Utility of a Validated Disease-Specific Measure to Assess Symptomatology in Patients with Indolent Systemic Mastocytosis (ISM)

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Background

- Systemic mastocytosis (SM) is a rare condition characterized by accumulation of neoplastic mast cells of more than one organ driven by the KIT D816V mutation.
- SM manifests as indolent systemic mastocytosis (ISM), an indolent form of SM, and advanced SM (AdvSM).
- Non-advanced SM, including ISM and SM, comprise 80-90% of total cases.
- ISM is associated with long diagnostic delays, decreased quality of life, and causes debilitating and unpredictable symptoms for patients, including-life-threatening anaphylaxis.
- The ISM symptom assessment form (ISM-SAF) was developed to measure disease symptomatology.
- This research assesses and describes the development and validation of the ISM-SAF, a symptom assessment tool developed specifically for ISM patient populations and explores its potential utility.

Methods

- A targeted review of peer-reviewed literature between 2015 and 2021 was conducted to systematically assess and summarize the development and validation of the ISM-SAF and explore its potential utility (PICO).
- The primary objective was to identify and synthesize data from publications reporting patient-level results using the ISM-SAF.
- The search was primarily conducted in PubMed, and supplemented through Google Scholar and Clinicaltrials.gov.
- Search terms in PubMed included: “systemic mastocytosis,” “symptom assessment,” “patient reported outcomes,” and “quality of life.”
- A targeted Google Scholar search aimed to capture abstracts, posters, and conference proceedings that were not captured in PubMed.

RESULTS

ISM-SAF Literature Review Results

- One full-text article on the development of the ISM-SAF, three presentations/publications on the application and validation of the ISM-SAF, and one observational trial met the inclusion criteria (Table 1).
- The ISM-SAF was developed using best practices for PRO development, including clinician and patient input on symptoms, cognitive debriefing interviews with patients, and regulatory feedback.
- The ISM-SAF assesses 11 relevant symptoms: abdominal pain, nausea, diarrhea, sores, itching, flushing, bone pain, fatigue, dizziness, brain fog, and headache (Figure 1) and has been validated in multiple languages.
- In addition to a total symptom score (TSS), reflective of overall disease burden, the ISM-SAF tool allows for evaluation of GI and skin-specific SM domain scores.

ISM-SAF Utility Results

- The ISM-SAF has been used in multiple research settings – randomized controlled trials, prospective observational studies, and a cross-sectional patient survey.
- Psychometric analyses have demonstrated the reliability, validity, and responsiveness of the ISM-SAF (Tables 1 & 2, Figures 3 and 4), and confirmed it is a fit for purpose tool to assess symptom severity in SM patients (Table 2).
- Measure change (i.e., improvement, increased severity) over time in SM-specific symptoms, calculated as a TSS at a single point in time (Figure 3).
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- Correlation is expected due to different scoring systems for SF and ISM.
- Differences between patients with moderate-severe versus mild SM disease (e.g., moderate-severe SM patients have TSS ≥ 28).
- The ISM-SAF is being used in the ongoing HARBOR clinical trial to assess the effects of a new ISM treatment on SM symptoms.

TABLE 1. STUDY CHARACTERISTICS

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Sample Size</th>
<th>Methods</th>
<th>Study Population</th>
<th>Study Parameters</th>
<th>Data Collection</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized Controlled Trial</td>
<td>103</td>
<td>ISM-SAF</td>
<td>Indolent SM</td>
<td>TSS</td>
<td>Test-retest reliability, ICC</td>
<td>Significant differences in TSS scores between groups (P&lt;0.05)</td>
</tr>
</tbody>
</table>

TABLE 2. COMPARISON OF RELIABILITY, VALIDITY, AND SENSITIVITY RESULTS FROM PIONEER 1R AND PROSPECTIVE OBSERVATIONAL STUDY

<table>
<thead>
<tr>
<th>Study</th>
<th>PIONEER 1R</th>
<th>Prospective Observational Study</th>
<th>Mean Relative Scores on TSS</th>
<th>Not reported</th>
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<tbody>
<tr>
<td>TSS</td>
<td>30.2</td>
<td>36.3</td>
<td>0.8</td>
<td>0.7</td>
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<tr>
<td>SS</td>
<td>95.0</td>
<td>98.2</td>
<td>0.6</td>
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TABLE 3. RESULTS FROM TOUCHSTONE SM PATIENT SURVEY (MESA 2020)

<table>
<thead>
<tr>
<th>Method</th>
<th>Sample Size</th>
<th>Key Outcomes</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
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<tr>
<td>TSS</td>
<td>77</td>
<td>12.7±5.0</td>
<td>12.5±5.0</td>
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<tr>
<td>SF-12</td>
<td>60</td>
<td>12.7±5.0</td>
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Figure 1. Flow Diagram for Review of ISM-SAF

Conclusions

- The development and validation of the ISM-SAF as a ‘fit for purpose’ tool to assess disease-related symptom severity in ISM patients in both clinical trial and observational research settings has been documented by peer-reviewed publications.
- Use of a reliable and valid symptom assessment tool that evaluates concepts relevant and important to individuals with a condition is important for determining clinical benefit of the new ISM treatment.
- The findings from this review highlight the utility of the ISM-SAF as a valuable tool to assess symptom burden and change in ISM symptoms over time.

As part of the validation, TSS scores have been shown to correlate well with commonly used measures of health status, quality of life (i.e., SF-12, PGIS).

Research has shown that a 35% individual percentage decrease in TSS is clinically meaningful improvement in ISM symptoms in the individual patients.

The ISM-SAF may offer clinicians a valuable tool to assess symptom severity and potential treatment benefits in clinical practice.

Related Validity, Known Groups

- The ISM-SAF total and domain scores based on PGIS, MC, and SF-12 scores have been shown to correlate well with commonly used measures of health status, quality of life (i.e., SF-12, PGIS).
- The ISM-SAF has been validated in multiple languages.
- The ISM-SAF tool allows for evaluation of GI and skin-specific SM domain scores.

Figure 2. ISM-SAF Symptoms Assessed, Domains, and Scoring

Figure 3. Correlation Between TSS and SF-12 PCS Among Touchstone SM Patients

Figure 4. Correlation Between TSS and SF-12 PCS Among Touchstone SM Patients

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