

## THERAPEUTIC HOTLINE: SHORT PAPER

## Injection site reactions with the use of biological agents

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**Abstract**

Injection site reactions (ISRs) are a local phenomenon defined as a constellation of symptoms, including swelling, erythema, pruritus, and pain around the site of injection. This article reviews the different aspects of ISRs, including their epidemiology and pathogenesis, and provides practical guidance to diagnose and treat such reactions. More focus is given to food and drug administration (FDA)-approved biological agents and biosimilars, which are licensed mainly for the treatment of dermatological conditions, including psoriasis, atopic dermatitis, and chronic urticaria. ISRs are major complications of all FDA-approved self-injectable biological agents, both in adults and children, with studies showing an incidence rate of 0.5–40%. The article emphasizes that ISRs are not correlated with drug efficacy or development of antidrug antibodies. Therefore, misunderstanding of the pathophysiology of the ISRs, most of them not being allergic or immunogenic reactions, might result in unnecessary discontinuation of the treatment. Almost all local reactions to subcutaneously administered biological agents can be prevented by changing the injection techniques, patient education, and training.

**KEYWORDS**

biological agents, drug reactions, injection site reactions, psoriasis

**1 | INTRODUCTION**

Biological agents are gaining much popularity as treatments for immune-mediated disorders, with more than 40 biologic agents approved for these conditions (Richardson & Gelfand, 2008). The use of these medications can be associated with adverse reactions that are divided into five types (Table 1; Corominas, Gastaminza, & Lobera, 2014; Pichler, 2006; Scherer, Spoerl, & Bircher, 2010). The most common cutaneous side effects are injection site reactions (ISRs), which are often defined as a constellation of symptoms, including swelling, erythema, pruritus, and pain around the site of injection (Zeltser et al., 2001).

In this article, we aimed to review the different aspects of ISRs, including their epidemiology and pathogenesis, and to provide practical guidance to diagnose and treat such reactions. More focus is given to the food and drug administration (FDA)-approved biological agents and biosimilars, which are licensed mainly for the treatment of dermatological conditions, including psoriasis, atopic dermatitis, and chronic urticaria (Supporting Information Table S1).

**2 | EPIDEMIOLOGY**

ISRs are a major complication of all FDA-approved self-injectable biological agents, both in adults and children, with studies showing an

incidence rate of 0.5–40% (Table 2; Henderson Berg & Carrasco, 2017; Langley & Paul, 2018; US Food and Drug Administration, 2017a, 2017b, 2017c, 2017d, 2017e, 2017f, 2017g, 2017h, 2017i, 2017j, 2017k, 2017l, 2017m, 2017n).

**3 | MECHANISM OF ACTION**

ISRs can be divided into two groups according to their mechanism of action: irritative reactions (immediate) and allergic reactions (immediate or delayed) to the excipient or to the drug itself (Figure 1a; Corominas et al., 2014). Type  $\alpha$  ISRs are irritative local reactions seen commonly at the injection sites of subcutaneously administered biologics, caused by the proinflammatory actions of the substances. The effect corresponds to a pharmacologic-toxic reaction, which can be dose related (Corominas et al., 2014; Scherer et al., 2010). Inappropriate injection techniques, injection close to blood vessels, the chemical and physical properties of the injected drug and a reaction to the vehicle component are several causes described in the literature resulting in irritative reactions (Corominas et al., 2014).

Hypersensitivity reactions can be categorized into Types I–IV according to Coombs and Gell classification, which are induced by IgE, IgG/IgM, complement or T-cells. Type  $\beta$  delayed ISRs are T-cell induced (Type IV), while immediate ISRs are caused by antibody

**TABLE 1** Pichler's classification of adverse drug reactions of biological agents

| Classification             | Type of reaction                                                                                                                                                                                                                                                                                                       |
|----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| $\alpha$ - type reaction   | <i>Immune stimulation as a direct effect:</i> There is increase in levels of systemic cytokines, by either exogenous administration or endogenous cell activation, which cause a variety of symptoms known as cytokine release syndrome                                                                                |
| $\beta$ - type reaction    | <i>Immunogenicity:</i> Hypersensitivity reactions involving IgE, IgG, complement or T cells                                                                                                                                                                                                                            |
| $\gamma$ - type reaction   | <i>Immune deviation from therapeutic protein:</i> Adverse events are either due to or part of intrinsic activity of the drug, which leads to impairment of the immune system by infection or malignancy, because of immunosuppression, or to an immune imbalance that manifests as autoimmune or inflammatory diseases |
| $\delta$ - type reaction   | <i>Cross reactivity with similar binding/antigenic molecules:</i> Due to the action of the drug on molecules that are generally overexpressed in tumor cells, but which are also expressed in healthy cells                                                                                                            |
| $\epsilon$ - type reaction | Nonimmunological adverse drug reaction                                                                                                                                                                                                                                                                                 |

induction (Types I–III; Henderson Berg & Carrasco, 2017). Zeltser et al. showed that ISRs after etanercept injection may be an example of a T-cell-mediated delayed-type hypersensitivity (DTH) reaction, as approximately 8% of patients developed “recall ISRs,” reactions at sites where medication was previously injected (Zeltser et al., 2001). González-López et al. (2007) also noticed that some patients treated with etanercept develop the same “recall ISRs” (Figure 1a). Histologic

**TABLE 2** Incidence rates of injection site reactions

| Incidence rates of ISRs (%) |                                   |
|-----------------------------|-----------------------------------|
| <5%                         | >5%                               |
| <i>Biologic agents</i>      |                                   |
| Ustekinumab (1–2%)          | Etanercept (2.97–37%)             |
| Secukinumab (<1%)           | Adalimumab (5–20%)                |
| Brodalumab (0.5–1.4%)       | Ixekizumab (13–17%)               |
| Guselkumab (0.5–2.4%)       | Certolizumab pegol (4.3–9.6%)     |
|                             | Golimumab (6%)                    |
|                             | Dupilumab (7–10%)                 |
|                             | Omalizumab (2.7–45%)              |
| <i>Biosimilar agents</i>    |                                   |
|                             | Adalimumab-atto (Amjevita; 5–20%) |
|                             | Adalimumab-adbm (Cyltezo; 5–20%)  |
|                             | Etanercept-szszs (Erelzi; 15–37%) |

ISRs: injection site reactions.

and immunophenotypic studies revealed a superficial perivascular lymphocytic infiltrate composed mostly of CD4-positive (CD41) lymphocytes in the case of ISRs and CD81 lymphocytes in recall-site reactions (Zeltser et al., 2001). In the two cases reported by Gonzalez-Lopez et al., the dermal infiltrate was predominantly composed of CD4+ T lymphocytes, suggesting that ISRs may also be the result of classic DTH directed by activated memory CD4+ T cells (Scherer et al., 2010). It is known that both CD4+ and CD8+ T cells may mediate DTH responses, but they differ in the molecular mechanisms by

**FIGURE 1** (a) The mechanism of action of injection site reactions (ISRs). (b) Techniques to reduce the incidence of ISRs

which antigens are processed (González-López et al., 2007; Werth & Levinson, 2001). Thus, whereas CD8+ T cells typically recognize intracellular antigens that are processed via the endogenous pathway, CD4+ T cells recognize extracellular antigens that are processed through the exogenous pathway (González-López et al., 2007; Werth & Levinson, 2001).

## 4 | CLINICAL FEATURES

ISRs can manifest as redness, itching, bruising, pain, swelling, and/or irritation at the site of injection (Moreland et al., 1999). They are usually mild reactions, which appear during the first week after each injection and manifest during the first or second month of treatment (Mocci, Marzo, Papa, Armuzzi, & Guidi, 2013). With etanercept, for example, ISRs are immediately evident or appear within 24–48 hr (Moreland et al., 1999). The mean duration of the reaction is 3–5 days and there is a gradual decrease in frequency and severity of ISRs with continuation of injections (Thielen, Kuenzli, & Saurat, 2005). Kim et al. (2015) conducted a multicenter retrospective study, in which only three cases resulted in withdrawal of treatment with etanercept. Very rarely, ISRs were categorized as severe and treatment was discontinued (Moreland et al., 1999; Thielen et al., 2005).

## 5 | DIAGNOSIS

Various techniques have been used in vitro and in vivo for diagnosis of adverse type reactions ( $\alpha$ - $\epsilon$ ) of biologic agents, such as detection of IgG or IgE antibodies, skin prick tests, intradermal tests, and patch tests (Corominas et al., 2014). Allergological diagnostics can in principle only be used for type  $\beta$  reactions. Skin tests, for example, are frequently nonspecifically positive due to the pathogenesis of type  $\alpha$  reaction (Scherer et al., 2010). In relation to ISRs, diagnostic possibilities are limited and not standardized.

## 6 | MANAGEMENT

At the moment, there is lack of scientific evidence how to approach ISRs, and most of the management strategies are based on FDA prescribing information. Patient education and counseling prior to the initiation of the treatment is important to avoid unnecessary early discontinuation of the medication (Figure 1b). The physician should inform the patient on the possibility of developing ISRs, especially during the first month (Mocci et al., 2013). The first injection should be performed under the supervision of a health care provider, and the ability to inject the biologic agent should be assessed during the second session (US Food and Drug Administration, 2017a, 2017b, 2017c, 2017d, 2017e, 2017f, 2017g, 2017h, 2017i, 2017j, 2017k). Injection sites should be rotated, with the most favorable sites being the thigh, stomach, and upper arm (US Food and Drug Administration, 2017a, 2017b, 2017c, 2017d, 2017f, 2017g, 2017h). The abdomen might be less painful compared to the extremities, but the patient needs to understand that other areas should be used as well (US Food and

Drug Administration, 2017a, 2017b, 2017c, 2017d, 2017e, 2017f, 2017g, 2017h, 2017i, 2017j, 2017k, 2017l, 2017m, 2017n). Injections should not be administered into sites where the skin is tender, bruised, red, or hard (Kim et al., 2015; US Food and Drug Administration, 2017b). In case of psoriatic patients, injection into raised, thick, red, or scaly skin lesions should be avoided (US Food and Drug Administration, 2017a). Areas with scars or stretch marks should also be avoided (US Food and Drug Administration, 2017b, 2017d, 2017k).

Proper sterilization techniques should be followed prior to the injection, and a cold compression can be applied on the injection site afterwards (US Food and Drug Administration, 2017a, 2017d, 2017f). Most of the biologic agents must be placed at room temperature prior to the injection (30–45 min) and the solution should be carefully inspected visually for particulate matter and discoloration prior to administration (Langley & Paul, 2018; US Food and Drug Administration, 2017b). The solution should be clear-colorless to yellow liquid, essentially free from particulates and should not be used if cloudy or if foreign particulate matter is present (US Food and Drug Administration, 2017a, 2017b, 2017h). Sometimes management with painkillers, topical steroids, or oral antihistamines is recommended (Langley & Paul, 2018; US Food and Drug Administration, 2017a, 2017b, 2017c, 2017d, 2017e, 2017f, 2017g, 2017h, 2017i, 2017j, 2017k). Injection in proximity to blood vessels is a common phenomenon with single-use prefilled syringe, thus patients should always withdraw prior to injection. If blood appears in the syringe patients should understand that they have accidentally entered a blood vessel and they should inject in a different site using a different syringe and needle (US Food and Drug Administration, 2017a, 2017k). To reduce the incidence of ISRs, autoinjectors should be used as they penetrate at the same level into the hypodermis, while self-injectors can result in injection of the medication in different layers of the skin (Langley & Paul, 2018; US Food and Drug Administration, 2017a, 2017f). Therefore, single dose autoinjector/pen should be preferred on the single-dose prefilled syringe, but further comparison studies should provide more precise safety profile.

## 7 | STUDY LIMITATIONS

The lack of reliable data and under-reporting of ISRs can affect the reported incidence rate. In addition, limited studies were performed on optimal approach to limit ISRs. Finally, this article is not a systemic review; we aim to review the different aspects of ISRs, including their epidemiology, mechanism of action, and practical guidance to diagnosing and treating such reactions.

## 8 | CONCLUSION

ISRs are a local phenomenon and misunderstanding of the pathophysiology of the ISRs might result in unnecessary discontinuation of the treatment. According to the FDA management strategies, local reactions to subcutaneously administered biologic agents can be avoided by educating patients and altering the injection techniques. However, most of the safety profiles of biological agents are limited to data from

randomized controlled trials. Therefore, further studies are needed to provide data to match existing safety profiles based on clinical trials.

## CONFLICT OF INTEREST

Yuval Ramot has received speaker honorarium and consultancy fees from Pfizer, AbbVie, Novartis, Janssen, and Eli Lilly.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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**Table 1. FDA–approved subcutaneous biological agents and biosimilars for the treatment of psoriasis, psoriatic arthritis, atopic dermatitis and chronic urticaria**

| <b>Drug (generic name)</b>    | <b>Mode of action</b> | <b>FDA indication</b>                                                                                                                                                                                                                      |
|-------------------------------|-----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Biologic Agents</b>        |                       |                                                                                                                                                                                                                                            |
| <b>Monoclonal antibodies</b>  |                       |                                                                                                                                                                                                                                            |
| Adalimumab (Humira®)          | TNF- $\alpha$         | Moderate to severe plaque psoriasis, active psoriatic arthritis, hidradenitis suppurativa, rheumatoid arthritis, juvenile idiopathic arthritis, ankylosis spondylitis, adult and pediatric Crohn's disease, ulcerative colitis and uveitis |
| Certolizumab-pegol (Cimzia®)  | TNF- $\alpha$         | Psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis and Crohn's disease                                                                                                                                                      |
| Golimumab (Simponi®)          | TNF- $\alpha$         | Psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis                                                                                                                                                                       |
| Omalizumab (Xolair®)          | IgE                   | Moderate to severe persistent asthma in patients 12 years of age and above, and chronic idiopathic urticaria in adults and adolescents                                                                                                     |
| Ustekinumab (Stelara®)        | IL-12/IL-23           | Moderate to severe plaque psoriasis (adults and adolescents), active psoriatic arthritis and moderately to severe active Crohn's disease                                                                                                   |
| Secukinumab (Cosentyx®)       | IL-17A                | Moderate to severe plaque psoriasis in adult patients, psoriatic arthritis, Crohn's disease                                                                                                                                                |
| Brodalumab (Siliq™/Kyntheum®) | IL-17R                | Moderate to severe plaque psoriasis in adult patients                                                                                                                                                                                      |

|                                          |                |                                                                                                                                                                                          |
|------------------------------------------|----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ixekizumab (Taltz <sup>®</sup> )         | IL-17A         | Moderate to severe plaque psoriasis in adult patients, psoriatic arthritis                                                                                                               |
| Guselkumab (Tremfya <sup>®</sup> )       | IL-23          | Psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis, plaque psoriasis                                                                                                   |
| Dupilumab (Dupixent <sup>®</sup> )       | IL-4R $\alpha$ | Moderate-to-severe atopic dermatitis                                                                                                                                                     |
| <b>Fusion proteins</b>                   |                |                                                                                                                                                                                          |
| Etanercept (Enbrel <sup>®</sup> )        | TNF- $\alpha$  | Psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, psoriasis in patients 4 years and older and juvenile rheumatoid arthritis                                             |
| <b>Biosimilars</b>                       |                |                                                                                                                                                                                          |
| <b>Monoclonal antibodies</b>             |                |                                                                                                                                                                                          |
| Adalimumab-atto (Amjevita <sup>®</sup> ) | TNF- $\alpha$  | Moderate to severe plaque psoriasis, rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease and ulcerative colitis            |
| Adalimumab-adbm (Cyltezo <sup>®</sup> )  | TNF- $\alpha$  | Moderate to severe plaque psoriasis, rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease and ulcerative colitis            |
| <b>Fusion proteins</b>                   |                |                                                                                                                                                                                          |
| Etanercept-szzs (Erelzi <sup>®</sup> )   | TNF- $\alpha$  | Moderate to severe plaque psoriasis, rheumatoid arthritis, polyarticular juvenile idiopathic arthritis in patients aged 2 years or older, psoriatic arthritis and ankylosing spondylitis |