Review paper

Reumatologia 2020; 58, 1: 26–33
DOI: https://doi.org/10.5114/reum.2020.93510

Desensitization to biological agents used in rheumatology

Joanna Makowska, Anna Lewandowska-Polak

Department of Rheumatology, Medical University of Lodz, Poland

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.

Biologicals 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.

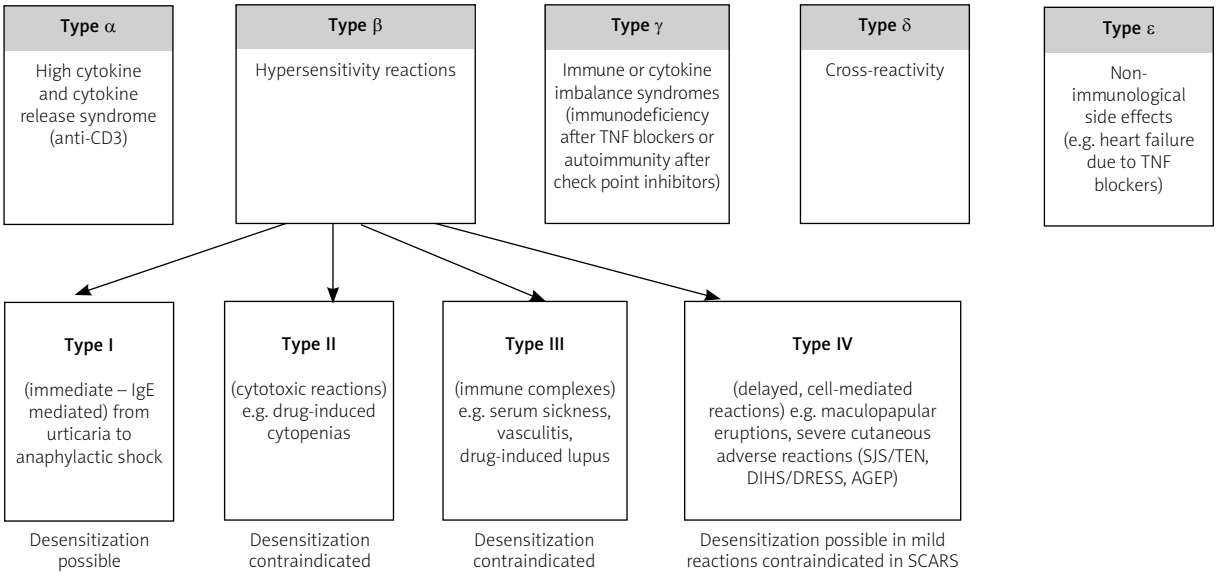
Classification of adverse drug reactions to biological agents

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:

Address for correspondence:
Anna Lewandowska-Polak, Department of Rheumatology, Medical University of Lodz, 1 Gen. Józefa Hallera Pl., 90-647 Lodz, Poland, e-mail: anna.lewandowska-polak@umed.lodz.pl

Submitted: 08.01.2020; **Accepted:** 13.02.2020



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 hypersensitivity IgE-mediated), type II (cytotoxic), type III reactions (serum sickness reactions) and delayed-type IV reactions (severe cutaneous reactions such as Stevens-Johnsons 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].

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

Drug	Author	Year of publication	No. of cases	Ref.
TNF inhibitors				
Infliximab	Puchner TC	2001	l	11
	Lelong J	2005	4	12
	Brennan PJ	2009	6	8
	Gallardo R	2010	1	16
	Madrigal-Burgaleta R	2013	10	15
	Caimmi SM	2014	1	17
	Mourad AA	2014	12	14
	Bavbek S	2016	1	19
	Behera S	2019	1	18
	Vultaggio A	2020	1	13
Etanercept	Bavbek S	2011	1	9
	Fellner MJ	2013	1	22
	Hall J	2013	1	21
	Bavbek S	2015	7	24
	de la Varga Martínez R	2017	2	23
Adalimumab	Rodríguez-Jiménez B	2009	1	26
	Quercia O	2011	1	27
	Bavbek S	2013	1	10
	Gutiérrez Fernández D	2014	1	28
	Demirel F	2015	1	29
	Bavbek S	2015	5	24
	Thévenot J	2019	2	25
IL-6 antagonist				
Tocilizumab	Justet A	2014	1	44
	Ye W	2016	1	45
	Cansever M	2018	1	46
	Erdogan T	2018	1	43
	Cortellini G	2018	1	47
	Demir S	2019	3	48
IL-1 antagonist				
Anakinra	Şoyyiğit S	2014	1	51
	Leroy V	2016	1	50
	Mendonca LO	2017	1	52
	I YIImaz	2018	1	53
IL-17 antagonist				
Ixekizumab	Jimenez RB	2018	1	49
Anti CD20				

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.

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 (SJS/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].

Table I. Cont.

Drug	Author	Year of publication	No. of cases	Ref.
Rituximab	Castells MC	2008	3	31
	Brennan PJ	2009	14	8
	Abadoglu O	2011		32
	Madrigal-Burgaleta R	2013	10	15
	Kuo JC	2014	2	33
	Fajt ML	2014	1	34
	Ataca P	2015	1	35
	Amoros-Reboredo P	2015	5	36
	Bavbek S	2016	1	19
	Dilley MA	2016	3	37
	Lebel E	2016	7	38
	Wong JT	2017	25	30
	Öztürk E	2017	3	39
	Della-Torre E	2017	1	40
	Pérez-Rodríguez E	2013	6	41
	Görgülü B	2013	24	42

No data on golimumab and certolizumab desensitization was present.

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,

Table II. Example of 16-step intravenous rituximab desensitization in patient with rheumatoid arthritis, Sjögren's syndrome, uveitis and lack of response to methotrexate and TNF blockers [20]

Step	Concentration of solution (mg/ml)	Rate of infusion (ml/h)	Time of infusion (min)	Dose administered during each step (mg)
1	0.002	2.5	15	0.001
2	0.002	5	15	0.002
3	0.002	10	15	0.004
4	0.002	20	15	0.008
5	0.031	2.5	15	0.019
6	0.031	5	15	0.038
7	0.031	10	15	0.077
8	0.031	20	15	0.153
9	0.306	5	15	0.383
10	0.306	10	15	0.765
11	0.306	20	15	1.53
12	0.306	40	15	3.06
13	3.036	10	15	7.59
14	3.036	20	15	15.179
15	3.036	40	15	30.358
16	3.036	80	174.375	705.834

Total time of infusion 6 h 40 min approximately. Cumulative dose administered 765 mg of rituximab.

Table III. Subcutaneous desensitization to adalimumab in patients with rheumatoid arthritis, ankylosing spondylitis and hypersensitivity reactions to adalimumab [24]

Step	Time (min)	Dose (mg)	Concentration (mg/ml)	Volume injected (ml)
1	0	0.5	0.5	1
2	30	0.75	5	0.15
3	60	1.25	5	0.25
4	90	2.5	5	0.5
5	120	5	50	0.1
6	150	10	50	0.2
7	180	20	50	0.4

Total time of desensitization 3 h. Cumulative dose 4 mg of adalimumab.

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 than 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 the safest and most reasonable option in the management of a patient with hypersensitivity reaction. However, in a certain clinical situation in which the culprit drug is irreplaceable or simply much more effective than an alternative drug, the desensitization procedure remains an important option.

It has been documented in a thousand patients that it is a safe and cost-effective procedure giving a chance for the patient to receive the most appropriate treatment for his condition. Close cooperation between the rheumatologist and allergologist is required to qualify the patient and safely perform the procedure of desensitization.

The authors declare no conflict of interest.

References

1. Vultaggio A, Castells MC. Hypersensitivity reactions to biologic agents. Immunol Allergy Clin North Am 2014; 34: 615-632, DOI: 10.1016/j.iac.2014.04.008.
2. Pichler WJ. Adverse side-effects to biological agents. Allergy 2006; 61: 912-920, DOI: 10.1111/j.1398-9995.2006.01058.x.
3. Sloane D, Govindarajulu U, Harrow-Mortelliti J, et al. Safety, Costs, and Efficacy of Rapid Drug Desensitizations to Chemotherapy and Monoclonal Antibodies. J Allergy Clin Immunol Pract 2016; 4: 497-504, DOI: 10.1016/j.jaip.2015.12.019.
4. Cernadas JR, Brockow K, Romano A, et al. General considerations on rapid desensitization for drug hypersensitivity – a consensus statement. Allergy 2010; 65: 1357-1366, DOI: 10.1111/j.1398-9995.2010.02441.x.
5. Demoly P, Adkinson NF, Brockow K, et al. International Consensus on drug allergy. Allergy 2014; 69: 420-437, DOI: 10.1111/all.12350.
6. Sancho-Serra Mdel C, Simarro M, Castells M. Rapid IgE desensitization is antigen specific and impairs early and late mast cell responses targeting FcεRI internalization. Eur J Immunol 2011; 41: 1004-1013, DOI: 10.1002/eji.201040810.
7. Kowalski ML, Ansotegui I, Aberer W, et al. Risk and safety requirements for diagnostic and therapeutic procedures in allergology: World Allergy Organization Statement. World Allergy Organ J 2016; 9: 33, DOI: 10.1186/s40413-016-0122-3.
8. Brennan PJ, Rodriguez Bouza T, Hsu FI, et al. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. J Allergy Clin Immunol 2009; 124: 1259-1266, DOI: 10.1016/j.jaci.2009.09.009.
9. Bavbek S, Aydin O, Ataman S, et al. Injection-site reaction to etanercept: role of skin test in the diagnosis of such reaction and successful desensitization. Allergy 2011; 66: 1256-1257, DOI: 10.1111/j.1398-9995.2011.02601.x.
10. Bavbek S, Ataman S, Bankova L, Castells M. Injection site reaction to adalimumab: Positive skin test and successful rapid desensitisation. Allergol Immunopathol (Madr) 2013; 41: 204-206, DOI: 10.1016/j.aller.2012.04.006.
11. Puchner TC, Kugathasan S, Kelly KJ, Binion DG. Successful desensitization and therapeutic use of infliximab in adult and pediatric Crohn's disease patients with prior anaphylactic reaction. Inflamm Bowel Dis 2001; 7: 34-37, DOI: 10.1097/00054725-200102000-00005.
12. Lelong J, Duburque C, Fournier C, et al. Desensitisation to infliximab in patients with Crohn's disease. Rev Mal Respir 2005; 22: 239-246, DOI: 10.1016/s0761-8425(05)85477-4.
13. Vultaggio A, Nencini F, Bormioli S, et al. Desensitization modulates humoral and cellular immune response to infliximab in a patient with an immediate hypersensitivity reaction. J Allergy Clin Immunol Pract 2020, DOI: 10.1016/j.jaip.2019.12.040.
14. Mourad AA, Boktor MN, Yilmaz-Demirdag Y, Bahna SL. Adverse reactions to infliximab and the outcome of desensitization. Ann Allergy Asthma Immunol 2015; 115: 143-146, DOI: 10.1016/j.anai.2015.06.004.
15. Madrigal-Burgaleta R, Berges-Gimeno MP, Angel-Pereira D, et al. Hypersensitivity and desensitization to antineoplastic agents: outcomes of 189 procedures with a new short protocol and novel diagnostic tools assessment. Allergy 2013; 68: 853-861, DOI: 10.1111/all.12105.
16. Gallardo R, Fobelo MJ, Pastor C, Orta-Cuevas JC. Protocol for inducing infliximab tolerance in a patient with psoriatic spondylarthritis. Farm Hosp 2010; 34: 94-96, DOI: 10.1016/j.farma.2009.10.001.
17. Caimmi SM, Caimmi D, Riscassi S, Marseglia GL. A new pediatric protocol for rapid desensitization to monoclonal antibodies. Int Arch Allergy Immunol 2014; 165: 214-218, DOI: 10.1159/000369299.
18. Behera SK, Selvarajan S, Mathews J, et al. A Novel Desensitization Protocol for Infliximab Hypersensitivity in a 13-Year Old Patient with Pustular Psoriasis. Curr Drug Saf 2019; 14: 158-162, DOI: 10.2174/1574886314666190119115632.
19. Bavbek S, Kendirlinan R, Çerçi P, et al. Rapid Drug Desensitization with Biologics: A Single-Center Experience with Four Biologics. Int Arch Allergy Immunol 2016; 171: 227-233, DOI: 10.1159/000454808.
20. Yang BC, Castells MC. Rituximab hypersensitivity and desensitization: a personalized approach to treat cancer and connec-

tive tissue diseases. Ann Allergy Asthma Immunol 2019; 123: 11-15, DOI: 10.1016/j.anai.2019.03.008.
21. Hall J, Findeisen J. Successful etanercept desensitization in a patient with severe injection site reactions. J Clin Rheumatol 2013; 19: 407-408, DOI: 10.1097/RHU.0b013e3182a705fe.
22. Fellner MJ, Yohe N. Etanercept urticaria in a patient with psoriasis desensitized using a new method. J Drugs Dermatol 2013; 12: 1168-1169.
23. de la Varga Martínez R, Gutiérrez Fernández D, Foncubierta Fernández A, et al. Rapid subcutaneous desensitization for treatment of hypersensitivity reactions to etanercept in two patients with positive basophil activation test. Allergol Int 2017; 66: 357-359, DOI: 10.1016/j.alit.2016.09.002.
24. Bavbek S, Ataman Ş, Akinci A, Castells M. Rapid subcutaneous desensitization for the management of local and systemic hypersensitivity reactions to etanercept and adalimumab in 12 patients. J Allergy Clin Immunol Pract 2015; 3: 629-632, DOI: 10.1016/j.jaip.2015.01.009.
25. Thévenot J, Ferrier le Bouëdec MC, Buisson A, et al. Rapid Desensitization to Adalimumab Is Associated With Decreased Basophil Sensitivity. J Investig Allergol Clin Immunol 2019; 29: 141-143, DOI: 10.18176/jiaci.0350.
26. Rodríguez-Jiménez B, Domínguez-Ortega J, González-Herrada C, et al. Successful adalimumab desensitization after generalized urticaria and rhinitis. J Investig Allergol Clin Immunol 2009; 19: 246-247.
27. Quercia O, Emiliani F, Foschi FG, Stefanini GF. Adalimumab desensitization after anaphylactic reaction. Ann Allergy Asthma Immunol 2011; 106: 547-548, DOI: 10.1016/j.anai.2011.03.014.
28. Gutiérrez Fernández D, Foncubierta Fernández A, Anguita Carazo JL, et al. Adalimumab desensitization protocol in a patient with a generalized urticarial reaction and angioedema following adalimumab administration. J Investig Allergol Clin Immunol 2014; 24: 273-275.
29. Demirel F, Kartal O, Gulec M, et al. Desensitization to Adalimumab: An Example of Repeated Desensitization to a Biological Agent. Drug Saf Case Rep 2015; 2: 7, DOI: 10.1007/s40800-015-0008-2.
30. Wong JT, Long A. Rituximab Hypersensitivity: Evaluation, Desensitization, and Potential Mechanisms. J Allergy Clin Immunol Pract 2017; 5: 1564-1571, DOI: 10.1016/j.jaip.2017.08.004.
31. Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. J Allergy Clin Immunol 2008; 122: 574-580, DOI: 10.1016/j.jaci.2008.02.044.
32. Abadoglu O, Epozturk K, Atayik E, Kaptanoglu E. Successful rapid rituximab desensitization for hypersensitivity reactions to monoclonal antibodies in a patient with rheumatoid arthritis: a remarkable option. J Investig Allergol Clin Immunol 2011; 21: 319-321.
33. Kuo JC, Hawkins C, Yip D. Treatment outcomes of rapid desensitisation protocols for chemotherapeutic agents and monoclonal antibodies following hypersensitivity reactions. Intern Med J 2014; 44: 442-449, DOI: 10.1111/imj.12320.
34. Fajt ML, Petrov AA. Desensitization protocol for rituximab-induced serum sickness. Curr Drug Saf 2014; 9: 240-242, DOI: 10.2174/1574886309666140509154056.
35. Ataca P, Atilla E, Kendir R, et al. Successful desensitization of a patient with rituximab hypersensitivity. Case Reports Immunol 2015; 2015: 524507, DOI: 10.1155/2015/524507.
36. Amoros-Reboredo P, Sanchez-Lopez J, Bastida-Fernandez C, et al. Desensitization to rituximab in a multidisciplinary setting. Int J Clin Pharm 2015; 37: 744-748, DOI: 10.1007/s11096-015-0136-x.
37. Dilley MA, Lee JP, Platt CD, Broyles AD. Rituximab Desensitization in Pediatric Patients: Results of a Case Series. Pediatr Allergy Immunol Pulmonol 2016; 29: 91-94. DOI: 10.1089/ped.2015.0615.
38. Lebel E, Ben-Yehuda D, Bohbot E, et al. Hypersensitivity reactions to rituximab: 53 successful desensitizations in 7 patients with severe, near-fatal reactions. J Allergy Clin Immunol Pract 2016; 4: 1000-1002, DOI: 10.1016/j.jaip.2016.05.013.
39. Öztürk E, Özyiğit LP, Öztürk AB, et al. Rituximab desensitization in three patients with severe rituximab allergy. Curr Probl Cancer 2017; 41: 349-354, DOI: 10.1016/j.currproblcancer.2017.07.003.
40. Della-Torre E, Conti A, Berti A, et al. Rituximab hypersensitivity in IgG4-related disease: successful desensitization in a patient with IgG4 rheumatoid factor. Int J Rheum Dis 2017; 20: 276-279, DOI: 10.1111/1756-185X.13021.
41. Pérez-Rodríguez E, Martínez-Tadeo JA, Perez-Rodriguez N, et al. Outcome of 490 Desensitizations to Chemotherapy Drugs with a Rapid One-Solution Protocol. J Allergy Clin Immunol Pract 2018; 6: 1621-1627 e6, DOI: 10.1016/j.jaip.2017.11.033.
42. Görgülü B, Seval GC, Kendirlinan R, et al. Rapid Drug Desensitization With Rituximab in 24 Cases: A Single-Center Experience. J Investig Allergol Clin Immunol 2019; 29: 468-470, DOI: 10.18176/jiaci.0445.
43. Erdogan T, Yasar Bilge NS, Kasifoglu T. Successful slow tocilizumab desensitization in a patient with adult onset Still disease. Biologicals 2018; 55: 17-18, DOI: 10.1016/j.biologicals.2018.07.002.
44. Justet A, Neukirch C, Poubeau P, et al. Successful rapid tocilizumab desensitization in a patient with Still disease. J Allergy Clin Immunol Pract 2014; 2: 631-632, DOI: 10.1016/j.jaip.2014.04.015.
45. Ye W, Fifield MC, Mayhew A, et al. Successful tocilizumab desensitization in an adult with juvenile idiopathic arthritis. Scand J Rheumatol 2016; 45: 75-76, DOI: 10.3109/03009742.2015.1074279.
46. Cansever M, Sahin N, Dursun I, et al. Successful Slow Desensitization to Tocilizumab in a 15-Year-Old Patient. J Investig Allergol Clin Immunol 2018; 28: 436-438, DOI: 10.18176/jiaci.0314.
47. Cortellini G, Mascella F, Simoncelli M, et al. Effective Desensitization to Tocilizumab in Delayed Hypersensitivity Reaction. Pharmacology 2018; 102: 114-116, DOI: 10.1159/000490419.
48. Demir S, Gelincik A, Coskun R, et al. A practical 16-day desensitization protocol in lenalidomide-induced non-immediate hypersensitivity reactions. Ann Allergy Asthma Immunol 2019; 123: 394-397, DOI: 10.1016/j.anai.2019.07.031.
49. Jimenez RB, Vera DG, Rivera-Diaz R, et al. Successful subcutaneous desensitization in a patient with allergy to ixekizumab.

J Allergy Clin Immunol Pract 2018; 6: 1761-1762, DOI: 10.1016/j.jaip.2017.12.036.
50. Leroy V, Lazaro E, Darrigade AS, et al. Successful rapid subcutaneous desensitization to anakinra in a case of delayed-type hypersensitivity reaction. Br J Dermatol 2016; 174: 1417-1418, DOI: 10.1111/bjd.14454.
51. Şoyyiğit S, Kendirlinan R, Aydin O, Celik GE. Successful desensitization with anakinra in a case with immediate hypersensitivity reaction. Ann Allergy Asthma Immunol 2014; 113: 325-326, DOI: 10.1016/j.anai.2014.06.017.
52. Mendonca LO, Malle L, Donovan FX, et al. Deficiency of Interleukin-1 Receptor Antagonist (DIRA): Report of the First Indian Patient and a Novel Deletion Affecting IL1RN. J Clin Immunol 2017; 37: 445-451, DOI: 10.1007/s10875-017-0399-1.
53. YIImaz I, Türk M, Nazik Bahçecioğlu S. Successful rapid subcutaneous desensitization to anakinra in a case with a severe immediate-type hypersensitivity reaction. Eur Ann Allergy Clin Immunol 2018; 50: 94-96, DOI: 10.23822/EurAnnACI.1764-1489.30.
54. Castells M, Sancho-Serra Mdel C, Simarro M. Hypersensitivity to antineoplastic agents: mechanisms and treatment with rapid desensitization. Cancer Immunol Immunother 2012; 61: 1575-1584, DOI: 10.1007/s00262-012-1273-x.
55. Scherer K, Brockow K, Aberer W, et al. Desensitization in delayed drug hypersensitivity reactions – an EAACI position paper of the Drug Allergy Interest Group. Allergy 2013; 68: 844-852, DOI: 10.1111/all.12161.
56. Castells M. Rapid desensitization for hypersensitivity reactions to medications. Immunol Allergy Clin North Am 2009; 29: 585-606, DOI: 10.1016/j.iac.2009.04.012.