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What does a prescriber think of biosimilars?

Biosimilaires : qu'en pense le prescripteur ?

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Résumé : Le prescripteur, jusqu'à récemment, était confronté aux génériques, des molécules simples, relativement faciles à reproduire. Mais cet article illustre que la biodisponibilité des génériques reste une préoccupation. Et maintenant interviennent les biosimilaires. En cancérologie, les biosimilaires sont pour le moment limités aux érythropoïétines et aux facteurs de croissance des globules blancs. Bientôt, ils seront rejoints par des biosimilaires d'anticorps monoclonaux avec activité antitumorale. Le prescripteur doit se demander, comme pour les génériques, si ces produits ont bien la même action que les originaux, si leur sécurité d'emploi est la même, si la qualité de la production est garantie. Et il exigera que l'on puisse savoir si le patient a bien reçu le produit prescrit, et non pas un autre. Le prescripteur va aussi s'attacher à ce que le prix moindre des biosimilaires permette vraiment de traiter les patients selon les recommandations internationales. Cela devrait être un bénéfice pour les patients et la communauté. ***Pour citer cette revue : Oncologie 13 (2011).***

Mots clés : Génériques – Biosimilaires – Prescription – Érythropoïétines – Facteurs de croissance

Abstract: Until recently the prescriber had to deal with generics, considered to be simple molecules which are easy to copy. But as discussed in this paper, the biodisponibility of generics remains a source of uncertainty. And now arrive biosimilars, limited for the time being in the cancer setting to granulocyte-colony stimulating factors (G-CSFs) and epoetins. Soon there will be biosimilar monoclonal antibodies with anticancer activity. The prescriber will ask, as for generics, if such drugs have the same activity as originators, if their safety profile is the same, if quality of the production process is guaranteed. The prescriber will want to know if the patient is indeed receiving the prescribed product, and not another. Finally the prescriber will want to check that the lower cost of biosimilars will allow to adhere to international guidelines. This should benefit patients and the community. ***To cite this journal: Oncologie 13 (2011).***

Keywords : Generic drugs – Biosimilars – Prescription – Erythropoietins – Growth factors

The recent marketing of biosimilars of epoetins and granulocyte-colony stimulating factors (G-CSFs) in oncology (and nephrology) has stirred up some discussion among the physicians who are prescribing these drugs. This paper will review some of the possible concerns.

Prescriber concerns about generics

Once drugs come off patent (in those countries where European-like patent laws are applied), manufacturers other than the original manufacturers can provide the same active agent. This has been the case over the last decades for small molecules, classical drugs which are supposed to be easy to reproduce. Conventional generics for an orally administered drug are considered to be therapeutically equivalent to a reference, once pharmaceutical equivalence (identical active substances) and bioequivalence (i.e. comparable pharmacokinetics) have been established in a crossover volunteer study and do not require formal clinical efficacy and safety studies [21].

It is important to realize that variations in interindividual handling of a drug (absorption, distribution and metabolism) can considerably influence such data; hence, authorities accept a wide confidence interval for the results of the tests. And this approach has led many clinicians to question its safety. Clinical practice has identified a number of drug classes for which generic substitution should be approached with caution. There are fears that use of this measure may be inappropriate in the case of a drug with a narrow therapeutic range or high intrasubject or intersubject variability [9]. The acceptance intervals show that the bioequivalence for the logarithm-transformed AUC and Cmax ratios lie within an acceptance range of 0.80–1.25 for the 90% confidence intervals [21].

These generic products should in principle reduce healthcare expenditure and create market competition, with drugs identical to the original branded reference drug product. In reality, despite all the laws that establish methods

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to demonstrate pharmaceutical equivalence and bioequivalence, thereby ensuring the safety and efficacy of the product, generic products can differ significantly from the reference drug, and amongst themselves, particularly in terms of pharmacokinetic properties. Such variations most often relate to pharmaceutical technical differences in the production of the active principle ingredient (like different crystalline forms or particle size), to the use of different excipients (such as sugars) or to the manufacturing process itself (such as tablet manufacture) [14].

There have been many studies and case reports describing insufficient efficacy, relapses and worsening clinical outcomes in patients because of the use of generics or after a switch from a brand name to a generic medication [17].

An example of biodisponibility issues is the following. The authors checked whether two generic formulations of amoxicillin, available on the Italian market, did fulfil the criteria for clinical pharmacokinetic bioequivalence vs the branded drug. Two generic amoxicillin products (generic A and B) were selected among four fast-release tablet formulations available on the Italian market. Twenty-four healthy adult volunteers of either sex participated to a single-dose, randomized, three-treatment, crossover, single-blind bioequivalence study designed to compare generic A and B with branded amoxicillin. Plasma samples were collected at preset times for 24 hours after dosing, and assayed for amoxicillin levels by high-performance liquid chromatography. Ninety-percent confidence intervals of AUC ratios were 0.8238 - 1.0502 (ratio 0.9302) and 0.8116 - 1.1007 (ratio 0.9452) for generic A and B vs branded amoxicillin, respectively. Ninety-percent confidence intervals of Cmax ratios were 0.7921 - 1.0134 (ratio 0.8960) and 0.8246 - 1.1199 (ratio 0.9610) for generic A and B vs branded amoxicillin, respectively. The mean pharmacokinetic profiles showed that the AUC value of branded amoxicillin was 8.5 and 5.4% greater than that estimated for generic A and B. These results indicate that one of the two marketed amoxicillin generics analysed in the present study is not bioequivalent to the brand leader product for Cmax on the basis of single-dose pharmacokinetic assessment [8].

From the patient's and clinician's perspective, changing from branded to generic drugs can give rise to concerns about switching. This was evaluated in a recently published Swiss study looking at the influence of patients, physicians and certain characteristics of the generics' market on generic substitution in Switzerland. Authors used reimbursement claims data submitted to a large health insurer by insured individuals living in one of Switzerland's three linguistic regions during 2003. All dispensed drugs studied were substitutable. The outcome (use of a generic or not) was modelled by logistic regression, adjusted for patients' characteristics (gender, age, treatment complexity, substitution groups) and with several variables describing reimbursement incentives (deductible, co-payments) and the generics' market (prices, packaging, co-branded original, number of available generics, etc). The overall generics' substitution rate for 173,212 dispensed prescriptions was 31%, though this varied considerably across cantons. Poor health status (older patients, complex treatments) was associated with lower generic use. Higher rates were associated with higher out-of-pocket costs, greater price differences between the original and the generic, and with the number of generics on the market, while reformulation and repackaging were associated with lower rates. The substitution rate was 13% lower among hospital physicians. The adoption of the prescribing practices of the canton with the highest substitution rate would increase substitution in other cantons to as much as 26%. The authors conclude that patient health status explained a part of the reluctance to substitute an original formulation by a generic. Economic incentives were efficient, but with a moderate global effect. The huge interregional differences indicated that prescribing behaviors and beliefs are probably the main determinant of generic substitution [7].

Prescriber concerns about biosimilars

If there can be so many challenges about generics of small molecules, what about large proteins like many biological agents? Indeed, the production process of these drugs is much more complex, and actually one should know that it is updated regularly by the companies that produce the originators, which might be actually producing "biosimilars" which do not bear that name. Thus a new terminology was needed to indicate a "similar biological medicinal product" and the term biosimilar was coined, although in the United States "follow-on biologics" has been often employed to characterize these products. Biosimilars are new biopharmaceutical agents that are "similar" but not identical to a reference biopharmaceutical product. Characteristics of biopharmaceuticals are closely related to the manufacturing process. Thus, biosimilars are unique molecules and are NOT generic versions of the innovator biopharmaceuticals.

When biosimilars were about to be introduced, many voiced concern about the need to ensure therapeutic equivalence. It was emphasized that inherent differences between biosimilars may produce dissimilarities in clinical efficacy, safety, and immunogenicity. Concern was also raised that minimal clinical experience with biosimilars at approval would mean that pharmacovigilance programs would be crucial to establish clinical databases [18].

But the official documents of the registration of biosimilars made available by the European Medicines Agency indicate that the biosimilar epoetin alfa and one of the biosimilar filgrastims have fewer

impurities and less modified product than their reference products [22]. Actually, as recently discussed, since the introduction of the first recombinant DNA-derived therapeutic proteins, the technology to produce and purify these products has greatly improved. Biosimilar manufacturers are consequently using a most recent state-of-the-art technology [22].

Several forms of G-CSF and epoetins are presently available. They have all been approved by the EMA in Europe under a special guidance discussed in another article of this special issue. The position of many groups is that such agents can be used safely. However, given that biosimilar products are not generic products, a switch from filgrastim or epoetin alfa to a biosimilar is considered a change in clinical management and should be done only under the guidance of a responsible clinician [10].

Due to multiple variations in the complex production process, biological products tend to differ from each other and from the previously approved agent. Consequently, to ensure traceability and thus robust pharmacovigilance, clinicians are encouraged to identify a product by brand name and ensure that no changes in treatment are made without informing both physician and patient [4].

Are such considerations relevant for daily practice? They most probably are. One is well aware that a drug which was not a real biosimilar but considered as such by many, epoetin delta, faced many production problems and was finally withdrawn, although it had received marketing approval several years before its launch [26].

Another consideration of the importance of traceability is certainly the well-known issue of pure red cell aplasia which was observed several years ago with one version of the original epoetin alfa produced in one factory, and recently with another one, actually a biosimilar. Being able to trace the clinical problem to its source, manufacturers have found the reason for the increased immunogenicity of the injectables, and corrected it. This would have been possibly impossible if one only knew that the patient was on "some epoetin" [6].

Relevant to this discussion about the difficulty to develop a biosimliar, let us give an example in the epoetin area. The authors of this work were independently checking the quality of several epoetins and observed a difference of activity. They then found that the potency of 10,000 IU ampoules of Eprex® was actually 10% higher than labelled upon repeated testing. The potency of epoetin zeta (Retacrit®) was found to be as labelled. So they concluded that the lower activity of epoetin zeta compared with Eprex® seems to be caused by a higher potency than nominal value of Eprex®. Why this difference was not encountered when biosimilar alfa was compared with the same innovator product was reported by the authors as unclear. They speculated that the developers of this biosimilar may have corrected the dosage based on potency testing in their clinical trials. The company marketing Retacrit® kindly provided the authors with the data on the different batches used during clinical development. Although there were differences in the bioactivity in the batches, Eprex® batches were found on average to have 9% higher bioactivity than the labelled strength and epoetin zeta batches have 1% higher bioactivity than the labelled strength. The authors note that all batches remained within the limits defined by the European Pharmacopeia, namely 80–125% (with error limits of 64–156%). On the contrary, the average specific bioactivity of the two proteins was similar (130.80 for Retacrit® vs 130.75 units/μg for Eprex®). The prescriber, reading such a paper, realizes that one is using agents which are relatively variable, and remains perplex about all the debate about "batch-to-batch reproducibility." One has to realize that many biologicals are used at doses which are safely within the limits of biological variability [20].

The approval of biosimilars has of course had an influence on existing guidelines for use of G-CSF, which at their recent update have recognized these important advances. One hopes that the availability of reliable and cheaper agents will allow all clinicians to follow the guidelines without obstacles. This should allow for lesser chemotherapy dose reductions when appropriate dose is crucial. It should allow for lesser hospitalizations, and for a lower overall cost of treatment.

Indeed, in spite of the clear indications for use of the EMA approval for G-CSF, reiterated in the recent update of the EORTC guidelines [4], many patients are suboptimally treated. The EMA approval requires the use of G-CSF beyond the white blood cell nadir, up to 11 days. Several studies show that treatment regimens vary along a continuum of days. In a French study, the mean treatment duration for filgrastim decreased from 7.8 days in 1999 to 5.5 days in 2006–2007 (with ranges from 1 to 10 or more days). Where in 1999, 45.3% of treatments exceeded 7 days, this rate was only 9.3% in 2006–2007 [11]. In a Spanish study, median injections of daily G-CSF were 6 for primary prophylaxis and 5 for secondary prophylaxis or treatment (with ranges from 1 to 13 days) [5]. An analysis of a large US claims database in 133 patients (322 cycles) with non-Hodgkin's lymphoma, 205 patients (482 cycles) with breast cancer, and 260 patients (522 cycles) with lung cancer revealed mean (± standard deviation) filgrastim treatment durations of 6.5 ± 3.1 days for patients with non-Hodgkin's lymphoma, 6.1 ± 2.9 days for breast cancer and 4.3 ± 3.1 days for lung cancer patients. This study shows that these shorter durations of treatment are paralleled with an increased rate of hospitalizations (NHL: OR 0.81, p = 0.003, breast: OR 0.77, p = 0.00, lung: OR 0.91, p = 0.084) [25].

The probability of a better outcome with guideline-adherent practice has been recently shown in a case-control study which showed a positive correlation in efficacy

Table 1. Recommendations of EORTC for prophylactic use of G-CSF [4]

Step 1. Assess frequency of febrile neutropenia associated with the planned chemotherapy regimen
IF risk is equal or greater than 20%, use prophylactic G-CSF
IF risk is below 10% prophylaxis is not indicated
Step 2. If risk is between 10 and 20%, consider if the patient is above age 65, a high risk factor. Other level I and II evidence risk factors include advanced disease, history of prior febrile neutropenia, no antibiotic prophylaxis (which is not recommended by EORTC). Other risk factors with limited evidence for increasing febrile neutropenia risk include poor performance/nutritional status, female gender, haemoglobin below 12 g/dL, liver, renal, cardiovascular disease.
Step 3. From step 2 determine if the patient has changed into a high febrile neutropenia risk category of 20% or more and use prophylactic G-CSF. If not, reassess at the next cycle.

Table 2. ESMO Guidelines for use of Epoetins [23]

Patients treated with chemotherapy and a Hb level ≤10 g/dL
Consider use of ESAs to increase Hb by <12 g/dL or to prevent further Hb decline
Patients not treated with chemotherapy:
No indication, and possible increased risk of death when ESAs administered to a target Hb of 12–14 g/dL
Continuing ESAs beyond 6–8 weeks in non-responders (Hb rise <1–2 g/dL or no decrease in transfusion requirement) is not beneficial
The Hb level should not exceed 12 g/dL; if it does, dose adjustments should be made

Table 3. Epoetins usage guidance in the United States [19]

ESAs are a recommended treatment option in patients with chemotherapy-associated anaemia and a Hb level <10 g/dL
ESAs are not recommended for the treatment of anaemia in cancer patients who are not receiving chemotherapy
An optimal level at which to initiate ESA therapy in patients with Hb 10–12 g/dL cannot be definitively determined from available evidence
Continuing ESAs beyond 6–8 weeks in non-responders (Hb rise <1–2 g/dL or no decrease in transfusion requirement) does not seem to be beneficial
Hb can be increased to the lowest level needed to avoid transfusions, which may vary by patient and condition

of epoetins to increase Hb value and guideline-adherent practice [2,3,24].

Whether similar data can be obtained for the use of G-CSFs is the object of an ongoing study, which has been described in two recent publications [12,13].

When using originators or biosimilars, the prescriber will pay attention to the limitations of use of the drugs, defined by the marketing authorization documents. The recommendations for use of these agents [4,19,23] are summarized in the following tables (Tables 1–3).

Concluding remarks

Recent studies have shown that generics do not always lead to the expected costs savings, reducing the impetus to proceed with compulsory generic switching [9]. Will this be true for biosimilars? Certainly, the economic decision makers have become more sophisticated with the mechanisms used to enhance a shift towards widespread use of generics and biosimilars. Not long ago many issues were raised to show how some health systems needed rethinking. For example, the English National Health Service was, according to some, reimbursing generics at too high prices and a significant proportion of the reimbursed price was stated to accrue to the distribution chain in a fashion that resembled an indirect subsidy [16]. An observational retrospective study has been conducted using administrative databases from across Europe, documenting changes in reimbursed utilization and expenditure of different proton pump inhibitors (PPIs) and statins between 2001 and 2007, alongside different reforms to enhance prescribing efficiency. There were considerable differences in the utilization of generics and patent-protected PPIs and statins among Western European countries. Prescribing restrictions, or a combination of education, prescribing targets and financial incentives, had the greatest influence on enhancing the utilization of omeprazole and simvastatin [15]. With such a background, one hopes that besides the EMA-mandated quality of the biosimilars, appropriate economical data [1] will lead to the acceptance of these agents by the medical community.

Conflict of interest statement : The author is a consultant for Amgem, Hexal, Roche, Sandoz.

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