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ORIGINAL ARTICLE

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Does Pharmaceutical Compounding of Vascular Endothelial Growth Factor Inhibitors for Intravitreal Use Alter the Risk of Post-injection Endophthalmitis?

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ABSTRACT

Purpose: To investigate the safety of pharmaceutically compounded syringes for intravitreal administration of anti-vascular endothelial growth factor (anti-VEGF) drugs.

Methods: Single center, retrospective chart review. From 2015 to 2019, Oslo University Hospital, Norway gradually implemented pharmaceutical compounding and splitting of bevacizumab, ranibizumab, and aflibercept vials into multiple prefilled syringes for intravitreal use. Medical records of all post-injection endophthalmitis (PIE) cases in this 5-year period were reviewed. The incidences of PIE associated with compounded and clinician-withdrawn syringes were compared.

Results: In 5 years, the total number of anti-VEGF injections was 112,926; 68,150 procedures (60%) utilized compounded syringes, and 44,776 procedures (40%) utilized clinician-withdrawn syringes. A total of 11 PIE cases were identified (incidence 0.10 per 1000; 95% CI 0.05–0.17). Five PIE cases were associated with compounded syringes (incidence 0.07 per 1000; 95% CI 0.03–0.17); 3 of these were culture positive. Six PIE cases were associated with clinician-withdrawn syringes (incidence 0.13 per 1000; 95% CI 0.06–0.29); 2 of these were culture positive. The relative risk of PIE following procedures utilizing compounded versus clinician-withdrawn syringes was 0.55 (95% CI 0.17–1.79; $p = 0.32$).

Conclusion: Use of compounded anti-VEGF drugs in a large clinical setting was not associated with an altered risk of PIE. The finding adds to the evidence that splitting of vials into prefilled syringes for intravitreal injections is safe, provided that an appropriate pharmaceutical compounding procedure is strictly followed.

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Post-injection endophthalmitis; pharmaceutical compounding; anti-VEGF; intravitreal injections

In the era of anti-vascular endothelial growth factor (anti-VEGF) therapy, intravitreal injections have become one of the most commonly performed ophthalmic procedures. In this regard, pharmaceutical compounding and splitting of drug vials into multiple prefilled syringes for intravitreal use are a cause of controversy. On the one hand, it has been alleged that the practice is hazardous and associated with an increased risk of post-injection endophthalmitis (PIE), and clusters of PIE following splitting of vials into several doses have indeed been reported.[1,2] On the other hand, appropriate pharmaceutical compounding expectedly adheres to higher hygiene standards than the label recommendation for preparation of ranibizumab (Lucentis®; Novartis, Basel, Switzerland) and aflibercept (Eylea®; Bayer, Leverkusen, Germany) in an office-based setting.[3,4] While the dispute over compounding remains unsettled, research contributes to resolve the safety concern regarding the practice. In particular, a large retrospective cohort study have demonstrated that off-label use of compounded bevacizumab across the United States was associated with a lower risk of PIE than approved use of ranibizumab and aflibercept.[4]

At Oslo University Hospital (OUH), Norway we have implemented pharmaceutical compounding of all intravitreally administered anti-VEGF drugs. The compounding procedure incorporates splitting of bevacizumab, ranibizumab, and aflibercept vials into multiple prefilled syringes. For practical reasons the compounding routine was gradually implemented, and over 5 years, all intravitreal anti-VEGF injections were performed with either compounded or clinician-withdrawn syringes under otherwise identical circumstances. Accordingly, to seek valuable real-life data on the safety of compounded syringes for intravitreal use, the purpose of the present study was to address the circumstances surrounding the PIE cases at OUH in this particular 5-year period.

Methods

The study took place at the Department of Ophthalmology at OUH, which is the largest provider of retinal care in Norway. It was conducted as a single center, retrospective chart review approved by the institutional data protection officer. Pharmaceutical compounding in the hospital pharmacy was gradually implemented from 2016, and toward the end of 2018, only prefilled syringes were used for intravitreal anti-VEGF treatment; therefore, the study period was defined as 2015 (the last year only clinician-withdrawn syringes were used) through 2019 (the first year only compounded syringes were used).

To determine the total number of injections, hospital episode statistics were searched for episodes of care that included the Nordic Medico-Statistical Committee´s Classification of Surgical Procedures (NCSP) code CKD05: intravitreal

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injection of drug. For each CKD05 episode, we registered the NCSP code for right, left, or bilateral procedure (ZXA 00, ZXA 05, or ZXA 10). Bilateral procedures were counted as two intravitreal injections. The number of compounded syringes was taken from the pharmacy´s production record.

The study identified all patients diagnosed with endophthalmitis (ICD-10 code H44.0: purulent endophthalmitis or H44.1: another endophthalmitis) following an intravitreal anti-VEGF injection at OUH. It should be noted that a diagnosis of endophthalmitis at OUH is ultimately made clinically on the basis of a typical medical history and ophthalmic examination, but a vitreous biopsy or pars plana vitrectomy for microbiological analysis is routinely performed as an aid to the diagnosis. Patients that had undergone intraocular surgery after the last intravitreal injection were excluded. Moreover, patients diagnosed with uveitis that did not receive endophthalmitis treatment (intravitreal antibiotics with or without vitrectomy) within 1 week were considered probable sterile endophthalmitis cases and excluded.

For each included PIE case, the medical record was reviewed for the circumstances surrounding the infection; use of a compounded or clinician-withdrawn syringe was registered, and it was evaluated whether the injection deviated from the standard procedure or there were known patient-related risk factors for PIE, e.g. active external infection or eyelid, adnexal, or ocular surface abnormalities.[5]

Generally, bevacizumab was the first-line anti-VEGF drug. Aflibercept was used in eyes resistant to bevacizumab treatment, in cases of diabetic macular edema presenting with decimal visual acuity <0.4, and in patients diagnosed with polypoidal choroidal vasculopathy. Ranibizumab was used in selected cases at the doctor´s discretion. Mainly, the intravitreal injections were performed in an ambulatory setting and took place in positive air pressure cleanrooms according to a standard procedure: The personnel used surgical masks and caps, and the doctor performing the injection used sterile gloves. An ophthalmic drape with adhesive aperture and an eye speculum were administered. Povidone-iodine 5% was applied as antiseptic. The exposure time was 60 s with the eye closed and an additional 30 s following placement of the eye speculum. No antibiotic prophylaxis was used.

In the case of same-day bilateral treatment, both compounded and clinician-withdrawn syringes were from separate vials. The compounded syringes were produced in the hospital pharmacy at OUH; commercially obtained bevacizumab, ranibizumab, and aflibercept vials were split and drawn into low dead space plastic syringes in an isolator unit and transfer chamber according to an aseptic production procedure. We used a filter needle to withdraw ranibizumab and aflibercept from the vials. The compounded syringes were prepared with a capped 13 mm needle. The prefilled syringes were stored in sterile plastic bags at 4°C in the dark. A compounded syringe had to be used within 7 days. If not, the syringe was discarded. Every 6 months, all pharmacy technicians underwent requalification, which included microbiological culture of compounded syringes.[6] Generally, an aflibercept vial could be split into three syringes and a ranibizumab vial into two syringes. A larger 4 ml bevacizumab vial was sufficient for approximately 40 syringes. Treatment of endophthalmitis at OUH is described elsewhere.[7]

As the compounding routine was gradually implemented, the daily number of compounded syringes delivered from the hospital pharmacy did not fully meet the demand, and additional clinician-withdrawn syringes had to be used. The choice to use compounded or clinician-withdrawn syringes was practical (on any day, compounded syringes were used first, if available) and without regard to individual patients.

The cumulative 5-year PIE incidence, Wilson score 95% confidence interval (CI), and relative risk (RR) of PIE following procedures utilizing compounded versus clinician-withdrawn syringes were determined. Statistical significance was defined as $p < 0.05$. Data are presented as mean (standard deviation) or median (range).

Results

The number of intravitreal anti-VEGF injections in the 5-year study period was 112,926. There were 4991 injections with ranibizumab, 56,044 injections with bevacizumab, and 51,891 injections with aflibercept; 68,150 procedures (60%) utilized compounded syringes, and 44,776 procedures (40%) utilized clinician-withdrawn syringes. A total of 11 PIE cases were identified (incidence 0.10 per 1000; 95% CI 0.05–0.17). All cases were unilateral and occurred sporadically. Median time from intravitreal injection to diagnosis of PIE was 8 (1–19) days.

Among the 4991 injections associated with ranibizumab, there was one PIE case (incidence 0.20 per 1000; 95% CI 0.04–1.13). Among the 56,044 injections associated with bevacizumab, there were 5 PIE cases (incidence 0.09 per 1000; 95% CI 0.04–0.21). Among the 51,891 injections associated with aflibercept, there were 5 PIE cases (incidence 0.10 per 1000; 95% CI 0.04–0.23).

Among the 68,150 procedures utilizing compounded syringes, there were five PIE cases (incidence 0.07 per 1000; 95% CI 0.03–-0.17). Three of the five cases were culture positive for Staphylococcus epidermidis. Two of the five cases were culture negative. Among the 44,776 procedures utilizing clinician-withdrawn syringes, there were 6 PIE cases (incidence 0.13 per 1000; 95% CI 0.06–0.29). Two of the six cases were culture positive: one for Staphylococcus aureus and one for Staphylococcus warneri. Four of the six cases were culture negative. The relative risk of PIE following procedures utilizing compounded versus clinician-withdrawn syringes was 0.55 (95% CI 0.17–1.79; $p = .32$).

Of the 11 PIE cases, the indication for anti-VEGF therapy was neovascular age-related macular degeneration in 8 patients, macular edema secondary to branch retinal vein occlusion in one patient, proliferative diabetic retinopathy in one patient, and choroidal neovascularization secondary to central serous chorioretinopathy in one patient. In all the 11 PIE cases, the preceding intravitreal injection adhered to the standard procedure, and patient-related risk factors for PIE were not identified. Table 1 displays a summary of the main findings.

Discussion

Implementation of pharmaceutical compounding and vial splitting of all intravitreally administered anti-VEGF drugs at OUH has led to several benefits, and numerous retina services in Norway and Finland have subsequently realized similar methods.[8] First, the prefilled syringes save time in the injection

Table 1. Main findings of post-injection endophthalmitis (PIE) cases associated with compounded and clinician-withdrawn syringes at Oslo University Hospital, Norway from 2015 to 2019. In all the 11 PIE cases, the preceding intravitreal injection adhered to the standard procedure, and patient-related risk factors for PIE were not identified.

Compounded syringes (60%) n = 68,150							Clinician-withdrawn syringes (40%) n = 45,286						
Case	Age	Sex	Diagnosis	Drug	Treatment	Pathogen in culture	Case	Age	Sex	Diagnosis	Drug	Treatment	Pathogen in culture
1	76	M	nAMD	R	dVB	-	1	78	M	nAMD	A	dVB	S. aureus
2	68	F	nAMD	B	PPV	S. epidermidis	2	89	F	nAMD	B	PPV	-
3	65	M	BRVO	A	dVB	S. epidermidis	3	86	F	nAMD	A	dVB	-
4	82	M	nAMD	A	PPV	S. epidermidis	4	55	F	DM I; PDR	B	PPV	-
5	68	F	nAMD	A	dVB	-	5	64	F	CSCR; sCNV	B	PPV	-
							6	92	F	nAMD	B	dVB	S. warneri
PIE incidence: 0.07 per 1000 (95% CI 0.03–0.17)							PIE incidence: 0.13 per 1000 (95% CI 0.06–0.29)						

A, aflibercept; B, bevacizumab; BRVO, branch retinal vein occlusion; CI, confidence interval; CSCR, central serous chorioretinopathy; DM I, diabetes mellitus type I; dVB, diagnostic vitreous biopsy; F, female; M, male; nAMD, neovascular age-related macular degeneration; PDR, proliferative diabetic retinopathy; PIE, post-injection endophthalmitis; PPV, pars plana vitrectomy; R, ranibizumab; S. aureus, Staphylococcus aureus; sCNV, secondary choroidal neovascularization; S. epidermidis, Staphylococcus epidermidis; S. warneri, Staphylococcus warneri.

room. Second, because all bevacizumab, ranibizumab, and aflibercept vials are split, the prefilled syringes reduce the public healthcare expenses associated with anti-VEGF drugs. Finally, the compounding procedure adheres to considerably higher hygiene standards than the label recommendation for preparation of the approved anti-VEGF drugs, and the prefilled syringes require less manipulation in the injection room. This can potentially lower the risk of contamination, and this study does not present evidence that the practice puts patients at increased risk of PIE, a finding that supports the conclusion of other safety studies of prefilled syringes.[4,9–11]

Unlike countries such as the United States, pharmaceutical compounding of bevacizumab for intravitreal use was formerly not customary in Norway. Instead, clinicians typically prepared the syringes, regardless of whether vials were split into several doses. Ultimately, two outbreaks of PIE associated with office-based splitting of anti-VEGF drugs ended the poorly regulated practice, and the Norwegian Board of Health Supervision now requires splitting of vials to take place in pharmaceutical compounding facilities.[12]

Among the five culture-positive PIE cases, we identified three instances of Staphylococcus epidermidis (associated with compounded syringes), one case of Staphylococcus aureus (associated with a clinician-withdrawn syringe), and one case of Staphylococcus warneri (associated with a clinician-withdrawn syringe). All bacteria are part of normal microbiota of skin and mucous membranes. In all PIE cases the preceding injection adhered to the standard procedure, and no patients had known risk factors for PIE. Accordingly, neither deviation from the standard injection protocol nor patient-specific circumstances seem to have biased the results. In regard to the one patient being treated for proliferative diabetic retinopathy, it is worth mentioning that although diabetes mellitus is a well-known risk factor for post-cataract surgery and endogenous endophthalmitis, it is not a proven risk factor for PIE.[5,9,13–16]

Some study limitations should be noted. First, culture-negative PIE cases were included. In addition to PIE, acute sterile endophthalmitis is a possible complication of intravitreal injections. It is reported to occur at roughly the same frequency as endophthalmitis.[17,18] Although we excluded inflammatory complication that did not receive antibiotics, instances of sterile endophthalmitis among the culture-negative PIE cases cannot be ruled out with certainty. Still, as the overall PIE rate in our study is similar to or lower than other reports, it does not indicate improper inclusion of non-PIE cases.[19] Second, other potential complications of intravitreal injections were not addressed. Finally, it should be emphasized that because PIE is a rare occurrence (overall incidence 0.10 per 1000 injections in this study), a study may lack statistical power to detect a true difference between groups.

In conclusion, use of repacked anti-VEGF drugs in a large clinical setting was not associated with an altered risk of PIE. Our study adds to the evidence that splitting of vials into prefilled syringes for intravitreal injections is safe, provided that an appropriate pharmaceutical compounding procedure is strictly followed.

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Disclosure statement

MSS is an investigator in an Alcon-sponsored clinical trial. ØKJ has received lecture fees from Allergan, Alcon, Bayer, and Novartis and is member of a Bayer, Allergan, and Roche advisory board. MCM has received lecture fees from Bayer and is member of a Bayer, Novartis, and Allergan advisory board.

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