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Review article

A review of toxic epidermal necrolysis management in Japan

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Abbreviations:
BSA, body surface area; DFPP, double filtration plasmapheresis; DIHS, drug-induced hypersensitivity syndrome; HLA, human leukocyte antigen; IVIg, intravenous immunoglobulin; mPSL, methylprednisolone; NSAID, non steroidal anti-inflammatory drugs; PE, plasma exchange; SCORTEN, score of toxic epidermal necrolysis; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; TNF, tumor necrosis factor

ABSTRACT

Toxic epidermal necrolysis (TEN) is a severe adverse drug reaction characterized by necrosis of the epidermis. Its incidence is approximately 1 per million a year and average mortality rate is high at 25–50%. TEN has a flu-like prodrome, followed by atypical, targetoid erythematous or purpuric macules on the skin. These macules coalesce to form flaccid blisters that slough off as areas of epidermal necrosis. Drugs such as allopurinol, sulfonamides, and carbamazepine are the most common causes. The human leukocyte antigen (HLA)-B*15:02 in Asians being administered carbamazepine and the HLA-B*58:01 antigen in patients of all ethnicities being administered allopurinol are known to be high-risk factors. Rapid diagnosis, discontinuation of the causative drug, and supportive treatment are essential for better prognosis and improvement of sequelae. Till now, systemic corticosteroids and intravenous immunoglobulins have been used as the most common active interventions; however, no gold standard has been established. In Japan, physicians follow a unique diagnostic criteria and treatment guideline to improve the diagnosis rate and streamline treatments. This may be a contributing factor for the lower mortality rate (14.3%). The efficacy of systemic corticosteroids, immunoglobulins, and plasmapheresis may have been beneficial as well. In Japan, TEN is defined as an epidermal detachment of over 10% of the body surface area (BSA), while the globally accepted definition established by Bastuji-Garin describes it as an epidermal detachment of over 30% of the BSA. In Japanese individuals, HLA-A*02:06, HLA-A*02:07, HLA-A*31:01 and HLA-B*51:01 may be linked to higher risks of TEN.

Introduction

Toxic epidermal necrolysis (TEN) is a severe adverse drug reaction characterized by necrosis of the epidermis. Keratinocyte cell death causes detachment of the skin and mucous membrane from the dermal-epidermal junction.[1] The incidence rate is 0.5–1.4 per million per year and the average mortality rate is 25–50%.[2–7] The mean patient age is 42.6 years and the incidence increases with age.[2,3] SJS and TEN have become to be classified under a single category, and the difference between them is the amount of epidermal detachment.[8] However, in this review, TEN specifically will be discussed because of its exceptional high mortality, rarity and intense symptoms compared to SJS. In a typical course of TEN, the first symptom is a flu-like prodrome.[9] Fever, malaise, and pharyngitis may occur before the onset of mucocutaneous symptoms. Clinically, atypical targetoid macules appear on the skin. These macules coalesce to form flaccid blisters that slough off as areas of epidermal necrosis (Fig. 1).[1] Drugs, especially antibacterial and antiepileptic drugs, are the most common cause. Specific human leukocyte antigen (HLA) alleles are high-risk factors as well. HLA-B*15:02 in Asians being administered carbamazepine and HLA-B*58:01 in people of all ethnicities being administered allopurinol have been reported to be high-risk factors for TEN.[1] Rapid diagnosis, discontinuation of the causative drug, and initiation of supportive treatment are essential for better prognosis and improvement of sequelae. Till now, systemic corticosteroids and intravenous immunoglobulins (IVIg) have been used as the most common active interventions; however, no gold standard has been established.[10] In Japan, as in the rest of the world, TEN is an important disease. In this review, the situation of TEN in Japan at the present will be discussed.

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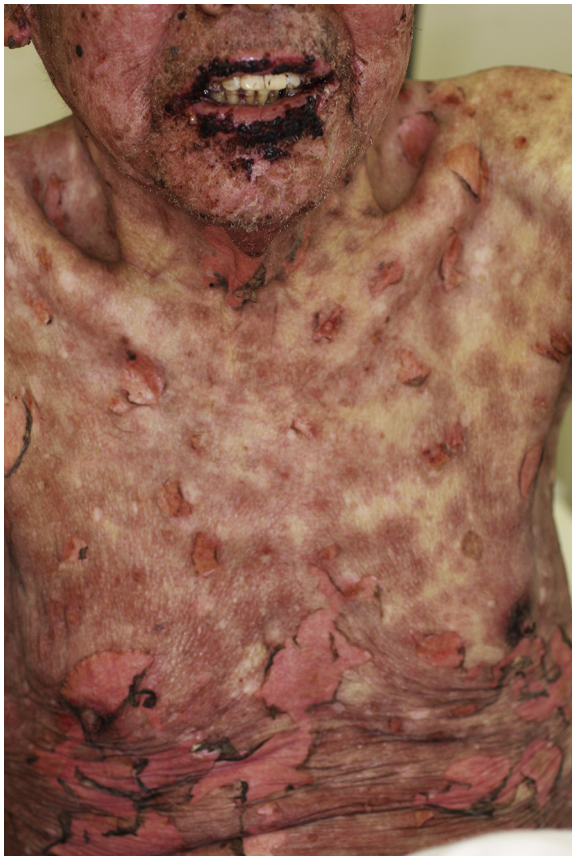

Fig. 1. Patient of toxic epidermal necrolysis with epidermal sloughing showing bare dermis. Coalescing violaceous macules can also be seen. There is widespread involvement of trunk and extremities. Erosions with hemorrahagic crusts on lips can also be seen.

Diagnosis

In Japan, TEN is characterized by an epidermal necrolysis greater than 10% of the BSA. Although it is recognized that TEN can occur following SJS, unlike in the rest of the world, there is no SJS/TEN overlap, where epidermal necrolysis occurs in 10–30% of the BSA.[11] Because it is a fatal disease, the Japanese Research Committee on severe adverse reaction has created a diagnostic criteria and treatment guideline to provide a speedy and accurate diagnosis and effective treatment. A scoring system different from SCORTEN, which is typically used worldwide has also been created to determine the severity of the condition. Besides total epidermal necrosis, area and severity of mucosal lesions, percentage of blisters or erosions, systemic symptoms (fever, respiratory failure, and liver impairment) are included.[12]

Support to TEN patients

Japan has a unique relief system for patients suffering from severe adverse drug reactions, and it was put in place in 1980. When a Japanese patient who was administered a medication for a reasonable licensed cause suffers from a severe drug reaction that requires treatment by admission or results in severe sequelae or death, the government financially supports the patient or his/her family for the treatment. This relief system also serves as a useful means of accumulating data on TEN in Japan for further analysis.[13]

Incidence rate, causes, and common symptoms

For 2005–2007, the incidence rate of TEN in Japan was 0.28–0.52 per million per year.[14] A retrospective study of 65 TEN cases in Japan between 2000 and 2006 through published medical journals, and another retrospective study of 35 TEN cases in 2 university hospitals in Japan between 2000 and 2013 provides the following insights (Table 1).[15,16] As per the Japanese guideline, patients with over 10% skin detachment, mucous membrane erosions, and skin lesions were diagnosed with TEN. SJS/TEN overlap cases were also considered to have TEN. The skin lesions were macules, atypical target-like lesions, bullae, or erosions. In the former study, 31 patients were men and 34 women, and the mean patient age was 45.7 years. All cases were caused by drugs, such as NSAIDs, antibiotics, and anticonvulsants. Cephalosporin was found to be the most common causative antibiotic with 10 cases, and carbamazepine the most common anticonvulsant with 8 cases. Patients developed symptoms within 2 weeks. The range of skin detachment was 10–70%, while the mean was 49.6%. Additional symptoms involving other organs, especially the liver and kidney, and the respiratory system were common in many patients. Hepatitis was the most common form of organ involvement, noted in 41 cases. Elevation of serum alanine aminotransferase level was the most common blood test abnormality, observed in 33 cases (100 IU/l–1000 IU/l). 7 cases of sepsis were also reported; in patients with SJS, only 1 case of sepsis occurred. Ocular complications were seen in 6 cases.[15] In the latter study, 17 patients were men and 18 women, and the mean patient age was 56.6 years. All cases were caused by drugs, such as NSAIDs, cold medicines, antibiotics, and anticonvulsants. Out of the cases where the causative drug was determined, antibiotics were the most common with 7 cases. The average interval until patients developed symptoms was 11.7 days. The range of skin detachment was 10–100% of BSA, while the mean was 44.7%. Additional symptoms involving other organs, especially the liver and kidney, and the gastrointestinal system were common in many patients. Hepatitis was the most common form of organ involvement, noted in 15 cases. 6 cases of sepsis were also reported; in patients with SJS, only 1 case of sepsis occurred. Keratoconjunctivitis including conjunctival injection and erosions, and pseudomembranes were seen in 17 cases. Labial and oral erosions were observed in 19 cases. Genital problems, found mainly by pain during urination, were observed in 17 cases of TEN.[16]

Mortality rate

Ranging from 6.2% to 32%, the most recent reported mortality rate for TEN was 14.3% (2000–2013).[13,15–17] The most recent

Table 1
Summary of the 2 studies of TEN patients in Japan by Yamane *et al.*[15,16]

Number of patients	65	35
Year	2000–2006	2000–2013
Background of patients	From articles of medical journals, review	2 university hospitals, case series
Male/female	31/34	17/18
Mean age	45.7	56.6
Most common causative drug	Cephalosporin	Antibiotics
Time until symptoms	2 weeks	Average of 11.7 days
Range of skin detachment	10–70% (Average 49.6%)	10–100% (Average 44.7%)
Most common organ involvement	Hepatitis	Hepatitis
Sepsis patients	7	6
Ocular complications	6	17
Mortality rate	6.20%	14.30%

TEN, toxic epidermal necrolysis.

mortality rate has decreased compared to the mortality rate of 21.6% (1981–1997), and this decrease may be due to the improvement in diagnosis and treatment.[17] Especially treatment options have increased, including steroid pulse therapy, rarely administered before 2000, plasmapheresis which became admitted coverage by health insurance in 2006, and high dose intravenous immunoglobulin (IVIg) which became admitted by health insurance in 2014.[15,16] In the retrospective study of 35 TEN cases in 2 university hospitals in Japan between 2000 and 2013, when comparing the mortality rate before and after plasmapheresis eligibility, there was a remarkable decrease from 23.5% (2000–2006) to 5.6% (2007–2013). Although steroid pulse therapy and the combination of IVIg therapy (<2 g/kg) with corticosteroid therapy were the mainstream until 2006, the frequency of cases treated with the combination of plasmapheresis and corticosteroid therapy increased remarkably after 2007, making it the most common treatment.[16] Common points in deceased patients in reports where details were provided, were that the mean age was over 50 years old, the majority women, majority treated with corticosteroids alone, and that majority had sepsis.[15,16]

Genetic susceptibility

There are specific HLA alleles that are associated with a high-risk for TEN, and especially for the Japanese (Table 2). HLA-B*15:02 in Asians administered with carbamazepine and HLA-B*58:01 in patients of all ethnicities administered with allopurinol are at high-risk for SJS/TEN.[6,14,18–25] The association of 2 of the most commonly known HLAs, HLA-B*15:02 and HLA-B*58:01, with TEN is different for the Japanese population. HLA-B*15:02 is not found in Japanese patients with TEN, but a similar HLA, HLA-B*15:11, is. This HLA is associated with TEN patients who were administered carbamazepine, and can be relatively commonly found in Japanese patients.[21–23] The odds ratio (OR) for HLA-B*15:11 in Japanese patients with carbamazepine-induced TEN was 9.76 (95% CI, 2.01–47.5). It has been suggested that some subfamilies of serotype HLA-B75 are involved in the onset of carbamazepine-induced SJS/TEN.[22] HLA-B*58:01 is a more global biomarker for TEN, as it is found in all patients regardless of ethnicity, including the Japanese.[19,20] In a case–control study of patients with allopurinol-induced adverse drug reactions (erythema exudavitum multiforme and SJS), 7 patients from Shimane University Hospital were selected between 2010 and 2012. The OR for HLA-B*58:01 was the highest at 65.6 (95% CI, 2.9–1497.0). None of the allopurinol-tolerated control patients had HLA-B*58:01.[23] In a multicenter study where HLA-B genotyping was performed on 58 Japanese SJS/TEN patients between July 2006 and April 2008, no HLA-B*15:02 carriers and 5 HLA-B*58:01 carriers were found. Four of the 5 HLA-B*58:01 carriers had allopurinol-induced SJS/TEN. The allele frequency was high when compared to that in the Japanese population (OR, 40.83, $p < 0.0001$).[25]

Table 2
HLA types and association with Japanese TEN patients.

HLA	Association with Japanese TEN patients
HLA-A*02:06	Found, related with ocular complications
HLA-A*02:07	Found (zonisamide)
HLA-A*31:01	Found (carbamazepine)
HLA-A*51:01	Found (phenobarbital)
HLA-B*15:02	Not found
HLA-B*15:11	Found (carbamazepine)
HLA-B*58:01	Found (allopurinol)

HLA, human leukocyte antigen; TEN, toxic epidermal necrolysis.

HLA-A*02:06 has been found in Japanese TEN patients, and is especially related with ocular complications. In the same case–control study, HLA-A*11:01 was found to suppress ocular complications. The OR for HLA-A*02:06 was 5.1 ($p < 0.0005$). HLA-A*02:06 is less commonly found in Caucasians and Han Chinese.[24] Another HLA found in the Japanese that could increase the risk of TEN is HLA-A*31:01. In a study conducted in 2011, the HLA-A*31:01 allele was found in 37 of 61 (60.7%) patients with carbamazepine-induced adverse drug reactions, compared with 47 of 376 (12.5%) carbamazepine-tolerant patients. The OR for HLA-A*31:01 was 10.8 (95% CI, 5.9–19.6). Combining the results of a replication study, the association of HLA-A*31:01 with SJS/TEN patients in a subgroup analysis had an OR of 33.9.[14] In the case of Japanese patients, allopurinol and carbamazepine should be prescribed with caution. Biomarkers for SJS/TEN caused by phenytoin, zonisamide, and phenobarbital have been investigated in Japan, and both HLA-A*02:07 and HLA-B*51:01 may be potential contenders. In a retrospective case–control study, HLA-A*02:07 was found to be associated with zonisamide-induced SJS/TEN ($p = 0.0176$), and HLA-B*51:01 with phenobarbital-induced SJS/TEN ($p = 0.0042$). HLA-B*51:01 was marginally associated with phenytoin-induced SJS/TEN as well. Phenobarbital and phenytoin have similar chemical structures, and are very different from carbamazepine. This similarity may be the reason for the association of HLA-B*51:01 to both drugs.[21]

Treatment

No major differences exist between TEN management in Japan and the world. Age and gender distribution, causative drugs, and clinical symptoms in Japan are similar to those reported elsewhere.[15] However, the most recent mortality rate in Japan is lower than that reported elsewhere.[5–7,16] A systematic review published in 2015 reported the absence of a globally accepted gold standard for TEN treatment.[26] Currently in the UK and US, no active interventions are recommended. In all studies on TEN, except for the randomized control trial of thalidomide by Wolkenstein that led to the discontinuation of thalidomide treatment in 1998, variations in treatment make interpreting the data difficult.

The Japanese guideline recommends systematic steroids, IVIg, and plasmapheresis as the 3 first-line treatments of choice. Starting from mPSL administered at 0.5–2 mg/kg/day, clinicians are recommended to refrain from blindly increasing the amount and to consider pulse therapy in the absence of improvement. Ocular symptoms, bullae or rapidly spreading detachment, and respiratory symptoms are signs for initiating pulse therapy. For pulse therapy, mPSL at 500–1000 mg/day for 3 days is recommended. The second choice of treatment after steroids is both IVIg and plasmapheresis. Either can be used, and often when either is not effective, the other treatment is considered. The guideline recommends a dose of 5–20 g/day for 3–5 days.[12] The amount of IVIg used in Japan is not always more than 2 g/kg, which is considered as an effective amount in reports from other parts of the world.[16,27] The use of IVIg at 0.4 g/kg/day for 5 days may have increased after 2014 when it was admitted coverage by health insurance. Before 2014, financial reasons probably decreased its use. In Japan, usually IVIg is used in combination often with corticosteroid, whereas in the rest of the world, most treatments include monotherapy. The use of plasmapheresis in TEN patients is licensed in Japan since 2006.[12] There have been several successful reports of treatment in Japan (Table 3).[28–31]

Systematic corticosteroids have been historically the first choice systematic treatment for TEN, with the first use reported in 1976.[32] For systemic corticosteroids, increased risks of gastrointestinal problems and infection leading to increased mortality are the

Table 3
Successful treatment reports of TEN in Japan.[28–31]

Author	Year of study	Type of study	Treatment	Details of treatment	Number of patients	Outcome
Araki *et al.*[28]	2009	Case series	Steroid pulse therapy	Methylprednisolone 500 or 1000 mg/day ×3–4 days	5	0/5 mortality
Hirahara *et al.*[29]	2013	Case series	Steroid pulse therapy	Methylprednisolone 1000 mg/day ×3 days + oral prednisolone (0.8–1 mg/kg/day) ± methylprednisolone 500 mg/day ×2 days	8	0/8 mortality
Aihara *et al.*[30]	2012	Case series	IVIg	IVIg 400 mg/kg/day ×5 days as an additional therapy to systemic steroids (≥20 mg/day of prednisolone equivalent) administrated ≥2 days; 1 patient: Maximum 30–60 mg/day prednisolone or prednisolone equivalent 2 patients: Methylprednisolone 1000 mg/day ×3 days	3	0/3 mortality
Yamada *et al.*[31]	2008	Review	Plasmapheresis	Simple plasma exchange or Double filtration plasmapheresis 44 patients Other type 3 patients	47	11/47 mortality

TEN, toxic epidermal necrolysis; IVIg, intravenous immunoglobulin.

biggest concerns hindering its use.[7,33,34] Administration of corticosteroids in the initial stage of SJS/TEN, including pulse therapy is suggested to be beneficial from articles set in Japan.[28,29] The efficacy of steroid pulse therapy in Japan has been reported. In a prospective case series by Araki *et al.*, 5 patients with SJS or TEN with ocular complications at the acute stage were given steroid pulse therapy of methylprednisolone 500 or 1000 mg/day for 3–4 days, within 4 days from disease onset. Ocular complications such as corneal or conjunctival epithelial defects, and pseudomembranous conjunctivitis present in all cases in the beginning, improved in all cases.[28] In another study by Hirahara *et al.*, 8 patients were given 1000 mg/day of methylprednisolone for 3 days. This was followed by oral prednisolone (0.8–1 mg/kg/day), which was tapered gradually. If high grade fever persisted or reduction in BSA was not observed after the last dose of pulse therapy, a course of half-dose methylprednisolone pulse therapy (500 mg/day for 2 consecutive days) was administered. No patients died during in the 3 months after, whereas predicted mortality was 1.6 deaths according to SCORTEN.[29]

IVIg has gained popularity as the first choice systematic treatment for TEN, since its advocation in 1998.[7] According to a systematic review published in 2012, IVIg alone is not beneficial; thus, its usability is limited.[35] However as a part of a combination therapy, its beneficial effect has been suggested in an article in Japan.[30] In a study by Aihara *et al.* in 2015, the efficacy of IVIg was evaluated. IVIg was administrated for 5 days consecutively, in an open-label, multicenter, single-arm study in patients with SJS or TEN. IVIg (400 mg/kg/day) administrated for 5 days consecutively was performed as an additional therapy to systemic steroids in adult patients with SJS or TEN. IVIg was started from 3 to 23 days after the onset of skin lesions. Efficacy on day 7 was evaluated. 8 patients, including 3TEN patients who did not respond sufficiently to systemic steroids were treated. Although because the degree of improvement did not fulfill the response criteria (SCORTEN reduction ≥6 on day 7) and 1 TEN patient was considered a non-responder, all the patients improved their symptoms, and survived. The efficacy on day 7 was 87.5% (7/8 patients). In the 7 SJS or TEN patients that responded to IVIg, epidermal detachment reduced from 9.4% to 0.3% when comparing day 1 and day 7 after symptoms appeared. Erythema reduced from 51.4% to 17.1%. Details of only one successful TEN patient were described in the study, and in that case, steroids were given one day after symptoms, and IVIg was given 9 days after symptoms, and 8 days after steroids. The symptoms ceased after IVIg, and re-epithelialization started 2 days after IVIg.[30] The combination of IVIg and corticosteroid, has been thought to reduce mortality rate from before.[36] The timing of IVIg to be beneficial has been suggested in other studies, to be before the epidermal detachment occurs in TEN, and earlier the better. This detachment is usually 4–6 days after the initial skin symptoms.[37,38] In the study by Aihara *et al.*, the timing of IVIg for the other 1 successful TEN case was 9 days after cutaneous symptoms, while the non-responder was 23 days. The timing could have contributed to the beneficial effect.[30]

Plasmapheresis has been reported to be effective, through case reports and a literature review especially in Japan.[31,39–44] Whether simple plasma exchange or double filtration plasmapheresis is more beneficial, remains to be known. In a literature review of TEN cases treated with plasmapheresis in Japan, 47 patients were treated until 2006. The rate of effectiveness was 80.9% and the mortality rate was 23.4% with 11 deaths. Thirty six of the cases had been used corticosteroids prior to plasmapheresis but had no effect.[31]

In the case of cyclosporine, an entire month is required to achieve its full therapeutic benefit and this is not feasible for an acute disease like TEN.[45] In case of anti-TNF therapy, except thalidomide, which is a contraindicated TEN treatment, etanercept and infliximab seem beneficial. N-acetylcysteine seems to be beneficial as well, but it has only been used in case reports thus far.[46–49] There are no case reports of TEN patients treated with cyclosporine, anti-TNF therapy or N-acetylcysteine in Japan.

The lower mortality rate in Japan could be partly because TEN is defined at 10% epidermal detachment and treatment is initiated at earlier stages. In the literature, pulse therapy is reported to be beneficial and its usage may improve the mortality rate in Japan. Moreover, the TEN treatment guidelines in Japan are efficient, with supportive therapy that overcomes the drawbacks of active interventions, especially corticosteroids.[12] Rapid diagnosis, discontinuation of the drug, and hospital admission are vital to TEN

treatment. HLA antigens and risk factors specific to the Japanese should be taken into consideration while prescribing especially high-risk drugs. The definition describing TEN as BSA detachment >10% is more effective as it prompts treatment for TEN rather than for SJS/TEN overlap. However, although the Japanese definition, diagnostic criteria, scoring system, and treatment guidelines are helpful in managing daily clinical situations, they make it difficult to compare cases with those reported from other parts of the world, which are usually diagnosed on the basis of the criteria described in the Bastuji study. As for the treatment, although only supportive therapy is considered to be the best treatment at present in other countries, active interventions of corticosteroids, IVIg, and plasmapheresis are employed commonly in Japan, and has been reported to be benefitical.[28–31]

The recent topic in management of SJS/TEN is that drug-induced hypersensitivity syndrome (DIHS) and SJS/TEN overlap often results in critical outcomes.[50,51] DIHS is characterized by fever, rash, hepatic dysfunction, hematological abnormalities and lymphadenopathy.[50] DIHS cases associated with skin manifestations similar to SJS/TEN have been reported. All or most of the criteria of DIHS was fulfilled, but also mucosal involvement and epidermal detachment was seen. DIHS is diagnosed based on its characteristic clinical course, multiple organ involvement, and detection of herpesvirus reactivation. The skin manifestations of DIHS include maculopapular rash, erythema multiforme, exfoliative dermatitis, acute generalized exanthematous pustular dermatosis-like eruption or erythroderma and can have mucosal involvement. There is no specific mucocutaneous symptom for DIHS. On the other hand SJS/TEN is diagnosed by characteristic mucocutaneous symptoms. Whether there is organ involvement does not matter. Therefore, a case diagnosed as SJS or TEN from its mucocutaneous symptoms, can also be diagnosed as DIHS from its clinical course and positive viral reactivation (Table 4).[10,51] Time of onset after the initiation of the causative drug does differ between DIHS and SJS/TEN. DIHS has a later onset of 2–6 weeks in 80% of the cases, most commonly at 4–5 weeks, while SJS/TEN has an early onset of within 3 weeks for 67% of cases. However, in the overlapping cases, the onset is 4–5 weeks after the start of the drug, just between the most common timing of SJS/TEN and DIHS. The overlapping cases were all caused by anticonvulsants.[51]

In another study by Teraki *et al.*, 8 patients diagnosed with SJS/TEN due to anticonvulsants were examined, and a similarity with DIHS was seen. Seven of the 8 patients developed symptoms >3 weeks after starting anticonvulsants. Hepatic dysfunction was present in 6 patients, leukocytosis and/or eosinophilia in 7 patients, reactivation of HHV-6 in 1 of the 4 patients.[50]

Table 4
Comparison of SJS/TEN, DIHS and overlap of SJS/TEN and DIHS.

	SJS/TEN	DIHS	Overlap of SJS/TEN and DIHS
Diagnosis	Skin and mucosal manifestation	Clinical course Organ involvement Detection of herpesvirus reactivation	Skin and mucosal manifestation Clinical course Organ involvement Detection of herpesvirus reactivation
Onset	67% of cases 0–3 weeks	80% of cases 2–6 weeks Most frequently at 4–5 weeks	4–5 weeks
Most common causative drugs	Anticonvulsant and antibiotics	Anticonvulsants	Anticonvulsants

DIHS, drug-induced hypersensitivity syndrome; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis.

Eye care

Consulting the ophthalmologist is essential to TEN. When there is ocular involvement, the combination of aggressive lubrication, topical antibiotics, topical corticosteroids and lysis of adhesions with a glass rod is necessary. However, this has had only a modest effect on long-term ocular complications. Recently, amniotic membranes transplant has been shown to be effective in preserving visual acuity and an intact ocular surface.[52,53] A physical barrier between the inflamed and denuded mucosal surfaces may minimize the formation of adhesions, and may be anti-inflammatory and antifibrotic.[53]

Conclusion

TEN is an important disease in Japan and the rest of the world. Although there are differences between diagnosis and recommended treatments, reducing the mortality rate has been the goal worldwide. HLA-A*02:06, HLA-A*02:07, HLA-A*31:01, and HLA-B*51:01 may be high-risk factors for TEN in Japanese individuals, and in the future, routine checks should be considered. Further research into the pathogenesis of TEN is warranted, and new findings may contribute toward a more effective active intervention.

Conflict of interest

The authors have no conflict of interest to declare.

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