Understanding the nocebo effect that can help in optimizing treatment outcomes with biosimilars

Mourad F Rezk

Abstract

Various theories have attempted to clarify the notable self-influenced consequence of some latent fixings as a result of patient's assumptions. The extended utilization of generics and now the expanding utilization of biosimilars have carried another definition to the consideration of clinicians who will in general depict the relationship between's negative assumptions or negative correspondences with negative emotional treatment results as the nocebo impact, a wonder that can cause the enlistment or the deteriorating of side effects by trick or dynamic treatments may represent some unfavorable occasions (AEs) announced by patients following treatment. Nocebo reactions may happen as unintended aftereffect of the necessity for medical services experts to clarify potential confusions and results while starting therapy.

Deluding or over negative correspondences may set negative expatiations at the patients' level which may at last trigger negative view of treatment results and a propensity to overreport unfavorable occasions and to pull out from treatment regimens. Appropriate reality based clarifications by medical care experts combined with procedures to console and draw in patients after starting or changing to a biosimilar are key in guaranteeing better therapy results and supportability on biosimilars to guarantee more extensive access for patients to complex biologics and lessen the monetary weight on medical care frameworks.

Introduction

Advanced biologic medicines have been widely used in changing the course of many chronic and lifethreatening diseases. The high cost of these biologics is an increasing burden to healthcare systems and limiting their sustainable accessibility to patients. The loss of exclusivity of many biologics and the setting of a clear and robust regulatory approval pathway have paved the way for the introduction of more affordable biosimilars that, once developed, are rigorously evaluated to ensure similar molecular structure, efficacy, and safety to their reference biologics. Since 2007, more than 20 biosimilars have been approved by the European Medical Association (EMA), including the first biosimilar monoclonal antibody (mAb) **CT-P13** (infliximab biosimilar), which was followed by SB4 (etanercept biosimilar) and SB2 (infliximab biosimilar) for the treatment of autoimmune diseases, such as rheumatoid arthritis. psoriatic arthritis. axial spondyloarthritis, psoriasis, and inflammatory bowel disease.

Further biosimilars that have recently received EMA approval include ABP501 (adalimumab biosimilar), GP2015 (etanercept biosimilar), and GP2013 and CT-P10 (rituximab biosimilars). Collectively, these biosimilars have helped reduce the overall spend and also increased patient access to effective biologic treatment.

Nevertheless, surveys of patients' and clinicians' views clearly demonstrate important gaps in their level of awareness and perception of biosimilars, which occasionally trigger feelings of uncertainty and ungrounded negative attitudes towards prescribing or receiving biosimilars. The role of negative perceptions and attitudes were previously described and are known to have the potential to negatively impact adherence and treatment outcomes.

Different publications have described this as the nocebo effect, which is the negative equivalent to a placebo effect, and have looked into its impact on adherence to medications. Special attention has been given to the nocebo effect on the adherence to generics, and different researchers have explored the potential nocebo

Mourad F Rezk

Medical and Scientific Affairs, Switzerland, E-mail: mouradfarouk.rezk@biogen.com

mechanisms and proposed approaches to minimize it. In our paper, we will specifically draw additional light on the nocebo effect to help optimize the use of, and adherence to, biosimilars and hence ensure favorable and sustainable clinical outcomes.

This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

Perception of Biosimilars: Awareness and Communication Gaps

For reference biologics, the aim of the developmental process is to demonstrate de novo the risk-benefit profile of the candidate product. However, during biosimilar development, the aim is to demonstrate high biosimilarity with the reference biologic in terms of structure, physicochemical attributes, and biologic activity, and to reconfirm the efficacy, safety, and immunogenicity profile as it was previously established by the reference biologic during its development process.

The majority of effort in establishing similarity is performed during comprehensive non-clinical comparability exercises, whereupon any potential difference in terms of critical quality attributes between the biosimilar and reference biologic are more likely to be detected. Following this, and to achieve regulatory approval, a phase I pharmacokinetic clinical study in humans must be carried out to demonstrate pharmacokinetic equivalence.

At least one phase III, randomized clinical trial is then performed in a sensitive patient population representative of those included in an approved indication for the reference biologic, to demonstrate equivalent efficacy and comparable safety and immunogenicity of the biosimilar and its reference biologic.

Post-marketing authorization studies, together with realworld data from registries and clinical centers, provide additional confirmation for the long-term effectiveness, safety, and immunogenicity of approved biosimilars. All this taken together comprises the totality of evidence for a biosimilar, highlighting the rigorous process in which biosimilars are developed and monitored.



However, despite biosimilars having been available since 2007 and, although vast amounts of preclinical, clinical, and real-world evidence confirming similar quality, equivalent efficacy, and comparable safety of the biosimilars to their reference biologic are available, a perception gap (likely due to low awareness of available data and lack of communication of these data) among physicians and patients still exists.

Although the majority of physicians are aware of biosimilars, knowledge gaps regarding the effectiveness and safety of these molecules can sometimes exist, which may lead to uncertainties around their use in daily clinical practice. Patient knowledge, understanding and perception of biosimilars also play an important role with regard to acceptance and treatment outcomes.

Patients who are aware of biosimilars tend to have more positive perceptions regarding biosimilars than patients who are unaware; however, perception regarding efficacy and safety of reference biologics is higher than for biosimilars. Therefore, low awareness and misconceptions of biosimilars may create, or widen, gaps in physician and patient perceptions, thereby impacting the use of biosimilars (as patients are less comfortable switching) and their outcomes.

In general, patient perception of treatment is also important when considering treatment adherence because a negative perception of treatment efficacy can cause non-adherence, as can lack of knowledge about a disease and its treatment. In addition, drug profiles play

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an important role, with patients more likely to discontinue treatment due to a poor side-effect profile or lack of efficacy of a medication. For example, in patients with rheumatoid arthritis, discontinuation rates due to inefficacy and adverse events were demonstrated in etanercept (17.5 and 22.4%, respectively), infliximab (44.1 and 36.7%, respectively) and adalimumab (50.4 and 31.2%, respectively) over a period of 12 years.These data highlight the importance efficacy and safety of a medication plays in patient adherence to treatment.

A Common Phenomenon Known as the Nocebo Effect Can Impact Outcomes

Perception gaps may be related to a nocebo effect that can lead to the induction or the worsening of symptoms induced by sham or active therapies. When a nocebo effect is seen with an active therapy, this is a nonspecific response in that the symptoms or physiologic changes cannot be explained on the basis of the known pharmacology of the drug and is not dose-dependent. Nocebo symptoms are typically generalized and diffuse, including drowsiness, nausea, fatigue, and insomnia.

Patients in general are highly receptive, but women, patients with psychiatric illness, or individuals with certain personality traits (e.g., aggressive or competitive) have been shown to be more susceptible to a nocebo effect. Psychologic mechanisms, including classic conditioning (when a neutral, inert or inactive stimulus can elicit a physiologic change if these have previously been repeatedly paired with a provocative stimulus), negative expectations and suggestibility can underlie the nocebo effect.

A perceived increase in dose of medication, suggestions by healthcare professionals (HCPs) that the medication triggers symptoms, observations of other people experiencing symptoms and higher expectations of symptoms are also strong predictors of the nocebo effect. Verbal and non-verbal communications from the HCP that may contain unintentional negative connotations, such as "this medication may help" or "let's try this drug", may also trigger a nocebo response in patients.

This effect has previously been observed in several therapy areas, including pain, Parkinson's disease, and

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cardiovascular disease. The nocebo effect was very recently demonstrated in patients receiving statins, where an excess rate of muscle-related adverse events were reported only when patients and their doctors were aware that statin therapy was being used, and not when its use was blinded. It is also very well recognized in patients who switch from a reference medicine to chemically identical generics.

Nocebo Effect in Patients Prescribed Biosimilar Agents

Recently, this nocebo effect has also been considered in patients switching from reference biologics to biosimilars. In observational studies, 16-28% of patients were found to discontinue CT-P13 biosimilar following ≥ 3 months of treatment.

Additionally, it was suggested that these discontinuation rates might have been slightly higher than those historically reported with the reference biologic and that this difference could be partially explained by perceived loss of efficacy and minor adverse events (such as fatigue, malaise, and headache), despite no changes in efficacy, safety. or immunogenicity being observed.

The authors concluded a nocebo effect was likely; however, they recommended further investigation to fully understand this phenomenon with regard to biosimilar use. The discontinuation rates stated in these publications are higher than those seen in registries and clinical center studies in patients treated with the etanercept biosimilar, with some reporting $\leq 9\%$ discontinuation rate following ≥ 5 months of treatment. Interestingly, these are far lower than those seen in Turkey, where medical billing records from patients with rheumatoid arthritis were analyzed, and 63 and 82% of biologic-naïve and switch patients (from INF to CT-P13), respectively. discontinued biosimilar treatment. However, the authors of these studies concluded further analysis was required to understand the reasons for these observations.

Overall Consequences of the Nocebo Effect

Considering that the nocebo effect has been shown to impact the number of adverse events experienced by a patient, result in perceived loss of efficacy, and lead to

Medical and Scientific Affairs, Switzerland, E-mail: mouradfarouk.rezk@biogen.com

non-adherence to a medicine, the consequences to the healthcare system are far-reaching. Not only does this affect patients' quality of life, but it can also affect how HCPs resolve these additional adverse events, which can lead to more complicated treatment regimens, or needless switching of the patient to previous treatments and possibly reducing their future treatment options. Collectively, dealing with nocebo effects results in additional patient clinic visits, which places more pressure on a healthcare system and can lead to the cost savings of biosimilars not being realized.

Strategies to Minimize the Possibility of a Nocebo Effect with Biosimilar Agents

Given that the nocebo effect can prompt non-adherence, which can have far-reaching consequences for a patient and healthcare systems, it is recommended that HCPs employ interventions to help minimize these effects from occurring. Invariably, owing to time restrictions in a busy clinic, it can be challenging to perform a thorough patient-physician discussion to ensure informed shared decision-making and reduce the likelihood of a nocebo effect from occurring. However, various strategies can be implemented in the clinic to help informed decision-making and negate the nocebo effect, including identifying patients at high risk, determining patient expectations of adverse events and providing reassurance if these are excessive, tailoring information to only provide pertinent details to the patient, reducing exposure of the patient to others experiencing side effects, and educating the patient on nocebo effects using case studies. Physicians should consider implementing motivational interviewing techniques into the clinic by subtly guiding the patient to think about and verbally express their reasons for and against change, so that the patient is making an informed and considered choice, which is likely to help reduce the nocebo effect.

In addition, any HCP who talks to patients about the potential use of a biosimilar must themselves feel fully confident and capable of transferring this confidence, and help a patient make an informed shared decision, without unintended negative suggestions, which may trigger an inappropriate negative bias and a nocebo response.

Information on biosimilars is now available from

several distinct sources that help to inform and build HCP confidence when making informed shared treatment decisions with their patients. This includes data from clinical trials, data from large observational from individual registries. data case studies. institutional experiences, and information guides released by regulatory bodies. Well-informed HCPs who are aware of these data are more likely to become confident and then be able to transfer this confidence in biosimilar medication to their patients, resulting in patient confidence regarding their choice, whether they eventually choose to switch or not, which should alleviate the nocebo effect.

Emerging research has shown how influential patientphysician interaction is on the perception of efficacy and safety of biosimilars, as it is with other therapies. For example, researchers at the Parker Institute, Denmark, have identified strong barriers and facilitators to the patient experience and highlighted patientphysician interaction as critical to ensure perceived treatment value for the patient. They highlighted that when treatment discussions with patients occur, it is important to appreciate that single biased words and gestures can have a significant impact and should be avoided to ensure minimal negative instructions and negative therapeutic context. Similarly, a recent openlabel study compared the effects of switching patients with a rheumatic disease from a reference product to a biosimilar agent (infliximab to CT-P13 in 2016 and etanercept to SB4 in 2017) using different communication strategies, including: notifying all patients at the same time; clearly informing patients about the reasons for the switch; providing 'soft skills' training for rheumatology and pharmacy staff to help them moderate patient concerns: and openly discussing possible nocebo effects.

They found that this led to higher patient acceptance and persistence rates compared with patients who did not receive this enhanced communication strategy. Further real-world data also show that comprehensive patient education and support (including face-to-face discussions; provision of patient information sheets on drug switch and biosimilars; access to a helpline number and regular clinical reviews) during the switch to a biosimilar product resulted in higher acceptance of these agents by patients, which may also help reduce the nocebo effect.

Conclusions

Although comprehensive comparability studies are used to ensure that biosimilars are approved according to the same quality, safety, and efficacy standards that apply to all biologic medicines, information gaps exist that can cause uncertainties amongst physicians and patients, and are heightened by the nocebo effect, which ultimately prevent the full benefits of biosimilars being realized. Given the important role biosimilars play in increasing physician treatment options and patient access to biologic medicine, it is important that HCPs are aware of this nocebo phenomenon and aim to reduce this effect when possible. As this effect could also occur when patients are switched from a reference biologic agent to biosimilar agents, HCPs should ensure they are fully familiar with the available data on biosimilar treatment from trials, registries, and case studies, and also be mindful of their potential to create bias in the mind of the patient through their choice of words and any perceived lack of confidence. Additionally, a thoughtful evaluation of patients' worries and perspectives and addressing them in a constructive and objective manner may further optimize patients' adherence to biosimilars and limit unwanted nocebo effects.

Acknowledgements

This article was funded by Biogen. Article processing charges were funded by Biogen. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published. Biogen provided funding for medical writing support in the development of this paper; Rugina Ali and Philip Ford, from INC Research/inVentiv Health, wrote the first draft of the manuscript based on input from authors, and Elisabeth Beatty from INC Research/inVentiv Health copyedited and styled the manuscript per journal requirements.

The authors had full editorial control of the paper, and provided their final approval of all content.

Disclosures

11th European Biosimilars Congress

April 26-27, 2018 | Rome, Italy

Mourad Farouk Rezk is an employee of Biogen

This work is partly presented at 11th European Biosimilars Congress, April 26-27, 2018 Rome, Italy

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International Gmbh and therefore receives a salary and may own Biogen stock. Burkhard Pieper is an employee of Biogen International Gmbh and therefore receives a salary and may own Biogen stock.