

Hypersensitivity Reactions to Quinolones

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Abstract: Quinolones are one of the most important classes of antimicrobial agents discovered in the recent years and one of the most widely used classes of antibiotics in clinical medicine. Their broad spectrum of activity and pharmacokinetic properties make them ideal agents for treating a variety of infections. Their clinical importance is further demonstrated by their activity against a wide range of diseases of public health importance such as anthrax, tuberculosis, bacterial pneumonia, and sexually transmitted diseases.

Like other antibiotics, quinolones can cause various, sometimes dangerous hypersensitivity reactions. The underlying pathomechanisms are only poorly understood. Some are thought to be partly non-immune mediated reactions, others are considered to be IgE- or T cell-mediated reactions. This review gives an insight into the different immunological mechanisms leading to the diverse symptoms of quinolone-induced hypersensitivity reactions, with special emphasis on the role of T cells in such reactions.

Key Words: Quinolones, Hypersensitivity, IgE-mediated, T cell-mediated, Crossreactivity.

INTRODUCTION

Quinolones are broad spectrum synthetic antibiotics which were introduced in the sixties with the launch of nalidixic acid, discovered as a by-product of anti-malaria research [1]. Eversince, it has been broadly used for the treatment of urinary tract infections but its narrow spectrum of activity, the development of resistance and the low serum concentration have restricted its use [2]. Nevertheless, it became the chemists' lead compound for further structural modifications to create new compounds in order to abolish its weaknesses. The addition, in the late eighties, of a fluoride side chain to the original quinolone antibiotic compounds yielded a new class of drugs, the fluoroquinolones, which showed a broader antimicrobial spectrum and improved pharmacokinetic properties [3]. Shortly thereafter, ciprofloxacin (CPFX), the prototypical agent of the original fluoroquinolones, became the most frequently used antibiotic throughout the world [4]. To date, more than 8000 analogues have established themselves as clinical drugs and more are to be introduced [5]. The first fluoroquinolones were widely used because they were the only orally administered agents available for the treatment of serious infections caused by gram-negative organisms, including *Pseudomonas* species. Moreover, this new generation of drugs has not only an activity against gram-positive and gram-negative bacteria, but also a potent coverage of atypical pathogens (activity against anaerobic bacteria, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*). Therefore, the fluoroquinolones offer considerable potential in the treatment of a wide variety of infections, from urinary tract infections to skin and soft

tissue infections, as well as for sexually transmitted diseases, respiratory tract infections, gastrointestinal diseases and bone infections [6].

QUINOLONES: MODE OF ACTION AND STRUCTURE

Quinolones target bacterial type II topoisomerases: DNA gyrase in gram-negative bacteria and DNA topoisomerase IV in gram-positive bacteria, which both are required for cell growth and division [7-9]. These enzymes introduce negative supercoils into DNA and separate interlocked DNA molecules [10], enabling the long bacterial DNA to fit into the cell. The molecular mechanism of inhibition of DNA gyrase by quinolones has been extensively investigated [11-13]. They antagonise the enzymatic activities, interfering with DNA replication, segregation of bacterial chromosomes, transcription, and other cellular processes as well as damaging DNA [14]. Gemifloxacin (GMFX), for instance, one of the newest fluoroquinolone put on the market, targets both topoisomerase IV and DNA gyrase simultaneously. This dual targeting makes it a very potent agent against *H. influenza* and *S. pneumoniae*, two major bacterial strains which show resistance to quinolones. In addition, it appears that some newer fluoroquinolones, like sparfloxacin, tosufloxacin and lomefloxacin, damage the bacterial cell membrane which leads to loss of cell content [5].

The quinolones share a common core consisting of a nitrogen-containing, eight-membered heterocyclic aromatic ring with a ketone group at position 4 and a carboxylic group at position 3 (Fig. (1)). The pyridine ring contains one nitrogen atom at position one and defines the quinoline derivatives. The cinnoline, naphthyridine and pyridopyrimidine derivatives differ in the addition of substituents at position 2, 8 or at positions 6 and 8, respectively. The fluoroquinolones have a fluorine substituent at position 6.

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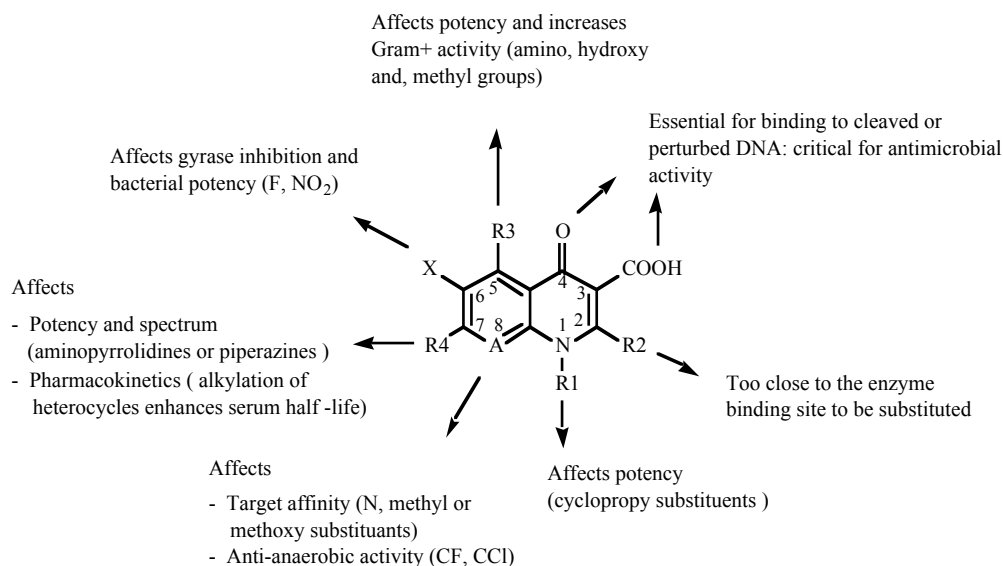


Fig. (1). Basic quinolone structure and summary of the antibacterial structure-activity relationship. The most effective additions are shown in brackets, details see text.

QUINOLONES: STRUCTURE-ACTIVITY RELATIONSHIP

- Pharmacological Activity

The structural features of quinolones do not only govern their antibacterial efficacy, but also influence their side-effect profile. Great improvements in the potency, spectrum and *in vivo* efficacy were achieved as a result of synthetic modifications. An excellent structure-activity relationship exists, which well defines the optimal groups for each position in terms of size, shape, and electronic properties (Fig. (1)). The features which most remarkably enhance antimicrobial effectiveness are: a halogen (F or Cl) at the 8-position, which improves oral absorption and activity against anaerobes; an alkylated pyrrolidine or piperazine at C₇ (the position directly interacting with DNA gyrase), which increase serum half-life and potency against Gram-positive and Gram-negative bacteria, respectively; and a cyclopropyl group at N₁ and an amino substituent at C₅, both of which improve overall potency [15]. In the same way, the 3-carboxylate and 4-carbonyl groups are essential for antibacterial activity because they mediate binding to the DNA-gyrase complex. The addition of a fluorine at C₆ (hence the name fluoroquinolones) causes an increase of up to 100-fold in gyrase inhibition and bacterial potency.

- Immunogenicity of Quinolones

The study of Manfredi *et al.* suggests that the IgE antibodies can only bind to the drug bound to a solid phase if positions C₂ to C₆ of the quinolone are accessible (Fig. (2)) [16]. Indeed, IgE tests were repeatedly negative in cinoxacin-hypersensitive patients, but positive when the sera were tested for the presence of IgE to other quinolones, which bind *via* the side chain at position 7 to the carrier molecule. However, the sera contained specific IgE to cinoxacin, since serum incubated with cinoxacin inhibited the binding of IgE to a pipedimic acid- and rifloxacin-sepharose solid phase.

Since cinoxacin is the only quinolone lacking a side chain at position 7, through which other quinolones bind to the solid phase, it can only bind to the sepharose *via* the carboxyl group at position 3. As the coupling to the spacer happens *via* the side chain at position 7 allows the detection of IgE antibodies, this side chain is probably not an epitope for IgE recognition. On the other hand, the 3-carboxyl group seems to be part of the epitope recognized by IgE.

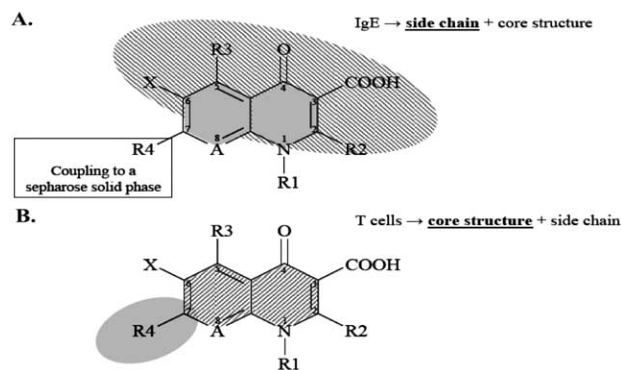


Fig. (2). Hypothetical epitopes recognized by Immunoglobulins E and T cells.

A. Coupling to solid phase *via* the side chain at position 7 allows detection of IgE antibodies, suggesting that this side chain is not an epitope for IgE. No IgE antibodies were detected if the binding to the solid phase was *via* position 3. Therefore, IgE antibodies interact mainly with the side chains at positions 2-6.

B. Quinolone-specific T cells never reacted to quinolones with only small side-chains at position 7. Therefore T cells generated in CPFX hypersensitivity might recognize the drug core structure together with the side-chain at position 7.

Similarly, some CPFX-specific T cells showed a broad crossreactivity, but never reacted to nalidixic acid (cinoxacin was not tested), which has only a small side chain (methyl group) at position 7. This part of the molecule might well be the epitope relevant for T cells recognition (Fig. (2)).

QUINOLONE HYPERSENSITIVITY REACTIONS

In general quinolones have a favorable safety profile, but serious and sometimes even fatal adverse reactions have been described. Severe reactions are very rare, less than one case among 50 000 treatments, and often suggest an underlying immune mechanism [17]. Those adverse events are not

detected by clinical trial programs which only identify such occurrences when occurring at frequencies of 1 per 1000 patients or higher [4].

A notable exception is gemifloxacin (GMFX). GMFX, one of the most potent antimicrobial agents against penicillin-, beta lactam- and glycopeptide-resistant staphylococci, pneumococci and enterococci, was found to cause maculopapular exanthema in about 3.6% of the 6775 patients treated (Fig. (3)). An analysis of the potential risk factors for these reactions revealed that rashes appeared more commonly in women under 40 years of age and in those patients submitted to longer treatment (>7d). A prospective study was per-

		Gemifloxacin (N = 6775)	Pooled comparators (Amoxicillin) (N = 5248)
Prevalence		3.6 %	1.1 %
Median onset		9 days	4 days
Gender	Males	2.4 %	08 %
	Females	4.7 %	1.4 %
Age	< 40 years	6.7 %	1.3 %
	> 40 years	2.5 %	1.1 %
Women > 40 year treated for 10 days	Rash rate	15.3 %	1.9 %

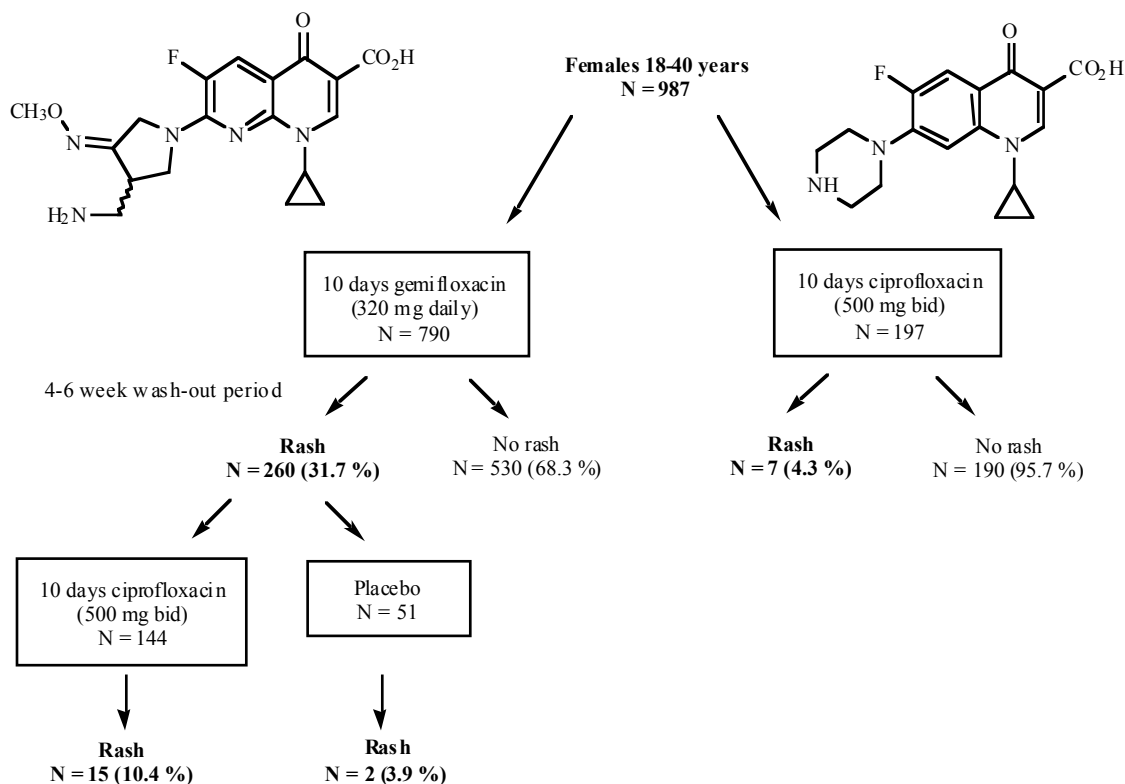


Fig. (3). Gemifloxacin, a new quinolone with potent activity, was evaluated in 987 healthy women aged 18-40 years. The incidence and recurrence of mostly mild rashes after first gemifloxacin intake and later rechallenge with ciprofloxacin is shown (details see reference [189]).

formed in 987 healthy women aged 18-40: 790 (80%) were treated with GMFX while the remaining 197 (20%) received CPFX for 10 days. An exanthema appeared in 260/790 (31.7%) GMFX-treated women but only in 7/197 (4.3%) CPFX-treated women, with a clear peak on day 8-10 after treatment onset. In the majority of the cases, the pathology was consistent with mild exanthematous eruptions, with biopsies revealing a moderate perivascular T cell infiltration in the dermis. This study emphasizes the important role of co-factors such as female gender, age and dose (duration of the treatment), in provoking exanthems. How estrogens boost the hypersensitivity reactions is unknown at present. However, the finding below, namely that T cells recognize quinolones, is well compatible with a strict dose-dependence.

Some structural features of quinolones do not only govern their antibacterial efficacy as discussed above, but are also known to be responsible for particular side-effects [18]: (1) halogen substituents at position 8 enhance the potency against gram-positive bacteria but are also related to severe phototoxicity which lead to the withdrawal of several agents (floxacin, Bay 3118, cinafloxacin); (2) temafloxacin, trovafloxacin and tosufloxacin, all having a difluorophenyl substitution at the 1-position, were withdrawn, suspended or associated with warnings because they caused severe, presumably immune-mediated side-effects in selected organs (haemolytic uraemic syndrome, hepatotoxic reactions and nephritis, respectively); (3) a fluoronaphthyridone core nuclear structure with a nitrogen at the 8-position is shared by tosufloxacin and trovafloxacin which caused hepatitis, nephritis and thrombocytopenia. However, more serious reactions, such as the temafloxacin-associated haemolytic-uraemic syndrome [19], and the unpredictable hepatic reactions associated with trovafloxacin [20], do not seem to have any structural relationship.

A medline review of literature since 1966 revealed 384 cases, reported by 166 authors, of unpredictable adverse reaction to quinolones, suggesting an underlying immune mechanism. Because of its high worldwide consumption, CPFX was the compound most frequently implicated with 152 cases, followed by ofloxacin, cinoxacin, nalidixic acid, pefloxacin, norfloxacin (NRFX), lomefloxacin, and piperidimic acid with 50 to 10 cases. Less than 10 cases have been reported for other quinolones.

The clinical presentation of those adverse reactions goes from transient and benign erythema to the severest forms. The most frequently described adverse reactions are of the immediate type, such as urticaria, angiodema and anaphylactic shock. Other presumably immune-mediated reactions are rarer: haemolytic-uremic syndrome [21, 22], haemolytic anaemia [19, 23, 24], thrombocytopenia [24-27], leukopenia [28, 29] or pancytopenia, acute interstitial nephritis [30-34], photosensitization [35-38], acute hepatitis [39-41] and cholestatic jaundice [42-44], Stevens-Johnson syndrome (SJS) [45, 46], toxic epidermal necrolysis (TEN) [45, 47-51], maculopapular exanthema [52, 53], acute pancreatitis [54-56], serum sickness-like disease [57, 58], angioimmunoblastic lymphadenopathy [59, 60], acute generalized exanthematous pustulosis [61, 62] and eosinophilic meningitis [63]. Fatal reactions have been reported with various quinolones (see Table 1).

IMMEDIATE ADVERSE REACTIONS

The adverse reactions to quinolones most frequently described are immediate and occur already within one hour after intake, suggesting a type I, IgE-mediated immune mechanism. Anaphylactic reactions, reported by 16 authors in 167 individuals, include pruritus, urticaria, angioedema

Table 1. Reported Fatal Reactions Induced by Various Quinolones

Drugs	Fatal reactions	References
trovafloxacin	Acute hepatitis	[39]
ciprofloxacin	Toxic epidermal necrolysis	[48, 202, 203]
	Acute interstitial nephritis	[34, 94]
	Pancytopenia	[204]
	Angioimmunoblastic lymphadenopathy evolving to malignant T cell lymphoma	[59]
	Schönlein-Henoch syndrome	[205]
	Fatal shock in an AIDS patient	[206]
temafloxacin	Haemolytic anaemia with kidney deficiency or with ischaemic colitis and disseminated intravascular coagulation	[19]
ofloxacin	Hepatitis	[121]
	Systemic haemorrhagic vasculitis	[207]
nalidixic acid	Haemolytic anaemia	[208]
gatifloxacin	Hepatitis	[122]
levofloxacin	Hepatitis	[123]
piperidimic acid	Toxic epidermal necrolysis	[50]

and shock. Among them, numerous cases were described with CPFX in AIDS patients [64-67]. Anaphylactic shock was experienced by 39 patients. To attain a diagnosis, skin prick and intradermal tests were performed but were often negative or not reliable because the same tests were also positive in some subjects of the control group [64, 68-71]. These false positive results were probably triggered by a direct histamine release by mast cells and basophils induced by quinolones. Indeed, when fluoroquinolones were orally administered at high doses (400 mg/kg) to dogs, the concentration of histamine in plasma was increased and accompanied by systemic erythema [72]. Thus, at least part of immediate reactions might be due to a non-immune mediated hypersensitivity syndrome (pseudo-allergy).

Due to the unreliable skin tests and the absence of a specific immunoassay suitable for the routine detection of IgE antibodies to quinolones, some authors used oral provocation tests as sole base for diagnosis, although challenges with drugs suspected to be responsible for an immediate reaction are considered to be dangerous because of the rapid onset of symptoms and the potentially fatal outcome. Indeed, with quinolones fatal reactions have been reported. Some performed provocation tests gave positive results even when skin tests were negative [70, 71, 73-77].

A formal prove that both, non-immune mediated, pseudoallergic reactions as well as IgE-mediated reactions can occur is based on the study carried out by Manfredi *et al.*. The study evaluated an *in vitro* assay to determine quinolone specific IgE [16]. The authors analysed 55 patients reporting 69 immediate reactions to quinolones, mainly urticaria or angioedema (85%), but also glottis oedema (35%) and shock (13%). In 64 reactions, the patients were taking the quinolone antibiotic only at the appearance of the symptoms. The presence of IgE was demonstrated using a solid phase obtained by coupling the drug to sepharose epoxy-activated 6B through a spacer arm *via* R4, a method described by Baldo and Harle for the detection of IgE antibodies to sulfo-methoxazole, penicillines, cephalosporins and other drugs [78-80]. The specificity of the assay was demonstrated using inhibition tests with quinolones, which inhibited the binding of IgE antibodies to the quinolone solid phase, while structurally unrelated drugs failed to induce an inhibition. Of note, this inhibition was achieved by soluble compounds, suggesting that the parent compound can bind to the specific IgE antibodies but is probably not able to crosslink the cell-bound IgE, and thus does not elicit mast cell degranulation. Serum IgE were detected for at least one quinolone in 30 out of 55 cases 1 to 48 months after the reaction, indicating that a substantial portion of patients with immediate reactions possess circulating, quinolone-specific IgE antibodies.

Moreover, a high degree of crossreactivity among quinolones emerged not only from the clinical history, but also from the *in vitro* test: 80% (24 out of 34) of the patients revealed IgE to more than one quinolone.

NON-IgE-MEDIATED, DELAYED-ADVERSE REACTIONS

In addition to immediate reactions, quinolones are also reported to elicit delayed immune reactions leading to a variety of symptoms such as hepatitis, different forms of exan-

thema, nephritis, serum sickness, blood cell discrasia, acute generalized exanthematous pustulosis, SJS and TEN.

Some of them are elicited by IgG-mediated cytotoxic mechanisms. In blood cell discrasia, the drug is thought to bind to the cell surface, thus turning the cell into a target for anti-drug IgG antibodies, and triggering clearance of the cell from the circulation, predominantly by tissue macrophages in the spleen, which bear Fc ϵ -receptors [81]. Serum sickness is immune complex-mediated: IgG antibodies recognise the circulating drug and the so-formed immune complexes are deposited in small vessels and activate complement and phagocytes [81].

However, many of those delayed hypersensitivity reactions, although clinically distinct, are T cell-mediated. Indeed, the observation of T cell infiltrates in drug-related allergic reactions that affect the skin, liver, and kidney, as well as drug-specific reactions found *in vitro* or indicated by skin tests, strongly suggest a T cell-mediated pathogenesis [82-87]. Some authors report positive patch skin tests [88] or positive lymphocyte transformation tests [89], and the presence of lymphocyte infiltrates in the lesions [41, 45, 76], confirming an involvement of T cells in quinolone-induced delayed adverse reactions as well. However, there are also negative lymphocyte transformation tests reported. A possible explanation might be that some quinolone-specific T cells are not detected in proliferation tests, but might be revealed by cytotoxicity assays. Indeed, Kuechler *et al.* detected drug-specific CD8⁺ TCR $\alpha\beta$ ⁺ T cells in different forms of drug-induced exanthems, which failed to proliferate upon drug presentation by antigen-presenting cells, but were cytotoxic in a drug-dependent way and featured some natural killer T cell-like features [90]. Cells with a similar phenotype were also reported in other severe drug reactions, namely in blister fluid of patients with SJS/TEN [91, 92].

In drug-induced interstitial nephritis, renal biopsies disclose extensive inflammatory infiltrates within the interstitium that are composed of lymphocytes and macrophages, which can produce many cytokines (TGF- β , IL-1, IL-4) [33, 93]. 28 authors have described 46 cases of quinolone-induced acute interstitial nephritis caused by an immune mechanism [34, 94-119].

Various fluoroquinolones have been implicated in cases of acute hepatitis and acute cholestatic jaundice [39, 42, 44, 102, 120-138] with an exceeding rate emerging for trovafloxacin. Because of the severity of the reactions – 152 cases of serious hepatic events, 6 patients needing liver transplants and five deaths – trovafloxacin was suspended in Europe and restricted in the United States in 1999. The association with hypersensitivity reactions (skin rashes) and the presence of eosinophils both in the liver biopsy and in the peripheral blood suggested an immune mechanism [39]. This is in line with the data of Tsutsui *et al.*, who could demonstrate the existence of drug-specific CD4⁺ T cells producing high amounts of IL-5 in patients with drug-induced allergic hepatitis [139].

The involvement of T cells has also been documented in drug-induced acute generalized exanthematous pustulosis by a frequently positive patch test reaction to the incriminated drug [140]. Immunohistochemistry of skin biopsies revealed

a massive cell infiltrate consisting of neutrophils in pustules and IL-8-producing CD4⁺ and CD8⁺ T cells in the dermis and epidermis. Drug-specific T cells could be obtained from the blood as well as from the skin [141].

In immunohistology, drug-induced maculopapular exanthems are characterized by a superficial mononuclear cell infiltrate consisting mainly of CD3⁺ T cells (40 to 70%) with a predominance of CD4⁺ cells [142, 143]. Not only do they show a cytotoxic function, but they also release and induce different cytokines like IFN- γ , IL-5 [144], IL-6, IL-1 β and TNF α [145], and chemokines like eotaxin and RANTES [144].

The immunopathologic pattern of SJS and TEN, the most severe form of drug-induced bullous exanthem, suggests a cellular immune reaction as well. Indeed, the dermal mononuclear infiltrate as well as the content of blister fluid is composed mainly of activated CD8⁺ T lymphocytes with some natural killer-like features and cytotoxic capacity [91, 92, 146].

Since the immune response elicited by one class of drugs or even by a single drug is a relatively rare event, clinically heterogeneous and unpredictable, our understanding of allergies to drugs evolves only slowly. Nevertheless, the above observations strongly suggest a T cell-mediated pathogenesis in numerous delayed adverse reactions. Therefore, T cells do not only recognize small peptide antigens, but they are also involved in immune reactions to small chemicals.

HOW DO T CELLS RECOGNIZE SMALL CHEMICALS/DRUGS LIKE QUINOLONES?

T cells recognize the antigen by their antigen receptors, which are heterodimers of 2 chains designated as either $\alpha\beta$ T cell receptors (the majority of T cells) or $\gamma\delta$ T cell receptors (about 5% of circulating T cells) (Fig. (4)). An enormous variety ($>10^{11}$) of T cell receptors (TCR) can be generated with distinct specificities because of different recombinations of genes coding for TCR and the addition of N-region nucleotide insertions. Each T cell displays thousands of identical T cell receptors, which bind a bimolecular complex displayed at the surface of another cell called an antigen-presenting cell, such as dendritic cells, Langerhans cells in the skin, B cells and macrophages. This complex consists of a fragment of a protein antigen (peptide) bound in the groove of a major histocompatibility complex (MHC) molecule. Two classes of MHC molecules present peptides of different origin and stimulate different T cells. Peptides that are derived from proteins synthesized and degraded in the cytosol are presented by MHC class I molecules and activate CD8⁺ T cells. The reactive CD8⁺ T cells secrete cytokines and are able to kill cells displaying foreign peptides derived from cytosolic pathogens, such as viruses. In contrast, MHC class II molecules present preferentially peptides derived from proteins degraded in endocytic vesicles. These structures interact with CD4⁺ T cells, which activate other immune effector cells by producing different cytokines (for example, macrophages, B cells, and CD8⁺ T cells) [81, 147, 148]. CD4⁺ T cells can also be cytotoxic [149, 150].

The main concept of recognition by B and T cells of small molecular compounds like drugs is based on the hapten

model [151-154]: drugs are compounds of less than 1kDa and are therefore thought not to be recognized *per se* by the immune system; they become immunogenic by covalent binding to a larger protein or peptide [151] (Fig.(4)). This hapten-protein complex is recognized directly by cell-bound or soluble immunoglobulins while T cells recognize it after intracellular processing and presentation on MHC molecules. The immunogenic peptides in the MHC groove can also directly be haptenated without the need of prior processing [155-157]. This concept implies that the hapten, i.e. the drug, is chemically reactive and thereby able to covalently bind to larger proteins or peptides. In the case of β -lactam antibiotics (for instance, penicillin-G) it has been shown unequivocally that the β -lactam ring can spontaneously open under physiological conditions and covalently bind to the ϵ -amino group of lysine residues [158].

Alternatively, if the drug is not intrinsically chemically reactive, it may gain immunogenicity through metabolism into reactive metabolites [154, 159] (Fig. (4)). Sulfamethoxazole (SMX) has been proposed as a typical example of a pro-hapten: SMX can be bioactivated to SMX-hydroxylamine (SMX-NHOH) by a cytochrome P450-dependent pathway and further oxidated to nitroso-SMX (SMX-NO) [159-161]. On one hand, the SMX-NO binds to cellular proteins that are further processed to peptides. The hapten-carrier complexes are then loaded on MHC molecules and presented on the cell surface to T cells. On the other hand, extracellular SMX-NO binds covalently either to serum or membrane proteins or directly to MHC-peptide complexes. Until recently, it was the prevailing concept that all SMX-related drug reactions are directed to reactive metabolites, but not against the inert parental compound itself [162]. However, recent studies in SMX-allergic individuals revealed that 77-96% of the generated drug-specific T cell clones (TCC) were exclusively specific for non-covalently bound SMX [163]. The response of SMX-NO-specific TCC was abrogated when the antioxidant glutathione – known to protect cells from reactive metabolites by conjugation and subsequent dissociation to SMX-NHOH and further to SMX [164] – was present during the covalent modification of APC. Furthermore, in lymphocyte transformation tests, the addition of the antioxidant glutathione to peripheral blood mononuclear cells of SMX-allergic individuals had no effect on the SMX-specific response but enhanced the proliferation to SMX-metabolites, presumably by transforming SMX-NO back to SMX [165]. These data show that in allergic individuals T cells recognize the non-covalently bound parent drug rather than APC covalently modified by reactive metabolites. Thus, this specific recognition of SMX – which is *per se* not able to covalently bind to a protein and is thus no hapten – by T cells takes place outside of the common hapten-carrier concept. For this reason, a third hypothesis has recently been proposed, termed pharmacological interaction of drugs with immune receptors or p-i concept (Fig. (4)) [150]. Chemically inert drugs, unable to bind covalently to peptides or proteins, may still activate certain T cells that happen to bear TCR that can interact with the drug. The medical effect of a drug usually arises through its binding into a pocket of a protein which serves as a receptor on the cell surface or within the cell, or as an enzyme, leading to activation or inhibition of the protein function (e.g. interaction of coxibs like celecoxib

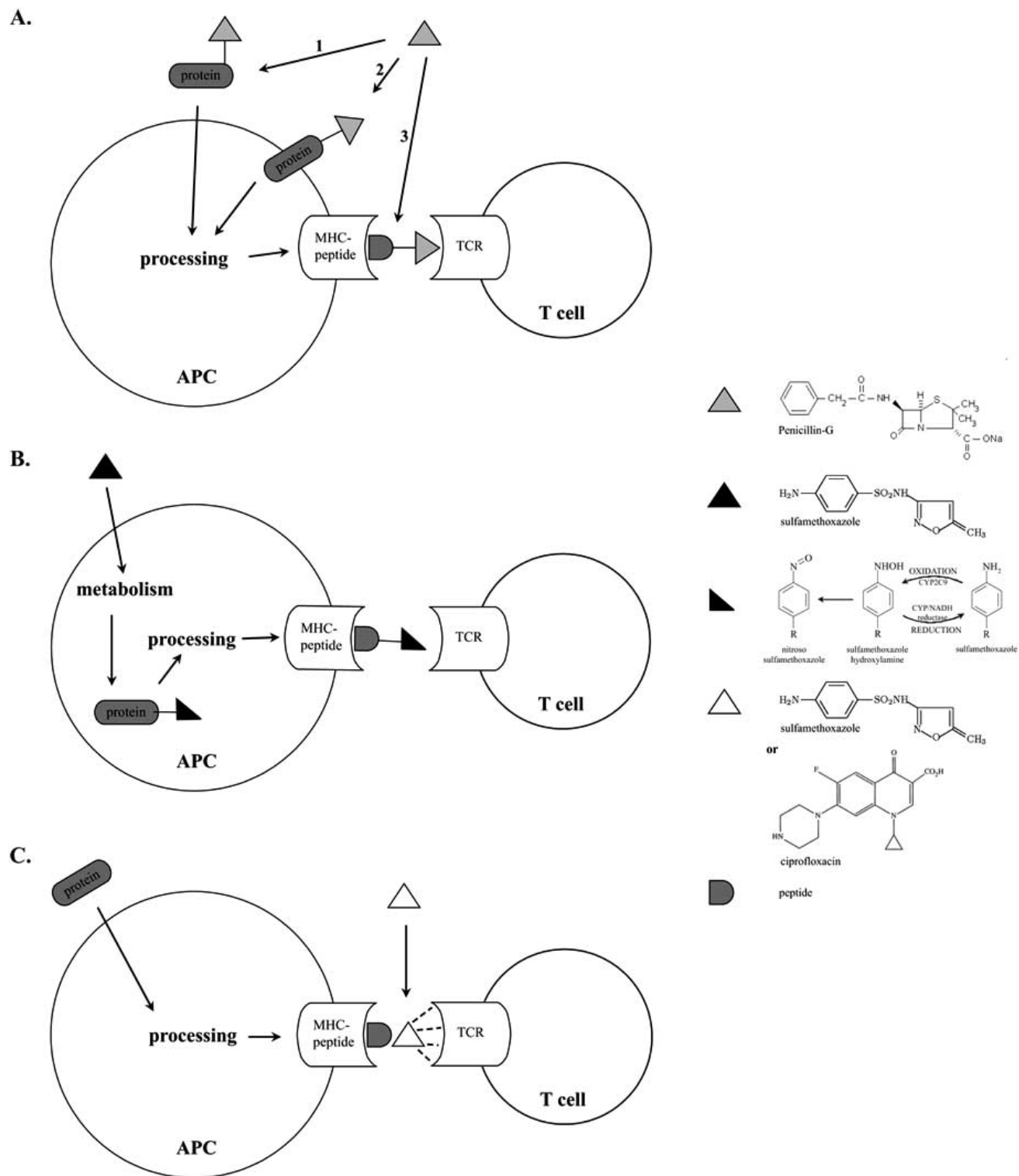


Fig. (4). The hapten, pro-hapten and p-i concepts.

A. Hapten-like drugs (e.g. penicillin) can bind covalently to both soluble (1) or cell-bound (2) proteins as well as directly to the MHC-peptide complex (3), eliciting both humoral and cellular immune responses.

B. Pro-hapten drugs (e.g. sulfamethoxazole) require metabolism to become chemically reactive and then act as hapten (nitroso-sulfamethoxazole).

C. The parent compound, which is chemically not reactive (sulfamethoxazole, quinolones,...), can still directly bind to the MHC-peptide/T cell receptors and stimulate T cells.

into a pocket of the enzyme cyclooxygenase). In the same way, certain drugs may bind the MHC-peptide complex or the TCR. If a drug would be able to fit into the three dimensional structure of the TCR complex, it could trigger a signal cascade within the T cell. If this signal is supplemented by MHC-peptide interaction, rapid T cell receptor-downregulation, cytokine production, proliferation and cytotoxic activities can be observed [141, 166-170]. This model has been extended by *in vitro* studies using T cells and TCC specific for drugs as SMX, lidocaine, mepivacaine, celecoxib, lamotrigine, carbamazepine, p-phenylenediamine, as well as T cells specific for quinolones and iodinated contrast media [168, 171-177, 202].

In particular, the p-i concept offers the only convincing explanation for the ability of drugs having no known metabolism that yields reactive metabolites (like lidocaine or radio contrast media) to induce delayed-type, T cell-mediated reactions.

Here in brief the main findings supporting this concept:

1. Glutaraldehyde-fixed antigen-presenting cells, by this way made unable to take up and subsequently process the antigen, can still present the drug and stimulate specific T cells [171]. This suggests that neither processing nor intracellular metabolism is involved.
2. Inhibiting the generation of reactive metabolites actually enhances the reactivity of T cells, suggesting that the inert drug but not the reactive metabolite is recognized [165].
3. Upon APC pulsing (incubation of APC with the drug, followed by washing steps), which removes the drug, no T cell stimulation was observed, whereas the hapten SMX-NO, which is able to covalently modify the MHC-peptide complex, was still able to stimulate hapten-specific T cells [168, 171]. The drug is thus bound in a labile way to the TCR-MHC-peptide complex.
4. Recognition of the drug by specific TCC occurs within seconds as revealed by $[Ca^{2+}]$ increase and immediate TCR downregulation in conditions in which the drug was clearly not covalently bound to the MHC-peptide complex, a timing not in accordance with the more than 6h needed for an intermediate metabolism and processing step [168].
5. This stimulation by inert drugs is MHC-dependent, implying that for full stimulation of the T cell, the TCR needs to interact with the drug and the MHC molecule [171, 172]. However between 5 and 22% of the clones are able to recognize the drug in an MHC-allele unrestricted way, which clearly indicates that a specific MHC molecule does not appear to be a limiting factor in drug presentation [178].

QUINOLONE INTERACTION WITH T CELLS

Quinolones are chemically inert drugs. Nevertheless, some metabolism exists. Both patterns of drug metabolism, the phase I reactions – oxidation, reduction or hydrolysis – and the phase II reactions – conjugation of a drug with an endogenous substance such as glucuronic acid, acetic acid,

sulphuric acid, or an amino acid [179] have been observed with the fluoroquinolones and several reactions are common to the agents [179]. The known metabolic pathways for quinolones are: glucuronidation of the carboxyl group, sulfonation of the secondary amine and the formation of a common bisconjugate [180]. Glucoronide conjugates have been identified as minor metabolites of pefloxacin, NRFX, and ofloxacin. Otherwise, biotransformation occurs at the piperazinyl moiety C-7 *via* microsomal oxidative mechanisms and other conjugation processes for some agents [179, 181].

Studies using ^{14}C -labelled CPFX showed that 80 to 90% of the excreted substance consist of the chemically inert compound, which makes it a possible relevant antigen *in vivo*. Alternatively, about 19% of the orally administered and 12% of the intravenously administered CPFX are secreted as metabolites in urine and faeces after metabolism in the liver mainly by the CYP p450 1A2 isoenzyme [199]. Thereby, four metabolites have been identified: desethylene-, sulfo-, oxo-, and formyl-CPFX, all structurally highly related to their parent compound, since they differ only in regard to their piperacinyloxy moiety. In view of the limited quinolone metabolism, it is questionable whether chemically reactive metabolites play a role in the induction of delayed adverse reactions. Moreover, some of the patients analysed by Schmid *et al.* [202] as well as by other authors [88] showed a positive patch test to CPFX after 24 and 48 hours. If a reactive compound is needed to induce an immune response, it is actually surprising to see such a skin reaction in answer to an inert drug, as it would imply that the drug-metabolite might be transported from the liver to the skin, or that some metabolism may also occur in the skin, as shown to a certain degree for SMX [160]. Concurrently, Rönna *et al.* tested the PBMCs of two CPFX- allergic patients with three CPFX metabolites (desethylene-, sulfo- and oxo-CPFX). Although the cells proliferated in response to different concentrations of the parent drug, none of the metabolites led to specific lymphocyte stimulation [89].

We recently further demonstrated that delayed drug-hypersensitivity reactions to quinolones are associated with a strong T cell immune response against the relevant quinolone and that quinolones are able to stimulate T cells in a specific, TCR- and MHC-dependent way [202]. Indeed, PBMCs of CPFX- and moxifloxacin-allergic patients showed a significant proliferation after stimulation with the parent compound CPFX or moxifloxacin, respectively (Fig. (5)) [182]. The generated T cell line and CD4⁺ TCC specific for CPFX were also directly stimulated by CPFX as the presence of fixed APC, unable to metabolize, was sufficient to elicit proliferation of CPFX-specific TCC.

These data suggest that quinolones behave like SMX [165], carbamazepine [183], lidocaine [184], and interact directly and in a rather labile way with the TCR and MHC-peptide complex. Incubating APC with the drug, followed by washing, removed CPFX and abrogated the stimulation of the drug-specific TCC.

CROSSREACTIVITY

Crossreactivity is a well known problem in quinolone hypersensitivity, especially since quinolones tend to be used more and more extensively. The structural similarity of qui-

inolones, the clinical data of crossreactions and some *in vitro* analyses suggest frequent crossreactivity [38, 68, 70, 73, 89, 185-188].

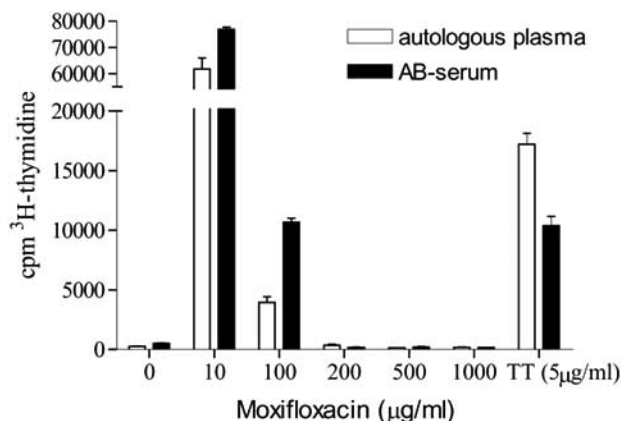


Fig. (5). LTT in moxifloxacin-induced delayed hypersensitivity.

The patient was treated with moxifloxacin over a period of 5 weeks. She developed a generalized exanthem during the last week of treatment. PBMC of the patient were cultured with different concentrations of moxifloxacin for 7 days (in autologous plasma or AB-serum) and [³H]-thymidine incorporation was measured. Tetanus toxoid (TT) was taken as positive control. The results are given as mean $\pm$ S.E.M of triplicates. Methods see reference [182].

Indeed, Manfredi *et al.*, who established a serological test capable of detecting IgE antibodies to CPFX and other quinolones, report several patients presenting anaphylactoid reactions to more than one quinolone. Moreover, the majority of the patients (80%) positive in the IgE test revealed IgE towards more than one quinolone [16].

In T cell-mediated CPFX-delayed hypersensitivity reactions, CPFX-specific TCC were also evaluated with a panel of 10 quinolones. Three patterns of crossreactivity could be outlined [202]. Some TCC reacted exclusively with CPFX, a second group responded to two quinolones (CPFX and NRFX) and the third group of clones showed a broad crossreactivity and could be stimulated by as many as 5 compounds. Those findings are supported by *in vivo* observations where oral provocation tests with different quinolones were positive in quinolone-hypersensitive patients [68, 70, 88]. Those data suggest that patients with severe reactions (IgE- or T cell-mediated) to one quinolone should not be treated again with another quinolone.

However, if the reaction is mild an attempt at a renewed treatment could be endeavored. Indeed, in the above mentioned prospective study on GMFX-hypersensitivity, the degree of clinical crossreactivity was also addressed [189]: 144 women who had developed a rash to GMFX were submitted to a 10 day CPFX treatment or to a placebo. 10.4% of the CPFX-treated women developed again a rash while only 3.9% of the women, who received a placebo, reacted (Fig. (3)). This study shows that in the same population structurally similar quinolones may have a notably different capacity to elicit maculopapular exanthems and that the risk of cross-reactivity in mild exanthemas is rather low. These and other

studies on crossreactivity in the sulfonamide, lidocain and penicillin model prompted Depta and Pichler [190] to conclude that the potential crossreactivity of a T cell with structurally related drugs is primarily determined by core and side chain determinants of the drug, suggesting that T cells are only crossreactive if the core structure is identical (e.g. the sulfanilamide structure in sulfonamide-containing antibacterials). Moreover, the affinity of the TCR to the drug, the frequency of drug reactive T cells, but also the TCR density is important: the higher the TCR density, the more likely as a substantial crossreactivity was found [191]. In contrast to T cell reactions, IgE-mediated reactions could be directed to smaller components, like the side chains alone, but the affinity of such antibodies might be rather low and the clinical relevance unclear [192].

GENETIC FACTORS

The idiosyncratic nature of drug-hypersensitivity reactions suggests that a genetic predisposition might be important in adverse drug reactions. However, years of research focusing mainly on pharmacogenetic factors yielded mainly promising concepts but no strong data [193]. The search for genetic associations in SJS and TEN caused by different drugs was frustrating. However, if not only the disease alone, but the disease AND the incriminated specific drug were considered together, some strong genetic risk factors were discovered. Recently three examples indicated a surprisingly high association with HL-A-B-alleles, emphasizing the T cell-mediated nature of some of these adverse reactions. Chung *et al.* described a strong association in Han Chinese between HLA-B*1502 and SJS induced by carbamazepine, a widely used anti-epileptic. The presence of this marker in 8% of Han Chinese but only in 1-2% of Caucasians could explain the higher incidence of carbamazepine induced SJS in Han Chinese [194].

In the same ethnic population, Hung *et al.* looked for a genetic marker for severe cutaneous reactions (drug hypersensitivity syndrome, SJS and TEN) caused by allopurinol, a medication widely used for hyperuricemia-related diseases such as gout [195]. After genotyping the individual HLA alleles, they noticed a significant increase in the frequency of the HLA-B*5801 allele. This allele was present in 100% of the patients with severe cutaneous reactions to allopurinol, but only in 15% of the allopurinol-tolerant control group and in 20% of the general population. However, there were tolerant patients who also carried HLA-B*5801, suggesting that this allele is necessary but not sufficient to induce allopurinol related severe cutaneous adverse reactions.

Abacavir, a potent HIV-1 nucleoside-analogue reverse-transcriptase inhibitor, can cause potentially life-threatening hypersensitivity reactions in about 5% of treated patients. An Australian study found that HLA-B*5701 was present in 14 out of 18 (78%) hypersensitive patients, versus 4 out of 167 (2%) tolerant patients [196]. HLA-DR7 and HLA-DQ3 were found in combination in 13 of the 18 (72%) patients, and 5 of the 167 (3%) tolerant individuals, while all three markers were present in 13 out of 18 (72%) hypersensitive patients, but in none of the tolerant patients. This association between MHC-alleles and abacavir hypersensitivity in HIV-1-positive individuals suggests a genetic susceptibility.

Those findings suggest that some particular MHC-alleles are a risk factor for certain severe drug-induced adverse reactions, but do not exclude the involvement of other risk factors, such as viral infections or other genes involved in the mechanism of pathogenesis.

No data exist regarding an immunogenetic or pharmacogenetic predisposition to quinolone-induced hypersensitivity.

CONCLUSIONS

The quinolones have evolved from antibacterial agents with a limited spectrum of activity and a restricted number of indications to a class of widely used antibiotics with extensive indications for infections caused by many bacterial pathogens in most body tissues and fluids. Nevertheless, like other antibiotics, they can cause immune mediated adverse side-effects, not only IgE-mediated but also T cell-mediated.

The evidences outlined above suggest that numerous delayed drug-hypersensitivity reactions to quinolones are associated with a strong T cell immune response against the relevant quinolone. It seems that the parent, chemically inert compound is recognized by T cells without the need of metabolism or processing.

In IgE-mediated reactions, crosslinking of bound IgE may be facilitated by binding to a protein. Most likely a reactive compound represents the relevant antigen, at least to some extent.

In T cell-mediated adverse effects, the drug interacts directly and in labile way with the TCR and MHC-peptide complex, unlike haptens, like SMX (SMX)-nitroso or penicillinG, which bind covalently to MHC-peptide complexes [157, 162]. Thus, a substantial number of side-effects (exanthema) to quinolones is induced by pathomechanisms similar to the ones already shown for other drugs (SMX, lidocaine, carbamazepine, lamotrigine) [167, 173, 174, 184, 197], and is compatible with the "p-i"-concept [198]. Nevertheless, other side-effects, for example hepatitis or anaphylaxis [16], may be due to the formation of active intermediates, which act as haptens forming neo-antigens by covalently binding to proteins/peptides subsequently initiating an immunological reaction [199]. Therefore, probably both, hapten - most relevant for IgE-reactions - and p-i mechanisms - most relevant for delayed T cell-reactions - can occur with quinolones and may even occur simultaneously [163].

The crossreactivity among quinolones at the IgE and T cell level is clinically well documented but no general pattern can be outlined, neither by *in vivo* observations nor by *in vitro* studies. As a consequence, patients with more severe hypersensitivity reactions to any quinolone should not be re-exposed to any of that class of antimicrobial agents.

A still open question is how to avoid those hypersensitivity reactions while keeping the effectiveness of those potential agents. How can we screen those hundreds of compounds as to preserve the patients from disagreeable and sometimes life threatening adverse reactions? This is not only an issue for the affected patient and treating physician, but also for the pharmaceutical industry, as a high frequency of such unexpected side effects caused by one drug might lead to a very expensive withdrawal of this drug from the market. Indeed, serious adverse drug effects in patients led to

the withdrawal or restriction of four quinolones in the past decade (temafloxacin, grepafloxacin, trovafloxacin, and sparfloxacin). Currently, there are no *in vivo* or *in vitro* tests available to predict the immunogenicity of chemically inert drugs. Genotyping for a particular HLA-allele could provide a better guidance for the prescription of a certain drug as suggested by the above described immunogenetic studies. A step towards an *in vitro* test has been achieved by Engler *et al.* who were able to induce a primary T cell response against SMX - which was directed to the inert, parent compound itself - using blood from healthy individuals previously not exposed to the drug [200]. Drug-reactive T cells could be detected after 14-35 days of culture after blood lymphocyte stimulation with the drug in presence of IL-2. This method should be refined and could then provide an opportunity to screen new drugs for their ability to interact with TCR. Another alternative could lie in the transfection of drug-specific T cell receptor into hybridoma cells. Vollmer *et al.* and Depta *et al.* were able to stably transfect nickel- and SMX-specific T cell receptors, respectively, into TCR negative mouse hybridoma cells [191, 201]. Those transfectants kept the specificity of the original T cell and, since they are continuously growing tumoral cells, are the best alternative to the cumbersome T cell cultures. Our group achieved the same with CPFX-specific TCR, and the cloning of highly quinolone-crossreactive TCR into hybridoma cells might be the key to open the door towards a stable, well established and standardized method to screen for other quinolones able to react with such TCR and able to induce a T cell response (Schmid *et al.*, submitted 2006).

It seems obvious that, although investigations run their course, further studies are needed to prevent and get a better understanding of quinolone-induced hypersensitivity reactions.

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ABBREVIATIONS

CPFX	= Ciprofloxacin
GMFX	= Gemifloxacin
NRFX	= Norfloxacin
SMX	= Sulfamethoxazole
TCC	= T cell clones
MHC	= Major histocompatibility complex
SJS	= Stevens Johnson syndrom
TCR	= T cell receptor
TEN	= Toxic epidermal necrolysis

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