

<b>GSK Medicine:</b> fluticasone propionate, beclomethasone
<b>Study No.:</b> WWE113159/WEUS650
<b>Title:</b> GPRD Cataract Study: Retrospective cohort study of cataract incidence among patients with Idiopathic Thrombocytopenic Purpura (ITP)
<b>Rationale:</b> SB497115 (eltrombopag) is a GSK TPO receptor agonist that boosts platelet production in patients with ITP. Cataracts have been observed in chronic toxicology studies of eltrombopag in mice and rats but have not been observed in dogs. The relevance of the findings in mice and rats to clinical trial participants is unknown. In humans there is no evidence that eltrombopag is associated with cataracts. However, additional knowledge of the occurrence of cataract in ITP patients will provide a better understanding of the benefit/risk assessment of eltrombopag. "Background rates" of cataracts among ITP patients will help provide a context to cataract risk in the "usual care" setting.
<b>Objectives:</b> 1.) To estimate the incidence and prevalence of cataract in the adult ITP population, stratified by age group, gender and medication use. 2.) To estimate the incidence and prevalence of cataract in a non-ITP population, in order to determine whether the risk of cataract is different in ITP patients compared with non-ITP patients.
<b>Indication:</b> IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP)
<b>Study Investigators/Centers:</b> GSK conducted study
<b>Research Methods:</b>
<b>Data Source:</b> UK Full-featured General Practice Research Database (ffGPRD)
<b>Study Design:</b> Retrospective cohort study
<b>Study Population:</b> ITP patients newly diagnosed between 1992 and 2005 and 18 years or older. The study population included patients with one year of medical history (including prescription history) in their patient record before their first ITP diagnosis and with at least three months of medical history in their patient record after their first ITP diagnosis (including prescription history).
<b>Study Exposures, Outcomes:</b> Use of oral systemic [cortico-] steroids was main exposure of interest. Outcome of interest was diagnosis codes for cataract or cataract surgery (as a proxy) in either eye in the computerised record. This included both prevalence of cataract (defined as a cataract or proxy cataract in any eye before the ITP diagnosis date or matched date for non-cases) and a newly-developed cataract in the follow-up period.
<b>Data Analysis Methods: Objective 1:</b> Cataract incidence among ITP patients. A retrospective observational cohort approach in following patients with ITP for a cataract outcome in a person-time analysis estimating incidence rates was adopted. Patients were followed from first ITP diagnosis date until censoring events: cataract diagnosis or cataract surgery, end of the study period, death, or the patient transfer out date, whichever came first. The use of steroid medications classified as oral, inhaled or intranasal steroids and risk of cataract was estimated and rate ratios and 95% confidence intervals were constructed. <b>Objective 2:</b> Cataract incidence in the source population that gave rise to the cases. Five-year age band and gender specific incidence rates in a sample of the underlying source population that does not have ITP was estimated. As above, analyses of incidence and prevalence rates as well as proportions of patients with cataracts in the interval analysis was performed. All these results were compared to the ITP population to determine if ITP patients are associated with cataracts .
<b>Limitations:</b> Prescribed medications are not always taken (potential misclassification bias). Cataracts may be more likely to be detected early (before they are symptomatic) in patients taking steroids because it is a known side effect of the drug (potential detection bias). Conversely, patients may not report to the doctor until the cataract is interfering with vision, and earlier-stage cataracts may be missed. Subtype of cataracts may not be captured (diagnosed by PCP). Also, little information is available on lifestyle risk factors for cataracts (e.g., drinking, UV light exposure, eye injury more than 1 year before ITP diagnosis) and certain medical risk factors (e.g. eye surgery more than 1 year before ITP diagnosis, family history of cataract) (potential unmeasured confounding). Difficult to understand acute versus chronic ITP disease; however, we followed patients from their first diagnosis for all of their follow-up time and thus capturing cataract incidence for the maximum possible outcome ascertainment.
<b>Study Results:</b>

**Table 1.** Description of study population (N=4470) for cohort study of cataracts among patients with and without idiopathic thrombocytopenic purpura (ITP) in the General Practice Research Database, 1993-2005, considering ITP patients with at least one year in database prior to first ITP diagnosis

<b>Cohort characteristics</b>	<b>Cases of ITP N (%)</b> N=745	<b>Non-cases N (%)*</b> N=3725
<b>Age</b>		
<b>Mean age (SD)</b>	56.44	56.38

	(19.67)	(19.58)
<b>Median age</b>	58.00	58.00
<b>Age range</b>	18.00 - 94.00	18.00 - 95.00
<b>n (%) female</b>	448 (60.1)	2240 (60.1)
<b>Mean (SD) follow-up time before index date</b>	6.67 (4.02)	6.66 (4.02)
<b>Mean (SD) follow-up time after index date</b>	4.13 (3.02)	4.21 (2.97)
<b>Cataract prevalence</b>		
<b>n (%) with cataract at any time prior to ITP diagnosis</b>	43 (5.77)	196 (5.26)
<b>n (%) with cataract surgery at any time prior to ITP diagnosis</b>	13 (1.71)	67 (1.8)
<b>n (%) with cataract OR surgery recorded for any eye</b>	49 (6.58)	217 (5.83)
<b>n (%) with cataract AND surgery recorded for any eye</b>	7 (.94)	46 (1.23)
<b>Steroid exposure in year prior to ITP diagnosis</b>		
<b>n (%) with any record of any steroids</b>	145 (19.46)	338 (9.07)
<b>Mean (SD) number of prescriptions</b>	4.33 (5.14)	4.96 (4.22)
<b>n (%) with any record of oral/systemic steroids</b>	104 (13.96)	144 (3.87)
<b>Mean (SD) number of prescriptions</b>	4.11 (5.73)	3.5 (3.54)
<b>n (%) with any record of inhaled steroids</b>	49 (6.58)	222 (5.96)
<b>Mean (SD) number of prescriptions</b>	3.57 (2.41)	4.86 (3.47)
<b>n (%) with any record of intranasal steroids</b>	6 (0.81)	40 (1.07)
<b>Mean (SD) number of prescriptions</b>	4.17 (4.58)	2.28 (1.60)
<b>n (%) with co-morbidities recorded at least 1 medical code prior to ITP diagnosis</b>		
<b>Diabetes Type I &amp; II</b>	60 (8.05)	186 (4.99)
<b>Hypertension</b>	179 (24.03)	817 (21.93)
<b>Schizophrenia</b>	9 (1.21)	31 (0.83)
<b>Glaucoma</b>	17 (2.28)	94 (2.52)
<b>Splenectomy</b>	29 (3.89)	4 (0.11)
<b>Smoking</b>		
<b>n (%) with recorded patient history on smoking status</b>	636 (85.45)	3061 (82.20)
<b>n (%) smoking status at time of ITP diagnosis</b>		
<b>Current</b>	142 (19.06)	760 (20.40)
<b>Former</b>	139 (18.66)	575 (15.44)
<b>Never</b>	355 (47.65)	1724 (46.28)
<b>n (%) steroid exposure any time (before or after index date)</b>	359 (48.2)	559 (15.0)

\*Frequency-matched to cases on 2-year age group, gender, duration of registration and medical practice.

**Table 2.** Characteristics of study population after index date (ITP diagnosis or matched date, for non-cases)

<b>Cohort characteristics</b>	<b>Cases of ITP N (%) N=745</b>	<b>Non-cases N (%) N=3725</b>
<b>Cataracts</b>		
<b>n (%) with cataract at any time after index date</b>	24 (3.22)	134 (3.60)
<b>n (%) with cataract surgery at any time at any time after index date</b>	10 (1.34)	54 (1.45)
<b>n (%) with cataract OR surgery after index date recorded for any eye</b>	30 (4.03)	157 (4.21)
<b>n (%) with cataract AND surgery after index date recorded for any eye</b>	4 (0.54)	31 (0.8)

<b>Steroid exposure any time after index date (follow-up until first cataract or surgery)</b>		
n (%) with any record of Any steroids	329 (44.16)	575 (15.44)
Mean (SD) number of prescription	10.79 (17.50)	12.18 (17.34)
n (%) with record of oral/systemic steroids	289 (38.79)	326 (8.75)
Mean (SD) number of prescriptions	8.78 (15.11)	6.56 (11.03)
n (%) with record of inhaled steroids	90 (12.08)	333 (8.94)
Mean (SD) number of prescriptions	10.29 (16.39)	13.05 (16.58)
n (%) with record of intranasal steroids	16 (2.15)	83 (2.23)
Mean (SD) number of prescriptions	5.44 (12.46)	6.24 (9.15)
<b>n (%) with co-morbidities recorded at least 1 medical code at any time before end of follow-up (first cataract or surgery) Baseline + FUP</b>		
Diabetes	81 (10.87)	278 (7.46)
Hypertension	257 (34.50)	1153 (30.95)
Schizophrenia	9 (1.21)	38 (1.02)
Glaucoma	28 (3.76)	122 (3.28)
Splenectomy	82 (11.01)	5 (0.13)

**Table 3.** Cataract incidence rates & 95% confidence intervals among ITP and non ITP patients, by age band and gender.

<b>Stratum</b>	<b>Among ITP (incidence rate per 1000 person- years, 95%CI)</b>	<b>Among non-ITP (incidence rate per 1000 person- years, 95%CI)</b>
<b>GENDER</b>		
<b>Males</b>	11.82 (6.29, 20.21)	13.95 (11.04, 17.39)
<b>Females</b>	8.97 (5.23, 14.37)	8.13 (6.43, 10.15)
<b>TOTAL</b>	10.02 (6.76, 14.31)	10.29 (8.74, 12.03)
<b>AGE GROUPS</b>		
<b>&lt; 20</b>	0 (-, -)	0 (-, -)
<b>20- 29</b>	0 (-, -)	0 (-, -)
<b>30 - 39</b>	0 (-, -)	0 (-, -)
<b>40 - 49</b>	2.16 (0.05, 12.06)	0.96 (0.17, 3.46)
<b>50 - 59</b>	-	3.38 (1.55, 6.43)
<b>60 - 69</b>	12.78 (4.69, 27.82)	9.84 (6.36, 14.52)
<b>70 - 79</b>	33.70 (19.63, 53.96)	29.04 (23.10, 36.05)
<b>80 - 89</b>	30.73 (11.27, 66.89)	32.75 (22.68, 45.77)
<b>90 +</b>	0 (-, -)	40.61 (13.18, 94.77)
<b>Positive history of oral/systemic steroids use before or after index date</b>		
<b>Users</b>	14.03 (8.68, 21.44)	16.92 (11.91, 23.33)
<b>Non-users</b>	6.01 (2.75, 11.41)	9.18 (7.61, 10.98)
<b>Positive history of intranasal steroids use before or after index date</b>		
<b>Users</b>	0 (-, -)	17.13 (9.12, 29.30)
<b>Non-users</b>	10.48 (7.07, 14.95)	9.93 (8.38, 11.69)
<b>Positive history of inhaled steroids use before or after index date(repeat by #of scripts analysis)</b>		
<b>Users</b>	10.99 (4.03, 23.92)	12.09 (7.58, 18.30)
<b>Non-users</b>	9.81 (6.28, 14.59)	10.05 (8.43, 11.89)
<b>Positive history of any steroids use before or after index date</b>		
<b>Users</b>	13.75 (8.72, 20.64)	15.56 (11.69, 20.30)
<b>Non-users</b>	5.29 (2.13, 10.91)	8.74 (7.13, 10.60)
<b>Conclusion:</b> No evidence of a difference in the risk of cataracts between an ITP and a comparable non-ITP population. However, in both ITP and non-ITP populations (as has been found in other populations) the use of oral steroids in particular was associated with an increased risk of cataracts.		

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