https://doi.org/10.31925/farmacia.2022.3.1 **REVIEW**

A PHARMACEUTICAL GUIDE TO ADALIMUMAB BIOSIMILARS

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Manuscript received: February 2022

Abstract

The development of monoclonal antibodies has revolutionized the pharmaceutical industry by offering clinicians a wide range of therapeutic agents for the treatment of a variety of disorders. Unlike small molecule drugs, monoclonal antibodies are large and complex molecules that are generated using genetically engineered living cells. Due to the high complexity of this class of molecules, producing exact copies is impossible and with several originator biological agents losing their patents in recent years, several pharmaceutical manufacturers are pursuing the development of generic biopharmaceuticals or what is known as "biosimilars" as alternative biological therapeutics. Adalimumab represents one of the most prescribed monoclonal antibodies in clinical practice. With the originator adalimumab losing its patency in 2018, several manufacturers are pursuing the development of adalimumab biosimilars with varying degrees of quality and thus exposing different markets to biosimilars of inferior quality or what is known as intended copies. These molecules could pose a major harm to patients as a result of the unexpected immunogenicity or lack of efficacy that results from their lack of similarity to the originator biologic. The aim of this review is to provide technical guidance for the pharmaceutical personnel working in research and development of adalimumab biosimilars in addition to regulatory assessors' worldwide reviewing biosimilars dossiers within public health authorities. The review article will detail all the development stages needed for the development of adalimumab biosimilars within the comparability exercise that is required by manufacturers to provide regulatory agencies with strong evidence of adalimumab biosimilarity.

Rezumat

Apariția anticorpilor monoclonali a revoluționat industria farmaceutică, oferind clinicienilor o gamă largă de agenți terapeutici pentru tratamentul multor afecțiuni. Spre deosebire de substanțele medicamentoase cu molecule mici, anticorpii monoclonali sunt molecule mari și complexe, generate de celule vii modificate genetic. Ținând cont de expirarea patentelor pentru agenți biologici inovatori, producătorii urmăresc dezvoltarea de biofarmaceutice generice sau ceea ce se cunoaște sub denumirea de „biosimilare". Adalimumab reprezintă unul dintre cei mai prescriși anticorpi monoclonali în clinică. O dată cu expirarea patentului adalimumabului în 2018, mai mulți producători urmăresc dezvoltarea de biosimilare. Acestea pot avea grade diferite de calitate și, astfel, expun pacienții la biosimilare de calitate inferioară. Aceste molecule ar putea aduce un prejudiciu major, ca urmare a imunogenității neașteptate sau a lipsei de eficacitate care rezultă din lipsa de similitudine a acestora cu substanța biologică originală. Scopul acestui *review* este de a orienta personalul farmaceutic care lucrează în cercetarea și dezvoltarea biosimilarelor cu adalimumab. Acest studiu detaliază toate etapele de dezvoltare necesare pentru biosimilarele cu adalimumab, cu scopul de a oferi agențiilor de reglementare dovezi privind biosimilaritatea.

Keywords: biosimilars, adalimumab, comparability, monoclonal antibodies, rheumatoid arthritis

Introduction

Monoclonal antibodies (mABs) revolutionized the standard treatment of a variety of common diseases including cancer, rheumatoid arthritis and other immune mediated disorders [1]. mABs fall under the umbrella of biopharmaceuticals, a class of therapeutics that include other protein-based drugs with less complexity such as insulin, erythropoietin and human growth hormone [2]. What differentiates monoclonal antibodies from other biological agents is the high complexity of their three-dimensional structure and significant manufacturing costs associated with their production [3]. The complexity of mABs poses significant limitations on the analytical techniques that are capable of characterizing the structural, physicochemical and biological properties of these agents when compared with classic small molecule drugs such as aspirin and other chemically synthesized medicines [4]. mABs are classified into chimeric, humanized and fully human antibodies [5]. This classification is based on the degree and presence of non-human components within the mAB structure with the chimeric antibodies displaying the highest degree of xenogenicity with the non-human components comprising 35% of the overall structure, while the fully human antibodies which are usually generated using advanced biotechnological techniques such as phage display libraries and transgenic mice technology producing mABs that are fully human

in their composition and contain (0%) non-human components within their structure. The decrease in the non-human composition of mABs as the case with the fully human antibodies is associated with reduced immunogenicity that is usually induced as a result of the foreign biological components embedded in the mAB structure and consequently would reduce the level of neutralizing antibodies produced by the immune system against mABs leading to a decrease in the efficacy of the mABs and increase the occurrence of immune relates adverse events [6, 7].

Adalimumab (Humira®) was the first fully human monoclonal antibody to be approved by regulatory agencies for the treatment of elevated TNF-alpha associated immune disorders [8]. The antibody is designed to bind tumour necrosis factor alpha (TNF-α) which is over expressed in several autoimmune related chronic inflammatory diseases and plays a major role in the pathogenesis of these disorders [9]. Humira® is approved in Europe for the treatment of RA, juvenile idiopathic arthritis (JIA), plaque psoriasis and psoriatic arthritis (PsA), ankylosing spondylitis (AS), adult and paediatric Crohn's disease, ulcerative colitis, hidradenitis suppurativa (HS) and uveitis [10].

Several originator biological agents have lost their patents in the recent decades which allowed other pharmaceutical manufacturers to pursue the development of generic biopharmaceuticals or what is known as "biosimilars" as alternative biological therapeutics that would provide substantial cost reduction for public and private health authorities [11]. The road to biosimilars development was facilitated with the introduction of a dedicated regulatory pathway for biosimilar registration by both the European medicines agency (EMA) and the US Food and Drug Administration (FDA) which resulted in the approval of EU's first biosimilar (Epoitein alpha) in 2007 and the approval of filgrastim in the US as the first biosimilar agent in 2015 [12].

As with several biological agents, Humira®'s patent has expired within the EU in October 2018 paving the way for the development, registration and approval of several adalimumab biosimilars worldwide. Currently, there are more than twelve adalimumab biosimilars approved both by EMA and the US FDA [13]. In 2021, Humira® has generated a record total revenue of 20.7 billion dollars. This record number in total sales for Humira® in addition to the patent expiry of adalimumab will allow several competitors to introduce adalimumab biosimilars with varying degrees of quality and thus exposing different markets to biosimilars of inferior quality or what is known as intended copies or biomimicks that do not meet the minimal rigorous regulatory threshold for biosimilar registration and approval set by regulatory authorities and consequently could pose a major harm to the patient population as a result of the unexpected immunogenicity or lack of efficacy associated with these kind of agents [14, 15].

In this review article, we aim to discuss the main technical components of the biosimilarity exercise required for the registration and regulatory approval of adalimumab biosimilars. This review will provide guidance for the pharmaceutical personnel working in research and development of adalimumab biosimilars in addition to regulatory assessors' worldwide reviewing biosimilars dossiers within public health authorities. The review will detail the minimal threshold technical requirements that are expected to be included within an adalimumab biosimilar dossier to ensure high similarity between reference adalimumab and its biosimilars. The EMA guidelines have set the primary principles for non-clinical and clinical requirements needed to establish the comparability between a reference mAb and its biosimilar [16]. Accordingly, the review will build on EMA guidelines and provide the detailed analytical, biological and clinical aspects needed for a rigorous biosimilarity exercise for adalimumab.

Non-Clinical Data

Physicochemical similarity

The first step in the establishment of biosimilar similarity for adalimumab biosimilars is to perform state of the art orthogonal analytical techniques to demonstrate the high similarity in the structure, post-translational modifications, higher order structure and physicochemical properties between the reference adalimumab and its biosimilars. This step is crucial for the confirmation of the biosimilarity of adalimumab biosimilars and is related to the complexity of the structure of mAbs and the effect of slight variation in its three-dimensional structure on the efficacy, immunogenicity and pharmacodynamics of the biosimilar. Table I Lists the major structural and physicochemical properties, analytical techniques acceptable limits that are expected to be performed in order to confirm biosimilarity and detect any potential variability that could affect the biological activity and binding of adalimumab to its target. The major properties to be investigated include: *primary structure* including post-translational modifications; *secondary and higher order structure*; *purity and related size and hydrophobic species* variants; *glycan profile and molecular weight of size* variants. The similarity for each property should be investigated by employing highly sensitive analytical techniques and tests for each property including liquid chromatography electrospray ionization mass spectroscopy (LC-ESI-MS), reverse phase high performance liquid chromatography (RP-HPLC), Edman degradation, FTIR Spectroscopy, reducing and non-reducing SDS PAGE, high performance size exclusion chromatography and others. The choice of the analytical technique should be chosen carefully in order to validate and authenticate the structural similarity of adalimumab's biosimilar.

Table I

Structural and Physicochemical quality attributes, parameters and analytical techniques required for adalimumab's biosimilarity exercise

Quality attribute	Specific parameter	Methods/Tests	Acceptable limits
Primary Structure including post-translational modifications	Amino acid sequence	Peptide mapping LC-ESI-MS	Identical amino acid sequence
		RP-UHPLC-UV	
	N and C Terminal Variants	LC-ESI-MS	Similar to reference
		Edman Degradation	
	Intact Molecular weight	LC-ESI-MS	Similar to reference
	Intact and deglycosylated subunit molecular weight	LC-ESI-MS	Similar to reference
	Disulphide bond	Reduced and non-reduced peptide mapping – LC-MS	Similar to reference
	Isoelectric point (pI)	Isoelectric focusing (IEF)	Similar to reference
	N-Glycosylation site	Peptide mapping	Similar to reference
	Extension coefficient	Acid hydrolysis – UV spectroscopy	Similar to reference
Secondary and Higher order structure	Secondary structural content	Far UV CD Spectroscopy	Identical
		FTIR Spectroscopy	
	Tertiary structure	Near UV CD Spectroscopy	Identical
		Intrinsic Fluorescence (IF)	Similar wavelength
		Thermal denaturation by DSC	Similar profile
Glycosylation	Mannosylation (M5), Galactosylation, Fucosylation and Sialylation	Glycan profiling using various chromatography techniques	Acceptable minor quantitative differences
	Galactose, Fucose, Mannose, GlcNAc and Sialic acid contents	Acid hydrolysis and RP-HPLC FD	Acceptable minor quantitative differences
	Glycosylation site occupancy	Mass spectrometry	Comparable amounts of site occupancy
Physico-chemical properties	Purity and related size species variants	Size exclusion chromatography	Highly similar profile
		Reducing and non-reducing SDS PAGE	Highly similar profile
		Reducing and non-reducing CE-SDS	Highly similar profile
		Capillary isoelectric focusing (cIEF)	Highly similar profile
	Purity & Related Hydrophobic Variants	Size exclusion chromatography	Similar to reference
	Sub-visible particle analysis	Microflow Imaging Technology	Similar to reference
	Sub-visible particle identity	Raman microscopy	Similar to reference
	Purity & Related charge related Variants	Cation Exchange chromatography (CEX-HPLC)	Similar to reference
	Process related impurities	Residual DNA analysis	Comparable amounts of residual DNA
		Host cell particles	Similar to reference

Functional similarity

The structural and physicochemical comparability of adalimumab biosimilars is supported by additional functional and biological comparability test as part of the non-clinical data required to support the similarity exercise. These biological characterization techniques include several assays that are required to detect any variability between the reference product and its biosimilar in regards to their biological activity. For adalimumab the *in vitro* analytical techniques and assays are designed to evaluate the Fab-related biological activities of adalimumab and its capability to bind soluble TNF-α, transmembrane TNF-α and induction of apoptosis. Additionally, the biological *in vitro* exercise should be able to evaluate the Fc-related biological activity of the biosimilar including the binding of the reference adalimumab and its biosimilar to FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa, FcRn, C1q binding, as well as ADCC and CDC activities. Table II lists the major *in vitro* studies and analytical techniques required to demonstrate adalimumab biosimilars functional similarity.

Table II

In vitro functional and biological quality attributes, parameters and analytical techniques required for adalimumab's biosimilarity exercise

Quality attribute	Specific parameter	Methods/Tests	Analytical Similarity Summary
Binding assays	Binding to soluble TNFα	Dye binding cell-based assay	Highly similar dose response curves and potency
		ELISA	
		Surface plasmon resonance (SPR)	
	Binding to transmembrane TNFα	Flow cytometry	Comparable binding activity
	FCγRI binding affinity	SPR	Comparable binding activity
	FCγRIIa binding affinity	SPR	Comparable binding activity
	FCγRIIb binding affinity	SPR	Comparable binding activity
	FCγRIII-a-F^{158} binding affinity	SPR	Comparable binding activity
	FCγRIII-a-V^{158} binding affinity	SPR	Comparable binding activity
	FcRn binding affinity	SPR	Comparable binding activity
	C1q binding ability	SPR	Comparable binding activity
***In vitro* bioassays**	ADCC	Cell based assay	Comparable activity
	CDC	Cell based assay	Comparable activity
	Apoptotic activity	Cell based assay	Comparable activity
	Macrophage induction	Cell based assay	Comparable activity

Non clinical in vivo similarity

The requirements of biosimilar manufacturers to perform nonclinical *in vivo* studies according to EMA and the US FDA follows a stepwise approach of analysing the results of the *in vitro* structural and biological comparability exercise to determine the need for additional *in vivo* animal pharmacodynamics studies. Accordingly, several mAb biosimilars are waived from performing such studies due to the extensive evidence of comparability as a result of the data provided in the structural and functional *in vitro* studies. However, for adalimumab biosimilars, additional *in vivo* animal studies are required in some cases to provide additional evidence to support the efficacy of the biosimilar through employing animal models that are designed to mimic the main pathological features of human Rheumatoid arthritis. This is usually performed on transgenic animals such as mice with over expressed TNF-α in order to reproduce the RA pathological features. The mice are treated with both the reference adalimumab and its biosimilar and evaluated using a defined macroscopic arthritis scores and histopathological joint related scores. Secondary pharmacodynamics and safety studies are not required for the comparability exercise of adalimumab biosimilars.

Toxicological data is also considered an essential part of other non-clinical studies required for demonstrating the safety of the adalimumab's biosimilar before proceeding to human clinical studies. These toxicological studies are usually performed on monkeys or rabbits and include single and repeated dose toxicity studies with the biosimilar and its reference adalimumab. The toxicological studies could be employed for the generation of toxicokinetic data and preliminary comparability pharmacokinetic profiling. However, all pharmacokinetic data should be extrapolated from human clinical studies.

Clinical Data

Pharmacokinetic clinical similarity

The clinical program of adalimumab biosimilars should start with a Phase I Pharmacokinetic study on healthy volunteers to determine the pharmacokinetic profile, safety and immunogenicity of the adalimumab biosimilar and its reference product. The design of the study should follow standard PK parameters and include either a single blind, parallel group design or a double-blind crossover design with a sample size convenient for PK data extrapolation. The study can be two or three armed including the biosimilar arm and at least one reference arm and in some cases two reference arms form different manufacturing sites. The main comparability PK endpoints that should be extrapolated form the study includes maximum concentration (C_{max}), area under the concentration-time curve (AUC) from zero time to infinity (AUC_{inf}) AUC from zero time to last quantifiable concentration (AUC_{last})T_{max}, K_{el}, $t_{0.5}$, V_d and Cl rate. Additionally, secondary endpoints such as tolerability and immunogenicity of the bio-similar and its reference product should be assessed accordingly. PK bioequivalence would be concluded if the 90% confidence interval (CI) of the geometric mean ratios of natural-log transformed AUC_{inf} and C_{max} for the test product and the reference product lies within 80% to 125%. The immunogenicity protocol should aim at detecting antidrug antibodies and neutralizing antibodies (Nabs) during the full duration of the study.

Clinical efficacy and safety

Following the determination of PK and immunogenicity studies, the clinical program should expand and build evidence on the step-wise approach of the comparability exercise of adalimumab biosimilars and their reference product and fill the final step required for the totality of evidence needed to demonstrate biosimilarity. At this stage, a comparative Phase III clinical trial should

be designed to demonstrate the comparable efficacy and safety of adalimumab biosimilar and its reference product taking into consideration that the aim of the study is not to demonstrate the efficacy of the biosimilar *per se*, but rather to demonstrate that there are no clinically significant differences between the biosimilar and the reference product. Accordingly, the design of the Phase III clinical trials should take careful consideration of the choice of the most sensitive patient sample and therapeutic indication, sample size, sample homogeneity, primary and secondary endpoints and clarification of the equivalence margins. For the adalimumab biosimilars, the most sensitive patient population would typically include patients with moderate to severe rheumatoid arthritis and the primary comparability endpoint being ACR20, a clinical score developed by the American College of Rheumatology that is defined as both improvement of 20% in the number of tender and number of swollen joints, and a 20% improvement in three of the following five criteria: patient global assessment, physician global assessment, functional ability measure (most often Health Assessment Questionnaire (HAQ)), visual analogue pain scale, and erythrocyte sedimentation rate or C-reactive protein (CRP). The sample size of the patient population should be justified based on proper statistical methodology and past literature relevant to clinical studies that were performed to address the efficacy of the originator adalimumab and the relevant therapeutic indication in addition to the duration of treatment. The EMA and FDA do not provide clear regulatory guidelines regarding the sample size of Phase III clinical trials designed for biosimilars comparability exercise which could provide ambiguity in the sample size design and prove to be a major barrier to biosimilar development due to the significant cost of Phase III clinical trials. However, it is suggested that an acceptable sample size for a comparability Phase III trial of adalimumab biosimilars should range between 290 as a minimal threshold and 620 as a maximal threshold for a randomized, parallel, active-reference controlled design trial for patients with moderate to severe rheumatoid arthritis and employing ACR20 as the primary comparability endpoint for the trial [17]. Figure 1 provides a summary of the technical and clinical requirements for performing the comparability exercise of adalimumab biosimilars.

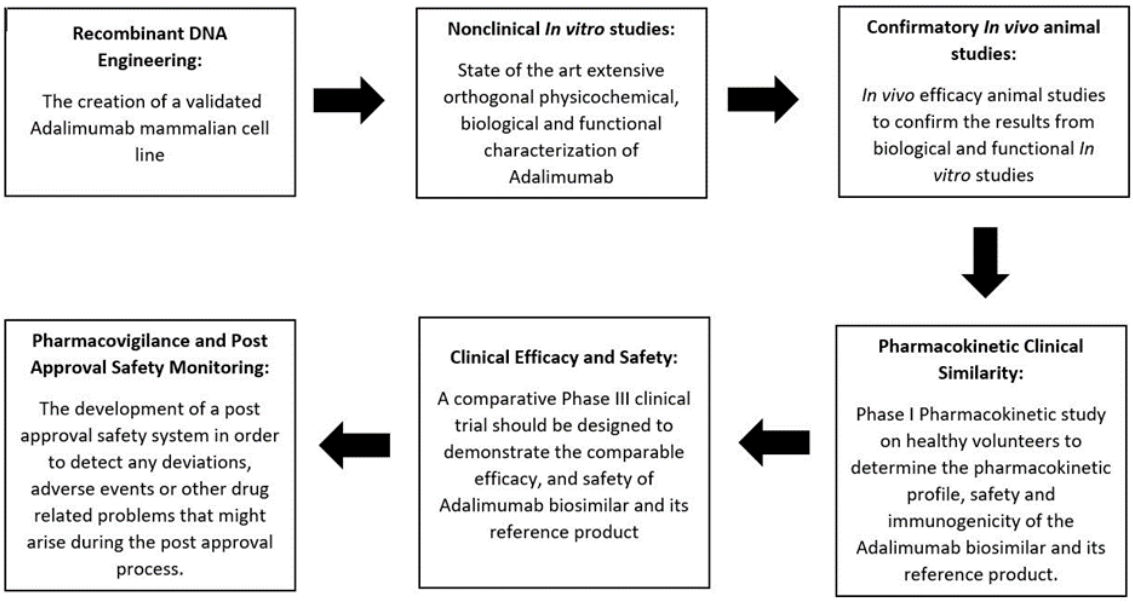

Figure 1.
The multiple stages of the comparability exercise for adalimumab biosimilars

Extrapolation of Indications

The regulatory pathway for the approval of adalimumab biosimilar does not require the manufacturer to perform comparable clinical trial for each of the approved indication for the originator adalimumab. The totality of evidence produced from the development program of the biosimilar and the comparability exercise performed including the Phase III trial on one indication allows the extrapolation of indications and is deemed acceptable [18]. This extrapolation in indication is justified when the pathogenesis of the different diseases is considered similar between the different indications for adalimumab as it is targeting the reduction of elevated levels of TNF-α [19]. From a regulatory point of view, the extrapolation of indication is indicated to reduce the time and costs associated with performing clinical trials for the different indications approved for the originator biologic. The majority of the approved adalimumab biosimilars has relied on rheumatoid arthritis as the main indication to be employed for extrapolation to other indications as it represents the

most sensitive and largest group of patients benefiting from the molecule itself.

Pharmacovigilance and Post Approval Safety Monitoring

Pharmacovigilance represents an important component of the post-approval program of biosimilars due to the immunogenic potential that might arise after long-term therapeutic use of the biological agent which in turn could lead to a significant effect on the safety and efficacy of the biosimilar. The immunogenicity of the biosimilar is closely monitored and evaluated during the comparability exercise as part of the development program and in comparison with the reference product. However, the manufacturer is responsible for developing a post approval safety system in order to detect any deviations, adverse events or other drug related problems that might arise during the post approval process. Regulatory agencies must also highlight the importance of pharmacovigilance for physicians and pharmacist working closely in the prescription and dispensing of biosimilars due to the unique characteristics of the products, their manufacturing and approval pathway which requires close monitoring to avoid any negative consequences that could pose a threat to the patients' safety and therapeutic outcomes.

Interchangeability and Automatic Substitution

Interchangeability of medications refers to the clinical practice of switching treatment from one biological reference (originator) agents to its biosimilar with the expectation that switching will produce the same therapeutic and clinical outcome for any patient in any clinical setting [20, 21]. Once interchangeability is confirmed, this is translated in medical practice into "auto substitution", a practice that allows the pharmacist to substitute any biological agent to its biosimilar without the approval or notification of the prescribing physician or the consent and knowledge of the patient. The subject of biosimilar interchangeability generated great discussion among regulators and is still being debated among many specialists [22]. The US FDA permits biological interchangeability provided that the manufacturer provides sufficient data to demonstrate biosimilarity and to prove that the biosimilar agent can produce the same clinical results in any given patient as the reference biological agent. Additionally, if the biosimilar should be administered more than once to any patient, the manufacturer must be able to provide sufficient data to demonstrate that switching from the originator biologic to its biosimilar will not pose any safety hazard or concern to the patient [23]. These requirements exceed the amount of data needed for biosimilar approval and consequently while in principle a biosimilar may be granted the status of "inter-changeability", the regulatory and clinical requirements demanded by the manufacturer would prove to be costly and burdensome. Additionally, if the biosimilar is granted "interchangeability" as stated by the FDA each state within the US has the decision to grant and allow automatic substitution. The situation within Europe is vague as there is no explicit regulatory definition and approval pathway for interchangeability and the decision for switching/auto substitution/ replacement lies within member states. This makes it clear that in the future the EMA and other health regulatory agencies should adopt clear guidance on the issue of interchangeability and substitution to avoid any confusion that might arise due to the use of biosimilars by the physicians and pharmacists. For the adalimumab biosimilars, the FDA has recently approved Cyltzeo® as the only interchangeable adalimumab biosimilar in the US. This approval can set the path for the regulatory requirements needed by manufacturers to achieve interchangeability and pave the way for other biosimilar medications to acquire such a status if the manufacturers choose to do so.

Summary and Conclusion

The total sales of the originator adalimumab in 2021 reported a record number of annual revenue exceeding 21 billion dollars. This puts adalimumab's originator (Humira®) as the top selling medication in the history of the pharmaceutical industry with the exception of the Pfizer Biontech vaccine which recorded a total of 38 billion dollars of total sales in 2021. Currently, there are 12 adalimumab biosimilar agents authorized by EMA for use within the European Union and seven by the US FDA. The number of adalimumab biosimilars will continue to increase due to the popularity of the medication in the treatment of several auto-immune mediated disorders and huge sales potential. In this article, we have listed the essential technical components of the biosimilarity exercise required for the registration and regulatory approval of adalimumab biosimilars. As more manufacturers pursue the development of adalimumab biosimilars, this review can provide personnel working in research and development of adalimumab biosimilars in addition regulatory officers worldwide the essential guidance needed for the development of adalimumab biosimilars. These guide-lines detailed in this review are not designed to meet the regulatory requirements of a specific regulatory agency *per se*, but are holistic and should meet the minimal threshold needed by all regulatory bodies who have specific scientific guidelines for mAb biosimilar registration and approval.

Acknowledgments

The authors are grateful to the Middle East University, Amman, Jordan and the deanship of research at Jordan University of Science and Technology for the financial support granted to cover the publication fee of this research article.

Conflict of interest

The authors declare no conflict of interest.

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