Review

Aspects of allergy in rheumatology

D. Spoerl[1], K. Scherer[1], A. Tyndall[2]

[1]Allergy Unit, Department of Dermatology University Hospital Basel, Basel, Switzerland;
[2]Department of Rheumatology, University of Basel, Felix Platter Spital, Basel, Switzerland.

David Spoerl, MD
Kathrin Scherer, MD
Alan De Vere Tyndall, MD

Please address correspondence and reprint requests to:
David Spoerl, MD,
Allergy Unit, Department of Dermatology,
University Hospital Basel,
Petersgraben 4,
4031 Basel, Switzerland.
E-mail: dspoerl@postmail.ch

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ABSTRACT

This review focuses on several basic mechanisms of allergy and when a rheumatologist should consider an external agent as being responsible for seemingly "rheumatic" manifestations. Typical allergic diseases are discussed in order to help the physician to recognise them. In addition, allergic aspects and adverse drug reactions of antirheumatic drugs and biopharmaceutical agent therapies will be discussed.

Introduction

Allergies, from the greek αλλεργία, reaction against "other", are undesired reactions against something that does not belong to "self". Allergy is a hypersensitivity reaction initiated by immunologic mechanisms to harmless foreign substances called allergens. Atopy is an individual and/or familial tendency, which usually manifests in childhood or adolescence, to become sensitised and produce immunoglobulin E (IgE) in response to ordinary exposures to allergens, usually proteins. The term atopy can not be used until an IgE mediated sensitisation has been documented by IgE antibodies in serum or by a positive skin prick test (1). The readiness to react to allergens is moreover greatly determined by many other concomitant factors which influence the immune system during exposure. The concomitant or sequential exposure to a combination of allergens, infection, physical exercise, psychological stress, alcohol, menstruation and/or concomitant medication may be necessary to provoke a reaction (2).

Definitions and classifications in allergic disease

The Coombs and Gell classification divides hypersensitivity reactions into four pathophysiological types, namely IgE-mediated anaphylaxis (type I), antibody-mediated cytotoxic reactions (type II), immune complex-mediated reactions (type III), and T-cell mediated delayed type hypersensitivity (type IV) (Table I) (3).

The term "allergy" should only be used when an immunologic reaction has been proven (4). Adverse drug reaction (ADR) on the other side is a wide definition including toxic, and both immunologic (including hypersensitivity reactions) and as yet not fully understood undesired drug effects. ADR on xenobiotics are usually classified in six groups (Table II) (5, 6). Most reactions are caused by the pharmacological or toxicological activities of the drug and are generally predictable (Type A). However, non-predictable, idiosyncratic (Type B) reactions count for approximately 15% of all reported ADR. Whenever a drug-induced hypersensitivity reaction is supposed but not established, physicians should either describe the clinical picture and the time-course, *e.g.* "macular exanthema 2 days after the start of penicillin administration" or use the term ADR. Recently, the diagnosis of drug allergy/hypersensitivity has been standardised by the European Network for Drug Allergy (ENDA) under the aegis of the European Academy of Allergology and Clinical Immunology (EAACI) and standard operating procedures have been published (7).

The often encountered term "infusion reaction" (IR) and "injection site reaction" (ISR) describes a subgroup of ADR against infused or injected (especially monoclonal antibodies) drugs. The classification of ADR to biopharmaceuticals is different from that of xenobiotics due to the particular effects of those drugs on the immune system. To distinguish it from the classification of side-effects to chemicals/drugs, the Greek alphabet is used for the five types (Table III) (8). This classification is a first attempt to bring some order in the increasing number of reports of ADR to biopharmaceuticals. Most of

Table I. Coombs and Gell's classification.

Type	Description	Clinical Example	Skin manifestations
Type I: IgE-mediated hypersensitivity; immediate hypersensitivity; anaphylaxis.	Takes 2-30 mins up to several hours to develop. Ag induces cross-linking of IgE bound to mast cells and basophils with release of vasoactive mediators.	Systemic anaphylaxis, allergic rhinoconjunctivits, early bronchial response in extrinsic asthma, allergic urticaria.	Urticaria, angioedema, flush, conjunctivitis.
Type II: Antibody-mediated, cell bound hypersensitivity.	Takes 1-8 hrs to develop. Antibody directed against cell-surface antigens mediates cell destruction or alters signaling.	Blood transfusion reactions, autoimmune haemolytic anemia, autoimmune urticaria, pemphigus vulgaris, ITP.	Non palpable purpura, bullae, urticaria.
Type III: Immune-complex mediated hypersensitivity.	Takes 2-16 hrs to develop. Antigen-antibody complexes deposited at various sites induce inflammation with complement activation.	Arthus reaction, serum sickness, exogen allergic alveolitis, urticarial vasculitis.	Palpable purpura, urticarial vasculitis, livedo racemosa.
Type IV: Cell-mediated hypersensitivity; Delayed type hypersensitivity.	Takes 4-72 hrs to develop. (usually T-) cell-mediated inflammation.	Contact dermatitis, Mantoux test, late bronchial response in asthma.	Eczema, maculopapular exanthema.

Table II. Classification of adverse drug reaction.

Type	Description	Example
Type A (Augmented)	Reactions which can be predicted from the known pharmacology of the drug. Dose-dependent, can be alleviated by a dose reduction.	Bleeding with anticoagulants, bradycardia with beta blockers, headache with nitrates, postural hypotension with prazosin.
Type B (Bizarre)	Immune system involved. Not dose-dependent, host-dependent factors important in pre-disposition.	Anticonvulsant hypersensitivity. Maculo-papular eruptions on penicillin.
Type C (Chronic)	Dose-related and time-related.	Hypothalamic-pituitary-adrenal axis suppression by glucocorticoids.
Type D (Delayed)	Occur after many years of treatment. Can be due to accumulation.	Secondary tumors after treatment with chemotherapy, analgesic nephropathy.
Type E (End of treatment)	Occur on withdrawal especially when drug is stopped abruptly.	Withdrawal seizures on stopping phenytoin, adrenocortical insufficiency on withdrawal of glucocorticoids.
Type F (Failure)	Failure of therapy or insufficient effect.	Hypertension on antihypertensive therapy.

Table III. Classification of adverse drug reaction to biopharmaceuticals. (?) means that the mechanism is yet unclear.

Type	Description	Example
Type α: High cytokine and cytokine release syndrome.	Side-effects might be connected to the systematic application of cytokines in relatively high doses or to high concentrations of cytokines released into the circulation.	Flu-like symptoms following Interferon alfa. Cytokine release syndrome following anti-thymocyte globulin (?).
Type β: Hypersensitivity.	Basically two forms of reactions can be differentiated: immediate and delayed.	Anaphylactic shock following OKT3 infusion. Infusion reaction (?). Local reaction to etanercept (?).
Type γ: Immune or cytokine imbalance syndromes.	Partly explicable by the effect of the drug. Can be further subdivided • immunodeficiency • autoimmunity • loss of tolerance	Uncontrolled infection under TNF inhibitors, *i.e.* tuberculosis flare. Induction of autoimmunity (?). Development of atopic dermatitis in patients undergoing infliximab therapy (?).
Type δ: Cross-reactivity.	Antibodies generated to an antigen expressed on tumour cells might also crossreact with normal cells, which express this structure as well, albeit to a lower degree.	Acneiforme eruptions in the frame of anti-EGFR treatment.
Type ε: Non-immunological side-effects.	Not directly related to the immune system, sometimes revealing unknown functions of the biopharmaceutical agents.	Cardiac failure in TNF-α inhibitor treatment (?).

Table IV. Differentiation between urticarial vasculitis and acute common urticaria.

	Urticarial vasculitis	Common urticaria
Synonyms	Hypersensitivity vasculitis; drug-induced vasculitis; leukocytoclastic vasculitis; cutaneous vasculitis; serum sickness or serum sickness-like reactions; allergic vasculitis.	Hives; nettle rash.
Clinical features of a single lesion	Painful, burning sensation; persistence over 24-72h; eventually purpuric; postinflammatory hyperpigmentation.	Pruritic; heals within 24h leaving no residual changes.
Associated conditions	HIV-, HBV- and HCV-Infections; Sjögren's syndrome; SLE; HUVS; Schnitzler's syndrome; Cogan's syndrome; Muckle-Wells syndrome; haematologic disease; amyloidosis; cryoglobulinemia; malignancy.	Angioedema; anaphylactic reactions; infections; physical and psychological stimuli.
Initial work-up	Search for physical signs of systemic disease, preceding infections and preceding drug ingestion, biopsy, complement studies including C1q Antibodies, complete blood count with differential, urinalysis, serum creatinine and liver enzymes, hepatitis B and C serologies, ANA, serum protein electrophoresis.	Search for eliciting allergen (food, hymenoptera, drugs) or physical stimuli; signs of infection; tryptase in serum.

them are only suppositions, showing that there still is the need to elucidate many mechanisms in immunology.

Urticaria: a dermatological manifestation of hypersensitivity or of rheumatic disease

The skin delineates the organism from the outer world and is therefore the predisposed organ where hypersensitivity reactions against exogenous allergens may take place.

This paragraph will focus on urticaria as one possible dermatological manifestation of hypersensitivity (Coombs Type I) or of rheumatic disease. In the first case, a trigger may be found through a thorough history while the latter will be accompanied by a flare of the underlying rheumatic disease. Other dermatological manifestations of rheumatic disease have been reviewed elsewhere (9, 10).

Urticaria (hives; nettle rash) is a morphological term describing an itchy weal on the skin. Hives can be seen in two clinical forms depending on the underlying disease: common urticaria and urticarial vasculitis. To differentiate between them might be difficult (Table IV). Urticaria is frequent and is, in the acute setting, a hallmark of anaphylaxis. It occurs in 40% with angioedema, which is thought to be prevalently due to bradykinin (11). The incidence in the population is 15% and it does not require further investigation if not chronic, that is by definition lasting more than 6 weeks, and the patient history is not strongly suggestive for an allergic cause (12). It is further classified into spontaneous urticaria (acute and chronic forms), physical urticaria (cold, pressure, heat, solar, demographic and vibratory urticaria) and urticaria due to other disorders (aquagenic, cholinergic, contact and exercise induced urticaria) (12). Acute urticaria is often due to common viral infections and a specific antigen trigger can rarely be found. The concept of autoimmune urticaria is increasingly being recognised but has still to be defined. A positive autologous serum skin test and autoimmune thyroiditis are frequent associated findings (13).

Urticarial vasculitis can present in a variety of ways, from a mild cutaneous form to a lupus-like disease with severe cardiopulmonary involvement. Urticarial vasculitis requires a biopsy to confirm the diagnosis. Histologically there are signs of leukocytoclastic vasculitis (14). In this disease, immune complex deposition leads to activation of the classic complement pathway, generating C3a and C5a. Those factors induce mast cell degranulation (with consequent urticaria) and neutrophil chemotaxis (causing the typical picture of leukocytoclastic vasculitis) (11). Urticarial vasculitis is an overlap disease where urticaria and leukocytoclastic vasculitis merge into another. It can further be subdivided in normo- and hypocomplementemic. Low complement levels and positive anti-C1q antibodies are markers of more severe disease (15), but are not specific. Anti-C1q antibodies can be found in 61% of patients with systemic lupus erythematosus (SLE), 38% in Hepatitis C virus (HCV) infected individuals, 20% of rheumatoid arthritis (RA) patients and in 15% in patients with scleroderma, Sjögren's syndrome or mixed connective tissue disease (MCTD) (16). In fact, in about half of cases where hypocomplementemia is present in urticarial vasculitis, diagnostic criteria of SLE are fulfilled (17). If not, hypocomplementemic urticarial vasculitis syndrome (HUVS) has to be considered. Urticarial vasculitis, if a cause can be found, may be a manifestation of a hypersensitivity reaction to drugs (cimetidine, diltiazem, potassium iodide, fluoxetine, non-steroidal antirheumatic drugs (NSAR) drugs and recently glatiramer acetate have been reported in the literature) and infections, in particular hepatitis B virus (HBV), HCV, Human immunodeficiency virus (HIV) and different bacterial pathogens (18). Urticarial vasculitis has been otherwise associated with many other diseases: Schnitzler's syndrome (typically with monoclonal gammopathy), Cogan syndrome (non syphilitic keratitis and vestibuloauditory dysfunction), Henoch-Schönlein purpura, Muckle Wells syndrome (together with deafness and renal amyloidosis) and more commonly, Sjögren syndrome (15, 19).

Is it allergy? When should a rheumatologist think of an external cause for the symptoms?

Patients with rheumatic disease often present with arthralgia and/or myalgia which, although common in the gen-

eral population, are very uncommon symptoms in allergic disease.

Myalgia: Myalgia has been reported among others as a "systemic symptom" in DRESS syndrome, the acronym for Drug Rash and Eosinophilia with Systemic Symptoms. The DRESS syndrome is an idiosyncratic reaction characterised by febrile maculopapular exanthema, occurring depending on the eliciting drug 3 weeks to months after the beginning of the treatment, accompanied by systemic symptoms, blood abnormalities (eosinophilia in 90% of cases, leukocytosis or atypical lymphocytosis, cytopenias) and interestingly a sequential reactivation of herpes viruses (20). It has a mortality of 10–20% and a protracted course in the remaining cases despite stop of the offending drug. The paradoxical worsening of clinical symptoms including febrile illness after withdrawal of the causative drug may lead to prescription of an empirical antibiotic treatment, which increases the risk of developing additional drug rashes. It has to be considered synonym to Drug Hypersensitivity Syndrome (DHS) and Drug Induced Hypersensitivity Syndrome (DIHS) (21). Anticonvulsants, sulfonamides, dapsone, allopurinol, minocycline and antiviral drugs are among the most frequent culprit drugs.

Myalgia is otherwise commonly reported by patients with multiple chemical sensitivity, an exclusion diagnosis in which psychiatric advice may be useful (22, 23).

Arthralgia: Arthralgia is typical in Coombs Type III hypersensitivity reactions. Urticarial vasculitis, hypersensitivity vasculitis, drug-induced vasculitis, serum sickness-like reactions and allergic vasculitis all probably describe the same entity. It is now known that arthralgia appears in approximately two-thirds of patients and that the joint involvement tends to occur after the rash has started, and resolves before the rash has vanished. A case of arthralgia due to a type IV hypersensitivity to prosthetic joints made from alloys to which the patient was sensitised has been reported (24).

Arthritis: Increased numbers of mast cells are found in the synovial tissue and fluid of patients with RA and especially at sites of cartilage erosion (25). Therefore, theoretically an "allergic arthritis" should be conceivable. Tumor necrosis factor alfa (TNF-α) production by synovial mast cells of RA patients has recently been shown *in vitro*, but the contribution of those cells in the inflammatory process *in vivo* is unknown (26).

Mast cells probably take part in the inflammatory process, but are unable to initiate it on their own and therefore, true arthritis due to a hypersensitivity reaction has not been reported so far. The question in the title of a paper, published in 1990 asking "is there an allergic synovitis?" remains unanswered (27).

Allergological aspects of selected disease modifying anti-rheumatic drugs (DMARDs)

Drug hypersensitivity reactions (Type B ADR) are a common clinical problem which may affect a considerable number of the treated patient population. Between 10 and 15% of patients may suffer from an ADR, 2–5% of these have to be hospitalised, and in 1–3% of hospitalised patients mortality may result. A maculopapular exanthema is the most commonly noted cutaneous adverse reaction pattern to all drugs, ranging between 51% and 95% of cases in various series (28). For most suspected drug reactions, there is no commercially available test to verify their tolerance and allergological work-up includes skin and in vitro tests eventually followed by provocation with the suspected drug or with an alternative drug if this appears too dangerous. As outlined above, not any rash appeared concomitantly to a new drug regimen is caused by a hypersensitivity reaction. Most patients often draw this conclusion resting their opinion merely on a chronological association and ask for desensitisation protocols. Many desensitisation protocols found in literature are rather graded re-administrations since no allergological work up has been previously performed and no induction of tolerance can be demonstrated. A general algorithm for drug desensitisation has recently been proposed in a consensus paper from the ENDA and the EAACI interest group on drug hypersensitivity (29). Drug desensitisation is defined as the induction of a temporary state of tolerance of a compound responsible for a hypersensitivity reaction. Only for some drugs (about 100), true desensitisation protocols can be found in literature.

Glucocorticoids

Most ADR to glucocorticoids are non type B (30). Allergic reactions to systemic glucocorticoids are rare, but are becoming more commonly recognised by clinicians. Glucocorticoids can develop hypersensitivity reactions of Coombs type I, III or IV (31, 32). There are more than 100 published reports of immediate hypersensitivity reactions (Coombs type I) occurring after oral and parenteral administration of corticosteroids. Type IV reactions are much more frequent with an estimated incidence of up to 4% for cutaneous reactions.

Excipients and preservatives in drugs are often implicated in type IV hypersensitivity reactions, but many cases of sensitisation to the pharmacological principle have been reported as well (33). In this case and in particular for topical glucocorticoids, the classification of glucocorticoids of Coopman and Goossens may be helpful to predict crossreactivity (34, 35). Desensitisation is one treatment option in patients for whom corticosteroids are essential and in whom cross-reactivity precludes the use of alternative steroid preparations (30) and successful desensitisation has been reported using oral and intravenously hydrocortisone (36, 37).

Methotrexate

Methotrexate may produce an acute granulomatous pneumonia mimicking an infection which must be ruled out by appropriate techniques (38). Criteria for defining methotrexate pneumonitis have been published (39). Anaphylaxis to methotrexate has been reported, but the authors could not identify specific IgE and tryptase was negative so that this supposition was based merely on skin test (40-42). Most anaphylactoid reaction have been reported after high dose methotrexate as a cancer treatment,

and desensitisation protocols have only been proposed for this indication (43, 44). Reassuringly, it seems that the combination of etanercept and methotrexate does not lead to new unexpected safety issues over 52 weeks of therapy (45). Moreover, concomitant methotrexate seems to protect from appearance of autoantibody and antibodies against biopharmaceuticals (46-48).

Antimalarials

The ADR of synthetic antimalarials are known, although not frequent, and they can involve the ocular, haematopoietic, gastrointestinal, cardiovascular and central nervous systems. Among adverse cutaneous reactions, dark discoloration is most often encountered, while bleaching of the hair, lichenoid reactions, maculopapular eruptions, psoriasis exacerbation and porphyria cutanea tarda are less common. Exanthematous pustulosis, allergic contact dermatitis and photosensitivity are rare (49).

Acute generalised exanthematous pustulosis (AGEP) has been reported as an ADR of hydroxychloroquine (50). AGEP is an uncommon Type B, Coombs type IVd ADR to a variety of drugs. The reaction results in formation of numerous sterile pustules on an extensive erythema associated with fever, neutrophilia and/or eosinophilia.

A desensitisation protocol has been recently published using an orally administered hydroxychloroquine solution in a patient with SLE after anaphylaxis (51).

Leflunomide

Leflunomide inhibits tyrosine kinases and thus suppresses the production of proinflammatory cytokines such as TNF-α. Suppression of a TNF-α induced cellular response may be one of the mechanisms of leflunomide efficacy in RA which could explain the induction of subacute cutaneous lupus erythematosus in a recently published case (52). The recent cases of lupus-like syndrome induced by anti- TNF-α treatment favour this hypothesis (53). Other severe adverse cutaneous reactions are Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), occurring in particular if the interaction with other drugs increases the amount of its active metabolite. Rifampicin is a known example, inducing the cytochrome (CYP) P450 2C9 enzyme. For those cutaneous adverse reactions no desensitisation protocol exists and because of their severity, re-administration of the culprit drug is not recommended.

Biopharmaceuticals

Initially, TNF-α antagonists were studied in the setting of acute sepsis in the intensive care units, but were abandoned due to unsatisfactory results (54, 55). ADR to TNF-α antagonists are not rare. Data comparing those drugs indicate that ADR are more common with mouse antibodies, followed by chimeric antibodies (75% human: *i.e.* infliximab), humanised antibodies (90% human, *i.e.* omalizumab) and rarest with human antibodies (*i.e.* adalimumab). The term ADR encompasses IR (for infused drugs) and ISR (for subcutaneous injected drugs), and does not tell anything about the pathogenetic mechanisms. IR usually occurs during or within a short time after infusion and ISR might take longer to develop, but this is not a rule. Whether these manifestations have to be considered type β or type γ reactions is still a matter of debate (56). Zeltser *et al.* compared recall ISR to fixed drug eruptions, known to be T-cell-dependent allergic reactions (57). This, together with the fact that IR rate depends on the degree of humanisation and that the presence of antibodies against the drug (*e.g.* antibodies toward infliximab (ATI) or Human Anti-Chimeric Antibodies (HACA) in case of infliximab) correlates with the risk of IR, speaks in favour of a type β reaction (58). ATI of the IgE isotype could be detected so far only in a few patients after IR and support this hypothesis (59, 60). On the other hand, the fact that IR often occur at the first dose supports the hypothesis that IR are type γ ADR. Consistent with this hypothesis was the finding that tryptase was negative in 11 patients with Crohn's disease who had an IR to infliximab and that it was possible to re-treat patients using specific protocols (61-63). In addition, fortunately patients who reacted to one TNF-α antagonist seem not be at risk for another ADR when they are switched to another TNF-α antagonist (64).

The formation of antibodies against the drug depends on cofactors such as the frequency of administration (scheduled vs. episodic, the latter being worst from this point of view) and the simultaneous administration of immunosuppressants (47, 65, 66). The latter may delay or reduce antibody formation and ADR frequency (67). Measurement of HACA and infliximab concentration has been shown to be useful because increasing the dose in patients who have HACAs is ineffective, whereas in patients with subtherapeutic infliximab concentrations this strategy may be a good alternative to changing to another anti-TNF-α agent (68). Most reported cases of antibody mediated hypersensitivity reactions have been associated with IgG, showing serum sickness like patterns. Recently, a serum sickness like reaction was reported for infliximab (69) and rituximab (70). Type I hypersensitivity response (Type β ADR) was reported with convincing evidence for injection site reactions to adalimumab (71).

Cytokine release syndrome (Type α ADR) is a common complication occurring with the use of anti-T and B cell antibody infusions (72). Severe cases are known as cytokine storms and present with a clinical pattern of a systemic inflammatory response syndrome (SIRS). Another ADR is the phenomenon of development of anti-DNA-antibodies and antinuclear antibody (ANA) with prolonged TNF-α blockade, the clinical significance of which remains unclear. Fortunately the associated drug induced lupus erythematosus (DILE) seems to be reversible after discontinuation of the suspected drug and the presence of those antibodies do not put the patient at risk for other ADR such as IR or loss of efficacy. TNF-α antagonist induced lupus erythematosus cases had a higher prevalence of antibodies to double-stranded DNA, rash, and hypocomplementemia than DILE due to other drugs. Fever is common in both types of DILE. Renal disease, which is rare in classic DILE, has been reported in cases of TNF-α antagonist induced DILE (73). The onset of chronic inflam-

matory skin disease is the most frequent cutaneous ADR of TNF-α antagonist in the skin, followed by infectious skin disease (74). Infliximab, etanercept and adalimumab can induce psoriasis, especially the palmoplantar pustulosis form. The prevalence of this adverse effect has been estimated at 1.5-5% of patients taking TNF-α antagonists (75). In a minority of patients, this ADR persisted upon discontinuation of the drug. Remission of psoriasis was similar whenever TNF-α antagonist were continued or stopped. The underlying paradoxical pathomechanisms of induction of psoriasis or psoriasiform exanthematic disease by TNF-α inhibitors remain elusive (76). Because no validated diagnostic tools exists to detect immunologically mediated and clinical relevant hypersensitivity to biopharmaceuticals, desensitisation protocols found in literature must be considered with caution (77-80). A protocol for adalimumab desensitisation has been proposed (81).

Conclusions

Knowledge of allergic disease is increasingly required in the clinical setting, both to exclude possible differential diagnosis, and to understand adverse effects of immune modulating drugs used in rheumatology. Because of limited experience with biopharmaceuticals, the risk-benefit evaluation for a given patient is often difficult (82). In the next years, it will be essential to develop adequate screening tools to evaluate the immunogenicity of therapeutic proteins (83). Only good understanding of the immune system will allow the identification of other application areas, *i.e.* in transplantation medicine and allergic immune response, and to recognise and maybe forecast ADR (84, 85).

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