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Anti-CD20 Directed Therapy of B Cell Lymphomas: Are New Agents Really Better?

Ciara L. Freeman[1] · Laurie Sehn[1]

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Abstract

Purpose of Review Since its initial approval in 1997, rituximab has revolutionized the treatment of CD20-positive lymphoproliferative disorders. Now, over two decades later, second-generation molecules are emerging that may have key biological advantages compared to rituximab, as well as biosimilars that may be more cost-effective. Clinicians, health policy makers, and payers will now need to critically appraise the available evidence for these competitors and decide which anti-CD20 to use.

Recent Findings Evidence has emerged directly comparing rituximab IV to a subcutaneous preparation, and head-to-head comparisons of rituximab versus next-generation anti-CD20 monoclonal antibodies have also been published. Trials comparing rituximab with newly developed biosimilars have also allowed for registration of these agents.

Summary In this review, we will present an overview of anti-CD20 monoclonal antibody development, discuss the mechanistic and clinical evidence for rituximab, as well as the novel compounds, and provide commentary on the possible advantages and limitations of these agents.

Keywords Lymphoma · CLL · CD20 · Monoclonal antibodies · Rituximab · Immunotherapy · Biosimilar

Introduction—The History of Anti-CD20 Monoclonal Antibody Development

The identification of the CD20 antigen in 1979 (then called B1) was the first step in what would become a therapeutic milestone [1, 2]. This glycosylated phosphoprotein is expressed on the surface of developing B cells but not the early progenitors nor mature plasma cells, and it was hypothesized (and later confirmed) that depleting these intermediate stage B cells in humans would be well tolerated without significant side effects [3]. Despite decades of study, the exact function of CD20 remains somewhat poorly understood. It is thought to play a role in calcium transport and is a member of the membrane spanning 4-A family with two small extracellular loops [4]. It is expressed at various levels by almost all B cell malignancies and is largely limited to B cells, identified early as a potential target for monoclonal antibody (mAb) therapy. Although the concept of immunotherapy had been around for almost a century, it took the Nobel-prize winning work of Köhler and Milstein in 1975 to begin this therapeutic revolution. They generated the first hybridoma cell lines capable of producing mAbs by immunizing mice against sheep cells followed by isolation of B-lymphocytes from the murine spleens and subsequent fusion of those cells with a myeloma cell line [5]. This was followed in 1980 by a proof of principle serotherapeutic trial in which a patient with multiply relapsed poorly differentiated "lymphocytic lymphoma" was treated with a murine anti-CD20 monoclonal antibody. A transient response was observed—with reduction in circulating cells—and the quest to mass-produce anti-CD20 mAbs began [6].

The first mAbs produced were murine. Early experience was disappointing with responses transient, half-lives short, and the formation of human anti-mouse antibodies' limited efficacy. Monoclonal antibodies are very large and complex molecules and variably glycosylated (which has impact on their function), and the originally produced hybridomas could not generate sufficient quantities for cost-effective therapy. Two main technical advances were required to overcome these limitations: first, recombinant DNA technology to make the mouse antibodies more like human ones and second,

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✉ Ciara L. Freeman
Ciara.freeman@bccancer.bc.ca

[1] BC Cancer, 600 W 10th Avenue, Vancouver, BC, Canada

engineered mammalian cells able to mass-produce sufficient quantities of the desired antibody to make treatment commercially viable (Fig. 1) [7].

The first success was in making "chimeric" antibodies—from the Greek mythological monster made up of many parts ("chimera")—these antibodies had murine variable regions that provided the antigen specificity and human constant regions that were able to interact with human host effector cells and complement. The human Fc portion also prolonged the half-life by interacting with receptors on endothelial cells lining the human vasculature [8, 9]. Subsequent advancements have led to the ability to produce "humanized" (less mouse-like) and fully human antibodies (Fig. 1).

The recombinant DNA that codes for the protein must be integrated into mammalian cells that can secrete large amounts of the desired antibody. It is important to bear in mind that the choice of mammalian cell used has impact on the composition of the N-linked sugars on the molecule which can impact the pharmacological properties of the mAb generated. A group at IDEC pharmaceuticals manipulated Chinese hamster ovary cells by genomic amplification with a linked dihydrofolate reductase gene and selection with competitive inhibition by methotrexate [7]. This technology was up-scalable. The Fc region of the chimeric antibody they produced was glycosylated in a way that allowed for interaction with human effector functions. This antibody, IDEC-C2B8, was later renamed rituximab.

Rituximab

Since its initial approval in 1997, rituximab has revolutionized the treatment of B cell malignancies [10••]. It is used as a monotherapy and in combination, at induction and relapse, and also as maintenance [10••]. Over the course of two decades, clinical trials were able to demonstrate clinically meaningful differences in progression-free and, in some cases, overall survival. Its favorable side effect profile has been well established [11], allowing for safe and tolerable combination therapy with both chemotherapeutics and novel agents. The success of rituximab spurred the development of second-generation molecules, aimed to improve efficacy, as well as biosimilars that may be more cost-effective. With these emerging compounds, it is time to ask what is the role of these newer agents?

Subcutaneous Rituximab

Rituximab was initially formulated as an intravenous (IV) infusion, due to the large volume required to administer doses considered therapeutic. By concentrating the solution more than 12-fold and co-administering with recombinant human hyaluronidase (rHuPH20), an enzyme that reduces resistance in the tissue by transiently depolymerizing interstitial hyaluronan, a subcutaneous (SC) preparation of the same active molecule was made possible [12•, 13]. As the IV infusion is typically administered over a period of 1.5–6 h, the SC preparation is an attractive alternative, with shortened administration time (5–7 min) and fixed dosing (1400 mg for NHL or 1600 mg for CLL) reducing mixing time as well as waste [12•, 14].

As the active molecule is the same, the studies conducted for regulatory approval were designed to demonstrate pharmacoequivalence. The objective of the initial dose-finding phase Ib SparkThera study was to determine a SC dose that would yield a similar trough concentration as the IV at the standard dose of

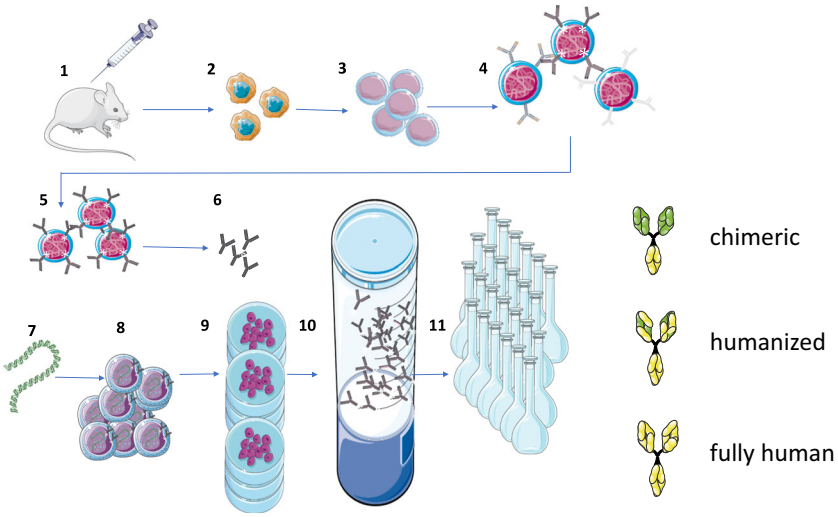

Fig. 1 Manufacture of monoclonal antibodies. 1. Immunize mouse (or other animal) with antigen of interest (human anti-CD20). 2. Isolate murine plasma cells expressing antibody targeting antigen. 3. Fuse with myeloma immortalized line of cells. 4. Generate hybridomas secreting the mAb. 5. Isolate clone producing the optimal antibody. 6. Assay antibody to ensure reactivity. 7. Clone antibody gene. 8. Express in Chinese hamster ovary cells. 9. Cell culture. 10. Bioreactor. 11. Harvest, filtration, purification, and quality control

375 mg/m^2 and a starting point for the CLL dose-finding study, SAWYER [15, 16]. The data generated suggested that even across all body surface area subgroups, the selected doses of 1400 mg for NHL and 1600 mg for CLL would result in adequate exposure compared with the IV dosing.

Pharmaco-equivalence and similar response rates compared to the IV version have been demonstrated across a number of settings: FL (SABRINA), DLBCL (MabEASE), and CLL (SAWYER), and this preparation has approval for use as induction, at relapse (FL and CLL) or as maintenance (FL) [17–19]. As the initial dose was still given IV across all the SC studies, the incidence of first-dose infusion-related reactions is unchanged, and the only significant difference in safety profile was an increase in administration-site and local cutaneous reactions [12•, 20].

While not intended to be better, in a prospective, randomized, open-label, crossover study involving 743 patients (PrefMab), 77–84% of patients reported a preference for the SC over the IV preparation. Identified reasons included "less time in clinic" and "feels more comfortable" [21]. There have also been numerous studies evaluating the impact on healthcare resource utilization. The SC preparation has been shown to reduce chair-time, preparation time, prescribing time, and waste [22–25]. A small pilot study even demonstrated the feasibility of self-administration as an outpatient with further reduction in costs [26]. Prescribers may also be reassured by the fact that SC rituximab is the same active molecule that underwent decades of evaluation in multiple clinical trials.

Next-Generation Development—Overcoming Rituximab Resistance

Investigation into the mechanism of action of rituximab led to the observation that anti-CD20 mAbs can largely be separated into two groups [27–29]. "Type I" mAbs comprise the majority (including rituximab), cause the CD20 molecule to cluster into lipid rafts on the membrane, and activate complement-dependent cytotoxicity (CDC) and possibly some degree of caspase-dependent direct cell death (DCD) (Fig. 2). The Fc portion of these mAbs is also capable of recruiting an effector immune response—antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent phagocytosis (ADP). By contrast, "Type II" mAbs do not cause clustering of CD20 into rafts, they are relatively ineffective at activating complement but evoke more potent caspase-independent DCD and are better at recruiting ADCC and ADP (Table 1) [30, 31, 34–37, 42, 43].

Despite extensive use of rituximab in the treatment of B cell–derived neoplasms, there are patients that fail to respond to initial therapy or relapse sooner than might be expected. Rituximab resistance has been somewhat arbitrarily defined lack of response during or relapse within 6 months of a rituximab-containing regimen [44]. Drivers of resistance have been extensively studied and may be tumor or host related. Exhaustion of complement, trogocytosis, lower affinity Fcgamma receptor polymorphisms, downregulation of CD20, upregulation of anti-apoptotic proteins, and host effector cell exhaustion have all been incriminated [45–48]. Strategies to overcome these mechanisms of resistance led to the development of next-generation molecules, aiming to be better than rituximab.

Ofatumumab

A fully human mAb directed against a unique epitope of the CD20 molecule, ofatumumab (OFA) was generated with a transgenic mouse and hybridoma technology [32, 49]. Postulated advantages over rituximab included the fact that it was fully human (thus less immunogenic), had a very low off-rate, and by virtue of its binding site being in closer proximity to the membrane could activate CDC more readily—with less reliance on effector mechanisms [32, 50]. In vitro, OFA demonstrated greater activity against CLL cells than rituximab and could lyse rituximab-resistant cells that expressed low levels of CD20.

It was initially approved in patients with relapsed and refractory (RR) CLL that had relapsed during or within 6 months of treatment with either a fludarabine-containing regimen or alemtuzumab. The investigator-determined overall response rate (ORR) in those refractory to fludarabine and alemtuzumab was 42%, with a median duration of response of 6.5 months [49, 51]. However, OFA in this population was later shown to be inferior to ibrutinib (IBR) with long-term follow-up of the RESONATE study (OFA vs IBR) demonstrating significantly prolonged progression-free survival (PFS) (3-year PFS, 59% vs 3%), and despite a 68% crossover, improved OS for IBR [52, 53].

In treatment-naïve patients unfit for fludarabine, OFA combined with chlorambucil (OFA+CLB) has proven superior to chlorambucil (CLB) alone [54]. It also prolonged PFS in R/R CLL compared with observation alone in a maintenance setting [55]. However, a recent meta-analysis suggested it may be a less cost-effective choice in the current era [56, 57].

So is ofatumumab *superior to rituximab*? Some debate exists over the relative importance of CDC in humans, with in vivo studies in transgenic mice suggesting effector-mediated mechanisms are the most important [58, 59••]. Available evidence from direct head-to-head comparisons with rituximab suggest that the advantages of OFA do not appear to translate into clinical superiority. In the ORCHARRD trial, patients with relapsed DLBCL were treated with DHAP (dexamethasone, high-dose cytarabine, cisplatin) combined with either OFA or RTX, and no advantage was seen between groups [60].

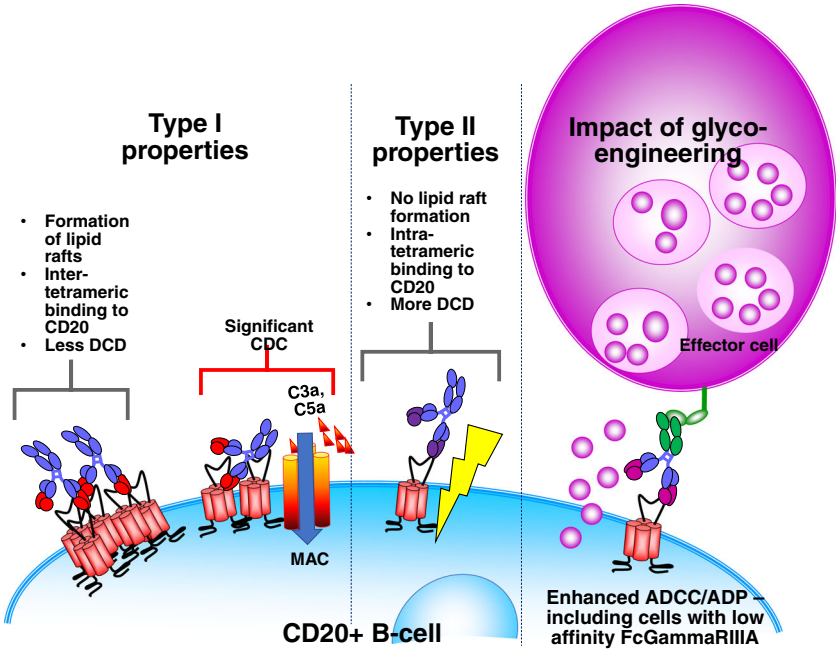

Fig. 2 Type I mAbs induce the formation of lipid rafts of CD20 and bind between tetramers, cause more complement-dependent cytotoxicity (CDC) and less direct cell death (DCD). By contrast, type II mAbs do not cause the formation of lipid rafts, nor do they significantly activate complement. They do generate more non-caspase-dependent DCD. The effect of low affinity polymorphisms of the Fcgamma receptor expressed on effector cells is thought to reduce antibody-dependent cellular cytotoxicity (ADCC). The impact of glyco-engineering the Fc portion of mAbs is to more effectively engage ADCC and antibody-dependent phagocytosis (ADP) facilitating binding and effector cell recruitment even in those patients with low affinity Fcgamma polymorphisms

Similarly, no difference was observed when patients with relapsed iNHL were randomized to single-agent OFA or RTX [61]. Both trials were closed early for futility.

Obinutuzumab

The only type II anti-CD20 mAb currently marketed, obinutuzumab (OBZ) was engineered to overcome proposed mechanisms of rituximab resistance. A humanized, rather than fully human, molecule, its type II properties together with a modified elbow-hinge region cause greater non-caspase-dependent DCD [62–64]. In contrast to RTX and OFA, it does not cause CD20 to form lipid rafts and does not significantly activate complement [27, 30, 31, 37]. Manufactured in cells with overexpression of glycosylation enzymes, the resultant antibody also has non-fucosylated sugars on the Fc portion, which improves binding to the Fc receptors and can evoke more potent responses from the host immune system (Fig. 2) [62, 65]. When compared to RTX in vitro, OBZ demonstrated greater DCD, ADCC, and ADP—regardless of the Fcgamma receptor phenotype [37, 42, 43, 62].

After demonstrating activity in single-arm studies of patients with R/R CD20–positive malignancies, OBZ underwent direct comparison with RTX across a variety of settings [66–68]. As monotherapy in R/R iNHL, investigator-assessed ORR favored OBZ over RTX (44.6% vs 33.3%; $p = 0.08$); CR rates were higher for OBZ (41.9% vs 22.7%, $p = 0.006$), but no difference in PFS was observed between groups [69]. In patients with CLL and comorbidities, compared to RTX+CLB, OBZ+CLB

Table 1 Proposed differences between type I and type II antibodies

Type I mAb	Type II mAb	Reference
Localization of CD20 into lipid rafts	No localization of CD20 into rafts	[30–33]
No homotypic adhesion	Homotypic adhesion	[30, 34, 35]
Minimal DCD	More potent DCD; largely caspase independent	[30, 34, 36–39]
Full CD20 binding capacity at saturating conditions	Half-maximal CD20 binding at saturating conditions	[32, 37]
Prominent CDC	Minimal CDC	[32, 37, 40, 41]

DCD, direct cell death; *CDC*, complement-dependent cytotoxicity

demonstrated significant prolongation of PFS (28.9 vs 15.7 months; $p < 0.0001$) and OS (median not reached vs 73.1 months; HR, 0.76; $p = 0.02$) [70, 71].

In patients with treatment naïve, advanced stage symptomatic FL, OBZ-chemo vs RTX-chemo (followed by maintenance with the randomized antibody in responding patients) prolonged investigator-assessed 3-year PFS (82% vs 75%; $p = 0.002$) although end-of-induction response and OS were not statistically different between groups [72, 73]. The benefit of OBZ over RTX in prolonging PFS and time-to-next-anti-lymphoma treatment (TTNALT) was seen regardless of chemotherapy backbone used (bendamustine, CHOP, or CVP); however, a higher proportion of fatal adverse events was reported in patients treated with bendamustine. The majority of these events occurred during the maintenance phase, in patients more likely to be older or with comorbidities, and bendamustine induction was associated with greater reduction in CD4+T-cells [72]. These results have led some to question the use of maintenance following bendamustine induction with any anti-CD20+ mAb and also the use of bendamustine in older, frailer patients [74]. For patients with previously untreated DLBCL, two phase III randomized trials (GOYA and GAINED) failed to demonstrate any advantage of OBZ over RTX combined with standard chemotherapy [75, 76].

The rationale for the selected dosing schedule of obinutuzumab has been extensively reviewed elsewhere [46, 77]. In preclinical experiments, obinutuzumab was superior to rituximab in causing DCD, ADCC, and lymphocyte depletion when identical concentrations of both agents were used. Further increasing the concentration of rituximab demonstrated a plateau in activity, which was not observed for obinutuzumab [37, 62, 78]. Furthermore, at saturating concentrations, obinutuzumab bound to B cells at levels approximately 50% less than rituximab. Taken together, preclinical evidence might suggest that for an equal antigenic mass, less obinutuzumab is necessary to evoke cytotoxicity and less is taken up by the antigenic "sink" of the tumor compared with rituximab [46, 62]. Regardless, the dosing strategy for obinutuzumab does result in the administration of more antibodies (Table 2) which is of similar molecular weight to rituximab [46]. If dose does matter, this would confer an advantage to obinutuzumab in the head-to-head comparative trials. However, as discussed, it may be the case that rituximab, more than obinutuzumab, has a dose-related ceiling of efficacy.

Is obinutuzumab better than rituximab? It does appear to be a more potent antibody with higher rates of minimal residual disease (MRD) negativity observed compared to RTX in both patients with CLL (CLL-11) and FL (GALLIUM) [70, 81]. Capitalizing on the ability to generate deep responses, combinations of OBZ with venetoclax (Bcl2 inhibitor) in CLL patients have demonstrated very impressive results with ORR ranging from 90 to 100% and MRD-negativity rates in peripheral blood of 87–92% [82, 83]. Further analysis of GALLIUM in FL suggests that OBZ-chemo reduces the risk of early progression compared with RTX-chemo by 34% at 2 years, potentially improving outcomes for the highest risk "POD-24" cohort that has been well described [84, 85]. There also may be a subset of DLBCL patients with increased expression of germinal-center genes that benefit from OBZ more than RTX [86]. However, the increase in adverse events (in particular infusion-related reactions and cytopenias) observed with OBZ compared with RTX along with the inevitable increase in cost (compared to subcutaneous rituximab or biosimilars) has led to great debate regarding its role.

Ublituximab

Like rituximab and ofatumumab, ublituximab (UBX) has type I properties, but targets a different epitope of the CD20 molecule and has, similar to obinutuzumab, been glyco-engineered [87]. Pre-clinically, UBX demonstrates similar levels of CDC and DCD compared with RTX, but enhanced ADCC was demonstrated—even in RTX-resistant cell lines [87–89]. Initial dose-finding investigation was promising, and the 900 mg dose was selected to move forward in a number of studies investigating its use combined with novel agents in R/R CD20+ lymphoproliferative neoplasms [90, 91].

Combination with a next-generation oral PI3Kδ/CK1ε inhibitor, umbralisib (TGR-1202) as well as ibrutinib (a chemotherapy-free "triplet") has been evaluated in a phase 1 setting enrolling patients with R/R NHL [92]. The combination of umbralisib (TGR-1202) and UBX ("U2") is also under evaluation in the three-arm UNITY-NHL phase 2b randomized trial (NCT02793583). The global registration directed UNITY-CLL phase 3 randomized trial (NCT02612311) is enrolling both treatment-naïve and R/R CLL patients and randomizing to U2 or OBZ plus CLB, similar to the CLL-11 trial. This agent has not yet received regulatory approval.

Is ublituximab better than rituximab? In vitro evidence suggests it may harbor some advantage, but without any direct comparisons to rituximab in the clinical setting, it may prove challenging to answer this question with any certainty.

Biosimilars—Making a Cost-Effective Alternative

With an estimated global expenditure of US$100 billion per annum on anti-cancer medicines, predicted to rise to $150 billion by 2020, comes a universal push to reduce spending by facilitating biosimilars [93]. The Food and Drug Administration (FDA) recently released an action plan to increase the availability of biosimilars, given that biologics represent 70% of the increase in drug spending between 2010 and

Table 2 Comparison of cumulative doses of obinutuzumab and rituximab in head-to-head clinical trials, from [46]

Clinical trial	Cumulative obinutuzumab dose	Cumulative rituximab dose	Reference
GAUSS	4000 mg	‡2700 mg	[69]
(induction – monotherapy for R/R iNHL)			
GAUSS	16,000 mg	‡10,800 mg	[69]
(monotherapy induction + ¶maintenance for relapsed iNHL without progression post induction)			
CLL-11	8000 mg*	5,175 mg*	[70]
(previously untreated CLL-with comorbidities unsuitable for fludarabine, combined with CLB)			
GALLIUM induction phase	8000 mg*	4526.5 mg*	[73]
(previously untreated FL – G-chemo vs R-chemo)			
GALLIUM maintenance phase	12000 mg*	7679 mg*	[73]
(previously untreated FL in a PR or greater post induction)			
GOYA	10,000*	5133.5*	[76, 79]
(previously untreated DLBCL – G-CHOP vs R-CHOP)			

*Median cumulative doses administered reported in supplementary material that accompanies each referenced publication

‡Based on an estimated average BSA from [80]

¶Assuming full-planned maintenance administration

2015 and the global biosimilars market is predicted to reach US$35 billion by 2020 [94, 95].

In order to claim that a molecule is *biosimilar* to the authorized reference product, it must be shown to have very similar structure, biological activity, efficacy, safety, and immunogenicity profile [96]. The European Medicines Association (EMA), which has been approving biosimilars since 2006, recommends rigorous evaluation—both pre- and post-approval [97]. Pre-clinically, high similarity in chemical and biological characteristics must be demonstrated. Clinical similarity then must be evaluated against the comparator directly. Trials should be designed to prove non-inferiority of both efficacy and safety against the reference product. There is also a post-approval commitment required to generate ongoing "real-world" evidence. Once biosimilarity has been demonstrated, data may be extrapolated to other indications already approved for the reference product, theoretically avoiding unnecessary repetition of trials already performed.

It is important to highlight several challenges regarding the development of biosimilars. As outlined earlier, the manufacturing process for these large molecules is highly complex, and differences in structural features such as fucosylation and protein folding can have significant impact on biological activity [96, 98••]. Even for rituximab, small changes in the glycosylation pattern have appeared over time and changes in the manufacturing process (site transfers, scale changes, etc.) have been found to alter the commercially available product [99].

Proprietors of the patented reference molecule are not obliged to disclose the exact details of their production process. Therefore, biosimilar manufacturers must develop their own methods, then demonstrate that the generated biosimilar exhibits comparable structural and functional properties prior to commencing further clinical evaluation [98••]. This does allow the biosimilar companies to capitalize on technical advances since the reference product was first developed.

The confirmatory clinical trials that support the approval of a biosimilar have been allowed to use ORR as a surrogate endpoint [97]. In the past, trials involving RTX or next-generation mAbs have used a variety of clinical endpoints including PFS, event-free survival, TTNALT, and OS. ORR is understandably an attractive endpoint—outcomes may be rapidly and easily obtained, expediting access to market for the biosimilar. Careful post-marketing follow-up will be crucial to ensure that response rates for biosimilars translate into meaningful longer term clinical outcomes. Finally, not all countries have the same regulatory approval process which means that not all biosimilars will be subjected to the same degree of pre- and post-approval scrutiny.

GP2013 (Rixathon)

GP2013 is a rituximab biosimilar that has been developed in accordance with EMAs guidance, including non-clinical and preclinical investigations and subsequent trials in rheumatoid arthritis and FL. In treatment-naïve–advanced-stage FL patients, equivalence was demonstrated between rixathon-CVP and RTX-CVP with ORRs 87% vs 88% respectively [100].

Follow-up was quite short at only 11.6 months. Safety, tolerability, and immunogenicity profiles were similar between groups. This was sufficient for EMA to issue broad approval for the biosimilar across all indications currently held for rituximab—although with the caveat that it "is subject to additional monitoring" [101].

CT-P10 (Truxima)

Similar to GP2013, CT-P10 has demonstrated its similarity with RTX pre-clinically and also underwent phase III randomized evaluation in previously untreated FL patients with advanced-stage disease. In this smaller study of 140 patients, ORR in the efficacy population was non-inferior at 97% in CT-P10 plus CVP arm vs 93% in the RTX-CVP arm. Again, no differences in pharmacokinetic properties, safety, or immunogenicity were demonstrated, and this has also led to a broad approval in Europe similar to rixathon [102].

Reditux

This intended biosimilar has been marketed since 2007 in India and was produced by the Indian generic manufacturer, Dr. Reddy's. Its launch price was 50% less than the originator and within 3 years of approval, had increased access for patients in India by sixfold [103]. India is a semi-regulated pharmaceutical market, and clinical trials required for approval of biosimilars only require evidence of safety and biologic equivalence. Reditux does have a different chromatography profile than rituximab and production differences between the two molecules exist. Approval in India was based on a single-arm clinical trial involving 17 patients [103, 104]. More recently, a limited retrospective evaluation has suggested a similar pharmacokinetic profile, toxicity, and response rates in DLBCL patients [105–107]. Since the launch of reditux in India, the manufacturer sought approval in other semi-regulated countries like Peru [103]. At the current time, reditux cannot seek approval in Europe or North America because of respective regulations governing biosimilars.

What is the role of biosimilars? If truly bioequivalent, the main advantage of biosimilars is cost. In an analysis performed to investigate the impact of replacing RTX with CT-P10 (truxima), assuming a reduction in acquisition cost by just 30%, data suggested savings across Europe could exceed €90 million within 12 months and projected a €570 million saving by 3 years, potentially giving an additional 47,695 patients' access to treatment [108]. 43.3% of the savings would come from the treatment of NHL and 19.8% from treating CLL. Authors noted their estimate for the price of CT-P10 might be conservative, with greater savings possible based on increasing competition and associated reductions in price.

Conclusion

Since its approval more than 20 years ago, rituximab has dramatically changed the treatment landscape for patients with CD20+ lymphoid malignancies and has been included in the WHO model list of essential medicines [109]. As a result of its impressive efficacy, but also high price, it remained the highest grossing anti-cancer therapeutic through to 2016 [3]. With the development of next-generation mAbs, subcutaneous rituximab, and biosimilars, clinicians (and payers) will have more options to consider. With respect to next-generation molecules, the proposed advantages of the frontrunner obinutuzumab over rituximab will need to be weighed against the higher toxicity profile, IV-only formulation, and greater cost. Switching to a biosimilar for many practicing around the globe may provide a practical option, particularly for those practicing in developing countries, where the current cost of cancer treatment often exceeds the average per capita income by many multiples [110]. As further data emerges, it will be important for clinicians to be informed with respect to the potential advantages, risks, and cost-effectiveness of available CD20 mAbs, such that they can optimize treatment selection.

Compliance with Ethical Standards

Conflict of Interest Ciara L. Freeman has received research funding through grants from Roche and Genentech, has served on advisory boards for AbbVie and Celgene, and has received honoraria for service as a consultant from Seattle Genetics.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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