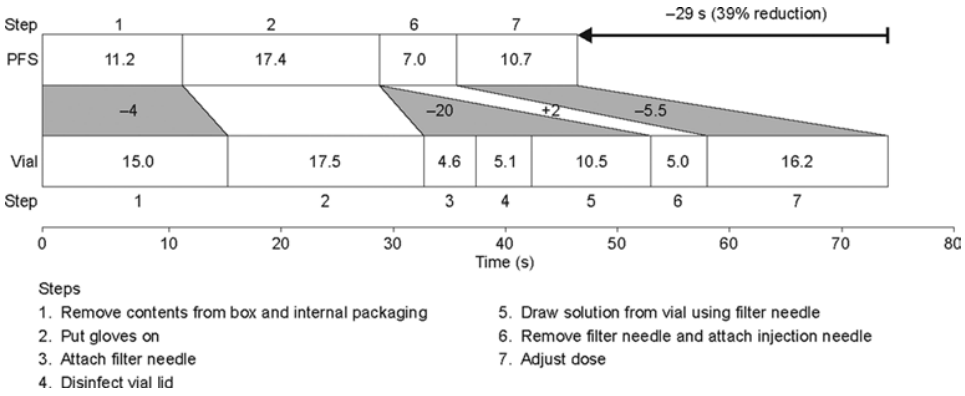

Fig. 2 - Breakdown of timing for the ranibizumab prefilled syringe (PFS) and vial at center 1. The total of the means for each step differs slightly from the overall preparation time. This is because some values for individual step timing were excluded from the analysis (e.g., owing to measurement error); however, the total preparation timing would still have been eligible for inclusion, hence the slight difference.

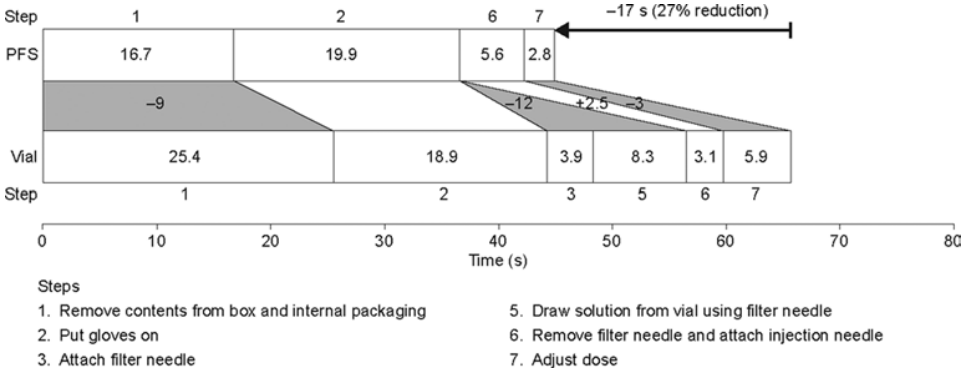

Fig. 3 - Breakdown of timing for the ranibizumab prefilled syringe (PFS) and vial at center 2. The total of the means for each step differs slightly from the overall preparation time. This is because some values for individual step timing were excluded from the analysis (e.g., owing to measurement error); however, the total preparation timing would still have been eligible for inclusion, hence the slight difference.

ation; range 34-47 seconds] vs vial, 75.3 ± 14.7 seconds [range 60-128 seconds]; p<0.001). Step 1 (removal of the contents from the box and internal packaging) was reduced by a mean of 3.8 seconds for the PFS relative to the vial (11.2 seconds vs 15.0 seconds, respectively). The mean time for step 2 (putting gloves on) was almost identical for both injection preparation methods; this was the most time-consuming step (PFS, 17.4 seconds vs vial, 17.5 seconds). Steps 3-5 (attaching the filter needle, disinfecting the vial lid, and drawing ranibizumab from the vial) were not performed in the PFS method and took a mean of 20.2 seconds in total when using the vial (step 3, 4.6 seconds; step 4, 5.1 seconds; step 5, 10.5 seconds). The mean time for step 6 (removing the filter needle and attaching the injection needle) was longer with the PFS than with the vial (7.0 seconds vs 5.0 seconds, respectively), while step 7 (dose adjustment) took a mean of 5.5 seconds less with the PFS than with the vial (10.7 seconds vs 16.2 seconds, respectively). Data are shown in Figure 2.

At center 2, the mean syringe preparation time was 17.0 seconds (27%) shorter using the PFS than using the vial (PFS 45.8 ± 9.8 seconds [range 29-64 seconds] vs vial, 62.8 ± 15.6 seconds [range 21-88 seconds]; p<0.01). Step 1 was a mean of 8.7 seconds faster with the PFS than with the vial. As at center 1, there was no significant difference between the PFS and the vial in the time taken for step 2. Steps 3 and 5 were not carried out in the PFS method and took a mean of 12.2 seconds when using the vial; step 4 was not performed at center 2. Step 6 was again slower when using the PFS setting than when using the vial (mean of 5.6 seconds vs 3.1 seconds, respectively). Step 7 was a mean of 3.1 seconds faster with the PFS than with the vial. Data are shown in Figure 3.

Qualitative results

At center 1, both the physician and the nurse in the treatment room were satisfied with the PFS because it required fewer preparation steps and, in their view, bubbles occurred less frequently when using the PFS than when using the vial. They thought that anti-VEGF therapy allowed more patients to be treated (physician) and older treatments such as photodynamic therapy and laser photocoagulation were described as being not very helpful (nurse). Both the physician and the nurse thought that the ranibizumab PFS was better than the vial. The primary reasons for this preference were that the PFS improved patient safety (potentially reducing the risk of ocular adverse events related to the injection procedure) and increased dosing accuracy (physician), and improved patient safety and increased efficiency owing to reduced injection time (nurse). The physician believed that patients would experience the greatest benefit from the PFS compared with the physician or nurse, while the nurse believed that the physician would gain the most benefit. The availability of the PFS was not likely to affect the physician's selection of anti-VEGF therapy.

At center 2, both the physician and nurses were satisfied with the PFS and thought that it was an improvement on the vial. This was because the PFS required fewer injection preparation steps and, in their view, bubbles occurred

less frequently than with the vial. They also believed that it was safer and saved time compared with the vial. The primary reason why they preferred the PFS to the vial was that it improved efficiency by reducing the injection time (physician) and improved patient safety by potentially reducing the risk of infection (nurses). The physician believed that nurses would experience the greatest benefit from the PFS, followed by physicians, while the nurses believed that the physician would benefit most. The physician thought that availability of the PFS was likely to affect physicians' selection of anti-VEGF therapy. Although nurses do not make decisions on therapy selection, they expressed a preference for using the PFS over other anti-VEGF therapy options.

Discussion

This study showed a significant reduction in syringe preparation time with the ranibizumab PFS compared with the ranibizumab vial in real-life clinical practice at 2 treatment centers in France. At center 1, preparation times were reduced by a mean of 29.3 seconds (39%) using the PFS, while at center 2, preparation times were reduced by a mean of 17.0 seconds (27%). The largest time savings were observed across steps 3-5 (attaching the filter needle, disinfecting the vial lid, and drawing ranibizumab from the vial, respectively), as these were not performed when using the PFS. In addition, the physicians and nurses thought there were fewer bubbles present when using the PFS, which reduced the time spent removing bubbles.

Health care professionals involved in the study reported a high degree of satisfaction with the PFS, citing various benefits to physicians, nurses, and patients to support this; for example, the administering physician was less dependent on a nurse being present throughout the preparation of the injection, thereby enabling staff reallocation to other duties. Fewer syringe preparation steps also reduced the possibility of errors. At center 1, it was thought that the risk of infection might be reduced for patients because disinfection of the vial lid was no longer necessary. Infection risk might also be reduced owing to fewer instances of handling components of the injection equipment using the PFS than when drawing the solution from a vial. PFSs also increase safety versus traditional vials, because fewer handling errors occur with the PFS (13). Finally, less waste is produced in the PFS procedure than with the vial; only 1 needle is required rather than 2, and the vial itself is no longer used.

The benefits in terms of speed of delivery, time-saving, reduced complexity of the syringe preparation process, and user satisfaction are consistent with earlier studies involving insulin and heparin PFSs (14, 15).

One limitation of the current study is that it focused only on the syringe preparation step of ranibizumab administration. Time could also be saved during other steps; for example, research on PFSs discussed above has documented time savings in steps such as waste disposal. The relatively small sample size is a potential limitation; however, the study was considerably overpowered given its inclusion of 122 syringe preparations versus the planned sample size of 48 preparations. In addition, the time-saving benefits of the PFS were clearly significant at both centers. A strength of the study is that it observed standard practice at 2 clinics, 1 private and 1 public, that are highly experienced in treating retinal diseases. Although data from the 2 centers could not be pooled owing to procedural differences, their results were in agreement that the PFS resulted in time savings.

In summary, the PFS improves speed and efficiency of ranibizumab administration versus the standard vial. This could enable physicians to treat more patients per treatment session, to treat the same number of patients in a shorter time, or to spend more time in discussion with patients; these points were also reflected in the feedback received from physicians and nurses.

Acknowledgment

Medical writing support was provided by Robert Gillies, PhD, PharmaGenesis London, UK. The authors thank the staff and patients at the treatment centers for their participation in this study.

Disclosures

Financial support: Funded by Novartis Pharma AG, Basel, Switzerland.

Conflict of interest: Eric Souied has received payment for consultancy, travel, and review activities from Allergan, Bayer, and Novartis; has been a board member and consultant for Théa; and has received payment for lectures and travel from Heidelberg. Salomon-Yves Cohen is a consultant for Bayer and Novartis. Claudia Leteneux and Alexandros Sagkriotis are employees of Novartis Pharma AG. Audrey Derveloy is an employee of Novartis Pharma France. Sascha Bayer and Guido Becker are employees of Q_PERIOR AG, which has received funding from Novartis to conduct this study. Sylvia Nghiem-Buffet has been a consultant for Novartis Pharma AG, Bayer AG, and Allergan.

Meeting presentation: A poster of this study was presented at the 14th European School for Advanced Studies in Ophthalmology (ESASO) Retina Academy meeting, Istanbul, Turkey, November 13, 2014.

References

1. Framme C, Wolf-Schnurrbusch UE, Lobsiger H, Bayer S, Wolf S. [Adapted and standardised patient management in the treatment of neovascular AMD in the outpatient setting of a university eye hospital.] Klin Monatsbl Augenheilkd. 2012;229:812-21.
2. Owen CG, Fletcher AE, Donoghue M, Rudnicka AR. How big is the burden of visual loss caused by age related macular degeneration in the United Kingdom? Br J Ophthalmol. 2003;87:312-7.
3. Bunce C, Wormald R. Leading causes of certification for blindness and partial sight in England & Wales. BMC Public Health. 2006;6:58.
4. Congdon N, O'Colmain B, Klaver CC, et al; Eye Diseases Prevalence Research Group. Causes and prevalence of visual impairment among adults in the United States. Arch Ophthalmol. 2004;122:477-85.
5. Menon G, Walters G. New paradigms in the treatment of wet AMD: the impact of anti-VEGF therapy. Eye. 2009;23(Suppl 1):S1-7.
6. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med. 1994;331:1480-7.
7. Brown DM, Kaiser PK, Michels M, et al; ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006;355:1432-44.

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