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AMERICAN ACADEMY OF OPHTHALMOLOGY®

Reports

The Pandemic Is Not Associated with Endophthalmitis Decrease after Anti−Vascular Endothelial Growth Factor Injections

The coronavirus disease 2019 (COVID-19) pandemic has been, and continues to be, a catastrophic global health adversity. A precipitous decline in patient visits to ophthalmologists occurred nationwide in the spring of 2020, but a lesser decline was observed in visits to retina specialists.[1] However, the introduction of new practices of care during the pandemic provide a unique window into understanding how potentially related clinical outcomes may have changed before and after the onset of the pandemic. One of those changes introduced during the pandemic is universal masking, both by the physician and by the patient, which permits the examination of the impact of masking on the risk of infectious complications of anti−vascular endothelial growth factor (VEGF) intravitreal injections. The overall risk of complications associated with anti-VEGF injections is low, but one vision-threatening complication is the occurrence of acute-onset endophthalmitis. The hypothesis is that mask use leads to a decrease in infections, such as endophthalmitis, by reducing the exposure to nasopharyngeal and oral flora and the dispersion of bacteria associated with speaking. Before the pandemic, anti-VEGF intravitreal injections did not necessitate the use of masks by ophthalmologists, and rarely by patients. The rate of endophthalmitis per intravitreal anti-VEGF injection has been reported to be 0.056% in a meta-analysis of 43 studies of 350 535 injections conducted between 2005 and 2012.[2]

Recent studies have compared rates of endophthalmitis before and after the onset of the pandemic. The Post-Injection Endophthalmitis Study Group retrospectively reviewed data from 12 centers in the United States from October 1, 2019, through July 31, 2020.[3] A total of 505 968 injections were classified into a no face mask group with a rate of presumed endophthalmitis of 0.0289% or a universal face mask group with a rate of 0.0213% (odds ratio [OR], 0.74; 95% confidence interval [CI], 0.51−1.18; $P = 0.097$). However, a decreased risk seemed to occur based on culture-positive endophthalmitis rates (OR, 0.46; 95% CI, 0.22−0.99; $P = 0.041$), but no difference was found based on oral flora-associated endophthalmitis rates (OR, 0.46; 95% CI, 0.05−4.46; $P = 0.645$). Naguib et al[4] evaluated the rates of endophthalmitis after any type of intravitreal injection retrospectively at 1 tertiary retina center in Houston, Texas. Based on a total of 134 097 injections both before and after COVID-19 masking protocols, a significant difference was not found (0.04% before COVID-19 vs. 0.03% after COVID-19; $P = 0.85$). A single-center study before the COVID-19 pandemic did not find a decreased risk of endophthalmitis based on physicians wearing a mask during intravitreal injections (0.0371% rate) versus physicians not talking during intravitreal injections (0.0298%; OR, 0.81; 95% CI, 0.41−1.57; $P = 0.527$).[5] Another study at a tertiary referral center found that the introduction of universal masking in 2020 did not reduce the rates of endophthalmitis (0.014% before COVID-19 vs. 0.011% during the COVID-19 pandemic; $P = 0.73$).[6]

The Academy's IRIS® Registry (Intelligent Research in Sight) is the largest single-specialty electronic health record clinical data registry in the United States. The data in the IRIS Registry database are aggregated and de-identified; therefore, institutional review board approval and written informed consent were not required for the analysis. All research adhered to the tenets of the Declaration of Helsinki. As of July 1, 2021, the IRIS Registry database included 69.2 million patients with 397.54 million visits from 3038 ophthalmic practices across the country, including most private practices. The methods of data extraction and aggregation have been described in the literature.[7] One of the singular applications of the IRIS Registry database is the focus on rare diseases and uncommon adverse events such as endophthalmitis.

Presumed cases of endophthalmitis were included if occurrence was within 21 days after an anti-VEGF intravitreal injection and were identified by the following International Classification of Disease, Tenth Revision, Clinical Modification codes: H44.001 through H44.003, H44.011 through H44.013, H44.021 through H44.023, and H44.111 through H44.113. Anti−vascular endothelial growth factor intravitreal injections were identified by the same-day presence of the Central Procedural Terminology code for an intravitreal injection (67028) with a Healthcare Common Procedure Coding System code that indicates the agent used (C9257, J9035, J0179, J0178, or J2778). A cutoff date of 21 days after anti-VEGF injections was used because most endophthalmitis cases occurred within 21 days after the injection. Cases were excluded if the patient was younger than 18 years, if there were any ophthalmic procedures other than intravitreal injections within 90 days before the documentation of endophthalmitis, a uveitis or panuveitis diagnosis preceding the occurrence of endophthalmitis, or if 2 anti-VEGF agents were listed on the same date. All patients were required to have at least 3 months of follow-up after the endophthalmitis event. A total of 4 206 234 anti-VEGF intravitreal injections were evaluated in the same 3 months, April through June, to account for possible seasonal factors across a 4-year period, 2017 through 2020 (Fig 1). The rates of endophthalmitis were similar across the years: 0.0334% in 2017, 0.0324% in 2018, 0.0292% in 2019, and 0.0303% in 2020. This range of rates of endophthalmitis is congruous with rates reported in recent studies.[4,5]

The limitations of the analysis include the lack of data on bacterial culture analyses to confirm cases of endophthalmitis definitively and the inability to confirm if masks were not worn before the pandemic or if masks were worn after the start of the pandemic. Although no data on bacterial cultures were available in the IRIS Registry database, the percentage of culture-positive endophthalmitis cases in the referenced studies is quite variable (26%−73%). Furthermore, if affected patients were treated at, or were referred to, a non-IRIS Registry practice, then these cases of endophthalmitis would not be captured in this analysis.

In summary, the results of this IRIS Registry analysis corroborate most of the prior findings described above, which did not

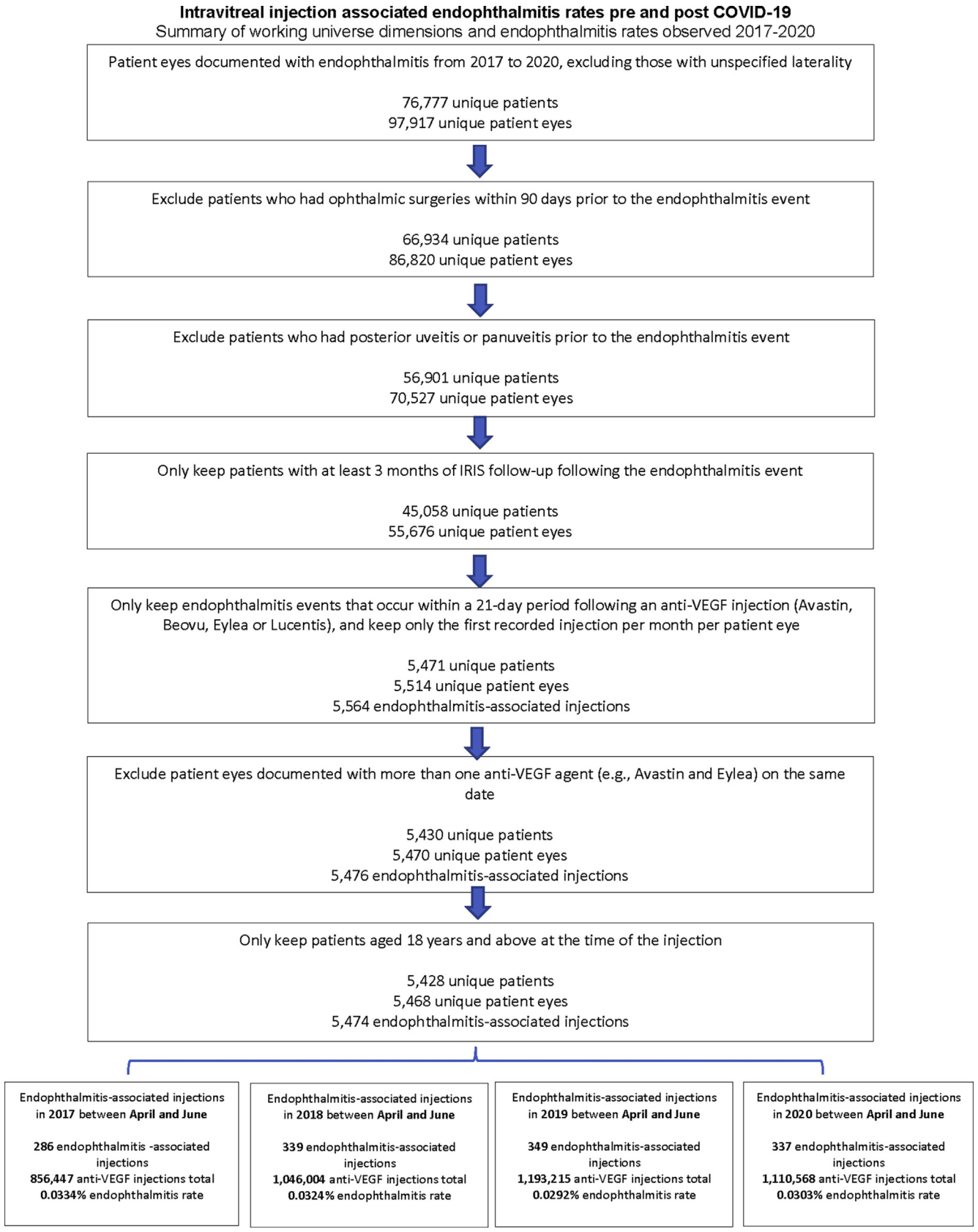

Figure 1. Flow diagram showing rates of presumed endophthalmitis-associated anti–vascular endothelial growth factor (VEGF) intravitreal injections in the IRIS® Registry (Intelligent Research in Sight) database. COVID-19 = coronavirus disease 2019.

identify a reduced rate of endophthalmitis after the start of the pandemic and universal mask wearing. It is also possible that the postulated reduced exposure to nasopharyngeal and oral flora and the dispersion of bacteria associated with speaking by surgeon mask wearing was balanced by patients' universal mask wearing that directed ventilation and exposure to nasopharyngeal flora towards their eyes. This analysis illustrates the ability to evaluate practice trends in a rapid and cost-effective approach using data from a large, geographically representative database that spans multiple periods.

Flora Lum, MD[1]
Siying Li, MS[1]
Lynn Liu, MS[1]
Charles Li, BA[1]
David W. Parke II, MD[1]
George A. Williams, MD[2]

[1]*American Academy of Ophthalmology, San Francisco, California;*
[2]*Oakland University William Beaumont School of Medicine, Rochester, Michigan*

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HUMAN SUBJECTS: No human subjects were included in this study. The data in the IRIS Registry database are aggregated and de-identified; therefore, institutional review board approval and written informed consent were not required for the analysis. All research adhered to the tenets of the Declaration of Helsinki.

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Correspondence:
Flora Lum, MD, American Academy of Ophthalmology, 655 Beach Street, San Francisco, CA 94109. E-mail: flum@aao.org.

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Time to Uveitis Control with Methotrexate and Mycophenolate Mofetil

Uveitis is a group of sight-threatening intraocular inflammatory diseases responsible for 5% to 20% of legal blindness in developed countries.[1] Timely control of inflammation is essential to prevent serious complications, and corticosteroid therapy is the mainstay of treatment for noninfectious uveitis. However, long-term exposure to corticosteroids has undesirable ocular and systemic side effects.[2] Among the available corticosteroid-sparing treatment options, the antimetabolites methotrexate and mycophenolate mofetil (MMF) are used commonly.

The First-Line Antimetabolites as Steroid-Sparing Treatment (FAST) Uveitis Trial (ClinicalTrials.gov identifier, pmid:NCT%2001829295) was a multicenter, randomized, observer-masked clinical trial that compared the effectiveness of methotrexate and MMF for achieving corticosteroid-sparing control of noninfectious uveitis.[3] The primary analysis found no difference in outcome between the 2 antimetabolites.[3] However, because immunomodulatory drugs can take months to have a full effect, participants were started on oral corticosteroids (1 mg/kg, up to 60 mg/day) at enrollment,[4] which was tapered according to the Standardization of Uveitis Nomenclature guidelines.[5] Ascertainment of all outcomes was masked to randomized treatment.

We present a subanalysis of the FAST Trial to compare time to corticosteroid-sparing control of ocular inflammation between methotrexate and MMF and to examine whether differences existed in corticosteroid exposure between the 2 antimetabolites. These are important metrics for effectiveness that were not analyzed in the primary outcome analysis.