Rituximab biosimilars in hematologic malignancies: the need for a real-world approach

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The introduction of rituximab biosimilars into healthcare systems can potentially help to control healthcare costs for the treatment of hematologic malignancies. However, there are currently several barriers to the uptake of biosimilars. This review discusses barriers to the adoption of rituximab biosimilars by stakeholders including patients and healthcare providers. We outline the importance of utilizing real-world evidence in providing additional clinical experience on rituximab biosimilars in hematologic malignancies to improve stakeholder confidence regarding their efficacy and safety. We conclude by offering recommendations for designing and conducting effective real-world studies. Such studies can provide evidence to help achieve lower-priced biologics and improved patient access to help sustain the treatment of hematologic malignancies with biologics, including rituximab biosimilars.

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In the USA, healthcare expenditure for cancer treatment is increasing, partly due to the cost of biologic drugs, which creates a challenge for the future sustainability of affordable cancer care [1]. The increase in cancer incidence due to a rise in life expectancy and improved survival rates has extended the length of time that patients receive treatment and contributed to the escalation in cancer healthcare costs [2,3]. Rituximab (MabThera[®]; Rituxan[®]) is a chimeric monoclonal antibody that targets the B-cell-specific antigen CD20, and this biologic drug has transformed standard therapies for the majority of lymphoid malignancies [4]. Rituximab is approved for the treatment of several conditions, including – but not limited to – follicular lymphoma (FL), diffuse large B-cell lymphoma, and chronic lymphocytic leukemia [5,6]. However, patient access to rituximab can be restricted, particularly in countries with limited financial resources [7].

As patent portfolios for biologics near end of term, the availability of biosimilar versions of these drugs may mitigate the total cost of care by potentially providing more affordable treatment options, thereby increasing patient access to these important therapies [1,8]. Biosimilars are biologic drugs that are developed to be highly similar in structure and function to licensed (i.e., reference or originator) products, with no clinically meaningful differences in efficacy, safety and purity [9,10]. The Biologics Price Competition and Innovation Act of 2009 (enacted as part of the Affordable Care Act) provides an abbreviated approval pathway for biosimilars [9,11]. As such, the introduction of rituximab biosimilars into healthcare systems can potentially help to control the treatment costs for hematologic malignancies [12].

The availability of rituximab biosimilars, however, does not automatically guarantee their adoption in routine clinical practice. Despite the availability of a filgrastim biosimilar, its uptake in the USA has been less than anticipated and has lagged behind other countries where granulocyte-colony stimulating factor biosimilars for use in cancer supportive care are available [13]. In order to realize the potential savings for US healthcare systems, several barriers to the uptake of rituximab biosimilars need to be overcome. These barriers include the perceptions of stakeholders

(including patients and healthcare providers), financial disincentives related to reimbursement, and regulatory policies (such as the interchangeability of reference products and biosimilars) [8,11,14]. Real-world evidence (RWE) can provide additional information to supplement the clinical data required by regulatory agencies as part of the abbreviated approval of biosimilars, to help overcome some of these barriers. The aim of this review is to discuss the current barriers to the uptake of biosimilars, the utility of RWE in providing additional clinical experience of the use of rituximab biosimilars for the treatment of hematologic malignancies, and recommendations for conducting effective real-world studies.

Regulatory guidance & rituximab biosimilars

To gain regulatory approval, biosimilars must be sufficiently similar to the corresponding reference product such that they are not expected to show any clinically meaningful differences in safety, efficacy and purity demonstrated through a robust regulatory pathway. Similarity of a proposed biosimilar to its reference product is established using a ‘totality-of-the-evidence’ approach, comprising data from comparative analytical, preclinical, pharmacokinetic and clinical studies [10,15]. These confirmatory clinical studies are conducted to establish similarity to the reference product in terms of quality, efficacy and safety [16]. Biosimilars have the same mechanism of action as their corresponding reference product [9,10]. As such, with appropriate scientific justification, regulatory guidance permits the approval of a biosimilar in all eligible indications held by the reference product, without a comparative trial in each indication. This is known as extrapolation across indications [9,10,17,18].

Many countries have now established regulatory pathways for the approval of biosimilars [9,10,18–22]. Rituximab biosimilars have been approved in the USA and the European Union through these pathways, using collective evidence from analytical, nonclinical and clinical studies. The comparative clinical studies were conducted in patients with either rheumatoid arthritis or FL, as these populations are adequately sensitive to detect meaningful differences in efficacy or safety between the biosimilar and reference rituximab (Table 1) [23–40]. There are also several rituximab biosimilars currently under development [41–44].

Real-world studies

The US FDA defines real-world data as “*data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources*” [45]. These sources go beyond the traditional clinical trial setting and include electronic patient health records, claims data, product and disease registries, patient-reported outcomes (PROs) and other emerging data sources, such as social media and industry collaborations (Table 2) [46,47]. RWE is the “clinical evidence on the use and potential benefits or risks of a medical product derived from analysis of real-world data” [45]. Real-world studies can provide insights into different aspects of treatment and patient outcomes to enhance the evidence generated from conventional clinical trials in selected patient populations [48,49]. For example, data from electronic patient records were used to evaluate changes in practice efficiency by comparing subcutaneous and intravenous administration of rituximab [50]. RWE has also been used to inform early treatment milestones, understand treatment patterns, and provide patient perspectives regarding disease management for chronic myeloid leukemia [49].

RWE can be used to gain a more accurate insight into patient outcomes, for example, disease progression and long-term survival can be studied over longer time periods than those used in clinical trials [48]. By providing additional clinical experience of rituximab biosimilars, RWE supplements the clinical data required by regulatory agencies for the approval of biosimilars, and thereby potentially alleviate some of the current barriers to their uptake (Table 3) [8]. In addition, the evidence that is generated can be systematically analyzed to identify possible ways to improve disease management. However, real-world studies also have limitations, including internal validity, confounding factors, lack of standardization in assessing response and progression, variable data quality and increased risk of bias [47,51]. Furthermore, different sources of real-world data have their own strengths and limitations [47]. Therefore, translating real-world data into robust, clinically relevant evidence can be a challenge.

Relevance of RWE to healthcare stakeholders

Currently, real-world data are accumulated from disease registries mandated by regulatory authorities as part of the pharmacovigilance requirements for the approval of a biosimilar [52,53]. Data accumulated through pharmacovigilance could be used to inform physicians on the utilization of rituximab biosimilars in clinical practice, and to help inform discussions about treatment decisions between physicians and patients [54]. The availability of RWE on the use of biosimilars may also increase understanding among physicians and prescribers that comparative clinical

Table 1. Rituximab biosimilars approved in the USA and the European Union for the treatment of hematological malignancies[†].

Product	Key clinical studies	Approved hematological indications [‡]	Regulatory authority (approval date)	Ref.
CT-P10 [#] (Truxima [®] [rituximab-abbs], Ritemvia [®] , Blizima [®] ; Celltrion)	Pharmacokinetics trial (n = 154) and extension study (n = 83); randomized, double-blind study in patients with RA (n = 372): – Similar PK and immunogenicity between CT-P10 and reference rituximab Randomized, double-blind studies in patients with previously untreated advanced FL (n = 140) and patients with LTB-FL (n = 258) – Similar PK, PD, efficacy, safety and immunogenicity between CT-P10 and reference rituximab – Similar PK, safety and efficacy between CT-P10 and reference rituximab	NHL; CLL [¶]	EMA (Feb 2017/Jul 2017); US FDA (Nov 2018)	[23–31]
GP2013 (Rixathon [®] /Riximyo [®] [§] ; Sandoz)	Randomized, double-blind efficacy and safety study in patients with RA (n = 173): – Similar PK, PD, safety, efficacy and immunogenicity between GP2013 and reference rituximab Randomized, double-blind study in patients with previously untreated advanced FL (n = 629) – Similar efficacy and safety between GP2013 and reference rituximab	NHL; CLL [§]	EMA (Jun 2017)	[32–35]
PF-05280586 (Ruxience [™] , rituximab-pvvr; Pfizer)	Pharmacokinetics trial (n = 220) and extension study (n = 185) in patients with active RA: – Similar PK, PD, safety and immunogenicity demonstrated between PF-05280586 and reference rituximab Randomized, double-blind efficacy and safety study in patients with untreated CD20-positive LTB-FL (n = 394) – Similar efficacy, safety, immunogenicity, PK and PD between PF-05280586 and reference rituximab	NHL; CLL	US FDA (Jul 2019) EMA (Apr 2020)	[36–40]

[†]As of April 2020.[‡]Some rituximab biosimilars are also approved to treat conditions including granulomatosis with polyangiitis, microscopic polyangiitis, pemphigus vulgaris and RA.[¶]CLL is not an approved indication for Ritemvia or rituximab-abbs.[§]Approved in the European Union as Riximyo under a duplicate marketing authorization for the treatment of NHL.[#]Clinical program was developed in consultation with the US FDA and EMA to support the global development of the product.

CLL: Chronic lymphocytic leukemia; FL: Follicular lymphoma; LTB-FL: Low tumor-burden FL; NHL: Non-Hodgkin lymphoma; PD: Pharmacodynamic; PK: Pharmacokinetic; RA: Rheumatoid arthritis.

Table 2. Sources of real-world data.

Setting	Examples
Research studies	Observational studies Post-approval safety studies
Clinical setting	Electronic patient health records Patient medical charts Patient registries (disease and product based)
Administrative claims databases	Patient medical claims
Pharmacy	Prescription records
Patient	Patient-reported outcomes Patient-powered research networks Information from wearables and fitness trackers
Emerging data sources	Social media Cross-industry data collaborations

Adapted from The Network for Excellence in Health Innovation 2015 [46] and Nabhan *et al.*, *JAMA Oncol.* 2019 [47].

studies of proposed biosimilars and the corresponding reference product are well-designed, and that data from these studies, which are required for regulatory approval, are reliable. In turn, this may improve the uptake of biosimilars.

In contrast to randomized clinical trials conducted in a selected patient population, patient populations in real-world settings are heterogeneous. RWE can therefore demonstrate the efficacy and safety of biosimilars in patient populations for whom clinical trial data are not available, such as children, the elderly, and those with concurrent medical conditions [13,14,48,55]. This aspect is of particular relevance in oncology as more than 95% of patients with cancer are treated outside of clinical trials [56]. In Europe, for example, real-world data from the Global Oncology Monitor (Ipsos Healthcare) have been used to evaluate prescription patterns for rituximab biosimilars [57]. This

Table 3. Barriers to the uptake of biosimilars in the USA.

Barrier	Issue	Role of real-world evidence
Perception of stakeholders (including physicians and patients)	Patients may be reluctant to switch from reference products to biosimilars Physicians lack confidence in prescribing biosimilars	To inform educational programs for physicians and patients on the efficacy and safety of rituximab biosimilars in more diverse patient populations
Pricing and reimbursement	Healthcare providers may not be able to adopt biosimilars if payers prefer the reference product in reimbursement models	To demonstrate the market value of rituximab biosimilars (e.g., by lowering treatment cost and improving patient access) to enable payers to make decisions on reimbursement
Regulatory policies	Prescribers are unsure whether clinical data on the interchangeability of reference products and biosimilars are reliable or whether extrapolation of data across indications is permitted	To provide data on the efficacy and safety of biosimilars in extrapolated indications, and provide data on switching between reference products and biosimilars

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online medical chart review study of the treatment of non-Hodgkin lymphoma (NHL) in five countries found that patients who had received first-line treatment, and had indolent disease and FL, were more likely to be treated with a rituximab biosimilar than with the reference product [57].

RWE can support physicians and patients when making decisions on nonmedical switching, to or from a reference biologic, for reasons relating to treatment cost or availability, rather than as a medical requirement [58,59]. Randomized clinical trials are powered to demonstrate efficacy and are largely limited to assessing known adverse events, whereas real-world populations are more appropriate for identifying previously unreported or rare adverse events [60,61]. Evidence from real-world settings could enhance confidence in the safety of biosimilars; for example, the post-market safety experience of granulocyte-colony stimulating factor biosimilars has demonstrated that real-world use in the USA is consistent with global safety data [62].

RWE can be used to determine potential cost savings for payers [55]. For example, researchers have compared the potential time and cost savings, which may be achieved from a US payer perspective, by using different formulations of the reference product and a rituximab biosimilar in the treatment of patients with NHL [63]. In this time- and cost-simulation analysis in patients with NHL receiving R-CHOP therapy (rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone), subcutaneous delivery of reference rituximab saved on both time and cost compared with intravenous administration. Moreover, intravenous dosing of a proposed rituximab biosimilar in an R-CHOP regimen provided time and cost savings when compared with subcutaneous administration of the reference product [63]. Further real-world studies are needed to determine the extent of the savings that could be achieved in clinical practice [60].

There is increasing interest from regulatory bodies in the use of RWE to support their decision-making, as highlighted in the “Framework for the FDA’s real-world evidence program” [45]. The guidance provides a framework for evaluating the use of real-world data to support approvals in new indications for a drug, and for post-approval study requirements, as set out in the 21st Century Cures Act [45,64]. The framework also highlights potential gaps in the current sources of real-world data; for example, it recommends that electronic patient health records and medical claims data should be utilized. The FDA recommends that strategies to address these gaps should be explored, including the use of mobile technologies and other tools for collecting PROs [45]. Real-world data can provide support throughout the development of all new drugs by identifying unmet treatment needs, generating hypotheses for clinical research, and providing insights on efficacy and safety for pre-regulatory approval and post-approval outcomes [46]. As such, RWE can be used to support the approval of drugs for expanded indications; for example, palbociclib is now approved to treat men with breast cancer, with its approval supported by real-world data from electronic health records and insurance claims [65].

Relevance of RWE in the era of biosimilars in hematology

As treatment options for hematologic malignancies increase, real-world data can be accumulated to expand the evidence base for disease management in clinical practice [42]. RWE has the potential to address outcomes in clinical practice, and increase understanding of adverse events, use of resources and economic burden [66–68]. This may facilitate evidence-based clinical decision-making and increase the uptake of biosimilars. Real-world studies have evaluated treatment patterns for novel therapies in patients with chronic lymphocytic leukemia to identify sequencing strategies and reasons for treatment discontinuation [69,70]. As more rituximab biosimilars become available, RWE could provide an understanding of the sequence in which patients should be treated with these

Table 4. Clinical and real-world studies for biosimilars.

Source	Advantages	Disadvantages
Randomized clinical trials	<ul style="list-style-type: none"> – Well-designed and controlled; high-quality data are collected – Patient baseline data are collected 	<ul style="list-style-type: none"> – May not reflect real-world patients seen by physicians due to strict inclusion and exclusion criteria – Limited indications are studied – Patients are followed up for limited time periods
Observational studies (prospective)	<ul style="list-style-type: none"> – Include different population subgroups (e.g., pediatric, pregnant and older patients) – Can be designed to address specific efficacy and safety questions to build confidence in biosimilars – Provide data on long-term patient outcomes – Demonstrate efficacy in extrapolated indications 	<ul style="list-style-type: none"> – Issues of selection bias and confounding factors
Observational studies (retrospective)	<ul style="list-style-type: none"> – Evaluate adherence to treatment with biosimilars – Evaluate switching between reference products and biosimilars 	<ul style="list-style-type: none"> – Patient baseline data may not be available – Issues of recall bias and confounding factors
Patient registries and electronic health records	<ul style="list-style-type: none"> – May identify rare side effects or trends in adverse events – More broadly representative of clinical settings and patient populations 	<ul style="list-style-type: none"> – Patient registries can have high set-up and maintenance costs
Review of insurance claims/pharmacy records	<ul style="list-style-type: none"> – Provide information on treatment patterns (comparing use of reference products with biosimilars) – Provide data on treatment costs 	<ul style="list-style-type: none"> – Prescribing decisions are not always evidence-driven, and can be affected by other factors, such as physician preference

drugs and offer invaluable insights into potential comparisons between rituximab biosimilars. Accumulating real-world data may help to reassure physicians and patients on the effectiveness of rituximab biosimilars in extrapolated indications [71].

Improving biosimilar uptake for the treatment of hematologic malignancies has the potential to reduce healthcare costs and expand patient access [14,17]. Increased competition between biosimilars may further reduce the costs of these drugs. However, there is a lack of consensus on the extent of these savings and, in any event, they are not likely to be as large as those obtained for generic drugs [72,73]. Additionally, biosimilars may improve patient care; for example, by enabling patients to receive treatment at an earlier stage of their disease [74,75].

The FDA's Biosimilars Action Plan recommends the increased use of real-world data to facilitate regulatory decision-making related to biosimilars [76]. RWE could also support safety assessments and the appropriate prescribing of biosimilars; for example, by considering data from the FDA's Adverse Event Reporting System and Sentinel Initiative, and data from insurance companies [76]. Real-world studies that accumulate data from a variety of sources, such as patient registries and insurance claims records, can provide further supportive data on the clinical experience of biosimilars. The results from such studies may help inform physicians, patients, manufacturers and regulatory bodies to guide decisions on the use of biosimilars in the treatment of patients across a range of conditions, including hematologic malignancies [55].

Designing effective real-world studies: challenges & recommendations

Challenges

As more rituximab biosimilars become available (including in extrapolated indications), there is a need for well-designed real-world studies to gain broader experience of their use in clinical practice and to gain the trust of the prescribing community [77,78]. However, obtaining reliable RWE for biosimilars with high-quality data can be a challenge. The key advantages and disadvantages of clinical and real-world studies in generating evidence on the use of biosimilars are summarized in Table 4. There are, however, several challenges to consider in the design of these studies, including data quality, biases, confounding factors, cost, patient confidentiality, access to data and governance [48,78]. Furthermore, there is a lack of knowledge and awareness of the systems and processes currently in place to support the collection of real-world data and the methods for analyzing these data [79]. Conducting real-world studies is typically less resource intensive than for randomized clinical trials; however, there is no agreed-upon design for an effective study, although checklists to ensure any data are of regulatory-grade quality have been proposed [56]. Pragmatic clinical trials can be conducted by physicians to test interventions in real-world clinical practice settings with a more representative range of patients than those included in randomized clinical trials, as eligibility criteria are not as strict [80]. One advantage of these trials is that they can be used to evaluate how an intervention works in various healthcare settings, such as hospitals, clinics or physician practices.

Physicians and their patients may have concerns about switching to a biosimilar in the middle of a treatment cycle for cost rather than medical reasons [8]. Therefore, some physicians and pharmacists might need additional sources of evidence on the effects of switching from the reference product to a biosimilar, as regulatory agencies generally do not require switching studies to be conducted for the approval of a biosimilar [81]. Oncologists must decide if and when treatment should be switched to biosimilars, either to or from a reference product or between different biosimilars [82]. Most physicians are unlikely to switch unless financial or other ‘toxicities’ emerge [83]. While the FDA requires switching studies for approved biosimilars to be designated as interchangeable, it does not require clinical trials in each extrapolated indication [81]. However, a lack of confidence in the efficacy and safety of rituximab biosimilars could lead to lower uptake. This in turn might increase the time required to collect sufficient data to undertake robust real-world studies, particularly if these are retrospective. Furthermore, stakeholders might require RWE that is based on region-specific data and they may not fully accept evidence based on data generated outside their region.

Recommendations

As rituximab biosimilars have only recently been approved for use in the USA, real-world data on their use in clinical practice are lacking; as such, initial studies should be prospective (e.g., a registry that captures patient-level data on the use of the biosimilar and reference product). As evidence on the real-world use of rituximab biosimilars accumulates, retrospective studies could be designed to address clinical and economic outcomes. Such studies may help to inform stakeholders and patients that RWE can be used alongside data from clinical trials to broaden the evidence base on the efficacy and safety of rituximab biosimilars [46]. These studies should also include additional information, such as PROs and economic analyses. PROs (e.g., health-related quality of life, and patient preference and satisfaction) could aid differentiation between competing products as more rituximab biosimilars are approved [55,84]. Documentation of PROs can contribute to an improved understanding of the overall efficacy of approved drugs; for example, by recording accurate information on patients’ symptom burden [84]. Such studies may enable biosimilar costs to be evaluated in relation to patient outcomes [85]. To ensure that real-world studies are designed to address meaningful questions, it is important to consider the views of all stakeholders, including patients [78]. However, best practices for involving different stakeholders when designing and conducting real-world studies are still being developed [78].

Collaborations are required between organizations that are adept at generating real-world data and groups with expertise in the analysis, interpretation and dissemination of these findings [55]. Biosimilar manufacturers and their collaborators could alleviate some of the concerns that physicians may have about the safety and effectiveness of biosimilars by designing real-world studies that provide supportive evidence for the safety of biosimilars. The American Society of Clinical Oncology’s ‘big data’ initiative, CancerLinQ[®], could potentially contribute valuable information on biosimilar use and effectiveness by integrating real-time data for clinical oncology practice and identifying safety concerns in real-world settings [86].

It will be important to identify whether further clinical evidence is required, and to prioritize specific questions regarding the use of biosimilars that can be addressed in real-world studies [55]. Evaluating the long-term use of biosimilars requires not only financial support from relevant stakeholders but also a consensus on the questions that should be addressed; for example, is the primary concern safety or efficacy and should real-world studies compare biosimilars with their reference product or with other rituximab biosimilars. Real-world studies also need to be designed using appropriate methods for data collection in each NHL indication. There is therefore a need to establish a working group to address the specific challenges of collating RWE on biosimilars for the treatment of hematologic malignancies, and to develop a consensus statement to ensure some level of evidence for the quality and comparability of data. Demonstrating the real-world value of rituximab biosimilars to all stakeholders is key to improving patient access and increasing the uptake of these drugs. As such, there are opportunities to design effective real-world studies to provide reliable long-term data on rituximab biosimilars.

Conclusion

Designing and conducting effective real-world studies for rituximab biosimilars may help to overcome barriers to their adoption by stakeholders. RWE can provide long-term data on the efficacy and safety of rituximab biosimilars in more diverse patient populations, particularly those not studied in clinical trials. This evidence could also support decision-making on non-medical switching, to or from a reference biologic. As randomized clinical trials are often costly to conduct, RWE can provide supportive evidence to help achieve lower-priced biologics and improve patient

access to these therapies. As such, RWE has the potential to help sustain the treatment of hematologic malignancies with biologics, including biosimilars.

Future perspective

Treatment options for hematological malignancies are anticipated to expand in the future as more rituximab biosimilars are approved. Stakeholders including patients and physicians will need more information to aid differentiation between biosimilars to support decision-making on the appropriate treatment for each patient. Real-world studies have an important role in providing reliable data on long-term patient outcomes, understanding the sequence in which patients should be treated with these drugs and demonstrating the efficacy of rituximab biosimilars in extrapolated indications. Mobile technologies (such as, wearable electronic devices) are likely to support real-world

Executive summary

Background

- Healthcare expenditure for cancer treatment is increasing, partly due to the cost of biologic drugs, creating a challenge for the future sustainability of affordable cancer care.
- As patent portfolios for biologics are nearing end of term, drug companies are developing biosimilars that may provide more affordable treatment options and increase patient access to these important therapies.
- Demonstrating the value of rituximab biosimilars to stakeholders (including patients and healthcare providers) in the real world is key to improving patient access; however, there are currently several barriers to the adoption of rituximab biosimilars.

Regulatory guidance & rituximab biosimilars

- To gain regulatory approval, biosimilars must be sufficiently similar to the corresponding reference biologic such that they are not expected to show any clinically meaningful differences in efficacy, safety and purity.
- Biosimilar approval is established using a 'totality-of-the-evidence' approach, comprising comparative analytical, preclinical, clinical pharmacokinetic, and efficacy and safety studies in an appropriate patient population.
- Some rituximab biosimilars have been approved in the USA and the European Union through these pathways and there are several other rituximab biosimilars currently in development.

Real-world studies

- Real-world studies can provide insights into different aspects of treatment and patient outcomes to supplement the evidence generated from conventional clinical trials in selected patient populations.
- Real-world data can be collected from a variety of sources including electronic patient health records, claims data, product and disease registries, PROs as well as from emerging data sources, such as social media and industry collaborations.

Relevance of RWE to healthcare stakeholders

- RWE can demonstrate the efficacy and safety of biosimilars in patient populations for whom clinical trial data are not available.
- Evidence on the use of biosimilars from real-world settings could enhance stakeholder confidence in the safety of these drugs.

Relevance of RWE in the era of biosimilars in hematology

- RWE has the potential to address outcomes in clinical practice, and increase understanding of adverse events, use of healthcare resources and the economic burden on healthcare systems.
- As more rituximab biosimilars become available, RWE may help inform physicians, patients, manufacturers and regulatory bodies to guide decisions on the use of these drugs for the treatment of hematologic malignancies.

Designing effective real-world studies: challenges & recommendations

- Obtaining reliable RWE for biosimilars can be challenging and there are several factors to consider when designing real-world studies, including data quality, biases, confounding factors, cost, patient confidentiality, access to data and governance.
- Real-world data on the use of rituximab biosimilars in clinical practice are lacking so initial studies should be prospective (e.g., registries to capture patient-level data on the use of the biosimilar and reference product).
- Retrospective studies could be designed to address clinical and economic outcomes, and acquisition of additional information such as PROs to aid differentiation between different biosimilars.
- Collaborations are required between organizations that are adept at generating real-world data and groups with expertise in the analysis, interpretation and dissemination of these findings.

Conclusion

- Providing real-world data on the efficacy and safety of rituximab biosimilars may help to overcome barriers to their adoption by stakeholders.
- RWE can provide supportive evidence to help achieve lower-priced biologics, improve patient access to these therapies and help sustain the treatment of hematologic malignancies with biologics, including biosimilars.

studies to collect data on PROs, such as health-related quality of life, and patient preference and satisfaction. Reassuring stakeholders on the efficacy and safety of rituximab biosimilars by accumulating reliable evidence through well-designed real-world studies can potentially help increase the uptake of rituximab biosimilars and, in turn, reduce healthcare costs for the treatment of hematologic malignancies.

Supplementary data

A Plain Language Summary is available for this paper. To view and download the Plain Language Summary, please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/fon-2020-0131

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