Cross-Reactivity With Drugs at the T Cell Level

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Abstract and Introduction

Abstract

Purpose of review: Cross-reactivity with drugs is an important clinical problem in drug hypersensitivity. Once a patient is labeled 'drug-allergic' all drugs of the same class are withheld and future therapeutic interventions are limited. Here we review cross-reactivity with drugs at the T cell level.

Recent findings: Analysis of T cell recognition of various classes of drugs (-lactam antibiotics, sulfonamides, local anesthetics) using T cell clones suggests that at the T cell level the whole structure, in particular the core and to a lesser degree side chains, are recognized.

Summary: It is necessary to differentiate cross-reactivity mediated by T cells and antibodies as only the latter seem to recognize side chains exclusively.

Introduction

Adverse reactions to drugs are a major problem in pharmacotherapy. Most of them can be related to the pharmacological/toxicological activity of the drug, but about 15-20% of all side effects are thought to be immune mediated.[1] Drug allergic reactions in humans[2] can be classified as immediate reactions such as anaphylaxis, urticaria, angioedema, with a predominant involvement of drug-specific immunoglobulin E antibodies.[3] Other clinical manifestations of drug allergy, like various forms of exanthema, interstitial lung disease, drug-induced hepatitis, and nephritis appear delayed and are thought to involve drug-specific T cells and the recruitment of various types of effector cells.[3-5*] A further subgroup of drug-allergic side effects affects mainly blood cells leading to thrombocytopenia, anaemia, leukopenia and is mainly due to immunoglobulin G or M antibody mediated mechanisms.[3]

Cross-reactivity is an important clinical problem in drug hypersensitivity. It is defined as the finding that a structurally similar drug, albeit previously not used, may elicit allergic side effects due to a preexisting immune response to a structurally related drug, to which the

individual was previously exposed and sensitized. Cross-reactivity is normally assumed if the symptoms appear more rapidly, and if a
previous drug-allergy is known, but in theory, a previous exposure without obvious clinical symptoms may have been sufficient. Symptoms
may be due to cross-reactivity with antibodies (immunoglobulins E and G) or T cells. While cross-reactivity with immunoglobulin E
antibodies was extensively discussed in previous reports,[6, 7] particularly with regard to penicillins and cephalosporins, the
cross-reactivity with T cells was less well-documented.[8-10]

Many types of drugs belong to certain chemical classes such as corticosteroids, -lactam antibiotics or quinolones, which have great
structural similarity. Moreover, many newly released drugs are derivatives of well-known, previously useful drugs. This makes it plausible
that cross-reactions exist within certain classes of drugs and cause a substantial clinical problem. For example, if a patient has a
hypersensitivity reaction to the antibacterial drug sulfamethoxazole, at present the whole group of 'sulfonamides' - many not belonging to
antibacterials - are recommended for avoidance in further treatments. This can dramatically limit the therapeutic repertoire. Therefore, it is
of great clinical interest to understand allergic cross-reactions to drugs to better advise the drug-allergic patient. Moreover, for the industry
and regulatory agencies it is important to exclude or predict the allergenic potential based on cross-reactivity of a new drug and to give
correct recommendations. In this short review we will focus on cross-reactivity by T cells to some drug groups and try to outline certain
differences between T cell and antibody mediated cross-reactivity.

T Cell Reactions to Drugs

Drugs are recognized by T cells. Depending on the chemical reactivity of the drug two main mechanisms have been proposed.

Hapten and Prohapten Concept

Drugs are small-molecular-weight compounds often with a molecular mass of less than 1 kDa. Therefore, they are considered to be per
se only poorly immunogenic. However, according to the 'hapten-carrier-model',[11] they can, after covalent binding to serum or cellular
proteins and subsequent uptake and processing, be presented by major histocompatibility complex (MHC) class I or II molecules to
reactive T cells.[2, 8, 9, 12] This pathway of drug presentation requires chemically reactive compounds with the ability to covalently modify
side chains of amino acids and some can even directly modify the peptide embedded in the MHC-molecule. Thus, the chemical reactivity

of the drug defines the allergenic potential.[12] This is the case for drugs that are per se reactive such as -lactam antibiotics.

Many drugs are not chemically reactive and thus lack these hapten-like features. Drug metabolism could lead to reactive metabolites that
are highly reactive and as a consequence, behave like haptens.[13-17] A typical example for such a prohapten is the reactive metabolite of
sulfamethoxazole. In this case, a nitroso-derivative is generated after cytochrome P450 dependent oxidation. Due to its gained reactivity it
can covalently modify SH groups of proteins.[18-20]

The Pharmacological Interaction of Drugs with Immune Receptors Concept-p-i Concept

Chemically inert drugs can, in spite of their small size and in contrast to previous dogmas, also elicit a T cell mediated immune
response,[21-23] as they might stimulate the T cell receptor (TCR) directly, although MHC interaction is still required: The ensuing immune
response is solely determined by the structure of the drug that is recognized by T cells in the context of MHC molecules but not by its
chemical reactivity.[24**] The concept postulates interaction of the drug with the TCR or MHC peptide complex in a way similar to drug
binding to pharmacologically relevant receptors (hence the 'p-i concept', pharmacological interaction of drugs with immune receptors).
This interaction is probably of low affinity, with a binding affinity (Kd) in the millimolar to micromolar range, as drug binding is easily
abolished by simple washing. It is still sufficient, however, to trigger T cells resulting in proliferative response, cytokine secretion, as well
as cytotoxicity.[21, 22] Neither covalent binding of the drug, nor internalization and processing or prior drug metabolism is required for the
stimulatory capacity of the drug [21, 22, 25]

In addition, it is possible that the drug has its primary affinity for the TCR and not for the MHC molecule that serves only as a stabilizing
scaffold. To fully activate T cells, antigen-presenting cells are needed.[22] However, the fact, (1) that up to 30% of drug-specific T cell clones
(TCCs) recognize the drug in a human leukocyte antigen-dependent but human leukocyte antigen-allele unrestricted way[23, 26] and (2)
that the recognition of the drug is independent of the peptide associated with the MHC molecule,[27*], lead to the assumption that the TCR
is the primary binding structure for the drug and not the MHC molecule, which only completes activation. This is in contrast to drugs that act
as haptens and are presented to T cells via MHC molecules.

Cross-Reactivity

Analysis of peptide-specific TCCs indicated that T cells might differ in the degree of specificity versus degeneracy of peptide
recognition.[28, 29] To explain this observation, there are two structural explanations as to why one TCR can recognize different, not related,
peptides: (1) These different MHC peptide complexes may have the same surfaces in terms of volume, charge and hydrophobicity allowing
engagement of the TCR in a similar way. (2) There may be a certain flexibility of the CDR3 loops that contributes to the TCR recognition of
different shapes of MHC peptide surfaces.[30-32**] This concept is important for the understanding of cross-reactivity with drugs at the T cell
level as the whole three-dimensional structure of the drug might be necessary for activation of the TCR as discussed below.

Sulfonamides

The SO2-NHX structure within a drug makes it a 'sulfonamide', which is present in many different drugs. Some sulfonamides are
anti-infectives and are used in combination with pyrimethamin as an antimalarial/antiprotozoal drug (together with sulfadoxin or
sulfadiazin), as an anti-infective drug in eye drops (sulfacetamid) and in combination with trimethoprim (sulfamethoxazole in
cotrimoxazole). Other drugs also contain a sulfonamide structure (celecoxib, furosemide, glibenclamide), but not the sulfanilamide
structure as in anti-infectives and have no anti-infective capacity.

To analyze the cross-reactivity within different sulfonamide derivatives, TCCs obtained from patients with sulfamethoxazole allergy were
generated and analyzed.[33] The TCCs showed a quite high diversity in their ability to respond to the different sulfonamide derivatives. On
the one hand, one half of the clones was highly specific and could be stimulated by sulfamethoxazole only. On the other hand, several
clones showed a broad cross-reactivity as they were responding to up to nine different compounds sharing only minute structural similarity
of the side chain.[33] But all cross-reactive compounds had the sulfanilamide-core structure in common. Quite interestingly, some
compounds have never reached the market and were not used or were only used in veterinary medicine, but still were able to elicit a
strong immune response in some TCCs.

The high heterogeneity of the observed cross-reactivity pattern in addition to the different V gene usage of the tested clones indicates that,
although oligoclonal outgrowth of drug-specific T cells has been described,[10, 34, 35] the T cell mediated response to sulfamethoxazole is
mainly polyclonal and heterogeneous.[33] This implies that each of the TCCs generated to sulfamethoxazole recognizes the drug in a

different way. Therefore, it seems likely that the per se non-reactive drug sulfamethoxazole has either the possibility to interact with MHC peptide complexes or TCR in several ways, generating distinct antigenic determinants or the small compound fits into various TCRs. Both options suggest that already during the induction phase of the allergy several quite distinct sulfamethoxazole-reactive T cells were stimulated.[28]

Furthermore, more than 300 sulfamethoxazole reactive TCCs generated from three sulfamethoxazole hypersensitivity patients were tested for cross reactivity with celecoxib. None of these revealed cross-reactivity with the sulfonamide celecoxib (Jan P.H. Depta and W.J. Pichler, personal observation). Another sulfonamide, furosemide, was not cross-reactive with sulfamethoxazole reactive T cells either.[21, 36] Both celecoxib and furosemide do not share the sulfanilamide core structure of sulfamethoxazole (Fig. 1). Thus, cross-reactivity by T cells is probably not determined by the presence of an SO_2-NHX-structure within the molecule, but requires a larger common denominator, such as the sulfanilamide-structure or similarity in the whole structure.

Figure 1. Cross-reactivity: misleading nomenclature

The chemical property defining the class of drugs is highlighted in grey. (a) Sulfonamides with sulfanilamide-structure with proven cross-reactivity at the T cell level. (b) -lactams with penicilloyl structure showing cross-reactivity at the T cell level. (c) Sulfonamides, which lack the sulfanilamide structure, are not cross-reactive with sulfonamides in (a). Cross-reactivity within (c) not analyzed in detail. (d) -lactams (cephalosporins) that are not cross-reactive with (b) (penicillins). Cross-reactivity of T cells within (d) is likely but not yet analyzed in detail. For T cells neither a sulfonamide-structure (a,c) nor the presence of a -lactam-structure (b,d) defines putative cross-reactivity. Most T cells appear to recognize more global structures.

Local Anesthetics

Lidocaine allergy of the delayed type is not uncommon, if used in a topical ointment. These patients develop a contact dermatitis to the local anesthetic, but might also react with subcutaneous applied local anesthetic with swelling, generalized urticaria and even erythema exsudativum multiforme-like reactions.[34] The analysis of 55 TCCs isolated from two different lidocaine-allergic patients revealed a

consistent cross-reactivity between lidocaine and mepivacaine.[37] Sixteen chemically related local anesthetics (including ester local

anesthetics, OH- and desalkylated metabolites) were used to identify structural requirements for T cell recognition. Each of the four clones

examined in detail was uniquely sensitive to changes in the structure of the local anesthetic. The obtained data suggest that two contact

residues within the amine side chain are required to interact with the TCR to induce T cell proliferation. Compounds with only one residue

(primary amines) are not capable of inducing cell proliferation. None of the ester compounds stimulated a T cell reaction.[37] The data

confirm findings from previous studies[38] that ester and amide local anesthetics do not cross-react in vivo and in vitro. Here again, T cells

appear to recognize the overall structure of the local anesthetics. Side chains or particular chemical properties are not sufficient for

activation of or cross-reaction with T cells. If cross-reactions appear, the overall structure of the drug is involved and has to be similar.

Beta-Lactam Antibiotics

The specific T cell response to a covalently binding drug like penicillin G and amoxicillin was analyzed by Padovan et al.[9] and

Mauri-Hellweg et al..[10] Again, the reactivity of penicillin G-specific T cell lines and clones isolated from different donors was evaluated

versus a panel of six different -lactam antibiotics. Two types of -lactam reactivity of T cells could be delineated: One group of patients

showed a rather restricted specificity, as T cell lines generated from such donors proliferated only to penicillin G, but not to other -lactam

antibiotics including cephalosporins, even if the side chain was identical (cephadroxil) (Fig. 1). This indicates that T cells recognize the

penicilloyl structure together with the side chain. The second group comprised patients with more broadly reactive T cells. They were

stimulated by both penicillin as well as by related penicillins like amoxicillin and ampicillin. Reactivity to amoxicillin and ampicillin always

occurred together, which is in agreement with the close similarity of these molecules, which differ only in an hydroxyl group at the side

chain in the para-position (Fig. 1). None of the T cell lines or TCCs reacted with any of the tested cephalosporins, even if the side chain

was identical (cephadroxil) to amoxicillin and the TCCs recognized amoxicillin. These findings imply that for T cells the penicilloyl core

structure is of general importance for recognition and that some TCCs react with the penicilloyl and side chain structure, while others react

mainly with the penicilloyl core structure, tolerating quite large modifications in the side chain.[10, 39] Thus, comparing sulfonamide, local

anesthetic and -lactam reactivity a common motif emerges: T cells tend to recognize the whole molecule, and not part of it; some T cells

recognize mainly the core structure, and possibly part of the side chain, but exclusive side chain reactivity seems to be rare. This would be in contrast to antibody-mediated reactions, as immunoglobulin E antibodies might react quite exclusively with the side chain, while the core structure might be altered (Fig. 2).[40] This concept implies that one should strictly differ between T cell mediated and antibody mediated reactions when advising a patient with regard to cross-reactivity. However, this concept is largely based on in-vitro studies and further in-vivo analysis would be required to prove this hypothesis.

Figure 2. Differences in recognition of drugs by B and T cell receptors

The core-structure of the drug sulfamethoxazole is highlighted in grey. The side-chain is given by a dotted line. The strength of the T or B cell receptor interaction is shown by the size of arrows. (a) TCRs interact with the whole structure, some TCRs tolerate changes in the side-chain. (b) B cell receptors recognize only drug-protein conjugates and some may even interact preferentially with the side chain of a drug. Changes in the core-structure might be tolerated.

Cross-Reactivity In Vivo

Based on the clonal analysis of T cell reactions to drugs, it is quite clear that in most instances the T cell reaction to a drug is polyclonal and also comprises TCCs able to react with a structurally related compound. Clinical reactivity does not always appear, however; and different factors might account for this (Fig. 3).

Figure 3. Relevance of structurally related drugs in clinical manifestation of cross-reactivity

Schematic representation of a pool of TCCs sensitized to drug A (gray shadow). T cells partially gray and densely dotted are specific for drug A and cross-reactive to drug A1, whereas lightly dotted T cells are cross-reactive to drug A2. The structure of drug A1 is very similar to A, while the structure of drug A2 is less related to drug A. If the patient would be sensitized to drug A, administration of drug A1 could lead to a clinically relevant cross-reaction, as it is more probable that TCCs exist that are cross-reactive to the structurally similar drug A1. Administration of drug A2 could be tolerated by the patient as only few

TCCs react, which are not sufficient to elicit clinical symptoms. If the immune response to A is strong and thus many TCCs
are generated, the likelihood of cross-reactivity is also greater tha n if the immune response is weak (low number of TCCs
stimulated).

The Structural Relationship to the Sensitizing Compound

A large part of the T cell reaction seems to be exclusively directed to the eliciting compound. Cross-reactivity was often not detectable at the
whole T cell level (stimulation of peripheral blood lymphocytes), but only after cloning, where less than 60% of the TCCs were
cross-reactive. Only part of the TCCs have a cross-reactive potential, even if the cross-reactivity might be directed to different compounds,
often only less than 5% of the TCCs are cross-reactive with a certain single related compound (Fig. 3). This cross-reactive potential might
differ in different individuals. Nevertheless, it is logical to assume that the closer the structures are, the more likely cross-reactivity might
occur.

The Strength of the Immune Reaction

The stronger the immune reaction is, the more likely a reaction might become clinically relevant: if the first immune reaction was already
scarcely causing symptoms, the restimulation of fewer TCCs by the second compound will not be sufficient to cause any symptoms. In
contrast, if the first immune reaction activated a wide pool of TCCs, the chances that a related drug also activates more TCCs is high.

Co-Factors

Sensitization to drugs might often not be clinically apparent. Only if co-factors like an underlying generalized viral infection or an ongoing
generalized autoimmune disease are present then the clinical symptoms might appear. If this co-factor is missing during the second
exposure, no symptoms might arise.

Multiple Drug Hypersensitivities

Multiple drug hypersensitivities are not so rare and are well documented by history, patch test or lymphocyte transformation tests and are
thought to occur in about 10% of well-documented patients with drug allergy.[41] Thus, some cases of presumed cross-reactivity might
actually represent a double sensitization and are not due to cross-reactivity.

Predicting Cross-Reactivity

Many newly developed drugs belong to a class of compounds with some allergenic potential. It would be of great value to predict the allergenic potential of a drug and its level of cross-reactivity with other compounds. For this purpose it is favorable to develop an assay that addresses cross-reactivity on the level of T cell responses.[42] To address this issue we transfected human drug-specific TCRs into mouse TCR negative T cell hybridomas.[43*, 44] These transfectants (generated to drugs such as fluoroquinolones, sulfonamides and radio contrast media) are stable and suitable tools for in-depth analysis of TCR-drug interactions because they are easy to handle and unlimited in growth compared with primary human TCCs. Furthermore, a battery of drug-specific TCR transfected hybridomas would give the possibility to test for putative cross-reactions. For example, sulfamethoxazole-specific TCRs can be used for analysis of cross-reactivity to non-anti-infective sulfonamides such as cyclooxygenase-2 selective drugs or diuretics. This would be of great advantage for patients, such as those labeled 'sulfonamide-allergic', which gives the erroneous impression that all sulfonamide-containing drugs are contra-indicated in such individuals.

Conclusion

Recent studies revealed that one has to distinguish between B and T cell mediated drug-cross-reactions. Whereas B cells can sometimes react exclusively with the side chain, T cells tend to recognize the global structure, which includes the core structure. These findings demonstrate that the classification of drug by a small chemical property such as SO_2-NHX can be misleading in the context of T cell mediated cross-reaction. In the development of a drug these features should be better considered and be included in the licensing. In addition, the physicians should become more aware of this problem and obtain tests to rule out cross-reactivity in a sensitized individual.

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