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Diffusion of biosimilar hemopoietic growth factors use in oncology practice: an Italian experience

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Abstract *Background* Biosimilars of hemopoietic growth factors present an important saving opportunity in oncology. However, while pharmacologists are aware of their potential benefits, biosimilars are still under-used in Italy. Improved information and guided clinical experience may help to increase the clinical acceptance of these drugs. To this aim, a collaborative educational project was set between an Hospital Oncology Unit and the Local Health Care Authority in Pavia, Italy.

Methods The project lasted 12 months. The strategy included an education-information seminar at startup, a reporting meeting at +6 months, electronic prescription monitoring and implementation of pharmacovigilance. The target was set to reach 90% of all naïve patients treated with biosimilars.

Results At the end of the study (2013), a dramatic relative increase in the prescription of biosimilar drugs was noted, with virtually 100% of new patients receiving biosimilar drugs during the last 4 months, with a positive impact on average per capita drug expenses. Active pharmacovigilance did not report any serious adverse drug reactions. An anonymous questionnaire showed that oncologists judged the experience quite positively, acquired a positive attitude toward these drugs and considered biosimilars a relevant saving opportunity, while adherence to prescription guidelines was maintained. Analysis of the year following the end of the project, 2014, showed a persistent prescription change.

Conclusions Results from this local experience suggests that specifically designed pragmatic interventions focused on information-education and monitoring may help in promoting the use and acceptance of biosimilar drugs in the real clinical setting.

Key-message

- Biosimilars of hemopoietic growth factors are a saving opportunity in oncology.
- An Hospital Oncology Unit and the Local Health Authority set a collaborative project based on education and monitoring with the goal to promote the use of biosimilar drugs in clinical practice.
- The target was set to reach 90% of all growth factor naïve-on chemotherapy outpatients treated with biosimilars by the end of the one-year project (2013), and this point was obtained at +8 month.
- The new prescribing attitude was maintained the year after the end of the study.
- Considering the local policy pricing for outpatients, the average per capita savings in the real clinical setting was approximately 31% compared to the year before the project.

1 Background

Biosimilar drugs are biological drugs similar to the originator and manufactured once the patent has expired. They present an opportunity to provide high-quality, financially

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sustainable care in oncology. Hemopoietic growth factors, erythrostimulating agents (ESA, erythropoietins) and myeloid growth factors (filgrastim), are among the first biosimilar drugs introduced onto the market. In Europe, these drugs are authorized by the European Medicines Agency (EMA) with a specific and selective registration process aimed at guaranteeing that a biosimilar drug does not differ significantly from the originator drug in terms of safety, quality and activity (EMA CPMP/ICH/5721/03 and CHMP/437/04 Rev 1) [1, 2]. Since biosimilars are usually cheaper (average price difference between the originator and the biosimilars range between 10% and 35% in Europe) [3], the Italian Pharmaceutical National Authority (AIFA) issued a judgement stating that biosimilars are not only comparable to originator drugs, but they should be preferred in *naïve* patients (not previously or recently exposed to the relevant drug) because of their lower price [4]. However, the use of biosimilar hemopoietic growth factors is suboptimal in Italy; figures for 2013 were of 20% of total doses for biosimilar erythropoietin alpha and 53% of total doses for biosimilar filgrastim in Italy, compared to 60% and 90% in Sweden, 28% and 74% in Spain, 24% and 75% in UK, and 55% for both biosimilars in Germany [5]. Poor knowledge is a factor: a survey conducted by the Italian Association of Medical Oncology (AIOM) on March 2013 showed that only 24% of Italian oncologists knew the exact definition of a biosimilar drug, and that 62% of them erroneously thought that biosimilars might function differently from originators [6]. On the other hand, oncologist acceptance of biosimilars was indicated among the key factors for their market penetration and success [7]. While strategies used for generics may not be currently appropriate to promote biosimilar uptake, programs based on information-education to clinicians, together with guided clinical experience with stress on pharmacovigilance, may be instrumental to this target. In this report, we described the results of a pilot collaborative project designed and operated by the Unit of Oncology of the IRCCS Policlinico San Matteo (Pavia, Italy) and the Local Health Authority (ASL-Pavia), with focus on the clinician's experience and on financial savings obtained.

2 Methods

The primary aim of the project was to promote the introduction of biosimilars of hemopoiesis stimulating agents in the clinical practice of the Oncology Unit of Fondazione IRCCS Policlinico San Matteo in Pavia (11 physicians). The target was set to reach 90% of all growth factor-naïve outpatients treated with biosimilars in one-year period of time (January-December 2013, project duration 12 months). The Day Hospital of the Oncology Unit treated 591 patients during the project activity, for a total of 4564 administered chemotherapy cycles, 41% for gastrointestinal, 31% for breast, 22% for lung and head and neck, and 6% for other types of cancers. Clinicians did not receive economic or other forms of incentives, and the project target was not settled as a goal in the budgeting process. Savings that might derive by the introduction of biosimilars were not destined to the Unit.

The change in management strategy included two meetings, both held by the Head of Pharmaceutics Unit of the Local Health Authority (Mirosa Dellagiovanna): a formal educational lesson on biosimilar biotechnology and authorization practices at the start of the project (with focus on complexity, immunogenicity, comparability exercise, and EMA and AIFA guidelines), and a second meeting held approximately 6 months later, at the time of the first assessment, aimed at identifying difficulties and analyzing differences from expected results (monitoring). Both meetings were held at the Hospital Oncology Unit, lasted approximately 2 hours each, and numbers of attending clinicians were recorded. In both instances, full participation of clinical oncologists was reached. Summaries were developed for each meeting. Other procedures were adopted to follow-up drug prescription and relative expenses: the clinician had to file a therapeutic planning record for each patient that was electronically submitted to the Local Health Authority. This record included: patient identification, type of growth factor (ESA or G-CSF, originator or biosimilar drug), dosage and expected duration of treatment. Since in oncology the indication to growth factors is limited to the time on chemotherapy, a single patient could have a maximum of two open records (one for ESA and one for G-CSF). Drugs were acquired in local pharmacy stores, prices were therefore determined by national negotiation (AIFA determined prices). All eligible patients were considered for the study and indication to growth factor use was intended to be in line with current guideline recommendations. With the aim to improve recording of possible side effects, drug prescription was limited to the oncologist team who filed the therapeutic planning record. By means of this procedure, patients were monitored every chemotherapy cycle (typically every 14 to 21 days) by experienced personnel, thus avoiding excessive use of growth factors and ensuring appropriate side effect reporting in clinical records.

The number of enrolled patients and drug prescriptions were analyzed on a monthly basis. Use of biosimilars vs originators and use of biosimilars vs total relative growth factor use (thus including lenograstim and pegfilgrastim for G-CSF and darbepoetin for ESA) were recorded. Yearly average expenditure for each treated outpatient (yearly total expenses of the Oncology Unit for hemopoietic growth factors divided by the number of outpatients treated per year) was compared with expenses of the year before (2012) and after the project (2014).

At the end of the study period, an anonymous questionnaire (12 questions) was distributed to oncologists to determine the impact of the project on knowledge and clinical

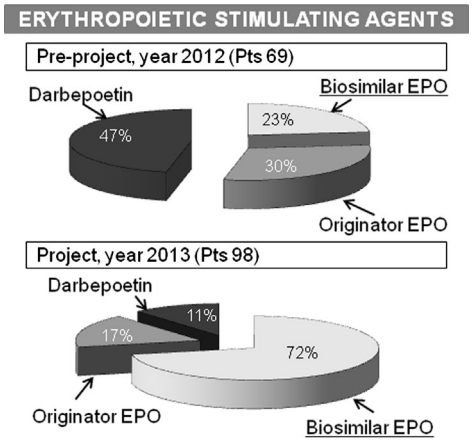

Fig. 1 Therapeutic planning records for ESA-treated patients at the Oncology Unit of IRCCS Policlinico San Matteo Hospital. Data during the project activity (2013) are compared with the previous year (2012). A marked increase in the number of planning records for biosimilar ESA was observed, and this was accomplished by means of both darbepoetin and originator drugs decline

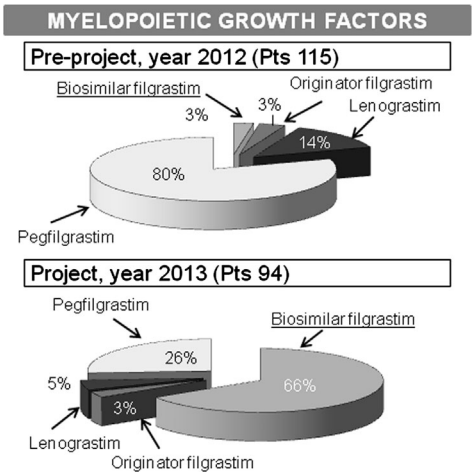

Fig. 2 Therapeutic planning records for myeloid growth factor-treated patients at the Oncology Unit of IRCCS Policlinico San Matteo Hospital. Data during the project activity (2013) are compared with the previous year (2012). As for ESA (Fig. 1), the striking increase in the number of planning records for biosimilar filgrastim is matched by a decline with the relative originator drug as well as with pegfilgrastim and lenograstim, two drugs for which no biosimilars are available yet

practice, and to draw information on any difficulties experienced and on preferences. To compare answers from experienced San Matteo oncologists with those from general oncologists, the questionnaire also included 5 questions from the March 2013 national AIOM survey on biosimilars [6]. All oncologists filed the questionnaire and responded to all the questions.

3 Results and discussion

3.1 Erythropoiesis stimulating agents (ESA)

Numbers of ESA planning records for the patients treated at the San Matteo Oncology Unit during the 12 months of the project activity (2013), compared with the previous year (2012), are shown in Fig. 1. A clear-cut change in drug prescription was observed, with a sharp increase in biosimilar drug records (from 23% to 72%) and an increase in the total number of ESA treated patients. Of note, darbepoetin, a growth factor for which there is no biosimilar drug yet, was the ESA most affected by increased biosimilar use, with a decrease from 47% to 11% of the total records (Fig. 1). The most valid explanation for this result is that clinicians considered the single weekly injection of 40.000 UI of biosimilar erythropoietin alpha a valid alternative for the more expensive 150 μg weekly dose of darbepoetin. Therefore, the prescription change involved the entire class of ESA. The total number of patients treated with ESA during year 2013 rose by approximately 42% (from 69 pts to 98 pts) compared to 2012. This was in line with both a relative increase of the number of patients treated at the recently constituted San Matteo Oncology Unit during 2013 (11% increase compared to 2012) and, more importantly, a relative increase of the number of chemotherapy treatments with drugs typically associated with chemotherapy-related anemia (plus 26%). However, it was also possible that the increase in ESA-treated patients could be partly caused by prescriptions that were not in line with current guidelines on ESA use, driven by the decreased price of the biosimilars. The results of the questionnaire and the data from myeloid growth factors reported below indicate that this possibility is unlikely.

3.2 Myeloid growth factors

Figure 2 shows the numbers of myeloid growth factor planning records for the patients followed at the San Matteo Oncology Unit during the 12 month project, compared with the previous year (2012). As it is the case for ESAs, a dramatic change in drug prescription was observed for myeloid growth factors, with a sharp increase in biosimilar drug records (from 3% to 66%). Again, the increased prescription of biosimilars was accompanied by reductions in growth factors for which there is no biosimilar drug, as in the case of lenograstim (from 14% to 5%) and pegfilgrastim (from 80% to 26% of total records). The re-introduction of schedules based on daily injections of short-acting biosimilars in place of the long-acting growth factor has been instrumental in this result. Oncologist proposed this schedule only to compliant and less fragile patients, and all patients accepted when informed about the aims of the project, and having understood the relevance of the issues. Although no proper questionnaire was given to monitor patient variation in quality of life, no complaints were reported. An explanation could be that the majority of patients treated with filgrastim were undergoing breast-cancer adjuvant treatment and

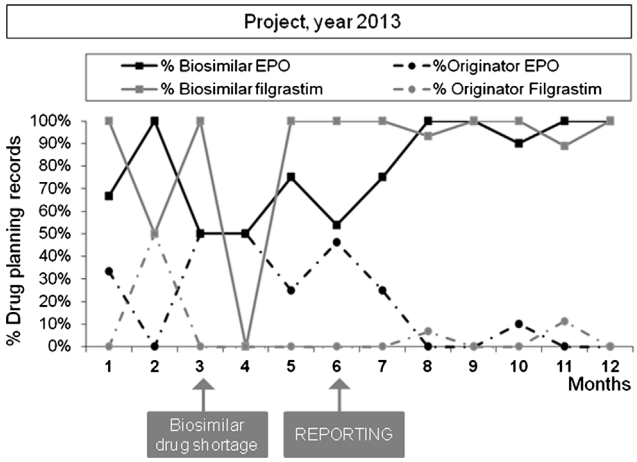

Fig. 3 Time variations in therapeutic planning records monitored during the study period, year 2013. The two crucial points are indicated: supplying shortage and first reporting meeting. The progressive increase in biosimilar planning records after reporting allowed reaching target by August 2013 (month +8, 90–100% of naïve patients treated with biosimilar drugs). This new prescriptive attitude was maintained for the remaining 4 months of study project

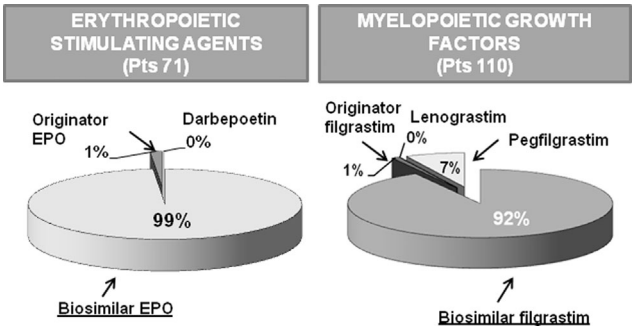

Fig. 4 Therapeutic planning records for hemopoietic growth factor-treated patients during the year following the project (2014). Biosimilars maintained a share above 90%, showing that the project was able to induce a stable change in prescription attitude

had already experienced single day injections of prophylactic low-molecular weight heparin after surgery. In addition, patients were instructed to stop daily injections in case of CTCAE grade 1 bone pain (indicating myelopoiesis recovery), a feature that helped to minimize typical side effects related to G-CSF use.

In contrast to the ESA data, the total number of patients treated with myeloid growth factors during the study, decreased by 18% (from 115 pts in 2012 to 94 pts in 2013). This latter finding does suggest that the relative lower price of the biosimilars did not promote incorrect behaviors in prescription activity, in line with the results of the questionnaire (see below).

3.3 Time variations in drug planning records

Time variations in patient therapeutic records monitored during the study period are shown in Fig. 3. Two moments were critical for the success of the project. The first, a negative one, was characterized by a sudden shortage of biosimilar drugs in pharmacy stores at month +2. Patients were sent back to the Oncology Unit for new drug records because pharmacists were unable to locate the requested drug. Prompt intervention by the Local Health Authority quickly solved the problem. However, prescriptions of originator drugs issued during the shortage window, which lasted around one month, influenced results up to month +5 (Fig. 3). The second key moment for the success of the project was the meeting for the first assessment at month +6 (Fig. 3). Officials from the Local Health Authority showed results for the first 6 months of activity (Fig. 3) and reassured oncologists about future biosimilar drug supplies. This key meeting, together with acquired awareness of the pharmacological safety and efficacy of biosimilars in the real clinical setting, encouraged the increased use of biosimilar drug records so that the project target was attained by August 2013 (month +8, Fig. 3: 90–100% of naïve patients treated with biosimilar drugs). This change in prescribing was maintained for the remaining 4 months of study project (Fig. 3).

3.4 Analysis of prescriptions in the year following the project (2014)

Figure 4 reports the numbers of hemopoietic growth factor planning records for the patients followed at the Oncology Unit at San Matteo Hospital during the year (2014) following the project activity. Biosimilar represented 92% and 99% of myeloid growth factors and ESA, respectively (Fig. 4). These results demonstrated that the project target (more than 90% of naïve patients treated with biosimilar drugs) reached at months +8 of 2013 (Fig. 3), was maintained after surveillance ceased, indicating a continuing positive attitude toward these biosimilars.

3.5 Savings analysis

In order to provide a figure of the savings that could derive from the prescription change, we calculated the yearly costs for growth factor use during 2012, 2013 (project) and 2014, and the number of patients treated. Figure 5 reports the average per capita spending (in Euros) for treating with hemopoietic growth factors an oncology outpatient receiving chemotherapy at the San Matteo Hospital, Pavia. Expenses were calculated according to drug prices officially registered at the National Pharmaceutical Authority (AIFA). In fact, as reported in the Methods section, these were the actual prices in Lombardy pharmacy stores. A marked expense reduction was observed, with a 31% saving compared to 2012. Analysis of 2014 costs, showed a 21% further reduction compared to the study period (2013), resulting in

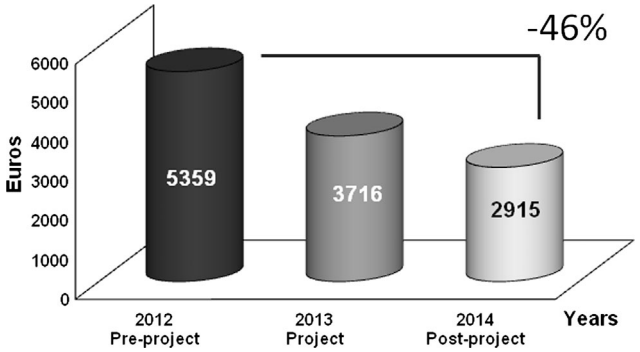

Fig. 5 Per capita average expenses (Euros) for treating with growth factors an oncology outpatient at San Matteo Hospital, Pavia, during 2012, 2013 (project activity), and 2014. Analysis showed a clear-cut decline of the per capita average expense, resulting in 46% saving on 2014 compared to the year before the project (2012). AIFA registered prices were used for calculations (see Methods)

46% saving compared to pre-study time (2012) (Fig. 5). These data do not take into account changes in the case mix of patients that might have occurred during the various years, such as the increase of 42% of ESA treated cases, the most costly ones, that was observed during the project time (Fig. 1) However, we believe that the present analysis provide a useful estimate of the impact that the introduction of biosimilar growth factors may have in the "real life" of an hospital oncology unit, where case mix may vary according to many variable factors, such as cancer type and stage, patient characteristics (age, fragility, line of chemotherapy) and chemotherapy drugs.

3.6 Safety and efficacy of biosimilars

Although the study was not specifically designed to address safety and efficacy of biosimilars, surveillance was implemented with a close follow-up (see Methods sections). No adverse effect was reported in approximately 200 patients treated, with the exception of 3 cases of grade 2 bone pain in patients treated with G-CSF. Oncologists did not note any difference in efficacy compared with their previous personal experience with originator drugs. Indeed, a recent review did not find any clinically significant difference on the safety profile of biosimilar and originator drugs [8].

3.7 The questionnaire—biosimilar drug acceptance

At the end of the project, a questionnaire (see supplementary material) that included a few questions drawn from the March 2013 AIOM survey on biosimilars (questions #1–5) was distributed to test the impact of the project on knowledge and clinical practice, and to gather information on perceived difficulties and observed preferences. Answers from San Matteo oncologists were in line with those from the national survey, but with a few notable exceptions, particularly on efficacy and safety issues; in particular, only 1 of 11 San Matteo oncologists (9%) thought that biosimilars might differ in activity compared to the relative originator, a concern expressed by the majority (62%) of AIOM oncologists (question#2); in addition, 55% of local oncologists did not see any critical issues on the use of EMA approved biological drugs (question #2), compared to 11% of the AIOM survey [6]. This somewhat unexpected high-degree of confidence can be related to the positive experience concerning safety and efficacy, from the deeper knowledge acquired during the pre-project formative session, and from the strict regulatory pathway applied in Europe for biosimilar drug marketing authorization. Another difference from the Italian national survey is that the San Matteo Hospital oncologists believed that biosimilar drugs may represent an opportunity for relevant savings (91% compared to 50% AIOM oncologists) without sacrificing efficacy and safety (question #3). The analysis of the specific questions related to the study raised some noteworthy issues. San Matteo oncologists showed varying attitudes to the project: approximately 60% of them thought that the study imposed in some way a limitation in their prescription freedom (question #9). This finding revealed that education-information needed to be implemented in this aspect, since preferred prescription of biosimilars (similar drugs, but sold at reduced price) should not be considered a question of "prescription freedom", but rather a matter of correct utilization of financial resources. On the other hand, 45% of them would be open to discuss a problematic issue, although rarely occurring in oncology, such as drug switching from an originator to a biosimilar drug (question #7). A final key point is that oncologist maintained adherence to international guidelines for growth factor use, despite the reduced price of the biosimilar drug (question #8). This is a relevant point, since any modifications of prescribing patterns laid down in the guidelines could abolish any savings related to enhanced biosimilar drug use. A relevant difficulty met in clinical practice was the temporary supply shortage, a problem that might have been related to unexpected high-prescription rates (question #11); thanks to the collaborative nature of the project between the Hospital and the Local Health Care Authority, the problem was solved rapidly, and constantly monitored thereafter.

4 Conclusions

Results from this local Italian experience indicated that it was possible, by means of a specifically designed professional learning and interventional project involving clinicians and the Local Health Care Authority, to promote efficiently and safely the introduction of growth factor biosimilars into oncology practice, attaining in a short span of time high prescription rates with a positive impact on related pharmaceutical expenses. The typical short-term use of

growth factors in oncology has certainly facilitated this task: shifting is generally not a problem in oncology (most oncology patients are drug-naïve) and immunization concerns that are typical of ESA chronically-treated patients, such as those in dialysis, do not apply to oncology patients. Answers from the anonymous questionnaire identified issues that were still critical and should be subject for future improvement. Nevertheless, the present experience showed that a simple collaborative educational project was powerful in this instance, and this should be considered in view of the next availability of biosimilar therapeutic monoclonal antibodies.

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