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Scientific rationale for extrapolation of biosimilar data across cancer indications: case study of CT-P10

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For a biosimilar to gain regulatory approval, a comprehensive comparability exercise must demonstrate that it is highly similar to its originator biologic, or reference product. Once biosimilarity has been shown, it is possible to approve the biosimilar for additional indications held by the reference product, without clinical trials in these indications. Extrapolation of clinical data is permitted by regulatory agencies as long as it is scientifically justified. CT-P10, a biosimilar of rituximab, was recently approved in Europe for all indications held by its reference product, incorporating both autoimmune diseases and hematological cancers. Here, we review the scientific rationale for extrapolation in biosimilar development using the example of CT-P10 as a case study.

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Biosimilars are highly similar versions of already licensed biologic products and represent a unique class of drugs requiring specific considerations for regulatory approval. Indeed, biosimilars undergo an expedited development and approval process that differs from that for novel or 'originator' biologics but that, nonetheless, are highly rigorous [1–6]. This process includes head-to-head comparisons of the biosimilar versus its reference product in all the stages of nonclinical and clinical evaluation that originator biologics pass through during their development, plus a comparative quality assessment. With respect to clinical trials, the nature and extent of the data required to approve an individual biosimilar depend on several factors, including: the level of evidence supporting biosimilarity in analytical, *in vitro* and, if performed, nonclinical *in vivo* studies; the occurrence of particular safety issues associated with the originator drug (or 'reference product') and the potential for extrapolation across indications. In this context, the term 'extrapolation' refers to the approval of a biosimilar for one or more additional indications held by the reference product, without the need for clinical trials of the biosimilar in those indications (Figure 1).

The general concept of extrapolation, for example from adult to pediatric patient populations or between drugs within the same class, is accepted as scientifically logical by key regulatory bodies, including the EMA and the FDA. In its concept paper on the extrapolation of efficacy and safety in medicine development, the EMA defines extrapolation as follows: "Extending information and conclusions available from studies in one or more subgroups of the patient population (source population), or in related conditions or with related medicinal products, to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the need to generate additional

KEYWORDS

• biosimilars • chronic lymphocytic leukemia • CT-P10 • diffuse large B cell lymphoma • extrapolation • follicular lymphoma • non-Hodgkin's lymphoma • rituximab • totality of evidence

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Figure 1. The role of indication extrapolation in biosimilar development. The pathways to approval of originator biologics and biosimilars are in some ways alike, involving the collection of analytical, *in vitro*, nonclinical *in vivo* and then clinical data. However, establishment of biosimilarity in comparative studies versus the originator biologic (or 'reference product'), alongside appropriate scientific justification, can permit 'indication extrapolation', allowing approval in all indications with fewer clinical studies.

PD: Pharmacodynamic; PK: Pharmacokinetic.

information (types of studies, design modifications, number of patients required) to reach conclusions for the target population, or condition or medicinal product” [7]. The EMA (and others) recognize that this process avoids unnecessary, and therefore unethical, clinical trials and encourages allocation of resources in areas where studies are most needed. For biosimilars, extrapolation reduces the burden of the development process, thereby potentially shortening the time to market and resulting in lower development costs that can be passed on in terms of reduced pricing. In this article, we discuss the scientific rationale for extrapolation in biosimilar development using the example of CT-P10 as a case study. For background, we begin by briefly discussing the general requirements of regulatory authorities with respect to extrapolation.

When is extrapolation permitted?

For approval of a biosimilar to be extrapolated across indications, regulators require: sufficient nonclinical and clinical data to prove biosimilarity to the reference biologic (often referred to as the ‘totality of evidence’); and scientific justification for extrapolation from source-to-target populations [4–6]. In practice, this requires collection of extensive nonclinical data comparing the structure and function of the biosimilar and reference product, as well as the performance of randomized controlled trials in an indication (or indications) considered sufficiently sensitive to detect clinically meaningful differences in efficacy or safety between the biosimilar and its reference product (if such differences were to exist). Scientific justification for extrapolation is often multifaceted and nuanced but usually centers on demonstrating either that the mechanisms of action and clinical profile of the reference product are the same in the source and target populations, or why any such differences between source and target populations would not be expected to result in clinically meaningful differences between biosimilar and reference product in the target population(s) [4]. If the molecular mechanism of action of the reference product is different across indications, or the contribution of different mechanisms is unknown, additional pharmacological data will be required to justify extrapolation and provide assurance that the two products will behave in a similar manner in the extrapolated indications [1]. Furthermore, special consideration may be required to justify extrapolation of immunogenicity data as there

are numerous influencing factors that can differ among indications, such as route of administration and concomitant medications [1].

Approval of CT-P10 in Europe

CT-P10 (Truxima®; CELLTRION, Incheon, Republic of Korea), a biosimilar of the anti-CD20 monoclonal antibody rituximab, was recently approved in Europe for all indications held by reference rituximab (MabThera®; Roche, Basel, Switzerland), including non-Hodgkin’s lymphoma (NHL) and chronic lymphocytic leukemia (CLL) [8]. Thus, CT-P10 became the first monoclonal antibody biosimilar therapy approved for use in hematological cancers (and in oncology in general). In NHL, CT-P10 is approved for use in combination with chemotherapy in previously untreated patients with stage III–IV follicular lymphoma (FL), as maintenance therapy in patients with FL responding to induction therapy, and in combination with CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisolone) in patients with CD20-positive diffuse large B cell lymphoma (DLBCL). It can also be used in combination with chemotherapy in treatment-naïve and relapsed/refractory CLL. Non-oncological indications are rheumatoid arthritis (RA) and granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) [8].

As we briefly discuss in the next section, approval of CT-P10 was based on the totality of evidence collected in analytical, *in vitro* and nonclinical *in vivo* experiments plus clinical data from randomized controlled trials in patients with RA and advanced FL. These trials demonstrated that there were no clinically meaningful differences between CT-P10 and reference rituximab (abbreviated hereafter as ‘RTX’) in these patient populations. Approval of CT-P10 in other indications held by RTX, including DLBCL and CLL, was based on extrapolation of data from these trials.

Establishing the biosimilarity of CT-P10 & reference rituximab

A comprehensive three-way comparability exercise was performed to fully characterize the structural and physicochemical properties of CT-P10 relative to both US-sourced and EU-sourced RTX (Rituxan® [Genentech, CA, USA] and MabThera, respectively) [8,9]. These analytical studies demonstrated a high degree of similarity between CT-P10 and both forms

of RTX [8]. *In vitro* biological and functional analyses also demonstrated comparable CD20-binding affinities and complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC) and apoptosis-inducing activities [8,10].

Randomized controlled studies compared the pharmacokinetics (PK), efficacy, safety and immunogenicity of CT-P10 and RTX in patients with RA and advanced FL [10–16]. Briefly, PK equivalence of CT-P10 and RTX was demonstrated in Phase I and III trials in patients with RA [10,12]. Efficacy profiles were also highly similar in this population, with the Phase III trial demonstrating therapeutic equivalence in terms of reductions in disease activity scores between baseline and week 24 [10,13]. The safety and immunogenicity profiles of RA patients treated with CT-P10 or RTX were also comparable [10,12–13]. B cell kinetics in patients with RA treated with CT-P10 or RTX were also shown to be similar: there was a reduction in median B cell count to below the lower limit of quantification at 4 h post-treatment, which remained low until the last measured end point at 24 weeks [10]. In patients with untreated advanced FL, the PK of CT-P10 and RTX was determined to be equivalent when each was given in combination with cyclophosphamide, vincristine and prednisone (CVP) chemotherapy [11]. Pharmacodynamic analyses up to treatment cycle 4 in this patient population showed that B cell levels decreased below the lower limit of quantification shortly after cycle 1 and subsequently remained low in both treatment groups. Safety and immunogenicity profiles up to cycle 4 were also comparable between groups [11].

Scientific rationale for extrapolation of CT-P10 clinical data across indications

As we have described, extrapolation from one indication of a reference product to another in which the biosimilar has not been clinically tested is permitted if the totality of evidence supports biosimilarity and it is scientifically justified. In the case of CT-P10, the decision of the EMA to approve it for all indications held by its reference product was based on the totality of evidence showing biosimilarity between CT-P10 and RTX in nonclinical evaluations and in clinical trials in RA and advanced FL, as well as on the further scientific justifications described below [8].

• Selection of source populations

Selection of the patient populations recruited to CT-P10 clinical trials involved careful consideration. According to regulatory guidelines, biosimilars should be evaluated in indications that are sufficiently sensitive to detect clinically meaningful differences in efficacy or safety between biosimilar and reference product. As there is a long history of RTX use in RA [17], there were extensive clinical data with which to define and validate efficacy equivalence margins for the statistical comparison of CT-P10 with RTX; similarly, the history of use of RTX in FL provided sufficient data on which to predict efficacy in that population. Ultimately, RA and FL populations were considered adequately sensitive to detect meaningful differences between CT-P10 and RTX. The EMA also recommends that, for clinical studies assessing biosimilarity, the source population should be homogenous [5]. Therefore, the selection of FL as a source population for trials comparing CT-P10 and RTX in patients with cancer was considered particularly appropriate as, compared with the biologically and clinically diverse DLBCL for example, FL is a relatively homogenous disease.

• Similarity in pathology between RA & B cell-related malignancies

A significant factor that permitted cross-indication extrapolation for CT-P10 is the primary role of B cells in the pathogenesis of RA and certain hematological malignancies [18,19]. In RA, B cell checkpoints that monitor self-tolerance are defective, leading to the accumulation of autoreactive B cells that promote leukocyte infiltration into joints, causing inflammation of the synovial membrane and bone destruction [18,20]. In B cell-related hematological malignancies, defective apoptosis and altered survival signaling of B cells leads to their accumulation in the blood or lymph nodes [19].

• Rituximab mechanisms of action

RTX is a monoclonal antibody that binds with high specificity to CD20. This cell surface antigen is present on normal and malignant B cells during cell maturation and antigen-stimulated activation but absent on lymphoid stem cells and plasma cells [21,22]. The benefit of targeting CD20 in B cell malignancies was first realized almost three decades ago [23], and led to RTX becoming the first monoclonal antibody

Figure 2. Main mechanisms of action of rituximab. Rituximab can deplete B cells through direct induction of apoptosis and activation of the immune effector mechanisms CDC and ADCC. ADCC: Antibody-dependent cell-mediated cytotoxicity; CDC: Complement-dependent cytotoxicity; MAC: Membrane attack complex.

approved for the treatment of cancer in the USA in 1997 and Europe in 1998. Depletion of B cells by CD20-bound rituximab has primarily been attributed to CDC, ADCC and apoptosis (Figure 2) [22,24–25]. Comprehensive literature searches have not identified evidence suggesting a difference in the CD20-mediated effects of RTX between autoimmune and oncology indications. However, the clinical significance of each mechanism within each RTX indication remains to be determined. Importantly, *in vitro* functional analyses of CT-P10 have demonstrated that it has highly similar CDC, ADCC and apoptotic activity compared with RTX [8,10]. Analyses of functional end points, potency and binding affinity relating to apoptosis, CDC and ADCC conducted using samples from patients with NHL and CL also supported CT-P10 indication extrapolation to oncology indications from data obtained in RA [8].

Complement-dependent cytotoxicity

Rituximab is a type I CD20 monoclonal antibody, with *in vitro* analyses showing it can bind to the complement component C1q and trigger the classical complement pathway [26,27]. This capability is dependent on the redistribution

of CD20 into lipid rafts within the target cell membrane, which is thought to make the cell more vulnerable to complement attack [26]. However, although some *in vivo* studies have indicated that this mechanism is important for the therapeutic effects of rituximab [28,29], others have found no evidence that complement is necessary for the drug's ability to deplete B cells [30]. Furthermore, the expression of complement inhibitors (CD46, CD55 and CD59) on tumor cells did not correlate with clinical outcome following rituximab treatment in patients with FL or CLL [31,32]. Therefore, although it is clear that rituximab can induce CDC, the importance of this mechanism in the therapeutic effects of the drug is not certain [24,25]. Furthermore, some evidence suggests that the CDC activity of rituximab is related to CD20 expression levels [33]. CLL cells are known to express lower levels of CD20 compared with FL, and it has been suggested that this may explain the poorer responses of CLL to rituximab [34]. This may not invalidate extrapolation between indications, however, as it is likely that other mechanisms (e.g., ADCC) may act in a complementary fashion [33].

Antibody-dependent cell-mediated cytotoxicity

ADCC depends upon recognition of the bound anti-CD20 antibody on the B cell surface by fragment crystallizable γ receptors (Fc γ Rs) present on natural killer cells [35]. These cells become activated through their Fc γ R and release cytotoxic granules to kill the antibody-coated CD20-positive cell. Evidence for the role of ADCC in the therapeutic activity of rituximab comes from correlations of receptor polymorphisms and drug responses. Genomic polymorphisms affect the affinity of Fc γ R for the Fc portion of the anti-CD20 antibody, and thus affect the killing activity of effector cells [36]. For example, a single nucleotide polymorphism in one form of the Fc γ R (Fc γ RIII) has been correlated with rituximab efficacy in FL [37] and RA [38]. This suggests the importance of Fc-mediated ADCC in effective therapy. However, the clinical relevance of such polymorphisms for rituximab immunotherapy on longer-term survival across B cell malignancies is still unclear, particularly when administered in combination with chemotherapy [39–41]. In particular, high-affinity variants were not associated with better responses in patients with CLL or DLBCL, suggesting other modes of action of rituximab such as CDC and apoptosis are more important in these cancers [39,41]. *In vitro* functional analysis has demonstrated that the FcRn-binding affinities of CT-P10 and RTX show almost identical equilibrium dissociation constants [8,10].

Cell signaling & apoptosis

Evidence suggests that direct ligation of CD20 by rituximab can impact intracellular signaling, leading to inhibition of antiapoptotic and survival signaling pathways [42]. This has been shown to induce apoptosis in CLL cells [43]. Inhibition of pathways, including the NF- κ B, by rituximab has also been shown to sensitize lymphoma cells to cytotoxic drugs [44]. Further *in vitro* analysis that used a modified rituximab that lacked the Fc fragment determined that these rituximab-mediated effects were Fc-independent, without the need for FcR cross-linking, and occurred as a direct result of rituximab binding to CD20 [45]. Although these studies suggest a role for rituximab in promoting cell death, the contribution of this mechanism to the clinical therapeutic effects of rituximab across indications is still unclear.

Conclusion

Extrapolation is fundamental to the biosimilar concept. It efficiently reduces the number of clinical trials that are needed, which allows the regulatory process to be expedited. This can lead to price reductions compared with innovator biologics and potential savings for healthcare systems. The EMA-approved CT-P10 for all indications held by RTX based on the evidence of biosimilarity demonstrated in the comprehensive comparability assessment, which included clinical trials in patients with RA and FL. Extrapolation to CLL, GPA, MPA and DLBCL was scientifically justified based on the strength of clinical data in the source populations, the similarity of disease pathology across indications and the known mechanisms of action of rituximab in B cell-related cancers and autoimmune diseases.

Future perspective

It is expected that postauthorization surveillance of CT-P10 will further support the EMA's decision to approve the biosimilar in all indications held by RTX. Such evidence will also provide confidence for clinicians, patients and healthcare providers in CT-P10 and biosimilars in general. As patent expiry of other biological therapies is reached, it is inevitable that these too will be followed by the approval and introduction of biosimilar versions into clinical practice. Strict adherence to published guidelines that recognize the importance of scientific justification will ease the potential safety concerns in cross-indication extrapolation, and will aid in the regulatory approval and market uptake of biosimilars.

Financial & competing interests disclosure

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EXECUTIVE SUMMARY

Background

- Extrapolation refers to the approval of a biosimilar for one or more additional indications held by the reference product, without the need for clinical data in those indications.

When is extrapolation permitted?

- Extrapolation is permitted by regulatory agencies as long as it is scientifically justified.

Approval of CT-P10 in Europe

- CT-P10 is a biosimilar of rituximab, an anti-CD20 monoclonal antibody approved for use in autoimmune and cancer indications.
- CT-P10 was approved for all indications held by reference rituximab based on the totality of evidence collected in the comprehensive comparability exercise.

Establishing the biosimilarity of CT-P10 & reference rituximab

- *In vitro* structural, physicochemical, biological and functional analyses have demonstrated that CT-P10 and reference rituximab are highly similar.
- Phase I and III randomized controlled trials have demonstrated pharmacokinetic equivalence between CT-P10 and reference rituximab and comparable efficacy, safety, pharmacodynamics and immunogenicity in patients with rheumatoid arthritis.
- Pharmacokinetic equivalence of CT-P10 and reference rituximab and comparable safety, pharmacodynamics and immunogenicity have also been shown in patients with advanced follicular lymphoma.

Scientific rationale for extrapolation of CT-P10 clinical data across indications

- Rheumatoid arthritis was an appropriate indication in which to compare CT-P10 with reference rituximab as it was considered adequately sensitive to detect clinically meaningful differences in efficacy and safety between products.
- B cells play a primary role in the pathology of disease for all indications of reference rituximab. The ability of CT-P10 and reference rituximab to deplete B cells is highly comparable.
- Depletion of B cells by rituximab has been attributed to complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity and apoptosis.
- The contribution of these mechanisms across indications is uncertain. However, it has been demonstrated that CT-P10 and reference rituximab are comparable in their ability to induce these activities.

Conclusion

- Based on the totality of evidence, the EMA concluded that CT-P10 was highly similar to reference rituximab and that it was scientifically justified to approve the biosimilar for all indications held by the reference product.

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• of interest; •• of considerable interest

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