Received: 1 February 2023 | Accepted: 1 February 2023

DOI: 10.1111/bjh.18695

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

COMMENTARY

Born in the UK: A registry to improve and broadcast knowledge on Waldenström macroglobulinaemia

Eric Durot | **Alain Delmer**

Department of Hematology, University Hospital of Reims and UFR Médecine, Reims, France

Correspondence
Eric Durot, Department of Hematology, University Hospital of Reims and UFR Médecine, Reims, France.
Email: edurot@chu-reims.fr

Registries constitute an interesting source of real-world data and bring complementary information to randomised controlled trials. They are of particular importance in rare diseases such as Waldenström macroglobulinaemia (WM), which can present with various clinical and biological features. In their paper Uppal and colleagues describe the development of the Rory Morrison Registry, the UK registry for WM and IgM-related disorders and highlight the profound changes in therapies both at first-line and relapsed settings in the recent years.

Commentary on: Uppal E. et al. The WMUK Rory Morrison Registry for Waldenström Macroglobulinaemia: the growth of a national registry for a rare disorder. *Br J Haematol*. 2023;201:905-912.

KEYWORDS
IgM-related disorder, real-world data, registry, Waldenström macroglobulinaemia

A rare disease is defined as one that affects less than five in 10 000 people. With an age-adjusted incidence rate of <0.5/100 000 person-years, Waldenström macroglobulinaemia (WM) fully meets the World Health Organization (WHO) definition of a rare disorder. Despite a nearly uniform molecular abnormality (presence of myeloid differenciation primary response gene 88 (*MYD88*)^{L265P} mutation in 90%–95% of patients), WM encompasses a wide spectrum of clinical presentations, ranging from smouldering WM to symptomatic WM and IgM-related disorders (peripheral neuropathy, cryoglobulinaemia, cold agglutinin disease, Bing-Neel syndrome …). This heterogeneity of presentation in addition to the rarity of the disease represents a challenge for prospective clinical trials to properly explore each condition of WM.

In their paper, Uppal et al.[1] describe the different steps of the development of the Rory Morrison Registry (RMR), the UK registry for WM and IgM-associated disorders, and present the first results on demographics, treatments and outcomes. Among the preliminary results reported, the authors point out the significant proportion of young patients (37% aged <60 years). This younger WM population will be interesting to study in more detail. Indeed, a few studies have addressed this question, mainly in recent years, with conflicting results on the life-expectancy compared to age- and sex-matched general population, probably due to different analysed periods with different therapies and/or different age cut-offs.[2,3] The other interesting observation of the RMR is the clear evolution of the landscape of WM-directed therapies with the wide use of chemoimmunotherapy (bendamustine-rituximab and rituximab-cyclophosphamide-dexamethasone) in first line and single-agent ibrutinib at relapse in the UK. This observation was made possible by the inclusion of patients with 'historic' diagnosis. Finally, data on survival are probably still immature and will need longer follow-up and better exhaustiveness of the causes of death.

Quality of life (QoL) can be altered in WM, even in patients with smouldering WM who do not meet treatment criteria but may experience mild symptoms. Although now routinely used in clinical trials, patient-reported outcome measures (PROMs) have been very infrequently analysed in WM. The WhiMSICAL study is the largest one reporting QoL information.[4] Using two questionnaires, this study showed that 10% of patients present stress levels identical to that of post-traumatic stress disorder and better QoL scores in patients treated with Bruton tyrosine kinase inhibitor. In their paper, Uppal et al.[1] briefly introduce their collection

of PROMs within the RMR using four questionnaires. They recently published a provisional report with QoL data on 155 patients from the RMR.[5] They demonstrate the feasibility of digital PROMs in their registry with high completion rates and highlight the need to develop WM disease-specific PROMs. Although limited by survival bias and selection bias, this field of research will be crucial to evaluate and improve quality of care, in particular in a population of older patients with comorbidities and/or in IgM-related disorders, such as IgM-related neuropathy.

Among real-world data (RWD) sources, registries are one of the most frequently used and can produce complementary data to randomised controlled trials (RCTs). The European Medicines Agency (EMA) defines patient registries as 'organized systems that use observational methods to collect uniform data on a population defined by a particular disease, condition or exposure, and that is followed over time' and provides guidelines on data collection, quality management and analysis to achieve high-quality registries. Regarding this aspect, all the regulatory steps necessary for the development of the RMR in order to ensure data protection and data quality have been followed and are well detailed by the authors.

As outlined by the authors, the use of RWD is expanding more and more. We just have to look at the increasing number of studies referenced in PubMed whose title contains the words 'real-world data' in recent years to realise this. WM appears as the ideal example of disease for a registry to study all aspects not covered by RCTs. RWD has made valuable contribution to the knowledge of WM, in particular in rare complications of WM and/or IgM-related disorders. The RMR has already captured data from 273 patients with IgM-related disorders, which will most likely help to develop knowledge in these entities. RWD can also be used to produce synthetic comparator arms or to compare treatments in a situation where prospective trials are unlikely to be performed. For example, a recent international collaborative study based on local database has compared two of the most frequently first-line treatments used in WM, fixed-duration chemoimmunotherapy (bendamustine and rituximab) and continuous orally treatment (ibrutinib).[6] Biases are inherent in RWD but can be limited by statistical methods such as propensity score matching.[7] RCTs are few in WM and it is known that patients enrolled in a RCT are highly selected, representing <5% of patients with cancer.[8] RWD helps to improve population representability and generalisability of results; however, a recent study conducted at the Department of Haematology of Lyon in France showed an enrolment rate of 54% in the REALYSA study, a prospective real-life cohort in lymphomas.[9] In summary, RWD and RCTs need to walk together to improve knowledge and to evaluate the safety and efficacy of new treatments, in particular in a disease such WM.

The RMR is dedicated to the memory of Rory Morrison, a BBC Radio 4 broadcaster, diagnosed with WM at age of 39 years. With >1300 patients registered from 22 centres; he would be impressed with how far the registry has come. Since November 2017, the RMR has grown significantly, has successfully passed into adulthood and has already given birth to numerous analyses presented at international haematology congresses and/or recently published.[5,10] With such a broadcast, we have not finished hearing about it!

ORCID

Eric Durot https://orcid.org/0000-0003-3463-0089
Alain Delmer https://orcid.org/0000-0002-1430-2574

REFERENCES

1. Uppal E, Khwaja J, Bomsztyk J, McCarthy H, Kothari J, Walton P, et al. The WMUK Rory Morrison Registry for Waldenström Macroglobulinaemia: the growth of a national registry for a rare disorder. Br J Haematol. 2023;201:905–912.
2. Varettoni M, Ferrari A, Frustaci AM, Ferretti VV, Rizzi R, Motta M, et al. Younger patients with Waldenström Macroglobulinemia exhibit low risk profile and excellent outcomes in the era of immunotherapy and targeted therapies. Am J Hematol. 2020;95(12):1473–8.
3. Chohan KL, Paludo J, Vallumsetla N, Larson D, King RL, He R, et al. Survival trends in young patients with Waldenström macroglobulinemia: over five decades of experience. Am J Hematol. 2023. https://doi.org/10.1002/ajh.26807 Epub ahead of print.
4. Tohidi-Esfahani I, Warden A, Malunis E, DeNardis PL, Haurat J, Black M, et al. WhiMSICAL: a global Waldenström's Macroglobulinemia patient-derived data registry capturing treatment and quality of life outcomes. Am J Hematol. 2021;96(6):E218–22.
5. Khwaja J, Uppal E, Bristogiannis S, McCarthy H, Kothari J, Rismani A, et al. Patient reported outcome measures in Waldenström macroglobulinaemia: a real-world data analysis from the WMUK Rory Morrison registry. EJHaem. 2022; accepted.
6. Abeykoon JP, Kumar S, Castillo JJ, D'Sa S, Kastritis E, Durot E, et al. Bendamustine rituximab (BR) versus ibrutinib (Ibr) as primary therapy for Waldenström macroglobulinemia (WM): an international collaborative study. J Clin Oncol. 2022;40(16_suppl):7566–6.
7. Bachy E, Le Gouill S, Di Blasi R, Sesques P, Manson G, Cartron G, et al. A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma. Nat Med. 2022;28(10):2145–54.
8. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. JAMA. 2004;291(22):2720–6.
9. Le Lan C, Belot A, Golfier C, Audin B, Sesques P, Bernier A, et al. Evaluation of participation and recruitment bias in a prospective real-life multicentric cohort « real world data in lymphoma and survival in adults » (REALYSA study) for newly diagnosed lymphoma patients over one year in a hematology Department of Teaching Hospital. Blood. 2022;140(Supplement 1):5210–1.
10. Khwaja J, Uppal E, Baker R, Trivedi K, Rismani A, Gupta R, et al. Bortezomib-based therapy is effective and well tolerated in frontline and multiply pre-treated Waldenström macroglobulinaemia including BTKi failures: a real-world analysis. EJHaem. 2022;3(4):1330–4. https://doi.org/10.1002/jha2.597

How to cite this article: Durot E, Delmer A. Born in the UK: A registry to improve and broadcast knowledge on Waldenström macroglobulinaemia. Br J Haematol. 2023;201(5):809–810. https://doi.org/10.1111/bjh.18695