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REVIEW

Use of anti-CD20 therapy in follicular and marginal zone lymphoma: a review of the literature

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Abstract

The identification of the CD20 antigen in 1979 was the first step in what would become a therapeutic milestone opening the use of immunotherapy in hematological diseases. This protein is expressed on the surface of developing B cells, but not the early progenitors or mature plasma cells. In 1997, rituximab was approved by the Food and Drug Administration, and since then it has revolutionized the treatment of B-cell malignancies. It is used as a monotherapy and in combination, at induction, at relapsed, and also in maintenance. Indolent non-Hodgkin lymphomas are characterized by a long and non-aggressive course. In this group of lymphomas, rituximab represented a great therapeutic improvement, achieving lasting responses with few adverse effects. Nowadays, second-generation molecules are emerging that may have important advantages compared to rituximab, as well as biosimilars that represent an important cost-effective option.

Keywords: anti-CD20, biosimilars, immunotherapy, indolent non-Hodgkin lymphoma

Citation

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Introduction

Hematologic B-cell malignancies represent a vastly heterogeneous group of lymphoproliferative diseases, encompassing about 85% of all non-Hodgkin lymphomas (NHLs).[1] Wide ranges of disorders are included in this group, from slow-growing indolent non-Hodgkin lymphomas (iNHLs), to more aggressive entities, such as diffuse large B-cell lymphomas (DLBCLs).

A variety of entities are included in the iNHLs group, such as follicular lymphoma (FL), marginal zone lymphoma (MZL), or non-aggressive mantle cell lymphoma (MCL). The iNHLs are incurable,[2] and their natural history is characterized by a long course, where relapses and progressive resistance to treatments define the disease. Until the last decade of the 20th century, treatments were based on a combination of chemotherapy (CT) regimens, achieving response rates of around 50%.[3] During the 1990s, the landscape of iNHL was revolutionized by the approval of CD20-directed monoclonal antibodies (mAbs). mAbs became a standard component of care for B-cell lymphoproliferative disorders in general, and iNHL in particular. In recent years, the development of biologic mAbs (biosimilars) has emerged and will play a leading role in the management of these disorders.

In this paper, we will discuss the role of mAbs in FL and MZL along with reviewing the current data about the use of biosimilar mAbs in these diseases. We performed literature searches with PubMed and Google Scholar focusing on FL and MZL. Due to the scope of this paper, CLL has been excluded from the discussion.

Overview of anti-CD20 monoclonal antibodies

Rituximab is a chimeric murine–human anti-CD20 constituted by heavy and light chain variable region sequence (murine) and an IgG1 kappa constant region sequence (human). Initial studies that allowed the development of ritxuimab began in 1975, but it would not be until 1997, when the US Food and Drug Administration (FDA) approved it for use in

relapsed/refractory NHL. The trials published by Maloney[4] and McLaughlin[5] were the pivotal studies for its approval. The study by McLaughlin and colleagues showed an overall response rate (ORR) of 48% and a median time to progression of 13 months. Subsequently, in 1998, rituximab was also approved by the European Medicines Agency (EMA).

The CD20 antigen is a transmembrane protein expressed mainly on healthy (late pre-B and mature) and malignant B cells, becoming an appealing target in NHLs as neither pre-B hematopoietic stem cells nor plasma cells show it on their surfaces.[6] The physiological role of the antigen is not well described, and it is not reported as a natural ligand for this protein. Nevertheless, Walshe and colleagues presented a possible influence of CD20 on calcium ion influx.[7] The toxicity of anti-CD20 therapy is limited and also preserves a stem cell pool, which is necessary for B-cell regeneration after treatment.[8]

The mechanisms responsible for the death of CD20+ cells by anti-CD20 mAbs rituximab specifically involve four different pathways, with the immune system playing an important role in three of them. Direct antitumor impact represents the only mechanism without a patient immunity role. The induced cell death is caspase-dependent and also independent, leading to cell elimination.[9] The caspase-mediated apoptosis requires the involvement of sac family kinases in a process triggered by the rearrangement of lipid rafts after the rituximab–CD20 binding.[10]

Immune system-related effector mechanisms are complement-dependent cytotoxicity (CDC) and Fcγ receptor (FcγR)-mediated effects. FcγR is expressed on several immune cells such as neutrophils, macrophages, and natural killer (NK) cells. Signaling through FcγR triggers antibody-dependent cell-mediated cytotoxicity (ADCC) and cell-mediated phagocytosis (ADCP).[11] The classical pathway of complement is responsible for the CDC activity due to binding between C1q and rituximab. Thus, this junction induces an increased constitution of membrane attack complex, enhanced phagocytosis activity secondary to opsonization, and greater recruitment of other effector immune components.[12] The ADCC pathway drives a cytotoxic response that is NK-cell mediated after the interaction between the mAb by the Fc region and the effector cell (FcγRIII). Activated NK cells cause the death of targeted cells by permeabilization of the membrane (releasing perforin granules) and inducing programmed cell death (via caspase mechanisms prompted through granzyme B).[13,14]A possible adverse effect of the CDC on the ADCC mechanism has been reported as both compete for the mAb–CD20 complex. *In vitro* studies show greater CDC activity with rituximab; however, *in vivo* models reported that ADCC is more effective.[15] Therefore, the overall impact of CDC on rituximab antitumor effect needs further data. Lastly, ADCP occurs when mAb interacts with other FcγRs enrolled on macrophages, monocytes, and neutrophils surface, leading to the phagocytosis of targeted cells.

Besides other modes of action, some data suggest the possibility of T-cell-mediated immune effects against tumor antigens triggered by rituximab. This could be the reason for late responses despite the removal of the mAbs.[16] In fact, an increase of T cells targeting specific idiotypes of FL cells has been reported following rituximab treatment.[17] These findings support the theory of a fifth mechanism, the 'vaccinal effect'.

The concept of rituximab relapsed/refractory patients has been postulated by several authors in different trials.[18,19]

A variety of resistance mechanisms to anti-CD20 mAbs (in particular rituximab) have been postulated. Most of them involve the effector pathways (CDC, ADCC, and ADCP). Some membrane proteins are complement inhibitors such as decay-accelerating factor (DAF) (CD55), membrane cofactor protein (MCP) (CD46), or CD59 that decrease the CDC activity.[20] Apoptosis could be impaired in extended rituximab treatments by disturbances in expression of pro-apoptotic BCL-2 proteins.[21] Clonal selection has been hypothesized as a resistance pathway due to the lack of CD20 expression in malignant cells as well as the tumor microenvironment (intake of immune mediators).[11] Trogocytosis, or shaving reaction, encompasses the elimination of the rituximab–CD20 formation from the surface of targeted cells, leading to the survival of those malignant cells.[22] In addition, mAbs–CD20 complexes could also be internalized and cleared as triggered by FcγRIIb.[23]

Development of new mAbs has been stimulated by the need to find new approaches for patients with relapse/resistance to rituximab. Ofatumumab was the first of these new mABs. It is a humanized mAb against the same antigen; however, the junction to CD20 is in a different location than rituximab making a tighter union that is longer lasting.[24] Due to its structural characteristics (CD20-mAb complex closer to the cell membrane surface),[25] and the more avid binding to C1q ofatumumab presents higher CDC compared to rituximab.[26] Despite the superior *in vitro* activity,[27] efficacy results of ofatumumab in monotherapy in refractory FL patients were minimal. The NCT00394836 study presented an ORR of 11% and 5.8 months for progression-free survival (PFS).[28] Outcomes obtained with ofatumumab in combination with CT (NCT00494780 trial) are considered equivalent to those who received rituximab–CT treatment.[18,29] Consequently, approval by the FDA (in 2009) for its use was only in chronic lymphocytic leukemia (CLL) patients.

Obinutuzumab is another anti-CD20 mAb developed with the intention to bypass rituximab-resistance mechanisms. Obinutuzumab has demonstrated a superior B-cell depleting activity in peripheral blood and lymphoid tissue in non-human primate models, along with greater antitumor efficacy *in vivo* (tumor regression).[30,31] Since then, clinical trials have been performed, leading to its approval by the FDA (in 2013) for CLL patients. [1823] After the first indication in CLL, the results of the phase III GADOLIN trial, in 2016, with obinutuzumab plus bendamustine was approved for relapsed/refractory FL patients treated with a rituximab-containing regimen.[32] More recently, obinutuzumab has been approved for frontline treatment of FL on the basis of the GALLIUM trial.[33]

Obinutuzumab is also a humanized mAb with some structure variations that make it different from rituximab. The Fc

Table 1. Anti-CD20 monoclonal antibodies (mAbs) currently approved for use in oncology settings.

Generic name	Brand name	Format	Type	Indication	FDA/EMA approval date
Rituximab	MabThera, Rituxan	Chimeric IgG1	Type I	NHL	1997/1998
Ofatumumab	Arzerra	Human IgG1	Type I, binds small CD20 loop.	CLL	2009/2010
Obinutuzumab	Gazvya Gazyvaro	Humanized IgG1	Type II glycomodified	CLL R/R FL FL	2013/2014 2016/2016 2017/2017

CLL, chronic lymphocytic leukemia; EMA, European Medicines Agency; FDA, Food and Drug Administration; FL, follicular lymphoma; IgG, immunoglobulin G; NHL, non-Hodgkin lymphoma; R/R, relapsed or refractory.

portion is optimized by glycoengineering technology, allowing an increased binding affinity to the FcγR on immune effector cells.[24] The development of this Fc sequence is based on the studies of 2002, that reported an FcγR polymorphism (FcγRIIIa–158V), which implies greater binding affinity to IgG. Some authors also described an improvement in clinical response in those cases.[34] Although both CD20 epitopes recognized by rituximab and obinutuzumab are close to each other, the different binding orientation from the latter confers an improved activity.[35] The variations lead to an increase in ADCC and ADCP functions as well as a higher direct cell death induction than rituximab.[36] This last pathway is a non-apoptotic mechanism being independent of caspases and Bcl-2. Rather, it depends on the release of lysosomal enzymes on the target cell.[37] CDC capacity is decreased as it has a different Fc portion that does not activate it.[30]

In treating patients today, two types of mAbs against CD20 are used. Type I, such as rituximab or ofatumumab characterized by a potent CDC effect due to its capacity to translocate CD20 into lipid rafts of the plasmatic membrane. Afterward, C1q recruitment is encouraged and the complement cascade is activated.[3] Also, each type I mAbs can bind two CD20 tetramers, whereas type II mAbs are not able to bind more than one.[30] Conversely, type II mAbs like obinutuzumab do not have the ability to aggregate CD20–mAb complexes, showing a decreased CDC activity overcome by stronger ADCC/ADCP effect just as direct cell death.[30]

New formulations of anti-CD20 mAbs have been designed. Subcutaneous rituximab (Rituxan™ in the USA and MabThera SC™ in the European Union) had shown non-inferiority results in terms of pharmacokinetics, safety, and efficacy compared to the intravenous rituximab as well as the efficacy and safety profiles. The drug is combined with recombinant human hyaluronidase that allows the administration of higher concentrated volumes of the anti-CD20 in the skin. Serum trough concentrations of subcutaneous rituximab, the lowest concentration reached before the administration of the next dose, was non-inferior in comparison to intravenous formulation.[38,39] Likewise, in the SABRINA trial, ORRs were similar in both arms (subcutaneous *versus* intravenous).[32] The subcutaneous rituximab has a fixed dose 1400 mg that could be administrated in 5 minutes as opposed to the intravenous (IV) infusion (375 mg/m^2), which can take multiple hours to administer. The subcutaneous rituximab can be a substitute after the first dose of IV rituximab for patients, if preferred.

With deeper understanding of different mAbs, physicians will be able to make better decisions in treatment choices for patients with iNHL. Table 1 summarizes the different mAbs and their approved indications.

Clinical impact of anti-CD20 in B-cell FL and MZL treatment

Follicular lymphoma

Follicular lymphoma is the most common B-cell lymphoma representing almost 20% of NHL. It has a long natural history, with multiple relapses, despite having a long median survival.

Observation continues to be the appropriate measure for asymptomatic patients with low bulk disease and no cytopenias (no GELF criteria). For patients needing therapy, most patients are treated with chemoimmunotherapy, which has improved response rates, duration of response and overall survival (OS). The OS of patients with FL has improved significantly since the introduction of rituximab.

Initial treatment of advanced stage disease

FL was the first hematologic entity with anti-CD20 rituximab treatment indication by the FDA in 1997. The first phase II study included 37 patients with relapsed lymphoma receiving rituximab at a weekly dose of 375 mg/m^2 for 4 weeks. Clinical response was observed in 17 patients (46%) of whom three reached complete remissions with a median time to progression of 10.2 months. Low toxicity and side effects were observed.[40] Another multicenter phase II/III study with

166 patients with relapsed FL obtained responses in 48% of cases with a time to progression of 13 months. All these data confirmed the efficacy and safety profile of rituximab.[6] During the following years, other studies confirmed these results.[41–43]

The benefit of rituximab combination with CT regimens in the treatment of FL was demonstrated in several studies, such as by Czuczman and colleagues. This group included 40 patients with FL who received six cycles of CHOP in combination with 6 infusions of rituximab. The overall response was of 95%, with a CR of 55% and PR of 40%, with a median duration of response and time to progression not reached after 29 months of study follow-up. About 74% of patients continue in remission during the follow-up period. This study demonstrated the benefit of the combination of rituximab with CT, enhancing the responses without adding significant toxicity.[44]

The use of rituximab combined with different CT schemes, such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), cyclophosphamide, vincristine, and prednisone (CVP), CVPH–interferon, bendamustine, all in the first-line of treatment in FL obtained high response rates and prolonged remissions.[45–48]

Bendamustine plus rituximab (B–R) has been compared to R–CHOP in a phase III randomized trial in 513 patients with indolent lymphoma, the majority of which were FL.[47] The median PFS was superior for the B–R arm (69.5 *versus* 31.2 months), with less toxicity. No difference in the OS was observed at a median follow-up of 45 months.

In 2014, Flinn and colleagues published the results of their BRIGHT study where the combination of B–R was non-inferior to R–CHOP and R–CVP with B–R having similar complete and ORRs.[49] The PFS was longer in the B–R group, but OS was similar, and more second malignancies were observed in patients treated under this combination.

All of these trials have demonstrated improved response rates, time to progression, and OS in the rituximab plus CT arms. Due to a large amount of scientific evidence, rituximab in combination with CT has positioned itself as the worldwide first-line standard treatment.

The utility of rituximab in the FL maintenance and rescue treatment has been shown as well. The role of maintenance treatment increases PFS but does not have a great impact on OS. The largest study designed to confirm rituximab maintenance was the PRIMA study (multicentric, international, randomized), with 1217 untreated FL patients included. These patients received immunochemotherapy according to the routine practice of each participating medical center. The patients (n=1019) who achieved response (CR or PR) were randomized in two arms: to 2-years maintenance with rituximab at 375 mg/m^2 every 8 weeks or observation. A total of 505 patients received maintenance, and 513 were assigned to the observation branch (one patient died during randomization). With a median follow-up of 36 months, the PFS was 74.9% (95% CI: 70.9–78.9) in the maintenance arm with rituximab and 57.6% (53.2–62.0) in the observation group. There was no significant difference in OS between both groups (HR: 0.87, 95% CI: 0.51–1.47). The presence of grade 3–4 side effects was of 24% of cases in the arm of rituximab and 17% in the observation. Infections were the most frequent side effect occurring in 39 and 24%, respectively.[50] In 2017, the results of the 10-year follow-up PRIMA study were published. The median PFS in the observation arm was 4.60 years and, in the maintenance, rituximab was 10.49 years (Log-Rank, $p<0.01$; HR: 0.6, 95% CI: 0.52–0.73). At 10 years, 51% of patients in the arm of rituximab and 35% in the observation arm were free of progression.[51]

Another randomized phase III trial using fludarabine, cyclophosphamide, and mitoxantrone examined whether abbreviated maintenance with rituximab had clinical benefit in patients ages 60–75 with previously untreated FL.[52] No statistically significant PFS benefit was observed.

Vidal and colleagues, in 2017, published the results of an individual patient data (IPD) meta-analysis including all the randomized studies of rituximab in maintenance in FL patients with the purpose to demonstrate the benefit of this strategy in the OS. A total of seven clinical trials, with 2315 patients included, were analyzed. The median age of all patients was 57 years (range 23–87). In all the trials, the vast majority of patients had advanced stage disease. Most patients received induction that included CT. Induction CT was CHOP based in 62% of the patients, CVP based in 23% of the patients, and fludarabine-based CT in 15% of patients with no difference between the patients randomized to maintenance rituximab (MR) and no MR. Induction included rituximab for 74% of patients in the IPD analysis. Median follow-up was 6 years. This meta-analysis demonstrated an OS benefit with MR treatment compared with no maintenance expressed as the number needed to treat being 29 patients to prevent 1 death within 5 years. Once again, improvement in the OS was observed in patients who received maintenance with rituximab compared with patients in observation (HR: 0.79, 95% CI: 0.66–0.96), but no clinical or disease characteristics associated with a greater benefit of maintenance were detected.[53] PFS was longer with MR treatment in all subgroups and models. The major toxicity was the increased risk of infection. Despite this study, the benefit in OS of maintenance with rituximab is still questionable.

The RESORT study is a clinical trial that was designed to compare maintenance with rituximab (MR) *versus* retreatment (RR) with rituximab in patients with low-tumor burden FL. Subjects were treated with 4 weekly doses of rituximab, and then subsequently randomized to either observation and retreatment at progression or rituximab maintenance for 2 years. A total of 289 patients were randomized to the RR or MR arms; with a median follow-up of 4.5 years, the median time estimated for treatment failure was 3.9 years in those who received RR and 4.3 in those who received MR ($p=0.54$). There was no difference in time to cytotoxic therapy, but it did show a possible favor in the MR arm. In patients with low-tumor burden FL, the strategy of re-treatment with rituximab

produces control of the disease comparable to that obtained in patients who received maintenance with rituximab.[54] More studies are needed to better determine maintenance with rituximab *versus* retreatment as an option in the future.

Phase II studies combining rituximab with lenalidomide (R2) showed that this combination is a good alternative compared to immunochemotherapy due to the low toxicity associated.[55] The RELEVANCE study is a phase III randomized study comparing rituximab–lenalidomide (R2) with R–CT in patients with FL, but not previously treated. A total of 1030 patients with high tumor burden were randomized to receive R2 (n=513) or R–CT (n=517, 72% R–CHOP, 23% R–B, 5% R–CVP). With a median follow-up of 37.9 months, it was impossible to establish the superiority of R2 *versus* R–CT.[56]

A significant number of patients with FL develop a disease refractory to rituximab over time. Both ofatumumab and obinutuzumab were developed to try to improve survival in these patients.

Treatment of relapsed or refractory (R/R) FL

Treatment for R/R FL ranges from rituximab alone, novel agents plus rituximab, combination R–CT, radioimmunotherapy and, for selected patients, stem cell transplantation.

Lenalidomide plus rituximab (R2) *versus* placebo plus rituximab has been studied in relapsed and refractory FL patients, and the results have been published under the AUGMENT trial name. The ORR was higher with the combination (70 *versus* 53%), and also the time to progression (1 year longer for the R2 regimen). Improved median PFS was observed for the combination (39 and 14%, respectively), with non-statistically significant improvement in OS.[57]

Several new humanized anti-CD20 mAbs have been studied in patients with R/R FL.

The study of ofatumumab published by Czuczman, in 2012, includes patients with FL refractory to rituximab, who received 8 weekly infusions of ofatumumab at a dose of 300 mg and subsequently 7 doses of 500 mg or 1000 mg. The overall response was 13% for the 500 mg dose and 10% for the 1000 mg dose. The ORR for the total population was 11%. Among patients refractory to rituximab as monotherapy, the overall response was 22%. The PFS was 5.8 months and 9.1 months in those who reduced the tumor mass in the first 3 months, with a good safety profile. The study demonstrates modest activity in highly pretreated patients with rituximab regimens.[22]

Obinutuzumab was approved in February 2016 for patients with relapsed or refractory FL to any regimen containing rituximab. The phase III GALLIUM study analyzed the utility of obinutuzumab in the first-line treatment in FL. Patients were randomized to receive induction treatment with obinutuzumab plus CT or rituximab plus CT and subsequently to 2-year maintenance with the anti-CD20 received in the induction. A total of 1202 patients were recruited with a median follow-up of 34.5 months. The arm of obinutuzumab presented a lower risk of progression, relapse, and death than the arm of rituximab (estimated ratio of 3-year PFS of 80 *versus* 73.3%; HR for progression, relapse, or death 0.66, 95% CI: 0.51–0.85; p=0.001). The response ratios were similar in both groups (88.5% with obinutuzumab and 86.9% with rituximab). Side effects were more frequent in the obinutuzumab arm (74.6 *versus* 67.8%).[27]

The value of obinutuzumab *versus* rituximab and post-induction maintenance appear to be relatively modest. However, one must be taking into account the POD24 concept (progression/relapse of FL within 24 months of chemoimmunotherapy) as a surrogate endpoint. In the case of obinutuzumab, the reduction in POD24 was associated with a 34% reduction in the risk of a PFS event at 24 months relative to R-chemo, including a marked reduction in the number of POD24 events. Post-progression survival for POD24 patients appeared to be similar in the two arms. 27.[33]

Another phase III study (GADOLIN) showed greater efficacy of the association of bendamustine plus obinutuzumab followed by maintenance with obinutuzumab *versus* bendamustine monotherapy, in refractory to rituximab FL patients.[31] An update of this study reported a benefit in the OS of bendamustine plus obinutuzumab and confirmed the benefit in the PFS.[58]

The lack of a survival benefit in this trial, the potential for increased toxicity (possibly connected, in part, with bendamustine use), and the requirement for maintenance therapy may have limited the adoption of obinutuzumab by some clinicians as part of initial FL treatment. Rituximab and obinutuzumab remain reasonable options as part of an upfront chemoimmunotherapy strategy for FL.

Marginal zone lymphoma

Marginal zone lymphomas are a group of rare hematologic malignancies, representing around 5–17% of all NHLs.[59] MZLs are subdivided into three different entities: extranodal MZL (EMZL) also known as mucosa-associated lymphoid tissue (MALT) lymphoma, splenic MZL (SMZL), and nodal MZL (NMZL).[60] These disorders share some morphological and immunophenotypic features whereas differ in other matters such as clinical presentation, molecular background, prognosis, and treatment approach.[61] A standard of care has not been established, and management for other iNHLs such as FL has been extrapolated as well as experience from retrospective series until randomized clinical trials will be performed.

There are no specific criteria in treatment choices for MALT lymphomas and it is usually individualized. In localized cases with microbial involvement, the eradication therapy could provide disease regression.[62] In those localized cases that fail to respond to antimicrobial treatment, radiation is a good alternative. In the 5-year analysis of the IELSG-19, the addition of rituximab to chlorambucil improved the event-free survival (EFS) and the CR compared to chlorambucil in monotherapy (68 *versus* 50%, p=0.002; 78 *versus* 65%, p=0.025, respectively).[63] For advanced-stage patients, rituximab–CT combinations have

to be considered. In the MALT2008-01 trial, EFS at 2 and 4 years after rituximab and bendamustine as front-line treatment were 93 and 88%, respectively.[64,65]

Different treatment approaches have been proposed for SMZL patients. A 'Watch & Wait' strategy is accepted for those asymptomatic patients, as other iNHLs.[66] If a patient presents with symptomatic splenomegaly, cytopenias, or B symptoms,[67] a variety of approaches can be used. Splenectomy, CT, rituximab, and combinations of the last two have all shown efficacy. Surgical removal of the spleen was the standard of care until the anti-CD20 mAbs development. Splenectomy achieved better survival rates than the other alternative (alkylating drugs);[68] however, rituximab approval changed this landscape. In a retrospective study, treatment with rituximab in monotherapy (6 weekly doses plus 1 to 2 years of bi-monthly infusions as maintenance) provides a 5- and 10-years OS of 93 and 85%, respectively. Whereas, freedom from progression rates at 5 and 10 years were 71 and 74%, respectively.[69] These results support the use of rituximab instead of splenectomy (historical data) as a greatly effective approach. Clinicians should determine the best treatment for their patients on a case-by-case basis.

Rituximab became the standard of care in this disease as front-line treatment. In disseminated or relapsed cases, combination therapy of rituximab–CT could be an option.[70] Furthermore, some studies show that the addition of CT to rituximab did not increase its efficacy.[71] Encouraging results have been observed in the recent first prospective trial (BRISMA study) that evaluates the B–R regimen, as first-line treatment, in 56 SMZL patients.[72] In this phase II trial, the 3-year PFS and OS rates were 90 and 96%, respectively. Therefore, B–R became an attractive option, being necessary in studies that compare it with rituximab in monotherapy. Obinutuzumab has demonstrated its efficacy in iNHLs, but no trial on SMZL has been performed to date.

With NMZL, the start of the treatment depends on the symptom burden or the existence of organ impairment. Thus, a 'Watch & Wait' strategy is recommended for asymptomatic patients, whereas in localized disease, radiotherapy is preferred.[73] In symptomatic cases, approaches in other iNHLs and MZLs are extrapolated. Therefore, combinations of CT and rituximab are used. Some retrospective series including NMZL patients reported 5-year PFS rates between 35 and 47% and OS rates around 55–85%.[74] Bendamustine could also be administrated with rituximab. However, studies carried out in NMZLs are needed, and we only have the scope of some subgroup analyses from studies in iNHL. Laribi and colleagues performed a retrospective study of this scheme as first line of treatment in 14 NMZL patients. Despite the small number of individuals, results are compelling with a FFS of 93% and OS of 100% after 22 months.[74]

In MZLs, the use of rituximab is mainly 'off label' as it is not officially approved. It is still recommended by numerous consensus guidelines. Recent studies in iNHLs include MZL patients without subgroup distinctions.[48,49] The lenalidomide–rituximab combination has been approved in relapsed/refractory MZL due to the AUGMENT trial results in May 2019, although no PFS difference was reported among treatment arms in the MZL patients.[57]

Biosimilar mAbs

A biosimilar is a biologic product produced using the same gene, which is highly similar to an approved biologic product. There must not be clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency.[75]

The development of a biosimilar is different from the process applied to a new biologic. The manufacturing process for the originator biologic belongs to the proprietary; therefore, a pharmaceutical company developing a potential biosimilar must analyze the originator extensively and use reverse engineering to develop a biologic product with a highly similar structure and function. The main issue is the difficulty of reproducing an identical chemical structure of complex proteins; many of them are produced using a biologic process which, in some cases, requires production in living cells.[76]

Clinical performance of biologic drugs may be affected by minor post-translational structural modifications due to the manufacturing process. In that sense, to develop a potential biosimilar requires substantial knowledge and expertise regarding the development and manufacture of biologics, allowing a biologic product with similar clinical efficacy and safety as the originator (Table 2).

With an estimated global expenditure of US$100 billion per annum on anticancer medicines and a prediction to rise to $150 billion by 2020, we must feel obligated to reduce spending by facilitating biosimilars.[77] Different Regulatory Offices around the world released an action plan to increase the availability of biosimilars, given that biologics represent 70% of the increase in drug spending between 2010 and 2015, and the global biosimilars market is predicted to reach $35 billion by 2020.[78,79]

Rituximab as the first mAb in hematology is also one of the first to encounter competition from biosimilar products as its patent expires. As rituximab plays an important role in the treatment of several hematological diseases, biosimilars represent an opportunity for less-expensive therapeutic development (Table 3).

The patent for rituximab expired in Europe, in 2013, and will expire in the USA in 2018; therefore, biosimilars are in development and emerging (e.g. Truxima™, Rixathon™/Riximyo™ approved in Europe).[80,81] The biosimilar therapeutic mAbs approved in the EU, the USA, and Japan are listed in Table 4.

In the process of developing rituximab biosimilar, structural evaluations of amino acid sequence and higher-order structure are performed. Likewise, the glycosylation state, the binding affinity, and the cell-killing efficacy of *in vitro* CDC and ADCC separately are characteristics that are evaluated as part of the approval

Table 2. Comparison of data for approval of an innovator product and a biosimilar.

Risk management plan	Risk management plan
Clinical studies • PK/PD • Safety and efficacy • Immunogenicity	COMPARATIVE clinical trials • PK/PD • Safety and efficacy • Immunogenicity
Non-clinical trials	COMPARATIVE non-clinical trials
Quality characterization	Quality characterization
	COMPARATIVE quality studies

PD, pharmacodynamic; PK, pharmacodynamic.

Table 3. Comparison of rituximab and biosimilars.

Considerations	Rituximab	Biosimilars
Time (years)	7–12	3–5
Phases of research	Discovery, development, preclinical, and clinical trial phases I–III consecutive	Development, preclinical, and clinical trial phases I–III
Estimated cost	1 billion	100 million

Table 4. Rituximab biosimilar mAb approved in the European Union, the USA, and Japan.

Innovator product	Biosimilar	Trade name	Company
MabThera	Rituximab	Truxima, Blitzima, Ritemvia, Rituzena,	Celltrion
MabThera	Rituximab	Riximyo, Rixathon	Sandoz
Rituxan	Rituximab BS1	Rituximab BS intravenous infusion (KHK)	Kyowa Hakko Kirin

process of a biosimilar drug. In the absence of surrogate markers for efficacy, it is usually necessary to demonstrate comparable clinical efficacy of biosimilars and the reference product in adequately powered, randomized, comparative clinical trials. Biosimilars generally require fewer clinical trials and, therefore, a shorter timeframe for approval. This is especially favorable for countries that have limited access to the original compounds or have a shortage of products. The confirmatory clinical trials that support the approval of a biosimilar have been allowed to use ORR as a surrogate endpoint.[82] In the case of past clinical trials with rituximab, different clinical endpoints including PFS, EFS, and OS were indicated.

Careful post-marketing follow-up will be crucial to ensure the response rates that biosimilars translate into meaningful longer-term clinical outcomes.

The biosimilars that are currently in the market are:

A) BCD-020: The market name is AcellBia and is the first mAb biosimilar developed in Russia. Some data report comparable results to the parent drug about pharmacokinetics/pharmacodynamics (PK/PD), safety, and efficacy.
B) CT-P10: Known as Truxima™, it is the first biosimilar to be granted marketing authorization by the EU in 2016. A phase I and a phase III trial were done to confirm safety, similar PK/

PD, and efficacy. Truxima™ was also tested in FL patients. These were randomized to either R–CVP or biosimilar-CVP. The ORR was 97.3% in the CT–P10–CVP group and 92.6% in the R–CVP, meeting the point of non-inferiority. These results led to the approval by the EMA for all rituximab indications.

C) GP2013: Or Rixathon™, is also approved for use in the EU, and is the second rituximab biosimilar for which an FDA application has been submitted in the USA. A phase III study (ASSIST-FL) included 629 untreated, advanced FL patients, who were randomly assigned to either R–CVP or GP2013–CVP. ORR was 87% with GP2013 and 88% with rituximab.

D) HLX01: It is a biosimilar produced in China, and has been tested in a clinical trial in DLBCL and severe RA. Since 2015, several clinical trials have been developed to determinate PK/PD of this biosimilar relative to rituximab. In 2016, CHOP with HLX01 was compared with R–CHOP in DLBCL to ensure similar efficacy.

Despite rituximab's long history of a successful application, much remains to be discovered. Until now, issues like the mechanism of cell killing *in vivo* or the ideal dosage schedules remain without a complete explanation. Likewise, there are no biomarkers to reliably predict the type of patients who will benefit from rituximab, or its inclusion in combination therapies. This scenario makes assessing next-generation anti-CD20 and rituximab biosimilars a challenging goal, providing opportunities for improvement as the relative efficacies of that new mAbs are evaluated (Table 4).

Conclusions

The profound and revolutionary impact of anti-CD20 mAbs on modern medical therapeutics is undisputed. The role of CD20 mAbs is well known and its use seems more than assured in the short term, and new developments in this area abound.

New generations of CD20 targeted drugs with better activity and properties modulation that may augment their clinical efficacy and safety are appearing as the result of modern pharmaceutical engineering methods. These novel therapy combinations also offer potential synergistic benefits to overcome resistant disease or improve response rates. Development of biosimilar mAbs is expected to decrease medical expenses and make it easier for patients to access medicines needed for treatment. Biosimilars are evaluated using rigorous analyses of the potential biosimilar *versus* the originator biological to confirm the similar structure, function, and clinical efficacy as well as safety. Biosimilars of rituximab may provide a practical option, particularly in developing countries. New data published will be important for clinicians to be informed of potential advantages, risks, and cost effectiveness of available CD20 mAbs to optimize the treatment. Ublituximab, a type I anti-CD20 with similar pharmacokinetics as obinutuzumab, is coming into the landscape. The initial dose was selected to move forward in several studies investigating its use combined with novel agents in R/R CD20 lymphoproliferative neoplasm. Currently, phase III studies are enrolling patients.

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