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Fracture risk tools performance and potential use in systemic lupus erythematosus

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ABSTRACT

Objective Skeletal fragility is a major comorbidity in systemic lupus erythematosus (SLE), yet the accuracy of fracture risk algorithms in this population remains uncertain. We compared the discriminative ability of Fracture Risk Assessment Tool (FRAX) and the Italian FRAX-derived tool (DeFRA) for fractures in SLE.

Methods This is a secondary analysis of the multicentre osteoporosis and FRagility fracture Among SLE patients (FRAIL - NCT05590390) cohort that included patients with SLE who underwent dual-energy X-ray absorptiometry with vertebral fracture assessment (VFA). Vertebral fractures were confirmed by radiography. For each patient, 10-year major osteoporotic fracture probability was calculated using FRAX and DeFRA. Discrimination was assessed with receiver operating characteristic curves and DeLong's test. Operational thresholds (FRAX ≥20%, DeFRA ≥20% and 15%) were evaluated for sensitivity, specificity, predictive values and number needed to scan (NNS=1/positive predictive value). Robustness of estimates was tested using 2000 bootstrap resamples with out-of-bag evaluation.

Results 106 patients with SLE were included in the study. Mean age was 53.6 years, 88.7% were female and 41.5% were on glucocorticoids. Morphometric vertebral fractures were identified in 23 patients (21.7%), including 15 previously unrecognised. For newly detected fractures, area under the curve (AUC) was higher for DeFRA (0.834, 95% CI 0.725 to 0.944) than FRAX (0.681, 95% CI 0.495 to 0.867; p=0.022). Similar results were observed when considering any vertebral fracture (AUC 0.902 vs 0.770; p=0.013). At operational thresholds, DeFRA ≥20% identified 9/15 new fractures (NNS=1.78) versus 7 with FRAX ≥20%, while lowering the cut-off to DeFRA ≥15% increased sensitivity (10/15 fractures, NNS=2.0) without loss of specificity. Bootstrap validation confirmed the robustness of rank ordering.

Conclusion In SLE, DeFRA outperforms FRAX in detecting vertebral fractures and offers a clinically efficient threshold for guiding targeted VFA, with potential implications for optimising imaging strategies and glucocorticoid management.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Fracture risk is often underestimated in SLE, and standard tools such as Fracture Risk Assessment Tool (FRAX) may not fully capture disease-specific factors, particularly glucocorticoid exposure and predominantly lumbar bone loss, leading to potential underdiagnosis of vertebral fractures.

WHAT THIS STUDY ADDS

⇒ In this multicentre cohort of patients with SLE, the Italian FRAX-derived tool (DeFRA) demonstrated significantly superior discriminatory ability compared with FRAX in detecting vertebral fractures, including those previously missed by imaging.

⇒ DeFRA thresholds, particularly the ≥15% threshold, showed a greater ability to identify patients with vertebral fractures while maintaining similar diagnostic efficiency; these results suggest the potential use of DeFRA to guide the decision to perform a vertebral fracture assessment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Using DeFRA to guide targeted imaging may improve the early recognition of skeletal frailty in SLE and support more informed glucocorticoid management. These findings encourage the integration of disease-specific risk assessment tools into routine SLE care and provide a framework for future validation of risk-based imaging strategies.

INTRODUCTION

Skeletal fragility is a major comorbidity in systemic lupus erythematosus (SLE).[1–3] Patients with SLE sustain fractures at a younger age and at higher rates than the general population,[4] due to the combined effects of chronic inflammation, systemic glucocorticoid (GC) exposure, vitamin D deficiency and SLE-related comorbidities.[5–9] Vertebral fractures, often asymptomatic, are of particular concern as they predict future fractures, disability and reduced quality of life.

Accurate fracture risk assessment is therefore critical in SLE. The Fracture Risk Assessment Tool (FRAX) is the most widely used algorithm to estimate 10-year probability of major osteoporotic fracture (MOF) based on clinical risk factors and femoral neck bone mineral density (BMD).[10] Although FRAX includes GC use and secondary osteoporosis, it does not account for GC dose or duration, and it only allows BMD input at a single skeletal site. As a result, FRAX may underestimate fracture risk in SLE.[11–13] In Italy, the FRAX-derived (DeFRA) algorithm was developed to refine risk prediction by allowing stratification of GC exposure by dose, by including BMD from multiple skeletal sites and by considering autoimmune diseases such as SLE among comorbidities.[14] Preliminary evidence suggests that DeFRA provides greater accuracy than FRAX in SLE, as shown in a recent monocentric study.[15] However, confirmatory studies in larger multicentre cohorts are lacking. In addition, the capacity of these algorithms to detect newly morphometric vertebral fractures, an outcome of clear clinical relevance, remains largely unexplored.

In this study, we conducted a secondary analysis of the multicentre osteoporosis and FRagility fracture Among SLE patients (FRAIL - NCT05590390) cohort[16] to compare FRAX and DeFRA in patients with SLE, with the dual aim of assessing their ability to discriminate unrecognised morphometric vertebral fractures and evaluating their performance at established clinical thresholds.

METHODS

Trial Design

This work represents a secondary analysis of the FRAIL cohort, a multicentre study involving five tertiary rheumatology centres in Northern Italy previously designed to evaluate the prevalence and determinants of vertebral fractures in clinically inactive patients with SLE.[16] Patients were recruited between December 2022 and January 2024. The original cohort included adult patients (≥18 years) with a confirmed diagnosis of SLE fulfilling the 2019 European Alliance of Associations for Rheumatology/American College of Rheumatology or Systemic Lupus International Collaborating Clinics 2012 criteria, and clinically inactive disease, defined as absence of new British Isles Lupus Assessment Group (BILAG) A/B scores in the previous 3 months. Exclusion criteria were those of the FRAIL study and included: metabolic bone disorders other than osteoporosis, malabsorption syndromes, uncontrolled endocrine disease, pregnancy or postpartum state, recent SLE flare and incomplete information on treatments. In the present analysis, we focused specifically on the comparative performance of FRAXs. For each patient, both FRAX and DeFRA estimates of MOF probability were calculated at baseline. Details of the original study design and procedures for data collection have been reported elsewhere.[16] All participants had provided informed consent, and the original ethical approval covered secondary analyses.

Measurement of BMD and assessment of vertebral fracture

At baseline, all patients underwent a clinical evaluation, and data were collected to compute fracture risk using both FRAX and DeFRA algorithms.

Information on prior vertebral fractures (either clinically diagnosed or radiographically documented) was retrieved from medical history. None of the patients had undergone dual-energy X-ray absorptiometry (DXA) in the last 5 years; baseline DXA (GE Lunar iDXA ME 212814) with vertebral fracture assessment (VFA) was performed as part of the study protocol. The presence of incident morphometric vertebral fractures was assessed on VFA images and subsequently confirmed by standard spine radiography.

Statistical analysis

Normality was evaluated graphically (Q-Q plots). Continuous variables were summarised as means±SD, and categorical variables as counts and percentages.

We evaluated the discriminative performance of DeFRA and FRAX with two receiver operating characteristic (ROC) analyses: (1) using morphometric vertebral fractures newly detected by baseline VFA and confirmed radiographically, (2) using any vertebral fracture (previously known plus newly identified) and (3) using any MOF, including both vertebral and non-vertebral sites, as the binary outcome. For each algorithm and outcome, we computed the area under the curve (AUC) with 95% CIs and compared AUCs on paired data with DeLong's test. We interpreted AUC values using conventional rule-of-thumb thresholds: 0.5 indicates no discrimination; 0.7–0.8 acceptable; 0.8–0.9 excellent; and >0.9 outstanding.[17]

To assess the clinical efficiency of risk algorithms, we evaluated the performance of DeFRA and FRAX at prespecified operational thresholds. Although our cohort had a relatively young mean age (53 years), we reasoned that in SLE, fracture risk is largely driven by disease-related and treatment-related factors (eg, GC exposure, inflammation, comorbidities), which may accelerate skeletal ageing and justify the application of thresholds typically used in older general populations.[3 18–20] For this reason, we adopted the same 20% 10-year MOF probability threshold for both tools in the primary analysis, allowing a direct comparison at equivalent nominal risk levels.[21–24] In addition, a sensitivity analysis was performed using the lower DeFRA ≥15% cut-off, in line with prior Italian experiences where lower values have been considered clinically meaningful when using DeFRA, reflecting its higher sensitivity and inclusion of disease-specific factors such as GC dose and comorbidities. For each cut-off, we calculated sensitivity, specificity, positive predictive values (PPV) and the number needed to scan (NNS=1/PPV), defined as the average number of VFA assessments required to detect one new morphometric vertebral

fracture. Reclassification between the two algorithms was explored with cross-tabulation and McNemar's test.

To provide more robust estimates of diagnostic performance, we used a bootstrap resampling procedure with 2000 replicates. For each replicate, patients were resampled with replacement and performance measures were recalculated in the out-of-bag (OOB) observations.[25–27] This approach allowed us to derive 95% CIs for PPV and the corresponding NNS at the predefined thresholds.

Missing values were very limited (<2%, see online supplemental materials). Imputation was performed using a random forest-based method implemented in Orange (V.3.37), following the approach described in Rotta *et al*.[16] Results were unchanged compared with complete-case analyses.

All analyses were conducted in R (V.4.4.3). Two-sided p values of 0.05 or less were considered statistically significant.

RESULTS

Population

We included 106 patients with SLE (94 women, 88.7%), with a mean age of 53.6±13.9 years and a mean disease duration of 17.4±12.5 years. The most frequently involved domain was articular (n=81, 76.4%), cutaneous (n=47, 44.3%), haematological (n=41, 39.4%) and renal (n=34, 32.1%).

Fractures were common: 15 patients (14.2%) reported prior vertebral fractures and 36 (34.0%) non-vertebral fractures, most frequently involving the wrist (n=8), ribs (n=6), femur (n=4), metatarsals (n=5), pelvis (n=2), elbow (n=2) and, less commonly, the knee, malleolus or tibia and humerus (n=1 each). At baseline VFA, 23 patients (21.7%) had morphometric vertebral fractures, including 15 (14.2%) cases that had not been previously recognised. Of these newly detected fractures, six occurred in patients who already had a known vertebral fracture. Overall, 49 patients (46.2%) had at least one fracture.

GC exposure was reported in 100 patients (94.3%), with 44 (41.5%) on ongoing treatment. Hydroxychloroquine use was highly prevalent (n=91, 85.8%). Antiresorptive therapy was prescribed in 34 patients (32.1%), including oral bisphosphonates (n=15, 14.2%), intravenous bisphosphonates (n=10, 9.4%), denosumab (n=6, 5.7%) and teriparatide (n=3, 2.8%). Vitamin D supplementation was reported in 92 patients (86.8%).

Full patient characteristics are presented in table 1, whereas osteoporosis risk factors are summarised in table 2.

Fracture risk estimation

The mean FRAX MOF probability was 10.6±9.6%, compared with 13.2±12.8% by DeFRA. When newly identified morphometric vertebral fractures were used as the outcome, DeFRA demonstrated superior discriminative ability compared with FRAX. The AUC was 0.834 (95% CI

Table 1 Demographic and clinical characteristics of the study population (n=106)

Demographics	
Caucasian, n (%)	94 (88.7)
Postmenopausal, n (%)	56 (52.8)
Age at menopause, years	48.5±4.3
Ever disease characteristics	
Disease duration, years	17.4±12.5
SLEDAI-2K	1.8±2.0
SDI score	1.0±1.4
Charlson Index	2.3±1.7
Arthritis, n (%)	81 (76.4)
Renal involvement, n (%)	34 (32.1)
Cutaneous involvement, n (%)	47 (44.3)
Fracture history and vertebral assessment	
Previous vertebral fractures, n (%)	15 (14.2)
Previous non-vertebral fractures, n (%)	36 (34.0)
Newly detected vertebral fractures, n (%)	15 (14.2)
DXA measures	
T-score lumbar spine	−0.85±1.39
T-score femoral neck	−1.08±1.11
T-score total hip	−0.79±1.10
Z-score lumbar spine	0.05±1.27
Z-score femoral neck	−0.39±0.82
Z-score total hip	−0.28±0.82
Bone turnover and vitamin D	
25OH-vitamin D (ng/mL)	33.9±11.7
CTX (ng/mL)	0.13±0.12
P1NP (ng/mL)	57.5±33.2
Glucocorticoid exposure	
Current GC therapy, n (%)	44 (41.5)
Cumulative GC dose, g (prednisone eq.)	13.6±16.3
Duration of GC therapy, months	115.9±128.2
Antiosteoporotic therapy	
Current antiosteoporotic therapy, n (%)	34 (32.1)
Oral bisphosphonates	15 (14.2)
i.v. bisphosphonates	10 (9.4)
Denosumab	6 (5.7)
Teriparatide	3 (2.8)
Vitamin D supplementation, n (%)	92 (86.8)
Calcium supplementation, n (%)	12 (11.4)

Values are expressed as mean±SD for continuous variables and n (%) for categorical variables.
CTX, C-terminal telopeptide of type I collagen; DXA, dual-energy X-ray absorptiometry; GC, glucocorticoid; i.v., intravenous; 25OH-vitamin D, 25-hydroxyvitamin D; P1NP, procollagen type I N-terminal propeptide; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

Table 2 Risk factors for osteoporosis in the study population (n=106)

Variable	Value
Age, years	53.6±13.9
Female sex, n (%)	94 (88.7)
Mean daily prednisone dose in users, mg/die	3.38±2.49
Current smoking, n (%)	14 (13.2)
Smoking, pack-years (mean)	21.7±10.7
Early menopause (<45 years), n (%)	6 (5.6)
Body mass index, kg/ m²	24.42±4.73
Personal history of fracture, n (%)	47 (44.3)
Family history of fracture, n (%)	12 (11.3)
Diabetes mellitus, n (%)	16 (15.1)

Values are expressed as mean±SD for continuous variables and n (%) for categorical variables.

0.725 to 0.944) for DeFRA versus 0.681 (95% CI 0.495 to 0.867) for FRAX; the absolute AUC difference was 0.153 (95% CI 0.021 to 0.284; DeLong p=0.022) consistent with a good discriminative performance of DeFRA and only modest discrimination for FRAX. ROC curves are shown in figure 1A.

When considering any vertebral fracture (including both previously known and newly detected cases), results were directionally consistent with the primary analysis, and the performance gap between the two algorithms further widened. DeFRA demonstrated excellent discrimination with an AUC of 0.902 (95% CI 0.829 to 0.974), compared with good discrimination for FRAX (AUC 0.770, 95% CI 0.636 to 0.903). The difference between tools was statistically significant (ΔAUC 0.132, 95% CI 0.027 to 0.236, DeLong Z=2.486, p=0.013) (figure 1B).

When considering any MOF, discrimination was comparable between tools: AUC 0.789 (95% CI 0.700 to 0.878) for DeFRA and 0.812 (95% CI 0.730 to 0.895) for FRAX. The paired DeLong test showed no significant difference (ΔAUC −0.023; 95% CI −0.091 to 0.045, Z = −0.67, p=0.503) (figure 1C).

Operational thresholds and Bootstrap validation

At matched thresholds (≥20% for both algorithms), DeFRA and FRAX classified most patients concordantly (McNemar p=0.22). DeFRA ≥20% identified 9 of 15 newly detected morphometric vertebral fractures (sensitivity 60%, specificity 92%, PPV 56%, NNS=1.78 (95% CI 1.25 to 3.35)), whereas FRAX ≥20% identified 7 of 15 fractures (sensitivity 47%, specificity 95%, PPV 58%, NNS=1.71 (95% CI 1.18 to 3.61)). Despite the slightly higher PPV of FRAX, DeFRA captured two additional true fractures that FRAX missed, resulting in a modest net improvement in classification (NRI=0.11).

In the sensitivity analysis using DeFRA ≥15% versus FRAX ≥20%, DeFRA identified 10 of 15 fractures (sensitivity 67%, specificity 89%, PPV 50%, NNS=2.0 (95% CI 1.37 to 3.68)). All patients above the FRAX cut-off were also above the DeFRA threshold, and three additional fractures were identified exclusively by DeFRA (McNemar p=0.013). Among the true positives at these operational cut-offs, ongoing GC therapy was present in 4/10 (40.0%) for DeFRA ≥15% and 4/7 (57.1%) for FRAX ≥20%.

Bootstrap resampling with 2000 OOB evaluations confirmed the robustness of these findings. For DeFRA ≥15%, the PPV was 0.50 (95% CI 0.17 to 0.83), corresponding to an NNS of 2.00 (95% CI 1.20 to 5.88). For DeFRA ≥20%, the PPV was 0.56 (95% CI 0.20 to 1.00) and NNS 1.78 (95% CI 1.0 to 5.0).

DISCUSSION

In this multicentre secondary analysis of the FRAIL cohort, we calculated both DeFRA and FRAX in a larger sample of patients with SLE, assessed their discriminative ability against newly identified morphometric vertebral fractures and against any MOF, and proposed an operational threshold for selecting patients eligible for VFA.

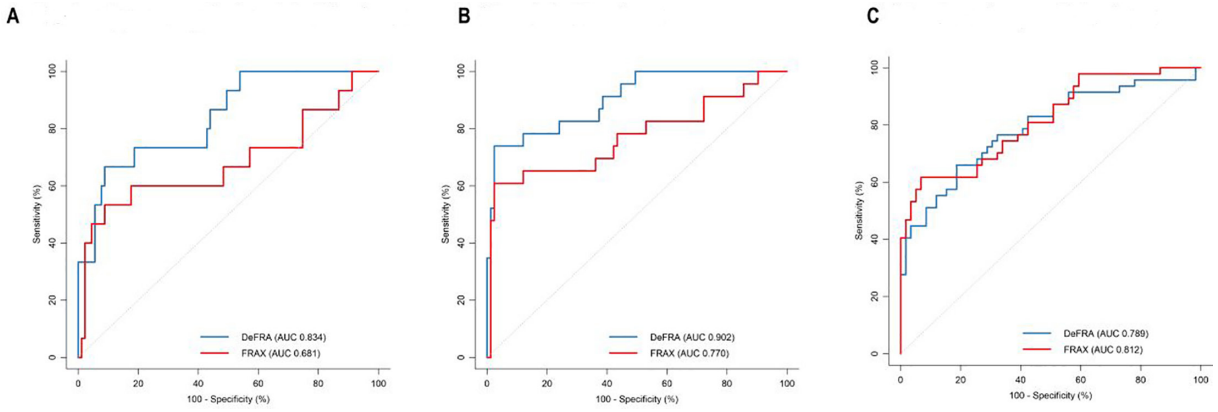

Figure 1 ROC curves comparing DeFRA and FRAX for fracture prediction. (A) Previously unrecognised vertebral fractures. (B) All vertebral fractures (previously known plus newly detected). (C) All MOF (including vertebral and non-vertebral sites). AUC, area under the curve; DeFRA, Italian FRAX-derived tool; FRAX, Fracture Risk Assessment Tool; MOF, major osteoporotic fracture; ROC, receiver operating characteristic.

This approach allowed us to quantify the clinical efficiency of such a strategy through the NNS.

Our results demonstrate that DeFRA performed better than FRAX in discriminating between patients with vertebral fractures from those without, while the two algorithms showed comparable performance when considering all MOF. This finding expands previous observations in smaller cohorts and is consistent with prior work by Ceccarelli and colleagues, who suggested that FRAX underestimates fracture risk in SLE compared with DeFRA.[15] There are plausible explanations for these results. It is well established that FRAX systematically underperforms in patients with SLE, as longitudinal studies have shown that it underestimates the 10-year risk of MOF in this population.[12 13 28] One key difference is the way GC exposure is modelled: FRAX treats it simply as present or absent, while DeFRA stratifies by dose, which is crucial in SLE given the central role of chronic steroid therapy in driving fracture risk.[29] A second difference concerns bone density input: FRAX is validated exclusively with femoral neck BMD, whereas DeFRA incorporates lumbar spine, femoral neck and total hip measurements. In patients with inflammatory diseases such as SLE, trabecular bone at the lumbar spine is particularly vulnerable to GC-induced loss, making its inclusion critical for accurate fracture risk estimation.[8 30–33] Finally, DeFRA includes SLE explicitly among causes of secondary osteoporosis and is calibrated on Italian epidemiology, which may improve accuracy in this clinical setting. When all MOFs were considered, DeFRA and FRAX showed similar performance. Although DeFRA accounts for disease-specific factors such as GC dose, inflammation and comorbidities, this advantage may have been offset by the predominance of non-vertebral fractures in our SLE cohort. These events are often multifactorial—related to disability, sarcopenia or falls—and therefore not fully captured by either model. Collectively, this likely explains why DeFRA achieved superior accuracy for vertebral fractures but showed comparable discrimination to FRAX when all MOF were analysed.

An additional novel finding is the proposal of a risk-based threshold to guide the diagnostic search for unrecognised vertebral fractures. Thresholds are routinely used in osteoporosis guidelines to determine therapeutic interventions, such as the fixed FRAX MOF ≥20% cut-off in the USA[34] or the age-dependent intervention thresholds adopted in the UK.[35] We show that a similar principle can be applied diagnostically, using a predefined cut-off to guide VFA. In our cohort, applying a risk-based approach with either algorithm improved the efficiency of identifying morphometric vertebral fractures (NNS=2). DeFRA, however, captured a higher number of true fractures at this same level of efficiency, supporting its potential value as a practical triage tool in SLE.

For context, based on the annual incidence of 3.5 vertebral fractures per 100 patient-years reported by Garcia-Carrasco *et al*, the predicted cumulative fracture risk would be approximately 7% at 2 years and 10% at 3 years, corresponding to an NNS of approximately 15 and 10, respectively.[36] compared with these estimates, a risk-based approach using DeFRA scores ≥15% would significantly improve the pretest efficiency of spinal imaging, allowing clinicians to prioritise patients most likely to have unrecognised vertebral fractures.

The threshold approach also has management implications. In our cohort, about 40% of patients identified by DeFRA at or above the cut-off were on chronic GC. Since GC remains one of the few modifiable risk factors in SLE, identifying patients at high risk of fragility fractures may support re-evaluation of long-term steroid use and facilitate therapeutic de-escalation, as also recommended by recent guidelines.[37] Importantly, our patients were all in clinical remission, suggesting that DeFRA-based stratification could provide a practical tool to encourage safe tapering strategies.

From an external validity perspective, our findings derive from a cohort recruited in tertiary rheumatology centres, composed of clinically inactive patients with SLE with regular follow-up and access to DXA/VFA. As noted in the primary FRAIL report, this setting represents a selected subgroup of the SLE population and may not reflect patients with active disease, community-based care or different ethnic and healthcare backgrounds. Therefore, caution is required when extrapolating these results beyond similar specialist settings.

The strengths of this work include its multicentre design, systematic identification of vertebral fractures by VFA with radiographic confirmation and the use of paired analyses to compare algorithms at predefined cut-offs, coupled with efficiency measures such as NNS. Limitations should also be acknowledged. Given the limited number of vertebral fractures, formal stratified analyses (eg, by GC exposure or prior fragility fractures) were not feasible and this should be considered when interpreting subgroup effects. The modest number of new morphometric fractures also reduces the precision of performance estimates; for this reason, CIs were reported to appropriately reflect this uncertainty. The cross-sectional design does not allow inference about prospective fracture risk, the sample size remains moderate and requires validation in larger external cohorts and generalisability is restricted to healthcare systems and populations where DeFRA is available and calibrated. Finally, as in the original FRAIL study, image readers were not formally blinded during VFA and radiograph evaluation; this inherent limitation also applies to the present secondary analysis and has been acknowledged accordingly.

In conclusion, in patients with SLE, DeFRA outperforms FRAX in discriminating vertebral fractures and shows promise as a practical tool for risk stratification. Rather than serving as a fixed decision threshold, higher DeFRA values (eg, ≥15%) may act as a clinical alert to prompt vertebral imaging and a review of modifiable factors such as GC therapy. Integrating DeFRA or FRAX into routine SLE management could therefore enhance the early recognition of skeletal fragility and optimise the

use of diagnostic and preventive resources. Prospective studies are warranted to confirm calibration, refine clinically meaningful cut-offs and determine the long-term impact of this risk-based approach on patient outcomes.

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Competing interests GA has received advisory board honouraria, consultancy fees and/or speaker fees from Theramex, UCB, Lilly, Galapagos, Fresenius Kabi, Amgen, BMS, Abiogen and Pfizer. DR declares speaker fees from Accord, GSK outside the submitted work. AF declares personal fees from Abiogen, Novartis and Neopharmed outside the submitted work. DG declares advisory board honouraria, consultancy fees and/or speaker fees from Abiogen, Celgene, Eli-Lilly, Neopharmed-Gentili, Pfizer and UCB outside the submitted work. MZ declares speaker fees from GSK, AstraZeneca, AbbVie and Pfizer outside the submitted work. OV declares advisory board honouraria and speaker fees from Gilead, Fresenius Kabi, Biogen, Eli-Lilly, UCB, AbbVie, MSD and BMS outside the submitted work. MR declares advisory board honouraria, consultancy fees and/or speaker fees from AbbVie, Eli-Lilly, Italfarmaco, Neopharmed-Gentili, Theramex, UCB, outside the submitted work. GO declares speaker fees from GSK, AstraZeneca, Novartis, Blueprint and Alexion outside the submitted work. All other authors declare no conflict of interest.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval The study was conducted according to the protocol 3875CESC approved by our local Ethics Committee, in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was collected for each participant. Patients provided consent for publication of anonymised data. GSK will not disclose the results to third parties without prior written approval from the sponsor.

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