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Review

The challenging definition of naïve patient for biological drug use

Martina Biggioggero [a], Marco Danova [b], Umberto Genovese [c], Francesco Locatelli [d], Pier Luigi Meroni [a,e,*], Fabrizio Pane [f], Francesco Scaglione [g]

[a] Department of Clinical Sciences and Health Community, University of Milan, Division of Rheumatology, Istituto G. Pini, Milan, Italy
[b] Department of Internal Medicine, Azienda Ospedaliera di Pavia, Pavia, Italy
[c] Department of Biomedical Sciences for Health, University of Milan, Division of Legal and Insurance Medicine, Milan, Italy
[d] Department of Nephrology, Alessandro Manzoni Hospital, Lecco, Italy
[e] Istituto Auxologico Italiano, Milan, Italy
[f] Department of Hematology and Marrow Transplantation, University Federico II of Naples, Naples, Italy
[g] Department of Medical Biotechnology and Translational Medicine, University of Milan, Milan, Italy

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ABSTRACT

Biosimilar is defined by The European Medical Agency as a biological medicinal product, which is similar but not identical to the biological drug already authorized. The biosimilar and its reference product are expected to display the same safety and efficacy profile and are generally used to treat the same conditions. The Italian Medicines Agency considers biosimilars as a valid therapeutic option with an economic advantage, especially in primary naïve patients with no previous exposure to the originator or with a sufficiently long wash-out period ("secondary naïve").

The identification of "secondary naïve" is not well defined and can be subjected to different variables, mainly the drug biologic effect and its immunogenicity. The first one depends on the type of biologics and on their mechanism of action. The second one is related to the fact that biologicals may be immunogenic and can trigger an anti-drug antibody response (ADA). ADA may behave as neutralizing antibodies blocking the active site of the biological but can also recognize other epitopes favoring the formation of immune-complexes that eventually affect the pharmacodynamics. Moreover, the concomitant immune-suppressive treatment can affect the immunogenicity, even if the exact mechanism remains unknown.

In conclusion, the development and use of biosimilars represent a tool for increasing health system sustainability. However it is of paramount importance to distinguish between the pharmacodynamics of a given drug and its immunogenicity being the two aspects unrelated. Thus a detailed definition of "secondary naïve" patients is challenging, and may be related to both the two parameters.

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* Corresponding author at: Centre for Biomedical Research and Technology — Istituto Auxologico Italiano, via G. Zucchi 18, 20095 Cusano Milanino, MI, Italy. Tel.: +39 3357469461.
E-mail addresses: martina.biggioggero@gmail.com (M. Biggioggero), marco_danova@ospedali.pavia.it (M. Danova), umberto.genovese@unimi.it (U. Genovese), f.locatelli@ospedale.lecco.it (F. Locatelli), pierluigi.meroni@unimi.it (P.L. Meroni), fabrizio.pane@unina.it (F. Pane), francesco.scaglione@unimi.it (F. Scaglione).

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1. Introduction

The clinical management and the course of immune mediated inflammatory diseases, anemia, as well as of several types of tumors have dramatically changed by the introduction of biologic therapies [1–3]. The main limitation of biologics is related to their costs and their use may result very expensive overtime. Patents for several biologics will expire over the next decade, removing a barrier to the development and marketing of biosimilars [2–4].

Biosimilars are defined by The European Medical Agency (EMA) as a biological medicinal product, which is similar to the biological drug already authorized, the so-called "reference medicinal product" or "originator". The active substance of a biosimilar medicine is similar to the one of the originator and is used in general at the same dose for treating the same disease(s) [5].

The biosimilar and its reference product are expected to display the same safety and efficacy profile and are generally used to treat the same conditions [6]. Biosimilars can be authorized only if highly similar to the original drug from an analytical and clinical perspective point of view and supported by a "comparability exercise" [5].

As biologics differ from small-molecule drugs because of their molecular size and complexity, multifaceted manufacturing process may induce micro-heterogeneity, and possibly immunogenicity. Biosimilars cannot be considered "generic versions" of currently approved biologics. The interchangeability between the originator and the biosimilar drug cannot be defined a priori and possible differences in inducing rare adverse events and anti-drug antibodies (ADA) should be evaluated. The decision on interchangeability and substitution relies on national competent authorities and is outside the remit of EMA.

2. The prescription status of biosimilars: in which patients should biosimilar be used?

The Italian Medicines Agency (AIFA) confirmed the previous EMA definition of biosimilars in a recent Position Paper [7]. Moreover, AIFA stated that biosimilars cannot be considered interchangeable or simple substitutes of originators and that in case of multiple indications the biosimilarity has to be demonstrated for each single medical condition [7].

The decision to prescribe an originator or a biosimilar remains a clinical indication entrusted to the prescribing specialist physician. AIFA considers biosimilars as a valid therapeutic option available to physicians, and preferable if they constitute an economic advantage, especially in naïve patients [7].

The term naïve patient refers to two specific categories: i) patients with no previous therapeutic exposure to originator ("primary naïve"), and ii) patients with previous exposure to the originator but with a wash-out period of time adequately long based on the judgment of the clinician ("secondary naïve") [7].

3. The problem of the definition of "secondary naïve" patients

The identification of "secondary naïve" patients is not well defined and can be subjected to different interpretations. Hence, it appears mandatory to clarify what exactly we should accept as "secondary naïve" patients and what variables can play a role in such a definition.

The variables potentially affecting the wash-out period can be the drug biologic effect itself and its immunogenicity.

3.1. Drug biologic effect

It is very difficult to generalize what is the correct wash-out period of time for defining a "secondary naïve" patient after a previous exposure to a specific biologic.

Primarily, it depends on the type of biologics and on their mechanism of action. For example, in the case of monoclonal antibodies, there is a big difference between the effect of an antibody targeted to a cytokine (i.e. infliximab) or to a cell surface molecule (i.e. rituximab).

Rituximab is a monoclonal antibody that selectively depletes B cells expressing the cell surface antigen CD20 [8]. CD20 is expressed on pre-B cells and mature B cells but not on stem cells, pro-B cells, or plasma cells [9]. Because CD20 is not expressed on stem cells or plasma cells, depletion of CD20 positive B cells does not appear to compromise either B-cell recovery (from stem cells) or immunoglobulin production (by plasma cells). Rituximab causes a rapid and complete depletion of CD20+ B cells in the bone marrow and incomplete depletion in the peripheral blood [10]. The effects of rituximab are exerted by antibody-dependent and complement-mediated cytotoxicity, as well as by apoptosis-inducing effects that last for a minimum of 16 weeks [11]. Studies in patients with Non-Hodgkin Lymphoma (NHL) have shown that treatment with rituximab results in a sustained but reversible depletion of peripheral CD20 positive B cells for up to 6 months following completion of treatment [12]. So, a therapeutic interval of more than 6 months could be reasonable taking into account the pharmacological effect of the drug, while its immunogenicity is unrelated to its pharmacological effect.

Likely, biological therapies targeting other cell membrane molecules (i.e. co-stimulatory molecules) may affect cell subpopulations in a similar way although no data are available as for anti-CD20 therapy.

Biologicals targeting soluble mediators (i.e. cytokines, growth factors) display a different pharmacodynamics, requiring shorter wash-out periods, when a therapeutic change is decided by the physician. No data are actually available, but a randomized clinical trial regarding the cycling from one tumor necrosis factor inhibitor (TNFi) to another TNFi suggests a wash-out period of at least 8 weeks for drugs with sub-cutaneous administration (i.e. adalimumab or etanercept) and 12 weeks for those with intravenous one (i.e. infliximab) [13], just considering their pharmacological effects.

3.2. Immunogenicity

3.2.1. Immunological memory

The immune system is characterized by the capacity to:

i) recognize self from non-self molecules (antigen specificity),
ii) produce a response against a given antigen (Ag) (Ag immunogenicity) through the expansion/activation of specific clones of effector cells (clonal selection), and
iii) maintain a specific memory of the Ag (immunological memory).

The clonal selection theory explains the cellular basis for both the immune response and the immunological memory [14]. The immunological memory is generated during the primary immune response. Most of the Ag-specific effector cells die in few days/weeks while memory cells are long-living after the original activation and display the same Ag-specificity. Immunological memory is almost life-long and can produce an anamnestic response if stimulated by the same Ag. For example, CD4 and CD8 positive T cells specific for the smallpox can be found even 75 years after the initial contact [15]. Their number is however decreasing over time in contrast with the anti-virus antibody titer that is usually kept constant, unless a new antigen stimulation takes place. The biological mechanisms responsible for the maintenance of the immunological memory are still a matter of research.

Biologicals, even when totally humanized, are immunogenic molecules that can be recognized as non-self Ag and able to trigger a detectable antibody response (ADA) [16]. Biologicals are given through a parenteral route and in most cases subcutaneously. Such a route is the best way to increase their immunogenicity like an active immunization (vaccination).

Patient related factors may influence immunogenicity [17]: i) differences in major histocompatability and human leukocyte antigen

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