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Non-IgE adverse reactions to biologics

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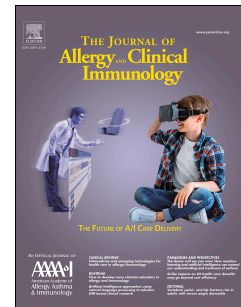
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Title: Non-IgE adverse reactions to biologics

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INTRODUCTION

Biologics encompass a class of new therapeutic agents that consists of monoclonal antibodies (moAbs), fusion proteins and nanobodies. Adverse reactions to biologics limit their use and have broad clinical impact since they affect all medical specialties¹.

Biologics are generally well tolerated, but due to their immunogenic structure, they can be recognized as non-self-epitopes inducing cellular and humoral immune responses². Hypersensitivity reactions (HSRs) to biologics have been reported with variable frequency depending on the agents¹. The structural differences of the IgG molecules can result in the generation of immunogenic compounds which elicit anti-drug antibodies (ADA), immunocomplex production and interactions with T cells. The generation of ADA relate to loss of drug efficacy and hypersensitivity reactions (HSRs)³. mAb can be chimeric, humanized or fully human in their Fab portion. Their immunogenicity is lower when human sequences are increased, but due to the carbohydrate side chains, is it not eliminated^{1,3}. Biologics induce the lysis of targeted cells with the subsequence release of proinflammatory mediators which are involved in the development of non-ADA-mediated HSRs⁴.

Current classification of drug HSRs is based on the clinical expression of symptoms (phenotypes) and their underlying cellular and molecular mechanisms (endotypes)¹. Biomarkers can help characterize and elucidate the endotypes, and skin testing, specific-IgE or tryptase have been used for the diagnosis of Type I/IgE-mediated reactions¹. Non-IgE-mediated reactions can present as immediate reactions during or shortly after the administration of moAbs and can be mediated by non-IgE anti-drug antibodies (ADA) and driven by the release of cytokines (CR). Sometimes both IgE and non-IgE mechanisms coexist inducing a constellation of symptoms which express as mixed reactions with fever, chills, urticaria, shortness of breath, desaturation and hypotension, among other symptoms, with elevated tryptase and IL-6^{1,4,5}. Delayed onset of non-IgE HSRs include serum sickness-like reactions, maculopapular rash and severe cutaneous adverse reactions^{1,6}.

NON-IgE-MEDIATED IMMEDIATE HSRs TO BIOLOGICS

ADA-mediated reactions

ADA-mediated HSRs are characterized by symptoms such as flushing, pruritus, urticaria/angioedema, wheezing, vomiting, diarrhea, hypotension, desaturation and can lead to life-threatening anaphylaxis similar to IgE-mediated reactions¹. Biologics can induce

different ADA-isotypes beyond IgE³. ADA titers are higher in patients who suffer HSRs compared with those who present with loss of efficacy². A prevalence of 56.6% specific-ADA have been detected in patients with infliximab HSRs⁵ and only 20% were IgE-ADA³. These findings suggest the existence of IgG-mediated HSRs to biologics. *In vitro* models have shown that the human FcγRIIA contributes to IgG-mediated reactions through mast cells activations during cutaneous passive and active anaphylaxis, and that basophils, neutrophils, monocytes and macrophages are involved during systemic anaphylaxis⁷. Biomarkers of these reactions include platelet-activating factor (PAF), histamine and MIP-α⁷ (Figure 1). Biologics can also generate drug-IgG-ADA immunocomplexes which can activate complement and release anaphylatoxins such as C3a and C5a. These bind complement receptors on mast cells and induce their activation and further release of mediators¹. These mechanisms could explain the negative skin testing in the 44% of patients with ADA-mediated HSRs to biologics¹. Interestingly, patients treated with rituximab who do not develop ADA during the 1st year of treatment are not at risk for developing HSRs on subsequent exposures⁸. Serum ADA levels may be explored as biomarkers to predict patients at risk for HSRs⁸. Sensitization to trastuzumab, infliximab and rituximab has been shown after a period of drug-interruption and re-exposure to be associated with HSRs^{1,3}.

Cytokine-release reactions

Two HSRs phenotypes have been described linked to systemic CR induced by biologics: infusion reactions (IR) and CR syndrome (CRS)¹. IR are self-limited and less severe on repeated exposures, and typically managed by anti-inflammatory pre-medications and by decreasing the infusion rate¹. CRS can be life-threatening reactions and can be managed through desensitization. Characteristics symptoms of CR-reactions are headache, back pain, dizziness, chills, fever and oxygen desaturation which can develop into hypotension and cardiovascular collapse¹. CRS reactions are seen for rituximab in up to 70% of patients during the 1st dose which can decrease to 40% in subsequent cycles with pre-medications⁴. The underlying mechanism is due to targeted-cell lysis and the activation of cells with FcγR, such as monocytes, macrophages and cytotoxic T-cells⁴. Detection of increased serum levels of TNF-α, INF-γ and IL-6, has been observed in patients with leukemia treated with rituximab⁴ (Figure 1). The elevation of IL-6 has been reported in patients with CRS during desensitization to Brentuximab and Obinutuzumab¹. Endothelium activation markers such as Ang-2 and von Willebrand factor have also been detected with a possible role in CR-reactions⁴. Negative ST

and elevation of IL-6 in serum during CRS reactions are the current biomarkers, and tumor lysis syndrome must be in the differential diagnosis⁴.

Mixed reactions

Mixed reactions are seen in patients presenting ADA-mediated and CRS-induced symptoms and may occur in up to 20% of HSRs to biologics¹. The biomarkers typically include tryptase and IL-6 elevations and most patients have positive skin testing¹.

NON-IMMEDIATE HSRs TO BIOLOGICS

The deposition of immunocomplex (soluble antigens aggregate with IgG/IgM) in target tissues can induce injection site reactions for subcutaneous biologics such as adalimumab¹, and serum sickness-like reactions, such as rituximab (1-20% of prevalence), infliximab and omalizumab⁹ (Figure 1). Symptoms appear around 7 to 14 days after the exposure and are usually self-limited⁹.

Delayed maculopapular rashes involving T-cells, macrophages and other cells have been described during treatment with biologics treatment and are typically self-limited with a good prognosis¹. SCARS are rarely induced by moAbs, with very few reported cases of symmetrical intertriginous and flexural exanthema to infliximab, Stevens-Johnson syndrome to rituximab and toxic epidermal necrolysis to cetuximab⁶ (Figure 1).

MANAGEMENT

Because of the potential side effects of desensitization, the need to reintroduce the same biological needs to be weighed against changing into an alternative treatment. However, switching first line treatments may impact the quality of life and patient survival¹. The reintroduction of biologics after a HSR should be based on the phenotype and endotype of the reactions and their severity (Figure 1). Rapid drug desensitization has shown to modulate humoral and cellular responses in patients after HSRs to rituximab, infliximab, trastuzumab, cetuximab, obinutuzumab and others¹⁰. Desensitization protocols should be adapted to address the initial reactions symptoms, including targeted premedications and IV fluids, which can further dilute the drugs and the mediators at the time of reactions¹. A case series of 104 patients including ADA-mediated, CRS and delayed maculopapular rash have been successfully

desensitized decreasing the prevalence and severity of breakthrough HSRs¹. Further studies are needed to better understand the role of desensitization in treating and preventing CR-reactions.

After a SCAR or severe non-immediate reaction to a biologic, discontinuation is indicated and the drug and similar drugs sharing common epitopes should be avoided⁹. Mild maculopapular delayed rash have been successfully addressed by rapid and slow desensitization protocols¹ (Figure 1).

CONCLUSION

Biologics can induce immediate and delayed HSR beyond the production of drug-specific IgE, which relates to the generation of ADA and the cell targeted release of proinflammatory cytokines. The activation of T cells and other cells during delayed reactions are also involved. More research is needed to better characterize the underlying mechanisms of these HSRs and their biomarkers to provide personalized diagnosis. Desensitizations are useful tools for the reintroduction of first-line biologics.

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204 Figure 1. Diagram outlining the proposed classification based on the underlying mechanisms,
205 potential mediators and management recommendations for non-IgE adverse reactions to
206 biologics¹.

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