TOPICAL REVIEW DOI 10.1111/j.1365-2133.2005.06721.x

Toxic epidermal necrolysis: current evidence, practical management and future directions

T.A. Chave, N.J. Mortimer, M.J. Sladden, A.P. Hall* and P.E. Hutchinson

*Departments of Dermatology and *Intensive Care Medicine, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester LE1 5WW, U.K.*

Correspondence
Toby Chave.
E-mail: toby.chave@rcht.cornwall.nhs.uk

Accepted for publication
12 January 2005

Key words:
apoptosis, ciclosporin, high-dependency care, intravenous immunoglobulins, plasmapheresis, toxic epidermal necrolysis

Conflicts of interest:
None declared.

Summary

Toxic epidermal necrolysis (TEN) is a rare disorder characterized by extensive epidermal death. Almost all cases appear to be caused by an idiosyncratic drug reaction. Proposed pathogenic mechanisms are conflicting, and the evidence for the benefits of individual treatments is inadequate, and in some cases contradictory. The mortality rate remains high. We review the literature pertaining to the pathogenesis of TEN and drug reactions in general. The rationale for therapeutic interventions, together with reported evidence of efficacy, are considered. We present a composite model of TEN, based on previous work and suggested pathogeneses of TEN, mechanisms of drug reactions and reported cytotoxic lymphocyte (CTL) cytolytic pathways. In this system, TEN, like some other cutaneous drug eruptions, is an HLA class I-restricted, specific drug sensitivity, resulting in clonal expansion of CD8+ CTLs. Cytotoxicity is mediated by CTL granzyme and possibly death receptor (DR) ligand (DR-L), probably Fas ligand (FasL). Particular to TEN, there is then an amplification sequence involving further DR-L expression. FasL is likely to be particularly important but tumour necrosis factor (TNF) may well contribute, via the TNF receptor 1 (TNF-R1) death pathway. Alternatively, we suggest the possibility of upregulation of an antiapoptotic TNF-R1–nuclear factor κB pathway, which would proscribe treatments which downregulate this pathway. None of the published data on individual treatment efficacies is sufficiently strong to suggest a definitive single treatment. Currently a multifaceted regimen appears indicated, targeting various likely intermediary mechanisms, including elimination of residual drug, immunosuppression, inhibition of DR pathways, general antiapoptotic strategies, and aggressive supportive care. Particular attention has been directed at avoiding potential conflicts between different treatments and avoiding agents that theoretically might have a net proapoptotic rather than antiapoptotic effect. Nursing on a specialized unit is of paramount importance.

Toxic epidermal necrolysis (TEN) is characterized by widespread epidermal death. Reported mortality varies from 30% to 50%. The estimated annual incidence is 1–2 per million population. In the majority of cases there is a history of recent drug ingestion.

A prodromal phase of fever, cough and malaise is followed by an acute macular exanthem, which rapidly becomes Nikolsky positive (epidermal separation induced by gentle lateral pressure on the skin surface). Subsequent shedding may remain localized, or may become very extensive. There is often severe involvement of mucosal surfaces. Systemic involvement in TEN is well recognized, but is very variable. In some cases there may be extensive involvement of the gastrointestinal tract,[1] and in up to 30% of cases respiratory involvement occurs,[2] sometimes with marked hypoxaemia in the absence of significant chest X-ray abnormalities. Sloughing of bronchial epithelium is seen on fibre optic bronchoscopy, and mechanical ventilation may be required.[2] Abnormalities in liver function tests are occasionally reported, but the incidence and exact nature of hepatic involvement are unknown. Significant leucopenia is a common finding, but it is not known whether there is direct bone marrow pathology specific to TEN, or if this merely represents a secondary phenomenon.

Increasing age, significant comorbidity and greater extent of skin involvement correlate with a worse prognosis.[3] Bastuji-Garin *et al.* have devised a validated measure of disease severity, the SCORTEN, that accurately predicts mortality using a seven-point checklist. This includes age, presence of malignancy, body

surface area involved, heart rate, serum urea, bicarbonate and glucose.[4]

The pathogenesis of TEN is not clear but there are several consistent histological and immunocytological findings, and recent studies relating to drug reactions and apoptotic mechanisms provide clues. Several treatments have been reported to be beneficial in case reports or uncontrolled series but there is no clear indication from the literature if any individual treatment or treatment regimen is optimal. The aims of this review are to consider pathogenic mechanisms in TEN, to evaluate current therapies at a theoretical level in relation to these, to evaluate the evidence of efficacy of reported treatments, and to define likely beneficial elements of an overall treatment strategy. Such a regimen would aim to interrupt likely intermediary pathogenic mechanisms, give general systemic support, but avoid agents with a possible promotive or ambiguous effect on apoptosis.

Search methods

We searched Medline and Pubmed for references from 1966 to 2004, using the search terms toxic epidermal necrolysis, TEN, Lyell syndrome, Stevens–Johnson syndrome and SJS. In continental Europe, TEN is arbitrarily classified as being present when more than 30% of the skin is involved; if less than 10% of the skin is involved it is termed Stevens–Johnson syndrome (SJS), and SJS/TEN overlap for between 10% and 30%. In the U.K., however, patients with SJS who develop any degree of Nikolsky-positive epidermal desquamation tend to be classified as having TEN. We considered all papers relevant to TEN as per U.K. criteria, and all papers were carefully scrutinized to ensure that other conditions in which epidermal desquamation can occur were excluded.

Mechanisms and pathogenesis of toxic epidermal necrolysis

We used the terms: apoptosis, cytotoxic T cells, death receptor (DR), caspase, tumour necrosis factor (TNF)-α, Fas, Fas ligand (FasL), TNF-related apoptosis-inducing ligand (TRAIL) and nuclear factor (NF)-κB. When other relevant terms were identified during the search, these were included. Papers describing the general mechanisms/pathogenesis of cutaneous drug reactions were also considered, where these were deemed relevant to TEN.

Treatment and management

We reviewed all papers and case reports which described the treatment and/or management of TEN. We used the search terms: treatment, management, steroids, corticosteroids, dexamethasone, immunoglobulin, intravenous immunoglobulins (IVIg), ciclosporin, cyclosporin, cyclophosphamide, insulin, zinc, granulocyte colony-stimulating factor (G-CSF), thalidomide, intensive care, intensive therapy, burns unit, nutrition, dressings, haemofiltration, dialysis and plasmapheresis.

Current evidence and theories of pathogenesis

The pathogenesis of TEN is not understood, but there are several relevant reported observations that any proposed mechanism must accommodate. There have also been recent observations relating to the pathogenesis of drug eruptions in general which are probably highly relevant.

Apoptosis

It is well known that the basic epidermal pathology in TEN is large-scale epidermal death, which has been convincingly shown to be the result of apoptosis.[5] Apoptosis is an orderly programmed disassembly of cellular DNA and the cytoskeleton. The basic effectors are usually caspases, a family of evolutionarily conserved cysteine proteases (Fig. 1). The caspase system may be activated by ligation of membrane-situated DRs which include TNF receptor (TNF-R) 1, Fas and TRAIL receptors (TRAIL-Rs). Normal epidermal cells express TNF-R1,[6] Fas[7–9] [which is upregulated by interferon (IFN)-γ[9,10]], and TRAIL-R1 and R2.[11,12]

There are other possible mechanisms of inducing cellular apoptosis independently of the DR pathways. These are via mitochondrial damage as may result from perturbation of the balance of proaptotic and antiapoptotic Bcl-2 proteins, e.g. from protein kinase (PK) B, p53 and granzyme activity, and activation of the ceramide pathway. Granzymes are serine proteinases that are components of cytotoxic T lymphocyte (CTL) and natural killer cell granules. They can induce apoptosis after perforin (expressed by activated CTLs) punches a hole in the cell membrane, either via caspases (by cleaving Bid, thus directly affecting the mitochondrial permeability pore and activating caspases), or via noncaspase-dependent pathways (Fig. 1). The most abundant, and most potent, in terms of apoptosis, is granzyme B. High levels are found in TEN blister fluid.[13]

Tumour necrosis factor as an effector of apoptosis?

A suggested pathological mechanism is that TNF is responsible for cell death in TEN.[5,14–16] TNF is abundantly present in the epidermis in TEN,[15,17] also in blister fluid mononuclear cells,[13] peripheral blood mononuclear cells (PBMC)[18] and macrophages.[19] Soluble (s)TNF and sTNF-Rs in blister fluid have also been reported.[20,21] The sTNF-Rs were more abundant in skin than in serum, suggesting epidermal processing of TNF.[20] One proposed source of TNF is necrotic keratinocytes which either release TNF, or provoke release from inflammatory cells.[17] However, the keratinocytes in TEN are apoptotic, rather than necrotic, and would not be expected to result in high levels of activation of inflammatory cytokines. It is notable that low levels of interleukin (IL)-1α, another primary inflammatory cytokine, are reported in TEN blister fluid, in comparison with burns.[22] Whether TNF release from keratinocytes is an active or passive process, TNF may well play a pathogenic role in TEN.

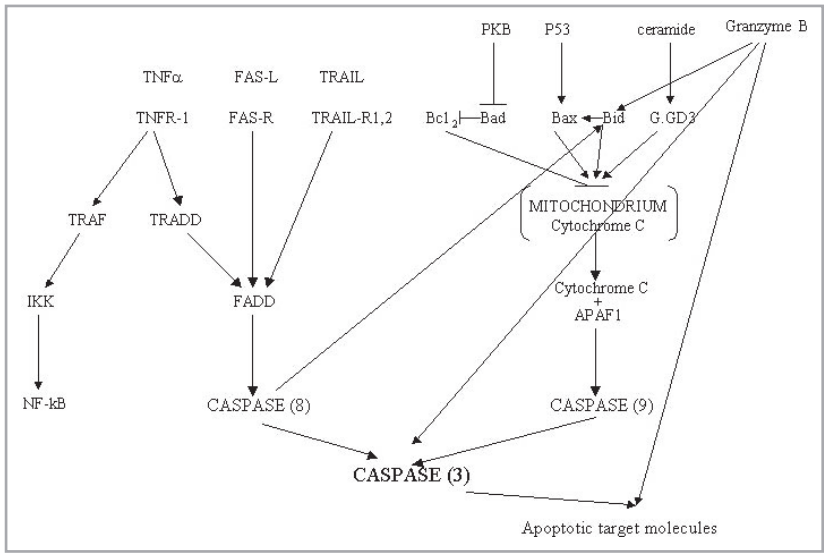

Fig 1. Intracellular apoptotic pathways in toxic epidermal necrolysis. To the left of the figure are the death receptor (DR) pathways for tumour necrosis factor (TNF)-α, Fas ligand (FAS-L) and TNF-related apoptosis-inducing ligand (TRAIL) which signal through Fas-associated death domain protein (FADD) to caspase 8 and cause apoptosis. Note that TNF-α can also signal to nuclear factor κB (NF-κB), which is antiapoptotic (see text). To the right are the non-DR pathways which work via the mitochondrial pore. Granzyme B can signal through this pathway or via noncaspase-dependent pathways. TNFR-1, TNF receptor 1; TRAF, TNF receptor-associated factor; IKK, I-κB kinase; TRADD, TNF receptor 1-associated death domain protein; FAS-R, Fas receptor; TRAIL-R1,2, TRAIL receptors 1 and 2; PKB, protein kinase B; G.GD3, galactoside GD3; APAF1, apoptotic protease activating factor.

The TNF-R1 apoptotic pathway (TNF-R1–TNF-R1-associated death domain protein–Fas-associated death domain protein–caspase 8) (Fig. 1) can be functional in keratinocytes.[23,24] It has been shown to be a mediator of ultraviolet (UV) B-induced apoptosis.[23] TNF-induced apoptosis has been implicated in CTL-induced alveolar cell damage in respiratory viral infection.[25] In addition, TNF is known to upregulate Fas and FasL,[26] which could be extra contributory factors in TEN. Thus the proapoptotic TNF-R1 pathway could be a cause of the apoptosis in TEN. However, the TNF-R1–caspase pathway is usually nonoperative in normal keratinocytes. TNF-R1 signals not only to caspases but also to NF-κB (Fig. 1), which is generally accepted to be associated with an antiapoptotic phenotype.[27–29] Upregulation of NF-κB has been shown to protect against apoptosis provoked by UV,[28] and apoptosis by TRAIL in transformed keratinocytes.[11] It has been suggested that upregulation of NF-κB by chemotherapy is a principal mechanism of inducible tumour chemoresistance.[30] This antiapoptotic activity may also apply to TNF-upregulated NF-κB, and this pathway has been shown to protect lung epithelial, neuronal or malignant cells from induction of apoptosis by TNF itself but also by Fas pathways.[27,31,32] Conversely, downregulation of NF-κB, for example in cell lines with genetic absence of NF-κB or in cells with aberrant, more effective, I-κBα (the inhibitor of NF-κB), may result in apoptosis.[27,30,32–35]

In TEN it is not known which TNF-R pathway is active or predominant, and whether TNF has a proaptotic or antiapoptotic affect, and studies on these pathways are needed. The anti-TNF agent thalidomide was reported to have a deleterious effect in the condition,[16] which would be compatible with active TNF antiapoptotic pathways. This raises questions in the context of our current knowledge, about the suitability of any treatment for TEN that might downregulate the TNF–NF-κB pathway.

Fas ligand as an effector of apoptosis?

This concept has been popular since Viard *et al.*[36] demonstrated lytically active FasL expressed on TEN keratinocytes and blockade of keratinocyte Fas pathways with antibodies present in pooled human IVIg. The inference from this study was that keratinocyte FasL ligation of Fas is the mechanism for apoptosis in TEN. It has subsequently been shown that IFN-γ-upregulated FasL on keratinocytes may result in apoptosis of both the upregulated keratinocytes and cocultured T cells *in vitro*,[26] although this observation was not in TEN. An alternative interpretation of FasL expression by keratinocytes is that it is a defence mechanism against immune attack,[37] i.e. it is involved with ligation of Fas on lymphocytes. This would be compatible with what Viard *et al.* actually demonstrated with the TEN tissue, which was apoptosis of lymphoid (Jurkat) cells rather than keratinocytes.

Recently, an alternative hypothesis, that the source of FasL is PBMC rather than keratinocytes, has been proposed by Abe *et al.*[38] These authors detected very little FasL on keratinocytes in TEN but found high serum levels of sFasL, which were increased when PBMC were exposed to the

causative drug. Sera of patients with TEN and SJS induced abundant keratinocyte apoptosis.[38] Of relevance to this is that in a previous study of mononuclear cells derived from patients' blood and lesional blister fluid, TNF, perforin and granzyme B were expressed in drug reactions of varying severity while FasL was expressed only in TEN and SJS.[13] sFasL has been found in high concentrations in TEN blister fluid[39] and in the sera of patients with TEN, but was virtually undetectable in patients with simple maculopapular drug reactions (MPR).[36] It has been suggested that sFasL may be involved in a 'secondary nonspecific extension of cell death leading to the massive lysis of epidermal cells'.[39] However, there is evidence that sFasL has less effect on induction of apoptosis compared with membrane FasL,[40] but the sheer quantity present might be expected to compensate for any reduction in potency.

Tumour necrosis factor-related apoptosis-inducing ligand receptor as an effector of apoptosis?

There is very little evidence regarding involvement of TRAIL-Rs in TEN. Such involvement seems unlikely as TRAIL-R pathways are generally not active in normal, nontransformed cells,[11,12] and anti-TRAIL antibody did not block TEN-derived CTL cytolysis.[39]

Nitric oxide synthetase as an effector of apoptosis?

Inducible nitric oxide (NO) synthetase mRNA and protein have been demonstrated in TEN by reverse transcription-polymerase chain reaction, and by immunoperoxidase staining in inflammatory cells in the lower epidermis and dermis.[41] The authors postulated that NO was the mediator of apoptosis in TEN.

Drug-induced immune reaction based on cytolytic CD8+ lymphocytes

It is increasingly recognized that various cutaneous drug eruptions are associated with drug-specific T-cell infiltrates.[42] In MPR it has been shown that T cells infiltrating the dermoepidermal junction express perforin and granzyme B, and that monocytes express IL-12 and IFN-γ.[43] Mauri-Hellweg *et al.* demonstrated *in vitro* the specific drug-induced activation of CD4+ and CD8+ T-cell subsets in PBMC from patients with drug allergy.[44] It has subsequently been established that the mechanism of this clonal expansion is major histocompatibility complex (MHC) restricted, usually resulting from labile association of unprocessed or metabolized drug with MHC.[45] Schnyder *et al.* reported a patient with sulfamethoxazole-induced skin reaction; CD4+ and CD8+ sulfamethoxazole-specific T-cell clones which exhibited a drug-specific, and MHC-restricted, cytotoxicity against keratinocytes were demonstrated. Pretreatment of the keratinocytes with IFN-γ was necessary, and the cytotoxicity was blocked by concanamycin A, suggesting perforin-mediated killing.[46]

Numerous authors have suggested that the pathogenesis of TEN is immunologically mediated and involves cytotoxic CD8+ lymphocytes.[14,17,22,47,48] There is good evidence for CD8+ involvement in TEN, as these cells are consistently reported to be the most common infiltrating cell in TEN histology.[47] They are the predominant cell in TEN blister fluid.[49] High expression of perforin, granzyme and FasL in mononuclear cells in TEN blisters suggests that the CD8+ cells are activated.[13] Recently the concept of specific drug-induced cytotoxicity has been taken further by the direct demonstration, in TEN-derived CD8+ lymphocytes, of drug-specific MHC class I cytotoxicity, mediated by granzyme but not by Fas or TRAIL.[39] However, this cytotoxicity was demonstrated to lymphocytes and not keratinocytes.

TEN would appear to fit into an increasingly recognized general pattern of cutaneous drug reactions which show drug MHC restriction and specific T-cell drug activation.[42,45,46]

A pathogenetic model

The histological, immunocytological and functional findings in TEN and other cutaneous drug reactions support the concept that TEN is a specific drug sensitivity reaction initiated by CTLs. It would seem likely that drug presentation is MHC class I restricted, there is clonal expansion of CD8+ CTLs, and these cells have the potential for granzyme-mediated cytolysis. However, these events do not appear specific for TEN, and the *in vitro* findings of Nassif *et al.*[39] in TEN are similar to those reported in MPR.[42,46] It seems unlikely, however, that the massive apoptosis in TEN can be fully explained by induction by CTLs; cell-to-cell contact is necessary and the CTLs are relatively sparse.

Fundamental questions are: what links the specific immune reaction to the massive epidermal apoptosis, and what apoptotic pathways are involved in TEN? Highly relevant observations are the raised serum levels of TNF and FasL, and the increased expression of FasL on keratinocytes. As described above, Viard *et al.* have proposed a central role for the Fas pathway.[36] The proposition was that apoptosis is activated by FasL expressed on the keratinocyte, although sFasL as suggested by Abe *et al.*[38] would seem a more likely candidate. This pathway may also be important in initial CTL-induced apoptosis where FasL is expressed on the lymphocyte. Studies in both drug reactions and TEN have demonstrated CTL-induced apoptosis mediated by granzyme and not Fas pathways.[39,46] However, CTL cytolysis is usually two pronged, involving granzyme and FasL,[50,51] and it would appear likely that the Fas pathway is at least subliminally active during CTL attack. The question then arises as to why FasL is massively upregulated in TEN. Recently, activation of Fas (and other DR pathways) has been shown to cause upregulation in the same cells of the respective ligands and this has been suggested as an autoamplification mechanism.[52] In addition, FasL is upregulated by IFN-γ, a likely source of which in TEN is the CTL. It could be argued therefore that upregulation of FasL expression by

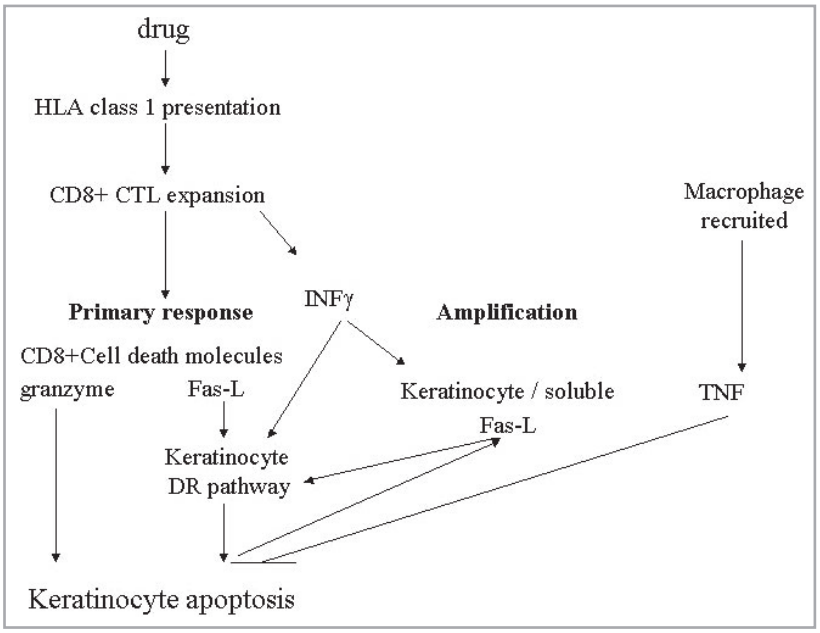

Fig 2. Possible apoptotic pathways in toxic epidermal necrolysis and their interactions. CTL, Cytotoxic T lymphocyte; IFNγ, interferon γ, Fas-L, Fas ligand; PBMC, peripheral blood mononuclear cells; TNF, tumour necrosis factor; DR, death receptor; - - - -, TNF acting as a proapoptotic agent; …, TNF acting as an antiapoptotic agent.

keratinocytes, and subsequent release into serum, is a response to CTL attack. An alternative source of FasL is the PBMC, as demonstrated by Abe *et al.*[38] Whatever the source, sFasL may amplify apoptotic signalling, as has been suggested for TNF in respiratory apoptosis.[25] Figure 2 shows a basic model of DR amplification, principally involving FasL, with either proaptotic or antiapoptic TNF pathways.

If this concept of DR amplification is correct, there is no explanation as to why this should occur in TEN as opposed to other drug reactions. A possible mechanism is that patients with TEN have a defective apoptosis regulatory system, possibly related to a rare polymorphism in an intrinsic apoptosis inhibitor. This would mean that Fas pathway autoamplification, possibly initiated by the initial CTL attack and facilitated by IFN-γ, would proceed unchecked. The same might apply to a TNF-R1 proapoptotic pathway.

In summary, in TEN the initiating drug induces an MHC-restricted immune response with clonal expansion of CD8+ CTLs, of central importance to which would be lymphocyte production of IL-2. Keratinocyte apoptosis may be a two-phase system: a primary CTL-driven process, as occurs in other cutaneous drug reactions, depending particularly on granzyme and possibly involving activation of DR pathways, and an amplification mode, specific to TEN, dependent on upregulation of DR ligand.

Current treatments: theoretical considerations and clinical evidence

General measures

Currently, virtually all authors agree that the most important aspects of managing TEN are prompt diagnosis, early withdrawal of all suspect drug(s), good supportive therapy, specialized nursing care, multidisciplinary teamwork, and management on a specialist intensive care or burns unit. However, there are no controlled trials of supportive care.

Prompt withdrawal of causative drug

Although intuitively logical, there is only limited evidence of an effect on the course of the disease. One observational study showed a reduction in mortality from 26% to 5% when implicated drugs with short elimination half-lives were withdrawn no later than the day when blisters or erosions first occurred. There was no difference for drugs with long half-lives.[53]

Another consideration is possible enhanced elimination of drug. Extracorporeal blood purification (EBP) techniques are commonly available. Continuous venovenous haemofiltration (CVVH) and modes of dialysis including haemodiafiltration are routine in a critical care setting. Small molecules, including most drugs, are readily filtered (provided they are not heavily bound to proteins like albumin). A further consideration is the elimination of potentially harmful cytokines.

Plasmapheresis would be expected to be more effective in respect of cytokine clearance. However, there is some evidence in the case of severe sepsis where a rapid reversal of pyrexia with CVVH has been attributed to either filtering or simply absorbing inflammatory mediators such as cytokines.[54–56] In current CVVH practice, molecules up to 40 kDa are filtered. The TNF monomer is 17 kDa but TNF typically exists as a trimer with a molecular weight of 54 kDa.[55] FasL is structurally similar and also forms a trimer. Both could be expected to behave similarly in respect of EBP techniques. There is currently much interest in the role of newer high cut-off haemofilters that appear more effective in eliminating cytokines of this size.[57,58]

Plasmapheresis is the only EBP therapy that has been used specifically in the treatment of TEN. Six case series and several isolated reports have been described. Combined, the six series indicate an overall mortality rate of 11% (five of 44), and suggest that plasmapheresis may be a safe and effective treatment for TEN.[59–64]

It is unclear whether any apparent benefit either is due to removal of the triggering drug/agent or perhaps reflects removal or at least attenuation of inflammatory mediators such as cytokines. Removal of TNF may be deleterious, as discussed above; however, simultaneous removal of sFasL is likely to compensate, and may well be highly advantageous.

EBP therapy can be rapidly established in an intensive care or high dependency setting. A large-bore double lumen intravascular catheter is required for all such cases. While clinical evidence is available only for plasmapheresis, there may be good reason to support at least the initial use of CVVH, particularly where plasmapheresis is either delayed or unavailable.

Supportive care

Most supportive therapies used in the treatment of patients with burns are applicable to patients with TEN. These include: careful protection of exposed dermis and eroded mucosal surfaces; prevention, early detection and treatment of infection; careful monitoring of fluid and electrolyte status with therapy for any imbalance; nutritional support; warming of the environment to reduce the increase in metabolic rate; and appropriate analgesia. There is no evidence that prophylactic antibiotics provide benefit, and most authors reserve antibiotic therapy for the treatment of proven infection. Clearly TEN carries a high risk of significant sepsis. This is an important consideration, as several current therapies involve immunosuppressant agents. Care must be taken in screening for sepsis and surveillance of lines/catheters to allow prompt intervention.

Early referral and management on a specialist unit

Most authors agree that because general principles of supportive management in TEN are similar to those in major burns, patients should be managed on a burns or intensive care unit. This seems logical, especially considering the multisystem nature of TEN. We identified eight retrospective case series ($n \leq 10$) supporting early referral to a specialist unit. There were no control data. Most of these studies suggested that early transfer to a specialist unit reduced mortality[3,65–70] and length of hospitalization.[71] In a small study ($n = 14$), no differences in mortality rate or infectious complications were noted in patients who were transferred late to a specialist unit but it was concluded that early transfer was important.[72] Only one study reviewing 15 patients admitted to a nonburn centre, in which no patient died, concluded that there is no need for burn centre care in the management of TEN.[73]

Overall, the data suggest that early transfer reduces the risk of infection and reduces mortality. The balance of evidence supports early transfer of patients with TEN to a specialized unit as a treatment priority.

Nutrition

TEN is a highly catabolic state necessitating appropriate nutritional support.[74] Energy and protein requirements appear to be related to amount of body surface area affected.[75] Eating may be painful and difficult if there is facial, oral or mucosal involvement, and nutritional requirements may well exceed the ability to eat. Nasogastric tube feeding with a soft fine-bore tube may allow appropriate supplementation of the diet (particularly overnight with 'normal' eating in the daytime). Enteral nutrition is preferable to parenteral nutrition, as it is better tolerated and can provide greater calorific intake.[76,77] Parenteral nutrition also requires central venous access, increasing the risk of significant sepsis as well as other complications of central lines.[78]

Hyperglycaemia in critically ill patients has been shown to be associated with increased morbidity and mortality.[79] Patients with TEN may be physiologically stressed, in pain, and have sometimes been treated with systemic steroids. These factors combined with hyperalimentation make hyperglycaemia likely. It is noteworthy that hyperglycaemia is an identified risk factor used in the SCORTEN severity scoring system predicting mortality in TEN.[4] Strict control of blood glucose with an insulin sliding scale infusion should be applied.[79] There is additionally some evidence that insulin has an antiapoptotic action that may be of some benefit in patients with TEN (see below).

Respiratory care and support

Pulmonary involvement is common in TEN. The hospital environment has a low humidity, compounding any airway damage. Treatment includes nebulized saline, bronchodilators and physiotherapy. Hypoxia may indicate involvement of respiratory epithelium and may require supplementary oxygen, or even mechanical ventilation.[2] Supplementary oxygen is both cold and dry; care must be taken to humidify inspired gases. In patients with TEN, face-masks are not well tolerated. Pressure and friction associated with a face-mask may increase skin loss around the nose and mouth. This applies particularly to a continuous positive airway pressure mask, an otherwise useful therapy when respiratory failure may be imminent.

Respiratory failure is a bad prognostic sign. Those individuals requiring formal ventilation can be expected to be ventilator dependent for some time and there is a risk of ventilator-associated pneumonia. Early tracheostomy may be beneficial, as it allows patients to avoid or reduce sedation, and to contribute more actively to ventilation, thus reducing respiratory muscle atrophy. Patients who are able to cough and actively contribute to clearance of sputum are at reduced risk of significant chest infection.

Biobrane dressings

A review of 10 patients with TEN (of whom two died) concluded that Biobrane® (a temporary semisynthetic skin substitute; Bertek) provided marked reduction in pain, eliminated the need for further dressings, and allowed early aggressive physiotherapy. Wounds healed completely within 14–21 days, with no significant scarring or need for skin grafting.[80] Another study of eight patients with TEN showed that Biobrane decreased pain and fluid loss, facilitated re-epithelialization, and decreased the risk of sepsis. No adverse side-effects were reported.[81] A series of three patients with TEN treated successfully with Biobrane demonstrated rapid re-epithelialization with no wound sepsis.[82] Another study reported that Biobrane was a safe and reliable method to achieve wound closure in TEN and avoided the cost and pain associated with repeated dressing changes.[83]

Extracutaneous involvement

Ocular involvement in TEN is common and can result in blindness. Ophthalmological treatment is generally supportive, with the use of lubricants and topical antibiotics. One small study suggested that amniotic membrane transplantation preserved normal ocular and eyelid surfaces and may prevent blindness.[84]

Immunosuppression

As there is considerable evidence that at least the initial process in TEN is immunological, there is good reason to consider the use of immunosuppressants in treatment. A general concern about the use of immunosuppressants is the possibility of promoting sepsis.

Corticosteroids

Corticosteroids have been used in the management of TEN for the last 30 years. Their use has been much debated and remains controversial. Proponents emphasize the importance of early intervention during the initial erythrodermic stage, with high doses for a few days only, to inhibit inflammation.[85,86] Opponents suggest an increased risk of sepsis, prolonged length of hospital stay, and increased mortality in TEN patients treated with corticosteroids.[87,88]

Corticosteroids are highly potent agents that target several intracellular processes to modify almost all the components of the inflammatory and immune response. Effects pertinent to TEN are on immunosuppression and apoptosis. Glucocorticoids inhibit T-cell activation via inhibition of transcription of IL-2 through inhibition of transcription factor AP-1.[89] A further key inhibited transcription factor is NF-κB, which is involved in regulation of production of a number of immunoregulatory and proinflammatory cytokines including ILs 1–6, 8, 11, 12, 15, 16 and, of particular relevance, IFN-γ and TNF.[90]

Whereas corticosteroids are proapoptotic in lymphoid cells, many haematopoietic cells and chondrocytes, they have been reported to be antiapoptotic in most other tissues,[91–99] including skin.[100] One mechanism of this effect may be inhibition of initiating pathways, e.g. downregulation of Fas/FasL in the apoptotic tissue.[93] In a model system of cocultured activated T cells and keratinocytes reported by Trautmann *et al.*,[100] apoptosis in keratinocytes was induced by lymphocytes secreting IFN-γ and sFasL and this was inhibited by dexamethasone (at high doses), ciclosporin, rapamycin and FK506 (tacrolimus).

Thus, in TEN, it appears that corticosteroids may have beneficial anti-inflammatory, immunosuppressive and antiapoptotic effects. However, a potential problem is the ability to downregulate NF-κB activity, particularly in the presence of an abundance of TNF. As with other causes of downregulation of NF-κB cited above, it has been suggested that downregulation by corticosteroids might result in apoptosis in the presence of TNF,[34] although the combination of TNF and dexamethasone has been shown to inhibit IFN-γ/anti-Fas antibody-mediated apoptosis in lung epithelial cells. However, there remain concerns that in the particular case of TEN, the inhibition of NF-κB by corticosteroids could result in a proapoptotic effect.

There are many individual case reports advocating the use of corticosteroids in TEN. In one series of 16 patients treated with high-dose corticosteroids, only one death was reported.[101] A series of 67 patients with SJS/TEN treated with steroids reported low mortality and minor side-effects, but the diagnoses were not clear and not all cases had mucous membrane involvement.[102] In a retrospective study of 15 patients with TEN treated with parenteral dexamethasone (8 mg daily in two divided doses) in Kerala, India, all made an uneventful recovery.[73]

Several studies ($n = 56$, $n = 39$, $n = 75$) have concluded that steroid treatment is not associated with altered mortality.[3,69,103] One large retrospective review ($n = 366$) showed no significant reduction in ocular sequelae.[104]

Systemic corticosteroids have been shown in several case series to be detrimental in TEN. One series ($n = 44$) reported excessive mortality associated with prolonged use of systemic steroid therapy.[70] In a retrospective study, multivariate analysis of prognostic factors indicated that steroid therapy was an independent factor for increased mortality.[71] Other studies also suggest that corticosteroids are contraindicated in the management of TEN.[80,87]

Many cases of TEN have been reported in patients already on high-dose corticosteroid therapy for pre-existing conditions. Two studies report frequencies of 5% (11 of 216)[105] and 7% (13 of 179).[106] Roujeau *et al.* reported that up to 9% of cases of TEN occur in patients already taking corticosteroids for other reasons.[107]

The balance of available evidence suggests that, at best, corticosteroids have no significant beneficial effect on TEN, and at worst are detrimental. Coupled with the theoretical concerns outlined above, corticosteroids cannot be recommended as a therapy for TEN.

Ciclosporin

Ciclosporin is a powerful immunosuppressant. The principle action is blockade of T-cell activation and proliferation by selective inhibition of calcineurin. This is a calcium–calmodulin-dependent protein phosphatase associated with activation of the IL-2 promoter. Clonal expansion of CD8+ cells involves an autocrine IL-2 loop and sIL-2 has been demonstrated in TEN blisters.[22] An inhibitory effect on CD8+ cells, and thereby an expected effect on all CD8+ cytotoxic mechanisms, is very attractive, as the relative importance of the cytolysis pathways in TEN is not well characterized. Ciclosporin, however, does not inhibit the cytolytic capacity of activated CD8+ cells. It could be argued therefore that by the time patients are seen there is a full complement of activated cells, in which case ciclosporin would not be expected to be effective, but it is equally possible that CD8+ activation is a continuing process. Ciclosporin also inhibits apoptotic pathways, which is of potential benefit in TEN. Decreased synthesis of TNF family members, including DR ligands such as FasL, has been reported.[108] In addition, ciclosporin has been reported to inhibit downregulation of NF-κB resulting from calcium signalling in epithelial tissue (bronchial), which would be expected to be antiapoptotic, and the reverse in lymphoid tissue.[109] It also inhibits apoptosis produced by a variety of agents in a range of tissues,[110–112] by inhibition of the mitochondrial permeability transition pore. The mitochondrial apoptotic pathway may be important in TEN as it is involved in some DR responses and partially in granzyme-induced apoptosis (via Bid: see Fig. 1).

In summary, ciclosporin has a number of potential benefits in TEN. It is strongly immunosuppressive and antiapoptotic, and does not downregulate NF-κB, although there may be some inhibition of TNF.

There have been nine individual cases and one case series of 11 patients published in the literature documenting the treatment of TEN with ciclosporin.[113–118] In the case reports all patients had severe TEN with a body surface area affected ranging from 35% to 80%. The dose of ciclosporin varied from 3 to 5 mg kg^{-1} daily given intravenously or orally. The duration of treatment also varied (8–24 days), but was generally given until the patient had re-epithelialized. All the reports claimed arrest of disease within 24–36 h. In the case series, 11 consecutive patients admitted to an intensive care burns unit received oral ciclosporin 3 mg kg^{-1} daily for 2 weeks.[118] The dose was then weaned over a further 2 weeks. Again, all patients had severe TEN with an affected body surface area ranging from 35% to 96% (median 90%). Outcomes were compared with a historical control group of six patients in the same centre who had been treated with cyclophosphamide and prednisolone. Time to arrest of disease progression and to complete re-epithelialization was found to be significantly shorter in the ciclosporin group. No significant nephrotoxicity was seen.[118]

Of all the 20 patients with TEN treated with ciclosporin in the literature, septic complications were reported in 12, although there were no fatalities. Complications included staphylococcal septicaemia[114,115] and *Enterococcus faecalis* septicaemia.[116] It is well recognized, however, that patients with TEN who receive no immunosuppression have a high incidence of septic complications, and treatment with ciclosporin does not appear to confer a higher risk.

Cyclophosphamide

Cytotoxic immunosuppressants, such as cyclophosphamide, are again powerful immunosuppressants. The mechanism of action of these agents is to induce apoptosis in immunocytes, resulting from DNA damage and mediated through p53 (Fig. 1). The apoptosis is not specific to immunocytes, and concerns arise that apoptosis in skin could be exacerbated.

Antiapoptotic measures

Intravenous immunoglobulins

The rationale for using IVIg is to block keratinocyte intracellular Fas signalling. In the studies of Viard *et al.*[36] cited above, where frozen sections of TEN tissue were found to induce apoptosis in overlying lymphocytes, it was shown that apoptosis could be completely abrogated by the addition of human pooled IVIg. Naturally occurring anti-Fas antibody was found to be present in the pooled IVIg, and when this was removed the antiapoptotic effects were negated. Preincubating IVIg with recombinant FasL did not abrogate FasL-induced apoptosis.

Following the *in vitro* studies cited above, 10 consecutive patients with TEN were treated with IVIg in doses ranging from 0·2 to 0·75 g kg^{-1} daily for 4 days. A dramatic interruption in disease progression was claimed and all 10 patients survived. Patient clinical details (basic demographics, comorbidities, severity of skin involvement) and the level of specialist supportive and nursing care provided were not given.

Treatment of TEN with IVIg has been reported in several case series, with conflicting results. Several series support the use of IVIg, reporting reduced mortality rates from the disease.[119–122] Other data are less encouraging.[123–125]

These studies are difficult to compare because of the wide variation in patients and treatment protocols. Various commercial brands of IVIg have been used, and different dosing regimens applied. IVIg are a diverse product developed from the pooled serum of hundreds of blood donors. Wide batch-to-batch variation in anti-Fas activity *in vitro* has been demonstrated,[121] and not all the contents and their biological activities are known.[126] Although data suggest that IVIg may be of use in TEN, study results are conflicting, and any mortality benefit is likely to be small. Accepting the above methodological problems, the overall mortality rate from the above eight studies was 20% (32 of 157).

Antitumour necrosis factor agents

Thalidomide inhibits the production of TNF and IL-6 by monocytes and lymphocytes. It was used in a double-blind

randomized controlled trial vs. placebo in TEN as an anti-TNF agent.[16] The trial was stopped prematurely because of increased mortality in the thalidomide group (83% compared with 30%). The increased mortality caused by thalidomide suggests that TNF could be antiapoptotic in TEN, as discussed above. In addition, there have been reports of TEN developing in patients being treated with thalidomide for other conditions.[127,128] However, thalidomide also acts as a potent costimulator of CD8+ cytotoxic T cells *in vitro*,[129] which would be anticipated to potentiate CD8+ cytotoxic damage. This is an alternative explanation for the deleterious effects.

Anti-TNF monoclonal antibody treatment has recently been reported in one case with a favourable outcome.[130] However, until the issue of which TNF-R pathway is operative in TEN is resolved such treatment would seem potentially hazardous.

Further possible treatments

As the primary pathology in TEN is widespread and progressive epidermal apoptosis, any safe agents with significant antiapoptotic effects could be of potential benefit. We consider two such agents below which could easily be utilized in a high dependency/intensive care unit setting.

Insulin

Both insulin and insulin-like growth factor (IGF) are ligands activating the PKB pathway (Fig. 1) via phosphatidylinositide-3′-OH kinase. IGF is a powerful constitutive antiapoptotic agent and upregulation is an important and unfavourable factor in certain cancers, e.g. Ca breast.[131] PKB inactivates Bad which can no longer inhibit the antiapoptotic Bcl-xL and inactivates caspase 9.[132] This therefore might be expected to inhibit particularly mitochondrial apoptotic pathways which may act as an amplification system for direct DR or granzyme pathways. A suitable delivery system would be glucose and insulin infusion on a sliding scale.

Zinc

Zinc protects against apoptosis induced by diverse physical, chemical and immunological stimuli,[133] including drugs,[134] in cultured cells. Zinc is maintained in discrete subcellular pools that are critical for the functional and structural integrity of cells, the labile pools regulating apoptosis.[135] Zinc also functions as an antioxidant and can stabilize membranes.[136] Interestingly, zinc supplementation is of known benefit in the treatment of necrolytic migratory erythema,[137] which has recently been shown to be an apoptotic process.[138] Furthermore, acquired zinc deficiency may cause the clinical picture of necrolytic migratory erythema.[139]

A potential problem of zinc administration in TEN is upregulation of T-cell immunity both by apoptotic and by nonapoptotic mechanisms. From studies of immunological function in zinc deficiency, it is evident that the effects of zinc include stimulation of mitogen-induced T-cell proliferation, secretion of cytokines (IFN-γ, IL-2, IL-2 receptor and TNF), an increased proportion of cytotoxic CD8+ precursors, and increased natural killer cell lytic activity.[140–142] In addition to a more direct immunostimulatory effect, zinc may also enhance lymphocyte homeostasis by inhibition of lymphocyte apoptosis.[133]

There is good evidence, however, that zinc in larger dosages is immunosuppressant.[143] *In vitro* at concentrations of 0·1 mmol L^{-1} (eight times the normal serum concentration), T cells are inhibited. At four times the serum concentration, mixed lymphocyte culture alloreactivity is suppressed.[143] This is supported by *in vivo* observations when zinc supplementation (elemental zinc 150 mg twice daily for 6 weeks) in healthy controls resulted in a reduction in the lymphocyte stimulation response to phytohaemagglutinin.[144] In addition, it has been reported recently that zinc administration prolonged cardiac graft survival in a rat model in a dose-dependent manner.[145] A subsequent study of the effects of zinc and ciclosporin (2 mg kg^{-1}) on allograft survival found their apparently beneficial effects to be additive.[146]

Thus, potential effects of zinc in TEN are inhibition of keratinocyte apoptosis and, if given in sufficient dosage, immunosuppression. Furthermore, it may complement treatment with ciclosporin.

Granulocyte colony-stimulating factor

Three case reports document the successful use of recombinant G-CSF in the treatment of TEN associated with leucopenia and neutropenia. In all cases the white cell count normalized rapidly after commencing treatment and all patients survived.[113,147,148] In another patient with TEN and severe aplastic anaemia, the skin disorder resolved within a few days of treatment with G-CSF and ciclosporin, although the aplastic anaemia only partially responded.[117] G-CSF may therefore be a useful adjunct in those patients who develop associated bone marrow suppression.

Conclusions

TEN is a rare but serious dermatological disorder with significant mortality, highlighting the inadequacy of current accepted treatments. Much work still needs to be done to elucidate the pathogenesis of TEN fully and to establish more effective therapy. Recent developments in our understanding of apoptotic pathways in keratinocytes and lymphocytes, and of specific immunological changes related to drug reactions, offer intriguing insights.

Combining the current available evidence relating to the efficacy of treatments, and the likely pathogenic mechanisms, certain conclusions can be drawn. All patients should be admitted to a specialist high dependency/intensive care unit as soon as the diagnosis has been established, for full assessment and expert supportive therapy. All possible triggering drugs should be stopped. There is a strong case for immediate

haemofiltration to remove any residual causative drug, and to reduce proapoptotic cytokine levels. It seems highly likely that TEN is immunologically mediated and early use of a powerful immunosuppressive would seem indicated. A potential problem with immunosuppression is that secondary infection, which is a major complication of TEN, may be precipitated or exacerbated. However, TEN currently has a high mortality and it is essential to combat the pathogenic process. Based on our current knowledge and the theoretical discussion outlined above, ciclosporin would seem to be the immunosuppressant of choice. IVIg have been extensively used but their value has not been definitely determined. A specific anti-FasL antibody, if developed in the future, may be of greater value. Insulin is now routinely used in the critical care environment to maintain strict normoglycaemia, and ill patients with TEN are likely to need it. There is a case for early recourse to this treatment in TEN in view of its antiapoptotic potential. Zinc is also an interesting potential antiapoptotic therapy, and may be worthy of investigation. Multicentre studies are needed to look further at potentially promising treatment combinations.

Acknowledgments

The authors thank Howard Pringle, Reader in Molecular Biology, Leicester University, Prof. Loems Ziegler-Heitbrock, Immunology Department, Leicester University and Heidi Robertshaw, Anaesthetics Department, St George's Hospital, London for their expert comment.

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