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New Insights in Toxic Epidermal Necrolysis (Lyell's Syndrome)

Clinical Considerations, Pathobiology and Targeted Treatments Revisited

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Contents

Abstract

Drug-induced toxic epidermal necrolysis (TEN), also known as Lyell's syndrome, is a life-threatening drug reaction characterized by extensive destruction of the epidermis and mucosal epithelia. The eyes are typically involved in TEN. At present, the disease has a high mortality rate. Conceptually, TEN and the Stevens-Johnson syndrome are closely related, although their severity and outcome are different. Distinguishing TEN from severe forms of erythema multiforme relies on consideration of aetiological,

clinical and histological characteristics. The current understanding of the pathomechanism of TEN suggests that keratinocytes are key initiator cells. It is probable that the combined deleterious effects on keratinocytes of both the cytokine tumour necrosis factor (TNF)-α and oxidative stress induce a combination of apoptotic and necrotic events. As yet, there is no evidence indicating the superiority of monotherapy with corticosteroids, ciclosporin (cyclosporine) or intravenous immunoglobulins over supportive care only for patients with TEN. However, the current theory of TEN pathogenesis supports the administration of a combination of antiapoptotic/antinecrotic drugs (e.g. anti-TNF-α antibodies plus *N*-acetylcysteine) targeting different levels of the keratinocyte failure machinery.

Drug-induced toxic epidermal necrolysis (TEN), also known by its eponym Lyell's syndrome,[1] remains one of the most dramatic dermatological emergencies. It represents a life-threatening disease characterized by extensive destruction of the epidermis and mucosal epithelia. TEN affects people of all ages, of all races and of both sexes. The yearly incidence of TEN reaches about 2–3 per million individuals in Westernized populations.[2-5] The mortality rate of 25–30% associated with TEN is mainly due to a series of secondary metabolic failures and to septicaemia following loss of epidermal integrity.[6,7] The invading microorganisms are varied and include bacterial species (mainly *Staphylococcus* spp),[8] and, more rarely, fungi (such as *Candida albicans* and *Mucor* spp).[9,10]

The clinical aspects of TEN, its differential diagnoses and the sequelae of the disorder have been thoroughly reviewed.[11-17] This review mainly focuses on new insights into the clinicopathological presentations and pathobiology of TEN, supporting the future rationale for innovative management of the disease.

1. Cutaneous Clinicopathological Aspects

A clinical classification of TEN, Stevens-Johnson syndrome (SJS) and erythema multiforme (EM) was attempted about 15 years ago[18] and slightly modified recently.[19] Accordingly, SJS and TEN are considered to be variants in severity of the same disease, which appears to be different from EM.[20]

EM presents as initial target-like lesions characterized by an erythematous raised and palpable rim surrounding a grey centre. Typical target-like structures exhibit at least three different zones corresponding to two concentric rings encircling a central disc (figure 1a). More atypical lesions have only two zones. The SJS/TEN spectrum exhibits flat target-like patches and/or macules (figure 1b). In sum, lesions belonging to the EM spectrum tend to be raised, whereas lesions of the SJS/TEN group are flat.[19] The initial EM and SJS/TEN lesions are commonly covered by blisters.[19] Only by closely correlating clinical, aetiological and histological factors can clinicians accurately distinguish EM, SJS and TEN.

EM lesions typically occur in younger males, and recur frequently without fever.[21] They are often confined to mucosae and cutaneous acral sites. However, some major EM presentations exhibit a widespread cutaneous distribution. EM is often a distant reaction to an infectious disease, most notably those due to *Herpes simplex* viruses and *Mycoplasma pneumoniae*. However, bullous EM is a rare complication of *M. pneumoniae* infection that had been reported in only 32 patients as at 2006.[22] No association is recognized with HIV infection[21] and drug reactions are rarely involved in EM.[23]

In the current classification, drugs appear to be the only cause of SJS/TEN. Accordingly, any diagnosis of post-infectious SJS should probably be revisited in favour of a major form of EM.

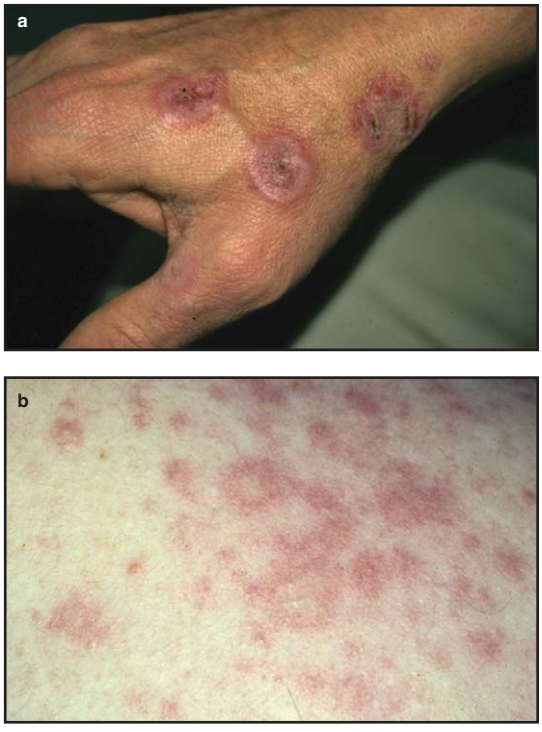

Fig. 1. Typical raised erythema multiforme target-like lesion with two concentric rings encircling a central disc (**a**) and flat toxic epidermal necrolysis target-like macules with only two zones (**b**).

However, it is possible that *M. pneumoniae*-related bullous dermatoses represent a distinct specific entity.[22] The clinical distinction between SJS and TEN is broadly established with reference to the extent of epidermal sloughing. In SJS, <10% of the body surface is affected, with a milder involvement of the mucosae (figure 2a). By contrast, TEN eroded lesions extend over >10% of the body surface in association with prominent destruction of mucosae (figure 2b). Despite a clinical presentation that is similar to TEN, the mortality rate of SJS remains limited, at 1–3%.[2]

In addition to these clinical and aetiological differences, EM and SJS/TEN conditions can be clearly distinguished histologically. EM presents as an inflammatory T-cell-rich dermatitis in contrast with the inflammatory cell-poor SJS/TEN lesions. In standard histological views, confluent necrotic keratinocytes are the hallmark of TEN. The dermo-epidermal junction exhibits changes ranging from vacuolar alterations to subepidermal blisters. The lymphoid cell infiltrate commonly remains superficial and sparse.[24] T lymphocytes usually predominate during the early phase of the disease but macrophages and factor XIIIa+ dermal dendrocytes (DDs) become rapidly predominant over subsequent days.[25,26] In addition, a strong tumour necrosis factor (TNF)-α immunoreactivity is typically found in TEN keratinocytes.[25] Some other biological markers represent ancillary parameters that distinguish EM from SJS/TEN. For example, serum interleukin (IL)-13 levels are increased in patients with SJS/TEN, but not in those with EM.[27]

2. Extracutaneous Involvement

Apart from the skin, TEN appears to specifically involve organs covered by a multistratified squamous epithelium such as the eyes (conjunctiva and cornea), oral cavity, oesophagus and vagina.[16] In addition, some segments of the excretory ducts of the large salivary glands and some foci of epidermoid metaplasia of the trachea and bronchioles exhibit a squamous multistratified epithelium. Thus, these surfaces are prone to development of TEN erosive ulcerations.

Early involvement of the eyes is noteworthy in TEN.[16] Indeed, we did not encounter a single patient without ocular involvement in a series of 75 TEN patients. In some instances, the ocular presentation is limited to conjunctivitis, but corneal erosions and other alterations are commonly present. In practice, a patient with an extensive cutaneous rash and presenting with ocular involvement probably has TEN; conversely, the absence of any ocular involvement means TEN can probably be ruled out.

A peculiar acute respiratory involvement occurs in about 25–30% of TEN cases.[28] This is primarily due to sloughing of bronchial epithelium in the proximal airways. This condition must be suspected when dyspnoea, bronchial hypersecretion and marked hypoxaemia develop during the early stages of TEN. Slightly protracted pulmonary complications, generally from day 7 to day 15, include pulmonary oedema, atelectasia, bacterial

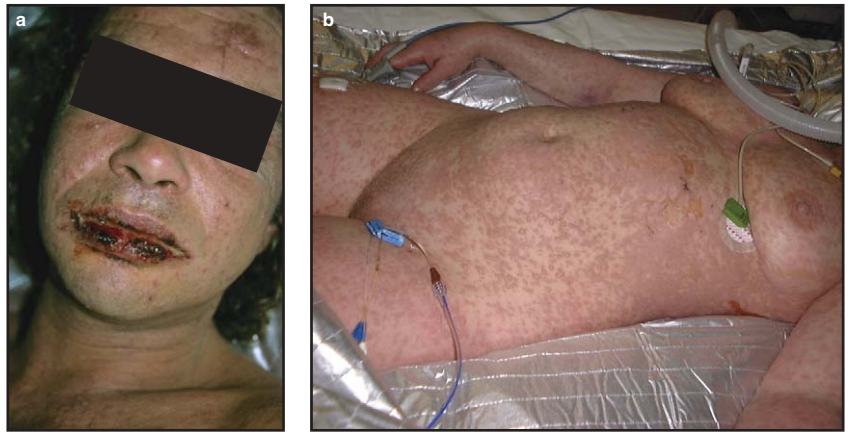

Fig. 2. Stevens-Johnson syndrome with moderate skin and mucosae involvement (**a**) and widespread epidermal blisters and detachment of toxic epidermal necrolysis (**b**).

pneumonia and adult respiratory distress syndrome.[28,29] Such protracted complications may result from metabolic disturbances in the absence of epithelial detachment.

A secondary multisystemic involvement is frequent in TEN.[30] Intestinal[31-33] and renal involvement,[34] acute pancreatitis[35] and haematological disturbances (lymphopenia, anaemia, disseminated intravascular coagulation) are possible.[36-38] Similar metabolic failure of other internal organs also probably follows and results from the primary destruction of large areas of stratified epithelia, leading to an apparent 'cytokine storm'.[30]

3. Differential Diagnosis

In the bullous stage of SJS/TEN, the main clinical differential diagnoses include grade IV acute graft-versus-host reaction (aGVHR), staphylococcal scalded skin syndrome (SSSS), acute generalized exanthematous pustulosis (AGEP) and generalized bullous fixed drug eruption.[39] The DRESS syndrome (drug rash with eosinophilia and systemic symptoms, formerly called drug hypersensitivity syndrome) must also be considered, although blistering is not the rule in this entity.

Despite the establishment of clinical, histological and immunohistochemical criteria, indisputable distinctions between some cases of TEN and lymphocyte-depleted aGVHR remain difficult to establish.[40-43] Indeed, close clinicopathological correlation is required.[43] Attention must be paid to the timing of the biopsy and to possible eye changes. For instance, ocular involvement is typically found in TEN patients, but only 10% of those with severe aGVHR have ocular manifestations.[42,43] The onset of the clinical signs of TEN is generally more dramatic than that of aGVHR, particularly in the immunosuppressed state of patients with aGVHR. The presence of some extracutaneous involvement (liver, gut) often helps to support the diagnosis of aGVHR. The density of the inflammatory infiltrate in the skin is generally as low in TEN as in drug-controlled aGVHR. Immunohistochemistry can help make the diagnosis by increasing the sensitivity of detection of epithelial alterations and the nature of the inflammatory cell infiltrate.[43] It must be emphasized that a restricted follicular involvement is more common in aGVHR than in TEN. Unlike in TEN, cytokeratin-15+ keratinocytes appear to be specifically targeted in aGVHR.[44,45]

SSSS is an exfoliative and bullous skin disease resulting from the effect of the exfoliative toxin-producing *Staphylococcus aureus*.[46] Mucosal and ocular involvement do not occur in SSSS. Bullae are thinner than in TEN and a typical Nikolsky sign is not present. Epidermal sloughing

results from intraepidermal cleavage occurring inside the granular layer. Scattered necrotic keratinocytes are admixed to lymphocytes and neutrophils. Immunohistochemistry confirms that TEN differs from SSSS by both the absence of CD15+ granulocytes and a stronger expression of the pro-apoptotic CD95 antigen in the epidermis.[46]

AGEP is an uncommon cutaneous eruption that is most often induced by drugs, acute *Enterovirus* infections or mercury poisoning.[47] It is characterized by acute extensive formation of non-follicular sterile pustules dispersed on an erythematous background. This condition is associated with fever and neutropenia.[47] Involvement of T cells in drug-induced AGEP is possible.[48,49] The histology and immunohistochemistry of acute AGEP skin specimens are quite typical. They are characterized by a massive inflammatory cell infiltrate composed predominantly of neutrophils collected in spongiform subcorneal or intraepidermal pustules, and admixed to T cells, both in subepidermal and perivascular locations.[48] In multilocular or generalized confluent fixed drug eruption, large irregularly distributed characteristic purplish-livid colour patches appear faintly discernible even after confluence.[13] Mucous membrane involvement and general symptoms are rare. Hence, AGEP follows a milder course than SJS/TEN. Histopathology shows a more pronounced inflammatory cell reaction and a marked oedema of the papillary dermis compared with SJS/TEN.

DRESS syndrome consists of a widespread erythematous eruption, fever, lymphadenopathies, hepatitis and haematological alterations, including eosinophilia and atypical lymphocytes.[50] Blistering of the cutaneous lesions may occur but is infrequent. The multivisceral involvement differentiates DRESS from TEN. Mucosal and ocular involvements are rare and generally subtle. A specific drug hypersensitivity is responsible for this reaction. However, unlike in TEN, disturbances in the drug detoxification pathway do not take place in the epidermis, but rather in other organs, including the liver.[51] The impaired ability to detoxify reactive drug metabolites primarily activates a T-cell response.[51] The most common histological finding in the DRESS syndrome is a dense superficial perivascular lymphocytic infiltrate, associated with spongiotic or lichenoid changes and a variable degree of oedema.

4. Aetiology

A large body of evidence suggests that TEN is an adverse drug reaction resulting from a specific alteration in drug metabolism.[2,13,31,46] More than 100 different drugs are recognized as causing TEN, but only a minority account for the vast majority of cases. These drugs are mainly represented by antibacterial sulfonamides (cotrimoxazole), aromatic antiepileptics (phenobarbital [phenobarbitone], phenytoin and carbamazepine), NSAIDs (phenylbutazone, oxyphenbutazone, isoxicam, piroxicam, selective cyclo-oxygenase-2 inhibitors), allopurinol and various antibacterials.[52-56] Among recently introduced drugs, strong associations have been documented for nevirapine (a non-nucleoside antiretroviral agent), lamotrigine (an antiepileptic), sertraline (a selective serotonin reuptake inhibitor), pantoprazole (a proton pump inhibitor) and tramadol (an analgesic).[57] The risk is generally greatest during the first 3 weeks of drug intake and is largely confined to the first 8 weeks of treatment.[58]

Although the only recognized cause of TEN is an adverse drug reaction, some clinical risk factors for the development of the disease have recently been identified. Among these are certain bacterial infections (*Klebsiella pneumoniae*,[59] *M. pneumoniae*,[60] *Yersinia enterocolitica*[61]), some vaccinations (measles-mumps-rubella, influenza, hepatitis B, varicella, combined *Haemophilus influenza* type b and measles-mumps-rubella),[62,63] allogeneic bone marrow[40,41,64] and stem cell transplantations,[65,66] systemic lupus erythematosus,[67,68] radiation therapy[69] and some oncological diseases.[70,71] However, as these conditions often require multi-drug treatments that introduce the risk of adverse events, it is often difficult to distinguish whether TEN is induced by the drugs or if the primary disease represents a risk factor for TEN. It is possible that these specific conditions alter the immune system, producing drug reactions different from those affecting the normal population.

AIDS patients are at dramatically increased risk for TEN.[72,73] At least three factors explain

this finding: (i) the large number of drugs administered to these patients; (ii) the altered immune system function of patients with AIDS; and (iii) the possible abnormal patterns of production and/or detoxification of drug metabolites in this patient group. In addition, HIV-1 is present in TEN blister fluid,[74] and molecular interactions have been demonstrated *in vitro* between HIV and human keratinocytes.[75] Moreover, severe cutaneous drug reactions, including TEN, are associated with specific anti-HIV medications.[76,77] By contrast, there is no association between TEN and other viral infections, including human *Herpesvirus* 6 and 7, *cytomegalovirus* and *parvovirus* B19.[78]

5. Prognosticators of Mortality

The main factors associated with TEN mortality are the occurrence of sepsis at the time of hospitalization (odds ratio [OR] 3.04, age (OR 1.11 per year of age) and total body surface area involved (OR 1.03 per percent of body surface area involved).[79] The presence of co-morbidities (OR 8.05) and corticosteroid intake (OR 2.32) are individually important but do not represent independent variables.[79]

The identification of independent risk factors for TEN mortality gave rise to the SCORTEN (Severity of Illness Score for TEN) scale.[80] SCORTEN is based on seven risk factors; namely, age >40 years, presence of malignancy, initial epidermal detachment of >10% of body surface, heart beat >120/min, blood glucose >252 mg/dL (14.0 mmol/L), serum bicarbonate level <20 mmol/L and serum urea level >27 mg/dL (10 mmol/L). The relationship between SCORTEN scores and mortality are shown in table I.

Table I. Mortality risk in relation to SCORTEN value

SCORTEN	Estimated mortality rate (%)
0–1	3.2
2	12.1
3	35.3
4	58.3
5	90.0

SCORTEN = Severity of Illness Score for Toxic Epidermal Necrolysis.[80]

SCORTEN varies over time, and its greatest predictive value is reached on day 3 after admission.[81] SCORTEN is generally considered an accurate estimator of the risk of death from TEN.[82-84] However, some authors consider that mortality is overestimated by SCORTEN in the setting of current treatment protocols.[85] Conversely, others claim that respiratory involvement[86] and tuberculosis[87] portend a poor prognosis that is not assessed by SCORTEN. Hence, although SCORTEN remains a useful tool for predicting mortality in TEN, it probably requires further refinement.

Recently, the extent of histological inflammation in TEN skin has been suggested to be a predictor of clinical outcome in a similar manner to SCORTEN.[88] However, the findings of this microscopic assessment do not constitute an independent predictive factor because the extent of inflammation varies according to the duration of the disease. In addition, objective quantification of the inflammatory infiltrate is particularly difficult to perform.[89]

6. Toxic Epidermal Necrolysis (TEN) During Pregnancy

Although only a few cases of TEN during pregnancy have been reported, they show that TEN may develop simultaneously in the mother and the fetus.[90-92] Clinically, the disease is generally lethal for the fetus. Three possible mechanisms of mother-to-fetus transmission are possible: common defects in detoxification pathways of reactive metabolites, a similar genetic predisposition to the development of TEN or the presence of drug-specific cytotoxic T cells initially in the mother's blood but subsequently circulating in the bloodstream of the fetus.[92] Interestingly, the placenta in pregnant women with TEN shows only mild chorioamnionitis.[92]

7. Sequelae

Long-term internal complications are rare in TEN survivors. These include diffuse heterotopic ossification,[93,94] chronic renal failure or pulmonary complications (persistent reduction in

carbon monoxide diffusing capacity, obstructive bronchitis/bronchiolitis, bronchiectasis)[95,96] and intestinal ulcers.[33]

The most common long-term morbidities involve the skin (81–100% of TEN survivors), eyes (27–54%), nails (36%) and oral/vulvovaginal mucosae (12.5%)[97-102] [table II]. Numerous post-TEN complications, particularly chronic eye involvement, significantly impair overall quality of life, emphasizing the need for long-term follow-up.

8. Pathobiology

8.1 Keratinocytes in the Initial Stage of TEN

TEN appears to be mediated by an immune cellular reaction. A humoral reaction is ruled out by the lack of specific immunoglobulins and complement deposits in TEN skin,[119] as well as by the absence of germinal centres and CD20+ B lymphocytes in TEN lymph nodes.[120]

Activated T lymphocytes and macrophages undoubtedly participate in TEN epidermal destruction.[26,121-123] However, they merely represent ancillary effector cells in the process. Indeed, keratinocytes likely represent the key initial cells in TEN epidermal destruction. A series of arguments supporting this pathogenic concept are summarized below.

First, most TEN lesions show a minimal inflammatory cell infiltrate.[24] In addition, the liver is generally preserved or has only moderate epidermal involvement. Therefore, it is unlikely that reactive metabolites originate from the liver, but rather that adverse drug bioactivation is primarily driven by keratinocytes.[124]

Second, keratinocytes exhibit prominent metabolic activity through various transport-associated and detoxifying enzymes.[125] The constitutive presence of the cytochrome P450 enzyme CYP3A and the potential induction of CYP1A are documented in the human epidermis.[125,126] For instance, covalent binding of carbamazepine-reactive metabolites to CYP isoforms has been demonstrated in TEN epidermis.[126] Biochemical investigations suggest an important role for flavin-containing mono-oxygenase 3 and some as yet unidentified peroxidases in the bioactivation of sulfonamides in human keratinocytes.[127] In addition, keratinocytes exhibit *N*-acetyltransferase-1 activity.[124,125] *N*-acetylation activity is decreased in the skin of TEN patients.[128,129] This feature may decrease the cutaneous clearance of

Table II. Persistent complications of toxic epidermal necrolysis

Organs	Clinical signs	References
Skin	Patchy hypo- and/or hyperpigmented areas	97-102
	Diffuse pruritus	98,99
	Hypertrophic/keloidal scarring	103,104
	Eruptive naevi	105
	Verrucous hyperplasia	106
Eyes	Dry eye syndrome	99,107-110
	Photophobia	
	Ocular pain	
	Loss of visual acuity	
	Chronic conjunctivitis sicca	
	Keratinization of the tarsal conjunctiva	
	Conjunctival synechiae	
	Ectropion	
	Entropion with trichiasis	
	Lid adhesion, symblepharon	
	Corneal neovascularization or opacification	
	Corneal abrasions, ulcers	
	Lachrymal duct scarring	
	Recurrent lachrymal cysts	
Nails	Dystrophy	98,101
	Ridging	
	Streaky pigmentation of the nail bed	
	Growth-stunted nails	
Oral cavity	Chronic tongue ulcerations	111
	Synechiae between tongue/lips and gingiva	112
	Xerostomia and Sjögren-like syndrome	113
	Cystic lesion of the parotid gland	114
	Hypopharyngeal stenosis and dysphagia	115,116
Genital mucosae	Vulvar adenosis	117
	Vulvar atrophy	98,118
	Chronic vulvar ulceration	
	Synechiae between the minor and major labia, at the fourchette or in the vagina	
	Vestibular or introital stenosis	
	Vaginal dryness	
	Phimosis	

the parent drug, allowing more drug to be metabolized through oxidative pathways.

Third, different proapoptotic systems are overexpressed by keratinocytes, beginning in the earliest phase of TEN and in the absence of any inflammatory cell infiltration.[25,130] In particular, TNF-α and Fas receptor/Fas ligand (CD95 receptor [CD95R]/CD95 ligand [CD95L]) appear to play prominent roles (table III). *In vitro* functional studies have demonstrated that keratinocytes in TEN patients express lytically active CD95L.[133,134] In addition, TEN keratinocytes express various pro-inflammatory cytokines and cytokine receptors, chemokines and chemokine receptors, adhesion molecules and human leukocyte antigen (HLA)-DR molecules potentially involved in TEN pathobiology (table III). However, none of these compounds are expressed specifically in TEN but are also found in other dermatoses and in healthy skin.

Fourth, the cytosolic calprotectin (L1-protein) complex is frequently expressed both in clinically involved and apparently uninvolved TEN epidermis.[130,141] The L1-protein involves a Ca^{++}-related process. Its presence in normal-appearing epidermis of TEN patients in the absence of inflammatory cells suggests that the increase in Ca^{++} concentration inside keratinocytes is one of the earliest biological events of TEN following drug metabolite formation.

Fifth, a unique case of antibacterial-induced TEN was reported in a patient who initially had prolonged severe methotrexate-induced pancytopenia without any leukocytes, including T lymphocytes and macrophages, in the blood and epidermis.[142] This observation suggests that the keratinocytes were responsible for their self-destruction without the intervention of any inflammatory cells.

8.2 Oxidative Stress in TEN Keratinocytes

Cytosolic glutathione-S-transferases (GSTs) form a family of phase II detoxification enzymes. Specifically, GSTs catalyze the conjugation of reduced glutathione (GSH) to a wide variety of endogenous and exogenous electrophilic compounds following activation of the GSH sulfhydryl

Table III. Keratinocyte expression and production in toxic epidermal necrolysis

Molecule	Pattern of expression	Method of detection	References
Pro/anti-inflammatory cytokines/cytokine receptors			
IL-10	Specific	PCR	131
CD40R	Specific	IHC	132
TNF-α	Specific	IHC	25,132
	Specific	PCR	131
CD95L (FasL)	Specific	PCR	131
	Specific	IHC	133,134
CD95R (FasR)	Non-specific	IHC	133,135,136
	Specific	IHC	132,134
Chemokines and chemokine receptors			
CCL27 (CTACK)	Specific	PCR, IHC	137
CXCR2	Non-specific	IHC	138
CXCR3	Specific	IHC	132
Adhesion molecules			
ICAM-1 (CD54)	Non-specific	IHC	46,139
HLA-DR	Non-specific	IHC	122,140

CCL = chemokine (C-C motif) ligand; **CD40R** = CD40 receptor; **CD95L** = CD95 ligand; **CD95R** = CD95 receptor; **CTACK** = cutaneous T-cell attracting chemokine; **CXCR** = CXC chemokine receptor; **FasL** = Fas ligand; **FasR** = Fas receptor; **HLA** = human leukocyte antigen; **ICAM** = intercellular adhesion molecule; **IHC** = immunohistochemistry; **IL** = interleukin; **PCR** = polymerase chain reaction; **TNF** = tumour necrosis factor.

groups. The isoenzyme GST-π is the most abundant form present in keratinocytes and plays a key role in the detoxification of electrophilic compounds.[143,144] Keratinocyte GST-π is overexpressed in TEN compared with other cutaneous adverse drug reactions and bullous pemphigoid.[145] Oxidative stress, which is one of the major inducers of GST-π expression, is probably involved in TEN epidermal destruction through reactive oxygen species (ROS) production by electrophilic xenobiotics.[146]

ROS act as intracellular chemical second messengers to increase gene transcription of inflammatory cytokines. This pathway follows transient activation by phosphorylation or allosteric modifications of redox-sensitive nuclear transcription factors such as nuclear factor-κB, activator protein-1 or USF43.[147-149] ROS induce IL-6, IL-8 and TNF-α production in keratinocytes.[150] In addition, ROS directly damage cellular components. They destroy the fatty acid esters of phospholipids, thus altering membrane semi-permeability.[151] By destabilizing membrane phosphoinositides, ROS-induced lipid peroxidation initiates apoptotic signal cascades through mobilization of Ca^{++} from the endoplasmic reticulum and activation of protein kinase C.[150] An increase in cytosolic Ca^{++} represents an early warning sign in TEN keratinocytes.[141]

GSH is a major detoxifying antioxidant of drug reactive metabolites in adverse cutaneous reactions. It directly scavenges various ROS and it serves as a substrate for GST-π and the glutathione peroxidase enzyme.[145] Human keratinocytes are resistant to toxic drugs such as sulfamethoxazole unless GSH is depleted, whereupon the cells become susceptible to the cytotoxic effects of the drug.[124] This may be of particular importance in HIV-infected patients who combine both low systemic and intracellular GSH levels[152,153] and an increased risk of TEN.[72]

8.3 Role of the Major Histocompatibility Complex

A genetic background involving the major histocompatibility complex (MHC) possibly contributes to TEN pathobiology. The association between *MHC* genes and drug reactions may be explained by the fact that MHC plays a role in the control of the immune response to drugs.

Drugs and their metabolites are small chemicals that are unlikely to trigger an immune reaction by themselves. A hapten hypothesis was raised for explaining drug reactions.[154,155] According to this hypothesis, specific antigenic drug metabolites are thought to covalently bind to some intracellular epitope peptides. *In vitro*, it has been shown that reactive drug metabolites, particularly for sulfamethoxazole, interact covalently with cellular macromolecules in normal human keratinocytes.[156] In this model, the major protein targets for sulfamethoxazole metabolites are found in compounds of 160, 125, 95 and 57 kDa.[124] These intracellular epitope peptides are as yet unidentified in TEN keratinocytes. The adducts potentially create toxic compounds or neoantigens recognized by the immune system. Their production is increased with GSH depletion.[124] Toxic compounds may accumulate to high levels over 7–14 days of drug therapy, which represents the time that commonly precedes the cutaneous toxic reaction and the demise of cells. The toxicity threshold of these adducts is expected to vary among individuals, possibly as a function of their detoxification capability, and may be the primary determinant for developing a drug reaction.[124] After cellular processing, these adducts may form endogenous antigens presented on the keratinocyte surface with MHC class I molecules, resulting in HLA-restricted CD8+ T-cell recognition and activation.

Another hypothesis relies on the p-i concept (pharmacological interaction with immune receptors) of direct non-covalent pharmacological interactions of drugs with MHC molecules.[157,158] Some findings favour the p-i concept in SJS/TEN.[159] Non-covalent interactions of drugs, such as carbamazepine or its metabolites, HLA-B-bound peptides, HLA-B molecules of antigen-presenting keratinocytes and T-cell receptors (TCRs), would trigger drug hypersensitivity.[159]

In summary, both the hapten and p-i hypotheses suggest that drug-induced SJS/TEN involves the interaction of specific MHC class I molecules, TCRs and drug-modified antigens.[160]

A significant increase in HLA-B12 and an almost significant increase in HLA-DR4 have been reported in Caucasian patients with TEN.[161] Significant associations have been found for HLA-A29 plus HLA-B12, and HLA-B12 plus HLA-DR7 in sulfonamide-related cases of TEN.[161] By contrast, oxicam-related TEN cases were linked to HLA-A2 and HLA-B12.[161] In Taiwanese Chinese patients, a strong association was shown between the gene alleles *HLA-B**1502 and *HLA-B**5801 and SSJ/TEN induced by carbamazepine[162,163] and allopurinol,[164] respectively. Similarly, *HLA-A**0206 was strongly associated with SJS/TEN with ocular complications in Japanese patients.[165] Because these findings have not been confirmed in Caucasian patients, the genetic markers for SJS/TEN do not appear to be universal and ethnicity seems to be of prime importance.[166-169] However, the high sensitivity/specificity of some HLA markers provides a likely basis for developing tests identifying individuals at risk for SJS/TEN in any given ethnic group.[160]

In addition to the involvement of the MHC system, specific extrathymic maturation and functions of T lymphocytes (e.g. following an infection of the host) or specific intrathymic selections in the TCR repertoire can also change the T-lymphocyte reaction and cause SJS/TEN.[170] Moreover, other non-HLA gene variations such as toll-like receptor 3 gene polymorphisms could be associated with SJS/TEN.[171]

8.4 Pathways of TEN Epidermal Destruction

Molecular and morphological features of apoptosis are present early in TEN-involved keratinocytes. This has been shown not only by electron microscopy but also by the characteristic ladder pattern of DNA cleavage and the presence of terminal deoxynucleotidyl transferase-mediated DNA nick end labelling.[172] However, the morphological hallmark of late apoptosis, i.e. the formation of apoptotic bodies, is not found in TEN epidermis; rather, full-thickness epidermal necrosis is observed.[173] Hence, it is assumed that the TEN pathomechanism likely combines early apoptosis and late necrosis. The involvement of mitochondria in TEN keratinocytes is a possible explanation for the simultaneous presence of these two mechanisms for cell death in TEN epidermis.[173] These features are summarized below.

According to the mitochondrial hypothesis, the TEN pathomechanism potentially involves four successive phases, the intensities of which vary according to the degree of keratinocyte maturation (figure 3).[173]

Phase I is determined by the immunogenic impact of xenobiotics. It involves a lack of balance between activation and detoxification processes in keratinocytes. Genetic factors (slow acetylation, hyperactive peroxidase systems, etc.) and/or acquired conditions (AIDS, etc.) could be involved in this early critical phase.

Phase II corresponds to early apoptosis. Generation of strongly electrophilic metabolites in TEN keratinocytes is thought to lead to disruption of the electron transfer chain in the mitochondria, followed by a decline in production of adenosine triphosphate (ATP). The electrical gradient across the mitochondrial inner membrane ($\Delta\psi m$) is lost. There is partial reduction of O_2 with production of ROS. Nitric oxide (NO) metabolism is also altered. Disrupting the electron transport chain alters oxidative phosphorylation and reduces ATP production, thus limiting the production of GSH. Hence, any decrease in ATP production leads to impaired detoxification. Loss of $\Delta\psi m$ in the mitochondria is thought to result in opening of large conductance channels in the outer membrane, allowing release of cytochrome C (Cyt C) from the intermembrane space into the cytosol. Cyt C activates caspase 9 and initiates the intracellular proteolytic cascade. The process ends with apoptosis. About 1–5% of electrons transferred to O_2 in the respiratory chain are directed to production of the superoxide anion O_2^- ($O_2 + e^- \leftrightarrow O_2^-$, where e^- represents an electron). The decrease in the coupling efficiency of electron chain transport in TEN increases the production of superoxides and ROS.[174] In TEN keratinocytes, it is likely that ROS, acting as second messengers, increase gene transcription of the TNF-α and CD95 pro-apoptotic systems. Indeed, increased expression of TNF-α and CD95 is present early in the course

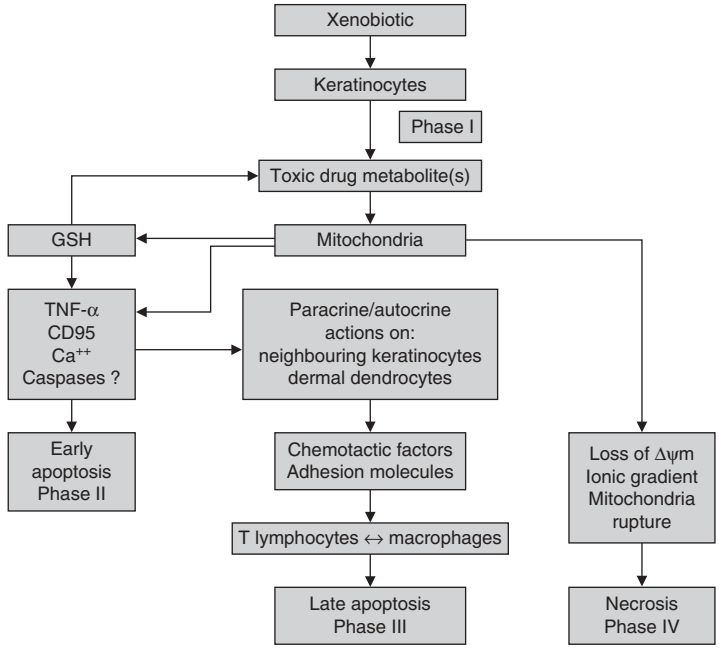

Fig. 3. Possible toxic epidermal necrolysis pathobiology. **Δψm** = electrical gradient across the mitochondrial inner membrane; **GSH** = glutathione; **TNF** = tumour necrosis factor.

of TEN, both in keratinocytes and blister fluid.[25,175,176] TNF-α probably acts as an autocrine/paracrine mediator spreading the epidermal destruction seen in TEN. In addition, TNF-α stimulates inducible NO synthase (iNOS), resulting in the production of large quantities of NO.[177] Increased iNOS expression has been demonstrated in TEN.[178] NO inhibits the mitochondrial respiratory chain, enhancing intracellular O_2^- production.[179] NO reacts with O_2^- to generate high levels of the potent oxidant peroxinitrite anion $OONO^-$ ($NO + O_2^- \rightarrow ONOO^-$).[179] The latter compound is capable of destroying Fe-S proteins and induces lipid peroxidation, thus causing irreversible damage to mitochondria and consequent intracytosolic release of Ca^{++}. CD95L+-activated keratinocytes are able to lyse other CD95R+ keratinocytes in TEN, particularly because CD95R is overexpressed on TEN keratinocytes.[133-135] Hence the CD95L/CD95R system is probably involved in early TEN apoptosis. ROS-induced lipid peroxidation makes the membrane 'leaky' to ions and initiates apoptotic signal cascades through Ca^{++} mobilization from the endoplasmic reticulum and activation of protein kinase C.[150] Indeed, increased Ca^{++} in the cytosol represents an early event in TEN keratinocytes.[141] Activation of caspases, hypercalcaemia and stimulation of pro-apoptotic cytokines such as TNF-α and/or CD95 lead singly or in combination to early apoptosis of keratinocytes, without any intervention of inflammatory cells. Similarly, early pathological features of TEN in the cornea reveal vacuolization of keratinocytes without any intraepithelial lymphocyte infiltration.[180]

In late apoptosis (phase III), the pro-inflammatory cytokine TNF-α is believed to act as an autocrine/paracrine factor on neighbouring keratinocytes, thus spreading epidermal destruction. In addition, TNF-α induces expression of the intercellular adhesion molecule (ICAM)-1 on keratinocytes, which is the ligand for lymphocyte function-associated antigen-1+ activated T lymphocytes.[181] TNF-α-activated keratinocytes further produce T lymphocyte chemokines such chemokine (C-C) motif (CCL) 27/cutaneous T-cell

attracting chemokine (CTACK).[137] Located in the vicinity of the superficial capillaries, factor XIIIa+ DDs are activated by keratinocyte-derived cytokines, particularly TNF-α.[25,26,182] DDs are thought to participate in TEN by acting as antigen-presenting cells and by attracting inflammatory cells upon secretion of appropriate cytokines.[25,26] Activated DDs in TEN show enlarged endoplasmic reticulum, as well as collagen fibre and mast cell granule phagocytosis.[183] They probably play a role in the regulation of the connective tissue remodelling that usually accompanies epidermal destruction. Phase III corresponds to the influx of inflammatory cells into the TEN epidermis. At first, these are predominantly composed of activated CD8+ T lymphocytes.[140,184,185] They express cutaneous lymphocyte antigen (CLA) molecules,[186-188] CD25 (IL-2 receptor),[189] CD56 (natural killer [NK] cell marker),[186] CD69 (activation marker),[188] CD45R0 (memory T cells),[26,140,188] CD94 (NK cell receptor),[186] CD158a/CD158b (NK cell receptor),[186] CD95L[133,139] and CCR10 (CTACK receptor).[137] Functionally, these functional subsets of lymphocytes are engaged in a Tc1 pathway, producing interferon-γ-inducing overexpression of MHC class I molecules on activated keratinocytes.[131,139,187] These cells are drug specific, MHC class I restricted and exhibit perforin/granzyme-mediated cytotoxicity.[190,191] In addition to having NK receptors, these T cells display functional NK cytotoxicity.[186] Thus, they are NKT-like cells (i.e. they share properties of both NK and T cells), but are distinct from regular CD1d-dependent NKT cells.[192] The exact areas of T lymphocyte activation in TEN remain to be established. TEN peripheral lymph nodes show only a discrete hyperplasia of the paracortical T-cell zone with a very low Ki-67 proliferation index.[120] Moreover, antigen-presenting cells such as CD1a+ Langerhans cells and factor XIIIa+ dendritic cells are sparse in TEN lymph nodes.[120] Some cytokines, such as IL-15, can locally induce functional NK-cell receptor expression (e.g. CD94) on T lymphocytes responding to superantigens or to alloantigens.[193] Subsequently, CD68+ macrophages form the most prevalent inflammatory cell population.[25,121,186,194] These cells interact strongly in mutual activation with T lymphocytes,[26] finally giving rise to a late and boosted apoptotic process.

In phase IV, the loss of $\Delta\psi m$ leading to permeability transition pore opening results in osmotic disturbances of mitochondria due to the matrix hyperosmolarity. There is expansion of the matrix space corresponding to swelling of organelles and subsequent rupture of their outer membranes. Cells with ruptured mitochondria are at risk of death through a slow non-apoptotic mechanism resembling necrosis.[174]

In summary, TEN epidermal destruction combines apoptosis at the beginning of the disease and necrosis as a later event. At each moment of the disease course, the relative proportions of the keratinocytes in early apoptosis (self-induced by the keratinocytes), late apoptosis (induced by inflammatory cells) and necrosis likely determine the clinical and histological manifestations of the involved area.[173]

In keratinocytes, ROS production may occur during the first 2 hours,[195] CD95 expression at about the third hour[131] and TNF-α production requires about 24 hours.[150] Loss of $\Delta\psi m$ and caspase activation occur over about 6–12 hours.[195] The apoptotic process may develop fully in 24–48 hours.[196] These short intervals mean that cutaneous TEN involvement is a very rapid process and requires emergency treatment.

Moreover, an immunological memory develops early after a first episode of TEN and persists for several years. This is evidenced by the rapid and generally dramatic TEN recurrence following accidental or provoked re-exposure to the culprit drug.[197-199] Provocation tests have previously been performed, but they are ethically unacceptable because of their inherent risks. These tests had positive results when they were performed soon after the acute onset of TEN (up to 3 months),[200] but gradually became negative as the interval after the previous eruption increased.[201]

9. Treatment

9.1 Supportive Care

Expeditious transfer of TEN patients to a burn unit helps considerably in reducing morbidity

and mortality.[9,202-204] Early withdrawal of the culprit drug is of paramount importance because this decreases the level of electrophilic metabolites in the body and guarantees a better prognosis.[205] As yet, there are no rapid and reliable *in vitro* tests for identifying the culprit drug in TEN.[206-209] The probability of involvement of a specific drug in TEN remains based on complex clinical and pharmacological algorithms rather than on *in vitro* tests.[210] Drugs sharing any chemical similarity with the initial culprit compound must be discarded when possible in the management of TEN since the risk of TEN recurrence and fatal cross-reactivity is high.[198,211] Immune modulating enteral nutrition might be considered.[212] Antibacterials should be administered only where there is evidence for a specific focus of infection.[12-17,213-215]

9.2 Local Treatment

Debridement of the necrotic epidermis is advocated.[12,14-17,97,215,216] This procedure is followed by immediate covering of the TEN erosions with biological or synthetic dressings. The biological dressings consist of skin xenografts,[217] skin allografts,[218,219] and autologous[220] or allogenic[103] cultured keratinocytes. Synthetic dressings include custom-knitted nylon fabric mechanically bonded to an ultrathin silicone membrane (BioBran®),[221-223] nanocrystalline silver dressings,[224] calcium alginate fibres[225] and hydrofibre silver dressings.[226] All these dressings are expensive and sometimes difficult to obtain.

The eroded surface is best treated with gauze dressing covered by an ointment containing antiseptics such as povidone-iodine (not on more than 20% of the body surface because of a potential effect on thyroid function) or chlorhexidine.[12-17,213-216,227] Silver sulfadiazine may be used only if TEN has not been induced by sulfonamides. Topical antiseptics and sulfonamides have been claimed to exert *in vitro* noxious effects on keratinocytes. However, in clinical practice, they provide protection against exogenous bacterial contamination and colonization, thus limiting local biocenosis and having a beneficial effect on re-epithelialization.[228] Moreover, skin healing is improved by a moist environment.

Air-fluidized beds help dry the skin and avoid maceration.[217] However, the regular air flow may increase the patient's daily evaporative water losses by 5–6 L, making management of fluid and electrolyte balance more difficult.[217,229] In addition, this approach may give rise to severe hypothermia.[229]

Amniotic membrane transplantation performed during the acute phase of TEN-induced conjunctival and corneal damage is effective in reducing inflammation and preventing scarring. In addition, this procedure helps to restore corneal epithelial integrity.[230-232]

9.3 Systemic Treatment

We hypothesized that disruption of the electron transfer chain in mitochondria by electrophilic metabolites of the culprit drug was the major event leading to both early apoptosis and late necrosis in TEN.[173] Accordingly, recovery of the electron transport chain might be a key target in TEN treatment. Treatments that only block the effects of the proinflammatory cytokines and receptors produced in TEN, without acting on the deregulation of the electron transport chain in mitochondria, probably have a limited effect on the course of TEN.[17] This may be the case for monotherapies consisting of intravenous immunoglobulin (IVIg), systemic corticosteroids, ciclosporin or anti-TNF-α agents.

9.3.1 Intravenous Immunoglobulin

The rationale for administration of IVIg relies on the presence of IgG antibodies directed to CD95R in commercial IVIg batches. These antibodies settle in the epidermis,[233] blocking the binding of CD95L to CD95R.[133,234,235] Since their initial use in TEN a decade ago,[133] a series of prospective and retrospective studies, as well as a meta-analysis, have assessed their benefit in the treatment of TEN. Their results were controversial, showing either a reduction in the mortality rate[82,235-242] or, conversely, no beneficial effect in comparison with supportive care alone.[243-247] IVIg therapy does not appear to

reduce the severity of ocular complications.[248] Differences in anti-CD95R activity in IVIg batches, in the usual doses of IVIg administered (doses >2 g/kg are generally associated with increased reductions in mortality) and in time from TEN onset to IVIg administration, may have contributed to the different outcomes.[235]

At present, there is no strong evidence supporting IVIg administration in TEN.[236,249] The cost/benefit ratio of IVIg therapy remains high. However, more studies need to be conducted to definitively evaluate the therapeutic potential of IVIg in TEN. The optimal doses should be determined. Subgroups of patients who could benefit from this treatment should be identified, particularly as it has been shown that IVIg does not curb the mortality rate when the SCORTEN risk of mortality is high.[236]

9.3.2 Corticosteroids

The use of high doses of corticosteroids in patients with TEN is a matter of debate. Case reports and short series of patients suggest that systemic corticosteroids contribute to a reduction in the mortality rate without increasing time to healing.[250] Other investigators noted no differences in mortality rates and infectious complications in patients who were taking corticosteroids compared with those who were not taking corticosteroids before admission to a burn unit.[251] Provocation tests in TEN patients showed that drug reactions were rapidly controlled by early administration of corticosteroids.[200] Conversely, TEN may occur in patients receiving long-term corticosteroid therapy before the onset of TEN.[252] In these settings, corticosteroid therapy may delay the onset of TEN but fails to block its progression. One study showed that systemic corticosteroid therapy for >48 hours was associated with a 5-fold increase in incidence of infection (especially *Candida* sepsis), a 2-fold increase in the duration of hospitalization and a 12.5-fold increase in mortality rate, independent of age, percentage of epidermal sloughing and leukocyte count nadir.[203]

Consideration of these contrasting findings suggests that corticosteroids may have a role to play in TEN treatment during the erythroderma stage before major skin loss has occurred.[202] In such a restricted condition, high doses of oral or parenteral dexamethasone,[250,253,254] prednisone[255] or prednisolone[256] could be administered on admission, but should not be used for >48 hours because more prolonged treatment is associated with a dramatic increase in TEN mortality and morbidity.[202] Moreover, when >20% of the total body surface has sloughed, corticosteroid therapy is contraindicated because of increased risk of sepsis.[202] The major limitation of corticosteroid therapy is the fact that it is often very difficult to diagnose TEN at an early non-bullous stage.

9.3.3 Ciclosporin (Cyclosporine)

Ciclosporin has been advocated as a potential agent for reversing TEN progression.[257,258] The suppressive action of ciclosporin is primarily directed at T-cell functions. In addition, the immunosuppressive effects of ciclosporin partly inhibit the activation of macrophages and the CD95 system. *In vitro*, ciclosporin abates the drug-induced expression of FasR and FasL messenger RNA (mRNA) and blocks drug-mediated apoptosis in some cell types.[257]

Only a few cases of TEN have been treated with ciclosporin, all in uncontrolled conditions.[259-265] Beneficial effects were generally reported. The effects of ciclosporin (5 mg/kg/day) on the epidermis of TEN patients were compared with those obtained with supportive care only.[257] Similarly to findings with use of IVIg, the apoptosis marker CD95R was downregulated in clinically involved TEN skin on completion of a 5-day course of ciclosporin.[136] This finding clinically confirmed the *in vitro* inhibitory effect of ciclosporin on the CD95 system. No significant effect of ciclosporin was evident in terms of an effect on the extent of the TEN inflammatory cell infiltrate. This might be considered surprising because ciclosporin exerts a potent inhibitory effect on activated T lymphocytes. However, the inability of ciclosporin to reduce accumulation of an inflammatory cell infiltrate in the skin has been noted previously in other conditions.[266] In comparison with supportive care alone, ciclosporin treatment did not improve re-epithelialization and did not significantly decrease morbidity and mortality in TEN.[136] It is

also noteworthy that TEN may develop in patients who had previously taken ciclosporin for other clinical disorders.[267]

In summary, ciclosporin partly inhibits the CD95 system in TEN patients. However, this drug does not appear to be sufficiently powerful in some patients to initiate a clinically relevant improvement in TEN prognosis.

9.3.4 Anti-Tumour Necrosis Factor-α Antibodies

The putative pathogenic importance of TNF-α in TEN suggests an innovative therapeutic approach consisting of selective blockade of TNF-α using specific antibodies. So far, only a few case reports have described the successful treatment of TEN patients with anti-TNF-α antibodies. Six patients were treated with infliximab[268-271] (3 or 5 mg/kg as a one-shot intravenous perfusion over 2 hours) and one patient with etanercept (one subcutaneous injection of 25 mg administrated 4 and 8 days post-admission).[272] In each case, treatment stopped the rapid progression of the disease. There were no specific adverse effects or increased susceptibility to infection. Immunohistochemistry showed that 24 hours after anti-TNF-α therapy, immunoreactivity for TNF-α was markedly decreased in lesional skin.[269] In parallel with protein immunoreactivity, TNF-α mRNA expression also dramatically decreased after anti-TNF-α therapy. The efficacy of anti-TNF-α therapy needs to be confirmed in larger groups of TEN patients.

9.3.5 N-Acetylcysteine

N-acetylcysteine (NAC) is a cysteine derivative precursor of GSH. Treatment with NAC may be effective in severe drug reactions via three mechanisms: (i) reacting with oxidative compounds and replenishing intracellular cysteine levels required for the production of GSH; (ii) blocking expression of the homing receptor for CLA; and (iii) inhibiting production of TNF-α and IL-1.[273] In addition, NAC increases the clearance of several drugs and their metabolites. A few patients have been successfully treated with high-dose intravenous NAC in open-label studies.[273,274] However, a randomized trial did not confirm the efficacy of NAC for the prevention of hypersensitivity reactions to cotrimoxazole in patients with HIV infection.[227] Moreover, high doses of NAC may inactivate not only the culprit drug but also other drugs potentially useful to the patient.[273] Further studies are required to confirm the beneficial therapeutic effect of NAC in TEN.

9.3.6 Other Systemic Medications

Use of pentoxifylline,[275,276] cyclophosphamide,[277,278] granulocyte macrophage colony-stimulating factor[279] and ulinastatin (urinary trypsin inhibitor)[280] has been successful in a few case reports. The lack of controlled studies and their putative mode of action make it difficult to propose these agents as appropriate treatments for TEN.

9.3.7 Plasmapheresis

Plasmapheresis has been used by itself or in association with IVIg, with some beneficial and promising results in TEN.[281-286] Plasmapheresis is thought to act by removing any drug excess, drug metabolites and cytotoxic mediators. However, plasmapheresis does not always substantially decrease blood and tissue cytokines. Indeed, the natural production and degradation of cytokines are often too rapid to be effectively controlled by this method.[283] Moreover, removal of plasma also necessitates provision of substitution fluid containing an appropriate amount of fresh frozen plasma. Such replacement is costly and, if sustained for long periods, represents a serious burden on the local blood bank. In addition, plasmapheresis removes soluble pro- and anti-inflammatory mediators simultaneously, which can negatively modify the patient's immunity.[287,288] Plasmapheresis also needs a vascular access which is a potential source of infection in TEN. Some authors believe that plasma exchanges do not achieve a significant therapeutic effect in TEN.[289] In summary, the lack of controlled studies, not only with respect to efficacy and safety but also in regard to its mechanism of action, make for difficulties in determining the true efficacy of plasmapheresis in TEN.

10. Conclusion

A variety of pathomechanisms are involved in necrolytic blistering diseases. TEN is a typical example of such a disease in terms of its widely diverse biological manifestations. Keratinocytes appear to be the most prominent mediators in the epidermal destruction associated with TEN. A combined process of apoptosis and necrosis is initiated by an altered detoxification pathway of the culprit drug within keratinocytes. TEN pathomechanisms lead to an enzymatic chain reaction with the production of different interactive proinflammatory cytokines in the epidermis. As yet, no single specific treatment has proven to be highly active in TEN, and no treatments are significantly superior to supportive care alone.[17,249] We suggest that several molecular targets that block different apoptosis/necrosis pathways should be attacked simultaneously in keratinocytes in order to achieve optimal efficacy in the treatment of TEN.

The treatments of TEN that have received most attention from clinicians are high-dose systemic corticosteroids and IVIg. The former is associated with potentially disastrous adverse effects. The latter has proven biological effects, but does not appear to be able to fully reverse the evolution of TEN. However, IVIg therapy might be useful in some TEN patients and is not generally associated with adverse effects. Based on the putative TEN pathomechanism, use of anti-TNF-α antibodies is a promising approach to TEN treatment, but new antiapoptotic molecules acting on keratinocytes are undoubtedly needed. Until effective chemical treatments are developed to neutralize the reactive electrophilic metabolites and to restore the electron transfer chain in TEN keratinocytes, several blocking agents (e.g. NAC combined with IVIg or anti-TNF-α agents) could be used simultaneously to achieve increased efficacy in TEN treatment.

Caution is necessary in initiating these studies, since previous studies have demonstrated that some theoretically useful molecules in TEN, such as thalidomide, have increased mortality in real-world clinical situations.[290] Moreover, the relevance of new clinical trials in TEN will probably be questioned given the rarity and gravity of the disease, which make organization of safe, double-blind studies with sufficient statistical power very difficult.

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