Use of second-line and beyond maintenance therapies in adult patients with primary immune thrombocytopenia in Europe: a parallel study of six prospective multicenter national registries

Guidelines for the management of primary immune thrombocytopenia (pITP) recommend avoiding long-term exposure to corticosteroids.[1,2] Although many therapeutic options are available, the proportion of patients exposed to maintenance (second-line) treatment is not known, neither is the pattern of maintenance treatment lines in Europe, which may be influenced by national guidelines and regulations (*Online Supplementary Table S1*), physician prescribing patterns, or patient preference. We evaluated the use of maintenance treatments in adult pITP patients diagnosed between 2010 and 2022 using a common extraction model and analysis plan in six prospective multicenter registries in Europe. Approximately 40% of patients with pITP received one maintenance treatment and 20% were exposed to a second maintenance treatment. The use of thrombopoietin receptor agonists (TPO-RA), particularly eltrombopag, has increased over the last decade, while the use of rituximab and splenectomy has decreased, with variations between countries. More generally, this study demonstrated the feasibility of conducting joint studies of national ITP registries at the European level, using a common extraction model and a common analysis plan.[3]

The European Research Consortium on ITP (ERCI) initiative to harmonize registries in Europe was launched in 2020. After describing patient enrollment and data collection in the existing European, multicenter, national, prospective registries of ITP patients in Europe,[3] we designed the present study to include data from six of these registries: the UK-Adult ITP Registry (established in 2007, prospective since 2010),[4] the CARMEN-France Registry (prospective, since 2013),[5] indeed the Pediatric and Adult Registry of Chronic ITP (PARC-ITP; enrolment since 2004)[6] limited to patients from Switzerland and Serbia, and the more recent prospective Italian Registry (started in 2019 with retrospective and prospective data from patients on active treatment or initiating treatment), the Norwegian ITP Registry (NOR-ITP) (started in 2017 with retrospective/prospective data collection), and the German Registry (prospective, since 2021). Adult patients (≥18 years of age) with a diagnosis of pITP between 2010 and 2022 were selected from each registry. We longitudinally assessed exposure to maintenance therapy (second and subsequent lines). We use the term "maintenance therapy" according to the updated definition of the International Working Group on Standardization of ITP Terminology (manuscript in prepartion), as opposed to 'initial' or 'emergency' treatments (i.e., corticosteroids, IVIg, anti-D, and platelet transfusions).

The proportions of patients exposed to any first and subsequent lines (maintenance) were calculated for each registry. Patients from the Italian Registry were excluded from the analysis because only patients on active treatment are recruited to this registry. Patients were also subgrouped according to age (<40, 40-59, 60-79 and ≥80 years), sex and time of ITP diagnosis (2010-2016 and 2017-2022). Analyses were performed in parallel by each registry using a common statistical analysis plan. This study was conducted in accordance with the European General Data Protection Regulation and the national regulations. No raw data were exchanged. Aggregated data were compared.

A total of 5,189 adult patients with pITP were included (3,020 from the UK, 1,263 from France, 604 from Italy, 172 from Norway, 105 from Germany, and 25 from Switzerland and Serbia). Patient characteristics are described in Table 1. The proportion of patients exposed to first-line therapy ranged from 61.9% (Germany) to 84.9% (France).

The proportion of patients exposed to maintenance therapy (second-line and beyond) ranged from 29.5% (Germany) to 53.4% (Norway) (Table 1). These proportions were stable by age group, sex, and study period in most countries (*Online Supplementary Table S2*). The proportion of patients receiving a second maintenance therapy ranged from 6.7% (Germany) to 23.3% (Norway) (Table 1).

Combining data from all registries, a total of 1,249 patients were exposed to eltrombopag, 806 to rituximab, 698 to romiplostim, 482 to mycophenolate (mostly in the UK), 299 to azathioprine (mostly in the UK), 140 to dapsone (mostly in France), 104 to hydroxychloroquine (mostly in France), 47 to avatrombopag (mostly in Norway), 46 to cyclosporine (mostly in Italy), 38 to fostamatinib, and 38 to danazol; 140 patients underwent splenectomy. Comparing the two study periods (Germany and Switzerland-Serbia were excluded because no patients were selected in the first and second study periods, respectively) the use of rituximab, other immunosuppressants, and splenectomy decreased from 2010-2016 to 2017-2022, whereas the use of TPO-RA, especially eltrombopag, increased (Figure 1).

First maintenance treatments are described in Figure 2 and *Online Supplementary Table S3*. The most commonly prescribed second line therapy was rituximab in Norway (54.3% of patients exposed to second-line therapy) and

the UK (24.6%), and eltrombopag in Germany (64.5%), Italy (65.7%) and France (55.4%). No major differences were observed by age group, except for rituximab in France (9.3% of second-line treatments in patients aged ≥80 years *vs.* 14.0-17.0% in other age groups) and Norway (no patients aged ≥80 years exposed) and the use of TPO-RA in Italy (45.1% in patients aged ≥80 years *vs.* >75% in other age groups). In the UK, azathioprine was used more frequently in women (14.8%) than in men (9.5%), as was hydroxychloroquine in France (17.9% *vs.* 8.0%). Over time, the use of TPO-RA increased in all countries except Norway, the use of rituximab decreased in all countries except Italy and Norway, and the use of dapsone decreased in France (*full data not shown*).

Second maintenance therapies by registry are detailed in *Online Supplementary Table S3*. The most common agents were eltrombopag in Norway (32.5% of patients exposed to a second maintenance therapy) and in the UK (27.5%),

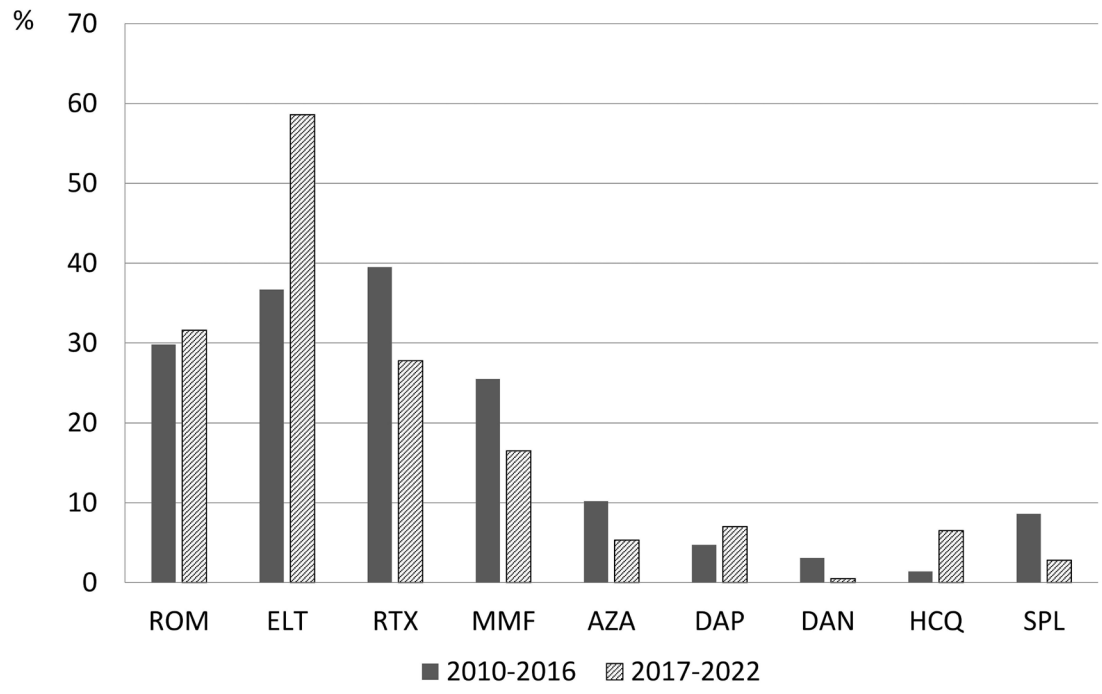

Figure 1. Proportions of patients initiating each major maintenance immune thrombocytopenia treatment during 2010-2016 versus 2017-2022. All treatment lines are combined, over the total number of patients exposed to any immune thrombocytopenia (ITP) maintenance treatment during these periods. AZA: azathioprine; DAN: danazol; DAP: dapsone; ELT: eltrombopag; HCQ: hydroxychloroquine; MMF: mycophenolate mofetil; ROM: romiplostim; RTX: rituximab; SPL: splenectomy.

Table 1. Patients' characteristics.

Characteristics	UK	France	Italy*	Norway	Germany	Switzerland and Serbia
N of patients with pITP	3,020	1,263	NA	172	105	25
Median age (Q1-Q3) at ITP diagnosis, years	56.6 (36.4-70.1)	62.0 (39.0-75.0)	58.7 (38.5-71.8)	50 (33-65)	66 (46-75)	47 (30.2-60.3)
Women, N (%)	1,613 (53.4)	668 (52.9)	336 (55.6)	97 (56.4)	43 (40.9)	13 (52.0)
Bleeding at ITP diagnosis, N (%)	1,328 (44.0)	763 (60.4)	NA	88 (51.2)	37 (48.7)**	18 (72.0)
Median platelet count at ITP diagnosis (Q1-Q3), $x10^9$/L	19 (6-49)	18 (6-49)	19 (7-39)	22 (5-37)	27 (6-69)	13 (7-60)
N of patients with pITP exposed to ITP treatment, N (%)	2,467 (81.7)	1,072 (84.9)	604 (NA)	145 (84.3)	65 (61.9)	18 (72.0)
N of patients with pITP exposed to ITP maintenance (second-line) treatment, N (%)	1,233 (40.8)	576 (45.6)	428 (NA)	92 (53.4)	31 (29.5)	9 (36.0)
N of patients with pITP exposed to ITP second maintenance (third-line) treatment, N (%)	607 (20.1)	272 (21.5)	134 (NA)	40 (23.3)	7 (6.7)	2 (8.0)

*In the Italian Registry, only patients on active treatment are included (at time of starting treatment or at first monitoring visit if already on treatment). Consequently, median age at primary immune thrombocytopenia (pITP) diagnosis, sex and platelet count at ITP diagnosis are presented only for patients who were on active ITP treatment. **Twenty-nine missing values. NA: not available.

romiplostim in Germany (42.9%) and Italy (32.1%), and rituximab in France (26.5%).

Overall, the proportion of patients treated with TPO-RA has increased during the last decade, while the proportion of patients treated with rituximab, other immunosuppressants, and splenectomy has decreased. The COVID-19 pandemic may have played a role, at least in part, in the years 2020 to 2022. In clinical practice, TPO-RA have increasingly been used earlier in the course of the disease in Europe, although they were initially limited by the approved indication for use in chronic ITP, defined at that time as 6 months from diagnosis.[7-10] This is due to the high response rate achieved with these agents, their safety profile (except in patients at high risk of thrombotic events),[11] and the possibility of achieving treatment-free sustained response after discontinuation.[12-14] The oral route and limited dose escalation steps of eltrombopag may explain its preferred use over romiplostim.[1,2,11] In contrast, this study confirms the repositioning of splenectomy after third-line treatment.[15]

International guidelines underscore a patient-centered and evidence-based approach to choosing the best maintenance treatment, emphasizing the use of drugs that have demonstrated efficacy and safety in randomized controlled trials (TPO-RA, fostamatinib, rituximab).[1] National guidelines in Europe do not rank the available maintenance treatments and recommend a choice based on ITP and patient profile. However, a number of drugs are specifically mentioned in some national guidelines, such as dapsone and hydroxychloroquine in France, which explains their almost exclusive use in this country (*Online Supplementary Table S1*). Similarly, the UK uses mycophenolate mofetil more than other countries, possibly due to its early adoption for ITP in this country. In addition to expert ITP guidelines, national regulatory restrictions may explain the discrepancies observed among countries (*Online Supplementary Table S1*).

This study has several limitations. To achieve our objectives, we included the European registries that enrolled adult patients with pITP regardless of the treatment received, and therefore excluded the multicenter drug study cohorts that included patients exposed to specific ITP treatments such as TPO-RA or fostamatinib. Some European countries are not represented in this analysis, so our results may not be representative of the whole of Europe.[3] The investigators are committed to including every new case of pITP in the registries. However, some cases of mild, silent thrombocy-

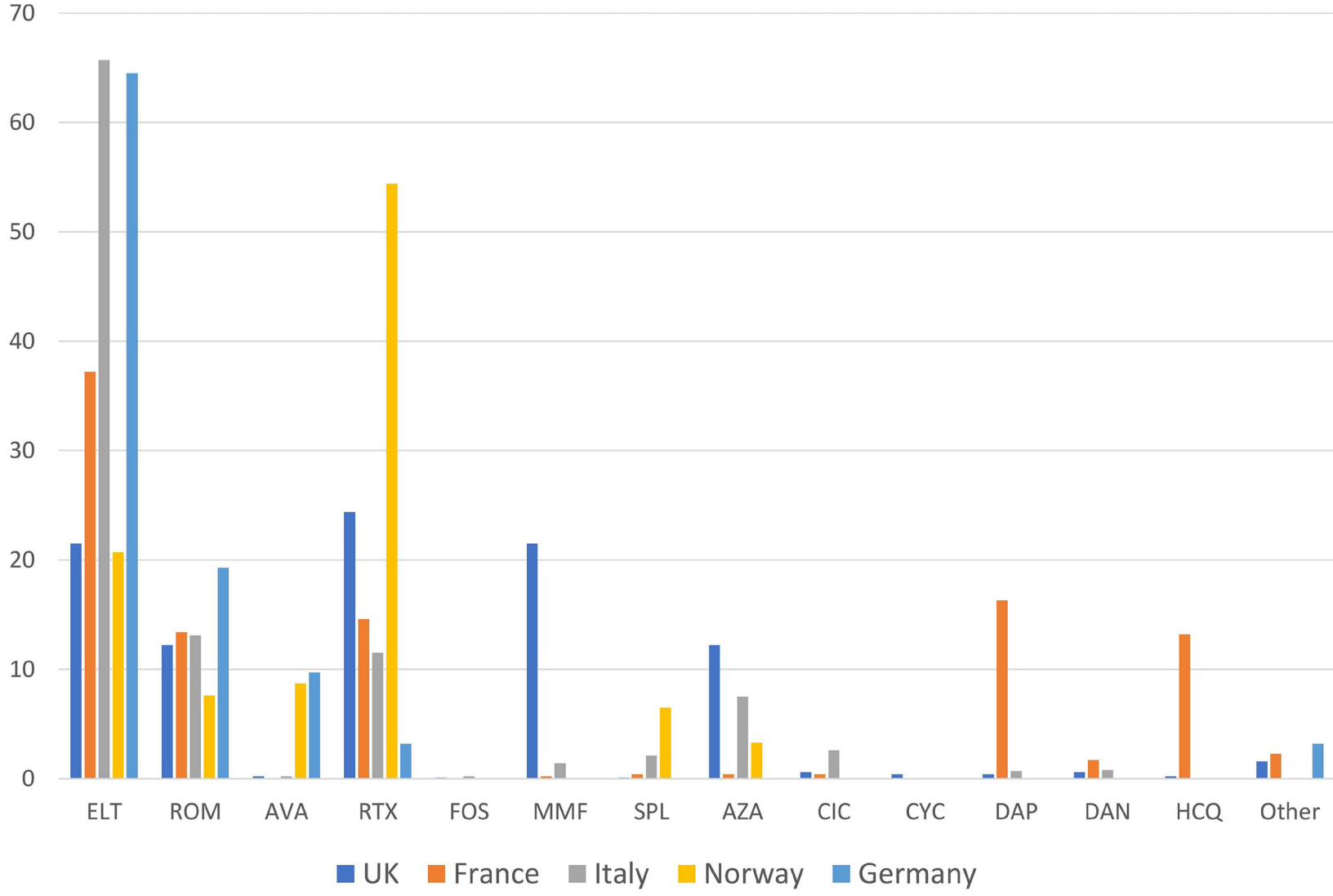

Figure 2. Proportion of first maintenance treatment in patients with primary immune thrombocytopenia over the total number of patients treated with maintenance therapy in each registry. The ITP-PARC registry (Switzerland and Serbia) was excluded due to insufficient number of selected patients (N=9). AVA: avatrombopag; AZA: azathioprine; CIC: cyclosporin; CYC: cyclophosphamide; DAN: danazol; DAP: dapsone; ELT: eltrombopag; FOS: fostamatinib; HCQ: hydroxychloroquine; MMF: mycophenolate mofetil; ROM: romiplostim; RTX: rituximab; SPL: splenectomy.

topenia may not be included by some investigators, which may lead to an overestimation of the percentage of patients treated in our study. More generally, there is no perfect source of country-level epidemiology that would identify all ITP patients; therefore, it is not possible to assess the percentage of pITP patients "captured" in each registry. Another limitation of the study is the very small number of patients exposed to newly marketed drugs (fostamatinib, avatrombopag) due to their recent introduction to the market. The German Registry started prospectively in 2021, and the ITP-PARC registry enrolled its last patient in 2017, which prevents any longitudinal analysis of changes in treatment patterns over time in these two registries. The minimum follow-up at the time of data extraction was 10 months, which may underestimate the proportion of patients exposed to maintenance therapies, especially in the third-line and beyond. Similarly, the ITP-PARC Registry is primarily a pediatric registry with few adult patients enrolled in a limited number of centers in Switzerland and Serbia. Finally, ITP treatment is changing rapidly and newly marketed drugs need to be evaluated to assess their real-world impact on ITP.

This international collaboration combining data from >5,000 patients demonstrates the feasibiity of conducting parallel pharmacoepidemiological studies by European ITP registries, using a harmonized core set of variables. The heterogeneity of treatment patterns across Europe highlights the importance of continuing comparative cross-national studies of real-world data provided by national registries on treatment strategies.

Authors

Guillaume Moulis,[1,2] Frederick Chen,[3] Giuseppe Carli,[4] Waleed Ghanima,[2,5] Karolin Trautmann-Grill,[6] Thomas Stauch,[7] Alexandra Schifferli,[8] Haroon Miah,[3] Manuela Rueter,[1] Lisanna Ghiotto,[9] Riccardo Tomasello,[5] Annabell Georgi,[6] Vickie McDonald,[10] Francesco Zaja,[2,11] Heidi Hassel Pettersen,[5] Thomas Kühne,[2,8] Maria Luisa Lozano,[2,12] Tomás José González-López,[2,13] Drew Provan,[2,3] Marc Michel,[2,14] Nichola Cooper,[2,15] Francesco Rodeghiero[2,9] and the ERCI Registry Harmonization Initiative Group[16]

[1]Department of Internal Medicine, Referral Center for Autoimmune Cytopenias in Adults, and Clinical Investigation Center 1436, Toulouse University Hospital, Toulouse, France; [2]European Research Consortium on Immune thrombocytopenia (ERCI) Vicenza, Italy; [3]ITP Center and UK Adult ITP Registry, Department of Clinical Hematology, Royal London Hospital, Barts Health NHS Trust and Queen Mary University of London, London, UK; [4]Department of Hematology, San Bortolo Hospital, Vicenza, Italy; [5]Østfold Hospital, Østfold and Institute of Clinical Medicine, University of Oslo, Oslo, Norway; [6]Medizinische Klinik und Poliklinik I, Universitätsklinikum Carl Gustav Carus der Technischen Universität, Dresden, Germany; [7]Universitätsklinikum Jena, Jena, Germany; [8]Department of Hematology/Oncology, University Children's Hospital Basel, Basel, Switzerland; [9]Hematology Project Foundation, Affiliated to the Department of Hematology, San Bortolo Hospital, Vicenza, Italy; [10]Guy's Hospital, London, UK; [11]DSM, Università degli Studi di Trieste, Trieste, Italy; [12]Hospital Universitario Morales Meseguer, Universidad de Murcia, IMIB-Pascual Parrilla, CIBERER, Murcia, Spain; [13]Hospital Universitario de Burgos, Burgos, Spain; [14]Mondor University Hospital, Créteil, France; [15]Imperial College London, London, UK and [16]Hematology Project Foundation, Vicenza, Italy

Correspondence:
G. MOULIS - moulis.g@chu-toulouse.fr

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Contributions

GM designed the study. FC, KT-G, AS, HM, MR, LG and RT conducted the analyses. All the authors participated in the interpretation of the results in each country. GM drafted and revised the manuscript. All authors approved the final version.

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Data-sharing statement

Please contact each registry coordinator. Data sharing will be assessed depending on national regulations.

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