Physician's global assessment is often useful in SLE, but not always: the case of clinical remission

We read with interest the paper by Aranow *et al*¹ where physician's global assessment (PGA) displayed excellent inter-rater reliability, which could rely on the inclusion of highly selected lupus experts, as stated by the authors themselves. Indeed, in previous studies, PGA showed a high intra-rater and inter-rater variability,^{2,3} consistently with PGA being a subjective measure.

The high inter-rater reliability observed by the authors is surprising considering that the timeframe for assessing disease activity significantly varied among respondents: 36.7% scored PGA over the previous 7–10 days, 36.7% over the previous month, the remainder over shorter or longer periods of time. Additionally, in almost one-third of respondents, lupus damage was considered when scoring PGA.

Notably, the authors suggest that PGA should be scored after considering laboratory results, owing to a better correlation with systemic lupus erythematosus (SLE) disease activity index-2000 (SLEDAI-2K) of postlaboratory versus prelaboratory PGA.

The finding that laboratory results, including serology, influence PGA performance raises some considerations.

In Aranow's study, each serological abnormality was associated with a median delta PGA prelab versus postlab of ≥ 0.3 ,¹ that is, the threshold for a *clinically* meaningful change in PGA. As PGA is incorporated in composite outcome measures including SLE-responder index and BILAG-based Combined Lupus Assessment (BICLA), the numerically significant impact of serology might reduce response rate in clinical trials, overpowering any clinical improvement.

Finally, a relevant question deals with the inclusion of PGA in a definition of *clinical* remission, which is a state of clinical quiescence, irrespective of serology.^{4,5} How could PGA fit in this definition? In Aranow's study, abnormal serology alone determined a median PGA increase of 0.54 for low C4, 0.41 for elevated anti-dsDNA antibody levels, 0.41 for low C3.¹ The DORIS definition of clinical remission includes a cut-off of <0.5 for PGA; therefore, one can argue that, by affecting PGA, abnormal serology could prevent the achievement of *clinical* remission definition or could lead to a loss of *clinical* remission status.

We recently tested in a multicentre cohort of 646 patients with SLE, followed up for five consecutive years, the performance of the items included in DORIS definitions, that is, PGA <0.5 (scored prior to reviewing complement and anti-DNA antibody test), clinical (c)SLEDAI-2K=0 and prednisone ≤ 0.5 mg/day, alone or in combination, in defining remission and predicting damage.⁶ We found that adding PGA <0.5 to cSLEDAI-2K=0 did not increase the performance of cSLEDAI-2K against damage progression while resulting in loss of remission in a relevant proportion of patients.

More recently, in the same cohort, we found that PGA ≥ 0.5 despite cSLEDAI-2K=0, which was observed in 195 patients, was associated with (1) nonspecific patient-reported symptoms (157/195, 80.5%) and (2) objectifiable clinical manifestations not included in SLEDAI-2K or not reaching the threshold to be scored in SLEDAI-2K (38/195, 19.5%) (table 1).

As remission should identify patients with better outcome, we compared damage progression, measured by SLICC/ACR Damage Index, between patients in clinical remission according to cSLEDAI-2K=0 plus PGA <0.5 and those in conditions (1) or

Table 1 Symptoms and manifestations which led to PGA ≥ 0.5 * despite cSLEDAI-2K=0 in a multicentre cohort of 646 patients with lupus

Patients with PGA ≥ 0.5 and cSLEDAI-2K=0	195/646 (30.2%)
1. Patients with subjective findings without objectifiable clinical manifestations likely due to SLE (condition 1)	
Musculoskeletal domain	98
Arthromyalgias	95
Low back pain	10
Morning stiffness	8
Asthenia/fatigue	66
Paraesthesia	1
Finger stings	1
Shortness of breath	1
Nausea	1
Burning mouth syndrome	1
Ocular pain	1
Dermatitis/urticaria	1
Multiple symptoms (arthromyalgias, asthenia, anxiety, panic attack, hallucinations, demoralisation, sleepiness, confusion, headache, memory deficit, dizziness, insomnia, vision loss, low-grade fever, chronic cough, paraesthesia, finger stings, chronic pharyngodynia, fast heartbeat, chronic itch, influenza syndrome, hand/foot ulcers, constipation, vaginosis and/or effluvium capillorum)	25
2. Patients with objectifiable clinical manifestations likely due to SLE (condition 2)	
Haematological involvement (i.e., lymphopenia, haemolytic anaemia)†	10
Monoarthritis	10
Proteinuria‡	6
Recurrent infections leading to withdrawal/reduction of immunosuppressive therapy	6
Chilblain lupus erythematosus	2
Lower limbs sensory neuropathy	1
Lymphadenopathy	1
Hand pitting scars	1
Impaired diffusing capacity of the lung for carbon monoxide	1
Tachyarrhythmia	1
Venous thrombosis in secondary antiphospholipid syndrome	1
Hepatic-pancreatic enzyme increase	1
Depression	1

*PGA was scored prior to reviewing complement and anti-DNA antibody test.

†not included in SLEDAI-2K.

‡Proteinuria ≤ 0.5 gr/day.

cSLEDAI-2K, clinical SLE disease activity index-2000; PGA, physician's global assessment; SLE, systemic lupus erythematosus.

(2). No difference was observed in the proportion of patients accruing new damage during follow-up (cSLEDAI-2K=0 and PGA <0.5 : 33.3%, condition (1): 26.8%, condition (2): 36.8%, $p=0.256$), suggesting that the symptoms/manifestations captured by PGA but not scored by cSLEDAI-2K could not affect damage. Thus, the inclusion of PGA in a definition of remission prevents the achievement of this status in a relevant proportion of patients without identifying a subgroup with a better prognosis.

Altogether, our data and those by Aranow *et al* highlight that inclusion of PGA in a definition of *clinical* remission gives relevance to serology, patient-reported symptoms and clinical manifestations unable to impair disease outcome while overshadowing the benefits of achieving remission according to less subjective disease activity indices.

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