EDITORIAL

Can we establish a hierarchy among trastuzumab biosimilar candidates?

The European patent for intravenous trastuzumab lapsed in 2017, and this stimulated research into a number of trastuzumab biosimilars. Quality assessment of their development and clinical results might enable establishment of a clinical hierarchy of these agents. This editorial will underline the key points for consideration when determining such an evaluation.

British Journal of Cancer (2018) 119:263–265; https://doi.org/10.1038/s41416-018-0171-1

MAIN

The extraordinary clinical achievements of trastuzumab have made history in the systemic management of breast cancer. Unfortunately, it is not uniformly available for routine use owing to its prohibitively high cost. With financial contingencies following the economic crisis together with rapidly increasing healthcare costs, even the richest countries are exploring ways to reduce their healthcare expenditures. In 2017, the patent for intravenous trastuzumab (Herceptin) expired across Europe, which stimulated the development of numerous trastuzumab biosimilar agents (Table 1).1–5 In this issue of the British Journal of Cancer, Lammers et al. report evidence establishing another step towards the registration of PF-05280014, a trastuzumab biosimilar candidate developed by Pfizer.6–8 This significant trial has provided clinical efficacy results of this candidate in patients with early breast cancer, and insight into its pharmacokinetic (PK) non-inferiority.

The development of a biosimilar drug requires the collation of extensive pre-clinical comparability studies to demonstrate similar structural, physicochemical, and functional biological characteristics with the reference medical product.9,10 PK comparability in animal models is required prior to the first in-human study, and this is usually aimed at demonstrating PK equivalence between the biosimilar candidate and the referent. These steps have already been successfully achieved for PF-05280014.6,7 Treatment with trastuzumab can result in the production of anti-trastuzumab antibodies; therefore, initial phase I trials for PK assessment include healthy male subjects, because they are less likely to require treatment with trastuzumab for breast cancer in the future. Notably, several previous studies have validated the absence of observable discrepancies in PK profiles for trastuzumab between healthy volunteers and patients.2,4,11,12 Iterative drug administration causes an accumulation of plasma drug levels, thus resulting in an increase of the average AuC(0–t). For trastuzumab exposure, large variability in the AuC(0–t) is observed up to cycle 5, beyond which the values become stable and homogeneous over time.13,14 Therefore, a large randomised study aimed at comparing the activities should also perform a PK assessment in patients receiving iterative administration.

A randomised clinical study represents the ultimate step in the path towards drug registration, with the intention of providing evidence for similar efficacy between the biosimilar candidate and the reference medical product in a sensitive population.10 The strength of the statistical demonstration of equivalence is a key parameter in the quality of this comparability exercise.15 The approach recommended by regulatory authorities for deriving equivalence margins relies on preserving the reference treatment effect, estimated using a meta-analysis focusing on major studies. These recommendations posit a 50–60% preservation of the reference treatment effect from the average effect, or from the lower boundary of the 95% confidence interval. Variable margins of equivalence using different ranges of confidence were pre-specified to define equivalence (Table 1).1–5 This variability reflects the difficulty in reaching a consensus on the acceptable and/or reasonable difference in efficacy of a biosimilar compound.

The second parameter of interest to consider is the population studied and the endpoint criterion used to claim equivalence. According to guidelines, clinical trials should be carried out on a sensitive and homogenous patient population, using endpoints that will; most easily detect differences between the biosimilar and the reference product.10 Archetypical survival endpoints dictate prolonged follow-up with associated increased development costs; these are in contradiction with biosimilar development strategies. Two population options are available: comparison at the metastatic setting based on objective response rate (ORR), or assessment at neoadjuvant setting using pathological complete response (pCR). The neoadjuvant setting is a more homogeneous population, meaning fewer uncertainty factors. In contrast, efficacy at the metastatic setting could be impacted by previous treatment exposures, including chemotherapy and anti-HER2-targeted agents, and by tumour burden or the type of metastatic sites involved. The neoadjuvant setting selects patients with localised disease who are naive to any anticancer therapy. Moreover, the neoadjuvant setting allows the use of pCR, which is a better efficacy assessment criterion and is related to survival outcome.16–18 ORR for metastatic lesions is not related to survival outcomes, and has not been used for the basis of any drug registration in breast cancer.10 Considering these points, the neoadjuvant setting is considered to be an important area for development in HER2-positive breast cancer.10 If a hierarchy based on clinical assessment could be developed for trastuzumab biosimilar candidates, then the agents with a favourable clinical assessment using pCR after neoadjuvant therapy might appear at the top of such classification (Table 1).1–5

A single clinical study, in either the metastatic or the neoadjuvant setting, is usually sufficient to prove the equivalent efficacy of a biosimilar drug. CPT-6 was previously assessed in studies using both settings, but this was due to small changes in the production process that required duplication of all the comparability exercises.4 For PF-05280014, clinical equivalence was based on a study in the metastatic setting, which was
Results of the randomised clinical studies achieved by major trastuzumab biosimilar candidates.1

Table 1.

| Amgen ABP980 | Biocon/Mylan MYL-1401O3 | Samsung BioEpis/Merck SB3 | Celltrion CT-P64a | Pfizer PF-05280014 |
|--------------|-------------------------|---------------------------|-----------------|-------------------|
| Neoadjuvant setting | | | | | |
| N | 725 | 475 | 549 | 226 |
| ORR | ✓✓ | ✓ | ✓ | ✓ |
| Metastatic setting | | | | | |
| N | 475 | 707 | 458 | |
| ORR | —— | —— | —— | —— |

Primary endpoint: Total pCR, Breast pCR, EBC: total pCR, EBC: PK (C\textsubscript{trough} > 20 \textmu g/ml at Cycle 5 (Cycle 6 predose)), MBC: ORR

Objective response rate (risk ratio), 95% CI ± 21%, EBC: 95% CI ± 15%, MBC: 95% CI ± 15%

EBC: early breast cancer; MBC: metastatic breast cancer, PK: pharmacokinetic; C\textsubscript{trough}: plasma concentration.

2. Stebbing, J. et al. CT-P6 compared with reference trastuzumab for HER2-positive early breast cancer: a randomised, double-blind, active-controlled, phase 3 equivalence trial. 
3. Rugo, H. S. et al. Effect of a proposed trastuzumab biosimilar compared with trastuzumab on overall response rate in patients with HER2-positive metastatic breast cancer. JAMA 317, 37–47 (2017).
4. Stebbing, J. et al. CT-P6 compared with reference trastuzumab for HER2-positive breast cancer: a randomised, double-blind, active-controlled, phase 3 equivalence trial. Lancet Oncol. 18, 917–928 (2017).
5. von Minckwitz G., Ponomarova O., Morales S., Zhang N., Hanes V. Efficacy and safety of Biosimilar ABP980 compared to trastuzumab in HER2-positive early breast cancer. Ann. Oncol. 28 (2017).
6. Yin, D. et al. A randomized phase 1 pharmacokinetic trial comparing the potential biosimilar PF-05280014 with trastuzumab in healthy volunteers (REFLECTIONS B127-01). Br. J. Clin. Pharmacol. 78, 1281–1290 (2014).

Additional Information

Competing Interests: T.P. declares no conflict of interest. X.P. is the Principal Investigator for SB3 and HD201, which are trastuzumab biosimilars. X.P. has received honorariums for consulting by SamsungBioEpis.

Correspondence: Xavier Pivot (xpivot@strasbourg.unicancer.fr)

References

1. Pegram M. et al. A randomized, double blind study of PF-05280014 (a potential trastuzumab biosimilar) vs trastuzumab, both in combination with paclitaxel, as first-line treatment for HER2-positive metastatic breast cancer. Ann. Oncol. 28 (suppl 5), 238PD (2017).
2. Pivot, X. et al. Phase III, randomized, double-blind study comparing the efficacy, safety, and immunogenicity of SB3 (trastuzumab biosimilar) and reference trastuzumab in patients treated with neoadjuvant therapy for human epidermal growth factor receptor 2-positive early breast cancer. J. Clin. Oncol. 36, 968–974 (2018).
3. Rugo, H. S. et al. Effect of a proposed trastuzumab biosimilar compared with trastuzumab on overall response rate in patients with ERBB2 (HER2)-positive metastatic breast cancer: a randomized clinical trial. JAMA 317, 37–47 (2017).
4. von Minckwitz G., Ponomarova O., Morales S., Zhang N., Hanes V. Efficacy and safety of Biosimilar ABP980 compared to trastuzumab in HER2-positive early breast cancer. Ann. Oncol. 28 (2017).
5. Yin, D. et al. A randomized phase 1 pharmacokinetic trial comparing the potential biosimilar PF-05280014 with trastuzumab in healthy volunteers (REFLECTIONS B127-01). Br. J. Clin. Pharmacol. 78, 1281–1290 (2014).
7. Hurst, S. et al. Comparative nonclinical assessments of the proposed biosimilar PF-05280014 and trastuzumab (Herceptin®). BioDrugs 28, 451–459 (2014).
8. Lammers P. et al. Neoadjuvant PF-05280014 (a potential trastuzumab biosimilar) versus trastuzumab for operable HER2+ breast cancer. Brit. J. Cancer. (2018). https://doi.org/10.1038/s41416-018-0147-1.
9. Agency EM. Guideline on similar biological products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf. (2015).
10. European Medicines Agency cfMpfHU. Guideline on similar biological medicinal products containing monoclonal antibodies—non clinical and clinical issues. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf. (2012).
11. Pivot, X. et al. A randomized phase I pharmacokinetic study comparing biosimilar candidate SB3 and trastuzumab in healthy male subjects. Clin. Ther. 38, 1665–73 e3 (2016).
12. Esteva, F. J. et al. A randomised trial comparing the pharmacokinetics and safety of the biosimilar CT-P6 with reference trastuzumab. Cancer Chemother. Pharmacol. 81, 505–514 (2018).
13. Leyland-Jones, B. et al. Pharmacokinetics, safety, and efficacy of trastuzumab administered every three weeks in combination with paclitaxel. J. Clin. Oncol. 21, 3965–3971 (2003).
14. Bruno, R. et al. Population pharmacokinetics of trastuzumab in patients with HER2+ metastatic breast cancer. Cancer Chemother. Pharmacol. 56, 361–369 (2005).
15. Pivot, X. et al. Challenges in the implementation of trastuzumab biosimilars: an expert panel’s recommendations. Anticancer Drugs 26, 1009–1016 (2015).
16. Cortazar, P. et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 384, 164–172 (2014).
17. Jackisch, C. et al. Subcutaneous versus intravenous formulation of trastuzumab for HER2-positive early breast cancer: updated results from the phase III HannaH study. Ann. Oncol. 26, 320–325 (2015).
18. Pivot, X. et al. A phase III study comparing SB3 (a proposed trastuzumab biosimilar) and trastuzumab reference product in HER2-positive early breast cancer treated with neoadjuvant–adjuvant treatment: final safety, immunogenicity and survival results. Eur. J. Cancer 93, 19–27 (2018).
19. Pivot, X., Thierry-Vuillemin, A., Villanueva, C. & Bazan, F. Response rates: a valuable signal of promising activity? Cancer J. 15, 361–365 (2009).
20. Pivot, X. & Cox, D. G. A new era for treatment development in HER2-positive breast cancer. Lancet Oncol. 19, 160–162 (2018).