

Drug Hypersensitivity Reactions Involving Skin

Oliver Hausmann, Benno Schnyder, and Werner J. Pichler

Contents

1	Introduction	30
2	T Cell Stimulation by Drugs	32
2.1	Stimulation of naïve T Cells (Sensitization Phase)	32
2.2	Effector Phase in Immune-Mediated Drug Hypersensitivity	34
3	Different Types of T Cell-Mediated Drug Hypersensitivity Reactions	41
4	Clinical Features and Pathophysiology of Cutaneous Reactions	43
4.1	Maculopapular Exanthem (MPE)	44
4.2	Acute Generalized Exanthematous Pustulosis (AGEP)	45
4.3	Bullous Exanthema, Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)	47
4.4	Drug (-Induced) Hypersensitivity Syndrome (DHS or DiHS) or Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)	49
4.5	Multiple Drug Hypersensitivity Syndrome	50
4.6	Flare Up Reactions	51
5	Conclusion	52
	References	52

Abstract Immune reactions to drugs can cause a variety of diseases involving the skin, liver, kidney, lungs, and other organs. Beside immediate, IgE-mediated reactions of varying degrees (urticaria to anaphylactic shock), many drug hypersensitivity reactions appear delayed, namely hours to days after starting drug treatment, showing a variety of clinical manifestations from solely skin involvement to fulminant systemic diseases which may be fatal. Immunohistochemical and functional studies of drug-specific T cells in patients with delayed reactions confirmed a predominant role for T cells in the onset and maintenance of immune-mediated delayed drug hypersensitivity reactions (type IV reactions). In these reactions, drug-specific CD4+ and CD8+ T cells are stimulated by drugs through

W.J. Pichler (✉)

Division of Allergology, Department of Rheumatology, Clinical Immunology and Allergology,
Inselspital, CH-3010 Bern, Switzerland
e-mail: werner.pichler@insel.ch

their T cell receptors (TCR). Drugs can stimulate T cells in two ways: they can act as haptens and bind covalently to larger protein structures (*hapten-carrier model*), inducing a specific immune response. In addition, they may accidentally bind in a labile, noncovalent way to a particular TCR of the whole TCR repertoire and possibly also major histocompatibility complex (MHC)-molecules – similar to their pharmacologic action. This seems to be sufficient to reactivate certain, probably in vivo preactivated T cells, if an additional interaction of the drug-stimulated TCR with MHC molecules occurs. The mechanism was named pharmacological interaction of a drug with (immune) receptor and thus termed the *p-i concept*. This new concept may explain the frequent skin symptoms in drug hypersensitivity to oral or parenteral drugs. Furthermore, the various clinical manifestations of T cell-mediated drug hypersensitivity may be explained by distinct T cell functions leading to different clinical phenotypes. These data allowed a subclassification of the delayed hypersensitivity reactions (type IV) into T cell reactions which, by releasing certain cytokines and chemokines, preferentially activate and recruit monocytes (type IVa), eosinophils (type IVb), or neutrophils (type IVd).

Keywords Drug hypersensitivity · T cells · p-i concept (pharmacological interaction of drugs with immune receptors) · Mechanism · Exanthema

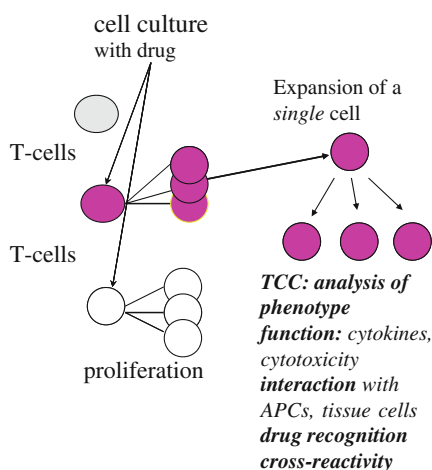
1 Introduction

Adverse drug reactions (ADR) can be classified into those that are predictable, common, dose-dependent, and related to the pharmacologic actions of the drug (type A reactions) and those that are unpredictable, uncommon, more or less dose-independent within the therapeutic range, and usually not related to the pharmacologic actions of the drug (type B reactions) (Rawlins and Thompson 1991). It is estimated that approximately 80% of ADRs belong to the type A category, and typical examples are gastrointestinal bleeding after treatment with NSAIDs, or bradycardia with β blocker treatment. Immune-mediated or allergic drug reactions (hypersensitivity reactions) are type B reactions. They account for 15–20% of all ADR (Lazarou et al. 1998). Unlike type A reactions, type B reactions are difficult to predict and are often not recognized until a drug is marketed and widely used in humans. It may then only affect a small number of patients, implying an individual susceptibility or predisposition. Indeed, the development of hypersensitivity reactions appears to depend on both genetic and environmental factors. Reactions in this category include *drug intolerance* (an undesired drug effect produced by the drug at therapeutic or subtherapeutic doses), *idiosyncratic reactions* (reactions that are not explainable in terms of the known pharmacologic actions of the drug, but are probably due to some individual genetic predisposition), and *allergic or hypersensitivity reactions* (reactions that are dependent on one or more immunological mechanisms).

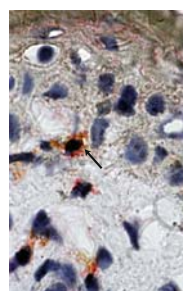
The effector phase of allergic reactions can be classified according to Coombs and Gell (Coombs and Gell 1968) into reactions that are mediated by drug-specific IgE antibodies (type I reactions), which are mostly immediate-type hypersensitivity reactions, cytotoxic and immune complex reactions, which are mediated by drug-specific IgG or IgM antibodies (type II and III reactions), or by drug-specific T lymphocytes (type IV), which are mostly delayed-type hypersensitivity reactions. This classification system has proven to be helpful in daily clinical practice to guide diagnostic and therapeutic decisions.

In this review, data and concepts of the role of T cells in drug hypersensitivity are presented, which evolved, on one hand, from in vitro studies of human, drug-specific T cells derived from blood and tissue of patients with various drug-induced hypersensitivity diseases (Fig. 1). These T cells were analyzed functionally regarding cytokine production and cytotoxicity after stimulation with the respective drug. On the other hand, the same functions were also evaluated by immunohistology of the organs affected by the drug allergy. The results led to new concepts in drug hypersensitivity: (1) a novel mechanism of drug stimulation of T cells could be defined, extending the hapten concept (Schnyder et al. 1997; Zanni et al. 1998; Pichler 2002; Schmid et al. 2006b), (2) the type IV reaction was further

Drug specific T-cell clones (TCC) from blood and tissue



Immunohistochemistry



Perforin red
CD4 brown

Fig. 1 Methods to study delayed drug hypersensitivity reactions in humans. (a) T cells – mainly from the peripheral blood, but also from tissue sections (skin, kidney), proliferate when exposed to drugs in cell culture. The proliferating cells can be expanded and then cloned by limiting dilutions, and functional and phenotypic analysis performed to evaluate how drugs are stimulatory for T cells and which functions they perform. (b) Immunohistology of skin (and kidney) using antibodies to cytokines, etc.: the example shows that in a maculopapular exanthema both CD4+ and CD8+ T cells also express perforin

subclassified into four subtypes based on the clinical, immunohistochemical, and functional heterogeneity of certain drug allergies (Pichler 2003); and (3) applying these two new concepts to the clinical situation provided an explanation of how and why skin symptoms are so predominant in drug hypersensitivity although most drugs are administered orally or parentally (Posadas and Pichler 2007).

2 T Cell Stimulation by Drugs

2.1 Stimulation of naïve T Cells (Sensitization Phase)

A classical immune response starts by stimulating the innate immune system, in particular dendritic cells. The antigen (bacterium, virus, etc.) activates pattern recognition receptors, e.g., Toll-like receptors (TLR) on dendritic cells and thereby provides an initial “danger signal”. The activated dendritic cells represent antigen-presenting cells (APC), which take up and process large and complex antigens. These are subsequently cleaved and presented as peptides to T cells via the MHC molecules in a suitable environment, mainly the secondary lymphoid organs such as lymph nodes. The ensuing immune response is directed against the original stimulus and is highly efficient; different antigens such as soluble or cell bound viral antigens elicit a distinct immune response, capable of eliminating the infectious agent without substantially harming the surrounding tissues.

Some therapeutic proteins such as mouse antibodies are intrinsically immunogenic because they represent foreign macromolecules. Many drugs, however, are neither proteins nor peptides, but are novel, unique structures and have a molecular mass of less than 1 kD. According to classical immunology (Landsteiner and Jacobs 1935), small molecules are not complete antigens and were considered to be incapable of directly inducing an immune response by priming of naïve T cells in their native state. For these agents to become immunogenic they must be chemically reactive (=haptens) and must be able to covalently bind to high molecular mass proteins (*haptens-carrier complexes*), which then undergo antigen processing and presentation, and are able to induce a novel immune response. Therefore, haptens need two essential features to elicit an immune response: activation of the innate immune system (=immunogenicity) and provision of novel antigenic determinants for the adaptive immune system (=antigenicity). An immune response to small molecular mass compounds is explained primarily by this *hapten hypothesis* (Landsteiner and Jacobs 1935; Griem et al. 1998; Aiba et al. 2003), which is well documented for certain chemicals such as *p*-phenylenediamine.

Some drugs, such as penicillin, are directly chemically reactive and bind spontaneously in a covalent way to other molecules, mostly proteins. Other drugs (prohaptens), however, must be metabolized or bioactivated to a chemically reactive form before they are able to covalently bind to proteins or other (intracellular) structures (Griem et al. 1998; Naisbitt et al. 2000; Aiba et al. 2003). Such

bioactivation is often accompanied by some toxic effect because the chemically reactive metabolite might bind and functionally disturb distinct proteins and metabolic or signaling pathways if it is not rapidly inactivated (e.g., by glutathione, etc.). Although bioactivation (transformation of a prohaptens into a haptens) is typically mediated by cytochrome P450 enzymes in hepatocytes, it may, albeit in a reduced amount, also occur at other sites, such as skin keratinocytes or dendritic cells (Kimber and Cumberbatch 1992; Reilly et al. 2000; Janmohamed et al. 2001; Swanson 2004; Roychowdhury and Svensson 2005).

2.1.1 Generation of Reactive Compounds Inside or Outside the Liver

Interestingly, metabolism in the liver and formation of neoantigenic determinants may not necessarily induce an immune response but rather immune tolerance (Crispe 2003). This might explain the observation that many drugs are converted to reactive compounds without causing an immune response. Consequently, it is difficult to infer that the generation of an intracellular haptens of a novel compound in the liver will lead to general immunogenicity. For example, paracetamol (acetaminophen) is metabolized in the liver to many metabolites, some of which are reactive and can act as haptens; however, true hypersensitivity reactions to paracetamol occur only very rarely. The mechanism of this hepatic tolerance is not yet fully understood, but it is very important from a clinical point of view because, for example, the immunosuppression needed for a liver allograft is moderate compared to other allografts, and it is even more important for daily living because most foods with their huge diversity of (novel) antigens are usually well tolerated when processed by the liver (Crispe 2003; Bowen et al. 2004).

It may be possible, that – particularly if high doses are given – the reactive drug compound generated in the liver may escape the tolerogenic hepatic environment via the lymphatic drainage to the local lymph nodes, where it can induce immune-stimulation, or it may enter the circulation and other tissues (Bowen et al. 2004). For instance, sulfamethoxazole (SMX) is metabolized by cytochrome P450 enzymes to a hydroxylamine-derivative (SMX-NHOH), which is not yet highly chemically reactive (Knowles et al. 2000). It may, however, be easily further metabolized (oxidized) by enzymes such as myeloperoxidase (e.g., in neutrophilic granulocytes) to SMX-NO, a potent haptens. Bioactivation is usually followed by a bioinactivating process, which abolishes the toxic and immunogenic properties of some metabolites, mainly via the glutathione pathway. In some cases, however, genetic or environmental factors may disturb the balance between these two processes leading to increased formation or decreased elimination of reactive drug metabolites.

2.1.2 Immunogenicity: Drug Stimulation of the Innate Immune System

How drugs might stimulate the innate immune system is presently being intensively investigated (Girolomoni et al. 1990; Becker et al. 1992; Neisius et al. 1999; Lipper

et al. 2000; Uetrecht 2001). Rarely, the drug may *directly* stimulate the innate immune system by binding to Toll-like receptors (such as binding of imiquimod to TLR 7 on dendritic cells) (Enk and Katz 1992). More frequently an indirect pathway is taken: the intracellular processing of a drug generates a hapten-like compound, which may bind to various intracellular structures and disturb their function. This may somehow “activate” the cells and upregulate certain molecules, some acting as “danger signals” (Lipper et al. 2000; Uetrecht 2001). If this metabolism occurs inside a professional APC such as a dendritic cell, these toxic signals may lead to upregulation of costimulatory molecules such as CD86 or CD40 on the cell surface. This feature of prohaptens/hapten-like drugs is already used in the screening of a potential immunogenicity of novel dermatologic compounds for treatment of skin diseases or skin care products (contact sensitizing potential) (Verrier et al. 1999; Hulette et al. 2005).

Some systemically applied drugs may also have such features; incubation of dendritic cells with SMX itself resulted in upregulation of CD40 molecules, and inhibitors of metabolism abrogated this stimulation (Sanderson et al. 2007). Albeit this effect was shown only for very high SMX-concentrations, it revealed that metabolism of a drug causing systemic immune reactions can occur inside APCs, and this may lead to enhanced antigen presenting capacity of the metabolizing cells. This could initiate an immune response to the drug, which is well documented if the reactive metabolite is given (SMX-NO) (Naisbitt et al. 2001).

2.1.3 Antigenicity: Drug Stimulation of the Adaptive Immune System

A second cardinal feature of haptens is the stimulation of the adaptive immune system (“antigenicity”): the hapten-binding to an autologous protein may modify it in such a way that it becomes a neo-antigen, which is processed and presented as hapten-modified peptides to T cells. A relatively large number of T and B cells are able to bind to hapten carrier complexes, and a vigorous immune response may arise. A predominant humoral immune response may occur if the hapten modification affects soluble and cell bound proteins, but exclusive T cell responses can be seen if the hapten binds directly to the MHC-peptide complexes. Thus, the type and target structure of the chemical modification of proteins already determines which type of immune reaction might develop (Pichler 2003).

2.2 Effector Phase in Immune-Mediated Drug Hypersensitivity

2.2.1 Antibody-Mediated Drug Hypersensitivity

Drug-carrier complexes may be antigenic for both T and B cells. Stimulation and proliferation of drug-specific T cell clones (sensitization) may provide help for the generation of a separate, B cell immune response to the hapten-carrier compound.

In a T helper cell type 2 (Th2)-cytokine milieu [interleukin (IL)-4, IL-5, IL-13], the B cell–Th2 contact (via CD40/CD40L) may allow a class switch to IgE, and drug (hapten)-specific IgE may be generated. The Fc- ϵ -RI-bound IgE on mast cells and basophils are the essential mediators for immediate type reactions such as urticaria and anaphylaxis (*type I reaction*). In a T helper cell type 1 (Th1)-cytokine environment (INF- γ , IL-12), IgG production is favored. Often no symptoms are seen, but under certain circumstances IgG- (and complement-) mediated cytotoxic effects may occur, which can lead to cell destruction such as in haemolytic anemia (*type II reaction*). Occasionally, an immune-complex-mediated disease with fever, urticaria, erythema multiforme, arthralgias, and lymphadenopathy may develop (*type III reaction*), for which in general a high cumulative dose of the respective drug is needed.

2.2.2 T Cell-Mediated Drug Hypersensitivity

Restimulation of Primed T Cells by Drug-Carrier Complexes (Hapten Model)

Upon reexposure to a drug acting as hapten or becoming a hapten after metabolism, the hapten-carrier-compounds are formed again and can be recognized by primed effector T cells. Recognition and the ensuing inflammation will take place in the involved tissue or in the corresponding draining lymph nodes. The tissue can be the skin, but also other organs where the drug or hapten-carrier compounds are present (Fig. 3a).

Stimulation of Primed T Cells by Native Drugs (p-i Concept)

Primary sensitization by drugs and protein allergens is asymptomatic. It has thus been a paradigm that in immune-mediated drug hypersensitivity, clinical signs or symptoms can be observed only on reexposure or longer lasting exposure (>3 days), allowing a clinically silent sensitization (Naisbitt et al. 2001). However, drug hypersensitivity reactions are rather frequently observed on first contact or after only a short period of time (hours). It has been assumed that such reactions on primary exposure are not mediated by the adaptive immune system and were therefore classified as “pseudoallergic”. However, more recent data in patients with iodinated contrast media hypersensitivity and without previous contact to the incriminated contrast medium revealed positive results in skin and cellular testing (lymphocyte transformation test, LTT). This suggests that clinically manifest hypersensitivity reactions to contrast media and other drugs (in particular neuromuscular blocking agents, NMBA) can occur on first exposure. Such reactions are best explained by a type of cross-reactivity, i.e., the T cells were originally primed by other drugs (such as pholcodine; Florvaag et al. 2006) or peptides, and happen to react with the drug as well. This would explain the rapidity of the reaction.

The p-i-Type of Stimulation of Peptide-specific TCR by Native Drugs

A detailed analysis of drug-reactive T cells revealed the surprising finding that most T cells do not react with the hapten (metabolite) but directly with the parent compound. This reactivity differed from hapten recognition; it occurred within minutes, before metabolism and presentation by the APC could take place. The drug binding was labile and could be washed away – in contrast to haptens, which bind covalently. Fixed APC, unable to take up and metabolize and process the drug were still able to provide interaction with the reactive T cell (Schnyder et al. 1997; Zanni et al. 1998; Pichler 2002; Schmid et al. 2006b). All these data (rapidity of reaction, independence of metabolism) led to the new p-i concept (pharmacological interaction of a drug with immune receptors) postulating that a drug might directly bind to TCR and stimulate the T cell. The interaction of the TCR with the MHC-molecule itself on APCs is well documented for TCR-MHC interactions and supplements this signal (Wu et al. 2002). This concept explains many clinical features of drug allergy better than the hapten concept, which is of particular importance for contact dermatitis but most likely not a suitable explanation for many generalized reactions to systemically administered drugs. This is particularly true for the frequent skin symptoms in drug allergy, which are explained in more detail (Fig. 3b, see Table 1 for differences between the p-i and hapten models).

The p-i Concept and Skin Symptoms

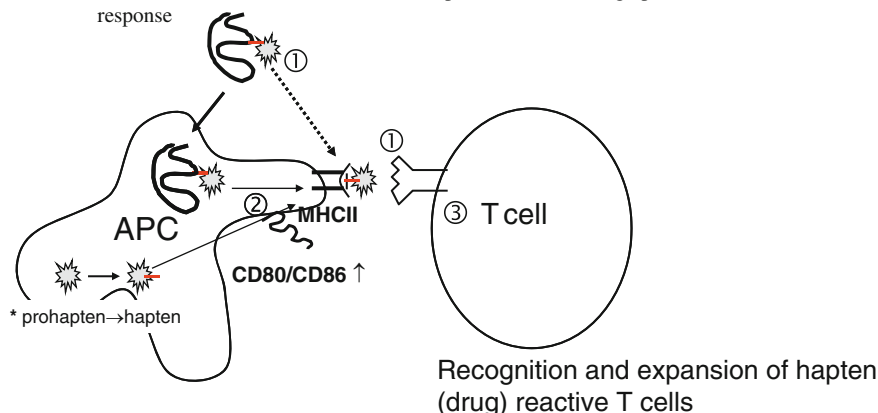
The systemic drug hypersensitivity reactions involving the skin are difficult to reconcile with the development of a classical immune response, where T cells primed in the lymph nodes home to the area where the antigen has entered and caused “danger signals”. Skin symptoms in systemic drug hypersensitivity reactions appear all over; there is no danger signal from the outside. One has to take into account (1) that drugs are ubiquitously distributed in the body, (2) the lack of extensive metabolism in the skin, (3) the well described sentinel function of some resident T cells in the skin, and (4) the p-i concept (Fig. 2) (Chung et al. 2004). As an explanation for the predominance of skin reaction we recently formulated the following hypothesis (Posadas and Pichler 2007):

- (a) Oral or parenteral uptake of drugs leads rapidly to a distribution throughout the body. This is particularly well documented for the skin, where, for example, antihistaminic drugs given orally can reach tissue levels in the nanomolar range within 45–60 min (Devillier 2006) and completely block H1 receptors and abolish skin test responses to allergens.
- (b) According to the p-i concept, a drug may not only interact with their appropriate pharmacological receptor (e.g., H1-receptor for antihistaminics), but also with T cell receptors (TCR) of certain T cells. Of note, no metabolism is needed to induce such an interaction. The stimulatory potential of this drug-TCR interaction may decisively depend on the readiness of the T cell to react to a “minor” signal such as a drug. In this context it is interesting that

A

The hapten concept

- 1 stable (covalent) binding of drug (=hapten) to protein/peptide or directly to peptide in MHC (.....→); *: prohapten becomes a hapten due to metabolism.
- 2 activation of dendritic cells and presentation of drug-modified peptide
- 3 stimulation of naive T cells and development of a *new*, drug-specific immune response



B

The p-i concept

- ① labile binding of drug to TCR directly
- ② The drug stimulates the T-cell via signalling by TCR.
- ③ The drug-induced signal is enhanced/supported by an additional MHC-interaction with the TCR

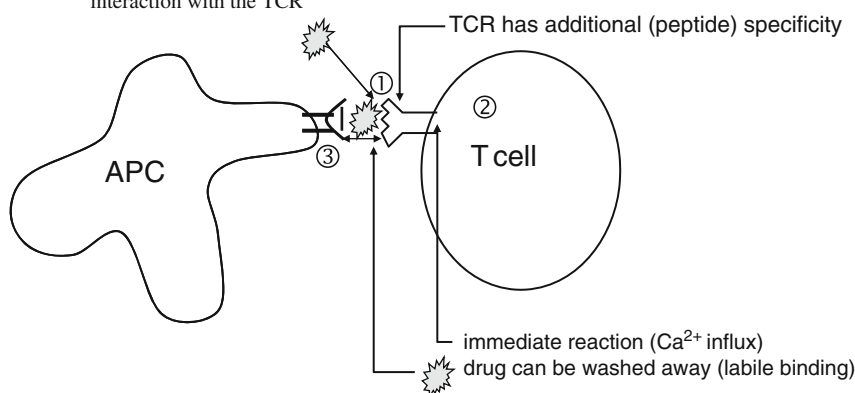


Fig. 2 Hapten/peptide and p-i concept of T cell stimulations by drugs. (a) Haptens: haptens are chemically reactive compounds. Drugs like penicillin are haptens: they bind to lysine amino acids in proteins or by the SH-group formed by opening the thiazolidine ring. This covalent binding can modify soluble or cell bound molecules. They can even bind directly to the immunogenic major histocompatibility complex (MHC)/peptide complex on antigen presenting cells (APC), either to the embedded peptide or to the MHC molecule itself. Thus, the chemical reactivity of haptens can lead to

Table 1 Important differences between hapten and p-i concept

Hapten concept	p-i concept
Activation of innate immunity required	Activation of innate immunity not required
Hapten-modified peptide is presented (stable covalent protein/peptide modification)	Direct (partial) interaction with TCR without presentation on MHC (no covalent binding)
Chemical modification (hapten)	Structural similarity (fitting into TCR)
Processing and metabolism	No processing/no metabolism
Directed to MHC-APC: serves to present the hapten-modified peptide	Directed to TCR-T cell: MHC interact with TCR, which is supplementing the drug stimulation of T cells
Activation of naïve and memory T cells	Activation of memory T cells only (?)
Strictly controlled and well-coordinated immune response	Uncoordinated and overlapping immune responses (e.g., Th1 & Th2 and cytotoxic)
Often combined immune responses (Ig, T cells)	Only T cell reactions of different types (exanthema, DRESS, AGEPS)

(c) The skin is a border region with an enormously dense network of APC and T cells, ready to mount an immune response (Keller et al. 2005; Clark et al. 2006). These “resident” T cells would fulfill sentinel functions and represent preactivated T cells with a high degree of reactivity. They can be characterized as chemokine ligand (CCL) 1 responders and express chemokine receptor (CCR) 8, while the immigrating inflammatory T cells are CCL20 responders and CCR6+. The frequent manifestation of drug hypersensitivity in the skin might be due to the readiness of such skin sentinel CCR8+, CD4+, TCR $\alpha\beta$ + T cells to be stimulated by drugs via the p-i mechanism. This initial activation provides stimulatory signals to local epidermal and endothelial cells and thus steers the immune reaction to the skin.

The possible steps of this new concept are outlined in Fig. 3b: In drug hypersensitivity, the local concentration of drugs in the skin may lead to a successful TCR engagement by drugs directly interacting with the TCR (p-i concept), supplemented by MHC interaction (through the close contact to the abundantly available

Fig. 2 (continued) the formation of many distinct antigenic epitopes, which can elicit both humoral and cellular immune responses. Other drugs are “prohaptens”: they require metabolic activation to become haptens (=chemically reactive), which happens mainly via cytochrome P450 enzymes. The metabolism leads to the formation of a chemically reactive compound (e.g., from sulfamethoxazole [SMX] to the chemically reactive form SMX-NO). The metabolite may then modify cell bound or soluble proteins, as described above for haptens. If this metabolite is available in the liver or kidney only, a localized immune response may develop. If it is available all over, a generalized reaction might ensue. (b) The p-i concept (pharmacological interaction with immune receptors): Drugs are often designed to fit into certain proteins/enzymes to block their function. Some drugs may also happen to bind into or onto some of the available and highly polymorphic T cell receptors for antigen. Under certain conditions (see text), this drug-T cell receptor interaction may lead to stimulation of the T cell. For full T cell stimulation by such a chemically inert drug (no hapten-like features), an additional interaction of the T cell receptor with the MHC-molecule is required. This type of drug stimulation would result in an exclusive T cell stimulation. A similar model is conceivable for the hypervariable antigen-binding sites of immunoglobulins, but has never been formally demonstrated

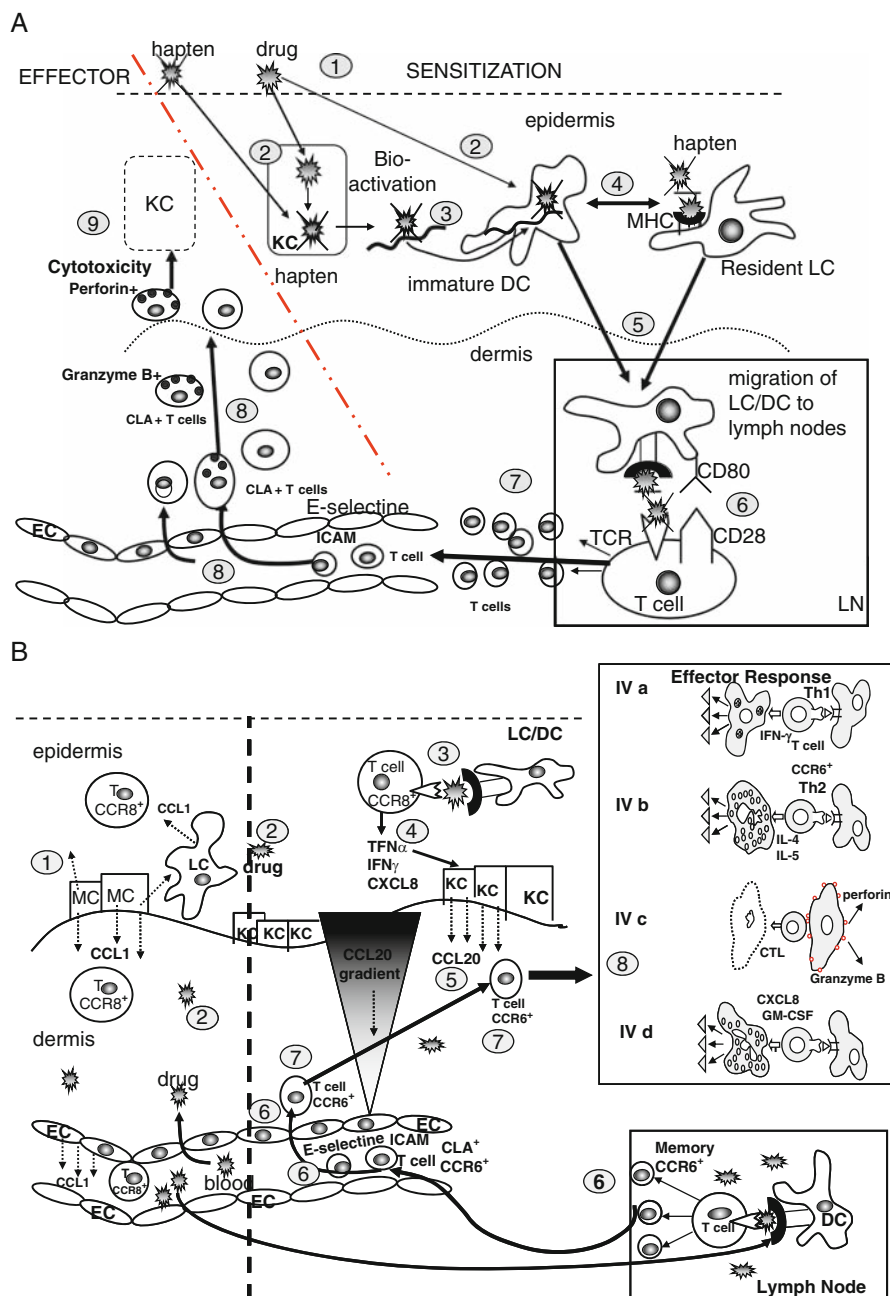


Fig. 3 Schematic representation of critical events involved in the frequent manifestation of drug hypersensitivity in the skin based on (a) hapten concept (contact dermatitis) or (b) p-i concept (generalized exanthema). Skin symptoms according to hapten/prohapten concept (a): contact dermatitis, drug applied on skin. Drugs, other chemicals or metal-ions enter the epidermis through the

epidermal antigen presenting cells (dendritic cells, DC and Langerhans cells, LC). The drug-stimulated CCR8+ T cells initiate an immune defense program by secretion of tumor necrosis factor (TNF)- α , interferon (IFN)- γ etc., which leads to an acute phase response via induction of inflammatory chemokines such as CXCL8 or CCL20 (= chemokine for CCR6+ T cells) in keratinocytes, upregulation of vascular adhesion receptors, and consequently recruitment of more leukocytes to the skin (steps 1–5; Fig. 3b). Since the majority of T cells in inflammatory conditions are CCR6-positive, they appear to be recruited and might have been activated outside the skin. Therefore, simultaneously with these local events in the skin, T cells in the lymph nodes may be activated by drugs, which are also found there because drugs are ubiquitously distributed in the body and do not need transport by the lymph or within DC/LC to the lymph nodes (like normal antigens). These T cells in the lymph nodes may be particularly responsive to the drug stimulation if they have been activated, e.g., by an infection. They will enter the circulation. Many may express CCR6 and other skin homing markers (e.g., cutaneous lymphocyte antigen, CLA), and therefore, upon arrival in the skin vasculature, they may adhere to the locally activated endothelium (due to the above described T cell stimulation in the skin) and emigrate from the vasculature to the skin following the CCL20 gradient (steps 6 and 7; Fig. 3b).

Fig. 3 (continued) stratum corneum or via the systemic circulation (1). This may already make a big difference. The hapten/prohapten concept may apply mainly to the contact dermatitis: the prohapten may undergo bioactivation in keratinocytes (KC) (2), but also in dendritic/Langerhans cells (DC/LC) (2), followed by intracellular protein haptenation. Haptens or reactive metabolites released from KC may haptenate extracellular proteins (3). These events may provide some local stimulation (“danger signal”), and in particular stimulate DC/LC (4), which process and present the hapten-protein complexes and emigrate (5) to the lymph nodes (LN), where they present the hapten-peptide complex to T cells (6). There, the engagement of the TCR of hapten-specific, naïve T cells in the presence of costimulatory signals (CD80/CD28) results in the generation of a hapten-specific immune response and clonal expansion of hapten-reactive T-effector cells (7). The activated T cells express skin homing receptors, which allow them to be recruited to the skin (8), where the local inflammation has already induced chemokine expression, which attracts these activated T cells. Local hapten presentation results in T cell (granzymeB/perforin)-mediated cytotoxicity and inflammation (9). Numbers refer to numbers in (a). (b) Skin symptoms according to p-i concept: drug-induced exanthema, drug coming from circulation. In the skin, many sentinel T cells reside (attracted by CCL1 released by melanocytes and Langerhans cells (1) and are in close apposition to Langerhans and dendritic cells (*left side*). The drug is ubiquitously distributed in the body and found in sufficiently high concentrations in the skin as well (2). Skin-resident CCR8+ CD4+ TCR $\alpha\beta$ +sentinel T cells are stimulated by the drug directly (p-i concept, *right side*) (3), and secrete diverse cytokines (4). This drug-induced activation of the local T cells occurs better the higher the molar concentration of the drug and is facilitated by the close contact of T cells to DC/LC in the skin, and this initial T cell stimulation provides signals to local epidermal and endothelial cells and thus sets an alarm signal (3) secrete diverse cytokines (4). The keratinocytes activated thereby secrete CCL20 (5). Simultaneously, T cells with a low activation threshold may be activated by the drug in lymph nodes, where they expand and then emigrate expressing the homing receptor CCR6 (6). The local CCR8+, but mainly the recruited CCR6+ T cells (7), evoke a *generalized* inflammatory skin response because the inflammation is not restricted to a localized area where an antigen penetrated the skin (like in contact dermatitis). This generalized reaction is typical for exanthema. The cytokine pattern released by the T cells (4) leads to different forms of the exanthem (8), which can be subclassified into IVa, IVb, IVc, and IVd type reactions. Numbers refer to numbers in (b)

Finally, the local sentinel CCR8+ and the recruited CCR6+ T cells (which represent the majority of T cells in inflamed areas) would evoke an inflammatory skin response. Its type might be determined by the profile of cytokines produced by the CCR6+ T cells, whereby the different responses (IVa, IVb, IVc, and IVd) described below might evolve. Why the immune response leads to a more IVa or IVb, etc., response is at present unknown (step 8; Fig. 3b).

This concept does *not* postulate drug metabolism in the skin and does *not* involve the hypothetical generation of a new immune response, but stimulates and expands *preexisting* effector or memory T cells, which already reside in the skin and lymph nodes (Pichler 2005). These T cells also already have peptide specificity. It is possible that a drug preferentially activates T cells with a particular peptide specificity, which might explain the puzzling finding that certain drugs elicit rather consistently similar clinical pictures (Peyriere et al. 2006).

This p-i concept adapted to the skin could explain:

(a) The preferential localization of drug hypersensitivity to the skin following oral or parental drug uptake. Other organs do not have such highly reactive sentinel T cells – and therefore the tissue is not “alarmed”, and activated T cells, even if they would express the appropriate homing receptors, cannot migrate there so easily.

(b) The dose dependency of many drug hypersensitivity reactions. Higher concentrations of drugs are more often associated with delayed drug hypersensitivity reactions (Uetrecht 2001), and higher doses would lead to higher tissue concentrations and thus a better stimulation of T cells.

(c) The observation that generalized viral diseases such as HIV or herpes virus infections are risk factors for drug hypersensitivity. In such diseases, lymphocytes (and DC/LC) are already activated, which may lower the threshold of reactivity to a minor signal like drug binding.

3 Different Types of T Cell-Mediated Drug Hypersensitivity Reactions

A detailed analysis of T cell subsets and functions over the last 20 years resulted in a better understanding of the heterogeneity of cellular immune responses, which should also be incorporated in the well-known Gell and Coombs classification. Therefore T cell-mediated type IV reactions were further subclassified into IVa–IVd reactions as proposed in Fig. 4 (Pichler 2003). This subclassification considers the distinct cytokine production by T cells and thus incorporates the well-accepted Th1/Th2 distinction of T cells. It includes the cytotoxic activity of both CD4+ and CD8+ T cells (IVc), and it emphasizes the participation of different effector cells such as monocytes (IVa), eosinophils (IVb), or neutrophils (IVd), which are the cells that mediate the inflammation and tissue damage.

Type IVa. Reactions correspond to Th1-type immune reactions. Th1-type T cells activate macrophages by secreting large amounts of IFN- γ , drive the production of

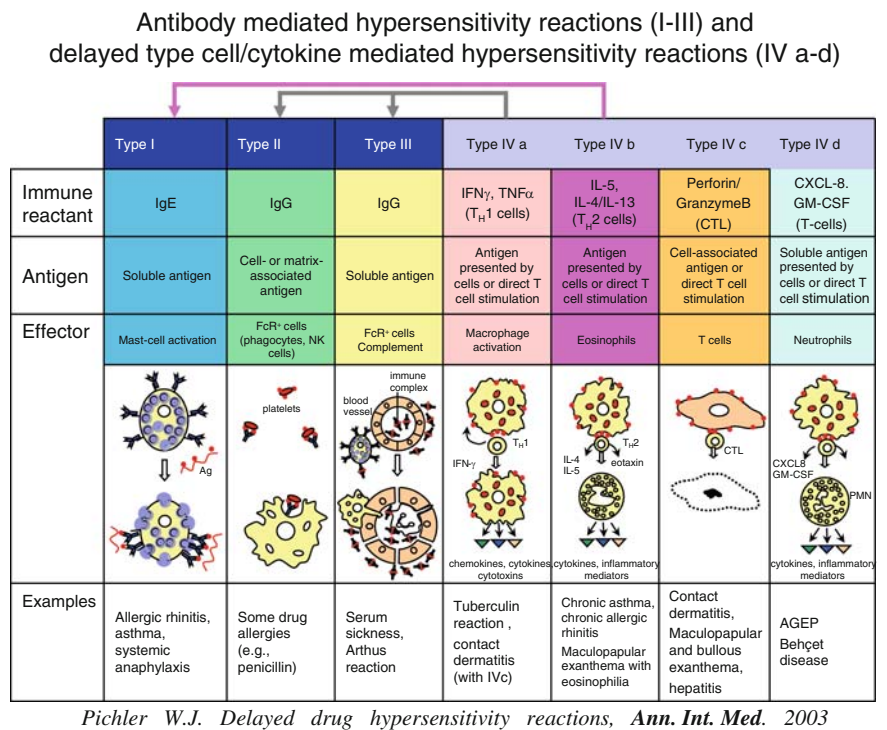


Fig. 4 Revised Gell and Coombs classification of drug reactions. Drugs can elicit all types of immune reactions. In fact, all reactions are T cell regulated, but the effector function relies mainly on antibodies (Type I-III) or more commonly T cells/cytokine secretion (type IVa to IVd). *Type I* are IgE-mediated reactions. Cross-linking IgE molecules on high affinity IgE receptors (FcεRI) on mast cells and basophils leads to degranulation and release of mediators, which cause a variety of symptoms (vasodilatation, increased permeability, bronchoconstriction, itch, etc.). *Type II* reactions are IgG-mediated, and cause cell destruction due to complement activation or interaction with Fcγ receptor bearing killer cells. *Type III* reactions are also IgG-mediated: Complement deposition and activation in small vessels and recruitment of neutrophilic granulocytes via Fcγ receptor interaction leads to local vascular inflammation. *Type IVa* corresponds to Th1-driven reactions with high IFN γ /TNF α secretion and involves *monocyte/macrophage* activation. Often, one can also see CD8+ T cell recruitment (type IVc reaction). *Type IVb* reactions correspond to *eosinophilic* inflammation and to a Th2 response with high IL-4/IL-5/IL-13 secretion; they are often associated with an IgE-mediated type I reaction. *Type IVc*: the cytotoxic reactions (both by CD4+ and CD8+ T cells) rely on *cytotoxic T cells* as effector cells. They seem to occur in all drug-related delayed hypersensitivity reactions. *Type IVd* corresponds to a T cell-dependent, sterile *neutrophilic inflammatory* reaction. It is clearly distinct from the rapid influx of neutrophils in bacterial infections. It seems to be related to high CXCL-8/GM-CSF production by T cells (and tissue cells). The role of IL-17 in these reactions is not yet defined

complement-fixing antibody isotypes involved in type II and III reactions (IgG1, IgG3), and are costimulatory for proinflammatory responses (TNF- α , IL-12) and CD8+ T cell responses. The T cells promote these reactions by IFN- γ secretion and possibly other cytokines (TNF- α , IL-18, etc.). An in vivo correlate would be, on the

one hand, monocyte activation, e.g., in skin tests to tuberculin or even granuloma formation as seen in sarcoidosis. On the other hand, these Th1 cells are known to activate CD8⁺ T cells, which might explain the common combination of IVa and IVc reactions (e.g., in contact dermatitis).

Type IVb. Corresponds to the Th2-type immune response. Th2 T cells secrete the cytokines IL-4, IL-13, and IL-5, which promote B cell production of IgE and IgG4, macrophage deactivation as well as mast cell and eosinophil responses. The high production of IL-5 leads to an eosinophilic inflammation, which is the characteristic inflammatory cell type in many drug hypersensitivity reactions (Pichler 2003). In addition, there is a link to type I reactions because Th2 cells boost IgE production by IL-4/IL-13 secretion. Thus, type IVb reactions may actually be involved in the late phase allergic inflammation of the bronchi or nasal mucosa (asthma and rhinitis), which were initiated by IgE on mast cells or basophils. Another in vivo correlate might be infestations with nematodes, eosinophil-rich maculopapular exanthema, or other T cell-dependent diseases with hypereosinophilia.

Type IVc. T cells themselves can also act as effector cells. They migrate to the tissue and can kill tissue cells such as hepatocytes or keratinocytes in a perforin/granzymeB- and FasL-dependent manner (Schnyder et al. 1998; Nassif et al. 2002, 2004; Kuechler et al. 2004). Such reactions occur in most drug-induced delayed hypersensitivity reactions, mostly together with other type IV reactions (monocyte, eosinophil, or neutrophil recruitment and activation). Cytotoxic T cells thus play an important role in maculopapular or bullous skin diseases as well as in conditions characterized by neutrophilic inflammation (acute generalized exanthematous pustulosis, AGEP), and in contact dermatitis. Type IVc reactions appear to be dominant in bullous skin reactions such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), where activated CD8⁺ T cells kill keratinocytes (Schnyder et al. 1998; Nassif et al. 2002, 2004). They may also be the dominant cell type in hepatitis or interstitial nephritis.

Type IVd. The possibility that T cells could also coordinate (sterile) neutrophilic inflammation has been rather neglected. Typical examples would be sterile neutrophilic inflammations of the skin, in particular acute generalized exanthematous pustulosis (AGEP). In this disease, T cells recruit neutrophils via CXCL8 release and prevent their apoptosis via GM-CSF release (Britschgi et al. 2001). In addition to AGEP, such T cell reactions are also found in Behçet’s disease and pustular psoriasis (Keller et al. 2005). The relationship of these T cells to the recently described IL-17-producing T cells (Th17) requires clarification.

4 Clinical Features and Pathophysiology of Cutaneous Reactions

The most frequent manifestations of drug allergies are delayed appearing *cutaneous reactions*, so-called “rashes”. They comprise a broad spectrum of clinical and distinct histopathological features which appear from 6 h to 10 days after drug

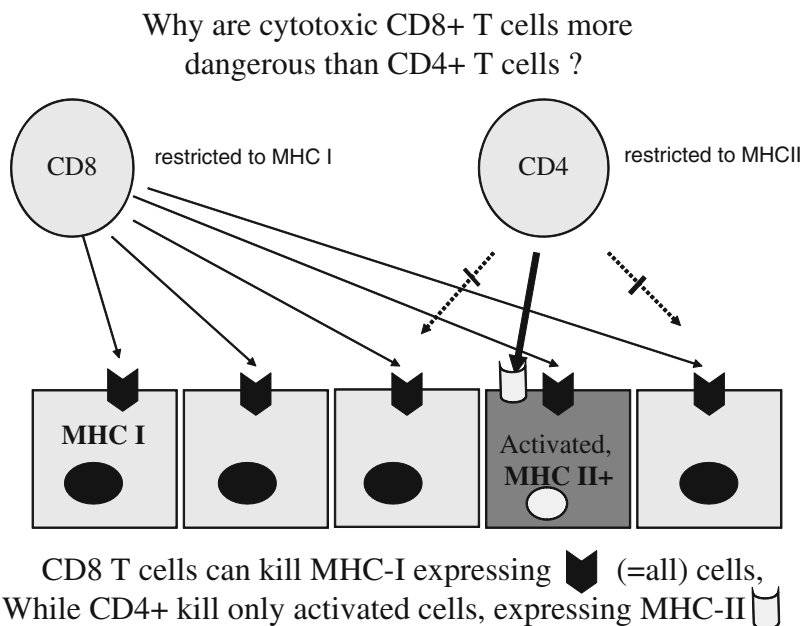


Fig. 5 Cytotoxicity of CD8+ versus CD4+ T cells: cytotoxic CD4+/CD8+ T cells recognize the drug in association with MHC and kill the respective target cell; if the killing is restricted to MHC class II (CD4+ T cells), only activated cells will be killed. If the killing process is targeted to MHC class I (CD8+ T cells), all nucleated cells, and in particular all keratinocytes (or hepatocytes), can be killed. This might explain the difference between the milder maculopapular exanthema and the more severe bullous exanthema

intake. In *all forms* of delayed drug-induced reactions, such as exanthema, interstitial nephritis, and probably hepatitis, cytotoxic mechanisms seem to play an important role. The clinical picture is determined by the *strength of cytotoxicity* (amount of drug-specific cytotoxic T cells and tissue destruction), which is also related to the proportion of cytotoxic CD8+ versus cytotoxic CD4+ T cells, because cytotoxic CD8+ T cells have a broader target cell repertoire (all nucleated cells express MHC I, which is recognized by CD8+ T cells, while CD4+ T cells require expression of MHC II which is only found on immunocompetent cells) (Fig. 5). Also important for the clinical picture is the type of associated effector mechanism (monocyte involvement or activation of eosinophilic and neutrophilic granulocytes).

4.1 Maculopapular Exanthem (MPE)

MPE is the most frequent drug hypersensitivity reaction, affecting 2–8% of hospitalized patients, especially after treatment with β -lactams, sulfamethoxazole,

quinolones, diuretics, and many more. It most commonly appears 8–11 days after the start of treatment – sometimes even 1–2 days after the end of treatment. In previously sensitized individuals it can appear on the first day. It is clearly a dose-dependent reaction. A study investigating exanthema after treatment with gemifloxacin (a quinolone) showed that females of childbearing age had a higher risk of exanthema, suggesting the influence of oestrogens (Schmid et al. 2006a). Most MPE – particularly if caused by β -lactams or gemifloxacin – are rather mild diseases, and treatment with an emollient cream, and possibly topical corticosteroids or systemic antihistamines for pruritus, is sufficient. Some patients can still be treated with the eliciting drug if needed without aggravation. The exanthema often heals with desquamation within 2–10 days after stopping the incriminated drug. It is rather unlikely that SJS/TEN will develop from a MPE because the involved cell types are different. On the other hand, some drugs may induce a mixed CD4+/CD8+ T cell activation. In such cases, prolonged treatment may lead to confluence of the papules; the patient may complain about malaise and fever, and liver injury tests indicate hepatitis (alanine aminotransferase $>3\times$ increase). In the blood, eosinophilia (>0.5 cells/l) as well as activated CD8+ T cells are found (Hari et al. 2001). This illustrates that even “mild” drug hypersensitivity reactions are *systemic diseases*, and that cutaneous manifestations may often be only the tip of the iceberg.

Immunohistology reveals a drug-specific CD4+ T cell infiltration (CLA+, CCR6+) in perivascular areas of the dermis (Yawalkar et al. 2000; Pichler 2003). Some T cells migrate into the dermoepidermal junction and epidermis, probably due to a gradient of chemokines produced by keratinocytes and melanocytes (e.g., CCL20 binding to CCR6). In the dermis and epidermis they encounter the drug-antigen again, and they are reactivated (they express MHC class II and CD25+) and may kill activated keratinocytes directly in a contact-dependent way by releasing perforin/granzymeB (Schnyder et al. 1998). Some keratinocytes undergo hydropic degeneration, but this apoptosis is not as extensive as with CD8+ T cell-mediated killing because not all keratinocytes express MHC class II. In addition, the immigrating CD4+ T cells exhibit a heterogeneous cytokine profile, including type 1 (IFN- γ) and type 2 (IL-4, IL-5) cytokines, which suggests that both Th1 and Th2 cells infiltrate the skin. The cytokine IL-5 is also detectable, both by immunohistochemistry and even in the serum (Hari et al. 1999). Tissue as well as blood eosinophilia can be found (Hari et al. 2001). The recruitment of eosinophils is also enhanced by the expression of the chemokines, eotaxin and RANTES, in MPE-lesions (Gerber et al. 1997).

4.2 Acute Generalized Exanthematous Pustulosis (AGEP)

Acute generalized exanthematous pustulosis is a rare disease (about 1:100,000 treatments) with an estimated incidence equal to severe bullous skin diseases (SJS and TEN combined) (Sidoroff et al. 2001). It is caused by drugs in $>90\%$ of cases (Table 2). Its clinical hallmark is the presence of myriads of disseminated,

Table 2 Drugs eliciting severe cutaneous or systemic reactions^a

Acute generalized exanthematous pustulosis (AGEP)	Stevens–Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN)	Drug induced hypersensitivity syndrome/Drug rash with eosinophilia and systemic symptoms (DiHS/DRESS) ^b
Aminopenicillins	Nevirapine	Carbamazepin ^c
Cephalosporins	Allopurinol ^c	Phenytoin
Pristinamycin	Phenytoin	Lamotrigin ^c
Celecoxib	Carbamazepin ^c	Minocyclin ^c
Quinolone	Lamotrigin ^c	Allopurinol ^c
Diltiazem	Cotrimoxazole	Dapsone
Terbinafin ^c	Barbiturate	Sulfasalazin
Macrolides	NSAID (oxicams)	Cotrimoxazole
	Sertraline	Abacavir ^c
	Pantoprazole	
	Tramadol	

^aList incomplete, only the most frequent elicitors are named
^bAbacavir and lamotrigine induced systemic reactions often lack eosinophilia, abacavir affects preferentially the respiratory and GI-tract, minocycline induces lymphadenopathy more frequently, etc.; compare (Peyriere et al. 2006)
^cThe type of reaction might be determined by the presence of a certain HLA-B phenotype (Hung et al. 2005)

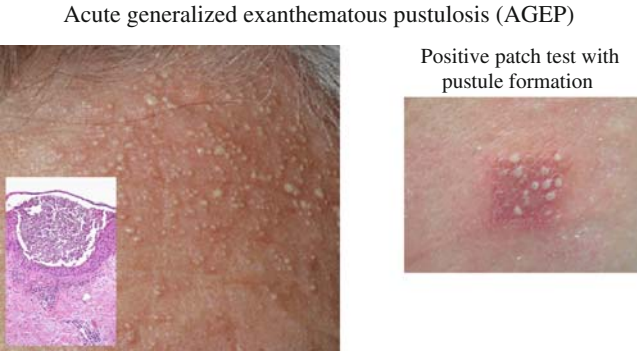


Fig. 6 Pustular drug eruption (AGEP): disseminated pustules cover the skin. Histologically, the pustules are intraepidermal and nonfollicular. A patch test reaction to the eliciting drugs can lead to a pustular reaction as well; for details see text

sterile pustules in the skin (Fig. 6), which appear rather rapidly, namely about 3–5 days after the initiation of treatment. The patients have fever and massive leukocytosis in the blood, sometimes with eosinophilia, but no involvement of mucosal surfaces. Epicutaneous patch test reactions during diagnostic work-up can cause a similar pustular reaction locally (Fig. 6). The latter feature allowed a study of the sequence of events in the development of pustules in sensitized patients using sequential biopsies of affected patients (Fig. 6).

Immunohistology of the acute lesion reveals subcorneal or intraepidermal pustules, which are filled with neutrophilic granulocytes and are surrounded by activated, HLA-DR-expressing CD4+ and CD8+ T cells. Keratinocytes show an elevated expression of the neutrophil-attracting chemokine, IL-8 (CXCL-8), and even the T cells migrating into the epidermis express CXCL-8 and GM-CSF. Analysis of sequential patch test reactions at 48–96 h suggests that drug-specific cytotoxic T cells migrate first and cause formation of vesicles by killing keratinocytes. Subsequently T cells and keratinocytes (stimulated by IFN- γ /TNF- α) release CXCL8, which recruits granulocytes into the vesicles, which are then transformed into pustules (Britschgi et al. 2001) (Fig. 6). Some pustules coalesce and may form bullae. The mortality rate is about 2–4% and older people are at the greatest risk. Healing occurs within 5 days after stopping the drug. This disease and the underlying T cell reaction seem to be a model for sterile neutrophilic inflammations (type IVd) such as pustular psoriasis and Behcet's disease (Keller et al. 2005). The relationship of these T cells to the recently described IL-17 secreting T-helper subset Th17 is unclear. Analysis of CXCL8-producing T cell clones isolated from skin lesions did not reveal elevated IL-17 production (Keller M, personal communication).

4.3 Bullous Exanthema, Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

The most severe bullous skin diseases are SJS and TEN. TEN and SJS are rare (incidence 1:1,000,000 for TEN, ca. 1:100,000 for SJS) (Mockenhaupt 2007). Nowadays, they are considered to be the milder and the more severe form of the same disease (SJS <10%, TEN >30% skin detachment), respectively. They are graded according to SCORTEN (Guegan et al. 2006), whereby age, underlying disease, and the amount of maximal skin detachment are the most important prognostic factors. According to the European Study Group of Severe Cutaneous Drug Reactions (EuroSCAR), SJS and TEN have mortalities of 13 and 39%, respectively. The intermediate form with 10–30% skin detachment is called SJS/TEN overlap syndrome and has a mortality rate of about 21%.

SJS/TEN are clearly different from erythema exsudativum multiforme, which is mainly caused by viral infections (Mockenhaupt 2007), is often recurrent, and affects younger persons (mean age 24 years). In about 6% of SJS/TEN cases, no drug treatment was reported the week before SJS/TEN started, and an infectious origin (*Mycoplasma* sp., *Klebsiella* sp.) is suspected. SJS/TEN can also be due to a graft versus host disease.

Most reactions start within the first 8 weeks of treatment (mean of first symptoms on the 17th day of treatment), with some differences according to the responsible drug (e.g., with sulfonamide antibiotics it may appear late). Once established, the disease can develop quite rapidly: initially often a macular, purple–red exanthema

is observed, which can become painful – an ominous sign. Within 12–24 h, bullae may already be seen, and the Nikolsky sign is positive. Stopping the eliciting drug at this time point may not prevent SJS from developing, but it might prevent an even more severe reaction (TEN). Mucous membranes (mouth and genitalia) are involved with blister formation as well as a purulent keratoconjunctivitis. The formation of synechiae may result in permanent eye damage.

The main causes for SJS/TEN are drugs (Table 2), which might differ in frequency in various regions due to genetic and ethnic background. The majority of cases are still due to some older drugs, and only a few newer drugs have a higher risk for SJS/TEN (Mockenhaupt et al. 2008). These include sertraline [RR=11 (2.7–46)], pantoprazole [RR=18 (3.9–85)], and tramadol [RR=20 (4.4–93)]. The most important risk factors are an HIV infection (low CD4, high CD8 counts), renal diseases, and active systemic autoimmune diseases such as systemic lupus erythematosus, Still's syndrome, Sjogren's disease, and rheumatoid arthritis, all being associated with immune stimulation.

In TEN, many dead keratinocytes are found, but cell infiltration is only rarely seen (Alanore and Roujeau 2007). However, the bullae – empty in histology – are actually filled with many cells, mainly cytotoxic CD8+ T cells, expressing CD56 and alpha/beta-T cell receptors, which may have migrated through the skin and have killed keratinocytes via perforin/granzyme B but not via the Fas-mediated pathway at this stage of the disease (Nassif et al. 2002, 2004). On the other hand, the massive cell death of keratinocytes is hard to reconcile with a cell-contact-dependent killing process. It has been proposed that the apoptosis of keratinocytes is due to Fas ligand (FasL), a soluble molecule of the TNF-family, which binds to keratinocytes via Fas and functions as a so-called death receptor (Viard et al. 1998). This FasL may also be expressed on or bound to keratinocytes, leading to a suicidal interaction between Fas and FasL. FasL bound to keratinocytes may also derive from mononuclear cells infiltrating/migrating through the skin in the early phase of the disease (Abe et al. 2003). Since blocking anti-Fas antibodies are found in immunoglobulin preparations, it has been proposed that patients with TEN should be treated with immunoglobulins. However, the efficiency of this treatment is controversial, and the content of such anti-Fas antibodies in immunoglobulin preparations is highly variable (Bachot et al. 2003).

Extensive research has not revealed a pharmacogenetic predisposition or low glutathione levels in most affected persons. However, recent data have shown striking HLA-associations with severe, CD8+ T cell-mediated drug hypersensitivity reactions (Mallal et al. 2002, 2008; Chung et al. 2004; Hung et al. 2005; Yang et al. 2007). Three factors play a role: (1) the type of drug; (2) the type of reaction – as it was found for cytotoxic CD8+ T cell mediated reactions only; and (3) possibly ethnic background; some associations were exclusively found in Han Chinese. The HLA-B allele, which is the most polymorphic HLA-allele, seems to be involved: in carbamazepine-induced SJS/TEN, it is HLA-B*1502, for allopurinol it is HLA-B*5801, and for abacavir it is HLA-B*5701 together with heat shock protein70 (Mallal et al. 2002; Chung et al. 2004; Hung et al. 2005). It seems that in these CD8+ T cell-mediated reactions a certain HLA-B allele favors the presentation of certain

peptides that are able to optimally present the drug acting as a hapten. Alternatively, certain MHC-class B alleles might supplement the direct T cell stimulation via these drugs (p-i concept) better than others, while absence of these alleles renders the T cell insufficiently responsive to the drugs (Yang et al. 2007).

The extremely high association of certain HLA-B alleles with hypersensitivity reactions to certain drugs may be used to prevent such side effects in the future. Specifically, HLA-typing may identify patients at risk, and their exclusion from treatment might reduce the incidence of side effects (Mallal et al. 2008).

4.4 Drug (-Induced) Hypersensitivity Syndrome (DHS or DiHS) or Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

Some drugs are known to cause a severe systemic disease with fever, lymph-node swelling, massive hepatitis, and various forms of exanthema (Table 2). Occasionally, patients develop colitis, pancreatitis, or interstitial lung disease (Knowles et al. 1999; Shiohara et al. 2007). Over 70% of these cases have marked eosinophilia (often $>10^9/l$), and activated lymphocytes are often found in the circulation similar to acute HIV or generalized herpes infections. This syndrome has many names; the most frequently used are drug (-induced) hypersensitivity syndrome (DHS or DiHS) or drug rash with eosinophilia and systemic symptoms (DRESS). Importantly, the symptoms can start up to 12 weeks after start of treatment, often after increasing the dose, and may also persist and recur for many weeks even after cessation of drug treatment. The clinical picture resembles a generalized viral infection, e.g., an acute Epstein-Barr virus infection, but it is distinguished by prominent eosinophilia. Many patients have facial swelling, and some have signs of a capillary leak syndrome (a side effect also observed in high dose IL-2 therapy), namely enhanced vascular permeability of small vessels with generalized edema, also affecting the lungs – similar to patients with a cytokine release syndrome or patients with a “cytokine storm” (Pichler and Campi 2007). Indeed, various cytokines are massively increased in the serum of these patients – not as high, but still similar to the incident with TGN1412 (a peculiar anti-CD28 antibody able to stimulate T cells to cytokine production and proliferation) – which has certain clinical similarities to this syndrome and supports the idea that certain drugs can act in a superagonistic/superantigen-like way (Pichler 2002).

A recent careful analysis of reported cases caused by antiepileptics, minocycline, allopurinol, and abacavir revealed quite consistent clinical pictures according to the eliciting drug, but also quite striking differences in the symptoms (Peyriere et al. 2006). For example, abacavir-induced reactions lack eosinophilia and hepatitis, but cause mainly gastrointestinal and respiratory symptoms, lamotrigine does (rarely) cause eosinophilia, while allopurinol-induced DRESS often involves the kidneys, etc.

The clinical picture is quite dramatic, and because the disease tends to persist in spite of stopping the drug, many patients are not diagnosed timely and correctly. However, every doctor using anticonvulsants should know about this syndrome because it occurs in up to 1:3,000 treated patients! The mortality is about 10%, and some patients only survive after an acute liver transplantation. This disease likely causes more deaths (mainly due to fulminant hepatitis) than anaphylaxis.

Patients with DiHS/DRESS have many activated T cells in their circulation. These drug-specific T cells are directly stimulated by the respective drug (p-i concept) and they secrete large amounts of IL-5 and IFN- γ (Naisbitt et al. 2003). A peculiar feature of this syndrome is its long-lasting clinical course despite withdrawal of the causative drug. There may also be a persistent intolerance to other, chemically distinct, rather innocuous drugs (e.g., acetaminophen), leading to flare up reactions weeks after stopping the initial drug therapy and further confusing the picture (see below). Sometimes the exposure to a new drug, e.g., for the treatment of a suspected complication such as a superinfection, might precipitate fulminant liver failure (observed for vancomycin after a DRESS developed due to sulfasalazine). Treatment often requires high doses of corticosteroids and careful and slow tapering, in particular if the hepatitis is severe.

Recently, it has been shown that, in many patients with this syndrome, human herpes simplex virus 6 (HSV-6), and/or cytomegalovirus (CMV) and/or Epstein-Barr virus (EBV) DNA can be detected in serum samples during the 3rd or 4th week of the disease (but not before), followed by a rise of antibodies to these herpes viruses (Hashimoto et al. 2003). Thus, similar to HIV infections where T cell activation can also enhance virus production, the drug-induced massive immune stimulation may reactivate these latent lymphotropic herpes-viruses, which subsequently replicate and possibly contribute to the chronic course and persistent drug-intolerance in the affected patients.

While in DRESS/DiHS the exanthema might help to suggest a drug hypersensitivity reaction, there are other drug hypersensitivity reactions without exanthema. Many drugs can induce isolated *hepatitis*, and some (penicillins, proton pump inhibitors, quinolones, disulfiram, etc.) (*interstitial*) *nephritis* (Spanou et al. 2006). The symptoms may start insidiously and cause substantial tissue damage and even death. In drug-induced interstitial nephritis, eosinophils can sometimes be detected in the urine (even in the absence of eosinophilia in the blood) (Spanou et al. 2006; Pichler 2007). Rarer are *interstitial lung diseases* (furadantin), *pancreatitis*, *isolated fever or eosinophilia* as the only symptom of a drug allergy.

4.5 Multiple Drug Hypersensitivity Syndrome

The term multiple drug hypersensitivity is used for different forms of side effects to various drugs. Some use it to characterize patients with multiple drug intolerance (“pseudoallergy” to various NSAID, etc.), others reserve this term for well-documented, repeated, and clearly immune-mediated reactions to structurally

unrelated drugs (Pichler 2007). Cross-reactivity due to structural similarity is therefore not included.

According to our experience, about 10% of patients with well-documented drug hypersensitivity (skin and/or lymphocyte transformation test positive) have multiple drug allergies (Neukomm et al. 2001; Gex-Collet et al. 2005). For example, a patient may react to subcutaneously injected lidocaine with massive angioedema, then years later develop a contact allergy to corticosteroids. Alternatively, a patient may react to amoxicillin, phenytoin, and sulfamethoxazole within a few months, but with different symptoms (MPE, DiHS/DRESS, erythrodermia). Most patients have had rather severe reactions to at least one drug. An IgE-mediated reaction can be followed by a T cell-mediated reaction. The reason for this accumulation of drug hypersensitivities in one individual is unknown. One explanation might be a deficient tolerance mechanism against small chemical compounds/xenobiotics. An immune reaction to a drug, be it via hapten or p-i mechanism, can be seen as a failure of tolerance, and the same patient might not only be prone to develop other drug allergies but also autoimmune diseases. Preliminary data suggest, indeed, that a previous drug allergy might be a risk factor for the development of a delayed hypersensitivity reaction to contrast media.

4.6 Flare Up Reactions

Multiple drug hypersensitivity should be differentiated from *flare up reactions* (Pichler 2007). In patients with systemic drug allergies such as severe MPE or DRESS/DiHS, the T cell part of the immune system is massively activated, similar to acute viral infections. Like in the latter, these patients seem to have a lower threshold to react to a new drug and might show a flare up of their rash to a new drug, which is often an antibiotic. The patient is then labeled as allergic to the first and second antibiotic, but testing after remission might reveal only a sensitization to the first antibiotic, and the second is well tolerated in provocation (personal observation). The T cell reactivity to the second antibiotic would require a massive T cell stimulation, which is absent under normal circumstances.

The clinical observation of a flare up reaction, and the previously mentioned cofactors for drug hypersensitivity reactions such as viral infections, etc., suggest that an efficient stimulation of T cells by a drug is the sum of drug-TCR affinity and readiness of the cell to react. Quite a few TCRs may have the ability to interact with drugs, probably with different affinities. If the immune system is resting, only drug-TCR interactions of high affinity may be able to stimulate T cells sufficiently to cause T cell expansion. If sufficient cells react, symptoms might arise. But even such a high affinity interaction may remain unnoticed if too few cells are stimulated. If the immune system is activated and the readiness to react is increased (lower threshold), even relatively low affinity drug-TCR interactions might suffice to activate many T cells thus resulting in a symptomatic reaction. After the cofactor is eliminated, the low affinity binding drug remains negative in skin tests and is later

well tolerated if the costimulatory conditions are no longer present. This hypothesis might also explain the transient nature of many exanthema caused by antibiotics in childhood; the viral cofactors are missing during later testing and provocation.

5 Conclusion

Drug hypersensitivity reactions often have a bizarre clinical picture, possibly due to an unusual and not well-coordinated stimulation of the immune system, bypassing many rules and immunological “checkpoints”. This situation is reminiscent of transplantation medicine, another “radical” intervention of modern medicine, where the allo-response caused unforeseen immunological problems. In both situations, the immune system is faced with a man-made challenge for which it was not trained during evolution – as neither transplantation nor the extensive use of xenobiotics had previously occurred. The better understanding of these puzzling diseases over recent years opens up the possibility of preventing many of them in the near future, as has been well demonstrated for abacavir and carbamazepine-induced reactions, where typing for immunogenetic markers dramatically reduced the incidence.

References

- Abe R, Shimizu T, Shibaki A, Nakamura H, Watanabe H, Shimizu H (2003) Toxic epidermal necrolysis and Stevens–Johnson syndrome are induced by soluble Fas ligand. *Am J Pathol* 162:1515–1520
- Aiba S, Manome H, Nakagawa S, Mollah ZU, Mizuashi M, Ohtani T, Yoshino Y, Tagami H (2003) p38 Mitogen-activated protein kinase and extracellular signal-regulated kinases play distinct roles in the activation of dendritic cells by two representative haptens, NiCl₂ and 2, 4-dinitrochlorobenzene. *J Invest Dermatol* 120:390–399
- Alanore L, Roujeau JC (2007) Clinic and pathogenesis of severe bullous skin reactions: Stevens–Johnson syndrome, toxic epidermal necrolysis. In: Pichler WJ (ed) *Drug hypersensitivity*. Karger, Basel, pp 267–277
- Bachot N, Revuz J, Roujeau JC (2003) Intravenous immunoglobulin treatment for Stevens–Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. *Arch Dermatol* 139:33–36
- Becker D, Mohamadzadeh M, Reske K, Knop J (1992) Increased level of intracellular MHC class II molecules in murine Langerhans cells following in vivo and in vitro administration of contact allergens. *J Invest Dermatol* 99:545–549
- Bowen DG, Zen M, Holz L, Davis T, McCaughan GW, Bertolino P (2004) The site of primary T cell activation is a determinant of the balance between intrahepatic tolerance and immunity. *J Clin Invest* 114:701–712
- Britschgi M, Steiner UC, Schmid S, Depta JP, Senti G, Bircher A, Burkhart C, Yawalkar N, Pichler WJ (2001) T-cell involvement in drug-induced acute generalized exanthematous pustulosis. *J Clin Invest* 107:1433–1441

- Chung WH, Hung SI, Hong HS, Hsieh MS, Yang LC, Ho HC, Wu JY, Chen YT (2004) Medical genetics: a marker for Stevens–Johnson syndrome. *Nature* 428:486
- Clark RA, Chong B, Mirchandani N, Brinster NK, Yamanaka K, Dowgiert RK, Kupper TS (2006) The vast majority of CLA+T cells are resident in normal skin. *J Immunol* 176:4431–4439
- Coombs PR, Gell PG (1968) Classification of allergic reactions responsible for clinical hypersensitivity and disease. In: Gell RR (ed) *Clinical aspects of immunology*. Oxford University Press, Oxford, pp 575–596
- Crispe IN (2003) Hepatic T cells and liver tolerance. *Nat Rev Immunol* 3:51–62
- Devillier P (2006) Comparing the new antihistamines: the role of pharmacological parameters. *Clin Exp Allergy* 36:5–7
- Enk AH, Katz SI (1992) Early molecular events in the induction phase of contact sensitivity. *Proc Natl Acad Sci U S A* 89:1398–1402
- Florvaag E, Johansson SG, Oman H, Harboe T, Nopp A (2006) Pholcodine stimulates a dramatic increase of IgE in IgE-sensitized individuals. A pilot study. *Allergy* 61:49–55
- Gerber BO, Zanni MP, Uguccioni M, Loetscher M, Mackay CR, Pichler WJ, Yawalkar N, Baggiolini M, Moser B (1997) Functional expression of the eotaxin receptor CCR3 in T lymphocytes co-localizing with eosinophils. *Curr Biol* 7:836–843
- Gex-Collet C, Helbling A, Pichler WJ (2005) Multiple drug hypersensitivity—proof of multiple drug hypersensitivity by patch and lymphocyte transformation tests. *J Invest Allerg Clin Immunol* 15:293–296
- Girolomoni G, Simon JC, Bergstresser PR, Cruz PD Jr (1990) Freshly isolated spleen dendritic cells and epidermal Langerhans cells undergo similar phenotypic and functional changes during short-term culture. *J Immunol* 145:2820–2826
- Griem P, Wulferink M, Sachs B, Gonzalez JB, Gleichmann E (1998) Allergic and autoimmune reactions to xenobiotics: how do they arise? *Immunol Today* 19:133–141
- Guegan S, Bastuji-Garin S, Poszepczynska-Guigne E, Roujeau JC, Revuz J (2006) Performance of the SCORTEN during the first five days of hospitalization to predict the prognosis of epidermal necrolysis. *J Invest Dermatol* 126:272–276
- Hari Y, Urwyler A, Hurni M, Yawalkar N, Dahinden C, Wendland T, Braathen LR, Matter L, Pichler WJ (1999) Distinct serum cytokine levels in drug- and measles-induced exanthema. *Int Arch Allergy Immunol* 120:225–229
- Hari Y, Frutig-Schnyder K, Hurni M, Yawalkar N, Zanni MP, Schnyder B, Kappeler A, von Greyerz S, Braathen LR, Pichler WJ (2001) T cell involvement in cutaneous drug eruptions. *Clin Exp Allergy* 31:1398–1408
- Hashimoto K, Yasukawa M, Tohyama M (2003) Human herpesvirus 6 and drug allergy. *Curr Opin Allergy Clin Immunol* 3:255–260
- Huilette BC, Ryan CA, Gildea LA, Gerberick GF (2005) Relationship of CD86 surface marker expression and cytotoxicity on dendritic cells exposed to chemical allergen. *Toxicol Appl Pharmacol* 209:159–166
- Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, Lin YL, Lan JL, Yang LC, Hong HS, Chen MJ, Lai PC, Wu MS, Chu CY, Wang KH, Chen CH, Fann CS, Wu JY, Chen YT (2005) HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci USA* 102:4134–4139
- Janmohamed A, Dolphin CT, Phillips IR, Shephard EA (2001) Quantification and cellular localization of expression in human skin of genes encoding flavin-containing monooxygenases and cytochromes P450. *Biochem Pharmacol* 62:777–786
- Keller M, Spanou Z, Schaerli P, Britschgi M, Yawalkar N, Seitz M, Villiger PM, Pichler WJ (2005) T cell-regulated neutrophilic inflammation in autoinflammatory diseases. *J Immunol* 175:7678–7686
- Kimber I, Cumberbatch M (1992) Dendritic cells and cutaneous immune responses to chemical allergens. *Toxicol Appl Pharmacol* 117:137–146
- Knowles SR, Shapiro LE, Shear NH (1999) Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. *Drug Saf* 21:489–501

- Knowles SR, Uetrecht J, Shear NH (2000) Idiosyncratic drug reactions: the reactive metabolite syndromes. *Lancet* 356:1587–1591
- Kuechler PC, Britschgi M, Schmid S, Hari Y, Grabscheid B, Pichler WJ (2004) Cytotoxic mechanisms in different forms of T-cell-mediated drug allergies. *Allergy* 59:613–622
- Landsteiner K, Jacobs J (1935) Studies on the sensitization of animals with simple chemical compounds. *JExper Med* 61: 643–656
- Lazarou J, Pomeranz BH, Corey PN (1998) Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 279:1200–1205
- Lipner GM, Arndt KA, Dover JS (2000) Recent therapeutic advances in dermatology. *JAMA* 283:175–177
- Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, Sayer D, Castley A, Mamotte C, Maxwell D, James I, Christiansen FT (2002) Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet* 359:727–732
- Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, Jagel-Guedes E, Rugina S, Kozyrev O, Cid JF, Hay P, Nolan D, Hughes S, Hughes A, Ryan S, Fitch N, Thorborn D, Benbow A (2008) HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl JMed* 358:568–579
- Mockenhaupt M (2007) Epidemiology and causes of severe cutaneous adverse reactions to drugs. In: Pichler WJ(ed) *Drug hypersensitivity*. Karger, Basel
- Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavinck JN, Sidoroff A, Schneck J, Roujeau JC, Flahault A (2008) Stevens–Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. *JInvest Dermatol* 128:35–44
- Naisbitt DJ, Gordon SF, Pirmohamed M, Park BK (2000) Immunological principles of adverse drug reactions: the initiation and propagation of immune responses elicited by drug treatment. *Drug Saf* 23:483–507
- Naisbitt DJ, Gordon SF, Pirmohamed M, Burkhart C, Cribb AE, Pichler WJ, Park BK (2001) Antigenicity and immunogenicity of sulphamethoxazole: demonstration of metabolism-dependent haptentation and T-cell proliferation in vivo. *Br JPharmacol* 133:295–305
- Naisbitt DJ, Farrell J, Wong G, Depta JP, Dodd CC, Hopkins JE, Gibney CA, Chadwick DW, Pichler WJ, Pirmohamed M, Park BK (2003) Characterization of drug-specific T cells in lamotrigine hypersensitivity. *JAllergy Clin Immunol* 111:1393–1403
- Nassif A, Bensussan A, Dorothee G, Mami-Chouaib F, Bachot N, Bagot M, Bousmell L, Roujeau JC (2002) Drug specific cytotoxic T-cells in the skin lesions of a patient with toxic epidermal necrolysis. *JInvest Dermatol* 118:728–733
- Nassif A, Bensussan A, Bousmell L, Deniaud A, Moslehi H, Wolkenstein P, Bagot M, Roujeau JC (2004) Toxic epidermal necrolysis: effector cells are drug-specific cytotoxic T cells. *JAllergy Clin Immunol* 114:1209–1215
- Neisius U, Brand P, Plochmann S, Saloga J, Knop J, Becker D (1999) Detection of increased tyrosine phosphorylation in murine Langerhans cells after stimulation with contact sensitizers. *Arch Dermatol Res* 291:22–27
- Neukomm CB, Yawalkar N, Helbling A, Pichler WJ (2001) T-cell reactions to drugs in distinct clinical manifestations of drug allergy. *JInvestig Allergol Clin Immunol* 11:275–284
- Peyriere H, Dereure O, Breton H, Demoly P, Cociglio M, Blayac JP, Hillaire-Buys D (2006) Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol* 155:422–428
- Pichler WJ (2002) Pharmacological interaction of drugs with antigen-specific immune receptors: the p-i concept. *Curr Opin Allergy Clin Immunol* 2:301–305
- Pichler WJ (2003) Delayed drug hypersensitivity reactions. *Ann Intern Med* 139:683–693
- Pichler WJ (2005) Direct T-cell stimulations by drugs–bypassing the innate immune system. *Toxicology* 209:95–100
- Pichler WJ (2007) Drug Hypersensitivity reactions: classification and relationship to T-cell activation. In: Pichler WJ (ed) *Drug hypersensitivity*. Karger, Basel, pp 168–189

- Pichler WJ, Campi P (2007) Adverse side effects to biological agents. In: Pichler WJ (ed) *Drug hypersensitivity*. Karger, Basel, pp 151–165
- Posadas SJ, Pichler WJ (2007) Delayed drug hypersensitivity reactions – new concepts. *Clin Exp Allergy* 37:989–999
- Rawlins M, Thompson W (1991) Mechanisms of adverse drug reactions. In: Davies D (ed) *Textbook of adverse drug reactions*. Oxford University Press, New York, pp 18–45
- Reilly TP, Lash LH, Doll MA, Hein DW, Woster PM, Svensson CK (2000) A role for bioactivation and covalent binding within epidermal keratinocytes in sulfonamide-induced cutaneous drug reactions. *J Invest Dermatol* 114:1164–1173
- Roychowdhury S, Svensson CK (2005) Mechanisms of drug-induced delayed-type hypersensitivity reactions in the skin. *Aaps J* 7:E834–E846
- Sanderson JP, Naibitt DJ, Farrell J, Ashby CA, Tucker MJ, Rieder MJ, Pirmohamed M, Clarke SE, Park BK (2007) Sulfamethoxazole and its metabolite nitroso sulfamethoxazole stimulate dendritic cell costimulatory signaling. *J Immunol* 178:5533–5542
- Schmid DA, Campi P, Pichler WJ (2006a) Hypersensitivity reactions to quinolones. *Curr Pharm Des* 12:3313–3326
- Schmid DA, Depta JP, Luthi M, Pichler WJ (2006b) Transfection of drug-specific T-cell receptors into hybridoma cells: tools to monitor drug interaction with T-cell receptors and evaluate cross-reactivity to related compounds. *Mol Pharmacol* 70:356–365
- Schnyder B, Mauri-Hellweg D, Zanni M, Bettens F, Pichler WJ (1997) Direct, MHC-dependent presentation of the drug sulfamethoxazole to human alphabeta T cell clones. *J Clin Invest* 100:136–141
- Schnyder B, Frutig K, Mauri-Hellweg D, Limat A, Yawalkar N, Pichler WJ (1998) T-cell-mediated cytotoxicity against keratinocytes in sulfamethoxazol-induced skin reaction. *Clin Exp Allergy* 28:1412–1417
- Shiohara T, Takahashi R, Kano Y (2007) Drug induced hypersensitivity syndrome and viral infections. In: Pichler WJ(ed) *Drug hypersensitivity*. Karger, Basel, pp 251–266
- Sidoroff A, Halevy S, Bavinc JN, Vaillant L, Roujeau JC (2001) Acute generalized exanthematous pustulosis (AGEP)–a clinical reaction pattern. *J Cutan Pathol* 28:113–119
- Spanou Z, Keller M, Britschgi M, Yawalkar N, Fehr T, Neuweiler J, Gugger M, Mohaupt M, Pichler WJ (2006) Involvement of drug-specific T cells in acute drug-induced interstitial nephritis. *J Am Soc Nephrol* 17:2919–2927
- Swanson HI (2004) Cytochrome P450 expression in human keratinocytes: an aryl hydrocarbon receptor perspective. *Chem Biol Interact* 149:69–79
- Uetrecht J (2001) Prediction of a new drug's potential to cause idiosyncratic reactions. *Curr Opin Drug Discov Devel* 4:55–59
- Verrier AC, Schmitt D, Staquet MJ (1999) Fragrance and contact allergens in vitro modulate the HLA-DR and E-cadherin expression on human epidermal Langerhans cells. *Int Arch Allergy Immunol* 120:56–62
- Viard I, Wehrli P, Bullani R, Schneider P, Holler N, Salomon D, Hunziker T, Saurat JH, Tschopp J, French LE (1998) Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. *Science* 282:490–493
- Wu LC, Tuot DS, Lyons DS, Garcia KC, Davis MM (2002) Two-step binding mechanism for T-cell receptor recognition of peptide MHC. *Nature* 418:552–556
- Yang CW, Hung SI, Juo CG, Lin YP, Fang WH, Lu IH, Chen ST, Chen YT (2007) HLA-B*1502-bound peptides: implications for the pathogenesis of carbamazepine-induced Stevens–Johnson syndrome. *J Allergy Clin Immunol* 120:870–877
- Yawalkar N, Egli F, Hari Y, Nievergelt H, Braathen LR, Pichler WJ (2000) Infiltration of cytotoxic T cells in drug-induced cutaneous eruptions. *Clin Exp Allergy* 30:847–855
- Zanni MP, von Greysz S, Schnyder B, Brander KA, Frutig K, Hari Y, Valitutti S, Pichler WJ (1998) HLA-restricted, processing- and metabolism-independent pathway of drug recognition by human alpha beta T lymphocytes. *J Clin Invest* 102:1591–1598