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Consensus statement on definitions of disease, end points, and therapeutic response for pemphigus

Dedee F. Murrell, MD, **Sarah Dick, MD**, **A.R. Ahmed, JD**, **Masayuki Amagia, MD**, **Maria A. Barnadas, MD**, **Luca Borradori, MD**, **Jean-Claude Bystryn, MD**, **Giuseppe Cianchini, MD**, **Luis Diaz, MD**, **David Fivenson, MD**, **Russell Hall, MD**, **Karen E. Harman, MD**, **Takashi Hashimoto, MD**, **Michael Hertl, MD**, **Nico Hunzelmann, MD**, **Pilar Iranzo, MD**, **Pascal Joly, MD**, **Marcel F. Jonkman, MD**, **Yasuo Kitajima, MD, PhD**, **Neil J. Korman, MD, PhD**, **Linda K. Martin, MD**, **Daniel Mimouni, MD**, **Animesh A. Sinha, MD, PhD**, **David Sirois, MD**, **Detlef Zillikens, MD**, and **Victoria P. Werth, MD**

Sydney, Australia; Philadelphia, Pennsylvania; Boston, Massachusetts; Tokyo, Kurume, Gifu, and Sapporo, Japan; Barcelona, Spain; Geneva, Switzerland; New York, New York; Rome, Italy; Chapel Hill and Durham, North Carolina; Ann Arbor and East Lansing, Michigan;‘ Leicester, United Kingdom; Standort Marburg, Koln, and Luebeck, Germany; Rouen, France; Groningen, the Netherlands; Cleveland, Ohio; Petah-Tikva, Israel; and Dallas, Texas

Abstract

Our scientific knowledge of pemphigus has dramatically progressed in recent years. However, despite the availability of various therapeutic options for the treatment of inflammatory diseases, only a few multicenter controlled trials have helped to define effective therapies in pemphigus. A major obstacle in comparing therapeutic outcomes between centers is the lack of generally accepted definitions and measurements for the clinical evaluation of pemphigus patients. Common terms and endpoints of pemphigus are needed so that experts in the field can accurately measure and assess disease extent, activity, severity, and therapeutic response, and thus facilitate and advance clinical trials This consensus statement from the International Pemphigus Committee represents two years of collaborative efforts to attain mutually acceptable common definitions for pemphigus. These should assist in development of consistent reporting of outcomes in future studies.

INTRODUCTION

Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are rare, chronic, potentially life-threatening, autoimmune vesiculobullous disorders. The incidence of disease is variable. Estimates range from 0.076 per 100,000 in Finland to 1.61 per 100,000 in Jerusalem; PF is less common than PV in most populations.

Although our scientific knowledge of PV and PF is quickly advancing and our armamentarium of therapies is rapidly growing, there is still a pronounced lack of well-designed studies and evidence-based practice guidelines. This dearth is not surprising given the rarity of the disease, as well as the absence of common terms, endpoints, and measurements to assess disease extent, activity, severity, and therapeutic response.

Reprint requests: Victoria P. Werth, Department of Dermatology, University of Pennsylvania, 2 Maloney Building, 36th and Spruce St., Philadelphia, PA 19104.

PURPOSE

The purpose of this consensus statement is to define common terms and endpoints of pemphigus so that experts in the field can eventually accurately measure and assess disease extent, activity, severity, and therapeutic response at agreed upon timepoints, and thus facilitate and advance clinical trials. This consensus statement reflects the collective opinion of experts in the field with extensive clinical experience diagnosing and managing pemphigus.

CONSENSUS METHODS

The need for common definitions and measurements for PV was addressed during a workshop organized by Drs. Lowell Goldsmith and Jean-Claude Bystryn at an International Pemphigus meeting organized by Drs. Bystryn, Luis Diaz, Sergei Grando, and John Stanley that was held at the National Institutes of Health (NIH) in June 2005. Subsequently, an international Pemphigus Definitions, Endpoints and Therapeutic Response Committee was organized. At the NIH, Dr. Victoria Werth was asked to chair the committee and Dr Dedee Murrell to assist. Dermatologists with expertise and special interests in pemphigus were contacted directly at the NIH meeting or by email and invited to participate (subsequently referred to as the International Pemphigus Committee). The committee first convened during the American Academy of Dermatology meeting in San Francisco, CA held in March 2006. Eleven dermatologists with expertise and special interests in pemphigus attended. During the meeting, there was (1) a systematic review of the terms and measurements used in the pemphigus literature and in ongoing PV studies (2) one round of review and revision of the proposed definitions of endpoints, complete and partial remission, relapse/flare, and failure, (3) a unanimous agreement regarding the definitions of endpoints, complete and partial remission, relapse/flare, and failure, and (4) an active discussion and proposals for common measurements of the extent of disease, disease activity, and the intensity of therapy. The pemphigus disease area index (PDAI) and the pemphigus severity score (PSS) were presented, reviewed and revised.

A second round of review of the definitions occurred at the Society of Investigative Dermatology meeting held in Philadelphia, PA May 2006. There were further discussions and proposals for common measurements of the extent of disease, disease activity, and the intensity of therapy. A focus group discussed the development of the pemphigus disease area index (PDAI) as well as the pemphigus severity score (PSS). Three pilot indices for the PDAI and a pilot PSS were presented and reviewed. There was unanimous agreement and no revisions were made.

A third round of review of the consensus statement definitions occurred at the European Society for Dermatologic Research Pemphigus Satellite Symposium in Paris, September 2006. Revisions of the definitions were made, including a consensus definition of disease control. Literature addressing outcome measures and currently used outcome measurement tools for PV were presented, and the PDAI and PSS were reviewed and revised. The autoimmune bullous skin disorder intensity score (ABSIS) was first presented to the International Pemphigus Committee at this meeting (1).

A fourth round of review of the European input to the Consensus definitions was made at the AAD 2007 annual meeting. In addition, data from the actual use of the PSS, PDAI and ABSIS in pemphigus patients was presented, with suggestions for modifying these being made by the group.

A last review of the definitions and suggestions for modification of the PSS, PDAI and ABSIS was made at the Society for Investigative Dermatology meeting in Los Angeles, CA in May 2007.

During each of the International Pemphigus Committee meetings, definitions and measurements were presented in written or diagrammed form, revisions were incorporated in written form at the time of the meeting, and a consensus was reached by the process of open discussion and reconciliation. This consensus reflects the fact that some countries utilize extended low doses of therapies after resolution of symptoms. In this consensus statement, we describe the agreed upon definitions for pemphigus.

THE CONSENSUS

Observation points

Early observation points of disease activity is the baseline. *Baseline* is defined as the day that therapy is started by a physician. Endpoints define control of disease activity, the end of the consolidation phase, and remission.

Early Endpoints—*Control of disease activity* (disease control) is defined as the time interval from baseline to the time at which new lesions cease to form and established lesions begin to heal. This is also considered the beginning of the consolidation phase. The expected interval of time to reach the control of disease activity is on the order of weeks, although it may be shorter.

The *end of the consolidation phase* is defined as the time at which no new lesions have developed for a minimum of 2 weeks and the majority (approximately 80%) of established lesions have healed. It is at this point that most clinicians begin to taper corticosteroid doses.

Late endpoints—Late endpoints of disease activity are identified as (1) complete remission off therapy and (2) complete remission on therapy, both of which only apply to patients who have had no new or established lesions for at least 2 months. A *complete remission off therapy* is defined as the absence of new and/or established lesions while the patient is off all systemic therapy for at least two months. A *complete remission on therapy* is defined as the absence of new or established lesions while the patient is receiving minimal therapy. *Minimal therapy* is defined as less than, or equal to, 10 mg/day of prednisone (or the equivalent) and/or minimal adjuvant therapy for at least two months. *Minimal adjuvant therapy* is defined as half of the dose required to be defined as treatment failure (see below). A *partial remission off therapy* is defined as the presence of transient new lesions that heal within one week without treatment and while the patient is off all systemic therapy for at least two months. A *partial remission on minimal therapy* is defined as the presence of transient new lesions that heal within one week while the patient is receiving minimal therapy, including topical steroids.

Relapse/Flare

A *relapse* of disease and a *flare* of disease are synonymous. They are defined by the appearance of 3 or more new lesions a month that do not heal spontaneously within 1 week, *or* by the extension of established lesions, in a patient who has achieved disease control.

Treatment Failure

Failure of therapy is defined as the failure to control disease activity (i.e., relapse/flare) with full therapeutic doses of systemic treatments. Treatment guidelines for pemphigus that are evidence-based have not been established by consensus and are not the purpose of this definitions paper. However, it is necessary to stipulate the therapeutic doses of such drugs needed for a minimum period of time for studies, in order that a treatment failure can be defined for clinical trials.

Hence, there is failure of therapy if there is continued development of new lesions, continued extension of old lesions, or failure of established lesions to begin to heal despite 3 weeks of therapy on 1.5 mg/kg/day prednisone equivalent with or without any of the following agents:

Cyclophosphamide 2 mg/kg/day for 12 weeks

Azathioprine 2.5 mg/kg/day for 12 weeks (if TPMT level is normal)

Methotrexate 20 mg/week for 12 weeks, or

Mycophenolate mofetil 3 gm/day for 12 weeks

The methotrexate and mycophenolate mofetil doses are based on an individual of 75kg. These doses reflect the fact that alternative therapies may be beneficial and a consideration for patients who are considered to be a failure of therapy.

CONCLUSION

Our scientific knowledge of pemphigus has dramatically progressed in recent years. However, despite the availability of various therapeutic options for the treatment of inflammatory diseases, only a few multicenter controlled trials have helped to define effective therapies in pemphigus. A major obstacle in comparing therapeutic outcomes between centers is the lack of generally accepted definitions and measurements for the clinical evaluation of pemphigus patients. The formation of the International Pemphigus Committee, this consensus statement with agreed upon common definitions, and the ongoing discussion and refinement of proposed common measurements for patients with pemphigus are the initial and necessary steps towards progress in the clinical evaluation and therapy of pemphigus. Further progress and advancement will require a continued unified effort.

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