Glucocorticoid-sparing in patients suffering from rheumatoid arthritis and treated with tocilizumab: the SPARE-1 study

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Abstract

Objective

To describe steroid-sparing in rheumatoid arthritis (RA) patients treated with tocilizumab (TCZ).

Methods

To evaluate the proportion of RA patients treated with more than 5 mg of prednisone (or equivalent)/day and starting TCZ who can receive less than 5 mg/day after 12 months without intensification of disease-modifying anti-rheumatic drugs (DMARDs), we conducted a non-interventional, multicentre, prospective study from 2011 to 2013. We included patients with moderate-to-severe RA, >18 years old, starting TCZ and receiving corticosteroids (GCs) at a dose greater than 5 mg/day of prednisone for at least 3 months.

Results

Amongst the 307 analysed patients (78% women, median RA duration: 8 years, mean DAS28-ESR: 5.1±1.3), 40% (95%CI=[35–46]) reached the targeted daily prednisone dose at M12, without conventional synthetic (cs)DMARD intensification. Predictive factors were RA duration of 5 years or less (OR=2.60, p=0.01), daily prednisone dose of 7.5 mg or less (OR=2.12, p=0.03), and low ESR value before the first TCZ infusion (OR=0.86, p=0.047). The proportion of patients with no more GCs increased up to 20% at M12. Disease activity improved over the 1-year period (DAS28-ESR LDA and remission in 41% and 33% of patients at M12, respectively). Amongst the 314 patients analysed for safety, at least one AE and at least one SAE were reported in 211 patients (67%) and in 48 patients (15%), respectively. No unexplained safety signal arose with TCZ.

Conclusion

A biological DMARD as TCZ allows reducing both GCs dose and disease activity in RA patients. Nevertheless, corticosteroid spare in real life is probably lower.

Key words

rheumatoid arthritis, epidemiology, glucocorticoids, tocilizumab, disease activity.

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Introduction

Rheumatoid arthritis (RA) is the most common of the chronic inflammatory rheumatic diseases, affecting 0.3–1% of the population, characterised by joint pain and swelling, progressive functional disability due to persistent synovitis, increased morbidity and mortality (1-4).

The RA management is based on a combination of symptomatic treatments and csDMARDs, the latter to be introduced as early as possible after diagnosis. Glucocorticoids (GCs) have been shown to decrease disease activity and attenuate the structural RA progression (4) but their adverse effects (5), although the acceptable benefit/risk ratio dosage remains debated, limit their use, especially in the long term (6). The recent EULAR recommendations stipulate that low to intermediate GC dose are beneficial as an initial, short-term treatment but should be tapered as quickly as possible (7).

Although there was a decline of mean initial prednisone use between 1980 and 2004, with long-term effectiveness of dosages less than 5 mg/day (8), a mean dose of 7.5 mg/day is taken by approximately 50% of patients initiating a biotherapy (9). As the aims of rheumatologists starting biologics are to reach remission or low disease activity (LDA) and to decrease corticosteroids without increasing in csDMARDs, it is interesting to evaluate in which proportion a biologic (b)DMARD allows GC doses reduction while preserving a LDA. A first answer was provided by a German cohort followed between 1999 and 2007, in which a decrease in GCs demand was associated with the initiation of anti-TNF therapy in RA patients (10). Out of 110 patients, 81 were able to reduce their GCs use including 28 who stopped it completely. The median dosage (quartiles) fell from 7.5 (5; 12.5) mg/day of prednisone or equivalent to 2.5 (0; 5) mg/day ($p<0.001$). After 12 months of treatment with the biologic agent, 75% of the patients were taking a daily dose of prednisone or equivalent of 5 mg or less. Finally, the best use of GCs in RA (initial dosage, long-term efficacy, duration of treatment), remains debated (8-12).

(TCZ) is the first humanised monoclonal antibody that inhibits both soluble and membrane-bound interleukin-6 receptors (13). After a clinical development programme including five large international double-blind phase III clinical trials (13-17), TCZ was indicated for the treatment of moderate to severe active RA in adult patients who failed, or were intolerant to, previous therapy with one or more csDMARDs or tumour necrosis factor (TNF) antagonists. TCZ efficacy was confirmed in a large phase IV research [Disease Activity Score (DAS) remission in 56% of the 1,681 analysed patients who failed csDMARDs or anti-TNFs (16).

To complete these findings, a non-interventional study appeared useful to provide a population-wide approach [*i.e.* aiming to describe practices without interfering with usual prescribing behaviours and treatment algorithms, (9)] and to describe the glucocorticoid-sparing effect of TCZ after 12 months of treatment, in RA patients.

Materials and methods

Although the rheumatologists knew the goal of the study, the trial was not conducted with the intention to reduce GC dosage but to collect in the real-life the activity of the disease, co-medication and safety in a group of patients starting TCZ. As the primary endpoint was the proportion of patients who reached a GC dose ≤5 mg/day of prednisone or equivalent, without intensification of csDMARDs, we included only patients with GC> mg/day of prednisone or equivalent.

Study design and regulatory issues

SPARE-1 was a French non-interventional, prospective and multicentre study conducted in RA patients. The study was managed in cooperation with an independent scientific committee including three hospital-based rheumatologists.

In accordance with French law regarding non-interventional studies, the SPARE-1 protocol was approved by the Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé (Consultative Committee on Information Processing for Research in the Field of

Health) and was validated by the Commission Nationale de l'Informatique et des Libertés (independent administrative authority protecting privacy and personal data), which guarantees confidentiality to the subjects. All patients were informed before study enrolment.

Rheumatologists recruitment and patients selection

Using a national database of 723 French hospital-based rheumatologists, all these specialists were invited by mail and phone in February 2011 to participate in the study, and 191 physicians agreed to do so. Each rheumatologist with an active annual file ≥20 RA patients was asked to include 3-15 consecutive patients fulfilling the eligibility criteria (adults with moderate to severe RA, starting TCZ and taking oral prednisone or equivalent >5 mg/day for at least three months at baseline, informed about the study orally and in writing and accepting their data to be processed). Patients participating in a clinical trial assessing RA treatment could not be included.

Data collection

The characteristics of participant rheumatologists [age, gender, main medical facility (university centre, hospital, or private clinic), and geographic location] were collected. Patients' data were collected during monthly routine visits by rheumatologists and semi-annually by patients. Patients' data were as follows: baseline characteristics, comorbidities and related ongoing treatments, and RA characteristics [history, previous treatments, treatments prescribed over the study period (TCZ infusions, daily GC doses, csDMARDs, symptomatic treatments), disease activity and scores]. Patients completed self-reported questionnaires at inclusion, M6 and M12: Rheumatoid arthritis Impact of Disease (RAID; covering all the potential RA effects (20), Health Assessment Questionnaire Disability Index (HAQ-DI; measuring RA-related functional disability) (21). Patient visual analogue scale (VAS) for global assessment of disease activity)was collected every month. Safety was assessed through recording adverse events (AEs) and Serious (S)AEs. The safety reporting period was defined as 28 days after the last TCZ infusion for non-serious AEs or 8 weeks after the last infusion for non-related SAEs or regardless of time for related SAEs. AEs having occurred afterwards were defined as "late".

Data were collected between March 2011 and April 2013 and were reviewed by the scientific committee.

Statistical methods

All tests were two-sided with α risk at 5%. Statistical analyses were performed using SAS v. 9.2 (SAS Institute Inc. Cary, NC, USA). Quantitative data were expressed as mean (standard deviation) or median (range) and qualitative data as numbers and percentages (calculated excluding missing data).

Efficacy analyses were performed on the patients fullfilling inclusion and non-inclusion criteria and who had received at least one TCZ infusion (Efficacy Population). Safety was analysed on the patients with at least one TCZ infusion (Safety Population).

The primary endpoint was the proportion of patients who reached a GC dose ≤5 mg/day of prednisone or equivalent, without intensification of csDMARDs, after 12 months of TCZ. It was described with its associated 95% confidence interval (CI). Patients with missing GCs dose at M12 or with missing data regarding csDMARDs intensification were considered as 'non-responders'. Sensitivity analyses were performed on 'completers' (patients with assessable response) and using the Last Observation Carried Forward (LOCF) method to handle missing GC doses. Factors associated with a reduction in GC dose were assessed, on 'completers', among baseline patients and disease characteristics using a marginal logistic model taking into account the correlation of patients within the centre. Univariate analyses were used to select (*p*-value ≤0.10) the explanatory variables to include in the multivariate model. Results were interpreted in terms of odd ratios with their associated 95% CI.

Secondary endpoints on steroid-sparing were described using 'non-responder' imputation. Monthly doses of prednisone over the study period as well as the monthly proportion of patients who discontinued GCs permanently were described using LOCF method. Therapeutic maintenance was analysed using Kaplan-Meier method. DAS28 LDA (DAS28-ESR ≤3.2) and remission (DAS28-ESR <2.6) were described using 'non-responder' imputation.

Determination of sample size was based on the width of a 95% CI. Around 400 patients allowed an estimation of 40 to 70% of patients reaching a GC dose ≤5 mg/day of prednisone or equivalent, without intensification of csDMARDs after 12 months of TCZ (10) with a 5% accuracy (width of the 95% CI around 10%) and a 5% type I error. Recruitment having been more difficult than expected, precision has been re-estimated before the end of inclusions. With 300 analysed patients (actual number at the time), the precision was of 5.2% and considered as sufficient.

Results

Rheumatologists' characteristics

Among the 191 rheumatologists who agreed to participate, 106 (55%) included at least one patient (15% of the 723 specialists included in the national database). Participant rheumatologists were distributed throughout France, with more hospital-based practice when compared to the national database.

Patients' characteristics

Of the 321 patients included in the SPARE-1 study, 314 received TCZ (Safety Population) and 307 met inclusion/exclusion criteria (Efficacy Population, Fig. 1). A total of 185 patients completed the study (*i.e.* underwent the M12 visit at the study end, with ongoing TCZ). Patients' characteristics are detailed in Table I. The mean age was 57±14 years, 78% were women, and 85% presented with at least one comorbidity or significant concomitant disease before the first TCZ infusion (arterial hypertension: 35% of patients; dyslipidaemia: 25%). The median RA duration was 8 years (Q1–Q3: [3; 15]), and mean DAS28-ESR was 5.1±1.3 before the first TCZ infusion.

There was no correlation between prednisone dose in patients and the levels of CRP (r=0.03; *p*=0.60)

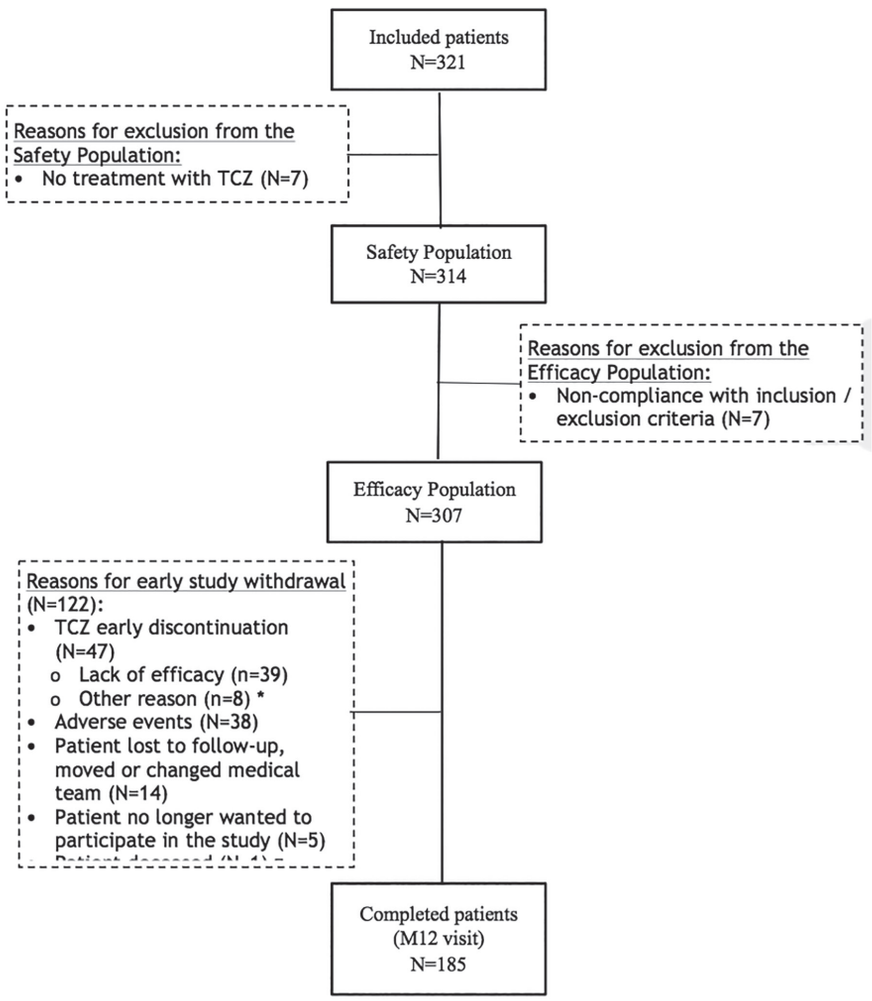

Fig. 1. Disposition of patients.
*Desire for pregnancy (n=3), patient wish due to lack of efficacy and poor tolerance (n=1), patient with specific psychological context (n=1), reason not provided (n=3)
†Geriatric cachexia with general status worsening, decubitus complications, and osteoporotic fracture (n=1). This fatal event, not related to tocilizumab, occurred more than 3 months after treatment discontinuation.

Steroid-sparing at M12 (primary criterion)

Considering patients with missing data for prednisone dose or for csDMARDs intensification at M12 as 'non-responders', the proportion of patients who reached the targeted daily dose of prednisone or equivalent (≤5 mg, dose at the visit + IV bolus the day of the visit if applicable) was 40% (95% CI=[35–46], Table II).

Amongst the 39 patients (13%) who permanently discontinued TCZ before the study end because of lack of efficacy, only 8 patients (21%) received a last daily dose up to 5 mg prednisone (or equivalent).

Predictive factors for this targeted GC reduction at M12 without csDMARD intensification were RA duration not more than 5 years (OR=2.60, 95% CI=[1.22–5.54], p=0.01), daily dose of prednisone not more than 7.5 mg (OR=2.12, 95% CI=[1.08–4.14], p=0.03) and low ESR value before the first TCZ infusion (unit=10mm/h; OR=0.86, 95% CI=[0.75–1.00], p=0.047).

Secondary analyses on steroid-sparing

Considering missing data as failure, the proportions of patients who reached a daily dose of prednisone ≤5 mg, without csDMARDs intensification, were 35% (95% CI=[29–40]) after 6 months of TCZ (*i.e.* a close proportion to findings observed after a 12-month treatment period), 40% (95% CI=[34–45]) after 12 months of TCZ and since at least one month, 36% (95% CI=[31–42]) if patients reached also a good or moderate EULAR response after 12 months of TCZ, 31% (95% CI=[26– 36]) if patients were also in DAS28 LDA after a 12-month treatment period, and 25% (95% CI=[21–30]) if patients were also in DAS28 remission after 12 months of TCZ treatment.

The proportion of patients treated with up to 5 mg/day of prednisone increased month by month (from 12% at M1 to 55% at M12) after the first TCZ infusion (Fig. 2). In parallel, the proportion of patients with no more GCs increased from 2% at M1 up to 20% at M12 (Fig. 3).

Amongst the 55 patients (30% of the assessable patients at M12) who did not reach the targeted daily dose of prednisone after 12 months of TCZ , the majority (n=39, 71%) had no changes in csDMARDs until M12 and only 8 patients (15%) had csDMARD intensification; the remaining patients (n=8, 15%) had other csDMARD modifications.

Disease activity

After the first TCZ infusion, monthly proportions of patients in DAS28-ESR LDA and remission rapidly increased as early as M1 (38% and 27%, respectively) and reached 41% and 33% at M12, respectively.

Mean TCZ infusions number over the 1-year study period was 10±4 per patient (median [Q1; Q3]: 12 [7; 13]) and 52% (n=159) of the patients received at least 12 TCZ infusions. Using Kaplan Meier method, 71% of the patients maintained the therapy at month 12.

We did not observe differences between the group with and without DMARDs (data not shown).

Safety

Until the end of the 1-year follow-up of the SPARE-1 study, 72% of patients maintained TCZ treatment [reasons for discontinuation in 28% of patients: lack of efficiency (45%), AEs (44%), other reasons (11%)].

Based on the Safety Population (n=314), at least one AE and at least one Serious AE (SAE) were reported in 211 patients (67%) and in 48 patients (15%), respectively over the safety reporting period. Amongst the

Table I. Patients' baseline characteristics (n=307).

Patient's characteristics	Total (n=307)
Age (years)*	57±14-57 [48; 66]
Women (n, %)	239 (78)
Osteoporosis (n, %)	95 (32)
Previous osteoporotic fracture (n, %)	31/85 (37)
Treatment for osteoporosis (n, %)	81/95 (85)
RA duration (years)*	10±9-8 [3; 15]
Positive Rheumatoid Factor or anti-CPP antibodies (n, %)	249 (82)
Erosive RA	237 (79)
Previous RA treatments	
Naive patients (n, %)	1 (<1)
Synthetic DMARD only (n, %)	87 (29)
Biological DMARD only (n, %)	9 (3)
Synthetic and biological DMARDs (n, %)	207 (68)
TJC*	9±7-8 [4; 14]
SJC*	6±5-4 [2; 8]
CRP (mg/L)*	19±23-9 [4; 26]
ESR (mm/h)*	29±23-23 [11; 39]
DAS28-ESR*	5.1±1.3-5.1 [4.2; 5.9]
CDAI*	27±12-26 [18; 34]
SDAI*	29±13-27 [20; 36]
DMARDs combined with tocilizumab (n, %)	191 (62)
Methotrexate (n, %)	147/191 (77)
Methotrexate dose (mg/week)*	17±4-15 [15; 20]
Last glucocorticoid daily dose† (mg of prednisone or equivalent) *	12±7-10 [8; 13]
HAQ-DI score* - n=216	1.6±0.7-1.6 [1.1; 2.0]
RAID score* - n=212	6.2±2.0-6.5 [4.9; 7.6]

RA: rheumatoid arthritis; CPP: cyclic citrullinated peptide; DMARD: (disease-modifying anti-rheumatic drug; TJC: tender joint count; SJC: swollen joint count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate); DAS: disease activity score; CDAI: Clinical Disease Activity Index; SDAI: Simplified Disease Activity Index; HAQ-DI: Health Assessment Questionnaire Disability Index; RAID: Rheumatoid Arthritis Impact of Disease.
*Mean ± standard deviation - median [1st quartile; 3rd quartile].
†Daily glucocorticoid dose at the medical visit arrival (before the first tocilizumab infusion) + IV bolus the day of the visit if applicable.

Table II. Proportion of patients who reached a daily glucocorticoid dose ≤5 mg prednisone or equivalent, without intensification of synthetic DMARDs, after 12 months of treatment with tocilizumab (n=307).

	Total n=307
Proportion of patients who reached the targeted glucocorticoid dose (non-assessable response = No) - 95% CI	124 (40.4%) - [34.9 ; 45.9]
Proportion of patients who reached the targeted glucocorticoid dose (LOCF, non-assessable response = No) - 95% CI	157 (51.1%) - [45.6 ; 56.7]
Proportion of patients who reached the targeted glucocorticoid dose (completed patients) – 95% CI (n=184*)	124 (67.4%) - [60.6 ; 74.2]

LOCF: last observed carried forward; CI: confidence interval).
*Amongst the 185 completed patients (*i.e.* patients who underwent the M12 visit with ongoing treatment with tocilizumab), 1 patient had no data reported for the primary criterion analysis.

652 reported AEs, the most frequent were infections and infestations (37%), gastrointestinal disorders (14%), general disorders and administration site conditions (12%), musculoskeletal and connective tissue disorders (12%), and blood and lymphatic system disorders (11%). Amongst the 72 reported SAEs the most frequent were infections and infestations (5%) and musculoskeletal and connective tissue disorders (4%).

A total of 130 patients (41%) experienced at least one AE related to TCZ and 27 patients (9%) presented with at least one TCZ-related SAE.

One hundred and forty-one patients (45%) experienced at least one AE of Special Interest (AESI *i.e.* anaphylaxis / hypersensitivity reactions, demyelinating disorders, gastrointestinal perforations and related events, malignancies, myocardial infarctions / acute coronary syndromes, infections including all opportunistic infections, hepatic events, bleeding events, and stroke) and at least one TCZ-related AESI was reported in 89 patients (28%). A total of 26 patients (8%) experienced at least one serious AESI and 20 patients (6%) presented with at least one serious TCZ-related AESI.

Regarding AESIs, 115 patients (37%) had infections and 15 patients (5%) presented with serious infections (including one patient with Pneumocystis jiroveci pneumonia and one patient with Legionella pneumonia which were assessed as related to TCZ). A total of 22 patients (7%) developed serious or medically significant hepatic events, including one patient with serious TCZ-related ALAT increase. Nine patients (3%) experienced spontaneous or serious bleeding events and four patients (1%) presented with serious events, including one patient with serious petechiae and purpura related to TCZ. Three patients (1%) experienced anaphylaxis events which were assessed as serious and related to TCZ in two patients (<1%). One patient (<1%) presented with serious TCZ-related ileal perforation. Three patients (1%) developed malignancy and one malignancy was assessed as related to TCZ (skin squamous cell carcinoma). Two patients (<1%) experienced non-related stroke. No myocardial infarctions / acute coronary syndromes occurred.

After the safety period, 3 patients (1%) presented with at least one late SAE. One pneumonia, one glioblastoma, and one death (Fig. 1) which occurred 3 months after the safety study period.

One pregnancy was discovered at 22 weeks of amenorrhoea in a 34-year old patient. TCZ and MTX were discontinued. The patient gave birth to a normal baby, and no adverse event was reported.

Discussion

The SPARE-1 study confirmed in real-life conditions that the prescription of TCZ allows sparing GC intake in pa-

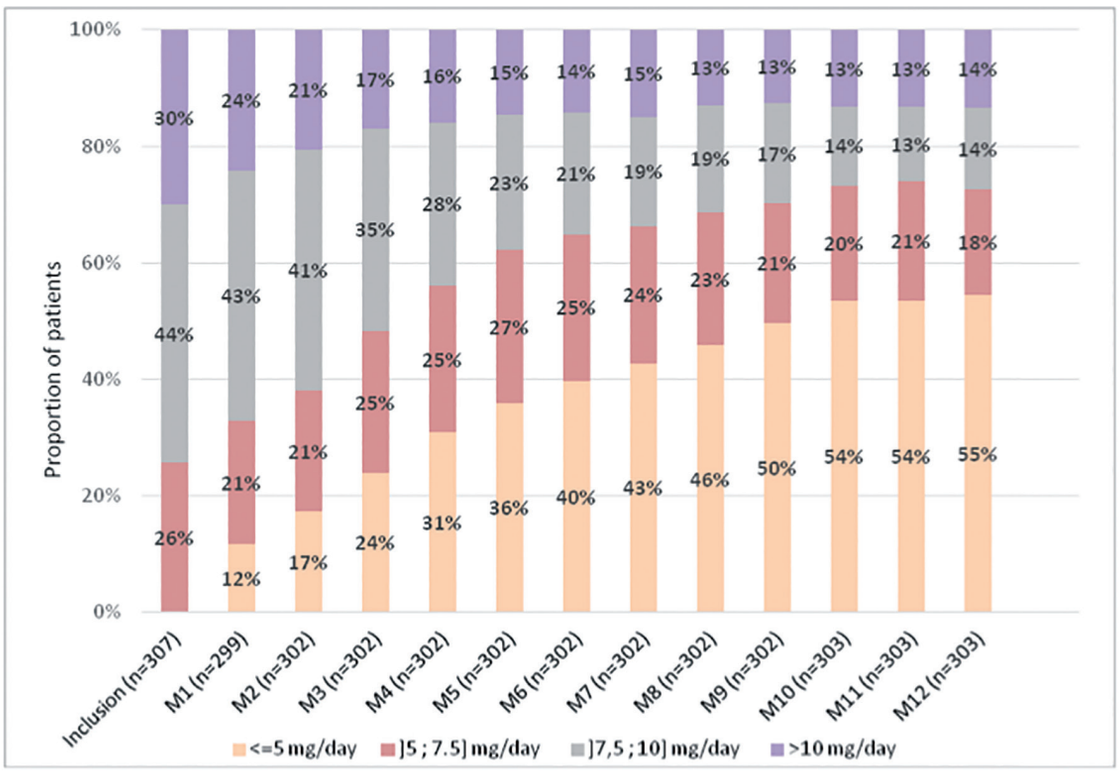

Fig. 2. Daily dose of prednisone equivalent, at each monthly visit (n=307).
Daily dose of prednisone or equivalent: dose at the medical visit arrival + IV bolus the day of the visit if applicable. For this analysis, the LOCF method (using last post-baseline values) was used.

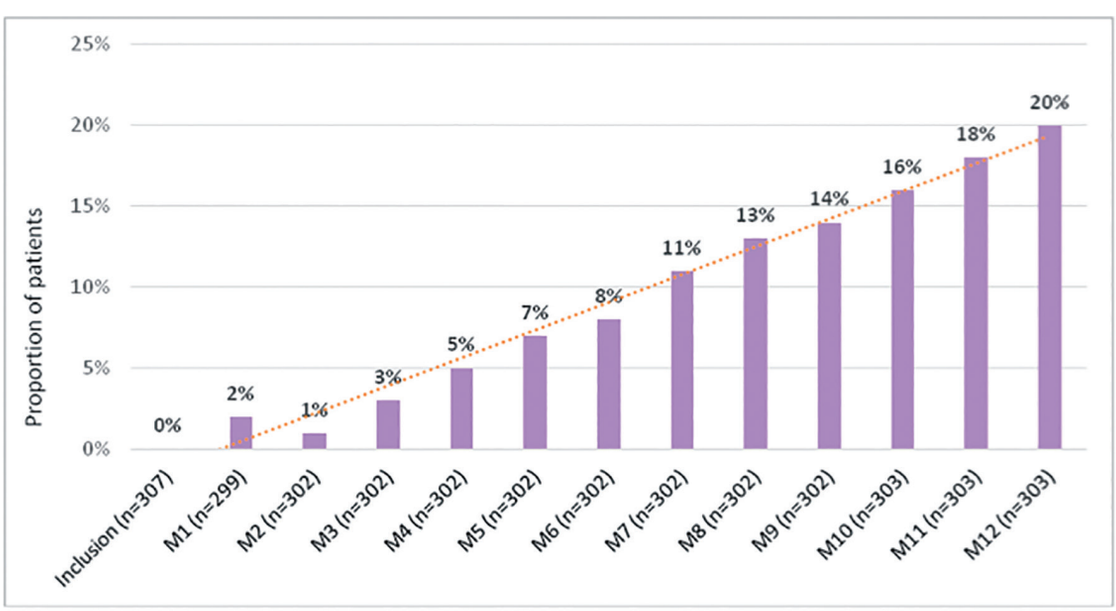

Fig. 3. Patients with discontinuation of glucocorticoid treatment, at each monthly visit (n=307).
For analyses, last post-baseline values were used.

tients suffering from moderate to severe RA (≤5 mg/day of prednisone or equivalent, without csDMARD intensification until M12): 40% of the patients (95% CI=[35–46]). Although usually seen in that type of observational study, the number of non-assessable patients for the evaluation of this primary endpoint (123/307) prompted us to further sensitivity analyses which showed higher proportions of patients having reached this target of steroid-sparing (around 2/3 of completed patients and more than half of the patients when using last post-baseline data). Furthermore, the proportion of RA patients with no more GCs increased over the SPARE-1 study period (up to 20% at M12).

72% of RA patients maintained TCZ treatment until the end of the 1-year follow-up. Close findings were observed in other non-interventional studies conducted in RA patients treated with TCZ: 65% of patients at Week 52 in the German ROUTINE study (22), 63% of patients after a 1-year follow-up in the Swedish ARTIS study registry (23), and 66% of patients after a 1-year follow-up in the DANBIO registry (24). In all these studies, the relatively high early treatment withdrawal proportions probably reflected the usual TCZ prescription after several unsuccessful RA

treatments in a real-life setting. Furthermore these patients were more likely to suffer from adverse events as 85% of them had at least one co-morbidity and 68% had received either a csDMARD, either a bDMARD when enrolled in the SPARE-1 study.

There are few data regarding the GCs sparing effect of biologics in RA. For TCZ, the GCs sparing effect was shown at 5 years in two interventional studies in which TCZ was initiated as monotherapy. In the Japanese STREAM study (25), 89% (78/88) of the completed patients reduced their GC dose and 32% (28/88) were able to stop GCs after completion of the 5-year open-label follow-up. The mean GC dose decreased from 6.9 mg/day (median: 7.5 mg/day) to 2.4 mg/day (median: 2.0 mg/day) at 5 years. A Japanese meta-analysis concerning 6 clinical trials and 5 long-term TCZ extension trials (26) showed that, of the 546 studied patients taking GCs at baseline, 78% were able to decrease their GC dose during the study period, while 35% discontinued this treatment. The mean GC dose fell from 6.7 mg/day (median: 4.0 mg/day) at baseline to 2.3 mg/day (median: 0.5 mg/day) at 5 years. For anti-TNF, this was shown in a German retrospective study conducted from 1999 over a 5-year period in 110 RA patients (27). Median GC dose could be significantly reduced from 7.5 (5; 12.5) mg/day to 2.5 (0; 5) mg/day (p<0.0001). GC doses were actually reduced in 81 patients and even stopped in 28 patients. So, SPARE-1 was the first prospective non-interventional study describing the GCs sparing effect in real life at 1 year, in a sample population of more than 300 RA patients. However, the main limit of this study is a possible better spare in this study than in real life due to the known objective of the study. So, we plan now to verify this sparing effect in a cohort of patients treated by TCZ but not designed for this goal, the REGATE registry. Nevertheless, a recently published (28) open observational retrospective multicentre study has also shown that TCZ introduction led to rapid and long-lasting CS sparing.

During the SPARE-1 study, an improvement of disease activity (DAS-28 LDA and remission) was also observed concomitantly with the GC dose reduction. Similar results were observed after a 1-year treatment period in other recent non-interventional studies (with intensification of csDMARDs or not): 37% of patients were in DAS28-ESR LDA in the Swedish ARTIS registry (21); 44% and 55% of patients reached DAS28-ESR LDA and remission, respectively in the German ROUTINE study (22).

Safety data from the SPARE-1 study, in particular the proportion of patients with at least one infection over the study period, confirmed previous findings about TCZ.

In conclusion, SPARE-1 was the first prospective, multicentre, non-interventional study showing that the prescription of tocilizumab is associated with a reduction of steroid doses in 40% of the patients suffering from moderate to severe RA. Over the 1-year study period, the improvement of disease activity was also confirmed in tocilizumab-treated patients. No new or unexplained safety signals were noted.

Key messages

- This is the first confirmation of the steroid-sparing effect in RA patients treated with a biological DMARD as tocilizumab, in a prospective study.
- A reduction of corticosteroid doses is observed in 40% of the patients suffering from moderate to severe RA.

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