Regulatory Note

Is Extrapolation of the Safety and Efficacy Data in One Indication to Another Appropriate for Biosimilars?

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Received 31 July 2013; accepted 19 September 2013; published online 11 October 2013

Abstract. CT-P13, the world's first biosimilar monoclonal antibody to infliximab, was approved for marketing in South Korea for all the six indications of infliximab, which Europe may follow, although the product was tested only in rheumatoid arthritis (RA) with a limited pharmacokinetic comparison in ankylosing spondylitis. However, the extrapolation of the efficacy and safety findings of CT-P13 in RA to the other indications appears scientifically challenging when assessed by the current regulatory requirements. RA is not a sensitive clinical model to detect potential differences between CT-P13 and infliximab, and other mechanisms of action than antagonizing tumor necrosis factor α appear to be also important, which could be different by the approved indications. Furthermore, the immunogenicity and safety profiles of CT-P13 were not sufficiently characterized in that immunogenicity potential was lowest in RA, which was even further suppressed by the concomitant use of methotrexate. Extrapolation of the safety and efficacy data in one indication to another may be inappropriate for biosimilars unless backed up by strong scientific justification, which may include the mechanistic exposure–relationship approach. Therefore, regulatory agencies need to exercise caution before granting extrapolated indications to biosimilars.

KEY WORDS: biosimilars; CT-P13; extrapolation of indication; infliximab; regulatory agency.

INTRODUCTION

In July 2012, the Korea Food and Drug Administration (KFDA, currently the Korean Ministry of Food and Drug Safety) approved CT-P13 (Remsima®, Celltrion), the world's first follow-on monoclonal antibody claimed to be biosimilar to infliximab (Remicade®, Janssen Biotech) (1). A year later, the European Medicines Agency (EMA) also recommended the marketing authorization of CT-P13 (2). The approval or recommended approval of CT-P13 was based on a single equivalence trial conducted in patients with rheumatoid arthritis (RA) (3), supplemented by a pharmacokinetic study on ankylosing spondylitis (AS) (4). What was unique about this approval was that four other indications of infliximab (i.e., Crohn's disease, ulcerative colitis, psoriatic arthritis, and plaque psoriasis) were granted to CT-P13 although the product was not tested in these indicated populations.

According to KFDA, it may be possible to extrapolate the efficacy and safety data of the follow-on biological product in one indication to the other indications of a reference biological product when *all* of the following conditions are met (5): (1) a sensitive clinical test model has been used that is able to detect potential differences between the follow-on and reference products; (2) the clinically

relevant mechanisms of action and/or the involved receptors are the same for the different indications; and (3) the safety and immunogenicity profiles of the follow-on product have been sufficiently characterized. The same requirements are found in the guidance by the World Health Organization (WHO) (6), whereas the US FDA appears to require more strict and detailed criteria for extrapolation across indications (e.g., *the most* sensitive clinical condition to detect clinically meaningful difference not only in efficacy, but also in safety including immunogenicity; caution for different safety risk profiles across indications due to different comorbidities and concomitant medications; added shield against different toxicities based on off-target effects as well as the enhanced pharmacological activity of the product; and scientific justification in terms of the pharmacokinetics and bio-distribution of the product in different patient populations) (7). EMA also provides a legal mechanism for possible extrapolation to other indications (8) (Table I). The objective of this paper is to discuss whether CT-P13 met the extrapolation requirements by the regulatory agencies, particularly KFDA, based on existing scientific and clinical data.

EXTRAPOLATION REQUIREMENTS

Is Rheumatoid Arthritis a Sensitive Clinical Model?

If the difference in efficacy between a treatment and placebo is small, it is difficult (i.e., less sensitive) to show a difference between the treatment and another treatment similar to that even

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Table I. Summary of Concerns and Current Thoughts of FDA, EMA, and WHO (KFDA) Regarding Extrapolation of Clinical Data for Follow-on Biological Products

Concern	FDA	EMA	KFDA (WHO)
MOA may be distinct in each therapeutic indication.	Extrapolation will be considered on a case-by-case basis. Where the MOA differs between indications or are not fully understood, separate clinical trials are likely to be necessary.		The clinically relevant mechanisms of action and/or the involved receptors should be the same for the different indications.
For a given MOA, several mechanisms may exist.	Almost superimposable biological data must be provided, covering all functional aspects of the agent, even if not considered clinically relevant. Where MOA are not fully understood, separate clinical trials are likely to be necessary.		See above.
Risk of undertreating patients/varied safety profiles in different patient groups.	Data should be produced using a patient population and clinical endpoint most sensitive to detect clinically meaningful differences in efficacy and safety.		A sensitive clinical test model should be used that is able to detect potential differences between the follow-on and reference products. The safety and immunogenicity profiles of the follow-on product should be sufficiently characterized.
Individual patient characteristics may influence the response.	Careful consideration must be given to comorbidities/concomitant medications and intersubject variability.	Homogeneous population should be used—differences in response can then be attributed to the biosimilar.	

Modified from a table by T. Dörner *et al.* (37) as courtesy

FDA Food and Drug Administration, EMA European Medicines Agency, KFDA Korea Food and Drug Administration, WHO World Health Organization, MOA mechanism of action

if there is. Suppose that there is a 20% clinically significant difference in efficacy between a reference product and its follow-on product. If the placebo-adjusted efficacy of the reference product is sufficiently large, e.g., 50 with 100 being the maximum attainable efficacy, the 20% difference will be 10, which may be detected rather easily. However, if the placebo-adjusted efficacy of the reference product is only 5, the difference that needs to be detected becomes extremely small (i.e., 1). To detect such a small difference with a sufficient power, the trial has to enroll a huge number of subjects; otherwise, the trial will not be sensitive enough.

That is why the noninferiority (or equivalence) margin for follow-on products should be narrow when the difference in efficacy between a reference product and placebo is small (9). The margin cannot be greater than the placebo-adjusted treatment effect of a reference product, often referred to as “M1” or the largest margin. Therefore, a narrow margin can offset the insensitiveness of a noninferiority or equivalence trial when the placebo-adjusted efficacy of a reference product is small. From the regulator’s point of view, this is reasonable because it can guard against the consumer risk of erroneously declaring the follow-on product to be noninferior or equivalent when, in fact, it is inferior or nonequivalent, respectively, to a reference product.

Of the six indications of infliximab, the greatest placebo-adjusted response was found in plaque psoriasis, followed by psoriatic arthritis and Crohn’s disease (Table II). In contrast, RA was associated with the smallest placebo-adjusted response to infliximab (8–25%, Table II). Given that “widely differing protein levels have the same clinical effect” for therapeutic proteins (10), the dosing in RA may be less than optimal to be sensitive enough. In fact, the label-recommended dose of infliximab in RA is 40% lower than the one in the other indications for both induction and maintenance regimens (i.e., 3 vs. 5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks, respectively) because infliximab is used as an add-on treatment in conjunction with methotrexate (11). However, additional efficacy was

obtained with infliximab doses of >3 mg/kg in RA, e.g., up to 42% placebo-adjusted response (12,13), which was 1.7 times as large as that seen with 3 mg/kg. The increased efficacy with higher doses of infliximab is also reflected in the label, which recommends “for some patients... increasing the dose up to 10 mg/kg or treating as often as every 4 weeks” (11).

In the equivalence study on CT-P13 in RA, CT-P13 or infliximab was given at a lower induction and maintenance doses of 3 mg/kg at 0, 2, and 6 weeks and then every 8 weeks throughout the entire study period, respectively (3). In this equivalence study, the 95% confidence interval for the treatment difference between CT-P13 and infliximab in the primary endpoint (i.e., ACR20 response at week 30) was –6% to 10% and –4% to 12%, respectively, for the intention-to-treat and per-protocol populations. Thus, these confidence intervals contained the smallest placebo-adjusted response to infliximab shown previously (i.e., 8%), although they fell within the range of the equivalence margin of –15% to 15%. In other words, RA is likely to be a less, if not the least, sensitive clinical model to detect a potential difference in efficacy between CT-P13 and infliximab, particularly as studied in the equivalence trial of CT-P13. Therefore, the similar efficacy between CT-P13 and infliximab in RA may not rule out the possibility that the efficacies of the two products are in fact different in other extrapolated indications, in which such differences can be more easily detected because they are more sensitive clinical models than RA.

Is Antagonizing Tumor Necrosis Factor Alpha the Same Mechanism of Action in All the Approved Indications of Infliximab?

The mechanism of action of therapeutic monoclonal antibodies is multifaceted, which has been only partially elucidated (14). Although both infliximab and etanercept antagonize tumor

Table II. Efficacy of Infliximab in the Approved Indications

Indication	Study	Efficacy Endpoint	Week	Response, %		
				Infliximab	Placebo	Difference ^a
Crohn's disease	Targan <i>et al.</i> (18)	Clinical response	4	81	16	65
		Clinical response	12	41	12	29
	ACCENT I (15)	Clinical remission	30	42	21	21
	Present <i>et al.</i> (16)	Fistula response	6	68	26	42
	ACCENT II (17)	Fistula response	54	46	23	23
Ulcerative colitis	UC I (38)	Clinical response	8	69	37	32
		Clinical response	30	52	30	22
		Clinical response	54	45	20	25
	UC II (38)	Clinical response	8	65	29	36
		Clinical response	30	47	26	21
Rheumatoid arthritis	ATTRACT (12)	ACR20	54	42	17	25
		ACR50	54	21	9	12
		ACR70	54	11	2	9
	ASPIRE (13)	ACR20	54	62	54	8
		ACR50	54	46	32	14
		ACR70	54	33	21	12
Ankylosing spondylitis	ASSERT (39)	ASAS20	24	61	19	42
		ASAS50	24	47	12	35
		ASAS70	24	28	4	24
Psoriatic arthritis	IMPACT 1 (40)	ACR20	16	66	10	56
		ACR50	16	46	0	46
		ACR70	16	29	0	29
	IMPACT 2 (41)	ACR20	24	54	16	38
		ACR50	24	41	4	37
		ACR70	24	27	2	25
Plaque psoriasis	EXPRESS (30)	PASI 75	10	80	3	77
	EXPRESS II (29)	PASI 75	10	76	2	74
	SPIRIT (42)	PASI 75	10	88	6	82

ACR20, ACR50, and ACR70 American College of Rheumatology 20%, 50%, and 70% response criteria, respectively; ASAS20, ASAS50, and ASAS70 Assessments in Ankylosing Spondylitis 20%, 50%, and 70% response criteria, respectively; PASI75 75% reduction in the Psoriasis Area and Severity Index score

^a Placebo-adjusted difference (i.e., infliximab–placebo) in percentage point

necrosis factor alpha (TNF- α), this shared mechanism of action does not translate into similar efficacy. For example, infliximab is efficacious in Crohn's disease (15–18), whereas etanercept is not (19) even though both infliximab and etanercept are effective to treat RA (12,13,20). Even for the same monoclonal antibody, different mechanisms of action other than antagonizing TNF- α appear to be prevailing in the treatment of Crohn's disease and RA. For instance, infliximab induced apoptosis of inflammatory cells in Crohn's disease (21), whereas it did not exert the same effect in RA (22). Furthermore, infliximab attaches to and inhibits membrane-bound TNF- α much stronger than etanercept (23). This stronger target affinity of infliximab may lead to several intracellular mechanisms of action, which makes extrapolation of the efficacy and safety data of infliximab scientifically more challenging (24). Collectively, these findings suggest that the clinically relevant mechanisms of action for infliximab, and thereby for CT-P13, could differ by the approved indications.

Have the Safety and Immunogenicity Profiles of CT-P13 Been Sufficiently Characterized?

Antidrug antibodies or unwanted *immunogenicity* is a primary safety concern for biologics, and follow-on products are not an exception (25,26). For example, a minor change in the manufacturing process of an erythropoietin product caused the

generation of autoantibodies to endogenous as well as exogenous erythropoietin, drastically increasing the incidence of pure red cell aplasia, a rare but fatal anemic condition (27). Similarly, after treatment with infliximab in Crohn's disease, antibody-positive patients were 2.9 times more likely to experience infusion reactions than antibody-negative patients (28).

Therefore, the regulatory agencies require that the immunogenicity profile of follow-on products be sufficiently characterized before extrapolation to other indications is sought (5–8). Furthermore, the immunogenicity profile should be studied “in the patient population that carries the highest risk of an immune response and immune-related adverse events” (emphasis added) (6). This requirement is scientifically justified as discussed in the previous section, i.e., the population with the highest immune response will be the most *sensitive* population to detect a possible difference in immunogenicity (7). In the same vein, a population for which immunogenicity is suppressed by any measure may not serve as a basis for extrapolation to other indications (6).

The proportion of patients developing immunogenicity after treatment with infliximab varied widely by indication; it was highest in Crohn's disease (up to 61%) (28) and ranging between 20 and 51% in psoriasis (29,30). RA, however, is the indication in which the smallest proportion of patients developed antibodies to infliximab (~10%), mostly at a low titer

(12,13,31,32). This low immunogenicity in RA may be related to co-administered methotrexate, an immunosuppressant (28). In other words, RA is not only a less sensitive population for detecting a difference in immunogenicity, but also an inappropriate population for extrapolation due to the mandatory use of methotrexate in addition to infliximab. Therefore, the immunogenicity profile of CT-P13, investigated mainly in RA, may not be extrapolated to the other indications of infliximab. This means that the safety profiles of CT-P13 in patients with Crohn's disease, ulcerative colitis, psoriatic arthritis, and plaque psoriasis may differ from those with RA.

CONCLUSION

As exemplified in the case of CT-P13, a follow-on infliximab, extrapolation of the safety and efficacy data in one indication to another is scientifically challenging for biosimilars, particularly when extrapolation is based on a less sensitive clinical indication such as RA. This notion has been recently shared by experts in the inflammatory bowel disease (IBD) groups, who emphasized the difficulty of "extrapolation across indications" for biosimilars (33) and required "rigorous testing in patients with IBD" (34). Their positions are appropriate in that most health-care professionals are not aware how and on what basis biosimilars are approved for marketing (35). Therefore, the regulatory agencies need to exercise caution before granting extrapolated indications to biosimilars, many of which might be hard to justify by the *current* regulatory standards unless backed up by strong scientific rationale. On the other hand, it should be also noted that extrapolation across indications is a keystone to the marketing approval of biosimilars because their development process is "abridged" in principle. In this regard, the exposure-response relationship approach based on extensive modeling and simulation experiments using a short-term clinical outcome variable or validated pharmacodynamic endpoint can be a practical alternative to the full-scale comparative clinical trials. This approach has been shown to be effective in the drug development program of etanercept, in which mechanistic modeling and simulation enabled the extrapolation of a new dosage regimen to untested indications (36). Of course, the exposure-response relationship approach should be applied on a case-by-case basis until its usefulness and validity is carefully assessed for biosimilars, which will be elucidated eventually as more complex biosimilars including monoclonal antibody are currently under development.

Conflict of Interest The author has no conflict of interest to declare.

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