Editors Frank G. Holz
Richard F. Spaide

Medical Retina

With 91 Figures, Mostly in Colour
and 13 Tables

Springer

Series Editors

Günter K. Krieglstein, MD
Professor and Chairman
Department of Ophthalmology
University of Cologne
Kerpener Straße 62
50924 Cologne
Germany

Robert N. Weinreb, MD
Professor and Director
Hamilton Glaucoma Center
Department of Ophthalmology
University of California at San Diego
9500 Gilman Drive
La Jolla, CA 92093-0946
USA

Volume Editors

Frank G. Holz, MD
Professor and Chairman
Department of Ophthalmology
University of Bonn
Ernst-Abbe-Straße 2
53127 Bonn
Germany

Richard F. Spaide, MD
Assistant Clinical Professor
Vitreous, Retina, and Macula Consultants
of New York, and
LuEsther T. Mertz Retinal Research Center
Manhattan Eye, Ear, and Throat Hospital
460 Park Avenue
New York, NY 10022
USA

ISBN 978-3-540-33671-6
Springer Berlin Heidelberg NewYork

ISSN 1612-3212

Library of Congress Control Number: 2007927503

Editor: Marion Philipp, Heidelberg, Germany
Desk Editor: Martina Himberger, Heidelberg, Germany
Production: LE-TeX Jelonek, Schmidt & Vöckler GbR, Leipzig, Germany
Cover Design: WMXDesign GmbH, Heidelberg, Germany

Printed on acid-free paper
24/3180Wa 5 4 3 2 1 0

Chapter 5

Intravitreal Injections: Techniques and Sequelae

5

Heinrich Heimann

Core Messages

- Through the introduction of new treatment strategies for exudative age-related macular degeneration, the number of intravitreal injections has increased dramatically over the past few years. It is likely that this form of therapy will become the most common surgical intervention in ophthalmology within a short period of time.
- Although severe ocular adverse events associated with intraocular injections are rare, the rate can increase significantly if certain standards for intraocular interventions are not followed. Several guidelines on the technique for intravitreal injections have been published in recent years. Strict adherence to these guidelines is advisable.
- Endophthalmitis is the most feared complication of intravitreal injections. It is usually caused by bacterial contamination during or immediately after the injection and occurs in about 0.1% of injections and in about 1% of patients with repeated injections.
- Ocular hypertension and cataract development are not typically seen after anti-VEGF therapy.
- Based on the studies and data currently available, no major difference in the risk profile of the anti-VEGF drugs used at present can be seen.
- Triamcinolone is associated with a higher rate of secondary ocular hypertension (40%) and need for glaucoma surgery (1%) than anti-VEGF agents. It also has a higher rate of cataract progression in about 40% of patients within the first year of treatment.

5.1 Introduction

The introduction of new drugs for the treatment of age-related macular degeneration (AMD) has led to a significant change in ophthalmological practice. Until a few years ago, intravitreal injections were reserved for a small number of rare diseases (e.g., endophthalmitis, viral retinitis). Within a short period of time, the numbers of injections have increased and are now second only to cataract surgery as the most common treatment in most tertiary centers across Europe and the United States. It is likely that intravitreal growth factor (VEGF) type of action will soon become the most common intraocular procedure performed worldwide. With intravitreal injection we can obtain a high intraocular concentration of a drug, with minimal systemic exposure.

This tremendous and rapid change indicates a significant challenge for ophthalmological units; a tidal wave of intraocular injections, re-injections, and follow-up examinations has to be integrated into daily routine without compromising patients' safety. It is therefore mandatory to maintain essential safety standards for all injections whilst avoiding unnecessary and costly examina-

the number of patients that can be treated, the workload associated with each patient has to be minimized within the treating unit; therefore, it is likely that more and more pre- and postoperative examinations will be shifted to places outside the centers where the injections are performed. In a relatively short period of time, ophthalmologists and optometrists who are currently not performing intraocular injections will be confronted with a larger number of patients following intravitreal injections. In this chapter, the techniques, complications, and guidelines for intravitreal injections are reviewed. Because of the recent shift in the application of intravitreal drugs, the chapter focuses on studies of anti-VEGF substances and triamcinolone.

5.2 Complications of Intravitreal Injections

With an appropriate technique, the intravitreal injection of a drug is a straightforward surgical procedure that carries a low rate of serious complications (Table 5.1). Yet, the first published multicenter study showed that the disregard

Table 5.1 Complications of intravitreal injections

Complication	Peri-operative	Early (>7 days)	Late (>7 days)	Incidence	Related to injected substance
Conjunctival hemorrhage	X	X		~20–40%	–
Conjunctival scarring			X		
Punctate keratitis	X	X		~30%	–
Pain	X	X		~30%	
Traumatic cataract	X	X	X	<1%	–
Cataract progression			X	First year: ~15% ~40% (triamcinolone)	X
Central retinal artery occlusion	X	X		<1%	–
Vitreous reflux	X	X		~20%	–
Vitreous hemorrhage	X	X	X	<1%	–
Vitreous floaters	X	X	X	~30%	X
Intraocular inflammation	X	X		~20%	X
Uveitis/pseudo-endophthalmitis		X		~1%	X
Endophthalmitis		X	X	~0.15% per injection ~1% per patient with multiple injections	X
Retinal detachment		X	X	<1%	–
Ocular hypertension	X	X	X	Triamcinolone ~40%	X

of basic standards for intraocular surgery can quickly increase the rate of complications to unacceptable levels. In the initial stages of the VISION trial, the rates of bacterial endophthalmitis were more than 4-fold higher than those after routine cataract surgery [8, 14]. Serious adverse events occurred in 19% of patients (169 out of 892), although serious adverse events were also noted in 15% of patients (45 out of 298) with sham treatment [8]. These figures underline that intravitreal injections should be treated as intraocular surgery and conducted according to the standards applied to all intraocular procedures, e.g., asepsis of the operating field and a sterile technique throughout the process. Even with the greatest care, complications associated with intravitreal injections will never be avoided completely; however, as demonstrated in the recent large prospective trials, in only very few cases will these complications lead to a long-term reduction in visual acuity or discontinuation of the treatment if dealt with in a timely and appropriate fashion [4, 8, 14, 29].

5.2.1 Methodology

In this chapter, the complications associated with intraocular injections are reviewed. A methodological review is flawed by several problems:

1. The most serious side effects of intravitreal injections (e.g., endophthalmitis, retinal detachment, glaucoma, cataract) are rare following anti-VEGF treatment and occur in less than 1% of injections and in about 1–2% of patients undergoing repeated injections. Only randomized prospective trials with large patient numbers are able to reflect the true rate of complications associated with the drug examined and the treatment protocol applied. Such trials have been published for pegaptanib and ranibizumab (Table 5.2) [4, 8, 14, 29].
2. For the two other currently most commonly used drugs, bevacizumab and triamcinolone, such studies do not exist and it is unlikely that this will be the case in the near future.
3. Other important, potentially sight-threatening complications of injections are intraocular inflammation, cataract development, and a rise in intraocular pressure (IOP). The examination methods, time points, and definitions for the detection of these complications vary from study to study.
4. Different protocols for the performance of intravitreal injections have been used. The differences in the injection technique (e.g., subconjunctival anesthesia, perioperative drug treatment, etc.) can have a significant influence on the complication rate.

5.2.2 Perioperative Complications

Complications following intravitreal injections can be divided according to their occurrence into perioperative, early postoperative, and late (Table 5.1). Furthermore, complications from the intraocular injection procedure itself have to be distinguished from possible biological side-effects of the injected substance.

5.2.2.1 Conjunctival Hemorrhage

Conjunctival hemorrhage is related to the trauma caused by manipulations during the injection, e.g., forceps or needle injuries. Obviously, when subconjunctival anesthesia is used, the need for two injections increases the risk of this complication. In one series, subconjunctival hemorrhages could be seen in 18% of patients with intravitreal injections and topical anesthesia versus 40% in patients with subconjunctival anesthesia [22]. Nevertheless, even with topical anesthesia, hemorrhage can be seen in up to 37% of patients [7].

In the vast majority of cases, conjunctival hemorrhages is more cosmetically disturbing than harmful. They clear spontaneously within 7–14 days and do not require any therapy. Very rarely, they can progress to cause significant anterior segment problems that require surgical intervention. The risk of significant conjunctival hemorrhage seems to be increased in patients with anticoagulant therapy, e.g., warfarin [15]. In contrast to their relative insignificance in the majority of cases, conjunctival hemorrhage is often perceived as a serious side-effect from the patients' point of view. Particularly in an outpatient setting without a scheduled short-term follow-up examination, patients have to be instructed about

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.