Expert Agreement on EULAR/EUSTAR Recommendations for the Management of Systemic Sclerosis

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ABSTRACT. ***Objective.*** The European League Against Rheumatism/EULAR Scleroderma Trials and Research group (EULAR/EUSTAR) has published recommendations for the management of systemic sclerosis (SSc). Members of the Scleroderma Clinical Trials Consortium and the Canadian Scleroderma Research Group were surveyed regarding their level of agreement with the recommendations.

Methods. A survey containing the 14 EULAR/EUSTAR recommendations asked participants to indicate their level of agreement with each on a 10-point scale, from 0 (not at all) to 9 (completely agree). The survey was sent to 117 people, and 66 replies were received (56% response rate).

Results. Exceptions to generally high agreement included the use of iloprost and bosentan for digital vasculopathy, methotrexate for skin involvement, and bosentan and epoprostenol for pulmonary arterial hypertension (PAH; all < 69% agreement, defined as ≥ 7 rating). Vasculopathy and PAH treatment had differences in agreement between North America and Europe ($p < 0.006$). Respondents who were EULAR/EUSTAR recommendation authors shared a similar level of agreement compared to those who were not, except for the use of proton pump inhibitors for the prevention of SSc-related gastroesophageal reflux disease, esophageal ulcers, and strictures.

Conclusion. EULAR/EUSTAR recommendations were relatively well accepted among SSc experts. Overall reduced agreement may be due to the modest efficacy of some agents (such as methotrexate for the skin). Some regional disagreement is likely because of access differences. (J Rheumatol First Release April 1 2011; doi:10.3899/jrheum.101262)

Key Indexing Terms:
SCLERODERMA SYSTEMIC SCLEROSIS TREATMENT GUIDELINES SURVEY

Kowal-Bielecka, *et al* have compiled a list of 14 evidence-based recommendations from the European League Against Rheumatism (EULAR) and the Scleroderma Trials and Research group (EUSTAR) for the treatment of the various manifestations of systemic sclerosis (SSc)[1]. It is known that guidelines are often not followed in practice for reasons including lack of awareness, familiarity, or agreement[2]; however, little is known about the agreement regarding guidelines or recommendations by other experts in a therapeutic area. By surveying members of the Scleroderma Clinical Trials Consortium and the Canadian Scleroderma Research Group, we compiled data regarding agreement with the EULAR/EUSTAR recommendations for the treatment of SSc.

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K.M. Walker's work was made possible by the Canadian Scleroderma Research Group Summer Student Award.

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Accepted for publication February 3, 2011.

MATERIALS AND METHODS

A survey was generated using Survey Monkey, which included the 14 EULAR/EUSTAR recommendations. Participants were asked to indicate how little or strongly they agreed with each recommendation on a 10-point scale, from 0 (not at all) to 9 (completely agree). The survey was sent to 118 participants; 3 opportunities were given to reply, and there were 66 replies (56% response rate). After excluding respondents not currently practicing in North America or Europe, 59 participants remained.

Mean agreement ranged from 5.3 to 8.9 out of 9, with a range of 40.3% to 98.3% agreement with various guidelines (as measured by the percentage of responses of 7, 8, or 9 on the 10-point scale) when North American and European rheumatologists were grouped together. Mean agreement of North American rheumatologists ranged from 5.2 to 8.9, with a range of 41.4% to 100% agreement. Mean agreement of European rheumatologists ranged from 5.5 to 8.8, with a range of 38.9% to 100% agreement.

RESULTS

Many but not all recommendations had strong support (Table 1). Experts from North America and Europe differed in the strength of agreement with digital vasculopathy recommendations, but iloprost is not available in North America and bosentan is not approved for digital ulcer prevention in North America. Pulmonary arterial hypertension (PAH) agreement was also different. We also studied agreement among the respondents who were authors of the EULAR/EUSTAR recommendations compared to the

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Table 1. Agreement with the EULAR/EUSTAR recommendations. Data are mean agreement (SD, range) and percent in the top 3 ratings of the survey scale (7–9).

Recommendations	Combined North America and Europe, n = 59		North America, n = 41		Europe, n = 18		p
SSc-related digital vasculopathy (RP, digital ulcers)							
1. Dihydropyridine-type calcium antagonists, usually oral nifedipine, should be considered for first-line therapy for SSc-RP, and intravenous iloprost, or other available intravenous prostanoids, for severe RP.	7.3 (1.6, 3–9)	74.5	7.2 (1.6, 4–9)	77.6	7.5 (1.6, 3–9)	72.2	0.673
2. Intravenous prostanoids (in particular iloprost) should be considered in the treatment of active digital ulcers in patients with SSc.	6.7 (2.5, 0–9)	67.8	6.1 (2.7, 0–9)	58.6	7.8 (1.8, 2–9)	88.9	0.001*
3. Bosentan should be considered in diffuse SSc with multiple digital ulcers after failure of calcium antagonists and, usually, prostanoid therapy.	5.8 (2.5, 0–9)	47.5	5.6 (2.4, 0–9)	43.9	6.3 (2.6, 1–9)	55.6	0.523
SSc-PAH							
4. Bosentan should be strongly considered to treat SSc-PAH.	7.7 (1.8, 3–9)	76.3	7.7 (1.8, 3–9)	83.0	7.5 (1.9, 4–9)	61.1	0.547
5. Sitaxentan may also be considered to treat SSc-PAH.	7.7 (1.8, 0–9)	83.1	7.5 (1.9, 0–9)	85.4	7.9 (1.5, 5–9)	77.8	0.445
6. Sildenafil may be considered to treat SSc-PAH.	8.1 (1.5, 2–9)	89.8	8.1 (1.5, 2–9)	95.1	8.1 (1.5, 4–9)	89.0	0.696
7. Intravenous epoprostenol should be considered for the treatment of patients with severe SSc-PAH.	7.8 (2.0, 0–9)	83.1	8.5 (1, 5–9)	95.0	6.5 (2.7, 0–9)	55.5	0.006*
SSc-related skin involvement							
8. Methotrexate may be considered for treatment of skin manifestations of early diffuse SSc.	5.3 (2.8, 0–9)	40.3	5.2 (3, 0–9)	41.1	5.5 (2.6, 0–9)	38.9	0.962
SSc-ILD							
9. Cyclophosphamide should be considered for treatment of SSc-ILD.	7.7 (1.4, 1–9)	84.7	7.7 (1.5, 1–9)	87.6	7.7 (1.2, 6–9)	77.8	0.755
SSc-SRC							
10. ACE inhibitors should be used in the treatment of SRC.	8.9 (0.6, 5–9)	98.3	8.9 (0.3, 9)	100	8.8 (0.9, 5–9)	94.5	0.187
11. Patients on steroids should be carefully monitored for blood pressure and renal function.	8.6 (1.0, 4–9)	96.7	8.6 (1.1, 4–9)	95.2	8.6 (0.7, 7–9)	100	0.626
SSc-related gastrointestinal disease							
12. PPI should be used for the prevention of SSc-related gastroesophageal reflux, esophageal ulcers and strictures.**	8.3 (1.5, 2–9)	89.9	8.2 (1.7, 2–9)	87.9	8.5 (0.8, 6–9)	94.5	0.518
13. Prokinetic drugs should be used for the management of SSc-related symptomatic motility disturbances (dysphagia, GERD, early satiety, bloating, pseudo-obstruction, etc.).	7.1 (1.9, 0–9)	71.1	7.1 (1.9, 1–9)	70.8	7.1 (2.0, 0–9)	72.3	0.828
14. When malabsorption is caused by bacterial overgrowth, rotating antibiotics may be useful in SSc patients.	8.3 (1.1, 4–9)	93.3	8.4 (1.1, 4–9)	95.2	8.1 (1.1, 6–9)	88.9	0.585

* Mean North American rheumatologist agreement vs European rheumatologist agreement that was statistically different ($p < 0.05$). ** Recommendations that had significantly different agreement ($p < 0.05$) by respondents who were EULAR/EUSTAR recommendation authors vs respondents who were not EULAR/EUSTAR recommendation authors. EULAR: European League Against Rheumatism; EUSTAR: EULAR Scleroderma Trials and Research group; SSc: systemic sclerosis; RP: Raynaud's phenomenon; PAH: pulmonary arterial hypertension; ILD: interstitial lung disease; SRC: scleroderma renal crisis; ACE: angiotensin-converting enzyme; PPI: proton pump inhibitors; GERD: gastroesophageal reflux disease.

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respondents who were not authors and found that the recommendation authors had significantly higher agreement ($p = 0.006$) with the use of proton pump inhibitors for prevention of SSc-related gastroesophageal reflux, esophageal ulcers, and strictures.

DISCUSSION

Despite high agreement for many recommendations, it is not known whether rheumatologists actually follow these recommendations. We surveyed only SSc experts, all of whom were aware of the SSc treatment recommendations. However, awareness of these recommendations by practicing rheumatologists and their actual adherence has not been studied. Sources of variability and limitation leading to decreased adherence may include practice size and experience, individual patient characteristics, geographic location and drug availability, health insurance, and the lack of a clear algorithm for the treatment and management of SSc.

Agreement was lowest in areas with randomized controlled trials (methotrexate for skin involvement and bosentan in the prevention of digital ulcers), which may be due to the modest efficacy or in the latter case, lack of availability of the drug for this indication[3,4,5,6]. Further, the lack of agreement with the indicated uses of methotrexate and bosentan is independent of accessibility, as agreement was low for both North American and European rheumatologists (Table 1). As expected, access to treatment influenced agreement with recommendations regarding the use of iloprost. European rheumatologists favored the use of iloprost for active digital ulcers more than North American rheumatologists, while North American rheumatologists favored the use of epoprostenol more than their European counterparts, as indicated by a larger degree of agreement with its use in SSc-PAH (Table 1).

Lacking from these recommendations are guidelines for diagnostic and investigational procedures. Because of the low incidence and heterogeneity of SSc, such information would be extremely valuable.

There were 10 rheumatologists involved in the guidelines who also answered the survey, and if we remove them, the results do not change.

There are limitations of the recommendations in terms of the areas of SSc that are not addressed. For instance, there are no guidelines on treatment of pain, treatment of gastric antral vascular ectasia, maintenance therapy after interstitial lung disease is treated with cyclophosphamide, treatment of inflammatory arthritis, and therapy for erectile dysfunction; and nonpharmacologic treatment was not addressed.

The EULAR/EUSTAR recommendations for the treatment of SSc are relatively well accepted among the world's SSc experts. How strongly rheumatologists follow these recommendations requires further investigation. The agreement was for the most part similar among experts who did and did not write the recommendations. There were some differences in agreement between European and North American rheumatologists, mainly because of variability in access to drugs or indications of some medications.

APPENDIX

List of study collaborators: Scleroderma Clinical Trials Consortium: Firas Alkassab, Jerry A. Molitor, Lee S. Shapiro, Barri J. Fessler, Jan Tore Gran, Avram Goldberg, Thomas A. Medsger Jr, Gabriele Valentini, Tatiana S. Rodriguez-Reyna, M.E. Csuka, Leroy Griffing, Ariane Herrick, M. Kari Connolly, Alessandra Vacca, Gabriela Riemekasten, Fredrick M. Wigley, Dominque Farge, Sindhu R. Johnson, Marco Matucci-Cerinic, Laszlo Czirjak, Sergio Miguel Angel Toloza, Tafazzul H. Mahmud, Tracy M. Frech, Alexandre E. Voskuyl, Peter A. Merkel, Robyn Domsic, Paul Emery, Virginia Steen, Lidia Rudnicka, Christopher P. Denton, Philip J. Clements, Soumya Chatterjee, Bashar Kahaleh, Samina Hayat, Luc Mouthon, Robert Lafyatis, Edward V. Lally, Thomas Krieg, Lorinda Chung, Luis J. Catoggio, Maureen D. Mayes, Marina E. Anderson, Richard Silver, Susanna Proudman, James R. Seibold, Jean-Luc Senécal, Wendy Stevens, Eric Hachulla, Murat Inanc, Frank Wollheim, Oliver Distler, Tamiko R. Katsumoto, Vivien Hsu, David H. Collier, Daniel Furst, Kevin McKown, Dinesh Khanna, Suncica Volkov, and Alessandro Mathieu. Canadian Scleroderma Research Group: Murray Baron, Elzbieta A. Kaminska, Nader A. Khalidi, Marie Hudson, Janet Markland, Ariel Masetto, and Peter Docherty.

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