Standardizing Assessment of Adverse Effects in Rheumatology Clinical Trials. Status of OMERACT Toxicity Working Group March 2000: Towards a Common Understanding of Comparative Toxicity/Safety Profiles for Antirheumatic Therapies

THASIA G. WOODWORTH, DANIEL E. FURST, VIBEKE STRAND, JOACHIM KEMPENI, HELMUT FENNER, CHAK SING LAU, FREDERICK MILLER, RICK DAY, JOHN LIPANI, and PETER BROOKS

ABSTRACT. This paper describes the background and current status of an OMERACT facilitated effort to improve the consistency of adverse event reporting in rheumatology clinical trials. The overall goal is the development of an adverse event assessment tool that would provide a basis for use of common terminology and improve the consistency of reporting severity of side effects within rheumatology clinical trials and during postmarketing surveillance. The resulting Rheumatology Common Toxicity Criteria Index encompassed the following organ systems: allergic/immunologic, cardiac, ENT, gastrointestinal, musculoskeletal, neuropsychiatric, ophthalmologic, pulmonary and skin/integument. Before this tool is widely accepted, its validity, consistency, and feasibility need to be assessed in clinical trials. (J Rheumatol 2001;28:1163–9)

Key Indexing Terms:
ADVERSE EFFECTS
CLINICAL TRIALS
RHEUMATIC DISEASES
ANTIRHEUMATIC THERAPIES

This paper describes the background and current status of an OMERACT facilitated effort to improve the consistency of adverse event reporting in rheumatology clinical trials. It was the experience of the individuals involved that the assessment of treatment associated adverse events in clinical trials is highly variable, resulting in challenges to assessment of risk/benefit during the regulatory review process, and lack of clarity in product labeling for communication to practitioners of comparative risks of various rheumatologic therapies. We ascribed this variability to differences in investigator experience and training, as well as to differences in sensitivity to the impact of various side effects on patient well being. In international clinical trials variability also likely occurs related to language and cultural differences. We also recognized that in many cases, baseline patient status due to the severity of disease likely influences assessment of severity of side effects. We hypothesized that the development of a standardized, face and content valid assessment tool with ease of use would facilitate improvements in consistency of reporting. Such a tool should provide uniform definitions of different types of toxicity, and also a basis for describing degrees of severity for observed adverse events, by also recognizing the influence of disease status on severity.

The overall goal for this project has been the development, for rheumatology clinical trials, of an adverse event assessment tool that would provide a basis for use of common terminology and improve the consistency of reporting severity of side effects within clinical trials and during postmarketing surveillance. The objectives are (1) to improve the consistency of assessment and reporting of toxicity in clinical trials; (2) to improve the ability of investigators, regulators, and practitioners to differentiate safety profiles of individual and combination therapies for rheumatic diseases; and (3) to facilitate data management of toxicity data.

In April 1996 a group of individuals interested in addressing the challenges of adverse event reporting in rheumatology clinical trials met at OMERACT 3, and the Toxicity Working Group was formed. We believed that this effort would be especially important in light of the numbers of new therapies, some with potentially narrow therapeutic indices, being developed for serious rheumatologic diseases, most with associated significant baseline signs, symptoms,

T.G. Woodworth, MD, Pfizer Groton R & D, Groton, CT, USA; D.E. Furst, MD, Virginia Mason Medical Center, Seattle, WA, USA; V. Strand, MD, Biopharmaceutical Consultant, Portola Valley, CA, USA; J. Kempeni, MD, Fujisawa Pharmaceuticals, Neustadt, Germany; H. Fenner, MD, Pharmaceutical Consultant, Basel, Switzerland; C.S. Lau, MD, Hong Kong, China; F. Miller, MD, Center for Biologics Evaluation and Review, FDA, Bethesda, MD, USA; R. Day, MD, University of New South Wales, Australia; J. Lipani, MD, Pharmaceutical Consultant, Scottsdale, Arizona; P. Brooks, MD, University of Queensland, Brisbane, Australia.

Address reprint requests to Dr. T.G. Woodworth, Clinical Sciences Department, Building 260, Pfizer Groton, Eastern Point Road, Groton, CT 06340, USA. E-mail: thasia_g_woodworth@groton.pfizer.com

and laboratory abnormalities. Current members include individuals from academia, industry, and regulatory agencies with substantial and diverse clinical trials experience.

Subsequently, meetings have been held at OMERACT 4, and at various other international meetings such as ILAR, EULAR, and the American College of Rheumatology (ACR), as well as by teleconference. Initially, the group conducted a review of available tools used in clinical trials by other subspecialties, such as oncology and infectious disease (AIDS clinical trials in the USA). Written materials for review were circulated to members prior to meetings, with the overall purpose of meetings being to gain input and consensus regarding the tools being proposed. These materials included the WHO Common Toxicity Criteria (CTC), the Common Toxicity Criteria of the US National Cancer Institute, and European Organization for Randomized Trials in Oncology, the Division of AIDS Tables for Grading Severity of Adverse Experiences, and various Modified CTC Tables developed by pharmaceutical companies and researchers involved in rheumatology clinical trials. We also tried to integrate our efforts with other groups engaged in revision of CTC, using Medical Dictionary for Drug Regulatory Affair (MEDDRA) terms.

At the November 1998 ACR meeting, a "working version" of the Rheumatology CTC was presented to the groups, and approved for posting on the ILAR website, to facilitate acquisition and use by clinical trial groups. A plan was established to pilot these CTC on a voluntary basis in clinical trials that were being conducted by groups interested in and willing to provide feedback to the Toxicity Working Group. We hoped that this approach would then allow review of experience with the application of these CTC at OMERACT 5. Our intent is to then revise the CTC as necessary, and establish a forward plan that will facilitate application of this assessment tool in a range of rheumatology indications (not only rheumatoid arthritis, but also systemic lupus erythematosus, scleroderma, and other serious, disabling indications to be studied).

In our view, key criteria for application of these guidelines include recognition that the CTC is a guideline, not a "laundry list"; many of the agents being studied are also being evaluated for treatment of transplantation and cancer; and there is a need for guidelines for stopping rules/thresholds for treatment discontinuation. Also to be considered are the technical requirements for Registration of Pharmaceuticals for Human Use, assuring compatibility with the International Committee on Harmonization Consensus Definitions:

Adverse drug reaction: Noxious/unintended response to a therapeutic agent at doses normally used for prophylaxis, diagnosis, or therapy of disease.

Adverse event: Any untoward medical occurrence that may be present during treatment with a therapeutic agent and that does not necessarily have a causal relationship with this treatment.

Side effect: Any unintended effect of a therapeutic agent at doses normally used, related to its pharmacological properties.

To develop acceptable terminology, we selected from the MEDDRA terms:

- intended for use in pharmaceutical development, especially postmarketing;
- based on UK Medicines Control Agency medical terminology (ADROIT);
- incorporating WHO-ART, HARTS, COSTART, and International Classification of Diseases ICD-9.

RESULTS

In the preparation of draft Rheumatology CTC, we attempted to recognize the following components for assessment of toxicity: frequency and duration of event, and severity of event, including importance to the patient with regard to impact on activities of daily living and instrumental and discretionary activities. In addition, we tried to accommodate the importance to the clinician, attempting to integrate the trade-offs of the occurrence of an adverse event with the benefit of the intervention.

The resulting Rheumatology CTC Index encompassed the following organ systems: allergic/immunologic, cardiac, ENT, gastrointestinal, musculoskeletal, neuropsychiatric, ophthalmologic, pulmonary, and skin/integument. Within

Table 1. Severity of symptoms as described in the Rheumatology Common Toxicity Criteria (RCTC).

Mild	Moderate	Severe	Life-Threatening
Asymptomatic	Symptomatic	Prolonged symptoms, reversible	At risk of death
Short duration (< 1 wk)	Duration (1–2 wks)	Major functional impairment	Substantial disability, especially if permanent
No change in lifestyle	Alters lifestyle occasionally	Prescription medication/partial relief	May be hospitalized
No medication or OTC	Prescription medications with relief	May require study drug discontinuation May be hospitalized	

OTC: Over-the-counter.

each system, a number of specific symptoms or signs are described, which specify/define the severity described as severity, as shown in Table 1.

Appendix 1 provides the Rheumatology CTC as it has been developed in its entirety. Those terms not found in the Index can be found in MEDDRA.

DISCUSSION

While the Rheumatology CTC (RCTC) has been developed iteratively, and clearly has face validity, due to its similarity to the widely used (for oncology clinical trials) Oncology Common Toxicity Criteria, there are a number of questions that need to be addressed before being widely accepted.

When considering the validity of this Index, one has to consider its face validity, content validity, consistency, and ability to differentiate the safety/toxicity profiles of various therapies, and the ease with which it can be used.

While face validity was established by the process by which the Rheumatology CTC were developed, the other aspects of validation still need to be examined.

We propose that a simple method for evaluating the use of these CTC should be developed, to assure that their use meets the objectives initially envisioned.

IMPLEMENTATION ISSUES

Implementation issues include the following considerations:

- Assure methods for feedback and revision.
- How to collect, collate, and assess input data on use of Rheumatology CTC?
- Updates to incorporate any progress by National Cancer Institute/US Food and Drug Administration (Harmonize with MEDDRA versions).
- Create feedback tool on ILAR website (ILAR.org)

VALIDITY QUESTIONS

Questions specific to validity of the Rheumatology CTC that remain include:

- How can we determine the content validity of the Rheumatology Common Toxicity Criteria?
- How can consistency of toxicity assessment be determined?
- Can RCTC be used to compare toxicities across trials?
- How can this index be used to improve adverse event reporting?
- How can this index be used to quantify and compare reported adverse events?

APPENDIX 1

A draft version of the Rheumatology Common Toxicity Criteria Index.

Appendix 1. Proposed Rheumatology Common Toxicity Criteria (10/1998), Version 1.0 [from Common Toxicity Criteria (CTC) MEDDRA Version 1.5], signs and symptoms.

	1 - Mild Asymptomatic, or transient Short duration (< 1 week) No change in lifestyle No meds/occasional OTC	**2 - Moderate** Symptomatic Duration (1–2 weeks) Alter lifestyle occasionally Meds (may be prescription) relieve	**3 - Severe** Prolonged symptoms, reversible Major functional impairment Prescription meds/partial relief May require study drug discontinuation	**4 - Includes Life Threatening** At risk of death Substantial disability, especially if permanent May be hospitalized
Allergic/immunologic				
Allergic reaction/hypersensitivity (including drug fever)	Transient rash; drug fever < 38° C, 100.4° F; transient, asymptomatic bronchospasm	Generalized urticaria responsive to meds; or drug fever > 38° C (100.4° F), or reversible bronchospasm	Symptomatic bronchospasm, requiring parenteral meds; symptomatic urticaria persisting with meds, allergy related edema/angioedema	Anaphylaxis, laryngeal/ pharyngeal edema
Autoimmune reaction	Serologic or other evidence of autoimmune reaction but patient asymptomatic; all organ function normal, and no treatment is required (e.g., vitiligo)	Evidence of autoimmune reaction involving a non-essential organ or functions, requiring treatment other than immunosuppressive drugs (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or other toxicity requiring short term immunosuppressive treatment (e.g., transient colitis or anemia)	Causes major organ dysfunction, or progressive, not reversible, or requires long-term administration of high dose immunosuppressive therapy
Rhinitis (includes sneezing, nasal stuffiness, post-nasal discharge)	Transient, nonprescription meds relieve	Prescription med required, slow response	Corticosteroids or other med with only partial relief	—
Serum sickness	Transient, nonprescription meds relieve	Symptomatic, slow response to meds	Prolonged; symptoms only partially relieved by meds; corticosteroids required	Major organ dysfunction; or requires longterm, high-dose immunosuppressive therapy
Vasculitis	Localized, not requiring treatment; or rapid response	Symptomatic, slow response to meds	Generalized, parenteral corticosteroids required, or hospitalization	Prolonged hospitalization, ischemic changes, amputation
Voice changes (includes hoarseness, loss of voice laryngitis)	Intermittent hoarseness	Persistent hoarseness, able to vocalize	Whispered speech, not able to vocalize	—

General				
Fatigue/malaise	Increase over baseline; most usual daily functions maintained	Interferes with daily function	Interferes with basic ADL	Unable to care for self, bed or wheelchair bound > 50% of day
Fever (pyrexia) (note: fever due to drug allergy should be coded as allergy)	Transient, few symptoms; 37.7–38.5˚C (100.0 to 101.5 F)	Symptomatic, recurrent, 38.6 to 39.9˚C (101.6 to 103.9 F); relieved by meds	≥ 40˚C (≥ 104 F); prolonged, persistent symptoms; partial response to meds	Debilitating, hospitalization; no relief with meds
Headache	Transient or intermittent, no meds or relieved with OTC	Persistent, recurring, non-narcotic analgesics relieve	Prolonged, with limited response to narcotic meds	Intractable, debilitating, requires parenteral meds
Rigors, chills	Asymptomatic, transient, no meds, or non-narcotic meds relieve	Symptomatic, narcotic meds relieve	Prolonged symptoms, with limited response to narcotic meds	Debilitating, hospitalization; no relief with meds
Sweating (diaphoresis)	Episodic, transient	Frequent	Frequent, drenching	—
Weight gain	5–9.9%	10–19.9%	20–30%	
Weight loss	5–9.9%	10–19.9%	20–30%	
Skin/integument				
Alopecia	Subjective, transient	Objective, reversible	Patchy, wig used, reversible	Complete or irreversible
Bullous eruption	Localized, asymptomatic	Localized, symptomatic, requiring treatment	Generalized, responsive to treatment; reversible	Generalized, or requiring hospitalization for treatment
Dry skin	Asymptomatic, controlled with emollients	Symptoms only partially controlled with emollients	Generalized, moist desquamation, partially responsive to treatment	—
Injection site reaction	Local erythema	Erythema, pain, edema, includes superficial phlebitis	Induration > 10 mm, ulceration; includes thrombosis	Major necrosis requiring surgery
Petechiae	Few, transient, asymptomatic	Dependent areas, persistent	Generalized, responsive to treatment; reversible	—
Photosensitivity	Transient erythema	Painful erythema & edema requiring topical treatment	Blistering or desquamation, requires systemic corticosteroids	Generalized exfoliation, or hospitalization
Pruritis	Localized, asymptomatic, transient, local treatment	Intense, or generalized, relieved by systemic medication	Intense or generalized; poorly controlled despite treatment	—
Rash (not bullous)	Erythema, scattered macular/papular eruption; pruritus transient, OTC or no meds	Diffuse macular/papular eruption or erythema with pruritus; dry desquamation; treatment required	Generalized, moist desquamation, requires systemic corticosteroids; responsive to treatment; reversible	Exfoliative or ulcerating; or requires hospitalization; or parenteral corticosteroids
Ophthalmologic				
Cataract	Asymptomatic, no change in vision, nonprogressive	Symptomatic, partial visual loss, progressive	Symptoms impairing function, vision loss requiring treatment, including surgery	—
Conjunctivitis	Asymptomatic, transient, rapid response to treatment	Symptomatic, responds to treatment, changes not interfering with function	Symptoms prolonged, partial response to treatment, interferes with function	—
Lacrimation increased (tearing, watery eyes)	Symptoms not requiring treatment, transient	Symptomatic, treatment required, reversible	Unresponsive to treatment with major effect on function	—
Retinopathy	Asymptomatic, nonprogressive, no treatment	Reversible change in vision; readily responsive to treatment	Symptoms with ophthalmological findings that are reversible, but symptoms that improve	Loss of sight
Vision changes (e.g., blurred, photophobia, night blindness, vitreous floaters)	Asymptomatic, transient, no treatment required	Symptomatic, vision changes not interfering with function, reversible	Symptomatic, vision changes interfering with function	—
Xerophthalmia (dry eyes)	Mild scratchiness	Symptomatic without interfering with function, requires artificial tears	Interferes with vision/function, corneal ulceration	Loss of sight
ENT				
Hearing loss	Transient, intermittent, no interference with function	Symptomatic, treatment required, reversible	Interferes with function; incomplete response to treatment	Irreversible deafness
Sense of smell (parosmia)	Slightly altered	Markedly altered	—	—
Stomatitis	Asymptomatic	Painful, multiple, can eat	Interferes with nutrition, not reversible	Requires enteral support
Taste disturbance (dysgeusia)	Transiently altered; metallic	Persistently altered; limited effect on eating	Disabling, effect on nutrition	—
Tinnitus	Intermittent, transient, no interference with function	Requires treatment, reversible	Disabling, or associated with hearing loss	Irreversible deafness

Xerostomia (dry mouth)	Transient dryness, readily by moisturizers	Relief with meds	Interferes with nutrition, not reversible	—
Gastrointestinal				
Anorexia	Adequate food intake, minimal weight loss	Symptoms requiring oral nutritional supplementation	Prolonged, requiring iv nutritional support	Requires hospitalization for nutritional support
Constipation	Asymptomatic, transient, responds to stool softener, OTC laxatives	Symptomatic, requiring prescription laxatives, reversible	Obstipation, requiring medical intervention	Bowel obstruction, surgery required
Diarrhea	Transient, increase of 2–3 stools/day over pretreatment (no blood or mucus), OTC agents relieve	Symptomatic, increase 4–6 stools/day, nocturnal stools, cramping, requires treatment with prescription meds	Increase > 6 stools/day, associated with disabling symptoms, e.g., incontinence, severe cramping, partial response to treatment	Prolonged, dehydration, unresponsive to treatment, requires hospitalization
Dyspepsia (heartburn)	Transient, intermittent, responds to OTC antacids, H-2 blockers	Prolonged, recurrent, requires prescription meds, relieved by meds	Persistent despite treatment, interferes with function, hospitalization, associated with GI bleeding, ulcer	—
GI bleed (gastritis, gastric or duodenal ulcer diagnosed — define etiology)	Asymptomatic, endoscopic finding, hemoccult + stools, no transfusion, responds rapidly to treatment	Symptomatic, transfusion ≤ 2 units needed; responds to treatment	Hematemesis, transfusion ≥ 2–4 units, prolonged interference with function	Recurrent, transfusion > 4 units, perforation, requiring surgery, hospitalization
Hematochezia (rectal bleeding)	Hemorrhoidal, asymptomatic, no transfusion	Symptomatic, transfusion ≤ 2 units, reversible	Recurrent, transfusion > 2–3 units	> 4 units, hypotension, requiring hospitalization
Hepatitis	Laboratory abnormalities, asymptomatic, reversible	Symptomatic laboratory abnormalities, not interfering with function, slowly reversible	Laboratory abnormalities persist, symptoms interfere with function	Progressive, hepato-renal, anasarca, or pre-coma or coma
Nausea, or nausea/vomiting (use diagnostic term)	Transient, intermittent, minimal interference with intake, rapid response to meds	Persistent, recurrent, requires prescription meds, intake maintained	Prolonged, interferes with daily function and nutritional intake, periodic iv fluids	Hypotensive shock, hospitalization for symptoms, signs unresponsive to outpatient management
Pancreatitis	Amylase elevation, intermittent nausea/vomiting, transient, responds rapidly to treatment	Amylase elevation with abdominal pain, nausea, occasional vomiting, responsive to treatment	Severe, persistent abdominal pain with pancreatic enzyme elevation, incomplete or slow response to treatment	Complicated by shock, hemorrhage (acute circulatory failure)
Proctitis	Perianal pruritus, hemorrhoids (new onset), transient, intermittent, relieved by OTC meds	Tenesmus or ulcerations, anal fissure, responsive to treatment, minimal interference with function	Unresponsive to treatment, marked interference with function	Mucosal necrosis with hemorrhage, infection, surgery required
Cardiac				
Arrhythmia	—	Transient, responds to meds	Recurrent/persistent; maintenance prescription meds	Unstable, hospitalization required; parenteral meds
Cardiac function decreased	Asymptomatic decline in resting ejection fraction by > 10%, but < 20% of baseline value	Asymptomatic decline of resting ejection fraction ≥ 20% of baseline value	CHF responsive to treatment	Severe or refractory CHF
Edema	Asymptomatic (e.g., 1+ feet/calves), self-limited, no therapy required	Symptomatic (e.g., 2+ feet/calves), requires therapy	Symptoms limiting function (e.g., 3+ feet/calves, 2+ thighs), partial relief with treatment; prolonged	Anasarca; no response to treatment
Hypertension (new onset or worsening)	Asymptomatic, transient, increase by > 20 mm Hg (diastolic),or to > 150/100 if previously normal, no therapy required	Recurrent or persistent increase > 150/100, or by > 20 mm Hg (diastolic), responds readily to treatment	Symptomatic increase, persistent, requiring therapy	Hypertensive crisis
Hypotension (without underlying diagnosis)	Transient, intermittent, asymptomatic orthostatic decrease in blood pressure > 20 mm Hg	Symptomatic, without interference with function, recurrent or persistent > 20 mm Hg decrease, responds to treatment	Syncope, or symptomatic, interferes with function, requiring therapy and sustained medical attention, dose adjustment or discontinuance of drug	Shock
Myocardial ischemia	Transient chest pain/ECG changes; rapid relief with nitro	Recurring chest pain, transient ECG ST-T changes; treatment relieves	Angina without infarction, no or minimal functional compromise, reduce dose or discontinue study drug	Acute myocardial infarction, arrthymia or/and CHF

Pericarditis/pericardial effusion	Rub heard, asymptomatic	Detectable effusion by echocard, symptomatic, NSAID required	Detectable on chest x-ray, dyspnea; or pericardiocentesis; requires corticosteroids	Pulsus alternans with low cardiac output; requires surgery
Phlebitis/thrombosis/ embolism (excludes injection site reaction)	Asymptomatic, superficial, transient, local, or no treatment required	Symptomatic, recurrent, deep vein thrombosis, no anticoagulant therapy required	Deep vein thrombosis requiring anticoagulant therapy	Pulmonary embolism
Pulmonary				
Asthma	Occasional wheeze, no interference with activities	Wheezing, requires oral meds, occasional interference with function	Debilitating, requires nasal O_2	Requires ventilator assistance
Cough	Transient, intermittent, occasional OTC meds relieve	Persistent, requires narcotic or other prescription meds for relief	Recurrent, persistent coughing spasms without consistent relief by meds, interferes with function	Interferes with oxygenation; debilitating
Dyspnea	Subjective, transient, no interference with function	Symptomatic, intermittent or recurring, interferes with exertional activities	Symptomatic during daily routine activities, interferes with function, treatment with intermittent nasal O_2 relieves	Symptomatic at rest, debilitating, requires constant nasal O_2
Pleuritic pain (pleurisy)	Transient, intermittent symptoms, no treatment or OTC meds relieve	Persistent symptoms, requires prescription meds for relief	Prolonged symptoms, interferes with function, requires frequent narcotic pain relief	Debilitating, requiring hospitalization
Pneumonitis (pulmonary infiltrates)	Asymptomatic radiographic changes, transient, no treatment required	Symptomatic, persistent, requiring corticosteroids	Symptomatic, requiring treatment including O_2	Debilitating, not reversible; or requiring assisted ventilation
Pulmonary function decreased (FVC or carbon monoxide diffusion capacity — DLCO)	76–90% of pretreatment value	51–75% of pretreatment value	26–50% of pretreatment value	≤ 25% of pretreatment value
Musculoskeletal				
Avascular necrosis	Asymptomatic MRI changes, nonprogressive	MRI changes and symptoms responsive to rest and analgesia	MRI changes, symptoms requiring surgical intervention	Wheelchair bound; surgical repair not possible
Arthralgia	Intermittent transient symptoms, no meds, or relieved by OTC meds	Persistent or recurrent symptoms, resolve with meds, little effect on function	Severe symptoms despite meds impairs function	Debilitating, hospitalization required for treatment
Leg cramps	Transient, intermittent, does not interfere with function	Recurrent symptoms, minimally interferes with function or sleep, respond to meds	Persistent, prolonged interference with function or sleep, partial or no response to meds	—
Myalgia	Occasional; does not interfere with function	Frequent, requires meds (non-narcotic); minor effect on function	Major change in function/lifestyle, narcotic pain meds	Debilitating, profound weakness, requires wheelchair, unresponsive to meds
Neuropsychiatric				
Anxiety or Depression (mood alteration)	Symptomatic, does not interfere with function; no meds	Frequent symptoms, responds to meds; interferes with ADL at times	Persistent, prolonged symptoms; partial or no response to meds, limits daily function	Suicidal ideation, or danger to self
Cerebrovascular ischemia	—	Single transient ischemic event, responsive to treatment	Recurrent transient ischemic events	Cerebrovascular vascular accident with permanent disability
Cognitive disturbance	Subjective symptoms, transient, intermittent, not interfering with function	Objective symptoms, persisting, interferes with daily function occasionally	Persistent, or worsening objective symptoms; interferes with routine daily function	Debilitating/disabling and permanent; toxic psychosis
Depressed consciousness (somnolence)	Observed, transient, intermittent, not interfering with function	Somnolence or sedation, interfering with function	Persistent, progressive, obtundation, stupor	Coma
Inability to concentrate	Subjective symptoms, does not interfere with function	Objective findings, interferes with function	Persistent, prolonged objective findings; or organic cause	—
Insomnia (in absence of pain)	Occasional difficulty sleeping, transient, intermittent, not interfering with function	Recurrent difficulty sleeping; requires meds for relief; occasional interference with function	Persistent or worsening difficulty sleeping; severely interferes with routine daily function	—
Libido decreased	Decrease in interest	Loss of interest; influences relationship	Persistent, prolonged, interfering with relationship	—
Peripheral motor neuropathy	Subjective, or transient loss of deep tendon reflexes; function maintained	Objective weakness, persistent, no significant impairment of daily function	Objective weakness with substantial impairment of function	Paralysis

Peripheral sensory neuropathy (sensory disturbance)	Subjective symptoms without objective findings, transient, not interfering with function	Objective sensory loss, persistent, not interfering with function	Prolonged sensory loss or paresthesias interfering with function	—
Seizure	—	Recurrence of old seizures	Repetitive with partial response to medication	New seizure
Vertigo (dizziness)	Subjective symptoms, transient, intermittent, no treatment	Objective findings, recurrent, meds relieve, occasionally interfering with function	Persistent, prolonged, interfering with daily function; partial or no response to meds	—
Abnormal laboratory test results (with associated consequences)				
Hematology				
Hb (g/dl) decrease from pretreatment	1.0–1.4	1.5–2.0	2.1–2.9; or Hb < 8.0, > 7.0	≥ 3.0; or Hb < 7.0
Leukopenia (total WBC) × 1000	3.0–3.9	2.0–2.9	1.0–1.9	< 1.0
Neutropenia (× 1000)	1.5–1.9	1.0–1.4	0.5–0.9	< 0.5
Lymphopenia (× 1000)	1.5–1.9	1.0–1.4	0.5–0.9	< 0.5
Platelets (× 1000)	75–LLN	50–74.9	20–49.9; platelet transfusion required	< 20; recurrent platelet transfusions
Chemistry				
Hypercalcemia (mg/dl)	1.1 × ULN–11.5	11.6–12.5	12.6–13.5; or symptoms present	> 13.5; or associated coma
Hyperglycemia (mg/dl), fasting	140–160	161–250	251–500	>500, or associated with ketoacidosis
Hyperkalemia (mEq/l)	5.5–5.9	6.0–6.4	6.5–7.0 or any ECG change	> 7.0 or any arrhythmia
Hypocalcemia (mg/dl)	0.9 × LLN–7.8	7.7–7.0	6.9–6.5; or associated with symptoms	< 6.5, or occurrence of tetany
Hypoglycemia (mg/dl)	55–64 (no symptoms)	40–54 (or symptoms present)	30–39 (symptoms impair function)	< 30, or coma
Hyponatremia (mEq/l)	—	125–129	120–124	< 120
Hypokalemia (mEq/l)	—	3.0–3.4	2.5–2.9	< 2.5
CPK (also if polymyositis-like disease)	1.2–1.9 × ULN	2.0–4.0 × ULN	> 4.0 × ULN with weakness but without life-threatening signs or symptoms	> 4.0 × ULN with signs or symptoms of rhabdomyolysis or life-threatening
Serum uric acid	1.2–1.6 × ULN	1.7–2.9 × ULN	3.0–5.0 × ULN or gouty symptoms	—
Creatinine (mg/dl)	1.1–1.3 × ULN	1.3–1.8 × ULN	1.9–3.0 × ULN	> 3.0 × ULN
SGOT (AST)	1.2–1.5 × ULN	1.6–3.0 × ULN	3.1–8.0 × ULN	> 8.0 × ULN
SGPT (ALT)	1.2–1.5 × ULN	1.6–3.0 × ULN	3.0–8.0 × ULN	> 8.0 × ULN
Alkaline phosphatase	1.1–2.0 × ULN	1.6–3.0 × ULN	3.0–5.0 × ULN	> 5.0 × ULN
T. bilirubin	1.1–1.4 × ULN	1.5–1.9 × ULN	2.0–3.0 × ULN	> 3.0 × ULN
LDH	1.3–2.4 × ULN	2.5–5.0 × ULN	5.1–10 × ULN	> 10 × ULN
Urinalysis				
Hematuria	Micro only	Gross, no clots	Clots, transfusion < 2 units	Transfusions required
Proteinuria (per 24 h)	300–500 g (tr/1+)	501–1999 g (2+)	2–5.0 g (3+) nephrotic syndrome	> 5.0 g (4+) anasarca
WBC in urine	—	—	Indicating acute interstitial nephritis	Associated with acute renal failure
Uric acid crystals	Present without symptoms	—	With stones or symptoms of stones (e.g., renal colic)	Causing renal outflow obstruction and hospitalization
Autoimmune syndromes, if not part of basic disease				
ANA (see also SLE-like disease)	Appearance of positive ANA to 1:80 or equivalent	1:160–1:320 or equivalent	> 1:320 or equivalent	—
dsDNA (see also SLE-like disease)	Appearance of positive dsDNA to 2 × ULN	2–3.9 × ULN	4.0–8.0 × ULN	—
Anti-choline receptor AB (see weakness)	—	Appearance of antibodies	—	—

Meds: medication(s); OTC: over-the-counter medication; ADL: activities of daily living; iv: intravenous; ECG: electrocardiogram; CHF: congestive heart failure; MRI: magnetic resonance imaging; Hb: hemoglobin; LLN: lower limit of normal; ULN: upper limit of normal; WBC: white blood cells; SLE: systemic lupus erythematosus; ANA: antinuclear antibodies. H-2 blockers: histamine-2 blockers; FVC: forced vital capacity.