

Macrolides Allergy

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Abstract: Macrolides are characterised by their basic structure which is made up of a lactonic cycle with 2 osidic chains. They are classified according to the number of carbon atoms in the cycle : 14 membered macrolides (erythromycin, roxithromycin, dirithromycin, clarithromycin...), 15 membered (azithromycin) and 16 membered (spiramycin, josamycin, midecamycin...) macrolides.

Epidemiological studies show that macrolides are amongst the safest antibiotics, but in these series, no drug allergy work up was performed. An immediate IgE dependent hypersensitivity has been shown with erythromycin in some cases. The mechanism is unknown and the skin tests are negative in most other cases. It would appear that the macrolide allergies are unlikely to be class allergies. Eviction is the treatment of choice. Desensitization has been successful in a few cases.

Key Words: Allergy, diagnosis, drug allergy macrolides.

INTRODUCTION TO MACROLIDES

Chemical Structure

Erythromycin, derived from *Streptomyces erythreus* and originally market in 1952, was the first macrolide antibiotic. It was seen as an alternative therapy to beta-lactams for the treatment of Gram-positive cocci infections [1]. Its activity against atypical pathogens (*Mycoplasma spp.*, *Chlamydia spp.*), *Legionella spp.* and *Helicobacter spp.* has provided a broader spectrum of clinical use for erythromycin. Despite these new features, erythromycin has some drawbacks [2-5]: poor oral bioavailability, inactivation in acidic environment (needing enteric coating formulations), gastrointestinal side effects – nausea, cramping, diarrhea and short half-life (requesting multiple daily dosing).

The newer macrolides were only released in the 1990s, when clarithromycin was introduced in 1992 and Azithromycin in 1994. These newer macrolides presented some advantages over erythromycin [2-5]: broader spectrum of activity, including fastidious Gram-negative bacilli such as *H. influenzae* and *Neisseria spp.*, once or twice daily dosing and marked reduction in gastrointestinal side-effects.

The main structural component of the macrolides is a large lactone ring that varies in size from 12 to 16 atoms (Table 1) [6]. Glycosidic bonds attach one or more sugars to the ring, and the ring is substituted by hydroxyl or alkyl groups [7]. The macrolides can be subdivided into 4 classes based on the number of atoms in the lactone ring (Table 1). The 12-membered ring macrolides have a ketone group at C-7 [7]. Methymycin and neomethymycin are naturally occurring aglycone rings with desosamine moieties attached at the

C-3 position via a glycosidic bond. Attempts at creating semisynthetic 12-membered macrolides have been made but, to date, none have demonstrated significant clinical activity. The development of a new class of 14-membered ring macrolides known as the ketolides, which differ from other 14-membered ring macrolides by the replacement of the C-3 L-cladinose moiety with a keto group, may offer alternative therapy for Gram-positive infections attributable to resistant pathogens. Ketolides differ from macrolides in that they do not induce resistance to macrolides or MLSB (macrolide-lincosamide streptogramin B) resistance in *Streptococcus pneumoniae* [8].

Pharmacokinetics

The macrolides are generally characterized by low to moderate (30 to 55%) oral bioavailability with the exception of roxithromycin with its enhanced bioavailability (72 to 80%) [6]. The rate of macrolide absorption is variable. Erythromycin ethylsuccinate, clarithromycin, roxithromycin, azithromycin, josamycin and flurithromycin reach peak serum concentrations in 2 hours or less, while the other macrolides need up to 4 hours.

The macrolides are lipophilic in nature and have a low degree of ionization [9]. This allows extensive penetration into tissues and fluids and results in a large volume of distribution [10]. Unlike β -lactams and aminoglycosides, macrolides and ketolides enter host defence cells, particularly macrophages and polymorphonuclear leucocytes [11].

With the exception of the dibasic macrolides (dirithromycin and erythromycylamine), the 14C membered ring macrolides display an affinity for cytochrome P450 (CYP) [12]. These agents are associated with potential drug interactions as their interactions with CYP interfere with the metabolism of a number of drugs. The 15 membered ring macrolide azithromycin and the 16 membered ring macrolides spiramycin and josamycin do not share this affinity for CYP.

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The newer macrolides, with the exception of josamycin, exhibit increased half-lives when compared with erythromycin. This allows less frequent administration of these agents [12].

Macrolide excretion is primarily accomplished through the bile [13]. Renal excretion of macrolides is relatively limited with clarithromycin being the only macrolide to exhibit any significant urinary concentrations [14, 15].

Drug Interaction

Macrolide antibiotics can induce hepatic microsomal enzymes [16]. Experimental studies with rats and laboratory studies have shown that macrolides inactivate CYP450 [17-35]. Many drugs are extensively metabolized in the liver using the CYP450 isoenzymes, including theophylline [36-39], cyclosporine [40-42], terfenadine [43, 44], phenytoin, phenobarbital and carbamazepine [45]. Erythromycin can impair these drugs clearance when coadministered [46].

Clarithromycin might increase the steady-state concentrations of drugs that are primarily dependent upon CYP3A metabolism, including astemizole, cisapride, pimozide, midazolam and triazolam [47]. This feature can be clinically significant for drugs with narrow therapeutic index, such as carbamazepine, cyclosporin, digoxin, theophylline and warfarin. Potent inhibitors of CYP3A (*e.g.* omeprazole and ritonavir) may also alter the metabolism of Clarithromycin and its metabolites [48-50]. Rifampicin and rifabutin are highly effective enzyme inducers and may significantly decrease serum clarithromycin concentrations [51, 52]. Coadministration with carbamazepine can lead to acute toxicity [53, 54]. Cimetidine has been shown to prolong the absorption of clarithromycin [55]. Clarithromycin alters both the pharmacokinetics and pharmacodynamics of midazolam, leading to such a significant increased effect [56-59] that if coadministration is considered midazolam dose should be reduced by 50 to 75%. By contrast azithromycin does not seem to affect midazolam pharmacokinetics [59].

There is evidence for interaction between clarithromycin or roxithromycin, but not azithromycin, and astemizole, resulting in serious and potentially life threatening prolongation of QTc intervals [26, 60].

Clarithromycin and cyclosporin A coadministration may lead to increase in plasma levels of cyclosporin, due to interferences with both hepatic and intestinal metabolism of cyclosporin, so that an appropriate dose reduction should be considered [61, 62]. In general Azithromycin is considered unlikely to interact with cyclosporine. Nonetheless, practitioners should be aware of this possibility and should monitor cyclosporine levels closely, especially in critically ill patients who have other complications [63-65].

Macrolides may increase the bioavailability of digoxin and result in severe toxicity cases [66-74]. Therefore, digoxin concentrations must be monitored carefully after coadministration of macrolides and the doses of digoxin may need readjustment.

Macrolide antibiotics inhibit the metabolism of HMG-CoA reductase inhibitors that are metabolized by CYP3A4 (*i.e.*, atorvastatin, cerivastatin, lovastatin, simvastatin). This interaction may result in myopathy and rhabdomyolysis, particularly in patients with renal insufficiency or those who

are concurrently taking medications associated with myopathy [75-84].

Table 1. Macrolide Antibiotics According to the Number of Atoms in the Lactone Ring

12-C Lactone ring
Methymycin
Neomethymycin
Picromycin
14-C Lactone ring
Clarithromycin
Dirithromycin
Erythromycin
Erythromycylamine
Flurithromycin
Mycinamycin
Oleandomycin
Roxithromycin
Sporeamicin A
Troleandomycin
15-C Lactone ring
Azithromycin
16-C Lactone ring
Josamycin
Kitasamycin (leucomycin)
Midecamycin
Miokamycin (midecamycin acetate)
Rokitamycin
Rosaramycin
Spiramycin
Tylosin

Although there might be some reduction of antiretrovirals' concentration when coadministered with macrolides, the combination of both drugs is generally well tolerated and can be coadministered without dose adjustment [85-89].

Coadministration of clarithromycin and rifabutin results in significant bidirectional pharmacokinetic interactions resulting in a significant increase in rifabutin serum levels that might lead to severe clinical manifestations, especially neutropenia. Physicians should be aware that all patients receiving rifabutin, especially if coadministered with clarithromycin, should be monitored carefully for neutropenia [90-95]. By contrast, pharmacokinetic interactions between azithromycin and rifabutin do not seem to be clinically relevant [90].

Clarithromycin has been shown to inhibit the metabolism of pimazolidine in human liver microsomal preparations and pimezolidine, but not clarithromycin or its primary metabolite, is able to prolong QTc interval in a dose-dependent manner in a rabbit model. As a result, serious interaction between clarithromycin and pimezolidine might occur and a sudden death has been reported in one patient treated with pimezolidine for Tourette syndrome [96]. Concomitant administration of both drugs is contraindicated.

Increases in International Normalized Ratio (INR) have been detected in the patients who have previously been stabilized on warfarin when they were simultaneously given a macrolide [97-103]. Thereafter clinicians should be mindful when prescribing macrolides in combination with warfarin, and INR values should be closely monitored.

Mechanism of Action

Macrolides reversibly bind to the 50S ribosomal subunit of pathogens and inhibit mRNA-directed protein synthesis. Champney and Burdine [104] have proposed that macrolides may secondarily inhibit 50S ribosomal subunit assembly. Their experiments demonstrated that addition of macrolides to bacterial cells caused a decrease in the specific activity ratio of 50S to 30S subunits. This decrease in 50S subunit formation suggests the possibility of a second ribosomal target for the macrolides.

Macrolide antibiotics are generally bacteriostatic, however, bactericidal activity may occur under certain conditions or against specific microorganisms [105-110].

The ketolides have also been reported to bind to 23S rRNA and their mechanism of action is similar to that of the macrolides. However, ketolides have been demonstrated to bind with 10- to 100-fold higher affinity to unmethylated ribosomes than erythromycin and, unlike erythromycin, also bind to methylated ribosomes, although less avidly than to unmethylated ribosomes [111, 112].

Spectrum of Action

Macrolides are more active *in vitro* against Gram-positive and atypical agents than against Gram-negative pathogens. Macrolides are generally active against *Streptococcus pneumoniae* isolates that are susceptible to penicillin; however, significant cross-resistance may occur to pneumococcus highly resistant to penicillin. Macrolides are active against pathogens responsible for sexually transmitted diseases (like *Neisseria gonorrhoeae*, *Haemophilus ducreyi* and *Ureaplasma urealyticum*). Azithromycin is the only Macrolide active against *Mycoplasma hominis*. Clarithromycin is the most active against *Helicobacter pylori* [1]. Macrolides are useless to treat infections caused by methicillin-resistant staphylococci or *Enterococcus spp.*

Macrolides Resistance

There are two main resistance mechanisms to Macrolides: altered target site and efflux [1]. Some pathogens, like *S. pneumoniae*, may produce ribosomal RNA methylases that lead to the methylation of an adenine residue in the 23S ribosomal RNA of the 50S subunit leading to Macrolide

resistance. Genes encoding for macrolide resistance may be plasmid or chromosomally based and expressed constitutively or be induced [108, 113, 114]. Efflux refers to the ability of organisms to pump antimicrobial agents out of the bacterial cells, resulting in an insufficient drug concentration within the cell thereby rendering the organism resistant. A review made by Carbon and Poole [115] indicated that prevalence of macrolide resistance is closely related to the extent they are used. These observations have been most notable for *Streptococcus pneumoniae* and *S. pyogenes* while *M. catarrhalis*, *M. pneumoniae*, *C. pneumoniae* and *L. pneumophila* have not developed macrolide resistance [115]. Macrolide resistant *Streptococcus pneumoniae* are a major concern, especially as prevalence rates have raised significantly in the 1990s. Mean macrolide resistance rates for pneumococcus were 22% [116] ranging from 78% in Hong Kong to 2% in the Czech Republic.

Clinical Use (Table 2)

Macrolides are useful in a wide range of clinical infections, with some differences between the agents with respect to specific indications. General indications include mild to moderate upper and lower respiratory tract infections and skin infections [1].

Oral azithromycin is approved for the treatment of urethritis and cervicitis caused by *C. trachomatis* or *N. gonorrhoeae* and genital ulcer disease caused by *H. ducreyi* in men. Intravenous azithromycin is indicated for the initial treatment of pelvic inflammatory disease caused by *C. trachomatis*, *N. gonorrhoeae* or *M. hominis*.

Clarithromycin is indicated for the treatment of acute sinusitis due to *Streptococcus pneumoniae*, *H. influenzae* and *M. catarrhalis* and is also indicated for mycobacterial infections (*M. avium* and *M. intracellulare*) combined with other drugs.

Adverse Reactions

An Adverse Drug Reaction is defined by the World Health Organization as a noxious and unintended response to a drug that occurs at a dose normally used in man [117]. Macrolides are among the safest antibiotics available for the treatment of mild-to-moderate community-acquired bacterial infections [16], even in children [118]. Overall adverse effect rates of 7 to 26% for erythromycin, 14 to 26% for clarithromycin and 6 to 27% for azithromycin have been described for children [119-124]. Most adverse reactions associated with the use of macrolide antibiotics are mild and resolve on discontinuation therapy.

Gastro-intestinal events are the most frequently reported adverse reactions associated with the administration of macrolide antibacterials. The stimulant effect of macrolides on gut contractility mediated through endogenous release of motilin accounts, in part, for the poor gastro-intestinal tolerance of the macrolides [125-127]. Symptoms such as nausea, vomiting, abdominal cramps and diarrhea may result from both oral and intravenous administration. The specific macrolide agent used, timing of oral drug administration in relation to meals, daily dosage and infusion rate are factors that may affect gastro-intestinal tolerance [128].

Table 2. Clinical Use of Macrolides

Indications	Macrolide	Comments
Clinical use as antibiotics		
Community-acquired pneumonia [184-194]	E, A, C, T	
Lower respiratory tract infections [195-199]	A, C, E, T	
POCD bacterial exacerbations [200-203]	A, C, T	
Sinusitis [204-219]	A, C, E, R, T	
Pharyngitis [121, 220-222]	A, C, E	
Otitis media [223, 224]	A, C, R	
Infective endocarditis prophylaxis [225]	A, C	
<i>Haemophilus influenzae</i> infections [226-228]	A, C, T	
<i>Helicobacter pylori</i> infection [229-233]	C	
Chancroid [234-236]	E, A	
Lymphogranuloma venereum [237-239]	E	
Chlamydia trachomatis [238-241]	A, E	
Lyme disease [242-246]	E, A	If early treatment
MAC prophylaxis [247-252]	A, C	
MAC treatment [253-255]	A, C	In combination with other MAC-active antibiotic
As anti-inflammatory drug		
Chronic asthma [256]	A, C, R	
Cystic fibrosis [257]	A	
Diffuse panbronchiolitis [258, 259]	E	
Psoriasis [260]	E	As adjunctive treatment

Macrolides (A – Azithromycin; C – Clarithromycin; E – Erythromycin; K – Kitasamycin; J – Josamycin; M – Midecamycin R – Roxithromycin; S – Spiramycin; T – Telithromycin; Tr - Troleandomycin); COPD – Chronic obstructive pulmonary disease; MAC - Mycobacterium avium complex.

Thrombophlebitis is a well described adverse effect with intravenous administration of erythromycin [129]. Macrolide-induced adverse effects also include transient sensorineural ototoxicity [130, 131]. The exact mechanism is not known, but is thought to involve the central auditory pathways. Perceptive hearing loss typically occurs at frequencies above 4000Hz. Clinical evidence indicates that ototoxicity is more likely to occur in patients who are elderly, renally or hepatically impaired or those receiving an erythromycin dosage exceeding 4 g/day. Hearing impairment is usually reversible within days upon discontinuation of the drug. Newer macrolides have also been rarely associated with ototoxicity when administered at high dosages with long term use (azithromycin 600 to 1200 mg/day, clarithromycin 1g twice daily) [132-137].

ANTIBIOTIC ALLERGY

Subtypes of Drug Hypersensitivity Reactions

According to the Nomenclature Review Committee of the World Allergy Organization, drug allergy refers to a hy-

persensitivity reaction for which a definite immunological mechanism, either IgE or T-cell-mediated, is demonstrated [138]. Adverse drug reactions that clinically resemble an allergy but for which an immunological process is not proven should be classified as non-immune hypersensitivity reactions [138].

Drug hypersensitivity reactions represent about one third of adverse drug reactions which can affect 7% of the general population and up to 20% of hospitalized patients besides being responsible for as many as 8% of hospital admissions. Antibiotics are the leading causes. Reactions are in most cases not declared but reported numbers can also be inflated by the lack of a definite diagnosis [139].

The revised nomenclature for allergy classifies allergic reactions to drugs as IgE-mediated or non-IgE-mediated [140]. It is important, however, to distinguish between immediate and non-immediate reactions. The former occur within the first hour after the last drug administration and are manifested clinically by urticaria, angioedema, rhinoconjunctivitis, bronchospasm and anaphylactic shock. Non-

immediate reactions occur more than 1 h after last drug administration. The main non-immediate reactions are maculopapular eruptions and delayed-appearing urticaria/ angioedema. In addition, drugs can elicit fixed eruptions, exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome, and toxic epidermal necrolysis (TEN) [141]. Immediate allergic reactions are IgE-mediated, and have been extensively studied, whereas the mechanisms involved in non-immediate reactions seem to be more heterogeneous [141].

Immunopathology of Drug Hypersensitivity Reactions

Although drugs are capable of inducing all the types of immunological reactions described by Gell and Coombs, they are in the vast majority immunoglobulin-E- or T-cell mediated reactions. Very often the allergic determinants are unknown, and sometimes several allergic mechanisms and non-allergic mechanisms may be responsible [142]. Three major but not mutually exclusive models are proposed to explain drug-induced immune reactions: the hapten (and pro-hapten)-carrier concept, the danger signal concept and the p-i concept [143].

The hapten-carrier concept postulates that small compounds become antigenic for both B- and T-cells after covalent binding to larger proteins. Heterologous sera, some enzymes (chymopapaïne...) and hormones (insulin...) have sufficient molecular weight to be immunogenic in a native state. Most other drugs have a low molecular weight and are immunogenic only because they haptenize endogenous proteins. Some drugs are intrinsically reactive (hapten concept), while other drugs require enzymatic or non-enzymatic conversion to a reactive intermediate (pro-hapten concept) [143].

The danger signal concept, initially proposed by Matzinger, states that an immune response can only be mounted when antigen-presenting cells (APC) receive activating signals from stressed or damaged cells [144]. Thus, drug-related cytotoxicity may also be of importance. According to this concept, the immune response to a drug-derived antigen requires the presence of co-stimulatory signals and cytokines, which propagate and determine the type of immune response. The "danger signal" might result from chemical, physical or viral stress [145]. Recent findings indeed suggest that the drug itself can give the danger signal as well.

However, many drugs are not reactive and can still be immunogenic. Thus, Pichler has described a model of T-cell stimulation by drugs, termed pharmacological interaction with immune receptors (p-i concept) [141, 146]. He states that certain drugs would interact with T-cell receptors and MHC molecules in a direct way, without covalent binding to the receptor and without priming by APC. The interaction would be sufficient to stimulate T-cells if an MHC interaction was provided.

Diagnosis of Drug Hypersensitivity Reactions

The diagnosis of drug hypersensitivity is difficult, and drug-allergic reactions are surely under diagnosed. This difficulty is related to the following factors: 1) the variability of

the clinical picture; 2) insufficient understanding of the pathophysiologic reactions of most drug hypersensitivities; 3) some weakness of the classification of allergic reactions into four types according to Gell and Coombs, which is helpful for some drug-allergic reactions but fails to explain the most common form of drug allergy - exanthema - as well as some severe reactions such as toxic epidermal necrolysis, or the so-called DRESS or hypersensitivity syndromes; 4) the limitation and/or lack of standardization of the available *in vivo* and *in vitro* test procedures to detect drug hypersensitivity reactions. In view of these difficulties, most doctors restrict themselves to a careful clinical history, reference books, local agencies monitoring drug hypersensitivity, and/or databanks describing side effects attributed to a certain drug. However, only a formal diagnosis of drug allergy allows one to bring into play the measures required for prevention and treatment [147].

Drug allergy evaluation work-up involve patient's history, *in vivo* skin testing (prick, intradermal and patch tests), *in vitro* laboratory tests and provocation tests [148].

Clinical History

A detailed history is of paramount importance for the question of whether a certain disease reflects drug hypersensitivity as well as the question of which drug is causing it. To facilitate this recording of an appropriate history and to harmonize this procedure in Europe, members of ENDA (European Network of Drug Allergy, which is the interest group on drug allergy of the European Academy of Allergy and Clinical Immunology) have developed a questionnaire which might provide a guide in this rather difficult area of clinical medicine [147].

Skin Tests

Different types of skin tests (prick, intradermal and patch tests) could be applied according to the suspected pathomechanism of the drug hypersensitivity [149-153]. They have been mainly used and validated for β -lactam allergies. In immediate, possibly IgE mediated reactions (manifested by anaphylaxis, bronchospasm, conjunctivitis, rhinitis, urticaria/angioedema) prick tests and/or intradermal tests with reading after 20 minutes can be used [148]. For non-immediate reactions, occurring more than one hour after drug intake, manifested mainly by cutaneous symptoms, patch tests and/or late-reading intradermal tests might be useful [148]. Intradermal tests are more sensitive than prick tests, but have a higher rate of false positive results and might even lead to an anaphylactic reaction in IgE-dependent reactions [148].

Drugs possibly interfering with skin tests mechanisms (mainly anti-histamines, oral and topical corticosteroids) should be discontinued prior to skin testing. Patients being tested after a drug induced anaphylactic reaction should be out of β -adrenergic blockers as they may interfere with treatment of a possible systemic reaction elicited by the skin test. Skin tests are not innocuous and some patients might experience systemic reactions after percutaneous and epicutaneous skin testing [148]. Patients that have experienced severe drug hypersensitivity (requiring hospitalization) or life threatening including anaphylaxis, severe skin reactions (e.g. Stevens Johnson Syndrome) or systemic reactions are at

a higher risk, even if there is a long time interval between the drug hypersensitivity and drug allergy testing [154]. In such high risk patients an individual risk-benefit assessment has to be done. If tests are to be preformed, they should be initiated using a higher dilution of the test preparations (e.g. 1/10 – 1/10000) [148].

For skin testing, preparations for parenteral (mostly i.v.) route should be used, using 0.9% NaCl for dilutions. For IDT, sterile solutions are obligatory. When drugs are only available as tablets, this can be smashed in a mortar and diluted with saline or petrolatum. Test concentrations should be given in mg drug/ml vehicle. For patch tests, substances should be diluted in 0.9 NaCl or in petrolatum, depending on the solubility and toxicity of the preparation [148].

Skin tests should be performed with a concentration that does not cause a reaction in a sufficient number of controls. For some drugs the optimal test concentrations have been published while for others they remain unknown and must be determined. The optimal test concentration is the highest concentration of a particular drug, which does not give any skin reaction in a group of exposed and unexposed controls, but may originate a positive reaction in patients with drug allergy [148].

The negative predictive value of skin tests is generally low. This may be partly due to the fact that physiologic metabolites rather than the active drug itself are responsible for the reaction and because many drugs are haptens, which have to be conjugated with a carrier protein before becoming an allergen. Thus, a negative skin test to a drug alone is unreliable for ruling out drug allergy. In the case of a negative skin test, progression to more hazardous drug provocation tests should be considered [148].

The positive predictive value of a skin test tends to be high, provided that a sufficient number of controls have been tested negative with exactly the same methodology [155].

Skin prick tests (SPT), intradermal tests (IDT) and patch tests (PT) have been used in macrolides allergy evaluation (see Table 5) and gave positive results in 25 to 50% of patients tested.

In specialized centers it might be prudent to confirm the diagnosis by use of a provocation test, in order to gain and publish information about false positive and false negative skin reactions, as well as positive and negative predictive values for specific drugs and clinical manifestations [148]. Details on skin tests procedures in diagnosis of drug hypersensitivity have been published by ENDA [148].

Laboratory Tests

Pascual *et al.* [156], using Sepharose as solid phase covalently linked to erythromycin, were able to detect **drug-specific IgE antibodies** in serum from a patient who experienced an allergic reaction to erythromycin, whereas specific IgE could not be demonstrated in control sera. The specificity of this assay is supported by the inhibition of binding of IgE antibodies in patient serum to erythromycin solid phase complex by incubation with the free drug, partial inhibition with another, structurally related macrolide antibiotic (diacetilmidecamycin) and lack of inhibition with a structurally unrelated drug (trimethoprim).

The **lymphocyte transformation test (LTT)** measures the proliferation of T cells to a drug *in vitro* – from which one concludes to a previous *in vivo* reaction due to a sensitization. The usefulness of the LTT has been confirmed by the generation of drug-specific T-cell clones and the finding that drugs can directly interact with the T-cell receptor, without previous metabolism or need to bind to proteins [157]. The main advantage of this test is its applicability with many different drugs in different immune reactions, as drug-specific T cell are almost always involved in allergic drug reactions. Its main disadvantages are that an *in vitro* proliferation of T cells to a drug is difficult to transfer to the clinical situation and that the test *per se* is rather cumbersome and technically demanding. In addition, its sensitivity is limited (for β -lactam allergy it is in the range of 60–70%) [157].

LTT have been uses in macrolides allergy evaluation giving positive results in 2 cases with erythromycin [158, 159] and a negative result with Clarithromycin. [160]

Serrano *et al.* [161] reported a positive histamine release test (HRT) in a patient with urticaria due to erythromycin, while Igea *et al.* [162] reported negative results in patients with DPT confirmed macrolides allergy using erythromycin and spiramycin.

Drug Challenges

A drug provocation test (DPT) is the controlled administration of a drug in order to diagnose drug hypersensitivity reactions. DPTs are performed under medical surveillance, whether this drug is an alternative compound, or structurally/pharmacologically related, or the suspected drug itself [163]. DPT is widely considered to be the “gold standard” to establish or exclude the diagnosis of hypersensitivity to a certain substance, as it not only reproduces allergic symptoms but also any other adverse clinical manifestation irrespective of the mechanism. It thus has advantages over all other test procedures and even can prove or disprove the clinical relevance of test results as obtained with other *in vivo* and *in vitro* test methods. But DPT should be performed only if other, less dangerous test methods do not allow relevant conclusions and if the outcome might thus help clarify an otherwise obscure pathologic condition [163].

DPT with a suspected drug should not be performed in pregnant women or in patients at increased risk due to comorbidity like acute infections or uncontrolled asthma, or underlying cardiac, hepatic, renal, or other diseases, where exposure might provoke a situation which is beyond medical control [163]. In most circumstances it is difficult to justify DPT with drugs that are nowadays mostly obsolete like sulfonamides (except in HIV-positive persons) or substances with debatable value like many herbal products or “lifestyle drugs” [164]. DPT should never be performed in patients who have experienced severe, life-threatening immunocytotoxic reactions, including vasculitic syndromes, exfoliative dermatitis, erythema multiforme major/Stevens-Johnson syndrome, drug induced hypersensitivity reactions (with eosinophilia)/ DRESS and toxic epidermal necrolysis [163].

DPT might be performed *via* different routes of administration, including oral, parenteral (i.v., i.m., s.c.) and topical (nasal [165], bronchial [166, 167], conjunctival [168, 169] or cutaneous [170]). In principle, the drug should be adminis-

Table 3. Epidemiology Studies Reporting Macrolide Hypersensitivity

Reference	Study Design / Population	Macrolide Allergy Reported	Macrolide Allergy Evaluation	Macrolide Allergy Confirmed	Other Comments
Kamada 1991 [261]	Retrospective review of 120 children (234 ADR) with MAS	32 macrolides / 234 ADR 26 E+sulfisoxazole / 234 ADR	None		
Martin 1995 [262]	10 years retrospective review of children admitted with serum sickness like reactions	1 Tr / 30	None		
Van Der Linden 1998 [263]	Retrospective review of antimicrobial ACDR in 13679 patients in general practice	5 / 135 ACDR	None		An adjusted incidence ratio for ACDR of 1.1 (95% CI, 0.4–3.0)
Wessel 1998 [264]	4 year retrospective review of allergy to antibiotics following anesthesia	1 E / 5 peroperative anaphylaxis due to antibiotics	None		
Mahboob 1998 [265]	482 with FDE observed during 1 year at a general hospital	35 E / 482 FDE	DPT	6 (17%) / 35	
Naldi 1999 [266]	4 years review of all ACDR reported spontaneously to the surveillance systems of 4 Italian regions	122 (5%) / 2224 ACDR 4 A + 3S / 171 Angioedema	None		
Park 2000 [267]	97 children with MAS referred to a drug allergy clinic	35% macrolide involved	None		
Sharma 2001 [268]	6 years prospective hospital-based study of ACDR in a tertiary hospital	6 E / 500 ADR	None		
Forman 2002 [269]	10 years retrospective review of all cases of EM, SJS or TEN at a university tertiary care pediatric hospital	4 E / 61 drug related	None		
Saissi 2003 [270]	6 years retrospective review of "serious pustular eruption" reported to the French Pharmacovigilance Centers	5 S + metronidazole / 207 reports	None		
Noel 2004 [271]	1 year prospective hospital-based study of ACDR in a tertiary hospital	1 A / 46 ACDR	None		
Messaad 2004 [272]	898 consecutive patients with suspected immediate drug allergy referred to an allergy clinic	102 / 898	DPT	14 (13.7%)	
Benahmed 2004 [176]	5 year review of suspected hypersensitivity to macrolide antibiotics referred to an allergy clinic	139 patients referred	107 DPT suspected drug	8/107 (7.5%)	
Lammintausta 2005 [175]	25 year retrospective review of oral challenge in 784 patients with suspected ACDR. Patients with severe (SJS, TEN) or systemic symptoms were not challenged	136 (13.5%) positive / 1001 DPT in 784 patients	37 DPT with macrolides	1 E / 37 (2.7%)	Patients with + SPT were challenged only in dubious cases
Rallis 2006 [273]	1 year review of children with ACDR during ENT infections	5 E + 2 C / 47 ACDR	None		
Dore 2007 [274]	8 year retrospective review of children admitted with drug induced exfoliative skin disease (EM, SJS, TEN)	A – 1 / 32 A + Ibuprofen – 6 / 32 C+Ibuprofen – 1 / 32	None		

(Table 3) contd....

Reference	Study Design / Population	Macrolide Allergy Reported	Macrolide Allergy Evaluation	Macrolide Allergy Confirmed	Other Comments
Lange 2008 [275]	6 month questionnaire-based survey of lifetime prevalence of ADR in a German pediatric university hospital	5 (4.6%) / 108 ADR	None		
Gomes 2008 [276]	Cross-sectional survey of life occurrence of ADR at the outpatient clinic of a pediatric hospital	1E + 2C / 39 compatible clinical histories drug allergy	DPT – all negative	0%	

Drug Allergy Evaluation (SPT – Skin Prick Tests; IDT – IntraDermal Tests; PT – Patch Tests; DPT – Drug Provocation Test); Macrolides (A – Azithromycin; C – Clarithromycin; E – Erythromycin; K – Ketasamycin; J – Josamycin; M – Midecamycin R – Roxithromycin; S – Spiramycin; T – Telithromycin; Tr – Troleandomycin); Clinical reaction (ADR – Adverse Drug Reaction; CADR – unspecified Cutaneous Adverse Drug Reaction; CD – Contact Dermatitis; EM – Erythema multiforme; FDE – Fixed drug eruption; HSP – Henoch-Schönlein Purpura; MAS – Multiple antibiotic sensitivity; MPE – Maculopapular exanthema; SJS – Stevens-Johnson Syndrome; TEN – Toxic epidermal necrolysis).

tered in the same way as it was given when the reaction occurred, the oral route is favored if possible, since absorption is slower and developing adverse reactions can thus be treated earlier as compared to DPT performed by the parenteral route [163].

Any medication that might interfere with DPT challenge (especially anti-histamines, some antidepressants and systemic glucocorticosteroids) should be avoided before challenges.

Before performing a DPT, an individual assessment of risk/benefit must be done and challenge only performed if this ratio is acceptable [164]: the drug must be important, *i.e.* it has to be substantially more effective than other alternatives, the condition being treated must be serious, no alternative testing method is available or the results are inconclusive. The patient must be informed of the consequences of both the use of alternative treatments and the risks involved in DPT. The patient should give written informed consent for the test [163].

DPT should be regarded as a serious and potentially dangerous test procedure. It is essential to have well-trained medical staff, that is immediately available in case of emergency, and facilities for continuous monitoring of the patient's condition. Intravenous access and intensive care room access/emergency treatment should be available depending on the severity of the previous reaction and the type of drug. Procedures like spirometry, monitoring of blood pressure, pulse and vital signs must be performed according to the patient's individual situation. Evolution of life-threatening reactions may make fast access to intubation essential [163].

DPT should be performed placebo-controlled, single blinded, and, in certain situations where psychological aspects may prevail, even double blinded. This is of utmost importance, since even in healthy students and hospital staff without any medication but placebo capsules, 41% reported (mostly subjective) symptoms like sedation, irritation, but even nasal congestion, fever, exanthemas and urticaria within a 3-day observation period [171].

Generally one should start with a low dose, carefully increasing this and stopping as soon as the first objective symptoms occur. If no symptoms appear, the maximum sin-

gle dose of the specific drug must be achieved, and the administration of the defined daily dose is desirable [163]. Depending on the drug and the patient's response threshold, DPT may be completed within hours, days or, occasionally, weeks [172].

Patients should be observed as long as severe exposure-related reactions may be expected. This depends on the type of previous drug reaction, the drug under investigation [173] and the individual situation of the patient. If mild reactions had occurred, observation after stabilization is recommended for at least 2 hours. After severe reactions hospitalization is mandatory because of the possibility of biphasic episodes that can be lethal if not recognized early and treated adequately [174]. After discharge, the patient should be equipped with an adequate emergency treatment if further symptoms seem possible (antihistamines, betamimetics, glucocorticosteroids).

A DPT can be termed positive if it reproduces the original symptoms [163]. Although considered the gold-standard for diagnosis of drug allergy DPT can result in false positive reactions (due to psychological symptoms, to preexisting symptoms like chronic urticaria, drug-induced exacerbation of preexisting disease or self-infliction). More important, a negative test does not always prove tolerance for future situations, since there might be false negative results (due to intake of antiallergic drugs, missing co-factors like co-medication, viral infections, physical exercise, insufficient dose exposure) [163].

General considerations on DPT in diagnosis of drug hypersensitivity have been published by ENDA [163].

In the 3 series published using DPT in evaluation of Macrolides antibiotics allergy drug challenges confirmed drug allergy in 2,7% (1/37 of cutaneous adverse drug reactions) [175], 7,5% (8/107 of suspected hypersensitivity reactions to macrolides antibiotics) [176] and 17% (6/35 suspected fixed drug eruption due to macrolides). [177]

MACROLIDE ALLERGY

Review of Published Cases

We performed an extensive search using the Medline® and Scopus® databases trying to identify all reports of mac-

Table 4. Case Series of Hypersensitivity Reactions to Macrolide Antibiotics

References	N° Cases	Clinical reaction	Chronology	Drug Allergy Evaluation					Other
				SPT	IDT	PT	DPT	CR	
Amblard 1969 [277]	1 S	TEN		ND	ND	ND	ND	ND	
Handa 1972 [278]	1 E	HSP		ND	ND	ND	ND	ND	
Van Ketel 1976 [279]	1 E	Urticaria	1 week	ND	ND	E-	ND	ND	Scratch test +
	1 E (Top)	CD	3 weeks	ND	ND	E+	ND	ND	
Naik 1976 [280]	1 E	FDE	Few hours	ND	ND	ND	ND	ND	
Cooksley 1977 [281]	1 E	Cholestatic hepatitis		ND	ND	ND	ND	ND	LTT +
Abramov 1978 [282]	1 E	Dispnea, laryngeal edema	Few hours	ND	ND	ND	ND	ND	MDT +
Zafrani 1979 [283]	9 E	Cholestatic hepatitis	Weeks	ND	ND	ND	ND	ND	
Piaggiaro 1979 [284]	1 S (OC)	CD, fever, asthma		S+	ND	S+	S+ (In)	ND	
Veien 1980 [285]	8 S (OC)	CD		ND	ND	S+	ND	ND	
Lombardi 1982 [286]	1 E (Top)	CD		ND	ND	E +	ND	ND	Recurrence with reexposure
Keefe 1982 [287]	2 E	Hepatotoxicity		ND	ND	ND	ND	ND	
Ortuno 1984 [288]	1 E	Cholestatic hepatitis		ND	ND	ND	ND	ND	
Mae Diehl 1984 [289]	2 E	Cholestatic hepatitis		ND	ND	ND	ND	ND	
Pigatto 1984 [290]	1 E	FDE	3 days	ND	ND	E-	E+	ND	
Moscato 1984 [291]	2 S (OC)	Asthma	14 years 6 months	ND	ND	S -	S+ (In)	ND	
Galland 1984 [292]	1 S	MPE, Pruritic purpura, Vasculitis	10-15 min 2 days	ND	ND	ND	ND	M -	
Kofoed 1985 [293]	1 E	TEN	5 hours	ND	ND	E+	E+	ND	
Perrier 1987 [294]	1 E	Hepatitis		ND	ND	ND	ND	ND	
Larrey 1987 [295]	1 Tr	Cholestatic hepatitis	7 days	ND	ND	ND	ND	ND	
Rigauts 1988 [296]	1 E	Cholestatic hepatitis	2 weeks	ND	ND	ND	ND	ND	
Malo 1988 [297]	4 S (OC)	Occupational asthma		ND	ND	ND	S+ (In)	ND	4/51 exposed workers
Pendelton 1989 [298]	1 E	MPE and pruritus	24 hours	ND	ND	ND	ND	ND	
Jacqz-Aigrain 1990 [299]	1 E	TEN		ND	ND	ND	ND	ND	CoAd. With sulfisoxazole
Dooms-Goossens 1990 [300]	K, M	Airborne CD		ND	ND	ND	ND	ND	
Florido-Lopez 1991[301]	1 E	FDE	5 hours	ND	ND	E+, J-, M-	E+	J-, M-	
Mutalik 1991 [302]	1 E	FDE		ND	ND	ND	ND	ND	
Ostlere 1991 [303]	1 S	MPE, Pruritus	8 weeks	ND	ND	ND	ND	ND	

(Table 4) contd....

References	N° Cases	Clinical reaction	Chronology	Drug Allergy Evaluation					Other
				SPT	IDT	PT	DPT	CR	
Igea 1991 [162]	1 E	MPE	5 min	E-, S-		E-, S-	E+, S+	E, S	HRT E-, S -
	5 S	Urticaria	30 min	E-		E-, S-	S+	E-	HRT E-, S -
		MPE	5 min	E-, S-		E-, S-	E+, S+	E, S	HRT E-, S -
		MPE	3 hours	E-, S-		E-, S-	S+	E-	HRT E-, S -
		Urticaria / Angioedema	3 hours	E-, S-		E-, S-	S+	E-	HRT E-, S -
		Urticaria	1 hour	E-, S-		E-, S-	S+	E-	HRT E-, S -
Shirin 1992 [304]	1 E	MPE, pruritus, fever, hepatitis	2 days	ND	ND	ND	ND	ND	
Estrada 1992 [305]	1 E	Red neck syndrome		ND	ND	ND	ND	ND	
Malet 1992 [306]	1 S (OC)	Rhinoconjunctivitis		S+	S+	ND	S+ (Nas)	ND	
Sanchez de Dios 1992 [307]	1 M	HSP		ND	ND	ND	ND	ND	
Lopez Serrano 1993 [161]	1 E	Urticaria and pruritus	10 min	E +, S -	ND	E -	E+	S -	HRT +
De Vega 1993 [308]	1 C	Vasculitis	1 day	ND	ND	ND	ND	ND	
Uzzan 1993 [309]	1 Tr	Hepatitis		ND	ND	ND	ND	ND	
Fernandez Redondo 1994 [310]	1 E (Top)	CD	Few hours	ND	ND	ND	ND	ND	
	1 E	Generalized eczema	5 days	ND	ND	E +	ND	ND	
Valero Prieto 1994 [311]	1 S	HSP		ND	ND	ND	ND	ND	
Oteo 1994 [312]	1 C	Thrombocytopenic purpura		ND	ND	ND	ND	ND	
Trevisi 1994 [313]	1 A	Erythematous-pustulosis eruption	16 hours	ND	ND	ND	ND	ND	C3 and C4 normal
Pascual 1995 [314]	1 E	Urticaria	30 min	E +	ND	ND	ND	ND	E (IgE - RIA) +
Martins 1995 [315]	1 E (Top)	CD	8 days	ND	ND	E +	ND	ND	
Lestico 1995 [316]	1 E	SJS	ND	ND	ND	ND	ND	ND	
Raymond 1995 [317]	1 E	TEN	6 days	ND	ND	ND	ND	ND	CoAd. with sulfafurazole
Martin 1995 [262]	1 Tr	Serum sickness like disease	ND	ND	ND	ND	ND	ND	
Gomez-Lechon 1996 [318]	1 E	Cholestatic hepatitis	ND	ND	ND	ND	ND	ND	
Jorro 1996 [319]	1 E	Anaphylaxis	30 min	E -	E -	ND	E +	ND	PK + IgE (RAST) -
Valsechi 1996 [320]	1 E (Top)	CD	12 days	ND	ND	E +	ND	ND	
Vangala 1996 [321]	1 C	Angioedema	2 hours	ND	ND	ND	ND	ND	
Moreno 1996 [322]	1 M	Cholestatic hepatitis		ND	ND	ND	ND	ND	

(Table 4) contd....

References	N° Cases	Clinical reaction	Chronology	Drug Allergy Evaluation					Other
				SPT	IDT	PT	DPT	CR	
Goossens 1997 [323]	1 E	Perivascular lymphocytic dermatitis		E-	E-	ND	ND	ND	LTT +
Thevenot 1997 [324]	1 M	Hypersensitivity syndrome, Pustulosis	4 hours	ND	ND	ND	ND	ND	
Hubner 1997 [325]	1 A, R	Churg-Strauss	3–5 days	ND	ND	ND	ND	A, R	
Wessel 1998 [264]	1 E	Peroperative anaphylaxis	< 24 h	ND	ND	ND	ND		
Alvarez-Fernandez 1998 [326]	5 E			E + (3/5)	ND	ND	E+	C-, S-, A-, R-, M-, J-	
Quinones 1998 [327]	1 E	Pustulosis	8 hours	E -	ND	E -	E +	C -	
Mahboob 1998 [265]	6 E	FDE		ND	ND	ND	E+	ND	
Acero 1998 [328]	1 S (OC)	CD		ND	ND	S+	ND	ND	
Alvarez 1998 [329]	5 S			S-, C-, R-, A-, M-, J-	ND	ND	S+	E+ (1/5), C-, R-, A-, M-, J-	
Igea 1998 [330]	1 C	MPE, Angioedema	8 hours	E-, S-, C-, M-	E-, S-, C-, M-	E-, S-, C-, M-	C+	S-, E-, M-	
Rosina 1998 [331]	1 C	FDE	3 days	ND	ND	C+	ND	ND	
Gavura 1998 [332]	1 C	Vasculitis	6 days	ND	ND	ND	ND	ND	
Borja 1998 [333]	1 M	MPE	8 hours	M-, C-, E-	M-, C-, E-	M-, C-, E-	M+, C-, E-	C-, E-	
Krupa 1998 [334]	1 R	Urticaria	30 min	R+, C+	E+	R+, C+	ND	ND	
Barbaud 1998 [335]	2 E	Urticaria		E-	E+	E-	ND	ND	
		MPE		E+	ND	E-	ND	ND	
	2 S	Urticaria		S+	ND	S-	ND	ND	
		Urticaria / Angioedema		S-	S-	S-	S+	ND	
	1 J	Urticaria		J-	ND	J-	J+	ND	
Horn 1999 [336]	1 E	Cholestatic hepatitis	1 day	ND	ND	ND	ND	ND	Recurrence with reexposure
Gallardo 1999 [337]	1 E	Urticaria / Angioedema	Few hours	ND	ND	ND	ND	ND	
Goldberg 1999 [338]	1 C	HSP	10 days	ND	ND	ND	ND	ND	
Naldi 1999 [266]	4 A	Angioedema		ND	ND	ND	ND	ND	
	3 S	Angioedema		ND	ND	ND	ND	ND	
Williams 2000 [339]	1 E	SJS		ND	ND	ND	ND	ND	
Schissel 2000 [340]	1 A	MPE in infectious mononucleosis		ND	ND	ND	ND	ND	
Sharma 2001 [268]	6 E	ACDR		ND	ND	ND	ND	ND	

(Table 4) contd....

References	N° Cases	Clinical reaction	Chronology	Drug Allergy Evaluation					Other
				SPT	IDT	PT	DPT	CR	
Hamamoto 2001 [341]	1 C	FDE	10 days	ND	ND	C-	C+	ND	
Gangemi 2001 [342]	1 C	Dyspnea, cough, bronchospasm	Few minutes	ND	ND	ND	C+	ND	Reaction during alternative DPT
Cascaval 2001 [343]	1 A	Hypersensitivity syndrome	5 days	ND	ND	ND	ND	ND	
Saenz 2002 [344]	1 E	FDE	6 hours	ND	ND	E+, C+, M+, R+, A-	A -	C+, M+, R+, A	
Forman 2002 [269]	4 E	EM, TEN or SJS		ND	ND	ND	ND	ND	
Nucera 2002 [182]	2 S	MPE		S-	ND	S-	ND	ND	
Masia 2002 [345]	1 C	Fulminant hepatitis and fatal TEN		ND	ND	ND	ND	ND	CoAd. with disulfiram in alcoholic patient
Dakdouki 2002 [346]	1 A	MPE in infectious mononucleosis	1 day	ND	ND	ND	ND	ND	
Gurvinder 2002 [347]	1 R	Urticaria /Angioedema	2 days	R+, C-, E-	ND	ND	ND	C-, E-	
Amichai 2002 [348]	1 R	Localized MPE	3 days	ND	ND	ND	ND	ND	
Saissi 2003 [270]	5 S	Severe pustular eruption		ND	ND	ND	ND	ND	CoAd. with metronidazole
Terzano 2003 [349]	1 C	Pulmonary infiltration with eosinophilia	3 days	ND	ND	ND	ND	ND	Recurrence with reexposure
Borras-Blasco 2003 [350]	1 C	HSP	4 days	ND	ND	ND	ND	ND	
Freymond 2003 [351]	1 J	MPE	2 days	J-	J-	J +	J+	ND	
Baz 2004 [352]	1 C	Fatal TEN	3 days	ND	ND	ND	ND	ND	
Ohnishi 2004 [160]	1 C	Eosinophilic pneumonia	3 days	ND	ND	ND	ND	ND	LTT negative
Mimesh 2004 [353]	2 A (OC)	MPE	6 years	ND	ND	A+	ND	ND	
Noel 2004 [271]	1 A	EM		ND	ND	ND	ND	ND	
Benahmed 2004 [176]	7 S	Angioedema	Few hours	ND	ND	ND	S+	ND	
		Fever	Few days	ND	ND	ND	S+	ND	
		MPE	1 day	ND	ND	ND	S+	ND	
		Urticaria	1-2 h	ND	ND	ND	S+	ND	
		Urticaria	< 24 h	ND	ND	ND	S+	ND	
		Urticaria	Immediate	ND	ND	ND	S+	ND	
		Urticaria / Angioedema	Few hours	ND	ND	ND	S+	ND	
	1 R	Urticaria / Angioedema	12 h	ND	ND	ND	R +	ND	

(Table 4) contd....

References	N° Cases	Clinical reaction	Chronology	Drug Allergy Evaluation					Other
				SPT	IDT	PT	DPT	CR	
Lammintausta 2005 [175]	1 E	Urticaria		ND	ND	ND	ND	ND	Reaction during DPT
Alonso 2005 [354]	1 C	FDE tongue	4 days	ND	ND	C-, A-, E-	C+, A-, E-	A-, E-	
Khalidi 2005 [355]	1 C	TEN	2 days	ND	ND	ND	ND	ND	
Schmutz 2005 [356]	1 A	SJS		ND	ND	ND	ND	ND	
Zink 2006 [357]	1 C	Vasculitis	3 days	ND	ND	ND	ND	ND	
Brkljacic 2006 [358]	1 A	SJS	10 days	ND	ND	ND	ND	ND	
Chew 2006 [359]	1 R	Hypersensitivity pneumonitis	4 days	R-	R-	ND	R+	ND	
Clay 2006 [360]	3 T	Hepatitis	2 days	ND	ND	ND	ND	ND	
		Hepatitis with hepatic failure	1 week	ND	ND	ND	ND	ND	
		Hepatitis leading to massive hepatic necrosis and death	2 weeks						
Rallis 2006 [273]	5 E	3 Urticaria, 1 FDE, 1 MPE,		ND	ND	ND	ND	ND	
	2 C	1 Urticaria, 1 MPE		ND	ND	ND	ND	ND	
Sanchez-Morillas 2007 [361]	1 S	Urticaria	5 min	S+, C-, E-	S+, C+, E+	ND	C-, E-	C-, E-	
Dellestable 2007 [362]	1 S	MPE		S-	S-	S-	S+	ND	
Milkovic-Kraus 2007 [363]	7 A (OC)	CD, Rhinoconjunctivitis	3 mon – 4 y	ND	ND	A+	ND	ND	7/21 exposed workers
		CD	3 mon – 4 y	ND	ND	A+	ND	ND	
		CD, Rhinoconjunctivitis	3 mon – 4 y	ND	ND	A+	ND	ND	
		CD, Rhinoconjunctivitis	3 mon – 4 y	ND	ND	A±	ND	ND	
		CD	3 mon – 4 y	ND	ND	A+	ND	ND	
		CD	10 years	ND	ND	A-	ND	ND	
		Urticaria, rhinitis, dyspnea	10 years	ND	ND	A-	ND	ND	
Bottenberg 2007 [364]	1 T	Anapylaxis, Laryngeal edema	Shortly after 1 st intake	ND	ND	ND	ND	ND	
Bedard 2007 [365]	1 T	TEN	Few hours	ND	ND	ND	ND	ND	
Dore 2007 [274]	6 A + ibu- profen	4 SJS; 1 EM; 1 TEN		ND	ND	ND	ND	ND	
	1 C + ibu- profen	1 SJS		ND	ND	ND	ND	ND	
	1 A	1 SJS		ND	ND	ND	ND	ND	

Drug Allergy Evaluation (SPT – Skin Prick Tests; IDT – IntraDermal Tests; PT – Patch Tests; DPT – Drug Provocation Test; CR – Cross-Reactivity; In – Inhaled; Nas – Nasal); Macrolides (A – Azithromycin; C – Clarithromycin; E – Erythromycin; K – Ketasamycin; J – Josamycin; M – Midecamycin R – Roxithromycin; S – Spiramycin; T – Telithromycin; Tr – Troleandomycin); Clinical reaction (CADR – unspecified Cutaneous Adverse Drug Reaction; CD – Contact Dermatitis; EM – Erythema multiforme; FDE – Fixed drug eruption; HSP – Henoch-Schonlein Purpura; MPE – Maculopapular exanthema; SJS – Stevens-johnson Syndrome; TEN – Toxic epidermal necrolysis); CoAd. – Coadministration; CR – Cross-reactivity; HRT – Histamine release test; LTT – Lymphocyte transformation test; MDT – Mastocytes degranulation test; ND – Not Done; OC – Occupational setting; PK – Prausnitz-Kustner test; Top – Topical.

Table 5. Summary of Macrolides Hypersensitivity Reports

	Macrolide										Total
	A	C	E	J	M	R	S	T	Tr	CoAd.	
Clinical reaction											
Anaphylaxis	0	1	3	0	0	0	0	1	0	0	5
Urticaria / Angioedema	5	3	9	1	0	3	14	0	0	0	35
MPE	5	1	5	1	1	1	7	0	0	0	21
CD	6	0	5	0	0	0	10	0	0	1	22
FDE	0	3	13	0	0	0	0	0	0	0	16
Severe bullous skin diseases (TEN, SJS)	4	2	7	0	0	0	1	1	0	10	25
Other vasculitis	0	6	23	0	1	0	2	0	0	0	32
Other	1	2	1	0	2	1	8	3	3	6	27
Unknown	0	0	11	0	0	0	5	0	0	0	16
Occupational exposure	9	0	0	0	0	0	17	0	0	0	26
Chronology											
< 1 h	0	1	4	0	0	1	5	1	0	0	12
1 – 24 h	1	2	9	0	2	1	6	1	0	0	22
> 24 h	12	12	17	1	0	3	6	3	1	2	57
Unknown	8	3	47	1	2	0	30	0	2	15	108
Drug allergy evaluation	9/21	6/18	32/77	2/2	1/4	4/5	40/47	0/5	0/3	0/17	94/199
SPT (+/n)		0/1	6/13	0/2	0/1	2/3	4/18				12/38
IDT (+/n)		0/1	1/4	0/1	0/1	0/1	2/4				3/12
PT (+/n)	7/9	1/4	8/13	1/2	0/1	1/1	10/22				28/52
DPT (+/n)		4/4	19/19	2/2	1/1	2/2	7+In, 1+Nas, 20+oral				56
Other (+/n)		1LTT-	1 ST +, 2 LTT+, 1 MDT+, 1 HRT+, 1 HRT-, 1 IgE (RIA)+, 1 IgE (Rast), 1 PK+				1HRT+, 5HRT-				
Cross-reactivity											
Yes		0	2	0	0	1	2				5
No		2	5	0	1	1	6				15

Drug Allergy Evaluation (SPT – Skin Prick Tests; ST – Scratch test IDT – IntraDermal Tests; PT – Patch Tests; DPT – Drug Provocation Test; In – Inhaled; Nas – Nasal); Macrolides (A – Azithromycin; C – Clarithromycin; E – Erythromycin; K – Kitasamycin; J – Josamycin; M – Midecamycin R – Roxithromycin; S – Spiramycin; T – Telithromycin; Tr – Troleandomycin); Clinical reaction (CADR – unspecified Cutaneous Adverse Drug Reaction; CD – Contact Dermatitis; EM – Erythema multiforme; FDE – Fixed drug eruption; HSP – Henoch-Schonlein Purpura; MPE – Maculopapular exanthema; SJS – Stevens-johnson Syndrome; TEN – Toxic epidermal necrolysis); CoAd. – Coadministration; CR – Cross-reactivity; HRT – Histamine release test; LTT – Lymphocyte transformation test; MDT – Mastocytes degranulation test; ND – Not Done; OC – Occupational setting; PK – Prausnitz-Kustner test; Top – Topical.

rolide drug allergy using the following queries: “(Macrolides [MH] OR Macrolides [TIAB] OR Erythromycin [TIAB] OR Roxithromycin [TIAB] OR Clarithromycin [TIAB] OR Troleandomycin [TIAB] OR Dirithromycin [TIAB] OR Azithromycin [TIAB] OR Josamycin [TIAB] OR Spiramycin [TIAB] OR Midecamycin [TIAB] OR Roxithromycin [TIAB] OR Kitasamycin [TIAB] OR Oleandomycin [TIAB]) AND (“Drug hypersensitivity” [MH] OR “Drug hypersensitivity” [TIAB] OR Allergy [TIAB])”. We selected papers written in English, French, Spanish or Portuguese, or those with an English abstract which allowed enough details on macrolide allergy.

[TIAB] OR Kitasamycin [TIAB] OR Oleandomycin [TIAB]) AND (“Drug hypersensitivity” [MH] OR “Drug hypersensitivity” [TIAB] OR Allergy [TIAB])”. We selected papers written in English, French, Spanish or Portuguese, or those with an English abstract which allowed enough details on macrolide allergy.

In Table 3 we present the data on macrolides' hypersensitivity epidemiology. Results presented confirm that macrolides are amongst the safest antibiotics, accounting for very few drug hypersensitivity cases reported. It is also important to note that in most series, macrolides allergy reports rely on self-reported or a convince history of drug allergy. In those series in which macrolide allergy evaluation was performed, it was actually proved by DPT in only 2.7 to 17% of cases.

In Table 4 are presented all case series of hypersensitivity reactions to macrolide antibiotics which are pooled again in Table 5. 199 hypersensitivity reactions to macrolides have been reported, with erythromycin (77) followed by spiramycin (47) and azithromycin being the most implicated drugs. Urticaria (35) was the most common reported clinical reaction. Hypersensitivity reactions occurring in an occupational exposure have been reported with spiramycin and azithromycin. Although in most reports the chronology of the reaction was unknown, late reactions (> 24 h after drug intake) appeared the most frequently reported. Macrolide allergy diagnosis relied only on a suggestive clinical history in more than half of the reported cases and only 94 out of the 199 reported reactions underwent some drug allergy evaluation:

DPT in some centers, patch tests (PT) in most diagnosed cases, followed by skin prick tests and intradermal tests. Some authors reported the use of other laboratory tests like specific IgE, LTT and HRT. The methodologies used in all these tests lacked standardization.

Macrolide Allergy Management

Cross-Reactivity

Macrolide antibiotics are unlikely to cross react with other macrolide antibiotics. However, cross-reactivity has not been studied thoroughly in the literature. When it was studied (20 cases), it was found in 5 cases (involving mostly spiramycin - erythromycin [358, 301]) and the 15 other patients tolerated a different macrolide antibiotic. Macrolide antibiotics may also cross-react with other non-antibiotic macrolides, like the new immunomodulators tacrolimus [178].

Tolerance Induction / Desensitization

Desensitizations for type I hypersensitivity reactions in penicillin allergic patients were first developed 50 years ago. Successful cases of rapid progressive penicillin readministration led to the concept of temporary clinical tolerization [179]. The administration of suboptimal doses of drug antigens followed by the full therapeutic dose was safely achieved in highly allergic patients, permitting the treatment of severe infections [180]. Temporary tolerization is achieved in hours and can be maintained if drug antigens are administered at regular intervals, depending on pharmacokinetic parameters. Rapid desensitizations should only be done in settings with one-on-one nurse-patient care and where resuscitation personnel and resources are readily available. After a successful desensitization, repeated desensitizations can be done in outpatient or inpatient settings with similar conditions [181].

Nucera *et al.* [182] performed a rush tolerance induction in 2 pregnant patients, suffering from toxoplasmosis, who

developed a maculopapular exanthema after treatment with spiramycin. In days 1–3 the doses were given every 30 min and on days 4 and 5 every hour. At the end of this treatment the patients were able to continue spiramycin treatment until the end of their pregnancies without any side effects, and 2 healthy children were born.

Recently, it has been described the use of omalizumab (an anti-IgE mAb) to treat a severe ongoing symptoms of insulin allergy, despite continuous treatment with antihistamines and systemic corticosteroids, appearing 9 months after a successful desensitization [183]. It might represent a promising treatment for severe drug allergies with essential drugs where other procedures (*e.g.* tolerance induction/desensitization) have failed.

CONCLUSION

Allergy to macrolides is extremely rare (0.4 to 3% of treatments). There is little information which does not allow a conclusion with regard to the diagnostic tests. An immediate IgE dependent hypersensitivity has been shown with erythromycin in some cases. However, the mechanism is unknown and the skin tests are more often negative, so drug provocation tests performed in specialized centers might be regarded as the gold standard for macrolides allergy diagnosis. The clinical manifestations are the same as those encountered with the β -lactams. It would appear that macrolide antibiotic allergies are unlikely to be class allergies. This is important as the eviction advice could be limited to the only responsible macrolide.

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