Development of Criteria for Evaluating Clinical Response in Thyroid Eye Disease Using a Modified Delphi Technique

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Objective: To identify components of a provisional clinical response index for thyroid eye disease using a modified Delphi technique.

Methods: The International Thyroid Eye Disease Society conducted a structured, 3-round Delphi exercise establishing consensus for a core set of measures for clinical trials in thyroid eye disease. The steering committee discussed the results in a face-to-face meeting (nominal group technique) and evaluated each criterion with respect to its feasibility, reliability, redundancy, and validity. Redundant measures were consolidated or excluded.

Results: Criteria were parsed into 11 domains for the Delphi surveys. Eighty-four respondents participated in the Delphi 1 survey, providing 220 unique items. Ninety-two members (100% of the respondents from Delphi 1 plus 8 new participants) responded in Delphi 2 and rated the same 220 items. Sixty-four members (76% of participants) rated 153 criteria in Delphi 3 (67 criteria were excluded because of redundancy). Criteria with a mean greater than 6 (1 = least appropriate to 9 = most appropriate) were further evaluated by the nominal group technique and provisional core measures were chosen.

Conclusions: Using a Delphi exercise, we developed provisional core measures for assessing disease activity and severity in clinical trials of therapies for thyroid eye disease. These measures will be iteratively refined for use in multicenter clinical trials.

Arch Ophthalmol. 2009;127(9):1155-1160

Graves disease is a multisystem autoimmune disorder targeting the thyroid, orbit, and skin. The orbital disease runs a biphasic course. The initial active phase can be dominated by inflammation of orbital soft tissues and expansion of fat accompanied or followed by progressive fibrosis and its attendant abnormalities of eye motility. Thyroid eye disease (TED), also referred to as thyroid-associated ophthalmopathy and Graves orbitopathy, encompasses the orbital and periorbital manifestations of Graves disease and causes substantial morbidity and reduced quality of life.[1-4]

The initial manifestations of TED can precede, coincide with, or follow the onset of thyroid dysfunction. Moreover, the severity and duration of TED are unpredictable. The characteristic clinical course in which the disease often waxes and wanes challenges attempts to develop adequate outcome measures required for randomized therapeutic trials.[5] Typically, the active inflammatory disease transitions to a chronic stable phase within 1 to 5 years of onset.[6,7] Treatment options for active TED have been limited by the absence of an evidence-based clinical response index (CRI).

Several immunomodulatory agents have been introduced over the past decade that target key putative components of autoimmune inflammation.[8,9] These have found increasing utility in the therapy of diseases associated with tissue remodeling that at least superficially resemble TED. They include antibody-based agents that either abrogate cytokine function or deplete specific subsets of lymphocytes.[10-15] A CRI-TED would aid in defining clinical disease states, including remission and progression. Similar hurdles were overcome in allied diseases, including rheumatoid arthritis and scleroderma, following development of a CRI using the Delphi and nominal group methods.[16-18] These tools have allowed precise definition of disease activity, severity, remission, and response to treatment. By iteratively evaluating the feasibility, validity, and sensitivity of each criterion composing the CRI, progressively more sensitive evaluation and discrimination of therapeutic effects have become possible. Well-validated, widely accepted combined-response indexes

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Group Information: The International Thyroid Eye Disease Society members who participated in this study are listed on page 1158.

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should prove more sensitive than individual measures. This flexibility should facilitate drug development and improve assessment of therapeutic agents. Scleroderma and TED present with similarly complex and heterogeneous clinical manifestations deriving from the inflammatory and fibrotic nature they share. While still in a developmental stage, a scleroderma-specific CRI has already culminated in therapeutic trials.[19]

Development of a CRI-TED reflecting practice patterns would complement and extend important earlier work, such as that conducted by the European Group on Graves' Orbitopathy.[20-24] In addition, several disease activity score systems have been developed over the years, including NOSPECS, CAS, and VISA.[25-28] Many individual parameters included in these scales have been validated and they can now be included as essential elements in a CRI-TED. In particular, the CAS system has been validated in patients receiving anti-inflammatory therapy. However, "activity scores" are confusing and a single version may be difficult to implement. In general, they are limited in scope, are not widely used, and have not benefited from iterative refinement. They have failed to predict therapeutic efficacy. Regardless of the relative merits of each system, without universal implementation, no system for patient evaluation can be optimally developed and refined. Our ultimate goal was to overcome these limitations by developing a CRI-TED that reflects with great fidelity the qualitative and quantitative features of TED pathophysiology. Since the assessment parameters destined to be included were identified during a process where participating clinicians were solicited, broad acceptance became more likely. Ideally, CRIs achieve the necessary sensitivity for grading disease without becoming cumbersome. Refinement and validation of the CRI-TED resulted from an iterative and data-driven process where parameters that were redundant or offered no incremental value were removed. As additional therapies targeting inflammation and fibrosis become available, an adequately validated and inclusive CRI-TED will become indispensable in their evaluation. Herein, we report the first steps in developing a CRI-TED using a modified Delphi technique. This technique allowed proposal and assessment of criteria relevant in TED. It included subjective features (symptoms), objective measures (divided anatomically into skin, conjunctiva, cornea, and orbit), functional measures (vision and motility), imaging measures, quality of life, global health, biomarkers, previous grading scales, genetics, and other items not further specified.

METHODS

A provisional set of criteria was developed using both Delphi and nominal group techniques. The Delphi technique systematically solicits and collates judgment on a particular topic through an algorithm consisting of sequential questionnaires temporally interspersed so as to allow summarization of feedback and modification based on written responses obtained from individuals rather than assembled groups of participants. This technique facilitates consensus building among experts on topics where exact definitions may be unavailable.[29,30] The essential elements include (1) anonymous response from participating individuals, (2) interaction between participants following each round of input from questionnaire responses and controlled feedback to participants, and (3) statistical group response. In contrast, the nominal group technique is a structured face-to-face meeting that is led by a facilitator. After discussion, a voting process determines the fate of the proposed items by grading their value. Our application of these techniques to the development of the CRI-TED follows success in instrument building for other autoimmune diseases, including adult and juvenile rheumatoid arthritis, gout, and scleroderma.[29-35]

INTERNATIONAL THYROID EYE DISEASE SOCIETY STEERING COMMITTEE MEMBERS' MEETING

The International Thyroid Eye Disease Society (ITEDS) steering committee consists of ophthalmologists with specialized expertise in TED. Prior to the Delphi exercise, this committee proposed "domains" relevant in TED that included subjective features (symptoms), objective measures (divided anatomically into skin, conjunctiva, cornea, and orbit), functional measures (vision and motility), imaging measures, quality of life, global health, biomarkers, previous grading scales, and genetics and others (items not further specified).

STRUCTURED DELPHI EXERCISE

Endocrinologists and ophthalmologists were invited to participate in the development of a CRI using e-mail questionnaires addressed to members of the Endocrine Society, American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS), European Society of Ophthalmic Plastic and Reconstructive Surgery, Orbital Society, North American Neuro-Ophthalmology Society, and European Group on Graves' Orbitopathy as obtained from published member lists. Respondents were invited to participate as a member of ITEDS, which is an independent, international, nonprofit organization dedicated to advancing clinical trial methods and developing treatments for TED (www.iteds.net). The organization has no financial conflicts of interest or affiliation with other organizations. However, unrestricted funding was provided by the ASOPRS Foundation and American Neuro-Ophthalmology Society.

ROUND 1 (DELPHI 1)

The Delphi exercise was initiated via e-mail in December 2006 by asking a cohort of clinicians who focus on TED to identify parameters that they believed could be used in development of a CRI-TED application to a 1-year multicenter clinical trial. This was followed up with 2 reminder e-mails, each at a frequency of 3 weeks.

ROUNDS 2 AND 3 (DELPHI 2 AND 3)

The 84 respondents to the first request were subsequently sent a second questionnaire (Delphi 2) and asked to rate the importance of each item for a "CRI-TED in a hypothetical 1-year, prospective, longitudinal clinical trial." Eight additional experts chose to participate at this stage, for a total of 92 investigators in Delphi 2. Each respondent rated the criteria on a scale of 1 (extremely inappropriate for a combined measure) to 9 (extremely appropriate for a combined measure). Each investigator was reminded twice by e-mail to complete the questionnaire. Descriptive statistics were calculated and a report containing the final questionnaire was sent to participants (Delphi 3). This report provided feedback to the respondents, remind-

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ing them of their previous ratings in Delphi 2 for each criterion compared with a group mean (standard deviation). The questionnaire requested that each participant again rate the criteria after they considered the mean group response. Each investigator was again reminded twice by e-mail to complete the questionnaire.

STATISTICAL ANALYSIS

Statistical analyses were conducted by calculating mode, mean, median, standard deviation, and 25th/75th percentile response values. The median of the sample constitutes the most "typical" value in the range of data, where no more than 50% of the data fall above or below. Following the RAND/University of California, Los Angeles, appropriateness method, median scores falling in the 1 to 3 range during Delphi 3 were excluded from further consideration. Those in the 4 to 6 range were considered potentially appropriate, and scores between 7 and 9 were included in the CRI-TED. Exceptions included median scores lower than 5 but with multimodal distribution, where a small group of respondents felt the criterion was of high importance. Additional determinations were undertaken by members of the steering committee, who attempted to err on the side of overinclusion. This practice pertained to criteria with low median, multimodal values and those that were viewed as surprising or inconsistent with the committee's collective expectations.

ITEDS STEERING COMMITTEE MEETING (NOMINAL GROUP TECHNIQUE)

The ITEDS steering committee members met in April 2008 to consider the feasibility, reliability, redundancy, validity, and sensitivity to change of each proposed parameter for use in a 1-year clinical trial. The committee focused on responses from Delphi 3 (153 items) with a median score of 6 or greater. After discussion, the committee voted on each. Consensus among 80% of those attending was required for acceptance.

RESULTS

Eighty-four respondents participated in Delphi 1 and collectively provided 220 unique parameters for 11 domains (available on request). Ninety-two participants (100% response rate) responded in Delphi 2 (including 8 additional clinicians), rating the 220 parameters on a scale from 1 (least appropriate) to 9 (most appropriate). The criteria were reviewed by the steering committee, which eliminated 67 redundant items. One hundred fifty-three criteria grouped in the 11 domains were selected for presentation in Delphi 3. Sixty-four investigators (76%) rated the 153 parameters included in Delphi 3. Criteria with a mean greater than 6 (136 items) were further evaluated by the steering committee for use in a 1-year multicenter trial (Delphi 3 parameters available on request).

The committee evaluated each proposed parameter. The final provisional core measures are shown in the **Table**. Those with high content validity, as provided in the Delphi exercise (ie, mean ≥6), but minimal evidence of validity in the literature were included in research criteria. Additional criteria, including a visual analog scale assessing disease severity and interval change from patients' and physicians' perspectives, were also included. These were considered important, both by the committee and the respondents of Delphi 3, although currently they are not data driven with respect to reliability and validity.

Table. Provisional Parameters for Development of a Clinical Response Index for Thyroid Eye Disease

Domain	Parameter	Median Score (n=92)[a]
Skin	Periorbital edema	8
	Periorbital redness	7
	Fluctuating periocular edema	7
	Diurnal variation of eyelid swelling	6
Conjunctiva and cornea	Focal injection over rectus muscles (increased size or number of vessels)	8
	Chemosis	8
	Corneal ulcer	7
	Corneal erosions	7
	Corneal staining	7
	Caruncular swelling	6
Eyelid and orbit	Proptosis	9
	Lagophthalmos	8
	Margin reflex distance 1	7
	Margin reflex distance 2	7
	Levator function	5
Vision	Pupillary defect	9
	Visual acuity	9
	Humphrey 24-2 field scotomas	8
	Periodic obscurations	7
	Decreased color on AAO	7
	Velocity of disease activity	7
Diplopia	Diplopia in primary gaze	9
	Diplopia in changing gaze position	8
	Rate of diplopia onset/progression	8
	Field of binocular single vision	7
	Orthoptic measurements	7
	Hess test	6
	Inability to control diplopia with prisms	6
	Abnormal patient head position	6
	Measurement of individual versions	6
Imaging measures	Apical crowding	8
	Muscle and fat volume or ratios	7
	STIR sequence MRI	7
	T2 appearance on MRI (assessment of muscles)	7
QOL, disability, function	SF-36 assessment	6
	QOL patient and physician assessment of severity and activity	8
Global health	Smoking history	8
	Endocrinologic assessment of systemic hyperthyroidism	8
Biomarkers	Thyroid-stimulating antibodies, TSH	8
Genetics	Family history of autoimmune disease	6

Abbreviations: MRI, magnetic resonance imaging; QOL, quality of life; SF-36, 36-Item Short Form Health Survey; STIR, short tau inversion recovery; TSH, thyrotropin.
[a] Score from 1 (least appropriate) to 9 (most appropriate).

COMMENT

The ability to evaluate therapeutic intervention in several autoimmune diseases has been enhanced by the development of CRIs using the Delphi technique. Thus, we

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International Thyroid Eye Disease Society

Members Who Completed Questionnaires

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have begun to develop a CRI-TED using this same strategy. For the first time, to our knowledge, the combined clinical judgment of a relatively large cohort of clinicians with expertise with TED was incorporated. This we believe has resulted in a set of core parameters that will allow meaningful assessment of therapeutic efficacy in TED. We have solicited and analyzed the judgment of interested clinicians. However, our results should be considered preliminary. They must now be validated in a 1-year observational trial to assess their feasibility, reliability, and validity. Unlike previous scales of TED activity, the CRI-TED will undergo iterative refinement. This instrument should allow meaningful assessment of potential therapies by facilitating the standardization, conduct, reporting, and interpretation of clinical trials.

Many criteria are considered "standard of care," including examination for inflammation, visual acuity, and thyrotropin levels. Others, such as the visual analog scale, have been used to assess disease activity and have been found feasible, reliable, valid, and respon-

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sive to change in recent multicenter clinical trials. Domains and parameters that lacked feasibility or could not be easily measured in a multicenter study were avoided. For instance, ultrasonographic assessment of extraocular muscles was avoided because wide interreader variability makes its standardization difficult.

Our primary goal was to develop an instrument that can be used in prospective, longitudinal, observational clinical trials. Based on the natural history of TED, a 1-year trial seems appropriate. At its conclusion, further assessment of the CRI-TED will be undertaken to assure that it reflects disease progression. A panel of experts should define domains demonstrating 30% or more improvement or worsening of TED. This process will involve a paper-based case study.

Our study has both strengths and limitations. First, we successfully conducted a Delphi exercise using the broad knowledge base of endocrinologists, ophthalmologists, and orbital surgeons. Each of the 3 exercises generated high response rates. The principal limitation was an initial reliance on processes associated with consensus building. However, iterative refinement of the CRI-TED parameters will be data driven. Acknowledging this limitation, the current study, for the first time to our knowledge, obtains combined clinical input from investigators on several continents. Development of core parameters provides the first step toward a robust and easily administered CRI-TED. The resulting instrument should greatly enhance our ability to conduct meaningful therapeutic trials.

Submitted for Publication: December 23, 2008; final revision received February 4, 2009; accepted February 10, 2009.
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Financial Disclosure: None reported.
Funding/Support: This study was supported in part by the American Society of Ophthalmic Plastic and Reconstructive Surgery; North American Neuro-Ophthalmology Society; National Institutes of Health grants EY008976, EY011708, DK063121, EY016339, and RR00425; an unrestricted grant from Research to Prevent Blindness; a Research to Prevent Blindness Career Development Award; and the Bell Charitable Foundation.

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Ophthalmological Numismatics

Russian-born Vladimir Petrovich Filatov (1875-1956) received his medical degree at the University of Moscow in 1897. He settled in Odessa in 1903 and in 1911 became professor of ophthalmology and the director of the Eye Clinic of Novorossiysk University (presently Odessa State Medical University). In 1936, he founded the Ukrainian Institute of Experimental Ophthalmology and was appointed its director. This institute is now known as The Filatov Institute for Eye Diseases and Tissue Therapy. Filatov was a gifted and courageous surgeon, perfecting the surgical techniques of keratoplasty, the tube flap method used in plastic surgery, and developing techniques for corneal grafts using cadaver eyes. He was also a pioneer in eyebanking corneal tissue.

While many ophthalmologists have been commemorated on medals, Filatov is the first to be honored for his contributions to ophthalmology on a commemorative coin, a circulating 2 gryvnias coin issued by the Ukraine in 2005. It is 30 mm in diameter and struck in copper-nickel by the National Bank of Ukraine. The obverse depicts Filatov's clothed facing bust on the right and to the left, in 7 parallel lines in Cyrillic: BO/LODI/MIR/FILA/TOV/1875/1956. The reverse depicts 3 concentric circles superimposed on which is a schematic eye; above in the curve of the second circle in Cyrillic: UKRAINE, above which is a coat of arms; in the left field in Cyrillic: 2/GRIVNI; in the right field within the eye upside down in Cyrillic: 2/GRIVNI; and below in the third circle: 2005.

Courtesy of: Jay M. Galst, MD, clinical associate professor, New York Medical College, and Yuriy A. Maryshev, MD, PhD, The Filatov Institute of Eye Diseases and Tissue Therapy.

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