

Contact Allergy to Topical Corticosteroids: Update and Review on Cross-Sensitization

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Abstract: Contact allergy to topical corticosteroids (TCs) is an emerging problem, whose diagnosis can be complex owing to the peculiar characteristics of steroid allergens and the possible inadequacy of current diagnostic methods, including concentration and vehicle used in patch testing. The occurrence of cross-reactions among different TCs is not rare, but prediction of these is not sufficiently reliable. Moreover, the distinction between true cross-reactivity and concomitant sensitization may be difficult. The original classification proposed by Coopman *et al.* has been distinguished corticosteroids into four groups according to their molecular structure. These authors hypothesized that allergic contact reactions were more frequent with corticosteroids belonging to the same group. However, the clinical practice has evidenced that cross reactivity exists also among corticosteroids belonging to different groups. The potential to cross-react among corticosteroids is thought to be related not only to the structural homology but also to the stereoisomerism and metabolism of these drugs. Recent evidence suggests that mechanisms responsible for cross-reactivity may occur at T lymphocyte level during antigen presentation. Further investigations are needed to gain a more complete understanding of this important topic. This article also reviews some patents related to the treatment of contact dermatitis and other inflammatory skin diseases.

Keywords: Topical corticosteroids, classification, chemical structure, contact sensitization, cross-sensitization, allergic contact dermatitis, immunological mechanisms, hypersensitivity reactions.

INTRODUCTION

Topical corticosteroids (TCs), introduced in clinical practice in the first 1950s, are broadly used to treat several inflammatory skin diseases thanks to their antiinflammatory, immunosuppressive and antiproliferative activities. There are several corticosteroid molecules available in different topical formulations, alone or in combination with other drugs, such as antibiotic and antifungal agents. TCs can induce a great variety of well-known adverse events, and many of these events are associated with prolonged use or local immune suppression. Contact allergy to TCs is another possible untoward effect, which was initially regarded as a paradoxical phenomenon, because TCs represent the cornerstone of treatment of contact dermatitis. Since the first descriptions of contact sensitization to TCs in 1959 [1, 2], other reports were subsequently published, but the real extent of the problem was well recognized only in the late 1980s [3]. Hypersensitivity to TCs is a problem of dermatological and allergological concern, that has been thought to affect only a minority of patients with a skin disease treated with such drugs. However, in view of the wide use of TCs, the incidence of TC sensitization is very likely to be underestimated, also considering the difficulty in diagnosing these complaints owing to the peculiar characteristics of steroid allergens and the possible inadequacy of current diagnostic methods [4, 5].

EPIDEMIOLOGY

The prevalence of TC-induced allergic contact dermatitis (ACD) ranges from 0.2% to 6% according to the different patient series [6]. This apparent variability of prevalence estimates may be due to differences in patch test methodology, in terms of vehicles, TC panel and concentrations, as well as reading times of test reactions. Differential use of TC molecules among various countries may be another cause of discrepancies in prevalence results.

In a study lasting nearly 2 years conducted in 2,073 patients who underwent patch tests to six TCs, Doooms-Goossens *et al.* found 61 patients (2.9%) with a positive patch test to at least one TC [7]. Moreover, in accordance with this investigation, TCs were the 7th most frequent contact allergens, with budesonide being the TC most commonly responsible for allergic sensitization, often in association with positive patch test reactions to other TCs. A multicenter study carried out by the European Environmental and Contact Dermatitis Research Group (EECDRG) evaluated TC contact allergy in ten European countries, showing an overall incidence of 2.6%, with extremely variable percentages in the different member states ranging from 6.4 % in Belgium to 0.4-0.6 % in Spain and Portugal [8]. In a 6-year retrospective study performed in the U.S. at the Mayo Clinic, of 1,188 patients patch tested with TCs, 127 (10.7%) had a positive reaction to at least one TC, while 56 patients reacted to multiple TCs [9].

CLINICAL FEATURES AND DIAGNOSTIC ASPECTS

The clinical presentation of ACD to TCs is frequently characterized by modest inflammatory changes, being clearly

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exudative lesions rarely seen. Subjects with atopic eczema, hand dermatitis, leg ulcers and stasis dermatitis are more prone to develop sensitization to TCs [10]. Diagnosis can be difficult but should be suspected when an inflammatory skin disease does not improve or even worsen during TC treatment. The evolution of the lesions is usually subacute or chronic. Unusual clinical pictures of ACD following the application of TCs on the skin include oedema, mostly affecting the face and genitalia, erythema multiforme-like eruption, or lesions resembling granuloma annulare, acute generalized exanthematous pustulosis, or lupus erythematosus [11-18]. Contact allergy due to inhaled corticosteroids can cause swelling of the lips and eyelids, stomatitis, perioral dermatitis, dysphagia, nasal congestion and pruritus/burning, worsening of rhinitis, nasal septum ulceration and perforation, diffuse pruritus, eczematous lesions with variable extension, and also generalized skin eruptions, such as macular exanthema or urticaria [19-23].

In subjects previously sensitized to TCs, the systemic absorption of these drugs through multiple routes of administration (oral, parenteral, or intraarticular) can induce the so called systemic contact dermatitis, which can present as generalized maculo-papular, papulo-vesicular, pustular, or erythematous eruption, as well as urticarial rash [24-27].

Clinical suspicion of ACD with TCs should be confirmed by patch testing. Patch tests with TCs in patients with contact sensitization to these agents can evoke false negative reactions because of the intrinsic antiinflammatory action of TCs which may suppress or delay the cutaneous response. Therefore, reading should be postponed on day 5 or 7 (namely up to 5 days after the usual evaluation in patch testing) [28]. At the first reading, the reaction may appear only at the edges of the test area, while it can be completely absent in its central portion, where the antiinflammatory effect of the TC is more evident because of the accumulation at higher concentrations. This phenomenon, named 'edge- or border-effect' fades away on successive readings after a few days.

The EECDRG recommends that tixocortol pivalate and budesonide are used for patch testing as TC allergy markers, thus permitting the identification of most patients who are allergic to TCs [28]. Recently also hydrocortisone-17-butyrate has been introduced among TC allergy markers. These markers can be used in patch testing separately or combined in mixes [3, 29]. There is not yet general agreement upon the optimal concentration and vehicle for patch testing with TCs [3-7, 30].

Currently, petrolatum is not regarded as the best vehicle to test hydrocortisone-17-butyrate. For budesonide and tixocortol pivalate either petrolatum preparations or ethanolic solutions seem to work equally well. The advantages of ethanol over petrolatum include a better penetration of TCs, a reduction of their concentration in patch testing and a quicker development of the skin reaction in allergic subjects [30]. A disadvantage caused by the use of ethanol as a vehicle is that some TCs can be degraded in ethanol solutions under particular storage conditions, whereas preparations in petrolatum are usually more stable [31]. The necessity to seek new vehicles for TC patch testing is an emergent topic which deserves further investigations.

HISTOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL FEATURES

ACD is an immunological reaction in which T lymphocytes are activated in response to contact of the skin with a specific allergen.

A histopathological study performed on punch-biopsies taken from positive patch test reactions to hydrocortisone showed a perivascular inflammatory dermal infiltrate consisting of lympho-monocytes with exocytosis and spongiosis phenomena in the epidermis, thus drawing histopathological pictures of classic ACD [32]. Later, an immunohistochemical analysis found no qualitative differences between ACD induced by tixocortol pivalate and that caused by nickel sulphate, providing evidence for the immunological basis of the hypersensitivity reaction in both forms [33]. In skin samples obtained from positive test reactions to tixocortol pivalate, there was an increased expression of the receptors for interleukin (IL)-1 α and tumor necrosis factor (TNF)- α in the dermis, as well an up-regulation of adhesion molecules on keratinocytes and endothelial cells.

MECHANISMS UNDERLYING SENSITIZATION TO TCs

T Lymphocytes are the immune response effector cells implicated in ACD, which represents a typical example of a delayed hypersensitivity cell-mediated reaction (CMR) type IV according to Gell and Coombs' classification. According to Pichler [34], ACD can be further classified as a type IVa CMR, consisting in a Th1-type reaction characterized by macrophage activation and release of large quantities of interferon (IFN)- γ and other cytokines, such as IL-12, IL-18 and TNF- α . *in vitro*, Wilkinson demonstrated the activation of the monocytic cell lineage from patients with ACD to hydrocortisone, as shown by the increased consumption and capture of tritiated thymidine [35].

The mechanisms triggering the immune response and T lymphocyte recruitment in TC contact allergy can be explained by the hapten theory, whereby the TC low molecular weight makes it insufficiently immunogenic unless it is covalently bound to a protein, producing a complete antigen [36]. Bongaard [37] suggested that in aqueous solution C21 of the cortisone molecule is degraded to a glyoxal steroid, thus allowing the side chains present on C17 to bind covalently to the guanidine groups of arginine. The transformation of the steroid molecule to a complete antigen would thus present the carbon rings of the molecule to the immunocompetent cells. Stable binding of the steroid to the serum or skin proteins would therefore make it immunogenic. However, the association of the hapten theory with the danger theory has been recently proposed to explain drug-induced allergic reactions. According to this theory, a drug and its metabolite must not only have a high affinity for the organism proteins but also a certain degree of toxicity, enough to trigger danger signals and hence activation of the immune system [38]. What these danger signals might be is not known, but they likely include cellular stress or necrotic products of dead cells. The release of proteins or chemokines signalling cell distress may be sufficient to activate the immune system to fight a foreign body.

ALLERGENIC CROSS-REACTIVITY TO CORTICOSTEROIDS

Corticosteroids are drugs with a fixed, well-defined chemical formula, consisting of a cyclopentanoperhydrophenanthrene structure on which precise modifications are operated, such as halogenation of specific sites on the molecule to increase the anti-inflammatory properties and/or skin or mucosal penetrability. Fig. (1) shows the basic structure of a corticosteroid molecule. The occurrence of cross-reactions among different TCs is not rare, but prediction of these is not sufficiently reliable. Our knowledge about cross-reactions among corticosteroids is very limited also considering that the optimal concentration and vehicle in patch testing have not yet been standardized.

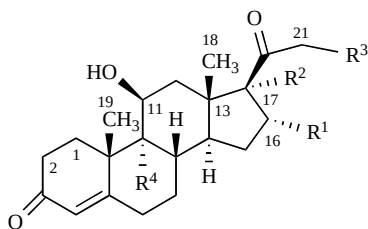


Fig. 1. Basic structure of a corticosteroid molecule.

Already by the early 1970s, Alani and Alani hypothesized the existence of a possible allergenic cross-reactivity among TCs [39], despite the difficulty in distinguishing between true cross-reactivity and concomitant sensitization owing to the impossibility of making a detailed reconstruction of the patient's history, including previous use of different TCs. In patients with ACD to TCs there is frequently a chronic evolution or aggravation of a pre-existing dermatitis, so that the patient or the physician tends to increase the use or prescription of TCs, employing ever more powerful molecules. This behaviour creates great confusion in the diagnostic assessment and collection of medical history.

The existence of allergenic cross-reactivity phenomena was confirmed by the results of some epidemiological studies conducted to investigate the incidence of ACD to TCs. In these studies some patients were found to present positive patch tests to corticosteroids not available on the market in the country where the study was carried [7], and obviously they could not have become sensitised through use of the molecule.

In 1989, after analyzing the literature data and performing patch tests with various TCs in a group of 19 patients, Coopman and colleagues [40] proposed a classification of corticosteroids based on the molecular structure, thus dividing them into four groups (A, B, C, and D) shown in Table 1 of which tixocortol pivalate, triamcinolone acetonide, betamethasone and hydrocortisone-17-butyrate are the corresponding markers, respectively. These researchers identified the D ring as the key factor that enables discrimination of one molecule from another. They hypothesized that allergic contact reactions occurred more frequently with corti-costeroids belonging to the same group, while cross-reac-tions were uncommon inbetween groups. In particular, in the authors' opinion, positive reactions appeared to be approximately six to seven times more frequently in well-defined groups of structurally-related substances than between corticosteroids of different groups.

Nevertheless, the clinical practice has partly denied the theoretical assumptions of Coopman *et al.* and it has been seen that cross reactivity exists also among corticosteroids belonging to different groups, particularly between those of group A and group D. Cross-reactivity between group B and group D is rarer. The potential to cross-react among corticosteroids may be related not only to the structural homology but also to the stereoisomerism and metabolism of these drugs [37, 41].

Lepoitteven *et al.* performed a computerized conformational analysis of the TC molecules demonstrating that groups A, B, and D were highly homogeneous within each group in terms of molecular structure (e.g., shape, volume

Table 1. Classes of Allergenic Cross-Reactivity Among TCs [40]

Class and Structural Characteristics	Main Examples of Related Drugs
Class A Hydrocortisone types with no modification of the D ring or C20-C21 or short chain esters on C20-C21	Hydrocortisone, prednisolone and methylprednisolone and their ester acetate, sodium phosphate and succinate, cortisone, prednisone, tixocortol pivalate
Class B Triamcinolone acetonide types with cis/ketalic or diolic modifications on C16-C17	Triamcinolone acetonide, fluocinolone acetonide, amcinonide, desonide, fluocinonide, halcinonide, budesonide, flunisolide
Class C Betamethasone types with a -CH ₃ mutilation on C16, but no esterification on C17-C21	Betamethasone, dexamethasone, desoxymethasone, fluocortolone, halomethasone
Class D Clobetasone or hydrocortisone esterified types with a long chain on C17 and/or C21 and with no methyl group on C16	Clobetasone butyrate, clobetasol propionate, hydrocortisone-17-aceponate, hydrocortisone-17-butyrate, beclomethasone dipropionate, betamethasone-17-valerate, betamethasone dipropionate, methylprednisolone aceponate, prednicarbate

and distribution of the charges). These authors were unable to represent the molecules of group C, that were comparable, in their view, to those of group A [41]. The investigation also showed the anomalous behaviour of budesonide, which exhibits two isomeric conformations, namely D-budesonide, that resembles the corticosteroids of group B, for instance acetonides, and L-budesonide, that mimics the hydrophobic pocket of the class of esters and would thus assign it to group D. This structural anomaly had already been reported by Japanese authors [42], who hypothesized that, thanks to the ability of the propyl substitute on the C terminal of the 16- α , 17- α -butyldene-dioxylic portion to rotate freely, budesonide could exhibit several conformational variants apart from D- and L-budesonide, including the racemic variant, which is extremely unstable.

The study by Coopman *et al.* [40] also confirmed that the allergenic characteristics of budesonide depend on its peculiar spatial structure, since patch tests performed with its main metabolites, 16- α -hydroxy-prednisolone and n-butyraldehyde and their further metabolites, 1-butanol, formaldehyde and prednisolone, were negative in subjects sensitised to budesonide.

Although, application of the above-mentioned classification in four groups has proven much simpler and more efficacious than other proposed classifications [43], various authors have raised some objections. For example, Wilkinson and coworkers proposed that the immunogenicity of cortisol should be attributed to the entire cyclopentanoperhydrophenanthrene structure [44]. In a study conducted in 96 patients with ACD to hydrocortisone, by mathematical analysis of the percentage of patients with positive skin reactions to patch tests with various TCs, they demonstrated that the modifications operated on the carbon rings and the skin test positivity were correlated in decreasing order with substitutions made on C6, C9, or both, and therefore that the B ring could be another site on the corticosteroid molecule affecting allergenic cross-reactivity [45].

It is possible that the presence of one atom of a halogenic element like chloride or fluoride on C9, by determining an electron-attractor effect on C11 [46], could not only cause folding of the steroid molecule, but it might also give it a notable conformational stability. This is indirectly shown by the fact that a halogenated TC like fluticasone propionate presents a single isomer whereas budesonide exhibits three variants, and that it has not been possible to produce a tridimensional representation of halogenated corticosteroids belonging to group C [41].

In a later study in which 46 subjects with positive reactions to budesonide underwent patch tests to 17 other topical TCs, Wilkinson *et al.* also suggested that the modifications on C21 favoured binding to the skin proteins, but had no immunological effect [47], since the keratinocytes possess an esterase that causes rapid hydrolysis of the ester present on C21 [48].

Enzymatic hydrolysis can thus alter the class to which a TC belongs, especially in the case of group D. A molecule in group D like prednicarbate, for example, a non halogenated drug with a high antiinflammatory activity, is a derivative of

prednisolone, that presents an ethylcarbonate on C17 and a propionate group on C21. It is rapidly hydrolyzed after skin absorption into prednisolone-17-ethylcarbonate, that also belongs to group D, and then prednisone, a member of group A [49].

Consequently, it is possible, when using group D TCs, to develop concomitant sensitization to molecules belonging to group A (non halogenated) and group C (halogenated). For this reason the classification proposed by Coopman *et al.* was revised and updated, subdividing group D into two subgroups:

- subgroup D1 (with fluorination on C9, methylation on C16 and an esterified side chain on C17, potentially cross-reacting with TCs in group C or causing co-sensitization to the latter, as in the case of clobetasol propionate);
- subgroup D2 (no halogenation on the carbon rings, neither methyl group on C16 nor ester on C17, like methylprednisolone aceponate, that can cause cross-reactions or co-sensitization to TCs in group A) [50].

The frequently associated skin sensitization to hydrocortisone (group A) and hydrocortisone-17-butyrate (group D) reported by other authors [51] seems to confirm this last possibility.

Wilkinson has also recently been obliged to revise his hypothesis that modifications only on C6/C9 are enough to affect allergenic cross-reactivity to TCs [52]. In fact, he now considers that the immunodominant sites affecting the immunogenicity of the basic hydrocortisone molecule and hence allergenic cross-reactivity phenomena are positions C6/C9 on B ring and positions C16/C17 on D ring, thus finally admitting the importance of the D ring.

Not all topical or systemic corticosteroid molecules can be included in the four groups of the classification proposed by Coopman *et al.* For instance, molecules like deflazacort, fluticasone propionate, mometasone furoate, owing to their peculiar structure (oxazoline ring on C16/C17 in deflazacort, esterification with short side chains on C17, the presence of a halogenated element on C21 and C17 as in fluticasone propionate and mometasone furoate) are difficult to classify correctly in the above-mentioned four groups without having to make some compromise. The particular structural formula of fluticasone propionate and mometasone furoate could also justify the low risk of allergic contact sensitization reported after their use [53, 54]. They could thus be an alternative molecule for use in patients with contact sensitization to two or more groups of TCs [55].

As a matter of fact, although the classification into four allergenic cross-reactivity groups is reasonably valid and reliable [56-58], its use is limiting in clinical practice. The modifications operated on D ring are not always enough to explain the lack of cross-reactivity among molecules in the same group [59,60] or the presence of cross-reactivity among molecules in different groups not ascribable to concomitant sensitisation. This is true for mometasone furoate, that seems to behave like class C TCs [61], but it may present cross-reactivity to group B TCs [62]. Moreover, sensitization to multiple TC molecules is an emerging problem which can not be explained only with concomitant reactions.

In order to better understand this problem, we also need to assess the behaviour of the effector cells of the immune response: the T lymphocytes.

CROSS-REACTIVITY AT THE T LYMPHOCYTE LEVEL

T Cells recognize antigen thanks to their antigen receptors, consisting of two heterodimer chains, alpha-beta (present on 95% of T lymphocytes) or gamma-epsilon (in the remaining 5%), that constitute the lymphocyte T cell receptor (TCR) which interacts with the antigen presenting cell (APC), like the Langerhans cell, in the skin [36]. After haptenization through binding to the serum or skin proteins, the hapten is internalized into the APC and presented to the lymphocyte TCR in association with the major histocompatibility complex (MHC) antigens. Two classes of MHC molecules, types I and II, present the hapten to the TCR, triggering different T lymphocytes. Antigens synthesized and degraded in the cell cytosol are presented in association with MHC I molecules and trigger a CD8+ T lymphocyte-mediated response of cytotoxic type. MHC II molecules present antigens that have been internalized in the vesicles by endocytosis and activate CD4+ T lymphocytes, that can orchestrate a wider, more complex immune response than that mediated by CD8+ cells. CD4+ cells trigger other immune effector cells like B lymphocytes, macrophages or even CD8+ T lymphocytes, causing the release of specific inflammatory cytokines. This antigen presentation can be induced by chemically reactive drugs, that can bind stably to the peripheral groups of the protein amino acids or even modify the peptides of the MCH molecules. Alternatively, the culprit drugs might be originally inactive but can be metabolically activated; in other words, such drugs have to be metabolised to become reactive haptens that can bind covalently to the proteins ('pro-hapten theory') [34, 36]. The activation of these pro-haptens generally occur through oxidation by endocellular P-450 cytochrome.

Iatrogenic haptens are presented in association with MHC molecule peptides to the T lymphocyte TCR. Studying the steroid hapten, Lauerma *et al.* have demonstrated that Langerhans cells and therefore MHC molecules have an important role in bringing about T lymphocyte recruitment and the development of an immune response to corticosteroids [63].

Despite the considerable progress made in the field of hypersensitivity reactions to drugs, the molecular mechanisms underlying recognition of the iatrogenic hapten by TCR, be it alpha-beta or gamma-epsilon, are still not completely known [64] or have been identified only for some drugs such as beta-lactams, local anesthetics with an amide group, and sulphonamides [65].

Since the allergenic cross-reactivity of corticosteroids mainly concerns 2 immunodominant sites, the D ring, with the cross-reactivities proposed by Coopman and colleagues, and the B ring, with the modifications proposed by Wilkinson [40,52], we could hypothesize that during molecule presentation to the TCR, the immunological recognition involves one site at a time (either the D ring and its modifications or the B ring with its modifications on C6 and C9). This would explain why allergic cross-reactivity does

not always occur among TCs considered structurally similar as regards only a single characteristic [59, 60].

Although *in vitro* studies have been made by isolating drug-specific T cell clones from drug-sensitive subjects and analysing their involvement in immunological recognition and cross-reactivity phenomena, such studies have largely focused on sulphonamides, beta-lactams and local anesthetics [65, 66], and never on corticosteroids. These studies suggest that T lymphocytes tend to recognize the overall structure of the drug including the core (e.g., the penicilloyl group in patients allergic to beta-lactams) [66], although in the case of sulphanilamides a very heterogeneous polyclonal-type T cell response has been observed to the various drugs containing an SO₂-NH reactive group of sulphanilamide type. However, this was not sufficient to induce the immune activation of T lymphocytes, that recognized the sulphanilamide structure of sulphomethoxazole but not drugs like furosemide and celecoxib, that present the SO₂-NH group but not the sulphanilamide structure [65, 66].

On this basis, it is possible that in corticosteroid allergy there may be T lymphocyte clones that recognize the modifications operated on the B ring, and lymphocyte clones that recognize those operated on the D ring. Anyway, since drug-specific T lymphocytes tend to recognize the basic molecular structure of the drug [66], T lymphocytes sensitized to corticosteroids should be able to recognize the crude cyclopentanoperhydrophenanthrene structure, consisting of 4 carbon rings.

Moreover, it has recently been proposed that even chemically inert drugs that are not able to bind to MHC molecule peptides can interact with the TCR of sensitized subjects in a weak manner, but enough to activate T lymphocytes (pharmacologic interaction of drugs with immune receptor, the so called 'p-i concept') [34]. This mechanism has been demonstrated for sulphomethoxazole, lidocaine, mepivacaine, carbamazepine, lamotrigine, celecoxib and p-phenylendiamine.

T Lymphocytes of sensitized patients thus undergo activation and proliferation independently of the MHC molecules, even if MHC-restricted. This implies that to achieve full activation of the T cell, the TCR needs to interact with both the drug and the MHC molecule that must send the activation signal, even if it does not "present" the drug in association with its peptides [34, 36].

Taking into account these recent studies, it can be hypothesized that exposure to various corticosteroids in a sensitized subject causes the activation of T lymphocytes by drug interaction with TCR. This ultimately leads to full recognition by T lymphocytes of the basic structure of the corticosteroid hormone, regardless of the modifications operated on it.

Direct evidence of this observation is provided by the fact that subjects with polysensitization to various TCs tend to react to corticosteroids whose structural formula prevents their assignment to one of the 4 groups of Coopman *et al.* [53, 54, 67], or to undergo extension of T lymphocyte activation to sex hormones [68], that also have the basic 4-carbon ring structure.

Paradoxically, this fine immunological recognition of the steroid allergens places patients at a disadvantage, as they will develop multiple sensitization to many TCs [58, 59] and even to systemic corticosteroids [27, 69, 70].

It has also been demonstrated that the density of TCRs on the cell surface can affect the degree of cross-reactivity, namely the ability of T lymphocytes to recognize drugs with a structure similar to that of the drug which originally induced the sensitization. The presence of a high number of TCRs on the lymphocyte surface increases this cross-reactivity, although the mechanisms determining the density of TCRs are unknown. They do not appear to depend on the iatrogenic allergenic dose [71], and it is not known whether this density can be pharmacologically down-regulated.

RECENT PATENTS

A recent invention provides methods for modulating lymphocyte activity. Such methods generally include contacting a pG6b-positive lymphocyte with a bioactive agent capable of modulating pG6b-mediated signaling in an amount effective to modulate at least one lymphocyte activity [72]. Novel compositions derived from antigen-binding sites of immunoglobulins having affinity for IL-31 are provided. The compositions exhibit immunological binding properties of antibody molecules capable of binding specifically to a human IL-31 [73]. The inventors of a product have surprisingly found that galectin-2 may be used to treat inflammatory skin diseases. They could show that in inflammatory skin diseases where there is an increased level of activated T cells such as contact allergy or psoriasis, galectin-2 could be successfully used to lower the level of activated T cells and/or to prevent an increase in the level of activated T cells. It is therefore to be expected that galectin-2 is useful in particular for atopic dermatitis, contact allergy, psoriasis, lichen planus and acne [74]. Another patent provides antibody conjugates comprising a targeting agent covalently attached to an antibody or fragment thereof. The antibody conjugates of the invention are particularly useful for imaging a tumor, organ, or tissue and for treating diseases and disorders such as cancer, inflammatory diseases, autoimmune diseases, infectious diseases, and neurological disorders. Kits containing the antibody conjugates described herein find utility in a wide range of applications including, for example, *in vivo* imaging and immunotherapy [75].

CURRENT & FUTURE DEVELOPMENTS

Although cross-reaction phenomena among TCs have been thoroughly studied and defined, further investigations are warranted to gain a more complete understanding of this problem. Studies of the molecular interactions between corticosteroid drugs and T lymphocytes, the effectors of allergic sensitization, need to be carried out *in vitro* and confirmed *in vivo*, both in subjects with positive patch tests to a specific group of TCs and in those showing multiple sensitization, to achieve a better insight into the mechanisms leading to TC allergy [76].

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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