Registries in immune thrombocytopenia (ITP) in Europe: the European Research Consortium on ITP (ERCI) network

Registries are essential tools for a better comprehension of rare disease epidemiology and management.[1] Immune thrombocytopenia (ITP) is a rare disease with an annual incidence rate of about three per 100 000 individuals.[2] Knowledge has been generated in ITP epidemiology during the last decade thanks to large cohorts of patients with ITP, including the recognition of factors related to variations in incidence, clinical course, predictors of chronicity, risk factors for bleeding, infection and thrombosis, as well as the determination of real-world treatment strategies.[3] Nevertheless, many issues remain unknown in ITP (Table S1). Linkage of registries presents several interests (Table 1). In June 2019, the European Research Consortium on ITP (ERCI) was founded by 10 experts in ITP in order to promote research in ITP among other objectives (Material S1).[4] One project supported by ERCI is to promote linkage of existing ITP registries in Europe. The first step of this project was to identify and describe the characteristics of

TABLE 1 Interests of European linkage of immune thrombocytopenia (ITP) registries

Interest	Description
Geoepidemiology	Assessment of epidemiological differences of ITP across countries
Comparison of ITP management between countries	Drug availability and national recommendations may differ, which makes comparison of different treatment strategies of particular relevance
Increase the number of informative patients for specific investigations	Incidence calculation and description of rare events, e.g. life-threatening bleeding and thrombosis
	Description of management of rare populations like multirefractory ITP
	Possibility of multivariable models for the identification of predictors of outcomes of interest (e.g. response to treatment, treatment-free remission), which is the first step towards a personalised treatment strategy
	Real-world assessment of exposed populations, effectiveness, and safety of newly marketed drugs, possibly restricted to patients unresponsive to standard treatments to start with, and therefore with an expected low number of exposed patients. This assessment is crucial for a better definition of global treatment strategies, and to help regulatory agencies assessing the true benefit-to-risk ratio of these drugs
	Collaborative studies on biological samples collected to better understand ITP pathophysiology and identify biomarkers
Identification of patients meeting inclusion criteria for clinical trials	Facilitation of patient enrolment by countries

TABLE 2 European registries of patients with immune thrombocytopenia (ITP) of the European Research Consortium on ITP (ERCI) network

Name	Country	Type	Design	Dates of start/end	Patients	No. of patients by 31 December 2020
Clinical registries (excluding pregnancy registries)						
PARC-ITP	Intercontinental	Clinical registry	Prospective	2004–ongoing	Children (<16 years) and adults with newly diagnosed ITP	4079 children and 478 adults
OBS'CEREVANCE	France	Clinical registry	Prospective	2004–ongoing	Children (<18 years) with chronic ITP	1074
UK-children ITP registry	UK	Clinical registry	Retrospective and prospective	2007–ongoing	Children (<18 years) with newly diagnosed or chronic ITP	2500
UK-adult ITP registry	UK	Clinical registry	Retrospective and prospective	2007–ongoing	Adults with primary ITP	4113
Italian adult ITP registry (NCT03465020)	Italy	Clinical registry	Retrospective and prospective	2019–ongoing	Adults with primary ITP initiating/ modifying/ stopping ITP treatment	511
CARMEN-France (NCT02877706)	France	Clinical registry	Prospective, aimed at completeness in the subarea of Midi-Pyrénées region (CARMEN)	June 2013–ongoing	Adults with incident ITP	1049
Norwegian ITP registry	Norway	Clinical registry	Retrospective and prospective	2017–ongoing	Children and adults with ITP	200
Spanish eltrombopag registry	Spain	Clinical registry	Retrospective and prospective	2013–ongoing	ITP adults exposed to eltrombopag	508
Spanish ITP Registry	Spain	Clinical Registry	Prospective	2018–ongoing	Newly diagnosed adults with ITP	197
Pregnancy registries						
TIGRO	France	Clinical registry (and case–control study)	Prospective	2015–2018	Pregnant women with ITP	171
UK pregnancy registry	UK	Clinical registry	Retrospective and prospective	2018–ongoing	Pregnant women with ITP	40
Spanish pregnancy registry	Spain and international collaboration	Clinical registry	Retrospective and prospective	2016–ongoing	Pregnant women with ITP	305
Population-based cohorts						
Nordic chronic ITP registry (the Nordic Country Patient Registry for Romiplostim - NCPRR)	Norway, Denmark, Sweden	Population-based, nationwide	Retrospective (but data acquired prospectively); validation of each case by medical chart review	2009–2018	Adults with chronic (>6 months) ITP	6024
Danish registry	Denmark	Population-based, nationwide	Retrospective (but data acquired prospectively); diagnosis codes validated	1980–2016	Adults with chronic (>12 months) ITP	2566

Recorded data					
Detailed bleeding	**Platelet counts**	**ITP treatment**	**Events (e.g. thromboses, infections, etc.)**	**HRQoL**	**Biobank**
Yes, at diagnosis, at 6 and 12 months and then yearly	Yes, at diagnosis, at 6 and 12 months, and then yearly	Yes, at diagnosis, at 6 and 12 months, and then yearly without precise dates of start and of end	Yes	No	EDTA blood samples, few centres only
Yes, at diagnosis and each visit, at least yearly	Yes, at diagnosis and each visit, at least yearly	Yes (name, dates of start and of end at each visit)	Yes	Not yet	DNA and plasma (2008–2011, for some patients notably those with Evans syndrome)
Yes, at diagnosis and each visit	Yes, at diagnosis and each visit	Yes, (name, duration, start and end details)	Yes	KIT at diagnosis, 6 months and yearly	DNA from all sites if patients consent
Yes, at diagnosis and each follow-up visit	Yes, at diagnosis and sequentially with treatment	Yes (name, dose, duration, start and end details)	Yes	No	DNA from all sites if patients consent (~50%)
Yes, at study entry and each annual visit	Yes, at diagnosis and during follow-up	Yes (name, dose, dates of start and of end)	Yes	SF-12, FACIT-F	Not yet
Yes, at diagnosis and during follow-up	Yes, at diagnosis and during follow-up	Yes (name, dose, dates of start and of end)	Yes	Not yet	In one centre (PBMCs)
Yes, at diagnosis and during follow-up	Yes, at diagnosis and lowest value every month thereafter	Yes (name, dose, dates of start and of end)	Yes	EQ5D, MFI-20 at baseline and annually, only for adults	In some centres blood, serum, plasma
Yes, at diagnosis and during follow-up	Yes	Yes (name, dose, dates of start and of end)	Yes	No	PBMCs (13.8% of patients)
Yes, at diagnosis and during follow-up	Yes, at diagnosis and during follow-up	Yes (name, dose, dates of start and of end)	Yes (12-months follow-up)	No	DNA, RNA, plasma, and PBMC (8% of patients)
Yes, during pregnancy	Yes, during pregnancy	Yes, during pregnancy	Yes, during pregnancy and including neonatal events	No	No
Yes, during pregnancy	Yes, during pregnancy	Yes, during pregnancy	Yes, during pregnancy and including neonatal events	No	Yes
Yes, during pregnancy	Yes, during pregnancy	Yes, during pregnancy	Yes, during pregnancy	No	No
No (hospitalisation for serious bleeding and hospital contact for bleeding only)	Yes	Yes (name, dates of start and of end by medical record review)	Yes (hospitalisations and out-hospital visits)	No	No
No (hospitalisation for serious bleeding and hospital contact for bleeding only)	No	Yes (out-of-hospital drugs: name, dates of dispensing, number of units)	Yes (hospitalisations and out-hospital visits)	No	No

Name	Country	Type	Design	Dates of start/end	Patients	No. of patients by 31 December 2020
FAITH (NCT03429660)	France	Population-based, nationwide	Retrospective construction (but data acquired prospectively); diagnosis codes validated	2009–ongoing	Children and adults with ITP	11 435 incident cases between July 2009 and June 2017

Abbreviations: EDTA, ethylene diamine tetra acetic acid; EQ5D, EuroQuol five-dimension scale; ERCI, European Research Consortium on ITP; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; HRQoL, health-related quality of life; ITP, immune thrombocytopenia (if not specified, both primary and secondary ITP are recorded); IVIg, intravenous immunoglobulin; KIT, kids ITP tools; MFI-20, Multidimensional Fatigue Inventory; PBMCs, peripheral blood mononuclear cells; SF-12, 12-item short-form health survey.

available registries of patients with ITP in Europe. This was the aim of this study.

The identification of registries has been made by ERCI founding members (Material S1). They selected multicentre cohorts of patients with ITP, with recent data (>2010). Both population-based cohorts (defined by cohorts of patients with ITP built using algorithms in health insurance databases or hospital registries) and clinical registries (where data were recorded specifically from patients into a dedicated database) were considered. A final list of 15 registries was obtained by consensus. Their coordinators were directly contacted to provide information about registry characteristics and collected variables, which has been obtained for all registries (Table 2).

Three of them were nationwide population-based cohorts built using health insurance databases, covering the entire population of the countries. They link sociodemographic, hospital and out-of-hospital data, such as drug dispensing data. Patients with ITP are identified using validated diagnosis codes/algorithms. In the Nordic chronic ITP registry, also called Nordic Country Patient Registry for Romiplostim (NCPRR), the diagnosis of ITP has been further validated by medical chart review of all included patients. These population-based registries are very useful tools to assess nationwide epidemiology and real-world exposure to drugs,[1] but they lack detailed clinical and biological data.

Among the 12 clinical cohorts, four include children with ITP and three are dedicated to follow pregnant women with ITP (Table 2). The Pediatric and Adult Registry on Chronic ITP (PARC-ITP) registry also includes patients from other continents (Asia, North and South America). In all, 10 clinical registries are, at least in part, with a prospective follow-up. Three clinical registries include incident cases of ITP only (PARC-ITP, the Spanish ITP registry, and *Cytopénies Auto-immunes: Registre Midi-PyréneEN* [CARMEN]-France) and one includes only patients initiating, modifying or stopping ITP treatment (Italian registry). All registries collect data about bleeding, platelet counts, ITP treatments and events during follow-up but with heterogeneity about the details of recorded data. Currently, only three clinical registries collect patient-reported health-related quality-of-life (HRQoL) assessments. Eight have biobanking collection.

The mapping of existing registries of patients with ITP in Europe showed good coverage of Western and Northern Europe. The sources of data, both population-based and non-population-based (above termed 'clinical registries'),[1] are complementary. Only three registries currently record patient-reported outcomes (QoL data), and reflection about improving this collection will be driven by the development of ITP-specific HRQoL scores.[5-7] Some of them collect biological samples, with the possibility of a better understanding of ITP pathophysiology (including gene predictors) and of the development of precision medicine.[8]

However, there is heterogeneity in the designs (retrospective/prospective) and data content which, at this stage, prevents any global common extraction model from all clinical registries. Consequently, depending on the research question, sources and data sets will be carefully chosen, which is not per se a methodological pitfall providing that the sources selected are representative of the population needed to answer the question and that enough patients are selected.

The future direction for the ERCI group is, when possible, to harmonise these databases in terms of data presentation, and to define a core data set that should be collected in each ongoing registry in order to improve data sharing and linkage.[1] This linkage approach is preferred to building a brand-new European registry, which would be much more time-consuming, costly and exposed to selection bias due to competition with other existing registries. From a regulatory point of view, a set of data from registries can be exported for common analyses in the European Union and other countries satisfying the General Data Protection Regulation, providing there is appropriate information of patients' rights on collected data with no opposition from patients, pseudonymisation, limitation to the minimal set of data needed for the study, safe transfer and storage of data with the level of protection needed for health sensitive data according to the law in each country.[9] An easier way to protect personal data is, in case of enough patients in the study population in each database, to conduct analyses separately in each country, and then to merge results of aggregated data using meta-analysis protocols. A feasibility study is currently ongoing to assess the clinical characteristics and real-world management of ITP in adolescents and young adults (AYAS), aiming at measuring the risk of chronic evolution (whether the natural history is close to childhood or adulthood profile) and identifying the

Recorded data					
Detailed bleeding	**Platelet counts**	**ITP treatment**	**Events (e.g. thromboses, infections, etc.)**	**HRQoL**	**Biobank**
No (only hospitalisation for serious bleeding)	No	Yes (name, dates of dispensing and number of units for out-of-hospital and in-hospital costly drugs like IVIg, rituximab)	Yes (hospitalisations or proxies)	No	No

risk factors of chronicity. An extraction model has been conceived to uniformly define chronic disease (disease activity ≥12 months after ITP, defined by platelet count of $<100 \times 10^6$/L or ongoing ITP treatment) and harmonise variables (e.g. names, units) from the PARC-ITP, CARMEN-France and OBS'CEREVANCE cohorts.[10] As regards population-based cohorts, the NCPRR is in itself an example of harmonisation of variable selection across three countries with common analysis plan (Denmark, Sweden, Norway).

In conclusion, this overview of existing registries of patients with ITP in Europe identified several cohorts that could be linked in the next future.

KEYWORDS

epidemiology, immune thrombocytopenia, pharmacoepidemiology, registries

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Guillaume Moulis completed data from the French CARMEN-France and FAITH cohorts and wrote the paper. All other authors participated in the data acquisition, critically reviewed and modified the manuscript and gave final approval for publication. The corresponding author attests that all the listed authors meet the authorship criteria and that no others meeting the criteria have been omitted. Guillaume Moulis is the guarantor. All authors are qualified representatives of the respective registries.

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