



# The Prevalence of Hypersensitivity Reactions to Antirheumatic Biological Agents and Results of the Skin Tests: Experience of a Tertiary Referral Allergy Center in Turkey

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## ABSTRACT

**Objective:** The use of biological agents (BAs) has increased dramatically for inflammatory diseases and this increase has led to a rise in hypersensitivity reactions (HSRs). The symptoms and diagnostic tools for HSRs are not standardized. We aimed to analyze the prevalence of HSRs to anti-rheumatic BAs and to evaluate the usefulness of skin tests (STs) as a diagnostic tool.

**Materials and Methods:** Our study was conducted at the Ege University Medical Faculty, Department of Internal Medicine, Division of Allergy and Clinical Immunology and Division of Rheumatology, Izmir, Turkey. Four hundred sixty patients who received BAs between Jan 1<sup>st</sup>, 2015, and Jan 1<sup>st</sup>, 2016, were reviewed in this retrospective cross-sectional study. The prevalence of HSRs was retrospectively evaluated. Ten patients with HSRs were evaluated with STs containing commercially available culprit drugs. The data was collected from hospital records. The age, sex, atopic diseases, primary rheumatic diseases, and anti-rheumatic therapies of the patients were recorded.

**Results:** Two hundred fifty patients were treated with rituximab (RTX), 45 with infliximab, 40 with tocilizumab (TOC), 36 with golimumab, 35 with etanercept, 34 with abatacept, 15 with certolizumab, and 5 with adalimumab. Fifty reactions with RTX and two reactions with TOC were infusion-related (IRRs). Ten HSRs were observed. Eight patients had immediate (7 immediate systemic reactions and 1 local injection site reactions), and 2 had late-onset cutaneous reactions. We detected the ratio of IRRs as 11.3%, immediate HSRs as 1.73%, IgE-mediated reactions as 1.08%, and anaphylaxis as 0.86%. STs were positive in 5 of 8 patients with immediate HSRs. Four of them had anaphylaxis, and remarkably, 3 of these had positive STs. None of the ten patients had high levels of specific IgE and only four had atopic diseases. Total IgE levels were not high and specific IgE levels were not positive in the presence of HSR to BAs ( $p=0.039$ ).

**Conclusion:** Five of the 8 (62.5%) patients with immediate reactions had positive STs, which suggested IgE-mediated reactions. The prevalence of HSRs to BAs was less than the ones mentioned in the literature.

**Keywords:** Hypersensitivity reaction, prevalence, biological agent, skin test

## INTRODUCTION

The treatments of immune-mediated diseases are successfully performed by the development of BAs which are protein molecules, different from other drugs. BAs can be fully human, humanized, and chimeric, but fully human is considered to be less immunogenic than the other kinds. Unexpectedly, fully human BAs can provoke adverse drug reactions (ADR) (1-4).

Initial ADRs to BAs are categorized into four groups by the recently published paper of Isabwe et al. The most common pattern is type 1-like (IgE/non-IgE) reactions (63%), followed by mixed reactions (21%), cytokine-release syndromes (CRS) (13%), and delayed-type IV reactions (3%) (2).

CRSs and IRRs to BAs can happen at the first dosage of the treatment and may arise with dermatologic (flush-

ing, itching, and erythema), cardiovascular (tachycardia, hypertension, and syncope), respiratory (dyspnea, chest tightness), gastrointestinal (vomiting, nausea), and constitutional symptoms (fever, chills, etc.) (2,3). IRRs could be limited by repeating the infusions and administration of the premedications. CRSs occur by the release of proinflammatory cytokines, mainly TNF- $\alpha$ , interleukin-1 (IL-1), and IL-6, from macrophages and other activated types of Fc $\gamma$ R receptor-presenting immune cells (2,3,5).

Immediate HSRs (type 1-like) to BAs can present with cutaneous (flushing, pruritus, urticaria, etc.), respiratory (shortness of breath, wheezing, etc.), cardiovascular (hypotension, tachycardia, etc.), gastrointestinal symptoms (vomiting, nausea, etc.) and the most importantly, anaphylaxis. The symptoms of HSRs to BAs are derived from the degranulating cells of the immune system, especially by the release of tryptase, histamine, leukotrienes, and prostaglandins from mast cells and basophils (2,6,7). Elevated serum tryptase levels measured at the time of the HSR and positive STs with a non-irritating concentration of a BA on immediate-read are strongly suggestive of an IgE-mediated allergy. Symptoms of IgG-mediated reactions would be similar to those observed in IgE-mediated reactions.

T-cell mediated, late-onset (type IV) HSRs to BAs can occur beginning from the 24<sup>th</sup> hour after the drug exposure to the several weeks after quitting the treatment (2,8,9). The cutaneous signs of the late-onset type HSRs can be presented at the subcutaneous injection sites, and also, they have a wide range of signs including nonsevere maculopapular rash to severe cutaneous adverse reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis) (2,10,11).

It should be kept in mind that mixed reactions can include the biomarkers of CRSs and type 1-like HSRs, and that the symptoms of both reactions could occur with BAs.

The increasing use of BAs has led to a rise in HSR. The symptoms and diagnostic tools for HSRs have not been standardized. We aimed to show the prevalence of HSRs to BAs in this retrospective cross-sectional study; in addition, to evaluate the usefulness of STs in diagnosis, and to demonstrate the underlying mechanisms of HSRs.

## MATERIALS and METHODS

### Study Group

The study group included four hundred sixty patients

who were treated with BAs by the Department of Rheumatology from Jan 1<sup>st</sup>, 2015 to Jan 1<sup>st</sup>, 2016. Infliximab (IFN), tocilizumab (TOC), and rituximab (RTX) were administered intravenously, and etanercept (ETN), adalimumab (ADA), golimumab (GOL), certolizumab (CZP), and abatacept (ABT) were administered subcutaneously.

Ten patients who were referred to the Department of Allergy and Clinical Immunology of Ege University due to immediate and late-onset HSRs to BAs at each exposure were enrolled in the study.

### Data under interest

The prevalence of HRSs was retrospectively evaluated and analysis of the allergic reactions to BAs was performed by using STs with the culprit drugs.

Written consent was obtained from all enrolled subjects according to the Declaration of Helsinki. The Ethics Committee of Ege University Hospital, Izmir, approved the study (70198063-050.06.04). No funding was received for this study.

Total serum IgE (normal value <100 KU/L) (ImmunoCAP PHADIA), serum specific IgE (normal value <0.35 KU/L), and qualitative multi-allergen test for inhalant allergens (Phadiotop, ImmunoCAP PHADIA) were evaluate to search the relationship between the presence of atopy and HSR to BAs.

### Definition of Hypersensitivity Reactions to Biological Agents

The HRSs were classified as IRR, immediate (type 1), and late-onset (type 4) reactions in our study group. Immediate HSRs were defined as local ISR, and systemic HSRs.

### Immediate Type (Type 1) Hypersensitivity Reactions

We classified the HSRs that occur within 24 hours of the injection as type 1 (immediate) HSRs. This type of reaction requires previous exposure to the drug for sensitization to occur. Various systems (cutaneous, respiratory, gastrointestinal, cardiovascular, and neurologic) are involved. We evaluated the patients with positive skin prick test (SPT) and/or intradermal test (IDT) as IgE-mediated immediate reactions and those without positive ST and/or IDT as non-IgE mediated immediate reactions. We accepted the patients with cutaneous symptoms at the site of injections

within the first 24 hours of injections as having local ISRs, which were characterized by erythema, edema, and itching at the site of subcutaneous administration (12).

#### Late-onset (Type 4) Hypersensitivity Reactions

We classified the HSRs that occur more than 24 hours after the injection of the drug and tend to resolve in the subsequent days as type 4. Late-onset HSRs can be seen at subcutaneous injection sites, and also present with systemic maculopapular and severe cutaneous drug eruptions (13).

#### Infusion-related Reactions

We classified HSRs that occur within the 1<sup>st</sup> hour of the injection of the drug, typically limit itself on repeated exposures, and respond to premedication on the subsequent injections as IRRs. Patients with IRRs may experience chills, fever, nausea, malaise, myalgia, and flushing (14).

We also evaluated the possibility of HSRs to concomitant therapy with disease-modifying anti-rheumatic drugs (DMARDs) (methotrexate, sulfasalazine, cyclosporine, azathioprine) and corticosteroids in all the patients.

#### Skin Tests with the Culprit Drugs

SPTs and IDTs were performed using commercially available drugs and prepared through serial dilutions. ST concentrations of culprit drugs are shown in Table I (15). SPT results were evaluated after 15 min and IDTs after 20 min. A minimum wheal area of 3 mm in diameter or an increase of area of >3 mm was considered positive for both SPTs and IDTs. Histamine was used as a positive control. When skin prick testing was negative, IDT was performed using 0.03 mL of a 1:100 dilution of a full-strength solution, and if results were negative, 1:10, and 1:1 (the full concentration of the commercial drug itself) dilutions were used (15).

**Table I: Proposed drug skin test concentrations**

Medication	Prick Test Concentration (mg/mL)	Intradermal Test Concentration
Rituximab	10	0.1, 1,10
Infliximab	10	0.1, 1,10
Tocilizumab	20	0.2, 2, 20
Adalimumab	50	0.5, 5, 50
Etanercept	25	0.25, 0.5, 5
Certolizumab	20	0.2,2,20

Patch tests were prepared using commercially available drugs with 10% and 30% dilutions with 0.9% NaCl for those in liquid form, and with petrolatum for those in powder form. Pure petrolatum was used as the negative control. Drug patch tests were performed on the upper back. Two patch test readings were done, the first on day 2 and the second on day 3 (16).

All of the drug tests were performed at least six weeks to six months after the resolution of the drug reaction, and 1 month after the cessation of systemic corticosteroids or immunosuppressive therapy, to avoid false-negative test results.

#### Statistical analyses

In descriptive statistics, percentage (%), frequency (number and percentage), mean (range) values were used for categorical variants as appropriate, and the chi-square and t-tests were used for comparisons of categorical variables. The non-parametric tests, Mann-Whitney U and Kruskal-Wallis H were used to compare numerical variables, where the numbers were <30. Statistical analyses were performed using the SPSS software package, version 23 (SPSS Inc., Chicago, IL, USA). Results with  $p < 0.05$  were evaluated as statistically significant.

#### RESULTS

Four hundred sixty patients were treated with various BAs. Two hundred fifty (54%) patients were treated with rituximab, 45 (9.78%) with infliximab, 40 (8.69%) with tocilizumab, 36 (7.82%) with golimumab, 35 (7.6%) with etanercept, 34 (7.39%) with abatacept, 15 with certolizumab (3.26%), and 5 (1.08%) with adalimumab (Figure 1).

#### Prevalence of HSRs

We detected the ratio of IRRs as 11.3% (52/460, 50 with RTX and 2 with TOC), the rate of immediate HSRs as 1.73% (8/460), the rate of IgE-mediated allergic reactions proved by positive-resulted STs as 1.08% (5/460), and the rate of anaphylaxis as 0.86% (4/460) (Figure 2). Additionally, we also detected the reaction prevalence for each drug (number of reactions/number of administered drugs). The prevalence of HRS to adalimumab was 20%, certolizumab was 6.66%, tocilizumab was 5%, infliximab was 4.44%, etanercept was 2.85%, rituximab was 1.2%. No HSR to golimumab and abatacept was observed (Figure 3).

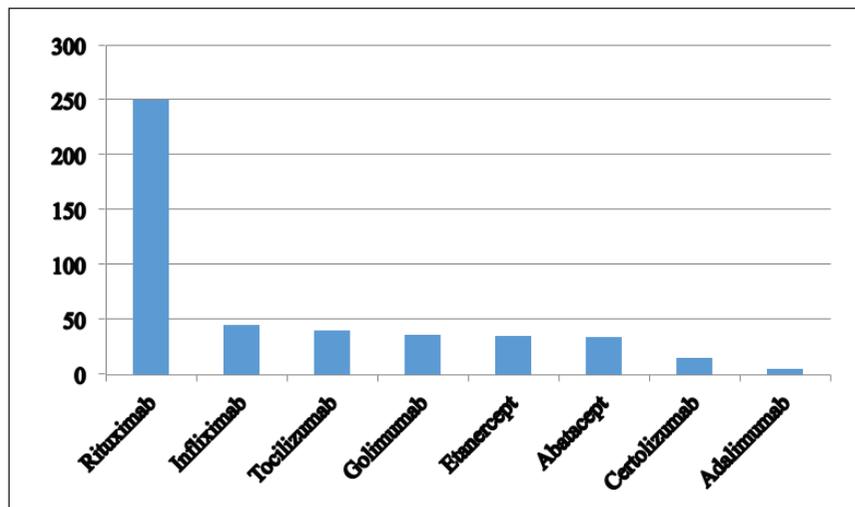


Figure 1. The distribution of the number of administered BAs.

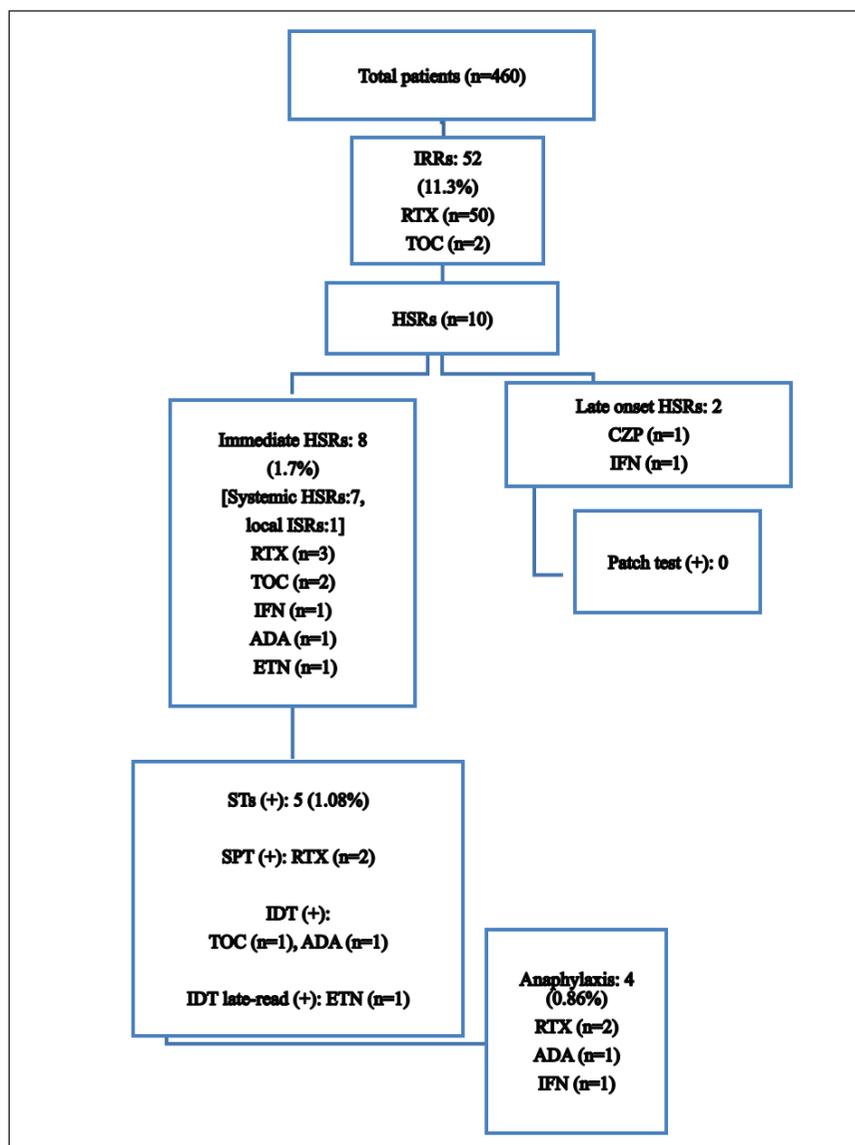
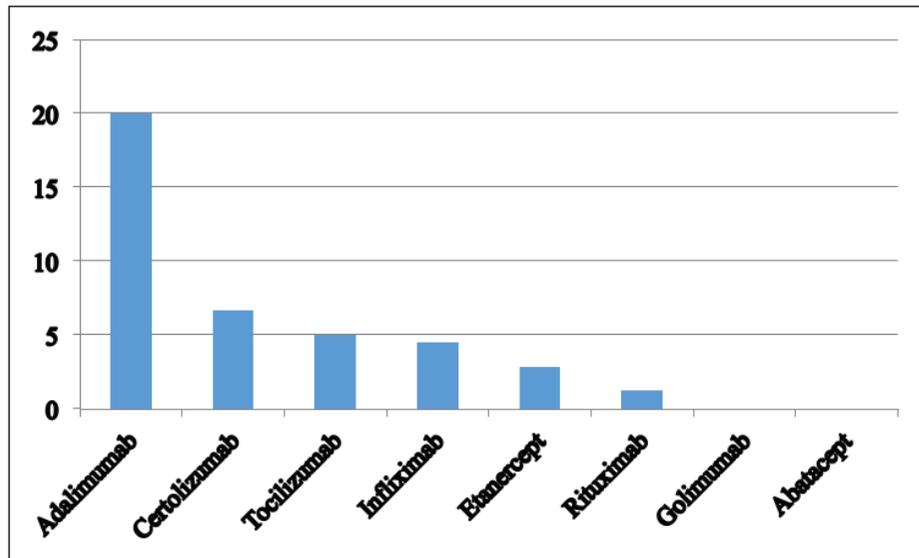


Figure 2. The distribution of the numbers and types of administered BAs. The HSRs and results of the STs to BAs are seen. **Abbreviations:** HSR: Hypersensitivity reactions, ST: Skin test, SPT: Skin prick test, IDT: Intradermal test, BAs: Biological agents, RTX: rituximab, IFN: infliximab, TOC: tocilizumab, GOL: golimumab, ETN: etanercept, ABT: abatacept, CZP: certolizumab, ADA: adalimumab.



**Figure 3.** The distribution of the HSRs for each of the BAs.

### Clinical characteristics of the reported hypersensitivity reactions and demographic features of the patients

Ten (4.6%) (6 females/4 males) patients with a mean age of 43.7 (range, 27-59) years, presented with HSRs to BAs during the one-year follow-up (Table II). Four had atopic diseases [2 had drug allergies (DA), 1 had non-steroidal anti-inflammatory drug-exacerbated cutaneous diseases (NECD), and 1 had asthma]. The distribution of the rheumatologic diseases was systemic lupus erythematosus (SLE, n=2), rheumatoid arthritis (RA, n=3), ankylosing spondylitis (AS, n=3), inflammatory bowel disease with seronegative spondylarthritis (IBD-SpA, n=1), and psoriatic arthritis (PsA, n=1). All of these patients were taking DMARDs while they were being administered BAs (Table II). Among these patients, ADRs developed in 21.2% of RTX (n=53/250) and 10% of TOC (n=4/40) infusions. Fifty reactions with RTX and 2 reactions with TOC were IRRs (Figure 2).

Cutaneous symptoms were the most frequent clinical features, in particular, immediate local reactions, flushing, urticaria, and itching. All of the reactions were recorded after the second infusion. Eight patients had immediate reactions (3 with RTX, 2 with TOC, 1 of each with IFN, ADA and ETN) (7 systemic immediate HSRs and 1 local ISR), and 2 had late-onset cutaneous reactions (1 with CZP and 1 with IFN). We detected HSRs particularly in patients with SLE, RA, and AS (Table II).

We detected a high level of total IgE [362 KU/L (0-100)] in only one patient with a late-onset cutaneous

reaction to IFN. All patients had negative levels of specific IgE (<0.35 KU/L). There were no high levels of total IgE and specific IgE in the patients with HSR to BAs (p=0.039). The patient with an ISR to ETN had high basal tryptase concentration [16 ng/mL (<11.4ng/mL)]. However, we detected a positive IDT at the late-read results (5/20 mm at the 24<sup>th</sup> hour and 5/10 mm at the 48<sup>th</sup> hour) and a positive drug patch test with a 30% dilution, suggestive of a T cell-mediated delayed-type hypersensitivity (Table II). We had a patient with AS presenting with anaphylaxis to ADA with a positive IDT (1/10 dilution) at the immediate-read result (10/45 mm) and two patients presenting with anaphylaxis to RTX with positive SPTs. Also, an immediate generalized cutaneous reaction to TOC was observed in one patient with a positive IDT (1/10 dilution) at the immediate-read result (5/10 mm). All of them were suggestive of an IgE-mediated mechanism (Table II).

### The safety and utility of skin testing to biologic agents

We analyzed whether HSRs had some specific clinical features in patients with ST positivity. Firstly, we observed a significantly higher incidence of ST positivity in patients with anaphylaxis (3/4) compared to the ones with mild-to-moderate events (2/6).

STs were positive in 5 of 8 patients with immediate HSRs (2 with RTX and 1 of each with TOC, ADA, and ETN) and four of those (2 with RTX, 1 of each ADA, and IFN) had anaphylaxis. There was no ST positivity with IFN. A patch test with the culprit drug was negative in the patient with a late-onset reaction to IFN (Table II). We could not perform

**Table II: The clinical characteristics of the patients and the results of the STs to the culprit drugs**

Patient no.	1	2	3	4	5	6	7	8	9	10
Sex	F	F	F	F	M	M	F	M	F	M
Age	41	59	27	30	45	46	45	38	49	57
Atopic Disease	-	DA	-	DA	-	NECD	-	Asthma	-	-
Primary Rheumatic Disease	CD	AS	SLE	SLE	AS	AS	PsA	RA	RA	RA
Anti-rheumatic Therapy	SSZ, AZA	MTX, SSZ	CsA, CS, MTX	CsA	SSZ	SSZ	MTX, SSZ	CS, MTX	CS, MTX	CS, MTX
Biological Agent	IFN	ADA	RTX	RTX	CZP	IFN	ETN	RTX	TOC	TOC
Biological Agent Dosage	3.	2. yrs	2.	4.	12.	2.	4.	4.	4. yrs	2. yrs
BAD at the Rxn.	3.	10.	2.	2.	11.	2.	4.	4.	12.	8.
Reaction Type	IR	IR	IR	IR	LOR	LOR	ISR	IR	IR	IR
Anaphylaxis	+	+	+	+	-	-	-	-	-	-
Cutaneous Sx.	-	+	+	+	+	+	+	+	+	+
Respiratory Sx.	+	+	+	+	-	-	-	-	-	-
Cardiovascular Sx.	+	+	+	+	-	-	-	-	-	-
Gastrointestinal Sx.	-	+	+	-	-	-	-	-	-	-
SPT	-	-	+	+	-	-	-	-	-	-
IDT	-	+	-	-	-	-	-	-	+	-
IDT/Late-read	-	-	-	-	-	-	+	-	-	-
Patch test	-	-	-	-	CLE	-	+	-	-	-

**Abbreviations:** BAD: Biological agent dosage, Sx: symptoms, SPT: Skin prick test, IDT: Intradermal test, ISR: Injection-site reactions, RTX: Rituximab, ETN: Etanercept, IFN: Infliximab, CZP: Certolizumab, ADA: Adalimumab, TOC: Tocilizumab, IR: Immediate systemic reaction, LOR: Late-onset reaction, DA: Drug allergy, NECD: Non-steroidal anti-inflammatory drug-exacerbated cutaneous disease, CD: Crohn disease, SLE: Systemic lupus erythematosus, AS: Ankylosing spondylitis, RA: Rheumatoid arthritis, PsA: Psoriatic arthritis, CLE: Cutaneous lupus erythematosus, MTX: Methotrexate, CS: Corticosteroid, AZA: Azatiopurine, CsA: Cyclosporine A, SSZ: Sulfasalazine.

a patch test with CZP since the patient had a gamma-type late-onset cutaneous reaction, and the biopsy confirmed it as cutaneous lupus erythematosus (CLE) (Table II). All of our ten reactive patients were treated with alternative BAs, even though only 5 had positive ST results. There were no unexpected adverse reactions to the ST procedure with the chosen dilutions of commercial drugs, including subjects with IgE-mediated reactions (n=5), and more importantly those who had experienced severe anaphylactic reactions (n=4).

## DISCUSSION

This study evaluated the prevalence rates of HSR to anti-rheumatic BAs and the usefulness of STs as a diagnostic tool in the patients who experienced HRs to BAs.

BAs could be fully murine, chimeric, humanized, and fully human. Even a fully human BA can elicit humoral or cellular immune responses. The humoral response

leads to T cell expansion, B cell activation, and anti-drug antibody (ADA) production (10,17). There are different ADA isotypes; IgG-ADA is involved in the majority of adverse events and loss of efficacy; IgE has been shown to cause immediate HSRs; and IgM is capable of activating the complement system. BAs engage with the cell-surface receptors, induce signaling, cytokine release, complement activation, and cell death. IRRs to BAs are due to target-dependent biologic effects (2,10,12,15,17).

A specific classification has been defined as type I-like reactions (IgE/non-IgE), CRSs, mixed reactions (both of type 1-like and CRS), delayed-type reactions, and IRRs (2). IRRs/CRSs occur within 1 h, immediate reactions within 6 h, local ISRs within 24 h, and delayed reactions occur from 1 h to 14 days after the infusion (3,4,12). CRSs/IRRs can occur in the first administration. The preformed cytokines (TNF-alfa and IL-6) are released due to the complement/antibody-mediated cell death by BAs (3,4,12,15). However,

only IRRs are self-limiting or can be limited by premedication (diphenhydramine, methylprednisolone, famotidine, acetylsalicylic acid, acetaminophen, albuterol nebulas, montelukast, and intravenous fluids) and by reducing the infusion rate (2). Premedication does not prevent ADA-mediated HSRs (10,12,15). Type I-like HSRs occur with the release of mast cell and basophil mediators; type III occurs when soluble antigens aggregate with IgG/IgM (immune complexes); and delayed types (type IV) are thought to be T-cell mediated (3-5,12,15). A sensitization phase to the drug is needed for type I reactions so that Th2 response and IgE production occur. IgE-ADA is closely associated with positive STs and severe HSRs. Mast cell/basophil mediators, IgG-ADA, FcγRIII, macrophages, and the platelet-activating factor are responsible for anaphylaxis (11).

Physicians should interrupt the infusion of the BA at the time of the immediate HSR at first. Epinephrine (0.3-0.5 mg intramuscular), proper positioning of the patient, crystalloid solutions, and oxygen should be used, where necessary. Diphenhydramine, methylprednisolone, famotidine, acetylsalicylic acid, acetaminophen, albuterol nebulas, and montelukast should be added to the therapy, according to the clinical signs. A blood sample should be obtained in the first 30-120 minutes of the HSR to assess the levels of the mast cell mediator, tryptase (3,5,12,15).

Patients with type I-like HSRs should be evaluated with STs containing culprit drugs. STs should be performed with the full strength of the commercial BAs at least 2-4 weeks after the initial reaction to minimize false-negative results. If the SPTs are negative, IDTs should be performed by using 0.03 mL of a 1:100 dilution of the full strength BA and if negative, 1:10 dilution (5,8,16,18).

If STs are negative, tryptase is within the normal range, and/or the HSR is not suggestive of a true, IgE-mediated type, the decision about administering rapid drug desensitization (RDD) is based on the severity of the initial reaction. If the initial reaction is mild, a graded challenge with the medication can be performed. If the challenge is positive, RDD should be performed; however, if it is negative, the patient can receive regular infusions. On the other hand, if the initial reaction is moderate to severe, and/or if STs are positive, offering a true, IgE-mediated reaction, RDD is recommended. RDD should only be performed when a BA is needed as first-line therapy and there is no acceptable treatment alternative in the situation of immediate HSRs. Delayed onset reactions are absolute contraindications for RDD (5,8,18).

During RDD, the medication is administered with a gradually increasing rate and concentration. Mast cells and basophils are the major targets; FcεRI receptor internalization, downregulation, and alteration of cellular signaling pathways are the mechanisms of RDD. A standard desensitization protocol is composed of 3 intravenous dilution bags, 12 steps; but if the initial reaction belongs to the high-risk group, RDD is increased to 16/20 steps. Tolerance is transient and should be repeated for every infusion (5,8,18).

Immediate HSRs to IFN occurs in about 10% of the patients (19-23). We observed a lower prevalence of HSRs to IFN than that reported in the literature (4.44%). Positive immediate STs to IFN and anti-IFN IgE were seen on average in 28% and 21% of reactive patients (23-25). In the study by Puxeddu et al., 8 patients had anaphylaxis to IFN, and IDTs were positive in 5 of them (19). However, we could not detect ST positivity to IFN both for the immediate and late-onset HSRs. Allergen-specific IgG antibodies might be involved in the mechanisms of those reactions. Late-onset reactions to IFN are rarely mentioned (19-24).

As reported in the literature, ISRs occur in 29.3% of patients with ETN and 15.3% with ADA (19,21,23). Bavbek et al. described an immediate ISR to ETN with a positive IDT (8). Campi et al. evaluated two patients with ISRs to ETN; the IDT was positive in one patient at the immediate-read, and in the second, only at the late-read (21). Puxeddu et al. evaluated 9 patients reactive to ETN and observed positive IDTs to ETN in 5 of them (17). We also observed positive IDTs at the late-read and patch test with ETN. We analyzed the prevalence of HSRs to ETN as 2.85%, much lower than that reported in the literature (3%) (19,21,23).

Despite being a fully-humanized BA, ADA can elicit immediate ISRs, HSRs, and also, delayed HSRs (8,26-29). Campi et al. referred to two patients with ISRs to ADA with positive IDTs at the late-read (21). Bircher et al. reported anaphylaxis to ADA with a positive IDT at the immediate-read (26). Benucci et al. reported a prolonged ISR to ADA with positive IDT at the late-read (23). An immediate local reaction to ADA with positive IDT was reported and the patient was successfully desensitized with a 6-step subcutaneous desensitization protocol (27). Among our cases, we observed anaphylaxis to ADA in a patient with a positive IDT at the immediate-read. This result is suggestive of an immediate-type allergic reaction, possibly IgE-mediated. Also, we observed no ISRs to ADA.

Anaphylaxis to adalimumab with a positive IDT has rarely been reported in the literature to date (8,26-29).

Puxeddu et al. reported the highest frequency and severity of reactions in patients treated with IFN, determining that 60.8% of all hypersensitivity reactions were attributable to IFN, 25.5% to ETN, and 11.7% to ADA. In contrast to our data, they determined the most serious anaphylaxis in 91.3% of IFN-related reactions, with anaphylaxis in 2% of the patients treated with ETN, and no reaction with ADA. The reactions to ETN and ADA were mainly local and mild (19). However, we detected the most serious anaphylaxis cases with IFN, ADA, and RTX.

In our study, we detected BAs acting through different mechanisms, which is why we observed the different frequencies of HSRs to BAs. When we evaluated the frequency and severity of HSRs in patients treated with BAs, we observed severe reactions with IFN and ADA. However, in regards to the frequency for each BA, we found it to be 20% for ADA, 6.66% for CZP, 4.44% for IFN, and 2.85% for ETN, in contrast to the data from the literature (8,19-23,26-29).

The incidence of ISR related to CZP ranged from 0.8% to 2.3%, and no anaphylactic reactions were reported (21,23). We detected one HSR to CZP in a patient with AS with late-onset cutaneous hypersensitivity. The prevalence of HSR to CZP was 6.66% in our study, similar to the rate reported in the literature (3,12,15).

Immediate HSRs to RTX occur on first exposure in about 25% of the patients with inflammatory disorders (3,12,15). Most of these reactions are consistent with a CRS/IRR caused by massive B-cell lysis. Reactions consistent with immediate HSR, potentially IgE-mediated, are estimated to account for 5 to 10% of cases (3,6,12,15,30,31). In addition, several RTX receiving patients in the literature may have had a positive ST result suggesting an IgE-mediated reaction, thus reinforcing the indication for desensitization (3,12,15).

In our study, 250 patients were administered RTX, and 53 had HSRs to the drug. Among them, 50 (20%) were evaluated as IRRs. We observed similar frequency reaction rates to RTX as in the literature. However, the rate of HSRs to RTX was only 1.2% among the RTX therapy-receiving patients. In particular, we detected a positive ST to RTX

with the commercial drug at the immediate-read results for anaphylaxis cases suggesting an IgE-mediated reaction. We strongly advise performing STs with RTX.

Immediate and delayed HSRs can occur secondary to the use of TOC (32-35). The role of TOC STs was assessed in 72 patients, where 5 presented with HSRs, and all SPTs were negative and IDTs were positive in 3 (33). We had 2 patients immediately reactive to TOC and one of them had a positive IDT to TOC.

CRSs/IRRs are described for RTX (up to 38% at the first administration of the drug) and IFN (4-21% of treated patients) (3,12,15). However, we detected the most frequent IRRs to RTX (21.2%) and TOC (10%) during the one-year follow-up.

There was a similar prevalence of atopy and ADRs in reactive and unreactive patients in previously reported data (36). Similar to the data from the literature, we found negative specific IgE concentrations for all patients. Our data were also compatible with the previous literature, which shows that high levels of total IgE and specific IgE were not found in the presence of HSR to BAs (36).

It has been demonstrated that the concomitant administration of immunosuppressive drugs reduces the rate of development of antibodies and also the rate of infusion reactions (12,15,19-21,25). All of our ten patients were receiving concomitant treatment with DMARDs, but we did not observe prevention of HSRs by these drugs.

The limitation of our study is the absence of a prospective design to define the role of STs in the identification of patients at risk of severe reactions and to analyze the results of STs in negative controls. According to several studies, among all of the initial reactions with BAs, the rate of severe reactions is considered as 25%. We observed the prevalence of immediate reactions to be lower than that previously reported in the literature. Although the ratio of ADRs to RTX was considered as 50-70%, our result was 20%. In addition, immediate ADRs to TOC have been considered rare, but our results showed TOC as the second most frequently responsible agent. In other studies, a possible difference in the number of infusion reactions had been observed and this result could be attributed to the rate of infusions and different diseases (3,8,12,15,19-21,25).

## CONCLUSION

On the basis of our results, especially to diagnose immediate-type HSRs to BAs, STs should be performed due to their simplicity and high sensitivity. A correlation was found between the clinical symptoms and STs, specially for the cases presenting with anaphylaxis. To perform IDTs are crucial for the diagnosis of immediate type HSRs to BAs. However, skin testing procedures have not been standardized for BAs, and still, we need to improve ST procedures to obtain definite results (20).

## Conflict of Interest

The authors declare that there is no conflict of interest.

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