REVIEW ARTICLE

Epidermal necrolysis (Stevens–Johnson syndrome and toxic epidermal necrolysis): Historical considerations

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ABSTRACT

Objective: To describe the history of toxic epidermal necrolysis, before and after the original report by the British dermatologist Alan Lyell in 1956.

Methods: Subjective expert choice of key advances in the comprehension of the nosology, classification, causality, and mechanisms of epidermal necrolysis (EN) over more than a century.

Results: Epidermolysis had been reported long before Lyell’s report, but most cases had likely been staphylococcal scalded skin syndrome. Concerning non-Staphylococcus EN, confusion with erythema multiforme dissipated and its relation to Stevens–Johnson syndrome was clarified.

Tremendous advances were made in understanding the causes and mechanisms, with increased acceleration in the last 10 years.

Conclusion: The next decade should be devoted to improve the prevention and management of a disease that is the most terrible form of drug hypersensitivity.

History of the disease: Nosology/classification, and diagnosis

Original description of toxic epidermal necrolysis

The name “toxic epidermal necrolysis (TEN)” was introduced in 1956 by Lyell1 to describe the clinical disorder characterized by extensive destruction of epidermis that resembled scalding. Since then, the eponym Lyell’s syndrome became widely accepted. As acknowledged later by Lyell,2 his original paper mixed three different disorders that all had been already described more or less clearly.

The first one was rapidly identified as staphylococcal scalded skin syndrome,3 and Lyell himself (Figure 1) contributed to the discovery of the toxin responsible for a superficial, subcorneal detachment that is histologically very distinct from the deep necrolysis characterizing TEN.5 This had been previously recognized and reported as “neonatal pemphigus”6–8 or von Rittershain disease.3

The second is now labeled as generalized bullous fixed drug eruption (GBFDE),9 a disease characterized by necrolysis of full-thickness epidermis on large well-demarcated blisters, which is similar to that of TEN; however, it is distinct from TEN in the absence or, if present, mildness of mucous membranes erosions, usual relapses, as well as with mild differences in histopathology.

Present knowledge remains insufficient to define the boundaries of GBFDE versus TEN clearly.

The description of TEN had already been provided by some predecessors to Lyell under different denominations: “unusual bullous eruption” (Lang and Walker in 195610), “erythroderma with epidermolysis” (Debré et al 193911).

Erythema multiforme, Stevens–Johnson syndrome, and related diseases: History and confusion

The initial description of erythema exudativum multiforme is attributed to von Hebra.12 I was not able to consult von Hebra’s original reports but from photographic pictures of Hebra’s drawings it seemed to encompass many skin diseases with a circinate pattern, of which some would probably be given a variety of other denominations today [e.g., erythema annulare, pyoderma gangrenosum, subacute lupus erythematosus (LE), Sweet’s syndrome].

Rendu in 1916,13 Fiessinger and Rendu in 191714 described a mucocutaneous eruption without clear cause that was later on reported as Fiessinger–Rendu syndrome or pluriorificial erosive ectodermosis, and retrospectively seems very similar to the two cases described in 1922 by Stevens and Johnson.15 In Germany Fuchs syndrome is used to describe a variant of erythema multiforme, and this syndrome mainly involves the mucosal surfaces. As the skin may be completely unaffected, it is an underrecognized diagnosis and often difficult to confirm.16

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Use of the terms “EM minor (erythema multiforme minor)” and “EM major (erythema multiforme major, EMM)” was proposed in the early 1950s for separating the classical mild cutaneous syndrome, as described by Hebra (erythema multiforme minor), from the usually more severe syndrome, with marked mucosal damage, as described by Stevens and Johnson, Fiessinger and Rendu, or Fuchs (all grouped under erythema multiforme major or majus).17

Because many physicians had observed the progression of cases from a phenotype of Stevens–Johnson syndrome (SJS) to a phenotype of TEN,18,19 TEN was included for years in an “EM spectrum”15 or in an even larger “mucocutaneous syndrome.”20

Attempts to clarify the confusion

Several facts were challenging the concept of the EM–SJS–TEN spectrum. First, the individual lesions that preceded detachment of epidermis were not suspected of being EM by Stevens and Johnson. In clinical reports of TEN, early lesions were clearly reported as “red or purple macules, often brown, occasionally purpuric, sometimes looking like ‘targets’ close to EM.”21 Second, it was difficult to explain why “EM is often provoked by herpes simplex infection, whereas I know of no evidence that this provokes TEN, if at all” (Lyell19).

A first proposal to split the “EM spectrum” was done by Ruiz-Maldonado, a Mexican dermatologist who proposed the classification of acute disseminated epidermal necrosis (ADEN) types 1, 2, and 3 for what we would call today SJS, overlap SJS–TEN, and TEN, respectively. ADEN was ipso facto separated from EM.22

In 1987, as a preliminary step to a large case-control study of the risk factors for EMM, SJS, and TEN, an international group of investigators had to agree on definitions and classification criteria. After reviewing several hundred photographs of historical cases, they proposed a classification based on the individual pattern and topographic distribution of the skin lesions and maximum extent of blisters/erosions (expressed as percentage of body surface area involved).23

Implicit to this new classification were the hypotheses that: (1) EMM is different from SJS, and (2) SJS and TEN are only severity variants of a single entity.

Both hypotheses were strongly supported by the results of the case-control analyses done on 552 patients and 1720 controls and showing that EMM differed from both SJS and TEN by demographics, associated diseases, causes, and severity, and that SJS, TEN, and overlapping cases differed only by the extent of detachment, and therefore severity.24 These results strongly suggested that a “spectrum from EMM to TEN” does not exist, but rather that there is on one hand a group of typical/atypical EMM and on the other a real continuum from SJS to TEN. The simplest way to express this continuum would be the denomination of epidermal necrosis (EN) that is used in this review.

Current classification

Most authors currently use the “Severe Cutaneous Adverse Reactions (SCAR) study” classification,25 presented in Table 1.

Diagnosis criteria are based on expert consensus and were never submitted to formal validation. These criteria are erosions of mucous membrane on at least two different sites, “spots” or “atypical targets,” skin blisters or erosions, skin pain, Nikolsky’s sign, and detachment of large epidermal sheets. The diagnosis is probable if three or more of the aforementioned criteria are present, definite if confirmed by unequivocal clinical photographs, and/or biopsy. The typical histology pattern shows extensive apoptosis of keratinocytes on the full thickness of the epidermis and mild interface dermatitis. Negative direct immunofluorescence findings are important in case of ambiguous histology.

Differential diagnoses are listed in Table 2, and Table 3 in J. Roujeau / Dermatologica Sinica 31 (2013) 169–174 presents the key dates and publications related to epidermal necrosis.

Epidemiology

The best available evidence on the incidence of EN was provided by studies done before the generalized use of current classification. There was obviously some room for ambiguity. For EMM, SJS, TEN, altogether the figure was four cases/million/year in the United States.24 In France, Germany, Italy, and Singapore, the incidence of TEN was reported to be one case/million/year26,27 using disease definitions encompassing what we would now call TEN (more than 30% detachment) and SJS–TEN overlap (10–29% detachment). Concerning SJS, more recent data suggest an incidence that is about equal to the total of TEN and SJS–TEN overlap.28 Taking all these data into account, a figure of two cases/million inhabitants/year can be considered highly plausible for EN in Europe. The incidence may be more elevated in other parts of the world because of risks related to ethnicity29 or to more frequent use of “highly associated” medications (Africa).

Severity

The high mortality associated with TEN was recognized very early. Actually the qualification of “toxic” chosen by Lyell referred to the
Table 2 Main differential diagnoses of SJS/TEN.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Context</th>
<th>Main clinical differences</th>
<th>Pathology</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSSS</td>
<td>Infants, renal failure in adults</td>
<td>No mucous membrane involvement</td>
<td>Subcorneal detachment</td>
<td>Staphylococcus toxins</td>
</tr>
<tr>
<td>AGEP</td>
<td>Recent initiation of medicines</td>
<td>Postules</td>
<td>Subcorneal postules</td>
<td>Medications</td>
</tr>
<tr>
<td>Burns</td>
<td>Unconsciousness</td>
<td>Lesions of &quot;spot&quot; or atypical targets</td>
<td>Epidermis involved on variable thickness</td>
<td>Thermal or chemical</td>
</tr>
<tr>
<td>aGVHDc</td>
<td>Bone marrow transplantation</td>
<td>Slower progression, gut and liver involvement</td>
<td>May be very close to that of TEN</td>
<td>Alloimmunity</td>
</tr>
<tr>
<td>LEb</td>
<td>SLE or SCLE</td>
<td>Slower progression, photo distribution</td>
<td>May be very close to that of TEN</td>
<td>Autoimmunity</td>
</tr>
<tr>
<td>Paraneoplastic pemphigus</td>
<td>Lymphoma</td>
<td>Slower progression, severe mouth lesions</td>
<td>Acantholysis, positive DIF</td>
<td>Ab-mediated autoimmunity</td>
</tr>
<tr>
<td>LABD, drug induced</td>
<td>Recent initiation of medicines</td>
<td>Some tense blisters</td>
<td>Subepidermal blister, no necrosis,</td>
<td>Medicationsc</td>
</tr>
<tr>
<td>E(E)MM</td>
<td>Children, young adults, frequent recurrences</td>
<td>Typical targets, no confluence</td>
<td>Less necrosis, more infiltrates</td>
<td>Infections, idiopathic</td>
</tr>
</tbody>
</table>

ACEP = acute generalized exanthematous pustulosis; aGVHD = acute graft-versus-host disease; E(E)MM = erythema (exsudativum) multiforme majus; LE = lupus erythematosus; LABD = linear IgA bullous disease; pos. DIF = positive DIF; SCE = subacute cutaneous lupus erythematosus; SLE = systemic lupus erythematosus; SSSS = staphylococcal scalded skin syndrome; SJS = Stevens–Johnson syndrome; TEN = toxic epidermal necrolysis.

c Frequently responsible drugs: amoxicillin, diltiazem, hydroxychloroquine, terbinafine.

b It is not yet clear whether aGVHD should be considered a cause of EN or a differential.

c Frequently responsible drugs: vancomycin, diltcenc, several antibiotics.

life-threatening severity of the disease and not to its causes or mechanisms as it was too often believed later. For years, SJS was considered much more benign, probably in large part because of confusion with EMM. A recent cohort study that included 460 patients with EN observed an overall disease-related mortality of 30% at 90 days after onset. The death rates were 20%, 30%, and 50% for subgroups of SJS, overlap, and TEN, respectively.28 In addition to very high mortality, EN is the cause of nearly constant sequelae, occasionally progressing and often invalidating.

Evolution of concepts on causality

The concept that medications were a frequent, if not the only, cause of TEN was rapidly accepted by the medical community... may be too quickly in the opinion of Lyell.19 Strong evidence of such causality (and also of relationship between SJS and TEN) was provided by several mass campaigns of prevention of infectious diseases by long-acting sulphonamides, as these resulted in “epidemics” of SJS and TEN.18,30

Table 3 Key dates and publications related to epidermal necrolysis.

<table>
<thead>
<tr>
<th>Date</th>
<th>Author(s)</th>
<th>Concept</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1866</td>
<td>von Hebra</td>
<td>Erythema exsudativum multiforme</td>
<td>12</td>
</tr>
<tr>
<td>1916, 1917</td>
<td>Rendu, Fiesinger and Rendu</td>
<td>Multiformal ectodermosis</td>
<td>13,14</td>
</tr>
<tr>
<td>1922</td>
<td>Stevens and Johnson</td>
<td>Stevens–Johnson syndrome</td>
<td>15</td>
</tr>
<tr>
<td>1939</td>
<td>Debré et al</td>
<td>Bullous erythroderma with epidermolysis</td>
<td>11</td>
</tr>
<tr>
<td>1956</td>
<td>Lyell</td>
<td>Toxic epidermal necrolysis</td>
<td>1</td>
</tr>
<tr>
<td>1968</td>
<td>Bergondt H et al</td>
<td>High risk of long-acting sulphonamides</td>
<td>18</td>
</tr>
<tr>
<td>1968, 1970</td>
<td>Billingham and Streilein, Streilein and Billingham</td>
<td>TEN and a graft-versus-host model in hamsters</td>
<td>37,38</td>
</tr>
<tr>
<td>1970</td>
<td>Mellish and Glasgow</td>
<td>Staphylococcal scalded skin syndrome</td>
<td>3</td>
</tr>
<tr>
<td>1972</td>
<td>Peck et al</td>
<td>Human graft-versus-host reaction as a cause of TEN</td>
<td>39</td>
</tr>
<tr>
<td>1972</td>
<td>Kauppinen</td>
<td>Drug rechallenge often negative in SJS and TEN</td>
<td>9</td>
</tr>
<tr>
<td>1985</td>
<td>Ruiz-Maldonado</td>
<td>ADEN types 1, 2, and 3</td>
<td>22</td>
</tr>
<tr>
<td>1985</td>
<td>Revuz et al</td>
<td>First international meeting on TEN, Créteil, France</td>
<td>—</td>
</tr>
<tr>
<td>1985</td>
<td>Lyell A (Créteil meeting)</td>
<td>The Jackpot hypothesis</td>
<td>—</td>
</tr>
<tr>
<td>1986</td>
<td>Roujeau et al</td>
<td>Mild links between HLA and TEN</td>
<td>58</td>
</tr>
<tr>
<td>1987</td>
<td>SCAR study group</td>
<td>Initiation of multinational case-control study on EN</td>
<td>—</td>
</tr>
<tr>
<td>1990</td>
<td>Roujeau and Revuz</td>
<td>Acute skin failure</td>
<td>64</td>
</tr>
<tr>
<td>1993</td>
<td>Correa et al</td>
<td>Studying T cells in blister fluid of TEN</td>
<td>43</td>
</tr>
<tr>
<td>1993</td>
<td>Bastuji-Garin et al</td>
<td>Consensus definition of EEMM, SJS, and TEN</td>
<td>23</td>
</tr>
<tr>
<td>1995</td>
<td>Roujeau et al</td>
<td>Results from first case-control study of drug risks in EN</td>
<td>32</td>
</tr>
<tr>
<td>1998</td>
<td>Wolkenstein et al</td>
<td>First RCT in TEN (thalidomide proved deleterious)</td>
<td>65</td>
</tr>
<tr>
<td>2000</td>
<td>Bastuji-Garin et al</td>
<td>SCORTEN; a prognosis score allowing comparisons between series</td>
<td>66</td>
</tr>
<tr>
<td>2002</td>
<td>Nassif et al</td>
<td>Drug-specific cytotoxic cells in blister fluid of TEN</td>
<td>48</td>
</tr>
<tr>
<td>2004</td>
<td>Chung et al</td>
<td>Carbamazepine (CBZ)-related TEN and HLA-B*15:02</td>
<td>29</td>
</tr>
<tr>
<td>2005</td>
<td>Hung et al</td>
<td>Allopurinol-related TEN and HLA-B*58:01</td>
<td>59</td>
</tr>
<tr>
<td>2008</td>
<td>Mockenhaupt et al</td>
<td>EuroSCAR case-control study of SJS/TEN</td>
<td>33</td>
</tr>
<tr>
<td>2008</td>
<td>Chung et al</td>
<td>Granulysin as the key cytokine in necrolysis</td>
<td>50</td>
</tr>
<tr>
<td>2011</td>
<td>Ko et al</td>
<td>Restricted TCR needed for CBZ-related SJS/TEN</td>
<td>52</td>
</tr>
<tr>
<td>2011</td>
<td>Genin et al</td>
<td>GWAS on a large European series of SJS/TEN cases</td>
<td>60</td>
</tr>
<tr>
<td>2012</td>
<td>Wei et al</td>
<td>Direct noncovalent link between CBZ and HLA-B1502</td>
<td>53</td>
</tr>
<tr>
<td>2012</td>
<td>Chen et al</td>
<td>Eradication of CBZ-induced TEN from Taiwan</td>
<td>63</td>
</tr>
<tr>
<td>2013</td>
<td>Sekula et al</td>
<td>SJS/TEN even more severe than suspected</td>
<td>28</td>
</tr>
</tbody>
</table>

ADEN = acute disseminated epidermal necrosis; EN = epidermal necrolysis; GWAS = genome-wide association studies; HLA = human leukocyte antigen; p-i concept = pharmaco-immune concept; RCT = randomized controlled trial; SCAR study = Severe Cutaneous Adverse Reactions study; SJS = Stevens–Johnson syndrome; TCR = T-cell receptor; TEN = toxic epidermal necrolysis.
It is anyhow important to keep in mind that no drug cause was suspected in the two original cases published by Stevens and Johnson. However, only one of the four original cases was reported by Lyell.

In 1990, I contributed a review on SJS and TEN stating that “Drugs are the most important, if not the only, cause of TEN ... Infections are well-recognized causes of SJS but not of TEN.” Both statements were erroneous: the hypothesis of different causes for SJS and TEN was wrong and so is the suggestion that TEN had no other cause than drugs.

The results of the SCAR case-control study clearly indicated that the “etiologic fraction” for “associated medications” was very similar for SJS, overlap SJS–TEN, and TEN and around 0.65 in all three groups. Because the etiologic fraction was calculated only for drugs with a statistically significant association, it was underestimated by lack of statistical power. Further experience on larger numbers of cases confirmed the existence of low percentage of cases without any exposure to medications (2–3%) and a larger number (10–15%) of cases exposed to several drugs that all were unlikely the cause. In 20–25% of cases, one or several medications were possibly the cause without any definite certainty. In conclusion, no more than 70–80% of cases are drug induced and the percentages are similar for SJS, TEN, and overlaps. The percentage of “idiopathic cases” is probably higher in children. Up to now only a very low proportion of cases of EN (≈1%) had an established nondrug cause. These causes include acute graft–versus-host-disease (GVHD), some variants of acute LE, and infections. Infection-related EN was especially demonstrated with Mycoplasma pneumoniae but other agents were also suspected (Klebsiella pneumoniae, viruses). Over dosages of methotrexate or colchicine may also induce damages of skin and mucous membrane that closely resemble EN.

Progress on comprehension of mechanisms

In early reports, the mechanisms leading to EN appeared very mysterious. Histological slides of skin lesions actually evidenced the total destruction of the epidermis upon a “silent dermis” with a very mild cell infiltrate, no lesion of vessels, no deposits of immunoglobulins (Ig) or complement.

Some important steps in the advancement of knowledge are summarized below.

Resemblance to GVHD

The first animal model resulting in necrosis of epithelial cell was established by Billingham and Streilein, two famous immunologists, in 1968 and 1970. The EN developed around a site of local GVHD in a complex model of cutaneous GVHD, at a time when the key role of dendritic cells was still unknown. In this model, an unidentified substance present in the plasma was able to cause epidermolysis.

In 1972, TEN was reported as a possible expression of acute GVHD in humans.

More recently, a Japanese team developed a mouse model of GVHD in transgenic mice expressing OVA in keratinocytes and developing epidermolysis after the transfer of OVA-specific cytotoxic T cells. The development of epidermolysis needed some immunosuppression and implied inactivation of regulatory cells.

Focus on blister fluid

The first attempts to study T cells at the site of lesions used immunofluorescence techniques and extraction of T cells from trypsinized sheets of necrotic epidermis. Very few cells were obtained and viability was poor. Tremendous progresses were made possible by studying cells present in the blister as first done by Osvaldo Correia et al in Portugal. Many advances were made by studying this blister fluid and characterizing the cells present in this fluid.

Drug-specific T cells

In the last 20 years, the key role of drug-specific T cells in drug allergy was definitely demonstrated by the establishment of human T-cell clones, derived from the blood lymphocytes or skin lesions of patients with a variety of reactions. T-cell clones demonstrated that drugs can be recognized by human T cells and suggested original pathways of activation. Clones have been obtained with most medications that induce allergic reactions in humans, including penicillin G, amoxicillin, sulfamethoxazole, phenobarbital, carbamazepine (CBZ), and lamotrigine. They were often of both CD4 and CD8 phenotypes, whatever the original type of eruption had been.

TEN drug-specific T cells were found in the blister fluid of patients with TEN, which were reported to kill autologous cells (lymphocytes and keratinocytes) in a major histocompatibility complex (MHC) class I-restricted pathway. In addition to the drug-specific CD8 memory cells, natural killer (NK) cells and NK T cells also contribute to apoptosis of epithelial cells.

Pharmaco-immune concept

With many drugs, a very original observation was that the drug could be presented to the T-cell receptor (TCR) and activate specific clone without prior processing by the antigen-presenting cell and through a noncovalent binding to the MHC or its embedded peptide. Because the noncovalent binding is reminiscent of the pharmacological interaction between a drug and its receptor, the denomination of pharmaco-immune concept has been proposed. This concept is supported by recent findings about direct links of medications (e.g., CBZ) with both human leukocyte antigen (HLA) and TCR.

Fas ligand

It was generally agreed that there were too few cytotoxic cells in the lesions of EN to explain the extent of epidermolysis and that soluble death mediators were also involved. A succession of cytokines had been suspected, such as tumor necrosis factor-α (TNF-α), perforin, granzyme B, but the most popular for more than 10 years has been Fas ligand. Activated keratinocytes express Fas-L and epidermal sheets of patients with EN-killed Jurkat cells (a lymphocyte cell line that is exquisitely sensitive to Fas-L-induced apoptosis). Human Ig inhibited the apoptosis of Jurkat cells. These findings were exaggerated as: (1) “collective suicide” of keratinocytes through Fas-L–Fas interactions (even though no evidence was provided that Fas L killed keratinocytes), and (2) possible inhibition of apoptosis of keratinocytes by human Ig (even though evidence points that the effect was only on Jurkat cells). Further studies have demonstrated the absence or very low impact of Fas-L on keratinocytes and no benefit from using high-dose human Ig (intravenous Ig) to treat patients with EN.

Regulatory cells

Clinicians noticed that patients developing EN suffered more often than controls from conditions that impaired immune response, advanced malignancy, autoimmune diseases, and long-term therapy with corticosteroids. In Azukizawa’s mouse model, development of EN needed prior inactivation of regulatory cells. Studies in humans strongly suggested that a deep depression in
number and functions of regulatory T cells was present at the acute stage of EN. Further studies are definitely needed on this topic.

Granulysin

In 2008, a key paper reported the work of the team directed by W.H. Chung and S.J. Hung demonstrating that granulysin was actually the main cytokine responsible for the apoptosis of epithelial cells in EN. Not only was granulysin present in the blisters at concentrations 100 times more elevated than perforin or granzyme B, but it also killed target cells in vitro and induced blisters with a necrotic roof when injected in the skin of normal mice at the concentration observed in blisters. Fas-L was detected in very low concentrations without any detectable effect. Granulysin was released by drug-specific cytotoxic CD8 T cells and NK cells. Macrophages often recruited in the lesions are also able to produce granulysin. These findings have several tremendous consequences: (1) clearly they demonstrate that the many other cytokines previously considered as contributing to EN (e.g., TNF-α, Fas-L, TRAIL, Tweak) have a mild and likely accessory role; and (2) they point to inhibiting the release and/or the effects of granulysin as the main goal in an emergency treatment of EN.

HLA associations

A mild association of EN with HLA had been reported more than 25 years ago but since 2004 several studies have shown strong and complete associations of HLA-B*15:02 allele with CBZ-induced EN and of HLA-B*58:01 with allopurinol-induced EN. Associated alleles show very different frequency distribution around the world being frequent in some parts of Asia and less frequent or rare in Europe. That association appeared both drug specific and phenotype specific and related to ethnicity. HLA associations are a field of intense and productive research. A direct link between the medication and the relevant HLA molecule was demonstrated for CBZ and abacavir as suggested years ago for penicillin. The demonstration that patients suffering from EN also have a restricted use of specific clonotypes of the TCR is a major progress to explain why a minority of persons harboring the HLA-B*15:02 phenotype developed EN when taking CBZ. Furthermore, the prevalence of CBZ-related EN was largely decreased from Taiwan, where it had been the primary cause, by testing for HLA-B*15:02 before prescription in recent years.

The Jackpot hypothesis

The “Jackpot” hypothesis was proposed by Lyell in 1985 during a discussion about the mechanisms of EN in the first international symposium on TEN. The disease is so rare that its occurrence needs the conjunction of several rare risk factors, including intake of “strongly associated” medication, adequate HLA, and certainly a few others such as adequate TCR variant and perturbation of regulatory cells.

The future

Looking back to the history of EN, it appears that in the past decades the knowledge about EN had improved tremendously, slowly initially but more rapidly in the last few years. Most of these more recent advances were provided by a leading Taiwanese team. With the important exception of HLA testing for CBZ in Asia, progresses in knowledge have not yet resulted in major benefits for the victims of what is the most severe form of adverse reaction to drugs.

The existence and development of international networks of researchers (e.g., RegiSCAR, J-SCAR, Asian-SCAR), active patient associations, and reference centers for treatment, provide a basis for new progresses and especially for translating progresses from laboratories to patient care.

Decreasing the incidence (detection of patients “at risk,” restriction of use of “strongly associated” medicines), earlier diagnosis and better care (reference centers, specific treatments), prevention and treatment of sequelae should be priorities for researchers and clinicians. No specific treatment has been proven to be effective until now. Therefore, increased focus is needed on agents inhibiting the release and/or blocking the effects of granulysin.

More implication of pharmaceutical companies and regulatory agencies in promoting research and helping the victims is definitely needed to decrease the burden of EN on public health.

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