Incidence of Central Retinal Artery Occlusion in the Neovascular Age-related Macular Degeneration Population - Protocol

Background

There has been persistent concern over increased risk of central Retinal Artery Occlusion (cRAO) following exposure to intravitreal aflibercept (Eylea®), for which neovascular (wet) age-related macular degeneration (nAMD) is the principal indication. There is a paucity of published data describing the incidence of cRAO in the general population. One US publication described the incidence of cRAO in Olmsted County, Minnesota from 1976 to 2005, but the description of the methods and findings are unhelpful with no breakdown of the event rates by age or sex, and the standardised incidence rates calculated used an unclear reference population (the 2000 census "U.S. white population"). [1] This means it isn't practically possible to apply these data to the nAMD population. A more recent publication derived from German claims data derived from AKO Baden-Württemberg has presented up-to-date stratified incidence rates and an overall incidence and prevalence figures standardised to the European Reference population. [2] In this case, the study has been published as a Research Letter and some details of the methodology & findings are lacking, although there is a breakdown of event rates by age but not sex. Given the different methodologies and presentation of the results, it in not practically possible to compare the Olmsted County and Baden-Württemberg findings.

Factors known to be associated with onset of nAMD are age (by far the strongest predictor), sex (females being at greater risk) and smoking history (with smoking being associated with greater risk). [3] Although ethnicity is associated with AMD in general (with European populations being at greater risk), this is not thought to be true for neovascular AMD. [3] Inconsistent findings in various epidemiological studies means that other factors potentially associated with nAMD such as exposure to sunlight, iris colour, alcohol consumption, hypertension and hyperlipidaemia, are not considered established risk factors. [3]

A request has been made for additional data on the incidence of RAO in the nAMD population to support the regulatory decision-making processes at the European Medicines Agency. The ready availability of IMRD-United Kingdom data made this the data source of choice. Pilot data in IMRD-UK (formally THIN) found only a very low level of usage of intravitreal aflibercept: this was unsurprising given it is intended for specialist (secondary care) use only and IMRD-UK predominantly records primary care drug exposures. However, it is thought there could be sufficient data to provide estimates of cRAO incidence in a population with the same demographic profile as the nAMD population.

Purpose

1. To establish the incidence of recorded cRAO in the general (IMRD-UK) population stratified by age, sex and smoking status.

2. To compare the incidence of recorded cRAO rate between IMRD-UK, AOK Baden-Württemberg and Olmsted County, Minnesota, USA.
3. To describe the demographic makeup of the population with recorded nAMD in IMRD-UK by age, sex and smoking status.
4. To derive an estimate of the incidence of recorded cRAO (and any RAO) standardised to the recorded nAMD population (stratified by both age & sex AND age, sex & smoking status).
5. To describe the actual incidence of recorded cRAO (and any RAO) in the nAMD population (accepting that numbers will be very low with both the underlying condition and outcome of interest being relatively rare).

Methods

Study design

This analysis will use data from IMRD-UK (formerly known as THIN) which originates from the computer systems of General Practitioners (GPs) across the United Kingdom. The data covers about 6% of the UK population and is broadly generalisable to the whole UK. Data on diagnoses and prescribing come from the GP system and are recorded as Read codes and Gemscript codes. The September 2019 version of IMRD-UK contains data from over 790 practices with a total of 17 million patients of which just under 3 million patients are "current".

Study population

IMRD-UK using the most recent data cut available. The population will be defined according to the first availability on the database for follow up (the latest of the subjects' date of registration with the GP practice, date of birth, date of Acceptable Mortality Reporting or date of practice computerisation) until the end of follow up (the earliest of transfer out date, date of death or date of last data collection. This will be assessed on a yearly basis from 2000 until 2018 (the most recent complete year of follow-up).

Study variables - Population at risk

The population at risk will be defined using Read code F425200 ('Wet senile macular degeneration') using only incident cases of newly diagnosed nAMD (defined using a minimum 1-year lookback period. Other related diagnoses will not be used (Table 1).

Table 1. Read code definition of the population at risk

cohort	Read code	description	ICD10 equivalent
nAMD	'F425200'	Wet senile macular degeneration	H35.3
other AMD	'F425.11' 'F425000' 'F425100'	Senile macular degeneration Unspecified senile macular degeneration Dry senile macular degeneration Wet senile macular degeneration	H35.3

Study variables - Outcomes

Three outcome definitions will be used: a narrow definition of cRAO only (Read code: F423100, "Central retinal artery occlusion"), other RAO, and a broader definition of any RAO incorporating both of these (Table 2). This mirrors the approach used by Pick *et al* where transient forms of RAO were not included. [2] Incident cases will be defined as a new-onset cases of RAO in patients with at least one-year of lookback in the database and no history of the outcome. Smoking status (classified as "current smoker", "ex-smoker", "never smoker") is regularly recorded for many patients in IMRD-UK. For this analysis the most recently dated smoking record prior to nAMD diagnosis for the "at risk" population (or year midpoint for the wider general population) will be used: where this is not complete (anticipated to be very low for the nAMD population) the next (subsequent) smoking status will be used. It is anticipated that there will be no smoking records for only a tiny minority of nAMD patients. A breakdown of smoking status will be described in the results.

Table 2. Retinal Artery Occlusion (RAO) outcomes definitions

outcome	Read code	description	ICD10 equivalent
central RAO	'F423100'	Central retinal artery occlusion	H34.1
other RAO	'F423200'	Retinal arterial branch occlusion	H34.2
	'F423211'	Branch retinal artery occlusion	H34.2
	'F423500'	Retinal partial arterial occlusion NOS	H34.2
	'FyuF500'	[X]Other retinal artery occlusions	H35.2
not used	'F423600'	Amaurosis fugax	G45.3
	'F423700'	Retinal transient arterial occlusion NOS	H34.0
	'F42yC00'	Retinal ischaemia	H35.8

Analysis

Incidence rates will be calculated as the number of incident cases of RAO divided by the total population follow up time and is described as the event rate per 100,000 person years (PY). This will be stratified by age (using categories as defined by the 1976 European reference population [4] used by Pick et al [2]), sex and smoking status. The distribution of incidence rates by age and sex for cRAO and all RAO will be displayed as histograms (Purpose 1). To allow comparison with previous incidence studies, incidence rates will be applied to the 1976 European reference population (Purpose 2). To establish the expected event rate in the nAMD population, event rates will be applied to the nAMD population stratified by age & sex, and age, sex & smoking status. To do this, the number of patients with nAMD in the IMRD-UK population will be stratified by age (using the same age categories described above), gender and (where applicable) smoking status (Purpose 3). The cRAO population event rates will then be applied to the nAMD population profile (Purpose 4) to generate and expected event rate. Confidence intervals for all standardised incidence rates will be calculated using the

approach of Rothman et al. [5] The actual rate of cRAO in the nAMD population will be calculated as the incidence number of cases divided by the patient years at risk during follow-up (Purpose 5) – although it is anticipated the number will be low: for the purposes of this analysis, patients known to have be prescribed intravitreal aflibercept or related medicines (Table 3) or other intravitreal injections (Read codes: '7270300' *Injection into vitreous body NEC*; '7270D00' *Injection of Ranibizumab into vitreous body*) will be excluded. Analyses will be conducted using SAS software.

Table 3. Medicines prescribed for nAMD

drugcode	description	frequency
53252979	Aflibercept 2mg/50microlitres solution for injection vials	12
53253979	Aflibercept 2mg/50microlitres solution for injection vials	14
73043978	Ranibizumab 1.65mg/0.165ml solution for injection pre-filled syringes	21
73044978	Ranibizumab 1.65mg/0.165ml solution for injection pre-filled syringes	4
84856998	Ranibizumab 2.3mg/0.23ml solution for injection vials	50
84863998	Ranibizumab 2.3mg/0.23ml solution for injection vials	8
85981998	Pegaptanib 300mcg/0.09ml prefilled syringes	1
86864998	Bevacizumab 100mg/4ml solution for infusion vials	6
86865998	Bevacizumab 100mg/4ml solution for infusion vials	6

Sensitivity analyses

Three outcome definitions will be used as described in Table 2: central RAO (the specific outcome of interest), other related form of RAO, and a combined category of *any* RAO.

Confounding variables

As a descriptive study, there are no particular concerns regarding confounding. Established risk factor for nAMD are age (by far the strongest predictor), sex (females being at greater risk) and smoking history (with smoking being associated with greater risk). All three can be measured in IMRD-UK and will be taken into account and adjusted for in the analysis.

Limitations

The principal limitation of this study will be the lack of data describing the validity of the codes used to identify AMD and RAO: the sensitivity or specificity might be poor, implying some "missing" diagnoses (false negatives) and/or the recording of non-cases (false positives). Given the severity of the conditions, there is a high likelihood of accurate recording of both RAO and AMD in primary care: however, this is assumed and not established. Other limitations are the relatively low numbers of patients with an outcome (RAO being a very rare condition) and a lack of differentiation between

"wet" and "dry" forms of AMD for some diagnoses (over 50% of Read codes are non-specific for the type of AMD although the proportion with precise diagnoses has increased with time). Finally, there is also a risk that a diagnosis of AMD may be made as an incidental finding at around the same time as RAO is diagnosed, but without the temporal relationship of the two pathophysiologies being clear. The extent to which this is an issue will be assessed by seeing if the rate of RAO events following a diagnosis of AMD remains constant with time, although number of events for such an analysis might be prohibitively low. Finally, studies in other databases have used more stringent case definitions (for example "a RAO code in one quarter of the year confirmed in one of the following three quarters or coded at least once as inpatient" [2]). Such approaches are generally specific to the nature of the data sources (e.g. claims-type data) and are not thought applicable to IMRD-UK.

Whilst acknowledging these limitations, it should be stressed that this study is set against a backdrop of a marked paucity of data describing the rate of RAO in the general population: such data as currently exist are poorly presented or methodologically unclear. In the absence of a "Gold Standard" study describing the incidence of RAO, data from IMRD-UK will add to literature around this, despite its limitations. The strengths of this study are that the data arise from complete, representative and well-defined population base.

Ethical / data protection considerations

This work uses de-identified data provided by patients as a part of their routine primary care. Only aggregate data will be presented. Cell counts of 1-5 will be suppressed in any output in order to prevent identification of individuals.

Pilot data

In the general population there were 1,794 incident case of cRAO 2,011 incident case of other RAO and 3,726 incident case of any RAO. There are 8,027 Read codes for nAMD.

Reference list

[1] Leavitt JA, Larson TA, Hodge DO, Gullerud RE. The incidence of central retinal artery occlusion in Olmsted County, Minnesota. *Ophthalmology* 2016;**123**:1999-2003

[2] Pick J, Nickels S, Saalmann F, Finger RP, Schuster AK. Incidence of retinal artery occlusion in Germany. *Acta Ophthalmol* 2020: doi: 10.1111/aos.14369 [Epub ahead of print]

[3] Mitchell P, Liew G, Gopinath B, Wong TY. Age-related macular degeneration. *Lancet* **2018**;392:1147-1159.

[4] EUROSTAT Methodologies and Working Papers. 2013 edition.

[5] Greenland S, Rothman, KJ. Introduction to Stratified Analysis. In Modern Epidemiology, Third Edition. Philadelphia, PA : Wolters Kluwer/Lippincott Williams & Wilkins Health, 2008