Rheumatoid arthritis patients achieved better quality of life than systemic lupus erythematosus patients at sustained remission

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Abstract Objective

In 2004 and 1999, respectively, recent-onset rheumatoid arthritis (RA) and systemic lupus erythematous (SLE) cohorts were initiated; the 36 item Medical Outcome Study Short-Form survey (SF-36) was applied beginning from enrolment. The objectives were to compare the SF-36v2 scores between patients from both cohorts who achieved sustained remission and to define the role of disease diagnosis as associated to SF-36v2 normative data in remission patients.

Methods

Sustained remission was considered when RA and SLE patients achieved at least 12 months of continuous follow-up with either SLE disease activity index 2000 update =0 or Disease Activity Score (28 joints) \leq 2.4, respectively. Up to December 2015, data from 172 RA patients and 211 SLE patients were reviewed. SF-36v2 scores were available for the totality of remission assessments. Logistic regression models were used to investigate factors associated with normative SF-36v2. Written informed consent was obtained from all patients.

Results

A higher proportion of patients achieved sustained remission sooner in the RA cohort than in the SLE cohort, 58% vs. 30.6% of the patients, after 30.8±23.9 vs. 59.4±37.5 months, respectively, p≤0.001. At sustained remission, RA patients scored better than SLE patients in 6 out of 8 domains of the SF-36v2 and the physical health component summary (PHCS); the opposite figure was true for the mental component. Age (β : 1.06, 95% CI: 1.02–1.1, p=0.03) and SLE diagnosis (β : 9.64, 95% CI: 3.61–25.75, p≤0.001) were predictors of not achieving normative PHCS.

Conclusion

RA patients in sustained remission achieved better quality of life than SLE patients.

Key words

rheumatoid arthritis, systemic lupus erythematosus, quality of life, sustained remission

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Introduction

In recent years, remission has been proposed as the expected target of various rheumatic diseases, including Systemic Lupus Erythematous (SLE) and Rheumatoid Arthritis (RA). In both conditions, remission has been associated with relevant outcomes such as survival in SLE patients (1, 2) and long-term damage and functional status in RA patients (3, 4). As a result, treat-to-target recommendations have been developed for both diseases, and remission is highlighted as the most relevant treatment target (5, 6).

Therefore, international efforts have been committed to define remission in each particular rheumatic disease. In SLE, several groups have validated indices to assess disease activity, damage and quality of life (QoL) (7-9); however, the criteria for disease remission have not been clearly established, except for the SLE Disease Activity Index (SLEDAI) (10). Meanwhile, in RA, different remission definitions had been validated, and the most frequently adopted definitions incorporate some of the core set of measures recommended to evaluate disease activity (11-14); ultimately, in RA patients, remission is operationalised as either a complete absence of disease activity or a level of disease activity so low that it is not troublesome to the patient and portends a good prognosis (15).

Through the course of SLE and RA, affected individuals have profound negative effects on their health-related QoL (HRQoL) (16, 17). The 36 item Medical Outcome Study Short-Form survey (SF-36) is a generic instrument that assesses HRQoL; the instrument has undergone extensive validation testing, has been adapted in multiple languages and cultures and allows comparison of outcomes among different conditions and to population's norms (18). It is also the most widely used measure to assess QoL in SLE (7, 19) and RA (20) patients. One relevant aspect about the association between disease activity status and HRQoL measures is that remission might have a different impact on patient's outcomes depending on the specific disease diagnosis. As such, it has been shown that RA patients in

the remission state almost achieved population norms in terms of HRQoL (21), unlike in the case of patients with ANCA-associated-vasculitides in remission, who showed substantially reduced HROoL (22). Furthermore, SLE outpatients had worse HRQoL and at an earlier age compared to patients with severe chronic conditions (23), and their SF-36 scores had been referred to as 30 to 40% lower than in the general population (7, 24). However, in SLE patients, a low correlation has been observed between disease activity (or damage) and SF-36 scores (7, 25), and there is little information regarding patients with remission.

The Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán is a national referral centre for rheumatic diseases located in México City. In 2004 and 1999, respectively, 2 incidental cohorts were initiated; the first cohort included recent-onset RA (26) and the second cohort included recent-onset SLE (27). Since then, patients from both cohorts have been followed with longitudinal evaluations of disease activity and HRQoL. In the present study, we sought to identify differences in HROoL between patients from both cohorts who had achieved and maintained a first remission state. The specific objectives of the study were:

- 1. To identify RA and SLE patients with first sustained remission and to describe their characteristics.
- 2. To compare SF-36v2 scores between RA patients in sustained remission and their SLE counterparts.
- 3. To identify factors associated with SF-36v2 normative data in patients from both cohorts with sustained remission and to define the role of disease diagnosis as a predictor of SF-36v2 normative data.

Materials and methods

The early SLE cohort (ESLEC)

In October 1999, an inception cohort of patients aged >16 years who were within 12 months of accrual of \geq 4 classification criteria for SLE (28) was assembled. At entry, patients had a standardised medical history, physical examination and complete laboratory tests, including at least routine chemi-



cal analyses, serum complements and anti-double-stranded DNA antibodies. Every 3 to 6 months, patients were seen at the lupus clinic and assessments of disease activity using the SLE disease activity index 2000 update (SLEDAI-2K) (29) and medications use and doses were confirmed.

The information was updated every year, including accrual damage using the Systemic Lupus International Collaborating Clinics damage index (SLICC) (30), the Hispanic version of the SF-36 measure (incorporate to routine assessments from 2005 onwards), any co-morbidities and traditional cardiovascular risk-factors. The information was stored in a database containing demographic, anthropometric, lifestyle habits, medical family history, obstetric variables, and lupus information. Two rheumatologists performed all the assessments.

Up to December 2015, 245 SLE patients were included into the cohort, of whom 211 had at least one year of follow-up that was required to meet the sustained remission definition.

The early RA cohort

In February 2004, an ongoing cohort of patients with recent-onset RA (within 12 months of symptoms onset) was initiated. At inclusion, the complete medical history and sociodemographic data were recorded in addition to the type(s) and levels of rheumatoid factor (RF) and of antibodies to cyclic citrullinated proteins (ACCP); consecutive medical evaluations were standardised and scheduled at regular intervals (at least 6 months apart), but included at least swollen and tender joint counts, acute reactant-phase determinations, patientand physician-reported outcomes (31), questionnaire SF-36v2 (32, 33), comorbidities and treatment assessments; all assessments were performed by one single rheumatologist. Traditional DMARDs were used in 99% of the patients with/without corticosteroids. Up to December 2015, the cohort comprised 180 RA patients of whom 172 had at least one year of follow-up.

Quality of life measurement: SF-36 and SF-36v2

The SF-36 is a generic measure of eight aspects of health status useful in describing and monitoring individuals suffering from a disease or illness. Both Hispanic versions (SF-36 and SF-36v2) include one scale for each of eight measures of health domains: physical functioning (10 items, [PF]), role participation with physical health problems (role-physical [RP], 4 items), bodily pain (2 items [BP]), general health (5 items, [GH]), vitality (4 items, [VT]), social functioning (2 items, [SF]), role participation with emotional health problems (roleemotional [RE], 3 items), and mental health (5 items, [MH]). All health domain scales are scored such that higher scores indicate better health. There are 2 component summary measures, physical (PHCS) and mental (MHCS), that aggregate 4 health domains each; the PHCS aggregates the domains of PF, RP, BP and GH and the MHCS aggregates VT, SF, RE and MH domains. There is an additional health domain scale, the self-evaluated transition and the data of this scale are not reported in the present study (32).

The SF36v2 differs from SF-36 (its predecessor) in that it contains a revised wording of instructions and survey items, a redesigned layout for questions and response choices, a greater comparability with the translations and cultural adaptations, a five-level response choice in place of dichotomous (yes/no) response choice for the items RP and RE, a five-level response choice in place of six-level response choice in the MH and VT scales and adoption of the T-score metric for both the health domain scales and the component summary measures, based on 1998 U.S. general population data (33).

Definitions

First sustained remission was considered (Yes/No) when patients achieved, for the first time, at least 12 months of continuous follow-up with either DAS28 \leq 2.4 for RA patients (31, 34) or SLEDAI=0 for SLE patients (10). The RA remission cut-off value of 2.4 (instead of 2.6) was chosen based on Aletaha et al. newly proposed definition of disease activity states (12). Nonetheless, we repeated the analysis considering first sustained remission when patients achieved, for the first time, at least 12 months of continuous followup with DAS28 \leq 2.6 and the same patients were identified (data not shown). Time in sustained remission was computed from the first time the state was achieved up to the last follow-up with either DAS28 \leq 2.4 for RA patients or SLEDAI=0 for SLE patients (Fig. 1). Disease flare was defined as DAS28>2.6 after sustained remission for RA patients and as SLEDAI >4 for SLE patients.

Norm and minimally important differences (MID) for SF-36v1.2 scores: normative data for each domain and the 2 summary measures were defined as \geq 50. MDI was defined as follows: PF of 4.3, RP of 4, BP of 5.5, GH of 7, VT of 6.7, SF of 6.2, RE of 4.6, MH of 6.7, PHCS of 3.8 and MHSC of 4.6 (32, 33).

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Statistics

Descriptive statistics, Student's *t*- and χ^2 tests were used, as appropriate. Sociodemographic data are presented as the mean \pm SD. Student's *t*-and χ^2 tests were used to compare normally distributed variables, and the Mann-Whitney U to compare non-normally distributed variables.

Logistic regression models were used to identify factors associated to SF-36v2 scores normative data in sustained remission patients. The selection of variables to be included was based on their statistical significance in the bivariate analysis; only age appears as a predictor. The analysis was separately performed for each cohort and for the entire population of patients with sustained remission where disease diagnosis, comorbidities and time to sustained remission were added (in addition to age) to the model.

Finally, we performed sensitivity analysis in the SR RA population considering either 2.4 or 2.6 as cut-off value for DAS28 sustained remission definition; we identified a total of 3271 time-point disease activity evaluations within the population described. Of them, 2378 were in DAS28-remission according to the 2.6 cut-off value and 2225 according to the 2.4 cut-off value; sensitivity was of 93.2%.

All statistical tests were 2-sided and evaluated at the 0.05 significance level. Statistical analysis was performed using the SPSS/PC programme (v. 17.0; Chicago IL).

The SF-36v2 licensee performed the rescoring of the SF-36 that was used in the ESLEC (32, 33). In all the cases, Spanish (for México) versions were used and scoring was adjusted by gender and age.

Ethics

The present study is in compliance with the Helsinki Declaration and was approved (IRE-274-10/11-1) by the Institution's internal review board "Comité de Ética en investigación del Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán". Written informed consent was obtained from all the patients.

The SF-36v2 license was purchased to guarantee that appropriate standards

Table I. Description of the ERAC and the ESLEC.

Characteristics	ERAC	ESLEC
Period of follow-up	04 Feb 2004 to 31 Dec 2015	24 Oct 1999 to 31 Dec 2015
n. of patients included	183	245
n. (%) of female	163 (89.1)	217 (88.6)
Age at cohort inclusion, years ¹	38.7 ± 12.9	27.2 ± 9.1
Years of formal education ¹	11 ± 3.9	12.7 ± 3.4
Disease duration at inclusion, months	5.3 ± 2.6	5.4 ± 3.8
Years of follow-up ¹	7.5 ± 3.2	10.6 ± 2.9
n. (%) of patients with active follow-up	p^2 152 (83.1)	171 (69.8)
n. (%) of patients lost to follow-up	29 (15.9)	37 (15.1)
n. (%) of patients dead ¹	4 (2.2)	37 (15.1)

Data presented as (mean±SD) unless otherwise indicated.

 $^{1}p \le 0.001$ for ERAC vs. ESLEC patients; $^{2}p=0.002$ for ERAC vs. ESLEC patients; ERAC: early RA cohort; ESLEC: early SLE cohort.

Table II. Comparison of sustained remission (SR) between patients from the ERAC and the ESLEC.

Characteristics of SR	ERAC	ESLEC	<i>p</i> -value
n. (%) of patients with SR	106 (57.9)	75 (30.6)	≤0.001
Follow-up to SR, months, mean±SD	30.8 ± 23.9	59.4 ± 37.5	≤0.001
Length of SR, months, mean±SD	33.3 ± 29.6	32.7 ± 24.5	0.802
n. (%) of patients who flare after SR	73 (68.9)	56 (74.8)	0.413
SR: 1 st sustained remission state; ERAC	: early RA cohort; ES	LEC. early SLE cohort.	

of cross-cultural adaptation techniques were used in the version developed of the SF-36 measure.

Results

Description of the cohorts

Table I summarises the cohort's characteristics. The ESLEC was established almost 4 years earlier than the ERAC; both cohorts were integrated primarily by middle-aged females (87.9%) although patients from the ERAC were older at inclusion and less educated than the ESLE patients. The majority of the patients had low-medium socioeconomic status (90.6%). Patients from both cohorts had recentonset disease and substantial follow-up that was longer in the ESLEC. Finally, there were fewer patients with current follow-up in the ESLEC, mainly attributed to a higher number of deaths.

Sustained remission and patient characteristics

A higher proportion of patients achieved sustained remission in the ERAC than in the ESLEC; additionally, the state of sustained remission was achieved earlier in patients from the former group. The length of time in remission and the number of patients who had a disease flare were similar as summarised in Table II.

The baseline characteristics of the patients who achieved sustained remission from both cohorts are compared in Table III; identical differences as those described for the entire cohort were found. In addition, patients from the ESLEC had more frequently comorbid conditions and higher Charlson scores (35) than patients from the ERAC and had more frequent inactive disease than patients from the ERAC (Table III). At baseline, the totality of the RA patients who achieved remission had active disease and corresponding SF36v2 evaluations. Due to a delayed incorporation of the SF-36 to the ESLEC, there were only 41 SF36v2 from the 75 SR-SLE patients, performed when patients had active disease (of note, these patients did not differ from the entire population of SLE patients who achieved sustained remission). Comparison of SF36v2 obtained at disease activity between RA and SLE patients with available data showed that patients from the former group scored significantly lower all the domains of the SF-36v2 (the GH domain showed a tendency) and both the PHCS and the MHCS measures than their counterpart (Fig. 2, Panel A).

Table III. Comparison of baseline characteristics from sustained remission (SR) patients from both cohorts.

Baseline characteristics	SR-patients from the ERAC, n=106	SR-patients from the ESLEC, n=75	<i>p</i> -value
n. (%) of female	91 (85.9)	68 (90.7)	0.403
Age at cohort inclusion, years	37.3 ± 12.3	28.3 ± 9.6	≤0.001
Years of formal education	11.1 ± 4	13.6 ± 3.7	≤0.001
Disease duration at inclusion, months	5.6 ± 2.5	6.3 ± 8.8	0.521
n. (%) of patients with comorbidity	12 (11.3)	20 (26.7)	0.012
Charlson score	1.2 ± 0.5	1.4 ± 0.8	0.013
Disease activity	DAS28: 5.4±1.5	SLEDAI: 6.3±5.6	NA
n. (%) of patients with inactive disease ¹	1 (0.9)	15 (20.3)	≤0.001
n. (%) of patients with at least moderate disease activity ²	101 (95.3)	49 (65.3)	≤0.001
n. (%) of patients with damage ³	12 (11.3)	8 (10.7)	0.732

Data presented as (mean±SD) unless otherwise indicated.

¹DAS28≤2.4 at baseline for ERAC patients and SLEDAI=0 at baseline for ESLEC patients;

²DAS28≥3.2 at baseline for ERAC patients and SLEDAI≥3 at baseline for ESLEC patients; ³Defined as with erosions on conventional hand and feet x-rays films for RA patients and as SLICC≥1

for SLE patients. NA: not applicable.

Comparison of SF-36v2 scores between patients from the ERAC and the ESLEC at sustained remission The vast majority of patients from both cohorts improved in their scores when they achieved their remission state; nonetheless, more RA patients than SLE patients improved their PHCS (104 [98.1%] vs. 29 patients [70.7%], $p \le .0001$) and their MHCS (96 [90.6%] vs. 30 [73.2%], p = 0.015).

RA patients in sustained remission scored higher than their SLE counterpart in the PF, BP, GH, VT, SF, and MH domains; the RP and RE domains were higher in SLE patients. The PHCS was higher in RA patients; the opposite result was true for the MHCS as shown in Figure 2, Panel B. Similarly, RA patients showed greater improvements in the PF, BP and SF domains and in the PHCS than SLE patients (Fig. 2, Panel C); the RE domain showed greater improvement in SLE patients. When the analysis was repeated in the restricted population of patients who improved their scores according to MDI cut-offs, similar results were obtained (data not shown). Finally, a minority of patients who achieved sustained remission had SF-36v2 domains scores within the norm at baseline evaluations, from 19.5% to 46.3% for SLE patients and from 2.8% to 14.2% for RA patients (Fig. 3, upper Panel). At SR, the number (%) of SLE and RA patients whose scores achieved the norm increased, although there was a greater proportion of RA patients who achieved PF, BP, GH, VT, SF, and PHCS norms when compared to SLE patients; these patients achieved more frequent RE and RP norms and tended to achieve a more frequent MHCS norm (Fig. 3, bottom Panel).

Factors associated with normative physical and mental health component summary in sustained remission patients

Sustained remission RA patients who achieved PHCS and MHCS norms were compared to those who did not; data





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from bivariate analysis showed differences in the age and presence of erosive disease between patients who achieved PHCS norms and their counterparts (data no shown). In the regression model, age appears to be the only associated factor to PHCS out of the norm, β : 1.12, 95%CI: 1.01-1.12, p=0.022, R²=0.11. Similarly, sustained remission SLE patients who achieved PHCS and MHCS norms were compared to those who did not; data from bivariate analysis showed differences in the age (data no shown). Age showed a tendency to be an associated factor to PHCS out of the norm, B: 1.05, 95%CI: 0.997-1.10 p=0.021, R²=0.07.

Finally, we tested the disease itself (RA vs. SLE) as a potential factor associated with achieving PHCS and MHCS norms among sustained remission patients; age, Charlson score and time to remission were also included as associated factors; age (β : 1.06, 95%CI: 1.02-1.11, p=0.031) and SLE diagnosis (β : 9.64, 95%CI: 3.61-25.75, p≤0.001) were both associated with not achieving normative PHCS (R²=0.22).

Discussion

Patient's perspective of disease activity represents an important aspect of the assessment of rheumatic diseases. Among these diseases, SLE and RA are known to impact the HRQoL of the patients with active disease (36, 37), although less is known about the HRQoL among patients in remission. The SF-36 is a valid and reliable tool that captures the physical, psychological and social impact of both diseases and has been recommended to be included in patient's assessments as a measure of self-reported quality of life (38, 39).

In the present study, we sought to identify patients who achieved their first sustained remission state from two incidental cohorts of SLE and RA and compared their SF-36 scores. The study involved two well-characterised cohorts of Mexican Mestizo patients with early disease and at least 10 years of follow-up. Complete and standardised assessments were performed by a limited number of dedicated rheumatologists. Equivalent definitions of remission were used for both diseases based on strict cut-offs of validated disease activity indices. We consider that both populations described are representative of 'real life' patients around the world, and the results presented have relevant clinical and practical implications.

First, we found that twice as many RA patients achieved their first sustained remission state compared to SLE patients (58% vs. 30.6%); in addition, remission was achieved earlier in RA patients. Similar rates, follow-ups to remission and times in remission had been described in RA and SLE patients from other populations, especially when less restrictive remission criteria are used (such as those permitting treatment) and data from patients with recent-onset disease are analysed (1, 40-42).

Second, as expected, patients from both cohorts improved their HRQoL at remission state; nonetheless, RA patients achieved better scores in the majority of SF-36 domains (but RP and RE) and in the PHCS compared with SLE patients. A greater proportion of RA patients in sustained remission achieved norms in five domains (from 71.7% for VT to 94.7% for PR) and in the PHCS (up to 90.5%) than SLE patients; these patients achieved more frequent RP and RE norms and scored higher MHCS than their counterparts. It might be

suggested that remission state impacts positively more health dimensions in RA patients than in their SLE counterpart. The discrepancy might be related to conceptual differences between the diseases in the construct of remission. Although the remission state was defined based on indices designed to assess disease activity, the DAS28 is a complex index that includes 2 patient's assessments, in opposition to the SLE-DAI. Additionally, the difference might be explained by a higher frequency of comorbid conditions in SLE patients compared to RA patients; nonetheless, patients from the former group showed higher comorbidity at baseline evaluation (that persisted at SR state), although their HRQoL was better than the HRQoL from RA patients, and the opposite figure was true at sustained remission. Also, there is evidence that the presence of different comorbidities influences the outcome's measure in RA and SLE patients; the most consistently mentioned in the literature are frequently unrecognised in our patients as depression (37, 43), fibromyalgia (44) and anxiety (45); recent fractures (46) and a wide range of additional medical chronic conditions integrated into a score (47) has also been related to poor HRQoL in patients with rheumatic conditions and could have been more represented in the SLE population at sustained remission. Finally, there might be a distinct impact of each disease in the HRQoL from patients achieving sustained remission, which has led to the recommendation to include patient's assessment when defining remission. Of note, SLE patients in sustained remission achieved more frequent RP and RE norms. Both roles explored limitations due to physical and to emotional problems, respectively, in different aspects of work or usual daily activities; we consider that their unexpected behaviour in SLE patients was determined by the re-scoring (from a categorical variable in the SF-36 version to a five level response choice in the SF-36v2) that might have respected the direction of the change (increase/ improvement vs. decrease/deterioration) and might have affected its magnitude and accordingly the percentage of patients achieving norms.

Third, at remission state, RA patients had greater improvement in all the SF-36 domains (except for the RE domain) and both summary components, than their SLE counterparts, despite having worse SF-36 scores at baseline evaluation; a higher deterioration of HRQoL in RA patients likely reflects high disease activity at cohort inclusion and accordingly a higher pain experience in such patients; meanwhile, clinical manifestations characterised by chronic pain are underrepresented in the spectrum of disease activity in SLE patients. In addition, reduced HRQoL had been shown in RA and SLE patients when compared to patients with other health conditions (37, 23). Fourth, in RA patients with sustained remission, age was the only factor associated with PHCS out of the norm, and a similar tendency was seen in SLE patients; also, SLE diagnosis (in addition to age) had the greatest impact on not achieving PHCS within norms. It is known that physical function declines with age (48) and that increased age reduces HROoL in aged RA patients (49) and is associated with fewer improvements in the majority of physical domains in SLE patients (36). We are unaware of a study that replicates the finding that SLE diagnosis prevents achieving PHCS norm in patients with remission; in addition to arguments already stated, it might be added that patients with RA have a reduced number of manifestations that potentially impact their HRQoL when compared to SLE patients in whom the spectrum is wider; finally, chronic pain is the main symptom of RA and it is known to impact physical function (50). Limitations of the study need to be addressed. We applied two different ver-

sions of the SF-36; the SF-36 from SLE patients were re-scored to SF-36v2 after the appropriate license was purchased; this re-scoring might have biased the results especially those related to roles. Specific comorbidities with a high prevalence in both diseases and known to impact SF-36, such as fibromyalgia, depression and anxiety, are not included in the Charlson score that was used in our study to evaluate comorbid conditions. Accordingly, we cannot rule out their impact on HRQoL outcomes. Due to a delay incorporation of the SF-36 to pa-

tient's assessments in the ESLEC, there were a significant number of missing data at disease activity, although it did not affect our main objective; in addition, patients with complete information did not differ from those with missing scores. Finally, the study was performed in patients from Latin-America; SLE and RA are known to have particular characteristics and prognoses in such populations (51) and the results might not be generalised to patients with dissimilar characteristics.

In conclusion, clinical remission has become a widely accepted treatment goal for patients with SLE and RA. However, there is no standardised conceptual definition of remission for either disease. In routine practice, remission is usually operationalised as the (complete) absence of disease activity and has a positive impact on HRQoL, although the magnitude of the impact might differ according to the disease in which remission is assessed. The present study showed that patients with recent-onset RA achieved the first sustained remission state earlier and more frequently compared to recentonset SLE patients; in addition, RA patients who achieved such state had better HRQoL than their SLE counterparts. Finally, age and SLE diagnosis were associated with not achieving HRQoL norms in patients with sustained remission. Important implications of our results might be related to the dimensions of the construct of remission in which the patient's perspective should be included.

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