Le basi scientifico-regolatorie del Secondo Position Paper sui biosimilari

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Dichiarazione di trasparenza/interessi*

Le opinioni espresse in questa presentazione sono personali e non impegnano in alcun modo l'AIFA

Interessi nell'industria farmaceutica	NO	Attualmente	Precedenti 2 anni	Da oltre 2 a 5 anni precedenti	Oltre 5 anni precedenti (facoltativo)
Interessi diretti:					
Impiego in una società	x				
Consulenza per una società	x				
Consulente strategico per una società	x				
Interessi finanziari	x				
Titolarità di un brevetto	x				
Interessi indiretti:					
Sperimentatore principale	x				
Sperimentatore	x				
Sovvenzioni o altri fondi finanziari	x				

* Patrizia Popoli, secondo il regolamento sul Conflitto di Interessi approvato dal CdA AIFA in data 26.01.2012 e pubblicato sulla Gazzetta Ufficiale del 20.03.2012 in accordo con la policy 0044 EMA/513078/2010 sulla gestione del conflitto di interessi dei membri dei Comitati Scientifici e degli esperti.

Secondo Position Paper AIFA sui Farmaci Biosimilari

AGENZIA ITALIANA DEL FARMACO

TUTELA RICERCA E SVILUPPO PER LA SALUTE

Premessa

Con il presente documento l'Agenzia Italiana del Farmaco (AIFA) fornisce agli operatori sanitari e ai cittadini informazioni chiare, trasparenti e convalidate sui medicinali biosimilari, in particolare riguardo i seguenti aspetti:

- definizione e principali criteri di caratterizzazione dei medicinali biologici e biosimilari;
- inquadramento delle normative regolatorie vigenti nell'UE in merito ai medicinali biosimilari;
- ruolo dei biosimilari nella sostenibilità economica del Servizio Sanitario Nazionale (SSN).

Indice

I biosimilari come alternativa ai prodotti originatori: la questione della sostituibilità

In Italia la posizione dell'AIFA chiarisce che i medicinali biologici e biosimilari non possono essere considerati sic et simpliciter alla stregua dei prodotti generici, o equivalenti.

La **sostituibilità automatica** (degli equivalenti) da parte dei farmacisti si riferisce alla pratica per cui il farmacista ha la facoltà, oppure è tenuto, conformemente a norme nazionali o locali, a dispensare, al posto del medicinale prescritto, un farmaco equivalente e intercambiabile, senza consultare il medico prescrittore.

Pur considerando che la scelta di trattamento rimane una decisione clinica affidata al medico prescrittore, a quest'ultimo è anche affidato il compito di contribuire a un utilizzo appropriato delle risorse ai fini della sostenibilità del sistema sanitario e la corretta informazione del paziente sull'uso dei biosimilari.

Come dimostrato dal processo regolatorio di autorizzazione, il rapporto rischio-beneficio dei biosimilari è il medesimo di quello degli originatori di riferimento. Per tale motivo, l'AIFA considera i biosimilari come prodotti intercambiabili con i corrispondenti originatori di riferimento. Tale considerazione vale tanto per i pazienti naïve quanto per i pazienti già in cura.

Riguardo al concetto di **intercambiabilità** riferita alla pratica medica si riportano le seguenti definizioni disponibili:

- Secondo la definizione dell'OMS è prodotto farmaceutico intercambiabile: "*un prodotto che si prevede abbia lo stesso effetto clinico di un prodotto comparatore e possa essere sostituito ad esso nella pratica clinica*" (Ref: WHO Technical Report Series, No. 937, 2006).

- L'intercambiabilità si riferisce alla pratica medica di sostituire un farmaco con un altro, che si prevede produca il medesimo effetto clinico in un determinato contesto clinico in qualsiasi paziente, su iniziativa o con l'accordo del medico prescrittore (definizione *Biosimilars Consensus Information Paper*).[8]

Utilizzo di biosimilari nell'ambito della Legge n.648/1996

In Italia sono in vigore disposizioni normative specifiche volte a facilitare l'accesso alle terapie in caso di assenza di valide alternative autorizzate.

In particolare, la legge n.648/96 ha previsto, tra l'altro, che per il trattamento di una patologia per la quale non sia disponibile una valida alternativa terapeutica possono essere impiegati ed

erogati a carico del SSN farmaci autorizzati per altra indicazione terapeutica (utilizzo *off-label*) e per i quali siano disponibili dati di sicurezza ed efficacia raccolti in studi clinici almeno di fase II, previo parere della Commissione consultiva Tecnico Scientifica

(CTS) dell'AIFA.

Utilizzo di biosimilari nell'ambito della Legge n.648/1996

Anche i prodotti biologici possono essere utilizzati per l'uso *off-label*, e quindi nel caso di un medicinale biosimilare il cui corrispondente medicinale biologico di riferimento sia già stato autorizzato per l'utilizzo *off-label* e sia, quindi, presente nel richiamato elenco, l'inserimento del biosimilare non è automatico, ma viene verificato caso per caso dalla CTS.

Utilizzo di biosimilari nell'ambito della Legge n.648/1996

In accordo con le raccomandazioni delle linee guida dell'EMA per le indicazioni autorizzate, l'estrapolazione delle indicazioni off-label da un farmaco originatore al rispettivo biosimilare debba essere condotta comunque caso per caso e nel rispetto dei medesimi principi, che sono in dettaglio:

1. individuazione di tutti gli elementi del *comparability exercise* riguardanti qualità, preclinica e clinica contenuti nell'EPAR e utilizzati dall'EMA per dimostrare che tra i due farmaci oggetto dell'esercizio di comparabilità non esistono differenze rilevanti che possano suggerire una modificazione del rapporto rischio/beneficio. Ciò dovrà essere valutato per tutte le indicazioni approvate direttamente o estrapolate da EMA. Si dovranno, ad esempio, valutare i dati e le conclusioni delle sezioni riguardanti la farmacodinamica pre-clinica e clinica e l'immunogenicità;
2. verifica volta ad appurare se il meccanismo d'azione del farmaco nell'indicazione autorizzata e rimborsata ai sensi della legge n.648/96 sia riconducibile o meno a caratteristiche della molecola diverse da quelle valutate e approvate nel comparability exercise;
3. verifica dell'assenza di specifiche tematiche di sicurezza (safety concerns) legati all'indicazione in esame.

Basi regolatorie

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Commission

Biosimilars in the EU

Information guide for healthcare professionals

Prepared jointly by the European Medicines Agency
and the European Commission

A robust regulatory framework for biosimilars

* Approval of medicines in the EU relies on a solid legal framework, which in 2004 introduced a dedicated route for the approval of biosimilars. The EU has pioneered the regulation of biosimilars since the approval of the first one (the growth hormone somatropin) in 2006. Since then, the EU has approved the highest number of biosimilars worldwide, and consequently has the most extensive experience of their use and safety.
* Over the years, EMA has issued scientific guidelines to help developers conform to the strict regulatory requirements for approving biosimilars. The guidelines have evolved to keep pace with rapid advances in biotechnology and analytical sciences, and they take on board increasing experience of clinical use.
* *The expertise acquired over the last 10 years has enabled EU regulators to integrate experience-based knowledge with the initial science-driven concept. This has helped to shape current requirements for approval.*

Data requirements for approval: a scientifically tailored package

* Medicines are approved when studies on their pharmaceutical quality, safety and efficacy convincingly demonstrate that the medicine's benefits outweigh the risks ('positive benefit-risk balance').
* For any biological medicine with a new active substance, a positive benefit-risk balance is determined mainly from evidence of safety and efficacy in pivotal trials in humans, supported by solid pharmaceutical quality data and non-clinical data.

Data requirements for approval: a scientifically tailored package

* For biosimilars, a positive benefit-risk balance is based on demonstrating biosimilarity, i.e. that the active substance is highly similar to the reference medicine. This is achieved via comprehensive comparability studies with the reference medicine and on the basis of solid pharmaceutical quality data. By demonstrating high similarity with the reference medicine, the biosimilar can largely rely on the efficacy and safety experience gained with the reference medicine.

Comparative trials are designed to confirm biosimilarity and clinical performance

* Clinical trials for biosimilars do not need to include all the pivotal studies conducted for the reference medicine to prove safety and efficacy in humans.

* Comparative clinical trials are specifically designed to rule out clinically relevant differences in safety or efficacy between the biosimilar and the reference medicine, and to confirm biosimilarity.

* Comparison of the biosimilar with the reference medicine involves extensive comparability studies to assess any possible impact on safety and efficacy. The approach is equivalent to when major changes are introduced to the manufacturing process for a medicine made by biotechnology

Efficacy equivalence margins

* Adequate equivalence margins should be chosen for the primary efficacy endpoint. Margins are established on the basis of knowledge of efficacy with the reference medicine, as well as on clinical judgement.
* Equivalence margins are set specifically for the indication studied and depend on the endpoint chosen. They should represent the largest difference in efficacy that would not matter in clinical practice; treatment differences within this range would thus be acceptable because they have no clinical relevance.

Table 6. Factors affecting the number and types of clinical studies to be carried out for approval

Determining factor	Reason for varying amount/type of data
Complexity of the molecule and comparability data available	For simpler molecules with well-established action (e.g. filgrastim) and where comparative quality data are solid, it may be sufficient to compare the effect of the biosimilar and reference medicine with PK and PD studies in healthy volunteers. For larger molecules (e.g. monoclonal antibodies), even when robust quality and in vitro comparability data are provided, a comparative study in patients using a conventional clinical efficacy endpoint is usually required.
Availability of a PD endpoint which correlates with efficacy	Conventional clinical efficacy endpoints are generally not needed if the PD endpoint correlates with clinical benefit.
Safety concerns with the reference medicine or pharmacological class	Safety data are collected throughout the clinical development programme, including during PK and PD studies. The amount of data normally depends on the type and severity of the safety concerns identified for the reference medicine. In principle, adverse reactions related to the pharmacological action can be expected at similar frequency for the biosimilar and reference product, if functional, analytical, PK, PD and efficacy comparability data are robust.

Determining factor	Reason for varying amount/type of data
Potential for immunogenicity	Analytical studies are the first step in assessing potential for immunogenicity. To complement this, clinical data on immunogenicity are generally required; animal studies are of limited value in predicting immune response in humans.
Possibility of extrapolating to other indications	Indications of the reference medicine can be approved for the biosimilar in the absence of specific clinical data generated with the biosimilar ('extrapolation of indications'). This can be accepted if all the scientific evidence available from the comparability studies establishes biosimilarity and can address the specific aspects of the 'extrapolated' indication (e.g. mode of action, potentially unique safety or immunogenicity aspects). Extrapolation of data to other indications is always supported by robust physicochemical and in vitro studies to assess all the possible mechanisms of action.

Extrapolation

* If a biosimilar is highly similar to a reference medicine, and has comparable safety and efficacy in one therapeutic indication, safety and efficacy data may be extrapolated to other indications already approved for the reference medicine. **Extrapolation** needs to be **supported by all the scientific evidence** generated in comparability studies (quality, non-clinical and clinical).

* Extrapolation is not a new concept but a well-established scientific principle used routinely when biological medicines with several approved indications undergo major changes to their manufacturing process (e.g. to introduce a new formulation). In most of these cases, clinical trials are not repeated for all indications and changes are approved based on quality and in vitro comparability studies.

Interchangeability, switching and substitution: EMA and Member States' responsibilities

* When EMA carries out the scientific review of a biosimilar, the evaluations do not include recommendations on whether the biosimilar is interchangeable with the reference medicine, and thus whether the reference medicine can be switched or substituted with the biosimilar.

* The decision on whether to allow interchangeable use and substitution of the reference biological medicine and the biosimilar is taken at national level

Basi scientifiche

Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial

Kristin K Jørgensen, Inge C Olsen*, Guro L Goll*, Merete Lorentzen*, Nils Bolstad, Espen A Haavardsholm, Knut E A Lundin, Cato Mørk†, Jørgen Jahnsen†, Tore K Kvien†, on behalf of the NOR-SWITCH study group*

Findings Between Oct 24, 2014, and July 8, 2015, 482 patients were enrolled and randomised (241 to infliximab originator, 241 to CT-P13 group; one patient was excluded from the full analysis and safety set for CT-P13) and 408 were included in the per-protocol set (202 in the infliximab originator group and 206 in the CT-P13 group). 155 (32%) patients in the full analysis set had Crohn's disease, 93 (19%) had ulcerative colitis, 91 (19%) had spondyloarthritis, 77 (16%) had rheumatoid arthritis, 30 (6%) had psoriatic arthritis, and 35 (7%) had chronic plaque psoriasis. Disease worsening occurred in 53 (26%) patients in the infliximab originator group and 61 (30%) patients in the CT-P13 group (per-protocol set; adjusted treatment difference –4·4%, 95% CI –12·7 to 3·9). The frequency of adverse events was similar between groups (for serious adverse events, 24 [10%] for infliximab originator *vs* 21 [9%] for CT-P13; for overall adverse events, 168 [70%] *vs* 164 [68%]; and for adverse events leading to discontinuation, nine [4%] *vs* eight [3%], respectively).

Interpretation The NOR-SWITCH trial showed that switching from infliximab originator to CT-P13 was not inferior to continued treatment with infliximab originator according to a prespecified non-inferiority margin of 15%. The study was not powered to show non-inferiority in individual diseases.

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ECCO Position Statement

ECCO Position Statement

ECCO Position Statement on the Use of Biosimilars for Inflammatory Bowel Disease—An Update

Silvio Danese,[a,b] Gionata Fiorino,[c] Tim Raine,[d] Marc Ferrante,[e] Karen Kemp,[f] Jaroslaw Kierkus,[g] Peter L. Lakatos,[h] Gerassimos Mantzaris,[i] Janneke van der Woude,[j] Julian Panes,[k] Laurent Peyrin-Biroulet[l]

ECCO Statements

* Clinical studies of equivalence in the most sensitive indication can provide the basis for extrapolation. Therefore data for the usage of biosimilars in IBD can be extrapolated from another sensitive indication.
* Switching from the originator to a biosimilar in patients with IBD is acceptable. Studies of switching can provide valuable evidence for safety and efficacy. Scientific and clinical evidence is lacking regarding reverse switching, multiple switching, and cross-switching among biosimilars in IBD patients.
* Switching from originator to a biosimilar should be performed following appropriate discussion between physicians, nurses, pharmacists, and patients, and according to national recommendation.

RHEUMATOLOGY

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Reviewing the evidence for biosimilars: key insights, lessons learned and future horizons

Till Uhlig[1] and Guro L. Goll[2]

Abstract

Biologic therapies have become central to the long-term management of many chronic diseases, including inflammatory rheumatic diseases. Over recent years, the development and licensing pathways for biosimilars have become more standardized, and several biosimilars have been made available for patients with inflammatory rheumatic diseases, such as RA. Pre-licensing requirements for biosimilars mandate the demonstration of comparability with reference products in terms of clinical activity, safety and immunogenicity, whereas post-marketing surveillance and risk minimization requirements are set in place to ensure that long-term, real-world safety data are collected to assess biosimilars in clinical practice. These measures should provide a foundation for physician confidence in biosimilars, which can be established further through clinical experience. Biosimilars may help to fill an unmet need by improving patient access to effective biologic treatments for chronic diseases. Greater access may result in additional clinical benefits, with appropriate use of biologic therapies according to treatment guidelines being associated with improved outcomes and the potential for reduced costs of care. Key challenges for the integration of biosimilars into everyday practice include questions about interchangeability, switching and automatic substitution. Several switching studies have shown that biosimilars can be used in place of reference products while maintaining efficacy and safety. Additional ongoing studies and registries may help to optimize the process of switching, and different funding models are examining the optimal mechanisms to ensure effective uptake of these new treatments.

Key words: biologics, immunogenicity, interchangeability, rheumatologic biosimilars, risk minimization, switching

Rheumatology key messages

- Biosimilar licensing is based on robust non-clinical and clinical evaluation of comparability with reference products.
- The NOR-SWITCH study has shown that switching to biosimilars does not affect clinical outcomes in chronic diseases.
- Biosimilars may enable improved access to biologic treatments for chronic diseases, such as RA.

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SYSTEMATIC REVIEW

Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes

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Abstract

Introduction To evaluate the possibility that switching from reference biologic medicines to biosimilars could lead to altered clinical outcomes, including enhanced immunogenicity, compromised safety, or diminished efficacy for patients, a systematic literature review was conducted of all switching studies between related biologics (including biosimilars).

Methods A systematic search was conducted using the Medline® and Embase® databases up to 30 June 2017 employing specific medical subject heading terms. Additionally, the snowball method and a hand search were also applied. Publications were considered if they contained efficacy or safety information related to a switch from a reference medicine to a biosimilar. Non-English, non-human studies, editorials, notes, and short surveys were excluded.

Results Primary data were available from 90 studies that enrolled 14,225 unique individuals. They included protein medicines used in supportive care as well as those used as therapeutic agents. The medicines contained seven different molecular entities that were used to treat 14 diseases. The great majority of the publications did not report differences in immunogenicity, safety, or efficacy. The nature and intensity of safety signals reported after switching from reference medicines to biosimilars were the same as those already known from continued use of the reference medicines alone. Three large multiple switch studies with different biosimilars did not show differences in efficacy or safety after multiple switches between reference medicine and biosimilar. Two publications reported a loss of efficacy or increased dropout rates.

Conclusions While use of each biologic must be assessed individually, these results provide reassurance to healthcare professionals and the public that the risk of immunogenicity-related safety concerns or diminished efficacy is unchanged after switching from a reference biologic to a biosimilar medicine.

La proposta del convegno nasce dalla pubblicazione del II position paper dell'AIFA sui biosimilari, che sancisce il **principio di intercambiabilità tra biosimilari e originatori di riferimento.**

La discussione sui biosimilari non dovrebbe essere limitata al puro aspetto economico.

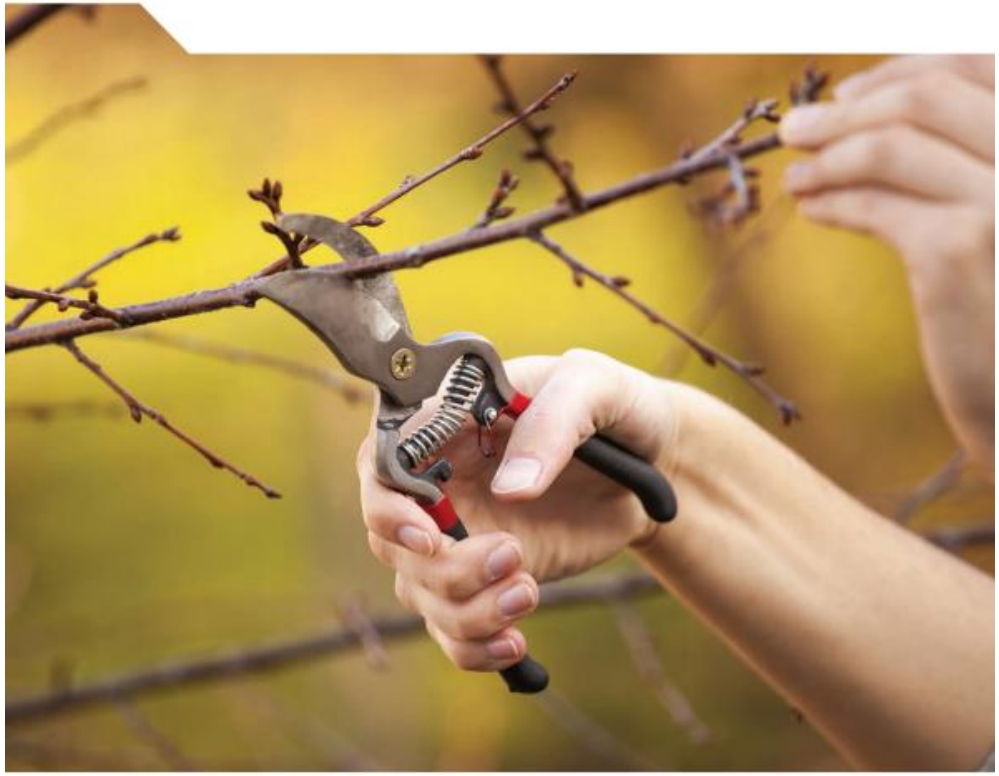
Dal momento che **il *position paper* riconosce al medico prescrittore la scelta del trattamento**, questo deve essere il filo conduttore del convegno.

Nel *position paper* si legge: al medico prescrittore è anche affidato il compito di contribuire ad un utilizzo appropriato delle risorse ai fini della sostenibilità del sistema sanitario e alla corretta informazione del paziente sull'uso dei biosimilari.

E’ una questione economica?

SI

Tackling Wasteful Spending on Health



OECD

PART II

Chapter 4

Reducing ineffective health care spending on pharmaceuticals

by
Karolina Socha-Dietrich, Chris James *and* Agnès Couffinhal

Box 4.1. **Current and future savings from the use of biosimilars**

In parallel with generic drug competition, opening the market to biosimilar competition could realise significant savings for health care systems. For example, between 2016 and 2020 eight key biologics are scheduled to lose patent protection. Analysis of data available for five European countries (France, Germany, Italy, Spain and the United Kingdom) and the United States suggests that a 20% reduction in price per treatment-day across these eight products could result in cumulative savings exceeding EUR 50 billion by the end of 2020 (IMS Institute for Healthcare Informatics, 2016). In 2015, following the introduction of biosimilar competition in one of the most often used classes of biologics – erythropoietins (EPOs) – the observed price reduction (across the class, i.e. for originators as well as biosimilars) varied from 39% in France to 55% in Germany (IMS Institute for Healthcare Informatics, 2016).

Regulation of market entry varies significantly between countries. The European Union approved the first biosimilar in 2006 and is the leader in the number of approved products: 20 as of June 2016. Yet biosimilars' use shows wide variation in the European Union. Even the first biosimilar still has little or no uptake in some countries (e.g. Greece, Ireland and the Slovak Republic), while in Poland it is used in almost all relevant therapies (Ekman and Vulto, 2016). The United States adopted the legislative framework for licensing biosimilars in 2010, but the first biosimilar was approved only in March 2015 (Belloni et al., 2016).

Some policies discussed in this chapter to increase uptake of generics can also be applied to biosimilars. For example, physicians and patients often worry that biosimilars will compromise quality of treatment (IMS Institute for Healthcare Informatics, 2016). Thus regulators should communicate their knowledge more actively and, most importantly, strive to take clear positions on interchangeability between biologics and biosimilars. In Norway and Denmark, where physicians are at the heart of decision making, uptake of biosimilars was rapid and sustained. Similarly, biosimilar competition is strong in Germany, where insurance funds invested in communication with physicians on the subject and subsequently introduced prescribing quotas for biosimilars (IMS Institute for Healthcare Informatics, 2016). A number of countries took a clear position on allowing a switch to biosimilars in the course of treatment, including Denmark, Finland, France, Germany and Norway (Ekman and Vulto, 2016).

E’ una questione economica?

SI, ma a parità di efficacia e sicurezza!

Grazie per la vostra attenzione

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