IRA **E-BULLETTIN**

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OUTCOME ASSESSMENT IN MYOSITIS

Currently, clinical remission is a realistically achievable goal for most patients of inflammatory myositis, and it must be pursued aggressively to optimise outcomes and reduce mortality. To adequately assess response to therapy and track long-term outcomes, there is a need for validated outcome measures.

The primary assessment of myositis includes core set measures (CSM) of disease activity and disease damage and measures of patient-reported outcomes. In clinical practice, distinguishing clinical features due to disease activity from damage is an essential part in the assessment of IIM patients.

Disease activity is defined as “extent and severity of reversible manifestations due to muscular and extra-muscular disease”. Damage is defined as “persistent changes in anatomy, physiology, pathology or function resulting from prior active disease, complications of therapy, development of comorbid conditions. Disease activity is reversible with therapy, whereas damage is often irreversible and cumulative.

International collaborative groups comprising clinicians and researchers with a special interest in IIM, which include the International MyositisAssessment and Clinical Studies Group (IMACS) and the Paediatric Rheumatology International Trials Organisation (PRINTO), have developed standardized,well-validated outcome measures to assess disease activity in adult patients with dermatomyositis(DM) or polymyositis(PM) and in children with juvenile dermatomyositis(JDM).

Core Set Measures (CSMs) are the minimum set of measures that are required to comprehensively assess disease activity and that should be carried out and reported in all clinical studies and therapeutic trials. There are six validated CSMs as shown in the table below:

Table 1. Core set measures in disease activity assessment (IMACS & PRINTO)

Domain	Core set measures	Included in IMACS-JDM& Adult IIM	Included in PRINTO- JDM
Patient or parent global activity	Patient or parent global disease activity assessment by Likert or VAS	Yes	Yes

Domain	Core set measures	Included in IMACS-JDM& Adult IIM	Included in PRINTO- JDM
Muscle strength	MMT on a scale of 0-10 points or expanded scale 0-5 points to include proximal, distal and axial muscles. CMAS(Childhood Myositis Assessment Scale)	Yes No	Yes Yes (Preferred)
Physical function	Validated patient/parent questionnaire of ADL(HAQ or CHAQ) CMAS	Yes No	Yes Yes (Preferred)
Laboratory assessment	Elevated serum enzymes at least two of AST/ALT/CPK/LDH/ Aldolase	Yes	No
Global disease activity, including extramuscular disease activity	Myositis Disease Activity Assessment Tool (MDAAT) to assess extramuscular organs, including constitutional, cutaneous, skeletal, Gastrointestinal, pulmonary and cardiac activity. DAS	Yes No	Yes Yes (Preferred)
Physician global activity	Physician global disease activity assessment by Likert or VAS	Yes	Yes

Drawback: CSMs do not adequately assess specific aspects of disease like skin/lung involvement important in myositis spectrum phenotypes such as Antisynthetase syndrome/ MDA5 disease

Clinical measures to assess skin disease activity and damage for adult and juvenile patients with dermatomyositis and to assess pulmonary disease for patients with interstitial lung disease (ILD) have been developed and partially validated for adult and juvenile dermatomyositis and polymyositis.

IIM response criteria

Response criteria provide standardized measurements of changes in disease activity in response to a therapeutic intervention. The CSMs of disease activity are responsive to changes in disease activity, as demonstrated in several therapeutic trials in JDM and in adults with DM/PM. The initial partially validated response criteria that were established for JDM and adult DM/PM included the preliminary definitions of improvement(DOI), which required ≥20% improvement in a minimum of three of six CSMs of disease activity to establish that patients showed minimal clinically meaningful improvement. The minimal clinically meaningful change in each disease activity measure has also been established as ≥20% improvement for all IMACS or PRINTO CSMs, except for ≥30% improvement in muscle enzymes. ACR and EULAR have approved response criteria in 2016 for adult and juvenile myositis with collaborative initiative that involved **IMACS** and **PRINTO.**

Composite response criteria using weighted changes in the core set measures of disease activity were developed and validated for adult and juvenile myositis patients. These composite response criteria are based on weighted scores that are applied to absolute percentage improvement in the six CSMs. Total improvement score (TIS) (scale of 0–100) is intended to provide a quantitative assessment of degree of response for each patient which can be compared between treatment arms using the mean or median scores of all enrolled patients.

The TIS is the sum of the improvement in each of the six CSMs of disease activity, but the individual CSMs are weighted, such that CSMs that are considered more important contribute more to the final score. Response criteria have different thresholds in JDM /adult DM to reflect the difference in responses between adults and children(Table 2)

The relative importance of each measure in assessing changes in disease activity has been determined using conjoint analysis, which identified muscle strength as the most important measure, followed by physician global activity (PGA) and extramuscular activity for adult and juvenile patients with dermatomyositis and adult patients with polymyositis.

Table 2: Total improvement score grading response in JDM/Adult IIM

Total Improvement Score	Grading of Response
DM and PM improvement category thresholds with total improvement	Minimal ≥20.0
score	Moderate ≥40.0 Major ≥60.0
JDM improvement category thresholds with total improvement score	Minimal ≥30.0 Moderate ≥45.0 Major ≥70.0

Table 3: Comparison of preliminary DOI with new response criteria

Preliminary criteria of improvement	Response criteria
A. Relative percent change and dichotomous "improvement" or "no improvement"	A. Absolute percent change and a continuous improvement score
B. Lack of clinical trial validation	B. Differentially weight the core set measures (with muscle strength and physician global weighted more weighed)
C. Equal weight to all core set measures.	C. Thresholds of minimal, moderate, and major improvement have been defined
D. Minimal clinical improvement	D. greater sensitivity to change

Disease state criteria

Disease state criteria, including criteria for inactive disease and remission, are being used as secondary endpoints in clinical trials. PRINTO developed criteria for clinically inactive disease (a point in time with clinically and biologically quiescent disease, either on or off therapy)in JDM, which include three of the four CSMs returning to normal or near-normal values, including creatine kinase, CMAS, MMT and PGA.

Criteria for inactive disease are not yet available for adult patients with DM/PM or IBM.

Various definitions on disease state are described in JDM, requires data driven validation

Table 4: Disease state definitions in IIM (IMACS &PRINTO)

Remission	≥6-month continuous period with no evidence of disease activity while not receiving any IIM therapy
Clinical remission	≥6-month continuous period of clinically inactive disease (on or off therapy)
Complete clinical response	≥6-month continuous period with no evidence of disease activity while receiving IIM therapy JDM, DM, PM and IBM

Remission	**≥6-month continuous period with no evidence of disease activity while not receiving any IIM therapy**
Disease flare or worsening criteria	Worsening of PGA by ≥2 cm on a 10 cm VAS and worsening on MMT-8 by ≥20%; extramuscular organ disease activity worsening by ≥2 cm on a 10 cm VAS; or ≥30% worsening in any 3 of 6 IMACS CSMs
Disease flare	Worsening by ≥20% in any 2 of 6 CSMs, with no more than one of the remaining variables improving by >30% (excluding muscle strength)

Table 5: Disease Damage Measures

Domain	Core set measures	IMACS-JDM/ adult IIM	PRINTO-JDM
Physician global damage	Physician global disease activity assessment by Likert or VAS	Yes	Yes
Global damage tool	Myositis Damage Index	Yes	Yes
Physical function **Muscle strength** **Growth and development**	Validated patient or parent questionnaire of activities of daily living (HAQ or CHAQ) CMAS Height and weight, menses and Tanner puberty stage	Yes	Yes
Quality of life **Health-related quality of life**	SF-36 (adult) CHQ–PF50 Physical Summary Score	Yes Yes	No Yes

MRI of muscle and immunological biomarkers are promising approaches to discriminate between disease activity and damage and might provide much-needed objective outcome measures requiring further validation in IIM.

To Summarize

1.Core set measures by IMACS and PRINTO paved way using in assessment of disease activity in IIM

2.Response criteria using CSM as degree of improvement has limitations – Dichotomous variable with relative percent change,no clinical trial validation, equal weight to CSM

3.ACR EULAR newer response criteria is hybrid criteria-used as continuous outcome providing Total improvement score(TIS) and categorical outcome-grading responses into minimal/moderate/major ,Muscle strength and PGA given more weightage among CSM , greater sensitivity to change and can be used in JDM/adult IIM.

4. Limitations do exist for newer response criteria – validated based on limited data, threshold for a major response is preliminary, cannot be used to define disease flare/worsening of disease/relapse/remission, cannot be used in everyday clinical practice as gadgets required to calculate scores and developed only for major clinical phenotypes(DM/PM/JDM)

5.Specific outcome scores assessing skin involvement and ILD in IIM require more validation

6.Disease criteria defining clinical inactive disease, remission and flare are proposed with limited data in JDM ,but adult definitions require more data to validate definitions.

7.Disease damage definitions are proposed with less data validation.

8.Quality of life assessment measures - SF36 in adult IIM/CHQ PF 50 in JDM are proposed by IMACS and PRINTO , they are not disease specific.

9.Imaging and biomarkers to differentiate disease activity and damage are coming up in the field of IIM to be used in future as outcome measures.

Suggested further reading:

1. Rider LG, Aggarwal R, Machado PM, Hogrel JY, Reed AM, Christopher-Stine L, Ruperto N et al Update on outcome assessment in myositis,Nat Rev Rheumatol. 2018 May;14(5):303-318. doi: 10.1038/nrrheum.2018.33.

2. Miller, F. W. et al. Proposed preliminary core set measures for disease outcome assessment in adult and juvenile idiopathic inflammatory myopathies. Rheumatology 40, 1262–1273 (2001).

3. Rider, L. G. et al. 2016 American College of Rheumatology/European League Against Rheumatism criteria for minimal, moderate, and major clinical response in juvenile dermatomyositis: An International Myositis Assessment and Clinical Studies Group/Paediatric Rheumatology International Trials Organisation collaborative initiative. Ann. Rheum. Dis. 76, 782–791 (2017).

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