Desensitization to biological agents used in rheumatology

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Abstract

Biological agents such as monoclonal antibodies and fusion proteins are widely used for the treatment of patients with various rheumatic disorders, influencing the quality of life, disability and even mortality in patients. However, biological agents can evoke adverse reactions of different grades of severity. Although drug avoidance remains a gold standard in the care of patients hypersensitive to medication, in certain clinical situations the culprit drug is the drug of choice and cannot be replaced by another equally effective compound. In such cases, desensitization can allow the patient to be treated within current guidelines and with the most effective treatment.

The authors searched Medline and Scopus databases for English-language sources using the following key words: hypersensitivity, desensitization, biologicals, adalimumab, etanercept, adalimumab, certolizumab, golimumab, rituximab, infliximab, ixekizumab, tocilizumab, anakinra and canakinumab.

The aim of our review is to present the current knowledge about desensitization to biological agents and some guidelines according to patient inclusion, contraindications, procedures, and safety requirements.

Drug desensitization is a new issue in rheumatology, and the solution to the problem of allergic reactions to biological drugs, which gives patients with rheumatic diseases the opportunity to extend and prolong their therapy. The present article is one of the first widely discussing this topic in the biological treatment of rheumatic diseases.

Key words: drug hypersensitivity, desensitization, biological agents, rheumatic diseases.

Introduction

Biological agents such as monoclonal antibodies and fusion proteins are becoming an everyday treatment of patients with chronic inflammatory disorders including rheumatoid arthritis, spondyloarthropathies, and systemic lupus erythematosus.

Biologics have a positive impact on the outcomes of the disease, influencing disability, mortality, and quality of life of rheumatic patients. These medications are however not without toxicity. Besides the side effects directly connected to their mode of action (e.g. increased susceptibility to infections in patients treated with TNF blockers or rituximab) they can also evoke hypersensitivity reactions. These reactions in the majority of cases are mild, but anaphylactic, life-threatening reactions can occur as well.

We searched Medline and Scopus databases for English-language sources using the following key words and their connections: hypersensitivity, desensitization with biologicals, adalimumab, etanercept, adalimumab, certolizumab, golimumab, rituximab, infliximab, ixekizumab, tocilizumab, anakinra, canakinumab.

Classification of adverse drug reactions to biological agents

Hypersensitivity reactions evoked by biological agents present a vast spectrum of clinical symptoms and underlying pathomechanisms [1]. Figure 1 presents the classification of adverse reactions to biological agents according to Pichler [2].

The proposed classification includes 5 types of adverse reactions to biologicals:
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Type IV (delayed, cell-mediated reactions) e.g. maculopapular eruptions, severe cutaneous adverse reactions (SJS/TEN, DIHS/DRESS, AGEP)

Desensitization possible in mild reactions contraindicated in SCARS

SJS/TEN – Stevens-Johnson syndrome/toxic epidermal necrolysis, DIHS/DRESS – drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms, AGEP – acute generalized exanthematous pustulosis.

Fig. 1. Classification of adverse drug reactions due to biological agents. Desensitization is possible in type I immediate reactions, some non-immune mediated hypersensitivity reactions and some mild type IV reactions. Desensitization is contraindicated in type II, type III and type IV severe reactions [2].

1) type α reactions are due to cytokine storm,
2) type β hypersensitivity reactions,
3) type γ – caused by immunological imbalance resulting in immunodeficiency syndrome or autoimmune disorders,
4) type δ – result of cross-reactivity between drug and autoantigens and
5) type ε – non-immunological adverse events, e.g. heart failure due to TNF blockers.

Among hypersensitivity reactions, we can distinguish reactions classified according to the classical Gell-Coombs classification. Biological agents can evoke both type I hypersensitivity reactions (immediate IgE-mediated), type II (cytotoxic), type III reactions (serum sickness reactions) and delayed-type IV reactions (severe cutaneous reactions such as Stevens-Johnson syndrome/toxic epidermal necrolysis) [2].

The reactions can be classified according to their severity into: grade 1 (mild) reactions – limited to the skin, grade 2 (moderate) reactions which meet the criteria of anaphylaxis and involve one or more organ systems with or without skin involvement, grade 3 (severe) reactions involving one or more organs with changes in vital signs such as hypotension, desaturation, throat syndromes or cardiovascular collapse [3]. Understanding of the underlying pathomechanism is crucial for further decisions about diagnostic procedures and management of hypersensitive patients.

Management options for patients with hypersensitivity to biologicals

Avoidance of the culprit drug and treatment with an alternative, non-cross-reactive drug remains a sensible, gold standard in management of patients with hypersensitivity to biological agents [4, 5]. However, in certain clinical situations, the culprit drug remains the optimal therapeutic option for our patient (e.g. a patient with adult-onset Still disease and tocilizumab hypersensitivity reaction). In such cases, inducing tolerance to the culprit drug by implementation of a desensitization procedure remains the method of choice [4].

In some patients, in the case of non-immune mediated, mild cutaneous reactions the adverse reactions can be prevented by slowing down the infusion rate or premedication H1 antihistamines [1]. However, in the case of “true” IgE-mediated hypersensitivity (confirmed by skin testing), it seems that such procedures are less effective, and reactions after the next exposure to the culprit drug can be augmented, becoming even life-threatening. In such patients desensitization to the biological can be indicated [1].
**Desensitization**

The term drug desensitization is currently used to define a process in which a patient’s immune response to a drug is modified to generate temporary tolerance [4]. In the proposed mechanisms underlying drug desensitization the mast cells and basophils are pushed into inhibitory pathways by small, incremental antigen doses, deactivating signal transduction and release of mediators [6].

The decision about the desensitization procedure requires not only close cooperation between the rheumatologist and the allergologist but also taking into consideration:
- medical indications for the procedure,
- pathomechanism of the reaction,
- contraindications to the procedure [4].

Assessment of pathomechanisms requires the implementation of diagnostic procedures such as skin testing or basophil activation test performance [5]. In the case of confirmed IgE-mediated reactions, desensitization is possible and successful in most cases [4]. There are some controversies in terms of safety and the possibility of desensitization of delayed reactions [7].

**Medical indications**

Desensitization is reasonable and recommended if:
- the drug is considered first-line therapy and there is no alternative treatment,
- the culprit drug is more effective than alternative therapy [4],
- non-cross-reacting therapeutic agents are unavailable. A recent publication proved that desensitization is a safe and cost-effective procedure [3].

Desensitization to drugs used in rheumatology such as TNF blockers [8–29], rituximab [8, 15, 18, 19, 30–42], tocilizumab [43–48], IL-17 blockers (ixekizumab) [49] and anti-IL-1 (anakinra) [50–53] has been described. Most of the described procedures were performed in patients with rheumatoid arthritis [8, 32] but desensitization in patients with lupus or spondyloarthropathies [24], adult-onset Still disease [43], IgG4-related disease [40] and autoinflammatory disorders [51–53] has also been performed with success. In most of the published cases desensitization was performed in patients with immediate reactions, but single reports on successful desensitization in delayed reactions [47] and serum sickness disease (type III reaction) [34] have been published as well. Table I presents the published cases of desensitization to biological agents used in rheumatic diseases.

**Table I.** List of published cases of desensitization to biologics used in treatment of rheumatic diseases

| Drug                  | Author                        | Year of publication | No. of cases | Ref. |
|-----------------------|-------------------------------|---------------------|--------------|------|
| TNF inhibitors        |                               |                     |              |      |
| Etanercept            |                               |                     |              |      |
| Adalimumab            |                               |                     |              |      |
| Etanercept            |                               |                     |              |      |
| Adalimumab            |                               |                     |              |      |
| IL-6 antagonist       |                               |                     |              |      |
| IL-1 antagonist       |                               |                     |              |      |
| Anakinra              |                               |                     |              |      |
| IL-17 antagonist      |                               |                     |              |      |
| Anti CD20             |                               |                     |              |      |
Pathomechanism of the reaction and desensitization possibility

Desensitization is a procedure of tolerance introduction in patients hypersensitive to the culprit drug. Desensitization is possible in IgE-mediated immediate allergic reactions and certain non-IgE-mediated, immediate reactions [8]. In general, the data on the mechanism of desensitization is available for immediate reactions (IgE-mediated) in which rapid desensitization induced mast cell tolerance, which is likely to be associated with stabilization of the membrane bound IgE receptors that are carrying drug antigen [54].

Contraindications are mainly based on safety of the patients as some of drug hypersensitivity reactions are life-threatening (e.g. Stevens-Johnson syndrome/toxic epidermal necrolysis) and there are no data that those patients can be safely desensitized. Based on this, the expert opinion and recommendation is to avoid desensitization in such cases [4, 7, 30, 55].

Contraindications to the procedure

Absolute contraindications include:

• previous severe/life-threatening cutaneous drug-induced disease (Stevens-Johnson syndrome/toxic epidermal necrolysis (SIS/TEN), drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms (DIHS/DRESS), acute generalized exanthematous pustulosis (AGEP),
• cutaneous and systemic vasculitis,
• serum sickness disease,
• drug-induced organ involvement (hepatitis, nephritis, pneumonitis) [7].

Relative contraindications include current treatment with beta-blockers and ACE inhibitors, and unstable underlying disease (e.g. asthma, coronary heart disease) [7].

Desensitization procedure

The route of administration will depend on the culprit drug. While the first papers described desensitization to monoclonal antibodies via the intravenous route (rituximab and infliximab) (see Table I) as the first registered monoclonal antibodies were administered intravenously, recently much more attention has been paid to the subcutaneous route of administration [24] (recommended for adalimumab, etanercept or anakinra).

Rapid intravenous protocol

The most common protocol of desensitization is the 12-step or 16-step rapid intravenous desensitization protocol from Brigham and Women’s Hospital in Boston [3, 8, 31]. One to four solutions are delivered in consecutive steps at increasing infusion rates. Each step takes about 15 minutes and the doses in successive steps are 2 to 2.5 times higher than in the previous steps [3].

The presented protocol is used to desensitize patients hypersensitive to biologicals and chemotherapeutics. The majority of desensitized patients develop no (74%) or a mild (19%) reaction, and only 7% of the patients present moderate to severe breakthrough reactions [31]. The majority of reactions are cutaneous, followed by respiratory and gastrointestinal symptoms, and usually develop during the last step of the protocol [3].

It is important to keep in mind that desensitization brings a temporal tolerance state, and as the time intervals between successive doses of biologicals can be very long (e.g. rituximab in rheumatoid arthritis patients), the procedure of desensitization should be repeated whenever the drug is administered. Table II presents the 16-step protocol of intravenous desensitization to rituximab.

Rapid subcutaneous protocols of desensitization

As some of the biologicals are administered via the subcutaneous route, case series of subcutaneous desensitization have been described as well [9, 10, 24]. According to the protocol proposed by Bavbek et al. [24] wadalimumab was administered every 30 minutes; the initial dose was 0.5 mg, followed by 0.75 mg, 1.25 mg,
2.5 mg, 5 mg, 10 mg and 20 mg (cumulative dose 40 mg of adalimumab). All patients were desensitized successfully and maintained on weekly adalimumab for 3 months with premedication. Adalimumab was then spaced to every other week without any signs of hypersensitivity [24]. Table III presents the protocol of subcutaneous desensitization to adalimumab [24].

**Desensitization outcomes**

In 30–50% of all desensitization procedures mild symptoms occurred, and there are no reported deaths resulting from desensitization protocol [31]. Most of the published desensitization protocols are well tolerated, but reactions during the procedure can appear. Usually, they are mild (flushing or urticaria) but severe reactions such as bronchospasm, desaturation, and hypotension can occur as well. In repeated desensitizations, the rates of hypersensitivity symptoms drop to 10% [7], but severe reactions can occur at every stage of subsequent desensitization [56]. Despite adverse events that can occur in desensitized patients, in general, the success rate of the desensitization procedure is very high and well over 90% of patients can achieve a state of tolerance [56].

**Safety measures during desensitization procedures**

The paper of WAO presents recommendations for safety measures that should be undertaken in patients before and during drug desensitization [7]. According to these recommendations desensitization can be performed both in hospital and outpatient settings; however,
all high-risk desensitization (patients after anaphylactic shock, unstable patients with severe cardiovascular disease) should be performed in the intensive care unit. Desensitization should be supervised by experienced, well-trained allergists and nurses [7]. Emergency equipment should be available on site. The procedure of desensitization should be closely supervised, as the first symptoms of the breakthrough reaction can be very subtle [7].

Conclusions

Drug desensitization is one of the methods of management of hypersensitivity reactions performed in some allergy clinics, but other specialists are not always aware about this possibility, which can help to reintroduce a drug crucial for treatment of rheumatic diseases. This is the first review on desensitization to biological agents used to treat various rheumatic disorders addressing rheumatology specialists. The avoidance of the culprit drug remains an important option. Close cooperation between the rheumatologist and allergologist is required to qualify the patient and safely perform the procedure of desensitization.

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