Case Summaries of Serious Skin Disorders

Case 1 Toxic epidermal necrolysis/Drug-induced hypersensitivity syndrome

Patient		Daily dose/ Treatment duration	Adverse reactions
Gender/ Age	Primary disease (complication)		Clinical course and therapeutic measures
Male 50s	Epilepsy Traumatic intracranial haemorrhage Paresis Aphasia Disorientation Osteoporosis Hepatitis alcoholic Pseudarthrosis Pleural effusion Hepatic atrophy	25 mg/day Consecutive 8-day treatment 50 mg/day for 38 days	Sodium valproate 1 200 mg/day had been administered for treatment of symptomatic epilepsy. Day 1 of administration: The patients visited to the emergency outpatient department because of epileptic seizure. Administration of lamotrigine 25 mg/day was started (concomitant use with sodium valproate) for treatment of epilepsy. 8 days after start of administration: The dose of lamotrigine increased to 50 mg/day. 20 days after start of administration: The patient visited to the emergency outpatient department because of a fall arising from dizziness. At that time, pyrexia and systemic smooth-surfaced papules were noted, accompanied by enlargement of the preauricular lymph nodes at a glance, thus rubella was suspected. 36 days after start of administration: During the visit to the outpatient neurology department, the patient did not complain of eruption. 43 days after start of administration: During the visit to the outpatient orthopedics department, the orthopedic surgeon found skin eruption and consulted a dermatologist, advising the patient to visit the dermatology department. When examined at the dermatology clinic, an adverse reaction associated with lamotrigine was suspected. However, since oral mucosal eruption was not found and laboratory test data were free of abnormalities, the patient would be followed-up with an anti-allergic drug and topical corticosteroid. The dermatologist instructed the patient to visit the clinic again. 46 days after start of administration: Discontinuation of lamotrigine was decided by discussion between the dermatologist and the attending physician. The patient was informed of the decision. 49 days after start of administration: During subsequent follow-up at the dermatology clinic, skin eruption tended to subside. 53 days after start of administration: Skin eruption disappeared. The outcome of the eruption was “improved.” 64 days after start of administration: At the time of visit to the attending physician, exacerbated skin eruption and pyrexia were noted. Interview of the patient revealed failure of the patient to comply with the instructions on discontinuation of lamotrigine. Administration of lamotrigine was discontinued and the patient was admitted to hospital. 3 days after discontinuation: At the dermatology department, immunoglobulin therapy (2 500 mg/day) and steroid mini-pulse therapy (prednisolone 500 mg/day) were administered for 3 days for drug-induced hypersensitivity syndrome (DIHS [TENS type]). 7 days after discontinuation: Sepsis occurred. Administration of meropenem (1.5 g/day) and thrombomodulin alfa (25 600 U/day) was started. Sputum culture showed gram-positive cocci (GPC) 4+ and blood culture showed GPC+. 10 days after discontinuation: The regimen was switched to prednisolone 100 mg/day. 12 days after discontinuation: The regimen was switched to cefazolin 6 g/day. Methicillin-sensitive *Staphylococcus aureus* bacteraemia triggered by skin eruption was definitely diagnosed. 13 days after discontinuation: Plasma exchange was performed (until 16 days after discontinuation of medication). 16 days after discontinuation: Skin eruption tended to improve. 21 days after discontinuation: Blood pressure decreased due to septic shock during cefazolin treatment. Vancomycin (1 g/day), meropenem (3 g/day), and thrombomodulin alfa (25 600 U/day) were administered. The patient was admitted to ICU. Poor response to calling and dark black skin occurred. 22 days after discontinuation Administration of intravenous injection of human antithrombin III was started (until 24 days after discontinuation of medication). 24 days after discontinuation *Pseudomonas aeruginosa* was detected from blood culture. 26 days after discontinuation The dose of prednisolone reduced to 80 mg/day. Skin eruption tended to improve, and the patient was transferred to an ordinary ward.

			33 days after discontinuation: The dose of prednisolone reduced to 70 mg/day. Circulation did not stabilize, and the general condition was aggravated. 35 days after discontinuation: Despite continued treatment, hepatic failure developed, leading to death.
Concomitant drugs (suspected drugs): minodronic acid hydrate, sodium valproate			

Laboratory Examination

Parameter	90 days before administration	Day 1 of administration	20 days after start of administration	64 days after start of administration	3 days after discontinuation	7 days after discontinuation	25 days after discontinuation	26 days after discontinuation	29 days after discontinuation	33 days after discontinuation
ALT (IU/L)	-	11	-	14	17	16	28	27	24	12
AST (IU/L)	-	36	-	52	29	38	71	63	57	51
T-Bil (mg/dL)	1.78	1.93	1.87	1.85	2.67	2.51	7.67	8.96	22.64	29.78
D-Bil (mg/dL)	-	-	-	-	-	-	-	5.46	18.82	24.48
Al-P (IU/L)	326	473	-	243	166	191	653	532	596	510
LDH (IU/L)	243	253	-	483	433	514	254	224	339	359
γ-GTP	16	26	-	27	24	36	-	-	58	43
WBC ($\times 10^3/\mu L$)	6.9	6.9	4.5	10.5	-	8.4	-	-	-	3.2
CRP (mg/dL)	-	0.20	0.59	2.9	-	14.18	-	-	-	8.85
PLT ($\times 10^4 \mu L$)	6.1	7.4	4.5	4.9	-	6.4	-	-	-	4.7
Cr (mg/dL)	0.66	0.82	0.83	0.67	-	0.69	-	-	-	2.71

Case 2 Drug-induced hypersensitivity syndrome

Patient		Daily dose/ Treatment duration	Adverse reactions
Gender/ Age	Primary disease (complication)		Clinical course and therapeutic measures
Female 60s	Bipolar disorder Depression Suicidal ideation Depressive symptom aggravated	50 mg/day for 25 days	61 days before administration: The patient was admitted to another hospital. Condition stabilized in response to treatment with fluvoxamine maleate 75 mg, flunitrazepam 2 mg, and levomepromazine maleate. 23 days before administration: The patient was discharged from the hospital. Day 1 of administration The patient had strong suicidal ideation. Administration of lamotrigine (50 mg/day) was started. Day 2 of administration: Olanzapine 5 mg was added. The dose of fluvoxamine maleate increased to 150 mg. Day 8 of administration: Clomipramine hydrochloride 75 mg was added. Day 19 of administration: The patient mentally stabilized. Date unknown: Suspected Stevens-Johnson syndrome and increased liver function test developed. Day 24 of administration: Pyrexia (40ºC) and systemic erythema occurred. Multiple organ failure (hepatic failure, renal failure) and DIHS developed. Day 25 of administration: Disturbed consciousness (JCS [Japan Coma Scale] II-30) was found and neuroleptic malignant syndrome was suspected, the patient was transported to this hospital. Hepatic failure, renal failure, sepsis, dysfunction thyroid, generalized erythema, and disturbed consciousness (AST, 20 323; ALT, 7 382; Cr, 3.22; BUN, 37.4; CK, 3 299) were noted and the patient urgently admitted to the hospital. Administration of lamotrigine was discontinued. 1 day after discontinuation: Steroid pulse therapy (continued until 3 days after discontinuation), continuous hemodiafiltration /hemodialysis were started. Plasma exchange (PE) for 8 sessions was performed (until 48 days after discontinuation). 4 days after discontinuation: The regimen was switched to water-soluble prednisolone 60 mg drip infusion, with dose level later reduced (continued until 48 days after discontinuation). 36 days after discontinuation β-D-glucan increased, and pyrexia (38ºC) and aggravation of disturbed consciousness were noted again. 42 days after discontinuation: Candida positive at the tip of the central vein catheter was found. General condition exacerbated due to sepsis. 48 days after discontinuation The patient died. Cause of death: Multiple organ failure, fulminant hepatic failure, drug-induced hypersensitivity syndrome, and renal failure Skin biopsy findings: Epidermal keratinocyte necrosis and lymphocyte infiltration into the epidermis seen (1 day after discontinuation). Post-mortem liver and kidney biopsy: Strong signs of drug-induced liver disorder
Concomitant drugs: clomipramine hydrochloride, fluvoxamine maleate, flunitrazepam, levomepromazine maleate, paroxetine hydrochloride hydrate, mirtazapine, alprazolam, zolpidem tartrate, duloxetine hydrochloride, olanzapine.			

Laboratory Examination

Parameter	59 days before administration	34 days before administration	Day 1 of administration	Day 23 of administration	Day of discontinuation	21 days after discontinuation
ALT (IU/L)	25	17	43	467	7382	56
AST (IU/L)	20	13	32	408	20323	61
T-Bil (mg/dL)	0.5	0.6	0.7	0.3	2.3	-
ALP	243	240	255	651	-	-
γ-GTP (IU/L)	15	15	15	120	-	-
LDH (IU/L)	147	139	154	501	18742	-
CK (IU/L)	-	-	-	-	3299	-
WBC (/μL)	5400	6000	3800	-	15120	15240

Case 3 Toxic epidermal necrolysis syndrome/Stevens-Johnson syndrome

Patient		Daily dose/ Treatment duration	Adverse reactions
Gender Age	Primary disease (complication)		Clinical course and therapeutic measures
Male 80s	Epilepsy Metastatic brain tumor Lung cancer Altered state of consciousness Atrial fibrillation Cerebral haemorrhage Hypertension Delirium Insomnia	25 mg/day for 9 days 50 mg/day for 22 days	Before administration: The patient was receiving treatment for lung cancer and metastatic brain tumor. Activities of daily living was almost possible without assistance. Day 1 of administration: The patient was taken to hospital by ambulance because of disturbed consciousness (JCS II-10) associated with seizure. Symptomatic epilepsy was diagnosed and the patient was admitted to the hospital. Administration of lamotrigine (25 mg/day) was started. MRI revealed a new metastatic brain tumor. Day 9 of administration: The dose of lamotrigine was changed to 50 mg/day. Date unknown: Oedema developed after gamma-knife treatment for metastatic brain tumor. Corticosteroid treatment was started. Day 28 of administration: Skin eruption (on back) occurred. Day 29 of administration: Stomatitis occurred. Day 30 of administration: Erythema multiforme (trunk) and erosion (buttocks, scrotum, extremities, lips, and oral cavity) developed. Administration of prednisolone 10 mg was started. Topical application of ethyl aminobenzoate and betamethasone butyrate propionate was started. *Escherichia coli* was detected from blood culture. Sepsis occurred. Administration of lamotrigine was discontinued. 1 day after discontinuation: Erosion (trunk, forehead) developed. Stevens-Johnson syndrome and toxic epidermal necrolysis syndrome was diagnosed. The dose of prednisolone increased to 15 mg. Administration of gentamicin sulfate and ceftriaxone sodium injection was started for treatment of sepsis. 6 days after discontinuation: Skin exfoliation (systemic) developed. 7 days after discontinuation: Despite high-dose gamma-globulin therapy and steroid pulse therapy (3 days), his condition failed to improve. 11 days after discontinuation: Pyrexia relapsed and enterococci were detected from blood culture. Sepsis was treated simultaneously. 19 days after discontinuation: The patient died. Cause of death: End stage cancer, rash, toxic epidermal necrolysis, skin eruption, erythema multiforme, skin erosion, scrotum erosion, stomatitis, lip erosion, mouth ulcer, skin exfoliation, and Stevens-Johnson syndrome
Concomitant drugs: clemastine fumarate, nitrazepam, lansoprazole, risperidone			

Laboratory Examination

Parameter	Day 1 of administration	14 days after administration	29 days after administration	1 day after discontinuation	4 days after discontinuation	5 days after discontinuation	6 days after discontinuation	11 days after discontinuation	12 days after discontinuation
ALT (IU/L)	39	26	26	40	92	-	76	52	-
AST (IU/L)	29	24	26	35	63	-	64	53	-
LDH (IU/L)	271	278	279	263	416	-	299	335	-
γ-GTP (IU/L)	-	19	-	24	-	-	67	62	-
CPK (IU/L)	207	239	-	142	-	-	125	52	-
Cr (mg/dL)	0.93	1.07	1.20	0.85	0.82	-	0.84	0.70	-
BUN (mg/dL)	14.9	21.9	29.0	18.1	17.6	-	24.6	35.4	-
WBC (/μL)	5500	6900	13400	2200	1900	1900	2400	2400	2300
CRP (mg/dL)	-	2.32	5.29	-	17.43	-	19.40	28.35	-