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Supply Chain Volatility of Repackaged Intravitreal Bevacizumab: A Survey of the American Society of Retina Specialists

Hasenin Al-khersan, MD[1], Miguel Busquets, MD[2], Ghassan Ghorayeb, MD[3], Dan Gong, MD[4], Anton Kolomeyer, MD, PhD[5], Ella H. Leung, MD[6], Philip Niles, MD[7], Nimesh A. Patel, MD[4], Ankoor R. Shah, MD[1], Charles C. Wykoff, MD, PhD[1], Jill Blim, MS[8], J. Michael Jumper, MD, FASRS[8], and Michael M. Lai, MD, PhD[9], on behalf of the ASRS Health Economics Committee

Abstract

Purpose: To characterize retina specialists' perceptions of the intravitreal (IVT) bevacizumab supply chain after the manufacturer, Pine Pharmaceuticals, announced they would no longer produce the formulation. **Methods:** A 22-question survey was created to assess retina physicians' use of IVT bevacizumab, perceptions of the supply chain, and how the decision will affect patient care. The survey was electronically distributed to all members of the American Society of Retina Specialists. **Results:** The survey was completed by 287 retina specialists. In the 3 months before the survey, 194 (67.6%) physicians reported receiving IVT bevacizumab from Pine Pharmaceuticals. Approximately 85% of physicians were either very concerned (158 [55.4%]) or concerned (85 [29.8%]) about their access to the medication in the next 3 months. Most physicians anticipated needing to delay or change patient appointments (142 [50.4%]) or change patient treatment plans (179 [63.9%]) because of shortages of IVT bevacizumab. Respondents overwhelmingly believed that patients with step-therapy requirements were most likely to be affected by appointment delays (119 [83.8%]) and changes in treatment plans (140 [78.2%]). **Conclusions:** The majority of retina specialists surveyed expect the decision to halt production of IVT bevacizumab will significantly disrupt access to the medication and adversely affect patient care. Most physicians predict delays and changes in treatment, particularly for patients with IVT bevacizumab step-therapy requirements. Therefore, to minimize negative effects on patient care, we recommend that carriers suspend step-therapy requirements, especially given that the disruption to the supply chain is likely to be longstanding.

Keywords

bevacizumab, antivascular endothelial growth factor, compounding pharmacy, healthcare supply chain

Introduction

Nearly 2 decades ago, the use of intravitreal (IVT) bevacizumab was first reported for neovascular age-related macular degeneration (nAMD).[1] Since then, the drug has been found to be noninferior to ranibizumab for the treatment of nAMD and is also effective for the treatment of diabetic macular edema.[2,3] The use of IVT bevacizumab has since become widespread for the treatment of various exudative retinal pathologies.[4] Although certain patients will benefit from alternative antivascular endothelial growth factor (anti-VEGF) therapies that are more durable and have drying effects, many retina specialists continue to use IVT bevacizumab because of its cost-effectiveness.[3,5,6]

Although it is used frequently, IVT bevacizumab has not received approval from the Food and Drug Administration for intraocular use.[7] In the United States, IVT bevacizumab is repackaged by compounding pharmacies into syringes designed for IVT injections. Interruptions in the supply chain from these compounding pharmacies can lead to significant disruptions in clinical care.[8] In addition, multiple outbreaks of contamination

[1] Retina Consultants of Texas, Houston, TX, USA
[2] Retina Associates of Kentucky, EyeCare Partners, Lexington, KY, USA
[3] West Virginia University, Morgantown, WV, USA
[4] Department of Ophthalmology, Massachusetts Eye and Ear, Harvard Medical School, Boston, MA, USA
[5] NJRetina, Teaneck, NJ, USA
[6] Georgia Retina, Atlanta, GA, USA
[7] Buffalo Niagara Retina Associates, Buffalo, NY, USA
[8] American Society of Retina Specialists, Chicago, IL, USA
[9] Retina Group of Washington, Chevy Chase, MD, USA

Corresponding Author:
Hasenin Al-khersan, MD, Retina Consultants of Texas, Houston, 4460 Bissonnet St, Ste. 200, Bellaire, TX 77401, USA.
Email: haseninrh@gmail.com

Table 1. Demographics of Survey Respondents.

Demographic	Respondents, n (%)
Years of experience	
0–5	45 (15.7)
6–10	52 (18.1)
11–15	50 (17.4)
>15	140 (48.8)
Practice setting	
Retina-only group (1–5 physicians)	103 (35.9)
Retina-only group (>5 physicians)	88 (30.7)
Multispecialty group	54 (18.8)
Academic center/hospital	35 (12.2)
Other	7 (2.4)
Region of practice	
Northeast	71 (24.7)
Midwest	55 (19.2)
South	87 (30.3)
West	69 (24.0)
Puerto Rico/Territories	5 (1.7)

resulting in endophthalmitis and blindness have been reported.[9,10] Further concerns include variable protein concentrations, even in samples from the same compounding pharmacies, and silicone oil found in the repackaged syringes.[11,12]

On October 11, 2024, Pine Pharmaceuticals, one of the largest producers of repackaged IVT bevacizumab in the US, announced that it would no longer produce repackaged IVT bevacizumab for intraocular use, raising concerns in the retina community regarding future access to the drug.[13,14] The current analysis sought to characterize retina physicians' perceptions regarding access to IVT bevacizumab.

Methods

This study adhered to the Declaration of Helsinki and was exempted from institutional review board approval. A 22-question anonymized survey was created that characterized retina physicians' historical use of IVT bevacizumab and concerns about its availability in the aftermath of the Pine Pharmaceuticals announcement (Supplemental Figure 1). Multiple retina specialists reviewed and validated the survey before it was electronically distributed in 3 mailings to all members of the American Society of Retinal Specialists (ASRS). A single response per participant was allowed. Responses were collected between October 24, 2024, and November 3, 2024.

Results

Demographics

Of 1955 retina specialists contacted, 287 (14.7%) responded to the survey. Most physicians (140 [48.8%]) had more than 15 years of experience and practiced in retina-only private practice groups, either with 1 to 5 (106 [36.9%]) specialists or more than 5 specialists (88 [30.7%]). Table 1 lists the full demographics of the survey respondents, including regional distribution.

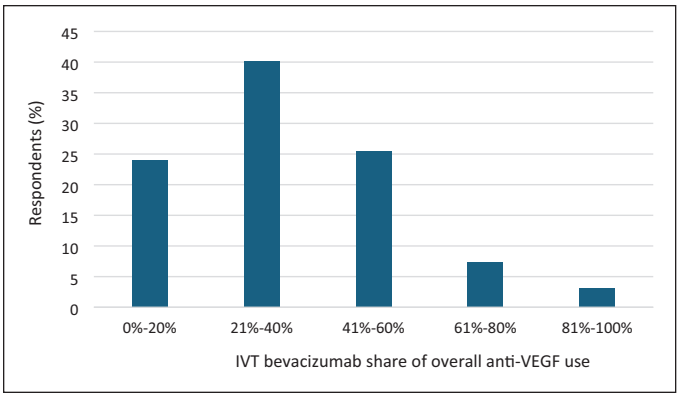

Figure 1. Intravitreal (IVT) bevacizumab as a share of overall antivascular endothelial growth factor (anti-VEGF) use among respondents.

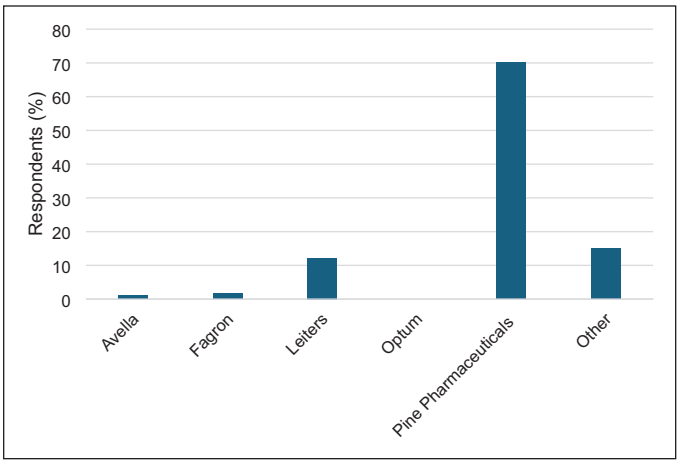

Figure 2. Pharmacies supplying the majority of physicians' intravitreal bevacizumab in the year before the survey.

Historical Bevacizumab Use

The distribution of IVT bevacizumab use among respondents in the year before the survey is shown in Figure 1. Of note, 84.7% (243) of retina specialists indicated that at least some portion of their use of IVT bevacizumab was for patients with a condition or indication that did not have a Food and Drug Administration-approved pharmacotherapy. Most physicians (201 [70%]) indicated that most of their supply in the year before the survey came from Pine Pharmaceuticals (Figure 2). In the 3 months immediately before the survey, 194 (67.6%) physicians reported receiving or using IVT bevacizumab from the manufacturer, with 124 (64.3%) physicians indicating the manufacturer was responsible for 81% to 100% of their supply.

Changes in IVT Bevacizumab Supply

Almost all respondents (273 [95.1%]) knew of Pine Pharmaceuticals' decision to halt production of IVT bevacizumab. Most respondents were made aware by announcements from either the ASRS (112 [41%]) or directly from the manufacturer (108 [39.6%]). Most physicians either strongly disagreed (50 [18%])

or disagreed (98 [35.3%]) with the notion that they felt adequately informed by manufacturers/suppliers about the overall status of the drug's availability.

Challenges to Access

A total of 191 (67%) physicians reported experiencing challenges to accessing IVT bevacizumab in the past year. In addition, most physicians were either very concerned (158 [55.4%]) or concerned (85 [29.8%]) about their ability in the next 3 months to access the drug. A majority of physicians believed Pine Pharmaceuticals' announcement would very likely (98 [35.3%]) or likely (87 [31.3%]) result in decreased use of IVT bevacizumab in the future. Furthermore, most physicians thought the announcement would very likely (89 [31.9%]) or likely (95 [34%]) lead to a decrease in the next 3 months of their use of the drug for naïve patients requiring anti-VEGF therapy.

Impacts on Patient Care

A majority of surveyed physicians anticipated needing to delay or change patient appointments (142 [50.4%]) or change patient treatment plans (179 [63.9%]) because of the manufacturer's decision to halt production of IVT bevacizumab. Respondents overwhelmingly believed that patients with insurance plans requiring step therapy were the most likely to be affected by appointment delays (119 [83.8%]) and changes in treatment plans (140 [78.2%]).

Step Therapy

In the 3 months before the survey, almost half (130 [45.8%]) of physicians reported pursuing bypasses to IVT bevacizumab step therapy; however, no physicians were successful with all of their appeals. Only 22 (16.8%) of those who applied for bypass were successful most of the time. Seventeen physicians (13%) reported being unsuccessful in all their attempts to obtain authorization to bypass IVT bevacizumab step therapy. Last, a majority of physicians reported feeling "not at all confident" (62 [21.8%]) or "not so confident" (135 [47.5%]) about navigating the process for obtaining step therapy bypass authorizations if such action would be needed.

Conclusions

The current survey identified serious concerns among retina specialists regarding the supply of IVT bevacizumab, both currently and in the past. Approximately two thirds of the retina specialists surveyed stated that even before Pine Pharmaceuticals' announcement, they faced challenges in obtaining the drug. The unstable supply of IVT bevacizumab has been an ongoing challenge most recently demonstrated by a large recall (approximately 370 000 units nationwide) in October 2023.[8] Moving forward, the decision to completely halt production of IVT bevacizumab will likely have adverse effects on patient care, as most retina specialist respondents reported receiving most of their supply from Pine Pharmaceuticals, previously the largest 503B supplier of IVT bevacizumab in the US. Some estimates indicated the company was responsible for nearly half of the IVT bevacizumab supply.[14] This is reflected by the fact that 85% of respondents felt either concerned or very concerned about their ability to obtain the drug in the next 3 months. Issues related to the supply of IVT bevacizumab represent a growing trend of supply chain disruptions across medicine.[15]

The results of this survey also showed that physicians believe Pine Pharmaceuticals' decision will directly affect patient care. Most physicians stated that they would likely need to delay appointments and change treatment plans moving forward. The overwhelming sentiment among respondents was that patients with insurance plans requiring step therapy would be disproportionately affected by these changes. The literature quantifying step-therapy plans in retina is sparse; however, 1 study of 7 large insurance carriers found that approximately 70% of ophthalmology plans incorporated step-therapy requirements across Medicare Advantage plans.[16] The case of bevacizumab step therapy is unique and particularly problematic because of the supply shortages of this required therapy. Accordingly, both the American Academy of Ophthalmology and the ASRS have called upon the Centers for Medicare & Medicaid Services and insurers to suspend step-therapy requirements given the uncertain supply chain.[17,18]

Nearly half of physicians reported attempting to obtain IVT bevacizumab step-therapy bypass authorization in the past 3 months before the survey, likely reflecting the volatile nature of its supply even before the manufacturer's announcement. Despite this experience, most physicians did not feel confident about navigating the process of obtaining step-therapy bypass authorization. This is reflected by the fact that no physicians reported being successful in all their attempts to obtain authorization, and only approximately 17% reported being successful in most of their attempts. More than 1 in 10 physicians were unsuccessful in all of their bypass attempts. The requirement to obtain step-therapy bypasses on a case-by-case basis can lead to undue administrative burdens on physicians.[19] In the setting of this large disruption of IVT bevacizumab supply, we recommend a suspension of step-therapy requirements to mitigate impacts on patient care, particularly given there is no imminent solution for this disruption of the supply chain.

Importantly, nearly 85% of those surveyed indicated that they used IVT bevacizumab therapy for patients with a disease that does not have an alternative FDA-approved pharmacotherapy. Anti-VEGF therapy has become an important mainstay in the treatment of a range of diseases, such as sickle cell retinopathy, choroidal neovascularization in central serous retinopathy, radiation retinopathy, and other pharmacotherapies that do not otherwise have FDA approval.[20–22] These patients may disproportionately suffer from shortages in the IVT bevacizumab supply chain.

Potential sampling and nonresponse bias are among the limitations of survey research. It is possible that respondents most affected by the decision were more likely to respond to our

survey, introducing bias. However, the respondents were broadly distributed across geographic regions, experience levels in the field, and practice settings. The response rate was also relatively low, which is explained in 2 ways. First, although 1955 retina specialists were contacted, ultimately we could not determine how many physicians opened the emails. Therefore, we opted to calculate the response rate more conservatively using the total number of specialists on the listserv. Second, in order to produce these data in a timely fashion, responses were collected over a brief period (<2 weeks).

The results of this survey emphasize the concerns among retina specialists regarding the uncertain supply of repackaged IVT bevacizumab. The decision to halt its production by Pine Pharmaceuticals has amplified this apprehension. Most importantly, a majority of retina specialists believe these developments will directly affect patient care, particularly those patients with step-therapy requirements. Given that there is no resolution on the horizon for this supply chain disruption, IVT bevacizumab step-therapy requirements should be suspended by the Centers for Medicare & Medicaid Services and insurance providers, allowing patients to continue receiving anti-VEGF therapies to preserve vision and prevent blindness.

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Ethical Approval

The present work was exempted from institutional review board approval. The study was conducted in concordance with the Declaration of Helsinki.

Informed Consent

Survey participants were informed that participation was voluntary and their responses would remain anonymous. Consent for participation was implied with completion of the survey.

Declaration of Conflicting Interest

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of the article: Dr. Al-khersan reports consulting fees from Alimera, Annexon, Apellis, Genentech, Ocular Therapeutix, and Regeneron. Dr. Busquets reports consulting fees from Ocular Therapeutix. Dr. Kolomeyer reports consulting fees from Alimera, Allergen, Apellis, Biogen, Genentech, Iveric, Oculis, Regeneron, Retina Labs, and Vial. Dr. Niles reports consulting fees from Regeneron. Dr. Patel reports consulting fees from Apellis, Alcon, Alimera, Allergan, Biogen, Dorc, EyePoint, Genentech, Kyoto, Life Science Regeneron, and Regenx Bio. Dr. Shah reports consulting to Notal Vision, Ocular Therapeutix, Regeneron, and RegenexBio. Dr, Lai reports consulting fees from Apellis and Genentech; Dr. Wykoff reports consulting fees from 4DMT, AbbVie, Adverum, Aerie, AGTC, Alcon, Alimera, Alkeus, Allgenesis, Alnylam, AMC Sciences, Annexon, Apellis, Arrowhead, Ascidian, Aviceda, Bausch + Lomb, Bayer, Biocryst, Bionic Vision, Boehringer Ingelheim, Cholgene, Clearside, Curacle, Emmecell, EyeBiotech, EyePoint, Foresite, Frontera, Genentech, Gyroscope, IACTA, InGel, Iveric Bio, Janssen, Kato, Kiora, Kodiak, Kriya, Merck, Merit, Nanoscope, Neurotech, NGM, Notal Vision, Novartis, OccuRx, Ocular Therapeutix, Ocuphire, Ocuterra, OliX, ONL, Opthea, Osanni, Oxular, Palatin, Perceive Bio, Perfuse, Ray, RecensMedical, Regeneron, RegenXBio, Resonance, Roche, Sandoz, Sanofi, Santen, SciNeuro, Stealth, Surrozen, Suzhou Raymon, Sylentis, THEA, Therini, TissueGen, Valo, Verana, Visgenx, and Zeiss and advisory board participation for Aerie and Kato. None of the other authors declared potential conflicts of interest with respect to the research, authorship, and/or publication of the article.

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ORCID iDs

Hasenin Al-khersan https://orcid.org/0000-0001-6114-0996
Miguel Busquets https://orcid.org/0000-0001-9522-8486
Dan Gong https://orcid.org/0000-0003-2055-9453
Charles C. Wykoff https://orcid.org/0000-0001-7756-5091

Supplemental Material

Supplemental material is available online with this article.

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