

Provincial Retinal Diseases Treatment Program

Analysis of Glaucoma Surgery Rates in PRDTP Patients Phases 1 to 3

April 2019



Background

- Early published observations of IOP rise after use of anti-VEGF medications in 2007/2008
- Retrospective chart reviews published between 2011-2013 suggest 6-9% of patients receiving anti-VEGF agents may develop sustained intraocular pressure (IOP) elevation
- BC retina specialists report cases of elevated intraocular pressure after anti-VEGF use 2017

Background

- Safety data linkage performed using PHSA/PRDTP, MSP, and PharmaNet databases in 2014 looking at vascular complications (MI, Stroke) related to intravitreal injections of anti-VEGF agents
 - Risk of Myocardial Infarction and Stroke With Single or Repeated Doses of Intravitreal Bevacizumab in Age-Related Macular Degeneration. Etminan M, Maberley DA, Babiuk DW, Carleton BC. Am J Ophthalmol. 2016 Jun;166:205.
- Same linkage subsequently evaluated for risk of glaucoma surgery after anti-VEGF intraocular injections
 - JAMA Ophthalmol. 2017 Apr 1;135(4):363-368. doi: 10.1001/jamaophthalmol.2017.0059. Association of Repeated Intravitreal Bevacizumab Injections With Risk for Glaucoma Surgery. Eadie BD1, Etminan M1, Carleton BC2, Maberley DA1, Mikelberg FS1.
 - Glaucoma surgery a robust end-point for glaucoma as drops often used in patients with high eye pressure but no glaucoma
 - Results:
 - Patients between 2009 and 2014 AMD receiving first Avastin injection
 - Followed for need of glaucoma surgery (n=75)
 - Found ≥ 7 injections per year increased risk of glaucoma surgery

Background

- **PRDTP Quality Review:** In January 2018 PHSA began a quality review to investigate glaucoma surgery among PRDPT Patients
- Phase 1, April 2018 - SPR (Surgical Patient Registry) and PRDTP linkage
 - Eye-level data
- Phase 2, June 2018 – MSP and PRDTP linkage
 - MSP data to define surgery
 - Included MSP procedures which were both inside and outside of OR
 - History of glaucoma determined by MSP diagnostic, procedure codes, Pharmanet
- Phase 3, March 2019 – MSP, SPR, and PRDTP linkage
 - MSP linkage with SPR data to determine true glaucoma surgery performed inside OR for a specific cohort of AMD patients
 - Previous history of glaucoma determined by MSP glaucoma procedure **and** glaucoma drug use (PharmaNet)

Phase 1 - Methods

- PRDTP linked with SPR data
- Data for patients entering program between January 2014 and December 2017
- Patients followed to December 2017 or until they had glaucoma surgery
- Excluded those with prior glaucoma surgery

Phase 1 - Results

- Average time from first injection to glaucoma surgery: 506 days
- Average number of injections before surgery: 10 injections
- Percentage of subjects who were female: 39%
- Average age at time of first surgery: 72 years

Data for left and right eyes evaluated separately, but results identical

Phase 1 - Results

Total Eyes in Cohort with and without surgery

- The preliminary data indicated the overall rate of PRDT patients requiring glaucoma surgery, in the four years 2013-2017, was just above 1%

	# of Eyes	# of Surgeries
No Glaucoma Surgery	26,363	-
Yes Glaucoma Surgery	305	386
Grand Total	26,668	386

Phase 1 – Total number of eyes needing at least one surgery

Information does not include multiple surgeries on the same eye

Received at least one surgery	# of eyes
OS - left eye	122
OD - right eye	120
Grand Total	242

Phase 1 – Percentage of surgeons' injections in eyes that required surgery (left eyes)

Percentage range of injections in eyes needing glaucoma surgery:

- 0% to 5% range for the PRDTP retinal specialists
- Not all 29 PRDTP retinal specialists' patients experienced increased glaucoma surgery rates as this was primarily focused among a small subset of retinal specialists

Phase 1 – Surgery numbers by drug(s) used (left eyes) [Avastin: Eylea: Lucentis]

Avastin Exposure Quartile and Exposure Mix	# of Eyes	% of all eyes
0-25 % Avastin	2	1%
20:0:80	1	1%
5:89:5	1	1%
26-50 % Avastin	7	5%
29:71:0	1	1%
35:65:0	1	1%
40:60:0	1	1%
48:0:52	1	1%
50:0:50	1	1%
50:40:10	1	1%
50:50:0	1	1%
51-75 % Avastin	6	4%
56:11:33	1	1%
58:42:0	1	1%
69:23:8	1	1%
70:30:0	1	1%
74:26:0	1	1%
75:25:0	1	1%
75-100 % Avastin	136	90%
78:22:0	1	1%
86:0:14	1	1%
93:7:0	1	1%
95:0:5	1	1%
95:5:0	1	1%
100:0:0	131	87%
Grand Total	151	100%

Phase 1 - Limitations

- Coding
 - SPR coding often entered by nurse or administrative assistant
 - By comparison, MSP coding is done by surgeon performing procedure – potentially more accurate
- In Phase 1, could not exclude patients with pre-existing glaucoma receiving eye drops (these people may have higher risk of surgery unrelated to anti-VEGF drugs)
- Follow-up interval (period at risk for surgery) was variable with this evaluation, makes it difficult to calculate incidence (rate) of glaucoma surgery

Phase 2 – Overview/objectives

- Investigate data to further clarify initial results in Phase 1
- Take advantage of a more fulsome data picture with data from PharmaNet and MSP linked to PHSA/PRDTP database
- Use a fixed follow-up interval for each patient
 - Set at two years
- Utilize more refined statistical methodology, including multivariate analysis (to control for potential confounders such as sex, age)

Phase 2 - Study cohort

- Inclusion: Patients receiving first intravitreal injection of Avastin, Lucentis, or Eylea for an indication of AMD, DME, or RVO, between January 1, 2011 and December 31, 2015 with two years of follow-up
- Exclusions:
 - Age <20 (not likely correct diagnosis)
 - Patients who received glaucoma surgery prior to first injection
 - Indication as Central Serous Retinopathy
 - Injection with Visudyne only (not at risk for glaucoma)
 - Cases with missing data in key data fields, e.g. sex, doctor code, underlying disease
- *NB: Phase 2 analysis conducted at patient level. This differs from Phase 1 as eye level information is not available from MSP data*

Phase 2 – Factors of interest

- Patient Characteristics
 - Age
 - Sex
 - History of glaucoma
 - Indication (Age-related macular degeneration [AMD], Diabetic Macular Edema [DME], Retinal Vein Occlusion [RVO])
 - Year of the first injection (2011, 2012, 2013, 2014, 2015)
- Provider/ Pharmacy Information
 - Treating retinal specialist
 - Most responsible pharmacy
- Treatment Strategies
 - Number of injections per year (≤ 3 , 4-6, ≥ 7)
 - Exposure to drug (only Avastin, only Lucentis, only Eylea, drug switchers)

Phase 2 - Statistical analyses

- Univariate analysis
- Develop a risk-adjusted model (adjust for patient characteristics specifically)
 - Estimate expected rates using the risk-adjusted model
 - Summarize observed and expected rates by year, doctor
 - Explore the variation among doctors using observed/expected ratios

Phase 2 - Univariate analysis

Surgery rate by injection year

- 'Surgery w/in 2 Years' column includes cases in year 1 and year 2

Year	Total	Surgery w/in 1 Year		Surgery w/in 2 Years	
		n	%	n	%
2011	2771	17	0.6%	43	1.6%
2012	2832	15	0.5%	46	1.6%
2013	3465	28	0.8%	66	1.9%
2014	4870	48	1.0%	108	2.2%
2015	4633	58	1.3%	125	2.7%
All	18571	166	0.9%	388	2.1%

Phase 2 - Univariate analysis

Demographics and Retinal Disease

Factor	Level	Total	2 Year Surgery Rate (%)	P-Value*
Demographic				
Age				0.106
	<65	3916	1.7	
	65-74	4265	2.4	
	75-84	5772	2.2	
	>=85	4618	2.0	
Sex				<0.0001
	Male	8651	2.7	
	Female	9920	1.6	
Retinal Disease				
Indication				<0.0001
	AMD	11830	1.8	
	DME	3941	2.1	
	RVO	2800	3.4	

Phase 2 - Univariate analysis

History of non-surgical glaucoma disease

Factor	Level	Total	2 Year Surgery Rate (%)	P-Value*
History of Glaucoma Disease				
	W/in 1 Year of first injection			<0.0001
	No	15100	1.3	
	Yes	3471	5.6	

Non-surgical glaucoma disease defined as patient receiving glaucoma drops within 1 year of first injection.

* P-value from Chi-squared test

Phase 2 - Univariate analysis

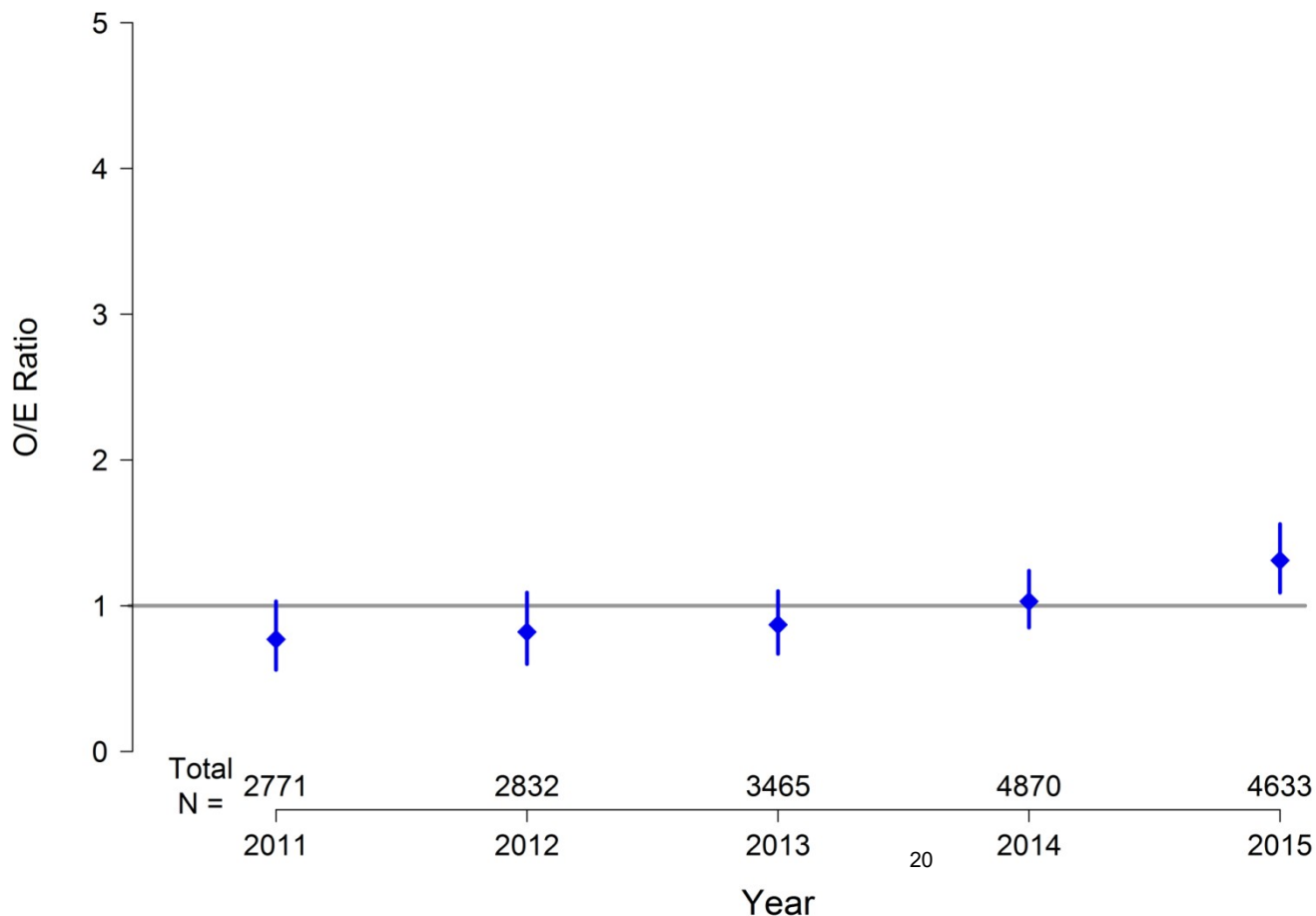
Treatment characteristics

Factor	Level	Total	2 Year Surgery Rate (%)	P-Value*
Treatment Received				
Number of Injections Per Year				0.0004
	<=3.5	7821	1.7	
	3.6-6.5	4429	1.9	
	>6.5	6321	2.7	
Drug Exposure				0.0171
	Pure Avastin	14778	2.2	
	Pure Lucentis	279	2.9	
	Pure Eylea	40	2.5	
	Drug Switchers	3474	1.4	

* P-value from Chi-squared test

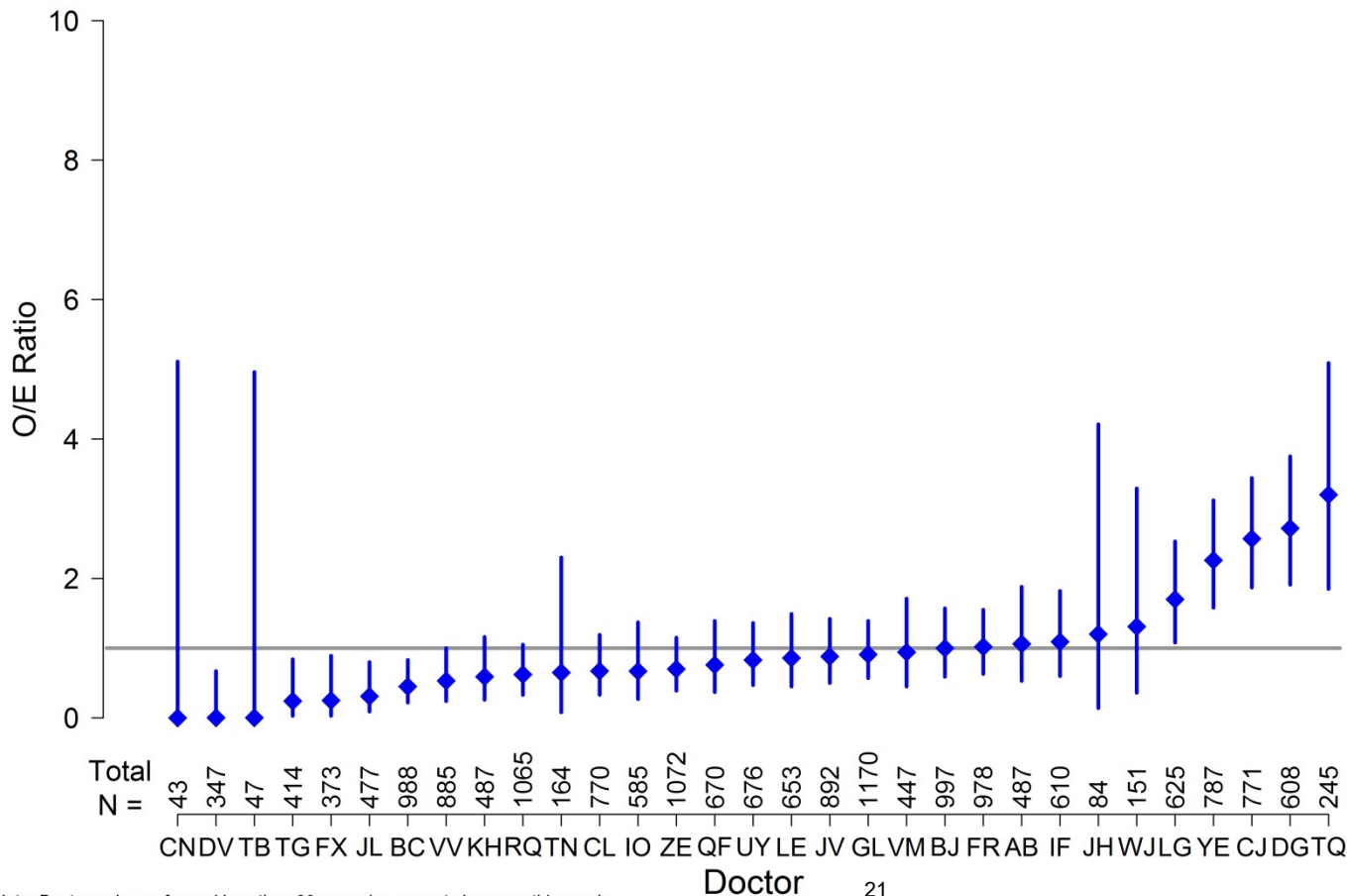
Phase 2 – Multivariate analysis: observed/expected ratio for 2 year surgery rate for each 2 year cohort

O/E includes 1, indicating ratio is as expected compared to other years



Phase 2 – Multivariate analysis: observe/expected ratio for 2-year surgery rate for each surgeon

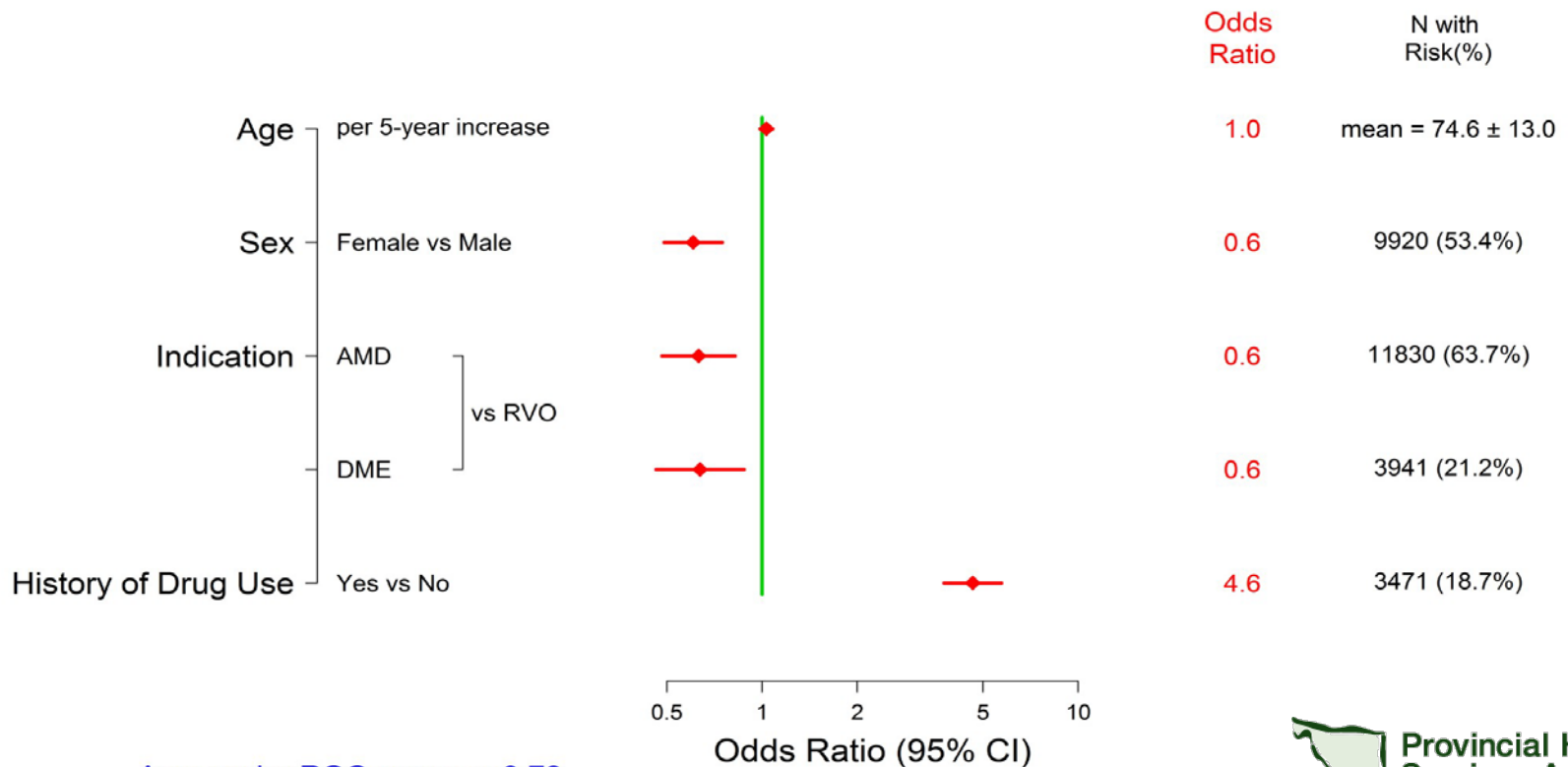
O/E includes 1, indicating ratio is as expected compared to other surgeons



Note: Doctors who performed less than 30 surgeries are not shown on this graph.

Phase 2 – Multivariate analysis: risk associated with specific factors

Odds ratio including 1, indicates no significant risk association with that factor and glaucoma surgery. 'Drug Use' refers to prior glaucoma drug use.



Phase 2 - Limitations

- Coding
 - MSP coding does not include data regarding whether left or right eye was treated surgically
 - Patient would have been included if surgery performed in non-injected (non-treated) eye
- Included patients with DME and RVO
 - Risk of glaucoma expected to be higher in both these conditions irrespective of anti-VEGF use
- Included office-based glaucoma procedures (such as laser trabeculoplasty – a procedure that can often be performed for early glaucoma or elevated intraocular pressure in the absence of glaucoma)

Phase 3 - Goals

Objective

Determine the crude rate of glaucoma surgery in an operating room in PRDTP program. AMD only patients over a 2-year follow-up window.

(Rationale - what is the rate of glaucoma surgery in patients who should not have an increased baseline risk of glaucoma.)

Outcome of interest

The outcome: a glaucoma surgery within two years of the first program Injection.

Phase 3 - Data sources

- The following databases were linked and used in this analysis for time frame January 1, 2011 to December 31, 2017

Database	Contains
PRDTP database	Contains injection level information for all program patients
Medical Service Plan (MSP) database	MSP glaucoma procedures for all PRDTP patients provided in OR, procedure room and physician offices. Includes surgical and non-surgical procedures.
Surgical Patient Registry (SPR) database	Surgical glaucoma procedures for all PRDTP patients
PharmaNet database	Glaucoma drug dispenses to PRDTP patients

Phase 3 - Cohort definition (exclusion)

Total 18,946 patients receiving first intravitreal injection of Avastin, Lucentis or Eylea, between January 1, 2011 and December 31, 2015

Exclusions:

- Indications as DME, RVO, CSR, other diagnoses
- Prior glaucoma drugs used up to 5 years before index injection
- Prior glaucoma surgery
- First drug = Visudyne
- Age < 20 years old
- Missing data

There were N=7833 patients with indication of Wet AMD included in the final cohort

Phase 3 - Cohort definition (exclusion rationale)

Number of excluded is not mutually exclusive and therefore cannot be summed up to the total exclusion number used to arrive at the final cohort

Exclusion	Clinical Rationale	# Excluded
PRDT patients < 20 years	Assumed to be data error	6
Patient gender = Missing/ Unknown	Assumed to be data error	300
DME, RVO, CSR, Other	Neovascular glaucoma is a well-recognized comorbidity of DME and RVO therefore are excluded - these patients may develop glaucoma not-related to program treatments	6973
Visudyne as drug of first injection	To ensure exclusion of CSR patients, since Visudyne is the first-line treatment for CSR. Patients with CSR can develop choroidal neovascularization, and then require anti-VEGF.	215
Any glaucoma procedure in MSP data prior to	MSP procedure prior to first injection indicates pre-existing glaucoma	457

program entry.		
Physician code missing	Assumed to be data error	15
Glaucoma drug use prior to program entry (within 5 years before program entry)	Glaucoma drug use as per PharmaNet data indicates pre-existing glaucoma. Since this analysis is concerned with de novo glaucoma within AMD patients we exclude these patients from analysis.	6489

Phase 3 - Case Definition (Strength of Data Linkage)

- Outcome: Glaucoma procedures performed in OR
- Determined by intersection of SPR and MSP databases
- Enhanced accuracy of glaucoma surgical outcome compared to Phase 1 and 2

2177 - GLAUCOMA – PERIPHERAL IREDECTOMY (ISOLATED PROCED.)

2178 - GLAUCOMA - FILTERING PROCEDURE, NON-MICROSCOPIC

2180 - GLAUCOMA – GONIOTOMY

2184 - GLAUCOMA – CYCLODIALYSIS

2187 - GLAUCOMA - FILTERING PROCEDURE, MICROSCOPIC

22070 - MOLTENO IMPLANT (INCLUDES PHASE 1 AND PHASE 2)

22185 - GLAUCOMA - CYCLOABLATIVE PROCEDURES

22187 - GLAUCOMA - COMPLICATED TRABECULECTOMY

Phase 3 - Methods (description of approach)

- The calculation of the 2-year surgery rate
 - 2-year surgery events = surgeries in the 1st year + surgeries in the 2nd year
 - 2-year surgery rate = 2-year surgery events / total patients who received their index injections in the preceding 2 years
- The average number of injections per year and the eye side of injection were determined over the 2-year follow-up period or time to the first surgery from the 1st program injection, whichever occurs first.
- The Spearman Rank Test was used to examine the time trend of 2-year surgery rates by year
- The Chi-Square Test was used to examine the univariate association between the average number of injections and 2-year surgery rates

Phase 3 – Methods

- Univariate analysis
 - 2-year surgery rates with 95% confidence intervals post index injection
 - Trend analysis for 2-year surgery rates
 - Average number of injections per year by injected eye side.
- Multivariate analysis
 - Not possible due to small number of surgeries in this cohort

Phase 3 - Results: Crude 2-year surgery rates post index injection by year, 2011-2015

Year of injection	Total AMD patients	Surgery events within 2 years	% with 95% CI
2011	1706	6	0.4 (0.1,0.8)
2012	1614	6	0.4 (0.1,0.8)
2013	1449	3	0.2 (0.0,0.6)
2014	1481	15	1.0 (0.6,1.7)
2015	1583	12	0.8 (0.4,1.3)
All	7833	42	0.5 (0.4,0.7)

P-value of 0.28 obtained from Spearman Rank Test for trend doesn't indicate any trend of 2-year surgery rates between 2011 and 2015

Phase 3 - Results – Univariate analysis: 2 year surgery rate by average number of injections per year grouped.

	Injected eye side over two year follow-up									All		
	Both			OD			OS					
	N	events	%	N	events	%	N	events	%	N	events	%
Average number of injections per year												
<=3	219	0	0.00%	1044	1	0.10%	1111	0	0.00%	2374	1	0.00%
3+ to 6	369	0	0.00%	807	3	0.40%	767	3	0.40%	1943	6	0.30%
6+ to 9	459	0	0.00%	719	3	0.40%	689	2	0.30%	1867	5	0.30%
9+ to 13	553	2	0.40%	326	7	2.10%	329	9	2.70%	1208	18	1.50%
13+	415	9	2.20%	16	3	18.80%	10	0	0.00%	441	12	2.70%
All	2015	11	0.50%	2912	17	0.60%	2906	14	0.50%	7833	42	0.50%

P-value (<0.0001) obtained from the Chi-square Test indicates significant association between the average number of injections per year and 2-year surgery rates.

Phase 3 - Conclusions

- The analysis of 2-year glaucoma surgery rates among a focused cohort of AMD only patients indicates an overall rate of 0.5% between 2011 and 2015
- Statistical analysis does not indicate the presence of a trend year over year in 2-year surgery rates
- Significant association between the average number of injections per year and 2-year surgery rates was observed based on the univariate analysis
- For the 11% of patients receiving 9-13 injections per year in one eye only, the 2 year rate was 2.4%