Prevalence of Diagnosed Adult Immune Thrombocytopenia in the United Kingdom

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ABSTRACT

Introduction: Data regarding the prevalence of immune thrombocytopenia (ITP) is limited, and is derived from North American population-based analyses. Therefore, the authors conducted the first study outside the United States (US) using the United Kingdom (UK) General Practice Research Database (GPRD) to estimate the adult prevalence of ITP in the UK. **Methods:** This study estimated the diagnosed prevalence of ITP in the adult population in UK using the GPRD from January 1, 1992 to December 31, 2009. **Results:** The unadjusted, overall 18-year period prevalence was 50.29/100,000 (95% CI: 48.51, 52.06).

The age- and gender-adjusted, overall 18-year period prevalence was 50.00/100,000 (95% CI: 49.20, 50.90). ITP prevalence was lower in adults aged 18–49 years of age (30.09/100,000, 95% CI: 28.27, 31.90) than in older adults aged 50–64 years of age (58.22/100,000, 95% CI: 53.88, 62.57) or ≥65 years of age (93.80/100,000, 95% CI: 88.76, 98.85). Prevalence was higher among females (59.32/100,000, 95% CI: 56.63, 62.01) than in males (40.66/100,000, 95% CI: 38.36, 42.96). Prevalence in the GPRD increased over time (1992 [16.33/100,000, 95% CI: 13.70, 19.00], 2000 [36.93/100,000, 95% CI: 34.50, 39.30], and 2009 [58.49/100,000, 95% CI: 55.80, 61.20]). **Conclusion:** This new analysis of general practice in the UK provides robust prevalence estimates of diagnosed ITP among adults in Europe. ITP prevalence is higher in women and increases with age and over time.

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INTRODUCTION

Immune thrombocytopenia (ITP) is an autoimmune disorder of adults and children

that is characterized by decreased platelet count ($<100 \times 10^9/L$), most commonly resulting from autoantibody-mediated peripheral platelet destruction and suboptimal platelet production.^{1–6} Among children, ITP is typically acute in duration (<6 months), while in adults it is usually a chronic condition lasting for many years^{6–11} with associated bruising, petechiae,⁷ and increased risk of clinically significant bleeding.⁶ Although ITP in adults can and does go into remission, patients are not considered ‘cured’ since the condition often relapses.¹²

ITP is a rare disease and knowledge of its incidence and prevalence is important, specifically to improve our understanding of the natural history of this disease. Current literature on the descriptive epidemiology of ITP is limited, and derives primarily from European, North American, and Japanese population-based studies. In published ITP incidence reports, estimates of adult ITP ranged from 1.6–3.9 per 100,000 adults per year in the United States (US), the United Kingdom (UK), and Japan.^{13–18} Due to the chronic nature of adult ITP¹² and the consequent accumulation of cases in the population, available prevalence estimates are appreciably higher,^{12,19–21} ranging from a 1-year prevalence of 9.5 per 100,000 persons²¹ to a high of 189.3 per 100,000 persons in a hospital-based study conducted in a US Veterans Administration patient population.²⁰ To the authors’ knowledge, there are no published estimates of the prevalence of adult ITP outside of the US.^{19–21} Therefore, using the General Practice Research Database (GPRD),²² the authors conducted the first study outside the US and estimated the prevalence (per 100,000 persons) of adults with a diagnosis of ITP in the GPRD from 1992–2009, unadjusted overall as well as age- and gender-specific (ie, adjusted to the 2009 UK population). In addition, the authors estimated the period prevalence of adults with a

diagnosis of ITP for each year from 1992–2009, overall and stratified by gender.

MATERIALS AND METHODS

Source of Data

This was a retrospective study using observational data from the GPRD; an electronic medical records database of a representative sample of general practices throughout the UK.²² The database currently includes information on diagnoses, prescriptions, referrals, outcomes, and laboratory results together with basic demographic information for approximately 9.6 million “research standard” patients from over 610 centers. The database is population-based and representative of the age, sex, and geographic regions of the UK.²² Inclusion is based on registration with a contributing general practice, rather than consultations, and there is no requirement that patients be actively receiving treatment to be considered for the database. Data are stored using Read codes for diseases that are cross-referenced to the International Classification of Diseases (ICD-9).²³ GPRD coding has been subject to a number of validation studies, which have found it an accurate identification tool for a wide spectrum of conditions and diseases.^{17,24–26} The quality of GPRD data is continuously monitored by the UK Medicines and Healthcare Products Regulatory Agency (MHRA). General practices are considered to be “up to (research) standard” and are included in the GPRD if they meet a series of quality checks on completeness and consistency of information that the general practice provides. Practices failing to meet these standards are excluded from participation. The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) of the GPRD for the MHRA.

Study Population

The study period ran from January 1, 1992 to December 31, 2009. Patients were included in the study if they provided at least 1 year of up-to-standard follow-up during the study period. Prevalent ITP cases included all adult individuals, aged ≥ 18 years, with at least one diagnostic Read code (42P2.11, D313.12, D313000, D313012) for ITP in the patient's medical records in the GPRD. Follow-up could start prior to the 18th birthday; however, ITP diagnosis must be on or after the 18th birthday.

Statistical Analyses

The overall prevalence of ITP in 1992-2009 was calculated as the total number of identified adult ITP cases from the population of all adults in the GPRD database, with at least 1 year of up-to-standard follow-up between 1992-2009, and then expressed as the number of ITP cases per 100,000 persons. Period prevalence for each year from 1992-2009 was calculated as the number of prevalent ITP cases within the population of all adult patients with continuous registration throughout that given calendar year, and then expressed as the number of ITP cases per 100,000 persons. Prevalent cases included all adult patients with a record of ITP during, or any time before, the current period of observation. Prevalence was calculated and stratified by gender as well as by the following age categories: 18-49 years, 50-64 years, 18-64 years, ≥ 65 years, and ≥ 18 years (all adults). CIs were calculated based on the binomial distribution. The overall age- and gender-adjusted prevalence and 95% CI were calculated by direct standardization to the age- and gender-distribution of the 2009 UK population.²⁵

GPRD physicians are not required to re-enter ongoing diagnoses unless there is some change in the patient's status, such as worsening of the

condition or a new treatment. Hence, to better understand recording trends over time, the authors calculated a 1-year period prevalence as the proportion of patients with ITP mentioned in that calendar year for each year individually from 1992-2009. The numerator for the 1-year period prevalence consisted of patients with ITP explicitly mentioned in that year (either newly diagnosed ITP cases or patients with previously diagnosed ITP who had an additional record for ITP in that calendar year). Previously diagnosed ITP patients without an ITP record in the current calendar year were not included in that year's period prevalence. The denominator included everyone followed in the GPRD for that calendar year.

RESULTS

Table 1 presents age- and gender-specific adult ITP prevalence and 95% CIs in the UK. The unadjusted, overall 18-year period prevalence was 50.29/100,000 (95% CI: 48.51, 52.06) persons for the 1992-2009 time period. The age- and gender-adjusted, overall 18-year period prevalence was 50.00/100,000 (95% CI: 49.20, 50.90) persons or 24,337 (95% CI: 23,948-24,775) diagnosed adult cases of ITP in the UK in 2009. ITP prevalence was lower in adults aged 18-49 years of age (30.09/100,000, 95% CI: 28.27, 31.90) than in older adults aged 50-64 years of age (58.22/100,000, 95% CI: 53.88, 62.57) or ≥ 65 years of age (93.80/100,000, 95% CI: 88.76, 98.85). Prevalence was higher among females (59.32/100,000, 95% CI: 56.63, 62.01) than in males (40.66/100,000, 95% CI: 38.36, 42.96).

Prevalence in the GPRD rose over time (1992 [16.33/100,000, 95% CI: 13.70, 19.00], 1995 [21.91/100,000, 95% CI: 19.30, 24.50], 2000 [36.93/100,000, 95% CI: 34.50, 39.30], 2005 [49.39/100,000, 95% CI: 46.90, 51.90], and 2009 [58.49/100,000, 95% CI: 55.80, 61.20])

(Figure 1). The pattern across the 1-year period prevalences demonstrate that the proportions of patients with ITP explicitly mentioned in any given year was higher in the second half of the study than the first half (1992 (3.29/100,000,

95% CI: 2.10, 4.50], 1995 [1.97/100,000, 95% CI: 1.20, 2.80], 1998 [3.05/100,000, 95% CI: 2.20, 3.90] vs. 2000 [4.51/100,000, 95% CI: 3.70, 5.40], 2005 (4.40/100,000, 95% CI: 3.70, 5.10], 2009 (4.57/100,000, 95% CI: 3.80, 5.30]) (Figure 2).

Table 1. Eighteen-year period prevalence of diagnosed adult immune thrombocytopenia (ITP) by age and gender in the General Practice Research Database (GPRD) population, 1992-2009.

Age (years)	Patient gender	GPRD population	ITP cases	Prevalence (95% CI) per 100,000 persons
18-49	All	3513085	1057	30.09 (28.27, 31.90)
50-64		1183364	689	58.22 (53.88, 62.57)
≥65		1414667	1327	93.80 (88.76, 98.85)
All		6111116	3073	50.29 (48.51, 52.06)
18-49	Female	1776034	699	39.36 (36.44, 42.27)
50-64		581523	410	70.50 (63.68, 77.33)
≥65		794795	761	95.75 (88.95, 102.55)
All		3152352	1870	59.32 (56.63, 62.01)
18-49	Male	1737051	358	20.61 (18.47, 22.74)
50-64		601841	279	46.36 (40.92, 51.80)
≥65		619872	566	91.31 (83.79, 98.83)
All		2958764	1203	40.66 (38.36, 42.96)

Figure 1. Eighteen-year period prevalence of adults with a diagnosis of immune thrombocytopenia (ITP) (per 100,000 persons) in the General Practice Research Database (GPRD) population, 1992-2009.

Figure 2. Period prevalence of adults with a diagnosis of immune thrombocytopenia (ITP) (per 100,000 persons) in the General Practice Research Database (GPRD) population 1992-2009.

DISCUSSION

Using a large population-based data source,²² these results provide evidence that the prevalence of diagnosed adult ITP is higher in females (59.32/100,000) than males (40.66/100,000), especially in the 18-49 years and 50-64 years age groups. These results are in line with previously published data reporting increased prevalence with advancing age and a higher prevalence among women.¹²

Results from this study also suggest an increase in diagnosed ITP over time, with a prevalence of 16.33, 36.93, and 58.49 per 100,000 persons in 1992, 2000, and 2009, respectively (Figure 1). The observed overall increase in prevalence from 1992-2009 may be related to the increase in incidence of ITP reported in a study by Schoonen et al. using the same GPRD database.¹⁷ Specifically, Schoonen reports a higher incidence of ITP in the period 2000-2005 compared to the periods 1990-1994 and 1995-1999. This increased incidence

after 2000 may be a contributing factor to the increased prevalence seen in the present study. In addition, the increase in prevalence may be due, in part, to increased awareness of the disease among physicians, more efficient diagnostic practices, and newly available therapies. It is possible that the increasing prevalence of adult ITP may be due, in part, to patients studied in the later years having longer accumulated medical histories and, hence, there is a greater opportunity of identifying all existing cases later in the study. On average, patients followed in 1992 had ≥ 3 years of prior history, while those followed in 2009 had ≥ 9 years of available information (data not shown). However, the 1-year period prevalence figures looking only at ITP records within the current year suggest that more patients had ITP records within the later years, irrespective of available medical history. Additionally, if the shorter available history had led to some existing prevalent cases failing to be identified in the early years, the incidence of ITP would be greater in the early years due to the

misclassification of existing patients as incident cases. This is not supported by the increase in incidence over time noted by Schoonen et al. These observations suggest that the overall increasing trend in prevalence is not solely an artefact of data collection or analysis, but rather is driven by an underlying increase in disease diagnosis. The authors believe that the later figures may be more likely to reflect the “true” prevalence of ITP diagnosed in adults, given an assumption that ITP in adults is essentially a chronic disease that may persist indefinitely.^{9–11,27}

Previously, the authors analyzed the Integrated Healthcare Information System (IHCIS) database, one of the largest US-managed healthcare claims databases, with over 70 million patients from more than 45 health plans. The authors reported a prevalence of diagnosed adult chronic ITP of 23.6 (95% CI: 23.4–23.8) per 100,000 adults, where prevalence of chronic ITP increased with age and was higher among females.¹⁹ This current analysis of GPRD data indicates the same pattern; prevalence of ITP was much higher in females in age groups 18–49 years and 50–64 years, than in males of similar ages. This was expected, given the female preponderance in ITP incidence.^{17,28} In GPRD, the difference in prevalence between elderly female patients ≥ 65 years of age (95.75/100,000, 95% CI: 88.95, 102.55) and males of a similar age (91.31/100,000, 95% CI: 83.79, 98.83) was less pronounced.

An analysis of the published ITP prevalence data requires careful consideration of case definitions and different methodologies employed, including different periods of data collection. Previous published reports indicated period prevalences between 9.5–189.3/100,000, for varying periods and populations; period prevalence within the present study was positioned within this range, 50.29/100,000. It is important to note that all previous published studies of ITP prevalence used cases defined by

administrative data,^{19–21} whereas cases within the present study were defined by electronic medical records. In addition, earlier data were from the US, whilst these were from the UK.

The authors believe this is the largest robust study to estimate the prevalence of ITP using a population database such as the UK GPRD. The present study has several strengths. First, the Read codes used to identify ITP codes are likely to reflect recording in UK general practice, having been reviewed by a physician with extensive experience managing adult patients with ITP in the UK National Health Service (NHS), who also formulated the strategy for the previous study using the UK GPRD.²⁹ Recording guidelines for GPRD encourage general practitioners (GPs) to enter signs and symptoms initially and only record a diagnosis, in this case a diagnosis of ITP, when there is a high diagnostic certainty. Exclusion diagnoses are not used routinely. GPs are also the point of entry to healthcare services in the UK and are encouraged to add all information deemed important for the ongoing clinical care of the patient, including diagnostic information from specialist services (eg, hematologists). Therefore, this data source is likely to capture ITP diagnoses reliably and be less sensitive to some recording issues, such as rule-out diagnoses, seen in other observational data. Second, the validity of coded records to identify ITP patients correctly has previously been confirmed by a review of the source medical records. In a study by Schoonen et al., validation of the computerized diagnosis of ITP against the source paper medical records indicated a high positive predictive value (PPV) of 91% (95% CI: 84%–96%).¹⁷

One limitation of the present study is that the GPRD coding system does not contain codes for ITP remission nor relapse; therefore, patients with acute ITP and patients with chronic ITP

were not able to be distinguished. However, chronic ITP is generally reported to represent the majority of ITP in adults;^{9,27} therefore, all chronic ITP cases in adults will most likely be captured with minimal overestimation of chronic ITP through the inclusion of acute cases.

Previously, the authors calculated an annual ITP prevalence in a US data source (where each consultation generates a new record of ITP) based on patients with an ITP record within the year of interest.¹⁹ In GPRD, diagnoses are routinely entered only once and considered ongoing unless the patient's status changes. Additional records may only be prompted by clinically important events, such as worsening of the condition or communication from specialists. The authors provide details of the annual "period" prevalence here in an attempt to provide additional insights into the temporal trend in ITP recording (Figure 2). However, the authors believe this underestimates true prevalence in GPRD since there is no requirement to re-enter "ongoing" diagnoses. "True" prevalence is presented based on any previous record of adult ITP within the patient's records.

For most patients with ITP and/or the patient's caregivers, effective management of the disease requires an understanding of the natural history of ITP, which often comes via counseling from healthcare providers. Improved understanding of the natural history of ITP among healthcare practitioners, such as GPs enrolled in the GPRD, will therefore assist ITP patients in making better informed choices regarding treatment and overall health, and substantially improving quality of life.

CONCLUSION

In conclusion, the present study provides a robust population-based prevalence estimate of ITP among adults, and indicates that ITP

prevalence increases with age and is higher in women. It also suggests an increasing prevalence over time of adults with a diagnosis of ITP. Moreover, educating and counseling patients with ITP and/or the patient's caregivers requires an understanding of the natural history of ITP; thus, this recent analysis of the prevalence of ITP in general medical practices in the UK adds another piece of important epidemiological evidence to our understanding of the natural history of this rare disease.

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REFERENCES

1. Ballem PJ, Segal GM, Stratton JR, Gernsheimer T, Adamson JW, Slichter SJ. Mechanisms of thrombocytopenia in chronic autoimmune thrombocytopenic purpura. Evidence of both impaired platelet production and increased platelet clearance. *J Clin Invest.* 1987;80:33-40.
2. Chang M, Nakagawa PA, Williams SA, et al. Immune thrombocytopenic purpura (ITP) plasma and purified ITP monoclonal autoantibodies inhibit megakaryocytopoiesis in vitro. *Blood.* 2003;102:887-895.

3. Gernsheimer T, Stratton J, Ballem PJ, Slichter SJ. Mechanisms of response to treatment in autoimmune thrombocytopenic purpura. *N Engl J Med*. 1989;320:974-980.
4. McMillan R, Wang L, Tomer A, Nichol J, Pistillo J. Suppression of in vitro megakaryocyte production by antiplatelet autoantibodies from adult patients with chronic ITP. *Blood*. 2004;103:1364-1369.
5. McMillan R, Nugent D. The effect of antiplatelet autoantibodies on megakaryocytopoiesis. *Int J Hematol*. 2005;81:94-99.
6. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood*. 2009;113:2386-2393.
7. British Committee for Standards in Haematology. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. *Br J Haematol*. 2003;120:574-596.
8. Cines DB, McMillan R. Management of adult idiopathic thrombocytopenic purpura. *Annu Rev Med*. 2005;56:425-442.
9. George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood*. 1996;88:3-40.
10. Karpatkin S. Autoimmune (idiopathic) thrombocytopenic purpura. *Lancet*. 1997;349:1531-1536.
11. Kumar S, Diehn FE, Gertz MA, Tefferi A. Splenectomy for immune thrombocytopenic purpura: long-term results and treatment of postsplenectomy relapses. *Ann Hematol*. 2002;81:312-319.
12. Fogarty PF. Chronic immune thrombocytopenia in adults: epidemiology and clinical presentation. *Hematol Oncol Clin North Am*. 2009;23:1213-1221.
13. Abrahamson PE, Hall SA, Feudjo-Tepie M, Mitrani-Gold FS, Logie J. The incidence of idiopathic thrombocytopenic purpura among adults: a population-based study and literature review. *Eur J Haematol*. 2009;83:83-89.
14. Frederiksen H, Schmidt K. The incidence of idiopathic thrombocytopenic purpura in adults increases with age. *Blood*. 1999;94:909-913.
15. Kurata Y, Fujimura K, Kuwana M, Tomiyama Y, Murata M. Epidemiology of primary immune thrombocytopenia in children and adults in Japan: a population-based study and literature review. *Int J Hematol*. 2011;93:329-335.
16. Neylon AJ, Saunders PW, Howard MR, Proctor SJ, Taylor PR. Clinically significant newly presenting autoimmune thrombocytopenic purpura in adults: a prospective study of a population-based cohort of 245 patients. *Br J Haematol*. 2003;122:966-974.
17. Schoonen WM, Kucera G, Coalson J, et al. Epidemiology of immune thrombocytopenic purpura in the General Practice Research Database. *Br J Haematol*. 2009;145:235-244.
18. Terrell DR, Beebe LA, Vesely SK, Neas BR, Segal JB, George JN. The incidence of immune thrombocytopenic purpura in children and adults: A critical review of published reports. *Am J Hematol*. 2010;85:174-180.
19. Feudjo-Tepie MA, Robinson NJ, Bennett D. Prevalence of diagnosed chronic immune thrombocytopenic purpura in the US: analysis of a large US claim database: a rebuttal. *J Thromb Haemost*. 2008;6:711-712.
20. Landgren O, Gridley G, Fears TR, Caporaso N. Immune thrombocytopenic purpura does not exhibit a disparity in prevalence between African American and White veterans. *Blood*. 2006;108:1111-1112.
21. Segal JB, Powe NR. Prevalence of immune thrombocytopenia: analyses of administrative data. *J Thromb Haemost*. 2006;4:2377-2383.
22. Garcia Rodriguez LA, Perez GS. Use of the UK General Practice Research Database for pharmacoepidemiology. *Br J Clin Pharmacol*. 1998;45:419-425.
23. Edwards CJ, Arden NK, Fisher D, et al. The changing use of disease-modifying anti-rheumatic drugs in individuals with rheumatoid arthritis from the United Kingdom General Practice Research Database. *Rheumatology*. 2005;44:1394-1398.
24. Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. *BMJ*. 1991;302:766-768.
25. Office for National Statistics (ONS). All releases of population estimates for UK, England and Wales, Scotland and Northern Ireland. Available at: <http://www.statistics.gov.uk/statbase/Product.asp?vlnk=15106>. Last accessed on February 7, 2011.

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26. Soriano JB, Maier WC, Visick G, Pride NB. Validation of general practitioner-diagnosed COPD in the UK general practice research database. *Eur J Epidemiol.* 2002;17:1075-1080.
 27. Cines DB, Blanchette VS. Immune thrombocytopenic purpura. *N Engl J Med.* 2002;346:995-1008.
 28. Fogarty PF, Segal JB. The epidemiology of immune thrombocytopenic purpura. *Curr Opin Hematol.* 2007;14:515-519.
 29. Sarpatwari A, Bennett D, Logie JW, et al. Thromboembolic events among adult patients with primary immune thrombocytopenia in the United Kingdom General Practice Research Database. *Haematol.* 2010;95:1167-1175.