British Journal of Healthcare and Medical Research - Vol. 11, No. 2
Publication Date: April 25, 2024
DOI:10.14738/bjhmr.112.15752.
Bandyopadhyay, A. K. (2024). Biosimilar Drug Development and Safety: Issues with Autoimmune Rheumatic Diseases (ARDs). British Journal of Healthcare and Medical Research, Vol - 11(2). 268-284.

SERVICES FOR SCIENCE AND EDUCATION

Biosimilar Drug Development and Safety: Issues with Autoimmune Rheumatic Diseases (ARDs)

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ABSTRACT

Biosimilar drugs including monoclonal antibodies (mAb) and cytokines, have become mainstream treatments in a few clinical settings starting from pain control, cardiovascular, oncology, and rheumatic arthritis (RA). Autoimmune rheumatic diseases share some observations like immune deregulation, and the presence of inflammatory mediators, can be treated with some effective Biologic disease-modifying antirheumatic drugs. In contrast, the structure and conformation of these medicine during infusion to the body yield anti drug antibody (ADA). Assessment of immunogenicity is an important component of drug safety evaluation. Risk based approach considers both probability of induction of immune response and expected clinical consequences. Tumor Necrosis Factor inhibitors (TNFi) are widely used in this aspect. Immunogenicity response on these treatments is crucial since the appearance of ADAs has consequences in terms of safety and efficacy. The risk of an immune response to a therapeutic protein may dictate treatment-related factors, including concomitant therapies, which may either decrease or increase. Patients with activated immune systems (for example, autoimmune rheumatic diseases orARDs) may be more used to immune responses to therapeutic proteins. Combination with immunosuppressive agents (e.g., methotrexate, MTX) during biologic therapy reduces the risk of ADAs production and may induce tolerance to biologic therapy in patients with ARDs. The frequency of ADAs formation also depends on the disease. For RA, the frequency of ADAs-IFX (infliximab) varies from 0–83% depending on the disease. Treatment of ARDs patients with a few biological agents and status of clinical immunogenicity are discussed.

Keywords: AS: ankylosing spondylitis, AxSpA: axial spondylarthritis, BLyS: B-lymphocyte stimulator, CTLA-4: Cytotoxic T-Lymphocyte Antigen 4, CD: Crohn's Disease, sJIA: systemic juvenile idiopathic arthritis, pJIA: polyarticular course juvenile idiopathic arthritis, mAb: monoclonal antibody, MTX, methotrexate, nr-axSpA:non-radiographic axial spondylarthritis, PsA: psoriatic arthritis, PsO: plaque psoriasis, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, TNF: tumor necrosis factor, UC: Ulcerative Colitis, UV: Urticarial Vasculitis, DMARDs: Disease-modifying antirheumatic drugs, bDMARDs: biologic Disease-modifying antirheumatic drugs, ARDs-Autoimmune rheumatic diseases, ADAs - Anti drug anti bodies, NAbs-Neutralization antibodies, (ACE): Affinity Capture Elution, TDM: therapeutic drug monitoring

INTRODUCTION

The Biosimilars Act was passed as part of the Patient Protection and Affordable Care Act.66. Under § 351(k) of the Biosimilars Act ("351(k) application"), which states that a biosimilar

manufacturer must demonstrate that its product is similar to a prior approved reference product [and to meet this standard, the statute requires that an applicant must show that the two products are “highly similar” and have “no clinically meaningful differences” in their safety or efficacy. Neither “highly similar” nor “no clinically meaningful differences “are well defined in statute. In the meantime, FDA developed the guidance to drive the product into development processes for regulatory pathway to approval [1-3]. Similar guidance was published by EU, and they approved a few drugs on the basis of their guidance [1-3].

It was observed that the biological molecules are complex and exist in several different structures- primary, secondary, tertiary, and quaternary. Further it interacts with different types of structures (e.g., tertiary, quaternary) to develop its stability and therapeutic values. Several factors are involved in protein folding including enzymatic interactions and the chemistry present in hosts. The subsequent purification, processing, and storage of such a protein may affect its structure or alter the function of a protein which may be related to the safety and efficacy of a drug [4,5]. In addition, post-translational modification occurs when enzymes present in a cell add various other molecules to the protein structure of the drug. The addition of these other molecules includes, for example, sugars (glycosylation) and phosphate groups (phosphorylation) [6]. Like structural changes, post-translational modification can affect the function, stability, bioavailability, and immunogenicity of a protein. Improper glycosylation of human erythropoietin or missing one or more glycosylation site may reduce the drug’s intended effect [7-11]. Biological drug is manufactured through recombinant DNA in different host; the product may be contaminated with host related impurities. So, the contamination may be due to: product related impurities, process related impurities, host related or other contaminates.

Again, the testing methods are product specific and proprietary, so each manufacturer has to develop product related methods, which may be different from the branded product. Similarly, they are required to prepare their own standards. During purification, the product may remain as monomer, dimer, or other conformations. The effectiveness of the different conformation of the molecule is required to determine with respect to safety. In addition, host related, or cell substrate derived impurities are required to develop the testing methods and purify the product to a minimum content of host derived proteins. The chemistry, manufacture, controls (CMC) information for each biological drug is so specific; manufacturers often develop product specific proprietary standards, test, and various other assays during the development. They maintained these procedures throughout the life cycle to ensure the standard of the biological product which are used in biological drug. Since the CMC information is proprietary, it is difficult for other manufacturers to produce the product in the same standard as originator. So, the knowledge and experience with these proprietary standards, tests and assays are essential to maintain the same standard of the products as originator. Complexities exist in clinical work as Clinicians like to review biosimilar’s action profile, storage, stability, expiration once in use, predictability of absorption from injection site, and bioavailability to build up their confidence limit for prescription to patients [12-15]. As mentioned earlier in impurity profile that protein impurities generated from product, process or host related, can increase immunogenicity making biological drugs especially vulnerable to immunogenicity issues [11,13]. Moreover, the patients develop various antibodies following the treatment with biological drugs and it may sometimes produce system translational modification of proteins [12-15].

URL: http://dx.doi.org/10.14738/bjhmr.112.15752.

Manufacturers overcame several of the difficulties and eventually produced several Biosimilar products, which are approved by Agencies. A list is provided in the previous publication (16). Biosimilar drugs include monoclonal antibodies (mAb) and cytokines. These products have become mainstream treatments in a few clinical settings starting from pain control, cardiovascular to oncology. Recombinant analogs of growth factors e.g., Type1 interferon's (IFNs) or interleukin-2(IL-2), insulin, or erythropoietin (EPO) are also used in the therapy. The critical part of the drug development process is to accurately assess drug exposure to determine the bioavailability of the drug. Immunogenicity is one of the issues for safety (Fig.1).

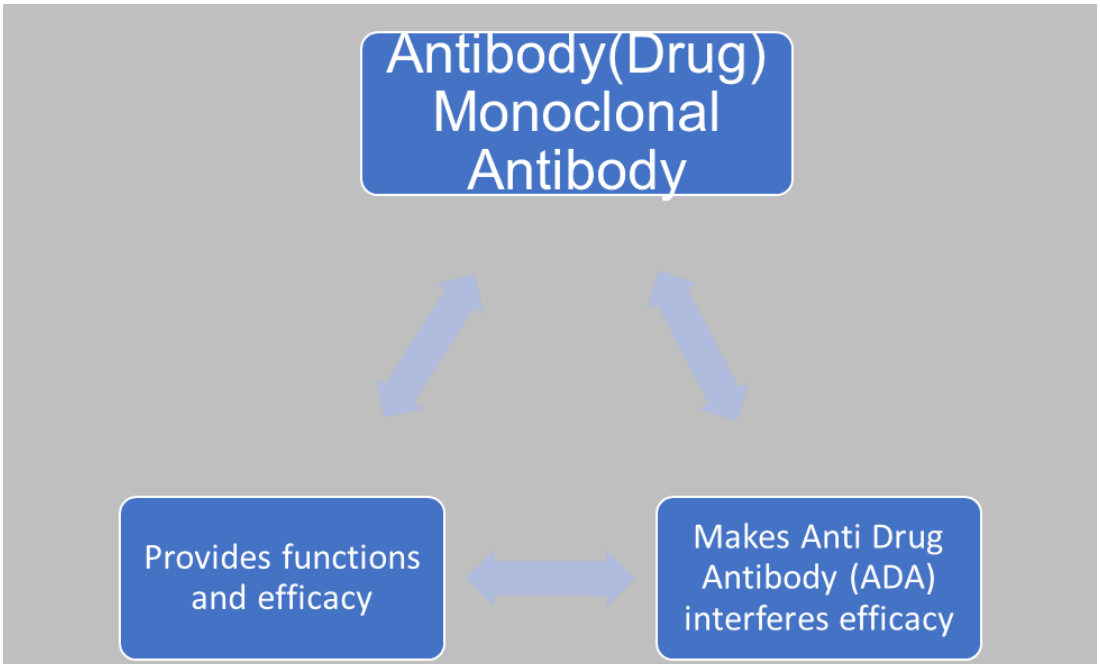
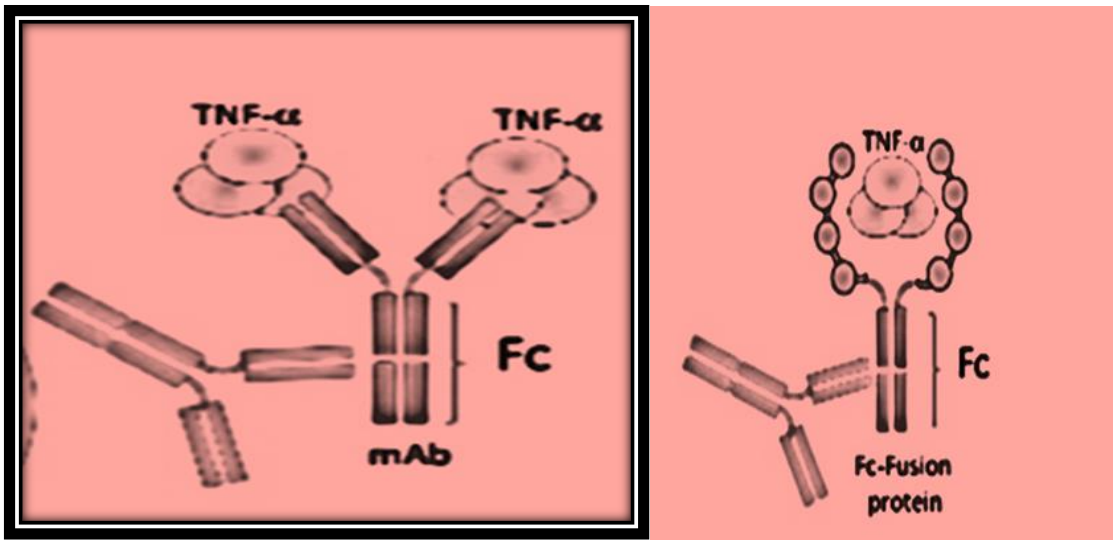


Fig. 1: Unwanted Immunity

On challenge the drug induces anti-drug antibodies (ADA) which may be either sustaining or clearing or neutralizing antibody (NAb) (Fig 2 & 3). Sustaining antibodies (Abs) prolongs the half-life by protecting it from normal clearance. In contrast clearing Abs more quickly decreases drug concentration below the therapeutic levels or removes the drug from circulation. The NAbs abrogates a drug's therapeutic effect and potentially induces serious side-effects. All of these clearing processes can affect pharmacokinetics (PK), pharmacodynamics (PD), and bioavailability analyses which in some cases minimize the potency of the drug on risk-based approach and can also limit the use of these drug products [15-26]. In contrast, repeated injection of these drug products to human in different physical condition can result in a break in immune tolerance to self-antigens leading to the product of adverse event response and sometimes immune complex disease or allergic reactions. Assessment of immunogenicity is an important component of drug safety evaluation, which is presently performed by estimating risk factors (Table 1) Risk based approach considers both probability of induction of immune response and expected clinical consequences. A combination of the two may result in high, medium, or low risk levels and will depend on the product, patient, and treatment related characteristics. Risk based evaluation was described in several publications [18-23]. Since Biosimilar manufacturing is different from the brand name or "reference drug" because of

variations in preparation from raw materials to finalized products [27,28], which may trigger unwanted adverse events (AE) [29].

As a result, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have issued several draft guidance related to quality consideration, reference product, labeling and interchangeability (Table 2).



(A) **(B)**

Figure 2. Anti-drug antibodies (ADAs). As discussed in the text, two types anti-drug antibodies are displayed. Non-neutralizing antibody (shown in (A) and (B), -bind to Fc- and remain inert to the drug-target interaction but indirectly decrease the drug level by increasing drug clearance via immune complex formation.

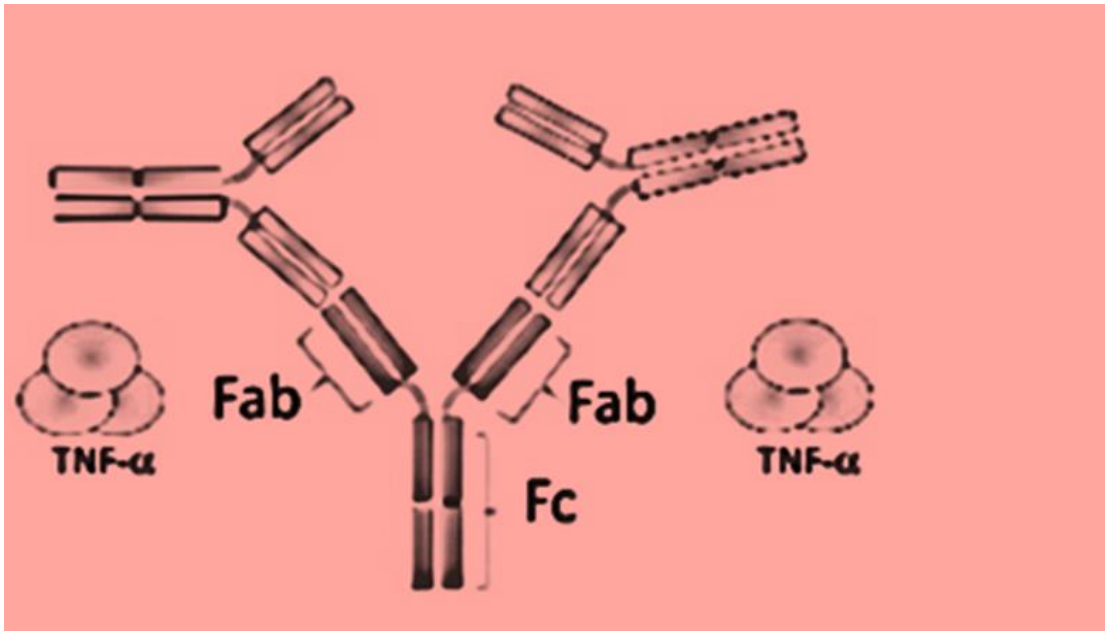


Figure 3: Anti-drug antibodies (ADAs). Neutralizing ADAs (Nabs) have an ability to bind with the drug at its target and show negative impact on functional drug level.

URL: http://dx.doi.org/10.14738/bjhmr.112.15752.

Table 1: Risk Assessment plan for immunogenicity.

Topics	Factors	Content
Product related	Intrinsic	Product profile, sequence homology
	Extrinsic	Process related impurities, Aggregates, Degradation Products, Stability of active ingredients in DP formulation
Immunogenicity related clinical risks		Cross-reactive Abs, Drug hypersensitivity responses, Abrogation of efficacy due to neutralizing Abs or quick clearance
Analytical Methods		Rationale for choice of methods, PK assay, ADA assay, assessment of cross-reactive potential, neutralizing Ab assay etc.
Nonclinical		Overview, ADA vs PK/PD, and other toxicities
Clinical		Studies contributing to immunogenicity, ADA responses, ADA vs PK/PD, ADA vs efficacy
		Impact of immunogenicity on overall assessment of benefit and risk
		Recommendations for risk management plan

Table 2: Recently Published FDA Guidance.

• Considerations in Demonstrating Interchangeability with a Reference Product; Draft Guidance for Industry (PDF - 229KB) CDER/CBER, January 2017
• Labeling for Biosimilar Products Guidance for Industry (PDF - 143KB) CDER/CBER, March 2016
• Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants; Guidance for Industry (PDF - 306KB) CDER/CBER, November 2015
• Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product; Guidance for Industry (PDF - 144KB) CDER/CBER, April 2015
• Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009; Draft Guidance (PDF - 104KB) CDER/CBER, May 2015
• Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Guidance for Industry (PDF - 169KB) CDER/CBER, April 2015
• Guideline on Similar Biological Medicinal Products - European
• Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues

Autoimmune rheumatic diseases (ARDs) are a cluster of heterogeneous disorders that share some clinical symptoms such as pain, tissue damage, immune deregulation, and the presence of inflammatory mediators. Disease-modifying antirheumatic drugs (DMARDs) are immunosuppressive and immunomodulatory agents classified as biologic agents (bDMARDs), which have become an important component of therapeutic strategies for many ARDs. However, these biologics are protein drugs that tend to induce an immune response against themselves (immunogenicity), particularly the formation of anti-drug antibodies (ADAs), which can have clinical consequences that depend on the type of the ADAs (neutralizing or non-neutralizing antibodies) and the resulting immune complexes that may form with the biologic agent [30-33].

Immunogenecity against a therapeutic protein depends upon many factors, which could be classified as patient- or drug-related factors. Patient- and disease-related factors stand out in the context of ARDs, as patients with triggered immune systems may be more used to immune responses to therapeutic proteins. In contrast, a combination with immunosuppressive agents

(e.g., methotrexate, MTX) during biologic therapy reduces the risk of ADAs production and may induce tolerance to biologic therapy in patients with ARDs [34-37]. The duration of dual Uno suppressive therapy is necessary to ensure tolerance to the biological component. Immunogenicity of biosimilars currently approved for rheumatic diseases, plaque psoriasis, or inflammatory bowel diseases is similar to that of their reference products. The lowest proportions of anti-drug antibodies were reported in trials of etanercept and its biosimilars, and the highest in the trials of adalimumab, infliximab, and their biosimilars. The purpose of this publication is to discuss the discrepancies in assessing and reporting clinical immunogenicity.

ISSUES IN VALIDATION OF NEUTRALIZING ANTIBODY

Immunogenicity of biological drug is detected through ADAs assay. Neutralization antibodies (NAbs) are a part of ADAs and they inhibit the binding of drug to target. Such inhibition may yield the neutralization of the drug's pharmacologic activity, potentially reducing efficacy. The biodrug may contain endogenous protein with non-redundant function, NAbs may cross react with the endogenous proteinpart and can have critical consequences for human safety (38). So, the immunogenicity of risk assessment is related to immunogenicity evaluation including NAb (39,40). In most cases NAb test is done following ADA assay. In rare instances, NAb testing may be performed in parallel with ADA testing and may hold one or more NAb group specifc assay (i.e., screen, confirm, titer). This parallel testing may be required in situations where NAb is used for trial inclusion/exclusion purposes, or to support high-risk products. Higher NAb concentration and/or higher binding affinity of NAb to the drug lowers the drug-target binding interaction. However, in the presence of high concentrations of residual circulating drug was often seen for drugs with longer half-lives or in repeat-dose studies, A team of experts within the American Association of Pharmaceutical Scientists' Therapeutic Product Immunogenicity Community across industry and the Food and Drug Administration addressed challenges unique to cell-based and non-cell based neutralizing antibody assays [41]. This team provides validation testing and reporting strategies and tools for the following assessments: (a) format selection; (b) cut point; (c) assay acceptance criteria; (d) control precision;(f) sensitivity including positive control selection and performance tracking; (g) negative control selection; (h) selectivity/specifcity including matrix interference, hemolysis, lipemia, bilirubin, concomitant medications, and structurally similar analytes; (i) drug tolerance; (j) target tolerance; (k) sample stability; and (l) assay robustness. Neutralizing antibody (NAb) assays typically rely on NAbs ability to block the drug-target interaction. Sometimes Abs may exist as drug bound complexes. In those cases, the NAb-drug complexes present in the sample could produce in the NAb being unable to block the drug-target interaction eventually yielding a false negative result. The residual free circulating drug present in the sample may bind to the target in the NAb assay thereby competing with the drug used in the assay and inhibiting the assay signal, resulting in a false positive response., Rathi et al (42) described multiple approaches involving acid treatment for traditional ADA assays to mitigate circulating drug interference issue. Two acid-treatment approaches that utilize the Dyna beads extraction with acid dissociation and Affinity Capture Elution (ACE) principle improves drug tolerance in NAb assays [42].

Elution (ACE) Principle to Improve Drug Tolerance in NAb Assays

Therefore, Smeijsters et al (43) developed the first LC-MS/MS method. Stable isotopically labeled infliximab antigen-binding fragments (SIL IFX F(ab')2) were used to bind and measure

URL: http://dx.doi.org/10.14738/bjhmr.112.15752.

ADAs indirectly. Protein A magnetic beads were used to capture IgG, including ADAs, where after SIL IFX F(ab')2 was added for labeling. After washing, internal standard addition, elution, denaturation, and digestion samples were measured by LC-MS/MS. Internal validation showed good linearity between 0.1 and 16 mg/L ($R2 > 0.998$). Sixty samples were used for cross-validation with RIA, and no significant difference between ADA concentrations was found. The methods had high correlation ($R = 0.94$, $p < 0.001$) an excellent agreement, intraclass correlation coefficient = 0.912 (95% confidence interval 0.858–0.947, $p < 0.001$). Furthermore, it presents the first ADA against the infliximab LC-MS/MS procedure. The authors claimed that the method is mendable for quantifying other ADAs, making it applicable as a template for future ADA methods [43].

TREATMENTS OF ARDS PATIENTS WITH BIOLOGIC AGENTS

Factors Related to Immune Response

When the patients were treated with therapeutic proteins, Patient- and disease-related factors, include genetic factors which modulate the immune response and factors related to a genetic defect. The immune system can detect small differences in the three-dimensional structure between the proteins. As stated previously the risk of an immune response to a therapeutic protein may dictate treatment-related factors, including concomitant therapies, which may either decrease or increase [20,40]. Patients with triggered immune systems (for example, autoimmune diseases) may be more used to immune responses to therapeutic proteins. There is evidence showing that concomitant use of certain DMARDs may maintain efficacy and prolong drug survival by reducing the immunogenicity of biologics in chronic inflammatory diseases. For example, the use of MTX in TNFi biologic therapies may attenuate the incidence of ADAs in RA, SpA, and CD [35-37,44]. This could be because the administration of immunosuppressive drugs could induce tolerance by suppressing B cells and consequently reducing ADAs production. The mechanisms of such immune tolerance are not yet clear [40].

As most of the vaccines are given via the subcutaneous (SC) route, the which is expected to be more immunogenic than the intravenous (IV) route. In contrast, many comparable clinical trials are not available for the safety and efficacy of SC and IV dosing regimens of therapeutic proteins or mAbs [45]. Clinical effects of immune responses in subjects can be highly variable, ranging from no measurable effects to extremely harmful effects. The immune response to biological agents, particularly the generation of ADAs, is a key aspect of therapy. ADAs can be generated by (A) a T-cell dependent/independent B cell activation or (B) T-cell independent/dependent B cell activation pathway. In the T-cell dependent pathway, mAbs act as antigens and are internalized by antigen-presenting cells (APCs), processed, and presented to T cells via the cognate interaction between the MHC class II molecules and T-cell eceptor. ADAs are generated when a T helper cell (Th) differentiates into a Th1 or Th2 phenotype and, following their cognate interactions with B cells, induces the proliferation of plasma cells (PC) that secrete ADAs. While biologics with multiple epitopes, such as mAbs, can cross-link B cell receptors (BCRs) via the T cell-independent pathway and then directly stimulate B cells to differentiate into PC to produce ADAs [46].

Two types of ADAs can be distinguished: non-neutralizing ADAs (or binding antibodies, Figure 2 A & B), which specifically bind the drug but do not affect the drug-target interaction, and neutralize ADA (NAb), which inhibit the biological activity of a therapeutic protein by binding to the epitope(s) within or close to the active site(s) of the molecule or by causing

conformational changes, thereby physically interfering with the ability of the drug to bind its target, Figure 3. Therefore, ADAs can alter a drug's pharmacokinetic (PK) and pharmacodynamic (PD) properties, reducing drug efficacy. Overall, depending on the circulating ADA titers, a reduction in the drug concentration can be clinically significant.

For example, in patients with low titers of ADAs, drug concentrations may remain high enough to be effective, while in patients who develop high titers of ADAs, a substantial portion of the drug will be neutralized and is likely to produce a clinical non-response and depends on the disease. For example, in RA, the frequency of ADAs-IFX varies from 8 to 62%, PsA 15–33%, JIA 26–42%, AS 6.1–69%, Ps 0–41%, CD 3–83% and UC 6–46%, then ranging from 0–83%. Although there is variability, the fact shows that the frequency of ADAs formation in patients treated with IFX can be low (0% in Ps) or exacerbated (83% in CD), but ADAs

TNF Inhibitors

TNF inhibitor is designated as TNFi, which is effective in lessening inflammation and diminishing symptoms. But, despite this a significant proportion of patients do not meet the requirements primarily or secondarily for AEs or non-efffectivity of drug. Currently, there are five FDA- and EMA-approved TNFi [47], out of which only three and three others are described below, highlighting the prevalence of antibodies to the drug (Table 3)

Table 3: Biologic agents approved for the treatment of ARDs by target.

Target	Biological Agent	Format	Indication
TNF -α	Infliximab	Chimeric mAb	CD, UC, PsA, PsO, AS, RA
TNF -α	Adalimumab	Fully human mAb	RA, PsA, PsO, AS, CD, JIA,
TNF -α	Etanercept	Fusion protein	RA, pJIA, PsA, AS, PsO
CD20	Rituximab	Chimeric mAb	RA, SLE
CTLA-4	Abatacept	Fusion protein	RA, PsA
IL-6R	Tocilizumab	Humanized mAb	RA, sJIA, pJIA

Legend: AS: ankylosing spondylitis; AxSpA: axial spondylarthritis; BLyS: B-lymphocyte stimulator; CTLA-4: Cytotoxic T-Lymphocyte Antigen 4; CD: Crohn's Disease; sJIA: systemic juvenile idiopathic arthritis; pJIA: polyarticular course juvenile idiopathic arthritis; mAb: monoclonal antibody; MTX, methotrexate; nr-axSpA: non-radiographic axial spondylarthritis; PsA: psoriatic arthritis; PsO: plaque psoriasis; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; TNF: tumor necrosis factor; UC: Ulcerative Colitis; UV: Urticarial Vasculitis

Infliximab (IFX):

IFX is a chimeric anti-TNF mAb approved for SpA, Crohn's Disease (CD), psoriasis (Ps), psoriatic arthritis (PsA), RA, and ulcerative colitis (UC) [33]. The development of immunogenicity to IFX has been reported in association with immune-mediated adverse events such as infusion reactions (due to the formation of ADAs). At least in RA, between 4 and 15% of patients treated with IFX could develop ADAs [34].

In a study by Menter et al. in 2007, after 50 weeks of treatment with IFX, between 35-50% of psoriatic patients developed antibodies against the drug (48). The factors related to a greater development of ADAs were a dose of 3 mg/kg *versus* 5 mg/kg, intermittent drug administration regimens or as needed *versus* scheduled, and no association with MTX as concomitant therapy. On the other hand, the presence of antibodies against IFX was associated with infusion-related adverse reactions only in the retreated group of patients and after an interval of 20 weeks from

URL: http://dx.doi.org/10.14738/bjhmr.112.15752.

the last administration (23% in patients positive for ADAs, compared to 8% in patients without ADAs). Furthermore, patients with antibodies were less likely to maintain a response at week 50 of follow-up (43-45). Similarly, in patients with active PsA treated with IFX, doses of 5 mg/kg were related to ADA production in up to 15.4% of cases, after 54 weeks with the drug. The development of anti-IFX antibodies was more frequent in patients who did not receive associated treatment with MTX at the beginning of the study (26.1% *versus* 3.6% in the patients who did receive it), showing an inverse correlation with the clinical response. The median percentage improvement in ACR20 for ADA-positive patients was lower (21.7%) than in those who did not develop antibodies (33.3%) at the end of the study [49].

The systematic review included 443 publications, of which 110 were related to IFX in different rheumatic diseases showing major differences in their results. The frequency of ADAs formation depends on the disease. For example, in RA, the frequency of ADAs-IFX varies from 8 to 62%, PsA 15–33%, JIA 26–42%, AS 6.1–69%, Ps 0–41%, CD 3–83% and UC 6–46%, then ranging from 0–83%. Although there is variability, the fact shows that the frequency of ADAs formation in patients treated with IFX can be low (0% in Ps) or exacerbated (83% in CD), but ADAs development is a real factor that must be taken in consideration because this can condition the success of the treatment [33].

Adalimumab (ADL):

ADL is a fully human anti-TNF mAb IgG1 approved for ankylosing spondylitis (AS), Crohn's Disease (CD), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), psoriasis (Ps), rheumatoid arthritis (RA), and urticarial vasculitis (UV).

The presence of anti-ADL antibodies was connected to a reduction in the efficacy of the drug to accomplish PASI75 (23.1% *versus* 72.7% in ADA-negative patients), with rapid loss of response (PASI <50) at week 52 of follow-up (50). Vogelzang et al. observed that ADL concentrations were significantly lower at 28 and 52 weeks of follow-up in 103 patients with PsA and positive ADAs, correlating in the same way with a lower clinical response. ADL concentrations reflect the amount of drug available in the serum that binds to its target molecule. If no free drug concentration is available or insufficient, inflammation cannot be effectively suppressed. Therefore, measuring drug concentrations in patients who do not respond adequately could provide more information on why there is an inadequate response (50).

A study of 143 patients, received biologics for a long term based on ACR criteria, were found to have ADL-ADA production [36]. Subsequently, in 2017 Strand et al. performed a systematic literature review and indicated that study design, assay methods as well as therapeutic schemes could raise the variability in the percentage of ADAs formation. Moreover, 80 of the publications refered a frequency between 0–54% of the patients with ADAs formation [33].

A multidisciplinary approach derived from the three different therapeutic areas – (rheumatology, troenterology, dermatology):-- on the use of the adalimumab biosimilar SB5 (ImraldiTM) do not suggest clinically meaningful differences between SB5 and reference adalimumab in terms of pharmacokinetics, efficacy/effectiveness, safety, or immunogenicity, either in patients who initiated SB5 or switched from adalimumab to SB5. Clinical studies suggest that the biosimilar SB5 is a safe and effective alternative to reference adalimumab. The patients of immune- mediated as inflammatory arthritis, inflammatory bowel disease and

psoriasis often require long-term biologic treatment. Biosimilar medicines (such as SB5) can provide useful treatments with reduced healthcare costs (51).

Etanercept (ETA):

ETA is a fusion protein between a human IgG1 Fc-tail and the TNF-receptor type 2(TNFR2) approved for its clinical use in AS, JIA, PsA, Ps, and RA. Although there are some reports which indicates that this biological drug has a high capability to produce the formation of ADAs, but. scientific reports show that ETA cannot induce ADAs formation.

Thomas et al., in 2015, performed a systematic review with meta-analysis (PRISMA) and conducted research using the preferred reporting items within the databases [52]. For RA, they reported that the mean for ETA-ADAs is only 3%, but this percentage represents only one within the found articles because in others it is 0%. In contrast, it is mentioned that in other autoimmune rheumatic diseases studied, the percentage remains to be 0%. Another report indicates the serum values of ETA-ADAs in RA were 0%. In contrast, the prevalence of ETA-ADAs in psoriasis reaches 18.3% [53-55]. Therefore, there is great variability in the mean percentages of ADAs, as reported by Strand et al., for example, ETA-ADAs serum levels in RA patients were found to be about 0–13%, 0% in PsA, 0–6% in JIA, 0% in AS and 2–5% in AS [33].

B Cell-Targeting Biologics

Rituximab (RTX):

RTX is a chimeric murine/human mAb IgG-1/kappa isotype that recognizes theCD20 antigen present on B-lymphocytes promoting its depletion. RTX was first used in non-Hodgkin lymphoma treatment but is now used in combination with MTX to treat RA that had not responded to one or more types of treatment, including TNFi [56]. RTX treatment is associated with a high degree of ADAs, which correlates with the efficacy of B-cell depletion.

The serum samples from 339 MS patients in a cross-sectional study, were collected prior to RTX infusion and ADAs were detected in 37% of relapsing/remitting MS and 26% in progressive forms of MS indicating a significant association between the presence and titers of ADAs and incomplete B-cell depletion [57]. In addition, in another clinical trial of 26 children treated with RTX for various immune-mediated diseases, six patients were ADA-positive (23.1%). In all ADA-positive patients, RTX concentrations were undetectable to ADA-negative patients, indicating that these ADA have a PK impact. Failure of B cell depletion was found in 5/6 ADA-positive. and 1/19 ADA-negative patients, showing that these ADA have a PD impact. Moreover, in SLE patients, 50.0% (n = 4/8) had developed RTX-ADA [58]. Specific patient groups may be more prone to develop ADAs. For example, after the first RTX cycle, no AAV (ANCA-associated vasculitis) patients were ADA-positive compared to 37.8% of the SLE patients [59].

T Cell Activation Inhibitor/Co-Stimulation Modulator (CTLA-4)

Abatacept (ABT):

ABT is a recombinant and glycosylated fusion protein that has as its target the human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4 or CD152). This biological drug has an Fc-modified portion (hinge, CH2, and CH3 domains) of the human over the immune system. It is used in patients with RA, PsA, or pJIA who have not responded to one or more DMARDs, such as MTX or other biologic drugs [60,61]. During clinical trials (phase II and III), IV ABT administered with or without MTX demonstrated transient, low-titer immunogenicity without clinical

URL: http://dx.doi.org/10.14738/bjhmr.112.15752.

consequence or influence on efficacy or safety. Patients (2237) with pre- and post-baseline serum samples were used for assessment. Of these, 0.9–2.1% of patients presented anti-CTL-4 antibodies, and among 20 patients positive for anti-CTLA-4 reactivity, 13 were eligible for assessment with the neutralization bioassay, and within these, 8 patients showed neutralizing activity [52]. Whereas in a phase IIIb non-inferiority study, ABT-induced antibodies occurred in 1.1%of SC ABT-treated patients and 2.3% of IV ABT-treated patients [54]. A study designed to evaluate the immunogenicity of ABT, with or without MTX and in the absence of an initial IV loading dose of ABT (ACCOMPANY phase III study), showed that 3.9% (combination) and 4.1% (monotherapy) of patients developed transient immunogenicity, and no patients were antibody positive at month 4 [60].

IL-6R Inhibition

Tocilizumab (TCZ):

TCZ is a recombinant humanized mAb, and its target molecule is the IL6 receptor (IL-6R) approved for RA, systemic juvenile idiopathic arthritis (sJIA), or polyarticular course juvenile idiopathic arthritis (pJIA). Clinical experience with TCZ, both IV and SC administration, has demonstrated low immunogenicity in several indications, including RA, Castleman's disease, and JIA [62]. Anti-TCZ antibodies developed among the small proportion of patients had no evident impact on PK, efficacy, or safety. ADAs were identified in 47 of 3094 (1.5%) and 69 of 5806 (1.2%) patients treated with TCZ in SC or IV, respectively, whereas NAbs were confirmed in 40 of 3094 (1.3%) and 54 of 5806 (0.9%) of these patients, respectively. ADA development was also comparable between patients who received TCZ monotherapy and those who received concomitant csDMARDs (0.7–2.0%) [62]. Similar data are reported in the SUMMACTA study to compare the efficacy and safety of SC versus IV formulations of TCZ in patients with RA with an inadequate response to DMARDs. Only five patients in each group were positive (0.8% and .8%) for both the confirmation and neutralizing assays post-baseline [62].

CLINICAL MONITORING

During the biotherapy, ADAs are formed in the blood of patients with the infusion of biodrug, Such ADA formation reduces clinical drug efficacy. This could be of concern because many factors potentially. related to biotherapy as well as clinical aspects of the patient are required to be considered. It became difficult for the physician to prescribe an appropriate drug for the first time [52,63]. Moreover, the formation of ADAs during drug infusion is also associated with AE, these infusion reactions are the most common ADA-related AE described for TNFi, and they are characterized by symptoms such as fever, pruritus, bronchospasm, or cardiovascular. collapse during or within the first day after drug administration. Infusion-related reactions can range from mild (e.g., rash, pruritus, dizziness, dyspnea) to severe (anaphylactic-like reactions such as hypotension and respiratory distress) [47].

The clinical effects of the generation of ADA are related to the amount of drug used in the formation of ADA and the amount of the free drug present. So, the therapeutic drug monitoring (TDM) of biodrugs could be helpful in several clinical settings, such as loss of response to therapy, the interpretation of side effects to therapy, and determining dose adjustments. Impportanttly, the TDM refers to the principle of using (a) drug concentration in blood (b) ADAs determination. All these points are important for therapeutic decision. Validated TDM assays are widely available. There are no adequate guidelines on whether and how to use them in clinical practice. Therefore, EULAR proposed a few points. together with the TDM assay so that

accurate information on the serum concentration of the drug, the formation of ADA, the optimization of the drug dose, the reduction of adverse events, or the potential impact of ADA on biologic therapy over time may be obtained [64]. Two EULAR task forces have agreed to define precise aspects for when it is necessary to evaluate the development of ADA and whether it affects the serum concentration of the drug as well as the outcome of therapy [65].

CONCLUSION

mAbs is used as therapeutic drug having different PK characteristics due to their particular physical properties, generally showing a smaller volume of distribution and a longer half-life, and their clearance is related to protein degradation and target binding. TDM of biodrug can also add the presence of ADA can provide insight into the reasons for clinical non-response to treatment. In contrast, there is contradictory evidence that the presence of ADA in a first TNFi predicts a better treatment response to a second TNFi. Switching from an immunogenic to a less immunogenic TNFi might be considered, as patients might also be more likely to develop ADA to a second immunogenic TNFi [66]. Intra-class and inter-class switches are both effective options in patients who fail the first biologics. In patients who develop secondary failure to the first biological drug due to ADA, a second biological drug within the same class may usually be considered [66,67].

It is to be noted that in clinical trial Blood concentrations and ADA, with other factors that influence these parameters such as dose, administration interval, body weight, methotrexate cotreatment, disease activity and adherence to treatment hold an important part of trial. In general, proactive use of TDM is not recommended due to lack of data from clinical trials, but reactive TDM could be considered in certain clinical situations. High-quality clinical trials of TDM in rheumatology are limited in number and require the optimum therapeutic range to be known in advance. However, relevant data from the original, dose-finding, licensing trials are generally not available. Therefore, the task force appeals to bio-drug companies to release these data into the public domain.

Patient and healthcare professionals' views around TDM have not been widely explored. Future research and education should focus on stakeholder (including patients, rheumatologists, and other health professionals) preferences and acceptability regarding TDM of biomedicines.

ACKNOWLEDGEWMENT

Thanks, aredue to Bharati Bandyopadhyay MD, Abin Bandyopadhyay MD, and Nina Bandyopadhyay MD for reviewing this article. I am grateful to Abir for designing the figures.

References

1. Bandyopadhyay A Complexities of Biosimilar Product. J Bioanal Biomed 2013; 5: 118-121. doi:10.4172/1948-593X.100009

2. Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research Guidance forIndustry: Questions and Answers on Biosimilar Development and the BPCI Act: September2021 Biosimilars //www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/

3. Rick NG Manufacture of Large Molecule APIs (Recombinant DNA Methods). (2nd Edn), Wiley-Blackwel, Hoboken, NJ, USA 2009; pp 340-348

4. Dimasi JA) New Drug Development in the United States from 1963 to 1999. Clin Pharmacol Ther (2001 ; 69: 286-296 PMID: 11371996 DOI: 10.1067/mcp.2001.115132

5. Khoury GA, Baliban RC, Floudas CA (2011) Proteome-wide post-translational modification statistics: frequency analysis and curation of the swiss-prot database. Scientific Reports. PMID: 22034591 PMCID: PMC3201773; DOI: 10.1038/srep00090

6. Larsen MR, Trelle MB, Thingholm TE, Jensen ON (2006) Analysis of posttranslational modifications of proteins by tandem mass spectrometry. Bio Techniques 40: 790-79 PMID: 16774123 DOI: 10.2144/000112201

7. Jenkins N, Murphy L, Tyther R (2008) Post-translational modifications of recombinant proteins: significance for biopharmaceuticals. Mol Biotechnol 39: 113-118. PMID: 18327554; DOI: 10.1007/s12033-008-9049-4

8. Delorme E, Lorenzini T, Giffin J, Martin F, Jacobsen F, et al. Role of glycosylation on the secretion and biological activity of erythropoietin. Biochemistry (1992); 3: 9871-9876. PMID: 1390770; DOI: 10.1021/bi00156a003

9. EU GMP Annex 2/ Manufacture of Biological Medicinal Products for Human Use https://www.gmp-compliance.org/files/guidemgr/2018_annex2_en.pdf

10. Spiker B (2009) Guide to Drug Development: A Comprehensive Review and Assessment. Wolters Kluwer Health &Lippincott Williams & Wilkins, 119-131

11. Rick NG (2009) Drugs: From Discovery to Approval.John Wiley & Sons, Canada 93-135.

12. Michael Hay, Jesse Rosenthal, David Thomas, John Craig (2011) Bio/Biomed tracker clinical trial success rates study, BIO CEO & Investor Conference, BIO

13. Class JN, Langis L (2012) A patient-centered paradigm for the biosimilars market. Communications 1: 17-21.

14. Rotenstein LS, Ran N, Shivers JP et al Opportunities and Challenges for Biosimilars: What's on the Horizon in the Global Insulin Market? (2012) Biosimilar opportunity within the insulin market. Presentation at GTC Bio Clinical Diabetes 2012; 30(4):19-20.16.

15. Bandyopadhyayy A Regulatory Progress of Bioosimilars: An Update Regulatory Focus 2018, November 7: 10-17;

16. Bandyopadhyayy A Regulatory Issues on Biosimilars. Curr Trends Biomedical Eng & Biosci. 2018; 15(3): 555912. DOI: 10.19080/CTBEB.2018.15.555912.

17. Bandyopadhyay A. Complexities of Protein Therapeutics and Immunogenicity. Journal of Bioanalysis & Biomedicine, 2015, 07 (3), pp.70-74. 10.4172/1948-593x.1000126. hal-0402130721.

18. Tovey MG, Lallemand C Immunogenicity and other problems associated with the use of biopharmaceuticals. TherAdv Drug Saf 2011; 2:113-128. PMID: 25083207; PMCID: PMC4110816; DOI: 10.1177/2042098611406318.

22. Bachmann MF, Zinkernagel RM Neutralizing antiviral B cell responses. Annu Rev Immunol 1997;15: 235-270. PMID: 9143688; DOI: 10.1146/annurev.immunol.15.1.235

23. Rosenberg AS Effects of protein aggregates: an immunologic perspective. AAPS J 2006; 8: E501-507. PMID: 17025268; PMCID: PMC2761057; DOI: 10.1208/aapsj080359

24. Ponce R, Abad L, Amaravadi L, Gelzleichter T, Gore E, et al Immunogenicity of biologically-derived therapeutics: Assessment and interpretation of nonclinical safety studies Regulatory Toxicology and Pharmacology 2009;54:164-182. PMID:19345250 DOI: 10.1016/j.yrtph.2009.03.012

25. Rosenberg AS Effects of protein aggregates: An immunologic perspective. AAPS J 2006; 8: E501-E507. PMID: 17025268 PMCID: PMC2761057 DOI: 10.1208/aapsj080359

26. Rosenberg AS, Worobec A () A risk-based approach to immunogenicity concerns of therapeutic protein products—Part 1—considering consequences of the immune response to a protein. BiopharmInt 2004; 17: 22-26.

23. Murphy, K, 2011, The Humoral Immune Response, in Janeway's Immunobiology, Garland Science Publishing: New York, 367-408

24. Test ST, Mitsuyoshi J, Connolly CC, Lucas AH () Increased immunogenicity and induction of class switching by conjugation of complement C3d to pneumococcal serotype 14 capsular polysaccharide infect. Immunol 2001; 69:3031-3040. PMID: 11292721; PMCID: PMC98257; DOI: 10.1128/IAI.69.5.3031-3040.2001

25. Schellekens H1 Immunologic mechanisms of EPO-associated pure red cell aplasia. Best Pract Res Clin Haematol 2005; 18: 473-480. PMID: 15792922; DOI: 10.1016/j.beha.2005.01.016

26. Hay, M., Rosenthal, J., Thomas, D., and Craig, J., Bio/Biomed tracker clinical trial success rates study, BIO CEO& Investor Conference, 2011. PMID: 24406927; DOI: 10.1038/nbt.2786

27. Chirino AJ, Ary ML, Marshall SA Minimizing the immunogenicity of protein therapeutics. Drug Discov Today 2004; 9: 82-90. PMID: 15012932; DOI: 10.1016/S1359-6446(03)02953-2

28. De Groot AS, Martin W () Reducing risk, improving outcomes: bioengineering less immunogenic protein therapeutics. CLIN Immunol 2009;131: 189-201. PMID: 19269256; DOI: 10.1016/j.clim.2009.01.009

29. Moore WV, Leppert P Role of aggregated human growth hormone (hGH) in development of antibodies to hGH. J Clin Endocrinol Metab 1980 51: 691-697. PMID: 7419661: DOI: 10.1210/jcem-51-4-691

30. Braun A, Kwee L, Labow MA, Alsenz J Protein aggregates seem to play a key role among the parameters influencing the antigenicity of interferon alpha (IFN-alpha) in normal and transgenic mice. Pharm Res 1997; 14: 1472-1478. PMID: 9358564: DOI: 10.1023/a:1012193326789

31. Wang W Protein aggregation and its inhibition in biopharmaceutics int. J. Pharmqacol. 2005; 289: 1- 30

32. Hermeling, S, et al., 2004, Structure-Immunogenicity Relationships of Therapeutic Proteins, Pharm Res, 21(6):897-903

33. Strand, V.; Goncalves, J.; Isaacs, J.D. Immunogenicity of biologic agents in rheumatology. Nat. Rev. Rheumatol. 2021, 17, 81–97.

34. Schaeverbeke, T.; Truchetet, M.E.; Kostine, M.; Barnetche, T.; Bannwarth, B.; Richez, C. Immunogenicity of biologic agents in rheumatoid arthritis patients: Lessons for clinical practice. Rheumatology 2016, 55, 210–220.

35. Maini, R.N.; Breedveld, F.C.; Kalden, J.R.; Smolen, J.S.; Davis, D.; Macfarlane, J.D.; Antoni, C.; Leeb, B.; Elliott, M.J.; Woody, J.N.; et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined withlow-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum. 1998, 41, 1552–1563.

36. Krieckaert, C.L.; Nurmohamed, M.T.; Wolbink, G.J. Methotrexate reduces immunogenicity in adalimumab treated rheumarthritis patients in a dose dependent manner. Ann. Rheum. Dis. 2012, 71, 1914–1915. [CrossRef]

37. Garces, S.; Demengeot, J.; Benito-Garcia, E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: A systematic review of the literature with a meta-analysis. Ann. Rheum. Dis. 2013, 72, 1947–1955.

38. Koren E, Smith HW, Shores E, Shankar G, Finco-Kent D, Rup B, et al. Recommendations on risk-based strategies for detection and aracterization of antibodies against biotechnology products. J. Immunol Methods. 2008;333(1–2):1–9.

39. Draft Guidance for Industry. Immunogenicity assessment for therpeutic protein products. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evalution and Research (CDER), Center for Biologics Evaluation and Research (CBER); 2013.

40. Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products Guidance for Industry, Draft Guiance. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health (CDRH). 2016.

41. Myler H, Vasconcelos JP, et al Neutralizing Antibody Validation Testing and Reporting Harmonization (WHITE PAPER) The AAPS Journal (2023); July 8 25-69 https://doi.org/10.1208/s12248-023-00830-

42. Rathi A, Rinker S, Niu H, Carter C, et al Assay development considerations to improve drug tolerance in direct competitive ligand binding neutralizing antibody assays - pretreatment strategies J. of Immunol. Methods. 2023:517:113484-93 https://doi.org/10.1016/j.jim.2023.113484

43. Smeijsters EH, Kim I, van der Elst CM, et al Optimization of a Quantitative Anti-Drug Antibodies against Optimization of a Quantitative Anti-Drug Antibodies against Infliximab Assay with the Liquid Chromatography-TandemMass Spectrometry: A Method Validation Study and Future PerspectivesInfliximab Assay with the Liquid Chromatography-TandemMass Spectrometry: A Method Validation Study and Future Perspectives. Pharmaceutics 2023; 15:1477-86. https://doi.org/10.3390/pharmaceutics15051477

44. Jani, M.; Barton, A.; Warren, R.B.; Griffiths, C.E.; Chinoy, H. The role of DMARDs in reducing the immunogenicity of TNFinhibitors in chronic inflammatory diseases. Rheumatology 2014, 53, 213–222.

45. Jarvi, N.L.; Balu-Iyer, S.V. Immunogenicity Challenges Associated with Subcutaneous Delivery of Therapeutic Proteins. BioDrugs 2021, 35, 125–146. [CrossRef] [PubMed]

46. Vaisman-Mentesh, A.; Gutierrez-Gonzalez, M.; DeKosky, B.J.; Wine, Y. The Molecular Mechanisms That Underlie the Immune Biology of Anti-drug Antibody Formation Following Treatment with Monoclonal Antibodies. Front. Immunol. 2020, 11, 1951.

47. Croft, M.; Siegel, R.M. Beyond TNF: TNF superfamily cytokines as targets for the treatment of rheumatic diseases. Nat. RevRheumatol. 2017, 13, 217–233. [CrossRef]

48. Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C, *et al.* A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis J Am Acad Dermatol, 56 (1) (2007), pp. 31.e1-31. e15 https://doi.org/10.1016/j.jaad.2006.07.017; View PDF; View article; Google Scholar

49. Kavanaugh A, Krueger GG, Beutler A, Guzzo C, Zhou, B, Dooley LT, *et al.* Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from the

IMPACT 2 trial Ann Rheum Dis, 66 (4) (2007), pp. 498-505. https://doi.org/10.1136/ard.2006.058339; View in Scopus; Google Scholar

50. EH Vogelzang, EL Kneepkens, MT Nurmohamed, AW van Kuijk, T Rispens, G Wolbink, *et al.* Anti-adalimumab antibodies and adalimumab concentrations in psoriatic arthritis; an association with disease activity at 28 and 52 weeks of follow-up Ann Rheum Dis, 73 (12) (2014), pp. 2178-2182 https://doi.org/10.1136/annrheumdis-2014-205554

51. Gisbert JP, Gaffney K, Young D, Ebbers HC, and Girolomoni G Current evidence on the use of the adalimumab biosimilar SB5 (Imraldi™): a multidisciplinary perspective Expert Opin Biol Ther 2022: Feb;22(2):109-121 PMID: 34918591; View article: CrossRef View in Scopus; Google Scholar DOI: 10.1080/14712598.2022.2012146

52. Thomas, S.S.; Borazan, N.; Barroso, N.; Duan, L.; Taroumian, S.; Kretzmann, B.; Bardales, R.; Elashoff, D.; Vangala, S.; Furst, D.E. Comparative Immunogenicity of TNF Inhibitors: Impact on Clinical Efficacy and Tolerability in the Management of AutoimmuneDiseases. A Systematic Review and Meta-Analysis. BioDrugs 2015, 29, 241–258. [CrossRef]

53. Bader-Meunier, B.; Krzysiek, R.; Lemelle, I.; Pajot, C.; Carbasse, A.; Poignant, S.; Melki, I.; Quartier, P.; Choupeaux, L.; Henry, E.; et al. Etanercept concentration and immunogenicity do not influence the response to Etanercept in patients withjuvenile idiopathic arthritis. Semin. Arthritis Rheum. 2019, 48, 1014–1018. [CrossRef]

54. Ara-Martín M, Pinto PH, Pascual-Salcedo D. Impact of immunogenicity on response to anti-TNF therapy in moderate-to-severe plaque psoriasis: results of the PREDIR study. *J Dermatolog Treat.* 2017;28(7):606–12. doi: 10.1080/09546634.2017.1296927. [PubMed] [CrossRef] [Google Scholar]

55. Tyring S, Gordon KB, Poulin Y, Langley RG, Gottlieb AB, Dunn M, et al. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. *Arch Dermatol.* 2007;143(6):719–26. doi: 10.1001/archderm.143.6.719. [PubMed] [CrossRef] [Google Scholar]

56. Leandro, M.; Isenberg, D.A. Rituximab—The first twenty years. Lupus 2021, 30, 371–377. [CrossRef]

57. Dunn, N.; Juto, A.; Ryner, M.; Manouchehrinia, A.; Piccoli, L.; Fink, K.; Piehl, F.; Fogdell-Hahn, A. Rituximab in multiple sclerosis: Frequency and clinical relevance of anti-drug antibodies. Mult. Scler. 2018, 24, 1224–1233. [CrossRef]

58. Oomen, I.; Nassar-Sheikh Rashid, A.; Bouts, A.H.M.; Gouw, S.C.; Kuijpers, T.W.; Rispens, T.; de Vries, A.; Wolbink, G.; Berg, J.M.V.D.; Schonenberg-Meinema, D. Anti-rituximab antibodies affect pharmacokinetics and pharmacodynamics of rituximab in children with immune-mediated diseases. Clin. Exp. Rheumatol. 2022, 40, 183–190. [CrossRef]

59. Faustini, F.; Dunn, N.; Kharlamova, N.; Ryner, M.; Bruchfeld, A.; Malmstrom, V.; Fogdell-Hahn, A.; Gunnarsson, I. First exposure to rituximab is associated to high rate of anti-drug antibodies in systemic lupus erythematosus but not in ANCA-associated vasculitis. Arthritis Res. Ther. 2021, 23, 211. [CrossRef]

60. Nash, P.; Nayiager, S.; Genovese, M.C.; Kivitz, A.J.; Oelke, K.; Ludivico, C.; Palmer, W.; Rodriguez, C.; Delaet, I.; Elegbe, A.; et al. Immunogenicity, safety, and efficacy of abatacept administered subcutaneously with or without background methotrexate in patients with rheumatoid arthritis: Results from a phase III, international, multicenter, parallel-arm, open-label study. Arthritis Care Res. 2013, 65, 718–728. [CrossRef] [PubMed]

61. Pombo-Suarez, M.; Gomez-Reino, J.J. Abatacept for the treatment of rheumatoid arthritis. Expert Rev. Clin. Immunol. 2019, 15,319–326. [CrossRef]\

62. Burmester, G.R.; Choy, E.; Kivitz, A.; Ogata, A.; Bao, M.; Nomura, A.; Lacey, S.; Pei, J.; Reiss, W.; Pethoe-Schramm, A.; et al. Low immunogenicity of tocilizumab in patients with rheumatoid arthritis. Ann. Rheum. Dis. 2017, 76, 1078–1085. [CrossRef]

63. Maneiro, J.R.; Salgado, E.; Gomez-Reino, J.J. Immunogenicity of monoclonal antibodies against tumor necrosis factor used in chronic immune-mediated Inflammatory conditions: Systematic review and meta-analysis. JAMA Intern. Med. 2013, 173,1416–1428. [CrossRef]

64. Kostine, M.; Finckh, A.; Bingham, C.O.; Visser, K.; Leipe, J.; Schulze-Koops, H.; Choy, E.H.; Benesova, K.; Radstake, T.R.D.J.; Cope, A.P.; et al. EULAR points to consider for the diagnosis and management of rheumatic immune-related adverse events due to cancer immunotherapy with checkpoint inhibitors. Ann. Rheum. Dis. 2021, 80, 36–48. [CrossRef]

65. CEBM. Oxford Centre for Evidence-Based Medicine—Levels of Evidence (March 2009). Available online: https://www.cebm.net/2009/06/oxford-centre-evidencebasedmedicine-levels-evidence-march-2009/ (accessed on 18 April 2023).

66. Krieckaert, C.L.; van Tubergen, A.; Gehin, J.E.; Hernandez-Breijo, B.; Le Meledo, G.; Balsa, A.; Böhm, P.; Cucnik, S.; Elkayam, O.; Goll, G.L.; et al. EULAR points to consider for therapeutic drug monitoring of biopharmaceuticals in inflammatory rheumaticand musculoskeletal diseases. Ann. Rheum. Dis. 2023, 82, 65–73. [CrossRef]

67. Siljehult, F.; Arlestig, L.; Eriksson, C.; Rantapaa-Dahlqvist, S. Concentrations of infliximab and anti-drug antibodies in relation toclinical response in patients with rheumatoid arthritis. Scand. J. Rheumatol. 2018, 47, 345–350. [CrossRef] [PubMed]