Commentary Article

rare tumors

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Real-world evidence for ultra rare cancers

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The data and evidence derived from real-world experience constitutes a substantial source of clinical knowledge. The US Food and Drug Administration (FDA) has defined real-world data (RWD) as data on patient health status and delivery of health care collected from various sources such as electronic health records, medical claims, product or disease registries and other sources. Real-world evidence (RWE) is the clinical evidence about the usage and risk or benefit of a medical product obtained from the analysis of RWD as opposed to the evidence acquired in the controlled environment in the confines of a clinical trial.

RWD have a well-established role on illuminating the pathophysiology and natural history of disease and documenting the safety and efficacy of a medical product after authorisation.[1] In particular, these data are instrumental for detection of rare side effects, and late and recurrent toxicities which can only be captured in larger populations over longer periods of time. In addition, they are critical for the evaluation of the long-term outcome of a treatment, the effectiveness of a drug in the general population as well as specific subgroups with comorbidities or on concomitant medications as opposed to the limited number of patients permitted to participate in a study by the strict inclusion criteria of the protocol.

With respect to ultra-rare cancers, the low incidence and geographical dispersion of patients makes the feasibility of clinical trials challenging. However, initiatives such as the Angiosarcoma Project (ASC Project) overcame this barrier by engaging and empowering patients to share samples and data remotely.[2] The whole exome sequencing of biospecimens revealed mutational signatures which elucidated the aetiology of the disease such as the one related to UV exposure in patients with head, neck, face and scalp (HNFS) angiosarcoma. This genomic information along with RWD of patients who received off-label anti-PD1 therapy who had durable responses catalysed the design of a clinical trial assessing the role of immunotherapy on HNFS angiosarcoma. The collected de-identified data are publicly available at cbioportal.org.

Another example of the utility of RWE in an ultra-rare cancer was the extension of the indication of palbociclib in male patients with breast cancer who were precluded from the large randomised trials as they represent less than 1% of new breast cancer cases. The FDA based the expansion of the indication on the favourable benefit/risk evaluation of palbociclib in females in the PALOMA-2 and PALOMA-3 trials and supportive RWD with descriptive information about outcomes in male patients.[3]

The utility of RWD in the pre-authorisation setting remains controversial.[4,5] The quality of RWD are inferior to those recorded in the context of a trial by trained personnel with protocol-specified procedures. Treatment assignment dependent on the decision of an individual physician on the basis of the likelihood of response can be a source of selection bias. The lack of randomisation results in introduction of confounders which would be otherwise evenly distributed across treatment groups. Other limitations may be the absence of control and the fact that these data are prone to multiple hypothesis testing and consequently inflated type I error. Therefore, any causal inference between treatment and clinical effect is problematic in real world situations.

Although it is tempting to use RWD to gain insight on drug effectiveness given their increasing availability, their utility for evidence generation to support regulatory decisions needs scrutinization. Towards this direction, in response to 21st Century Cures Act of 2016 which was introduced to accelerate medical product development, the FDA developed a framework to evaluate RWD and RWE. This takes into

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consideration the fitness of RWD, the appropriateness of the trial design to provide adequate scientific evidence and whether the study conduct meets FDA regulatory requirements.

In conclusion, RWD/RWE have a clear role in providing insight on the natural history of disease and documenting the safety and effectiveness of a drug post-authorisation. However, their role to guide regulatory decisions remains a work in progress.

Author contributions

LM researched literature and wrote the first draft of manuscript. RLJ conceived the study. LM, RLJ, PH and AN reviewed and edited the manuscript and approved the final version of the manuscript.

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