

Practice Patterns and Outcomes of Intravitreal Anti-VEGF Injection for Retinopathy of Prematurity

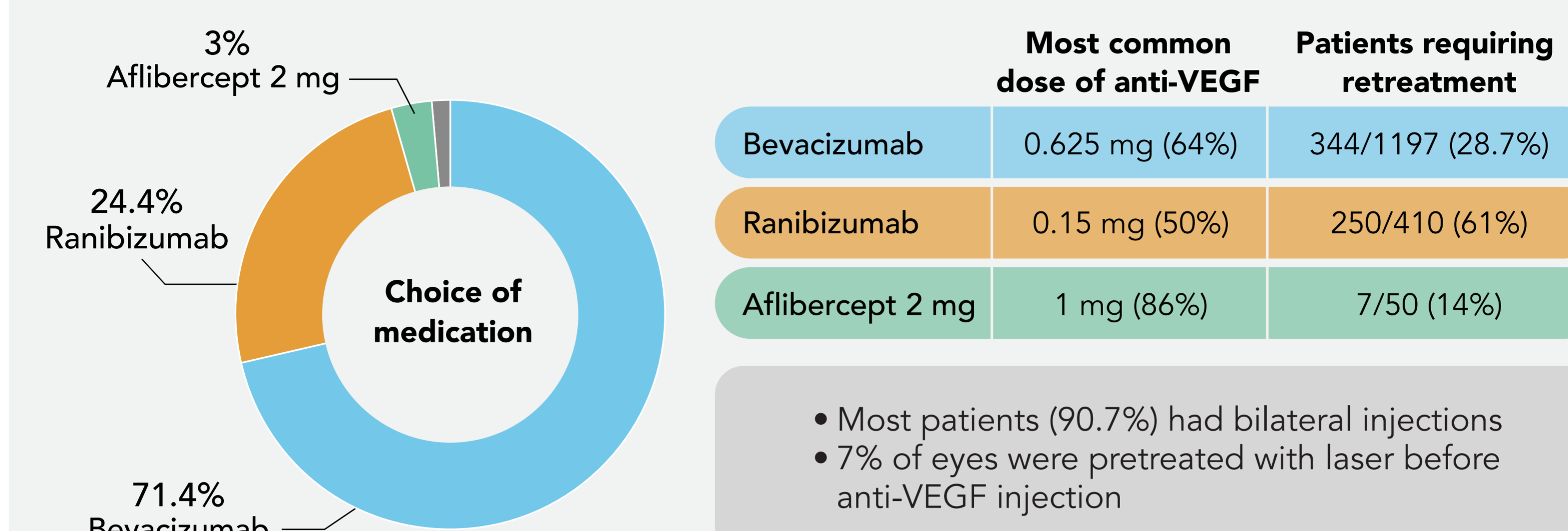
An International Multicenter Study

Patel NA, Acaba-Berco LA, Hoyek S, et al. *Ophthalmology*. 2022;129:1380-1388. doi:10.1016/j.ophtha.2022.07.009

This study reports practice patterns of intravitreal injections of anti-VEGF for retinopathy of prematurity (ROP) and outcomes data with a focus on retreatments and complications. Designed as a multicenter, international, retrospective, and consecutive series, the study assesses patients with ROP treated with anti-VEGF injections from 2007 to 2021.

Twenty-three sites (16 United States [US] and 7 non-US) participated and the data collected included demographics, birth characteristics, examination findings, and methods of injections. Comparisons between US and non-US sites were made. Primary outcomes included number and types of retreatments as well as complications. Secondary outcomes included specifics of the injection protocols, including types of medication, doses, distance from limbus, use of antibiotics, and quadrants where injections were delivered.

Bevacizumab was the most common anti-VEGF (71.4%), with a dose of 0.625 mg in 64% of cases



1677 eyes were included across 23 international sites over 14 years to report practice patterns and outcomes of intravitreal anti-VEGF injections

Characteristics of Patients with ROP in Global, US, and Non-US Groups

	Overall	US Group	Non-US Group	P Value, US Group versus Non-US Groups
Sites	23	16	7	
Eyes	1677	873	804	
Sex, n (%)				
Male	762 (56.7)	405 (61.3)	357 (52.3)	
Female	582 (43.3)	256 (38.7)	326 (47.7)	
Mean gestational age at birth, wks	25.7	24.5	26.9	<0.0001*
Mean birth weight, g	787	665.6	912.7	<0.0001*
Mean postconceptual age at first injection	36.3	36	36.6	0.0003*
Zone of ROP (most posterior), n (%)				
I	489 (29.7)	298 (35)	191 (24)	<0.0001*
II	1088 (66.1)	545 (64)	543 (68.3)	0.087
III	70 (4.2)	9 (1)	61 (7.7)	<0.0001*
Stage of ROP at injection, n (%)				
1	41 (2.5)	13 (1.5)	28 (3.5)	0.009*
2	215 (13.1)	114 (13.4)	101 (12.8)	0.763
3	1346 (82)	704 (82.6)	642 (81.4)	0.398
4	36 (2.2)	19 (2.2)	17 (2.2)	0.945
5	4 (0.2)	3 (0.3)	1 (0.1)	0.341
Average total clock hours	9.2	9.2	12	0.1232
Plus disease, n (%)	1392 (85.4)	747 (88.7)	645 (81.9)	0.0001*
Aggressive ROP, n (%)	282 (17.9)	217 (26.2)	65 (8.7)	<0.0001*

ROP = retinopathy of prematurity; US = United States
*P <0.05 (statistically significant)

In the short term, a repeated anti-VEGF injection can be used as a bridge to buy time for patient systemic stabilization and further retinal vascularization, which can both diminish the area that requires photocoagulation

Retreatments and Complications in Global, US, and Non-US Groups

	Overall	US Group	Non-US Group	P Value, US Group versus Non-US Groups
Total retreatments, n	604	509	95	
Injection-only retreatment, n (%)	64 (10.6)	30 (5.9)	34 (35.8)	<0.0001*
Laser-only retreatment, n (%)	482 (79.8)	428 (84.1)	54 (56.8)	<0.0001*
Laser and injection retreatment, n (%)	58 (9.6)	51 (10)	7 (7.4)	0.829
Laser before injection, n (%)	116 (7)	40 (4.6)	76 (9.6)	0.0001*
Laser after injection, n (%)	540 (32.2)	479 (55)	61 (7.2)	<0.0001*
Total reinjections, n	122	81	41	
Reinjection, n (%)	110 (6.7)	73 (8.5)	37 (4.7)	0.0016*
Two reinjections, n (%)	6 (0.4)	4 (0.5)	2 (0.3)	0.4617
Bevacizumab, n (%)	1197 (72.2)	595 (68.2)	602 (76.7)	<0.0001*
Aflibercept, n (%)	50 (3)	7 (0.8)	43 (5.5)	<0.0001*
Ranibizumab, n (%)	410 (24.8)	270 (31)	140 (17.8)	<0.0001*
Average time to retreatment, days				
Injection	58.1	62.2	48.7	0.0821
Laser	124.3	134.2	36.4	<0.0001*
Laser and injection	124.6	130.2	41.3	<0.0001*
Complications, n (%)				
None	1639 (99.1)	857 (98.7)	782 (99.7)	0.0976
Cataract	3 (0.2)	2 (0.2)	1 (0.1)	
Endophthalmitis	0	0	0	
Vitreous hemorrhage	7 (0.4)	5 (0.6)	2 (0.2)	0.3668
Corneal abrasion	1 (0.06)	1 (0.1)	0	
Subconjunctival hemorrhage	2 (0.12)	2 (0.2)	0	
Conjunctivitis	2 (0.12)	2 (0.2)	0	

*P <0.05 (statistically significant)

Major findings:

- 1) Complications after anti-VEGF injections are rare and similar across practice patterns and locations
- 2) Injection retreatments are performed less frequently and earlier than laser retreatments
- 3) Infants with ROP in the United States tend to be younger and smaller and were treated at earlier PCAs than non-US patients

Advances in neonatal care have led to increased survival of younger and smaller infants

In a recent single-center longitudinal study^a of infants with ROP, the researchers noted that over a 30-year period, there was **a decrease in gestational age and birth weight with each decade**. This was attributed to advances in neonatal care and its quality that led to increased survival of younger and smaller infants.

The increased survival of smaller and younger neonates in high-income countries has been reported and is thought to be the consequence of advancements in neonatal care, including optimization of oxygenation protocols, monitoring, and treatment with corticosteroids and antibiotics.

^aBerco LA, Fan KC, Al-Kharsan H, et al. Retinopathy of prematurity: advances in the screening and treatment of retinopathy of prematurity using a single center approach. *Am J Ophthalmol*. 2022;233:189e215.

Complications after anti-VEGF injections were rare and serious complications were absent

Overall, **complications after anti-VEGF injections were rare (0.9%)** and included:

- Vitreous hemorrhage
- Cataract formation
- Conjunctivitis
- Subconjunctival hemorrhage
- Corneal abrasion

Serious complications, such as endophthalmitis or retinal detachments, were absent.

Conclusion

- **In this large-scale study on the use of anti-VEGF therapy for ROP in a clinical setting, intravitreal injections were well tolerated with no cases of endophthalmitis, despite a variance of practice patterns in and outside the United States**
- **Retreatment rates were found to be higher than those previously reported in clinical trials. Delayed laser therapy was far more commonly used than reinjection, especially in the United States; however, the intention seems to be primarily for prophylaxis rather than for worsening disease**
- **Infants receiving injections in the United States tended to be younger and smaller, have higher rates of aggressive-ROP, be treated earlier, and require more retreatments than non-US neonates with ROP**