VOLUME 24/NUMBER 5/OCTOBER 2004

RETINA®

THE JOURNAL OF RETINAL AND VITREOUS DISEASES

LIPPINCOTT WILLIAMS & WILKINS

ISSN 0275-004X

RETINA®

THE JOURNAL OF RETINAL AND VITREOUS DISEASES

RETINA® The Journal of Retinal and Vitreous Diseases is indexed in *Biological Abstracts, EMBASE/Excerpta Medica, Index Medicus,* and *Current Contents.*
RETINA® The Journal of Retinal and Vitreous Diseases (ISSN 0275-004X) is published bimonthly for the Ophthalmic Communications Society, Inc., by Lippincott Williams & Wilkins, 16522 Hunters Green Parkway, Hagerstown, MD 21740-2116. Business offices are located at 530 Walnut Street, Philadelphia, PA 19106-3621. Production offices are located at 351 W. Camden Street, Baltimore, MD 21201-2436. Periodicals postage paid at Hagerstown, MD and at additional mailing offices.

Address for subscription information, orders, or changes of address (except Japan, India, Bangladesh, Sri Lanka, Nepal, and Pakistan): 16522 Hunters Green Parkway, Hagerstown, MD 21740-2116; phone: 1-800-638-3030; fax: 301-223-2400; in Maryland, call collect, 301-223-2300. In Japan, contact LWW Igaku-Shoin Ltd., 3-23-14 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan; phone: 81-3-5689-5400; fax: 81-3-5689-5402. In India, Bangladesh, Sri Lanka, Nepal, and Pakistan, contact Globe Publication Pvt. Ltd. B-13, 3rd Fl, A Block, Shopping Complex, Naraina Vihar, Ring Road, New Delhi 110028, India; phone: 91-11-579-3211; fax: 91-11-579-8876.
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RISKS OF INTRAVITREOUS INJECTION: A COMPREHENSIVE REVIEW

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Purpose: To evaluate the prevalence of the most common serious adverse events associated with intravitreous (IVT) injection.

Methods: A systematic search of the literature via PubMed from 1966 to March 1, 2004, was conducted to identify studies evaluating the safety of IVT injection. Data submitted in New Drug Applications to the U.S. Food and Drug Administration for drugs administered into the vitreous were included where available. Serious adverse events reported in each study were recorded, and risk per eye and risk per injection were calculated for the following serious adverse events: endophthalmitis, retinal detachment, iritis/uveitis, intraocular hemorrhage, ocular hypertension, cataract, and hypotony. Rare complications also were noted.

Results: Data from 14,866 IVT injections in 4,382 eyes were analyzed. There were 38 cases of endophthalmitis (including those reported as pseudoendophthalmitis) for a prevalence of 0.3% per injection and 0.9% per eye. Excluding cases reported specifically as pseudoendophthalmitis, the prevalence of endophthalmitis was 0.2% per injection and 0.5% per eye. Retinal detachment, iritis/uveitis, ocular hypertension, cataract, intraocular hemorrhage, and hypotony were generally associated with IVT injection of specific compounds and were infrequently attributed by the investigators to the injection procedure itself. Retinal vascular occlusions were described rarely in patients after IVT injection, and it was unclear in most cases whether these represented true injection-related complications or chance associations.

Conclusion: The risk of serious adverse events reported after IVT injection is low. Nevertheless, careful attention to injection technique and appropriate postinjection monitoring are essential because uncommon injection-related complications may be associated with permanent vision loss.

RETINA 24:676–698, 2004

Over the last 2 decades, the use of intravitreous (IVT) injection has gained increasing acceptance in the therapeutic management of many intraocular diseases, particularly disorders affecting the posterior segment. A highly effective and frequently used means of administering antiviral agents in the treatment of cytomegalovirus (CMV) retinitis, direct injection of antiviral agents into the vitreous of patients with acquired immunodeficiency syndrome maximizes intraocular drug levels while minimizing the risk of toxicity associated with systemic administration of these agents.[1–11] In addition, IVT injection of various gases has been used as a less-invasive alternative to scleral buckling for the management of retinal detachment in the setting of pneumatic retinopexy[12–14] and for the administration of tissue plasminogen activator ([TPA] Retavase; Centocor, Malvern, PA)[15,16] in the treatment of submacular hem-

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Although the term "intravitreal" is used colloquially quite often, we have used "intravitreous" as the grammatically correct and preferred term in this review.

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orrhage and acute central retinal vein occlusion. Needle aspiration of the vitreous—procedurally similar to IVT injection—is used routinely to biopsy the vitreous. In addition to the long-standing practices of vitreous Gram staining, microbial culture, and sensitivity analysis in the setting of suspected endophthalmitis,[17] vitreous sampling may also be used to obtain DNA for polymerase chain reaction–based analyses for patients suspected of having necrotizing herpetic retinitis[18–22] or toxoplasmic retinochoroiditis.[23]

Recent investigations into the treatment of retinal neovascularization, retinal edema, and posterior segment inflammation have led to the development of new biologic and pharmacologic agents that are optimally administered directly into the vitreous. IVT injection of these compounds is being investigated, both as a method of achieving vitreous concentrations beyond those obtainable with systemic administration and as a means of avoiding potential systemic adverse effects. Several of these investigational agents, such as the therapeutic aptamer oligonucleotide pegaptanib sodium (Macugen; Eyetech Pharmaceuticals, New York, NY)[24–26] and the monoclonal antibody fragment ranibizumab (Lucentis; Genentech, San Francisco, CA),[27,28] are currently undergoing clinical evaluation for the treatment of neovascular age-related macular degeneration (AMD) and, in the case of pegaptanib sodium, for diabetic macular edema and retinal vein occlusion. In addition, the off-label use of IVT triamcinolone acetonide (Kenalog; Bristol-Myers Squibb, New York, NY) injection is under investigation for a number of disorders, including macular edema[29,30] and retinal neovascularization.[31–34]

Because the potential advantages of IVT injection have become more widely appreciated and the number of possible applications has grown, questions have arisen regarding risks associated with this route of administration. Several potential complications of IVT injection, such as endophthalmitis, retinal detachment, traumatic cataract, and intraocular hemorrhage, can be vision threatening. A sufficient body of literature now exists to support a thorough review of the risks associated with IVT injection in managing ocular diseases. To that end, as background, we present a brief historical overview of the use of IVT injection in humans over the last century and a synopsis of recently published studies on the pharmacokinetic properties of agents administered directly into the vitreous. We then present the results of a comprehensive, systematic review of the literature from which we calculated prevalence estimates for the most common complications associated with IVT injection.

The analyzed reports of IVT injection varied considerably in size, design, and indication, and in most instances, the reported rates of the various complications were quite low. Although efforts were made to distinguish the risks associated with the specific agents being administered from the risks related to the IVT injection procedure per se, in some instances, such distinctions were difficult to make. Together, these factors limit to some extent the generalizability of cross-study comparisons and analyses. Despite these inherent shortcomings, to our knowledge, this review represents the most extensive assessment of the risks associated with IVT injection compiled to date.

A Historical Perspective on the Use of IVT Injection

IVT injection has been used in the treatment of human ocular disease for nearly a century. Figure 1[24,25,27,28,34–48] presents a timeline of important advances in the use of this technique from its earliest therapeutic application through the present. Although this timeline is intended to highlight some of the major achievements in the development of IVT therapeutics, it is not meant to be an exhaustive compilation or to acknowledge the many excellent investigative studies that served as a foundation for these advances. Initially reported in 1911 by Ohm[35] as a means to introduce air for retinal tamponade and repair of detachment, the IVT administration of pharmaceutical agents was pioneered in the mid-1940s with the use of penicillin to treat endophthalmitis.[36,37] Unfortunately, at that time drug administration often was delayed for days or even weeks after the infection became established, making most of these early attempts unsuccessful. The technique was used infrequently, therefore.

During the 1950s and 1960s, the use of IVT injection still was limited to the administration of air[38] or silicone oil[39] in the treatment of retinal detachment. By the 1970s, the advent of newer antimicrobial agents, combined with the continued poor success of alternative treatment options, led to renewed interest in IVT therapy for endophthalmitis. Animal studies demonstrating the safety of this route of administration[49,50] were followed by the publication of two case series describing successful treatment of endophthalmitis using IVT injection in patients.[40,41] Although still considered experimental at that time,[51] wider use of IVT injection to treat endophthalmitis was being advocated due to the poor treatment outcomes reported with systemic administration of antibiotics, which generally produced suboptimal drug levels in the vitreous.[52]

The development of IVT injection for the treatment of ophthalmic conditions other than endophthalmitis and retinal detachment lagged even further behind,

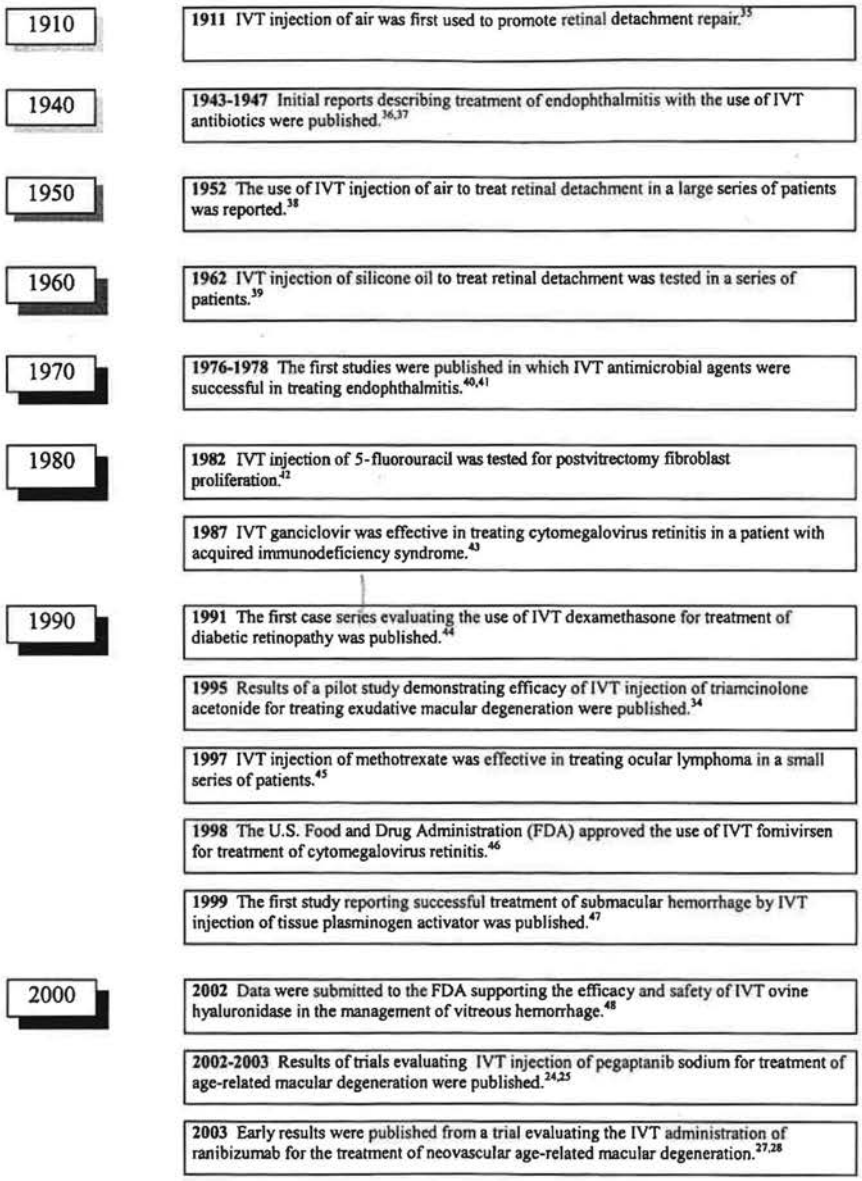

Fig. 1. A timeline of important advances in the use of intravitreous (IVT) injections to treat human ocular diseases.

perhaps because of perceived risks related to the procedure and because endophthalmitis and retinal detachment generally have the greatest likelihood for acute and irreversible vision loss. Although IVT injection of corticosteroids was evaluated in an animal model of ocular inflammation in the early 1980s,[53,54] there were no publications describing the use of IVT corticosteroids in humans until the 1990s. The first new application for IVT injection was not tried until 1982, when a pilot study assessing the efficacy and safety of 5-fluorouracil delivered as an IVT injection for the prevention of postvitrectomy fibroblast proliferation in patients with proliferative retinopathy was initiated.[42] This was followed in 1987 by the use of IVT ganciclovir sodium (Cytovine; Roche Pharmaceuticals, Nutley, NJ) in the treatment of CMV retinitis in a patient with acquired immunodeficiency syndrome.[43]

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