Successful long-term remission through tapering tocilizumab infusions: a single center prospective study

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Abstract

Background

Strategic drug therapy for rheumatoid arthritis (RA) patients with prolonged remission is not well defined. According to recent guidelines, tapering biological Disease Modifying Anti-Rheumatic Drugs (bDMARDs) may be considered. We aimed to evaluate the long-term maintenance of tocilizumab (TCZ) treatment after the progressive tapering of infusions.

Methods

We conducted an exploratory, prospective, single-center, open label study, on RA patients with sustained remission for at least 3 months and treated with TCZ infusions every 4 weeks. The initial re-treatment interval was 6 weeks for the first 3 months. Thereafter, the spacing between infusions was determined by the clinician. Successful long-term maintenance following the tapering of TCZ infusions was defined by patients still treated after two years by TCZ with a minimum dosing interval of 5 weeks.

Results

Thirteen patients were enrolled in the study. Eight out of thirteen were still treated by TCZ after two years. Successful long-term maintenance was possible in six patients, with four patients maintaining a re-treatment interval of 8-weeks or more. We observed 5 patients with TCZ withdrawal: one for adverse drug reaction (neutropenia) and four with secondary failure. Patients achieving successful long-term maintenance with TCZ were significantly younger than those with secondary failure (p<0.05). In addition, RA patients with positive rheumatoid factor and anti-citrullinated peptide antibodies, experienced a significantly greater number of flares during our 2-year follow-up (p<0.01).

Conclusions

A progressive tapering of TCZ infusions seems possible in most of the patients. However, larger studies, including more patients, are needed to confirm this therapeutic option.

Background

Rheumatoid arthritis (RA) is the most common inflammatory rheumatic disease. New licensed biological agents are now largely used in RA treatment. Recent recommendations from the American
College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) highlighted the need to treat RA patients quickly in order to obtain clinical remission without radiological damage (1). This therapeutic goal aims to prevent structural damage and disease progression. Clinical remission is defined by the absence of symptoms of disease activity and numerous validated indexes are able to classify patients (DAS28 < 2.6 or CDAI < 2.8; SDAI < 3.3 or Boolean criteria) (2,3). The new EULAR guidelines stress the importance of a “treat-to-target” strategy and outline recommended changes in therapy for patients exhibiting disease remission. In the context of persistent remission (up to 6 months), ending steroid treatment as quickly as possible is recommended (4). Then, if the patient remains in remission, clinicians can consider tapering biological disease-modifying anti-rheumatic drugs (bDMARDs), either through reduction of dose or extension of interval between applications (‘spacing’) (4). Furthermore, the updated EULAR recommendations for the management of RA with synthetic and bDMARDs highlight early RA, the depth of improvement, and the duration of remission as predictors of the likely success of tapering (4).

Increasing the spacing or stopping treatment with biological agents may also be desirable due to safety and health economics issues (5). As biologics are more expensive than conventional synthetic (cs) DMARDs, and may cause more serious adverse events, the next step in RA therapy management should be to assess the possibility of sustaining remission without the use of biologics. Some studies of tumor necrosis factor α (TNF-α)-targeting drugs found that dose reduction or discontinuation of biological agents can be achieved in a relevant proportion of RA patients without loss of disease control or radiological damage (6–8). Indeed, more than one-third of RA patients with low disease activity (LDA) or in remission did not experience a disease flare within the first year of tapering or stopping DMARD treatment (9).

Tocilizumab (TCZ) is the first therapeutic agent targeting IL-6 to be effective in RA treatment. TCZ is approved for the treatment of active, moderate-to-severe RA in patients who have had an inadequate response to one or more csDMARDs and/or TNF antagonists (10). Recent studies suggest that TCZ
could induce drug-free remission in a low proportion of patients (11,12). However, few data reporting the efficacy and safety of TCZ tapering are available and the follow-up of patients is short (less than one year) (13). We hypothesized that increasing the interval or spacing between TCZ infusions, rather than stopping the treatment in RA patients with remission, may represent a better strategy to reduce the risk of flare. We assumed that TCZ dose reduction, instead of dosing interval extension, may not be equivalent in efficacy for pharmacokinetics/pharmacodynamics reasons (14). However, we chose the spacing strategy because it was more convenient and less costly in “real life” practice reducing hospital stay. Thus, our aim was to evaluate the long-term maintenance of remission after progressive TCZ tapering in RA patients.

Methods

Patients’ characteristics

We conducted a prospective, exploratory, single-center, open label study with RA patients fulfilling the 2010 ACR/EULAR criteria (NCT02909998-ClinicalTrials.gov). We included patients in remission for at least 3 months and treated by TCZ infusions every 4 weeks. Criteria for remission were previously defined by DAS28 < 2.6 with only one swollen joint authorized in a 44-joint swollen count. The RA patients were without corticosteroids for at least 4 weeks and with a stable dose of csDMARDs for at least 3 months.

The study was approved by the local ethics committee (CPP IV Sud-Méditerranée, Montpellier, France) in accordance with the Helsinki Declaration and informed consent was obtained from each patient (NCT02909998; N°2008-A01087-48). Patients were recruited when they reported for their regular monthly infusion.

Design

The initial assessment included clinical, biological, and Doppler ultrasound (US) parameters for hands and feet. Doppler US was performed at baseline for all patients by the same radiologist with experience in rheumatic and musculoskeletal diseases. Sera of the patients was collected the day prior to the start of spacing to define levels of plasma TCZ and antidrug antibodies (ADAb). Samples were analyzed in the department of Immunology using LISA-TRACKER® enzyme-linked
immunosorbent assay (ELISA) kits (Theradiag, Marne La Vallée, France).

Retreatment interval (RTI) was fixed at 6 weeks spacing for the first 3 months. Thereafter, if possible, TCZ tapering to 8 weeks was advised, although the exact spacing pattern was left to be determined by the clinician. A flare could occur during the prolongation of TCZ administration interval and was defined by a DAS28 > 2.6 with a progression in the DAS28 > 0.6 compared to previous DAS28 (2). In case of flare, patients could be returned to a 4 or 6-weeks interval. Other options for clinicians were also possible, such as maintaining the RTI through decreasing TCZ doses, optimizing csDMARDs or introducing corticosteroids.

**Outcome assessment**

A successful long-term maintenance after tapering was defined after 2 years by the percentage of patients still treated by TCZ and with at least a 5-weeks interval between two infusions. The rate and time to flare after progressive TCZ spacing and predictors of maintaining remission or flare after tapering were analyzed. Possible reasons for TCZ withdrawal or spacing failure were also analyzed.

**Statistical analysis**

A general description of the sample was performed using the frequencies for qualitative variables and the mean, standard deviation and range is reported for quantitative variables. Comparisons between groups of patients were performed using Wilcoxon-Mann-Whitney test for averages and Fisher’s exact test for percentages with 95% confidence intervals. The significance level was set at 5% for all tests. Statistical analysis was performed using Prism version 6.0c (GraphPad Software Inc., La Jolla, CA, USA).

**Results**

**Characteristics of patients**

Thirteen RA patients were included from July 2011 to September 2012. Baseline patient characteristics are summarized in Table 1. Most patients were female (69.2%) with a mean age of 48.2 ± 14.5 years. The mean disease duration was 11.5 ± 9.4 years. Mean duration of treatment with TCZ before spacing was 18.4 ± 7.3 months. The mean time of remission was 7.5 ± 6.2 months. Ten patients (76.9%) presented erosions at baseline and seven (53.8%) were positive for rheumatoid
factor (RF) and anti-citrullinated peptide antibodies (ACPA). Prior to TCZ treatment, the mean number of previous csDMARDs and bDMARDs used were 2.1 ± 0.9 and 1.7 ± 1.2, respectively. Six patients received concomitant treatment with methotrexate (MTX), three with leflunomide, and five received TCZ in monotherapy. At the start of the progressive spacing, the mean DAS28 score was 1.6 ± 0.9.

**Patient outcomes after tapering TCZ infusions:**

After a 2-year follow-up, 8/13 patients remained on TCZ therapy after a spacing attempt. Six patients (46.1%) succeed to taper TCZ with a long-term controlled disease and a minimum 5-week interval between infusions (Table 2). Among these patients, four were treated every eight or more weeks RTI, and their mean DAS28 score at 24 months was 1.58 ± 0.6.

The successful long-term maintenance group (6/13) experienced on average one flare ± 0.9 during the study, with a mean delay of occurrence of 4.4 ± 4.9 months after the start of spacing. Only two patients remained on a 4 week RTI of TCZ infusions. A switch to another biologic was needed for five patients. Among them, four were due to a secondary failure (one is taking anti-TNF-α and three are taking abatacept), while the remaining patient developed a severe TCZ-induced neutropenia.

**Predictors of maintaining remission or flare after tapering**

In order to evaluate potential predictors of maintaining remission following TCZ tapering, we compared patients experiencing “secondary failure” (n=4) with those experiencing “successful long-term maintenance” (n=6) (Table 3). Patients with secondary failure were significantly older than patients in the group “successful long-term maintenance” (mean age: 60.7 ± 6.7 and 41.8 ± 15.2 respectively; p=0.038). Hand and feet US characteristics were similar in each group. TCZ plasma level was similar in both groups and none of them developed ADAAb. There was non-significant tendency (p=0.07) for patients in the “successful long-term maintenance” group to experience fewer flares during the 2 years of the study (mean number of flares: 2 ± 0 versus 1 ± 0.9).

Lastly, we compared patients who experienced one flare or less during the whole study with the remaining patients who experienced 2 or more (Table 4). While none of the baseline clinical, biological, and imaging characteristics were associated with successful tapering of TCZ infusions, we found that RF and ACPA positivity were both associated with a greater number of flares (p=0.004).
Discussion
Our observation of sustained remission in 8 out of 13 studied patients suggests that maintenance of TCZ therapy may be feasible following attempts to increase the spacing infusions. In addition, six out of thirteen of the patients successfully transitioned to long term-maintenance with tapered TCZ infusions. Four patients developed a secondary failure after beginning the spacing infusions, while one patient developed a severe neutropenia associated with TCZ. The age of patients may influence the success of the long-term maintenance of TCZ, as younger patients were more likely to experience successful transition and less likely to experience secondary failure. Moreover, RF and ACPA positive RA patients experienced more episodes of flares during our follow-up, underscoring a greater severity of the disease.

Guidelines concerning initiation of bDMARDs and how to induce remission are well established (15). However, data on patient responses to therapy once remission is reached are scarce. Stopping bDMARDs after achieving remission is challenging due to a potential tradeoff between the important health economic impact that could be achieved on one hand and the potential risk of recurrence on the other (16). New EULAR recommendations propose that clinicians consider changes in therapy, either through changes in dose or increasing the spacing between treatments, especially for patients in long-term remission in association with csDMARDs (4). However, no strategy is clearly yet recommended and the consequences of such changes are not well understood. Cost-analysis studies clearly demonstrate that decreasing doses of bDMARDs decreases costs (17). What remains unclear is consequences for patients, both in terms of identifying the long-term consequences of extension of dosing (radiographic changes, flares ...) as well as identifying characteristics that may aid clinicians in identifying patients in which down-titration or discontinuation of bDMARDs could be possible (17). Several studies have examined the discontinuation or the spacing of bDMARDs in RA patients with prolonged remission. Results suggest that discontinuation of anti-TNF-α agents does not allow a sustained remission in most drug-free patients [6,18]. Indeed, the prospective observational study of Van der Mass et al. found that discontinuation of anti-TNF-αtherapy was feasible for only 16% of their patients[6]. The PRESERVE study compared three strategies of RA’s drug management (maintenance,
half dose reduction and complete discontinuation of etanercept) in a randomized controlled trial of RA patients showing sustained remission in the past one year (18). After 1 year, low disease activity (LDA) was observed in 46% of patients in the placebo group versus 82.6% in patients maintained on etanercept therapy. In addition, the ADMIRE study with adalimumab (19), CERTAIN study with certolizumab pegol (20) and DOSERA study with etanercept (21) all demonstrated that withdrawing anti-TNF-α therapy did not allow maintenance of patients in sustained remission, with rates of sustained remission of 13%, 17% and 13% respectively. In the light of these results, others have tried down-titration of bDMARDs, rather than discontinuation, to maintain RA patients in sustained remission. In the PRESERVE study, Smolen et al. found that the risk of relapse and structural damage progression at 1 year of patients in the half-dose group was statistically indistinguishable from those maintained with a full dose (18). In the recent STRASS study comparing the effect of down-titration of TNF-blockers injections to their maintenance for RA-patients in remission (DAS28 < 2.6), relapse was observed more frequently in the progressively spacing TNF-blockers’ injections group (76.6% vs 46.5%, p=0.0004), however equivalence of the two strategies couldn’t be demonstrated due to an underpowered trial (22).

Concerning TCZ tapering, several strategies have been tried, including discontinuation TCZ infusions (11,12), and gradual spacing or extended RTI to a fixed interval (eg. 6-weeks)(13). We conducted the present study to determine if tapering TCZ through progressive spacing of infusions would be a better strategy to maintain patients under TCZ in remission. This approach was adopted because we believed that it might be the best option for our patients as well as from a medico-economical standpoint. A recent study extending dosing interval of TCZ infusions to 6 weeks for RA patients in sustained remission in the past 3 months appeared to provide an acceptable option, with 88% retaining remission after 54 weeks (13). By contrast, sustained remission following cessation of TCZ treatment was much lower: in the DREAM study (12), after cessation of TCZ used in monotherapy, drug free remission or LDA was present in 35.1%, and 13.4% of patients after 24 and 52 weeks respectively, and in the ACT-RAY study, remission rate dropped to 16% after stopping TCZ (23). In our study, we observed that a majority (61.5%) of our patients sustained remission at month 24 and
46.1% had successful long term maintenance with tapering of TCZ infusions, results is comparable to those of Kikuchi et al (13).

Some factors contributing to prolonging the duration of DAS28 remission and LDA after discontinuation or tapering of biologics have been previously identified. A lack of disease severity factors may be a selection criterion informing decisions to increase spacing of TCZ infusions (12). In the BeST study and in early arthritis cohorts, successful discontinuation was associated with the absence of ACPA, male gender, rapid achievement of remission, non-smoking and absence of HLA shared epitope (8,24). A shorter disease duration, better functional ability at discontinuation, and shorter symptom duration before starting any treatment were also predictive of successful discontinuation of bDMARDs (16). Our analysis of various clinical, radiological, biological and immune variables (Plasma TCZ level and ADAAb), identified only absence of FR and ACPA as being significantly associated with less flares.

Our study is mainly limited by the small number of included patients. As such, this preliminary analysis represents a “proof of concept”. In addition, our cohort was composed of patients with very severe disease (more than 75% with erosions, and long disease duration), none of whom had started TCZ as a first line of bDMARD. We also chose a very strict definition of remission in order to reduce the risk of relapse. The risk of relapse could likely be reduced by slowly tapering infusions. Indeed, the relatively quick tapering may be responsible of some relapses observed. We also found that plasma level of TCZ as well as ADAs were not useful to predict flares after TCZ tapering.

Conclusions
TCZ maintenance seems to be possible through progressive spacing of infusions in RA patients with sustained remission. Further studies should be conducted with a larger number of patients to confirm this hypothesis, and to identify factors identifying patients that could benefit from this strategy.

Abbreviations
ACR: American College of Rheumatology; ACPA: anti-citrullinated peptide antibodies; ADAAb: antidrug antibodies; bDMARDs: biological Disease Modifying Anti-Rheumatic Drugs; cs DMARDs: conventional synthetic Disease Modifying Anti-Rheumatic Drugs; EULAR: European League Against Rheumatism
LDA: Low disease activity; MTX: methotrexate; RA: Rheumatoid arthritis; RF: Rheumatoid factor; RTI: Retreatment interval; TCZ: tocilizumab; TNF-α: tumor necrosis factor α; US ultrasound

Declarations

**Ethics approval and consent to participate**

The study was approved by the local ethics committee (CPP IV Sud-Méditerranée, Montpellier, France) in accordance with the Helsinki Declaration and informed consent was obtained from each patient (NCT02909998; N°2008-A01087-48).

**Consent for publication**

Not applicable.

**Availability of data and materials**

Please contact authors for data requests (Pers YM, M.D, Ph.D - email address: ympers2000@yahoo.fr).

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contributions**

Conceptualization, Yves-Marie Pers; Investigation, Pierre Le Blay, Emma Rubenstein, Rosanna Ferreira Lopez, Thierry Vincent, Ahmed Larbi, Christian Jorgensen and Yves-Marie Pers; Methodology, Yves-Marie Pers; Formal analysis, Chayma Ladhari; Writing—original draft preparation, Chayma Ladhari and Yves-Marie Pers.; Writing—review and editing, all authors.

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Tables
Table 1: Baseline RA patients’ characteristics included in the study.
### All patients (n=13)

| Age, mean (SD), years; (min-max) | 48.23± 14.5, (21-67) |
|----------------------------------|-----------------------|
| Female, n (%)                   | 9 (69.2%)             |
| Disease duration, mean (SD), years; (min-max) | 11.46 ± 9.44; (2-36) |
| TCZ exposure before tapering, months (SD); (min-max) | 18.38 ±7.34; (5-29) |
| Remission achievement delay, months (SD); (min-max) | 2.38 ±2.63; (0-8) |
| Remission duration, months (SD); (min-max) | 7.53 ± 6.21; (3-24) |
| RF positive, n (%)              | 7 (53.8%)             |
| ACPA positive, n (%)            | 7 (53.8%)             |
| Erosive status, n (%)           | 10 (76.9%)            |
| Previous number of sDMARDs; (min-max) | 2.15 ± 0.9; (1-4) |
| Previous number of bDMARDs; (min-max) | 1.7 ± 1.18; (0-3) |
| Swollen joint count; (min-max)  | 0.08 ± 0.27; (0-1)    |
| Tender joint count; (min-max)   | 3.14 ± 3.4; (0-10)    |
| Hyperemia at Doppler            | 2 (15.4%)             |
| Number of patients with active synovitis | 7 (53.8%) |
| Number of active synovitis      |                       |
| Hands                           | 14                    |
| Feet                            | 5                     |
| Concomitant therapy             |                       |
| MTX, n (%)                      | 6 (42.9%)             |
| LEF, n (%)                      | 3 (21.4%)             |
| DAS28; mean (SD); (min-max)     | 1.65 ± 0.93; (0-2.6)  |
| ESR, mm/h; mean (SD); (min-max) | 7 ± 9.12; (1-27)     |
| CRP, mg/L, mean (SD); (min-max) | 2.21 ± 2.34; (0.2-7.4) |
| TCZ plasma level, mg/L; mean (SD); (min-max) | 7.35± 6.41; (0-16) |
| ADA positivity                  | 0                     |

RA: rheumatic arthritis, SD: standard deviation, n: number, TCZ: tocilizumab, RF: rheumatoid factor, ACPA: anti-citrullinated peptide antibodies, MTX: methotrexate, LEF: leflunomide, DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, ADA: antidrug antibodies
Table 2: Evolution of RA patients’ disease activity during the 24-months follow-up.

| Patient | DAS 28 | Day 0 | W6  | M3   | M6   | M9   | M12  | M18  | M24  |
|---------|--------|-------|-----|------|------|------|------|------|------|
| P1      | 1.76   | 3.14  | 2.43| 2.43 | 1.76 | 1.55 | 5.18 | 1.64 |
| RTI     | 4      | 6     | 6   | 6    | 6    | 8    | 8    | 6    |
| Dose    | 4      | 4     | 4   | 4    | 4    | 4    | 4    | 4    |
| P2      | 1.69   | 2.35  | 2.79| 2.89 | 2.69 | 3.14 | 1.34 | 2.13 |
| RTI     | 4      | 6     | 6   | 8    | 6    | 8    | 4    | 4    |
| Dose    | 8      | 8     | 8   | 8    | 8    | 8    | 8    | 8    |
| P3      | 2.4    | 2.07  | 2.57| 3.92 | 2.14 | 3.7  | 3.68 | 2.61 |
| RTI     | 4      | 6     | 6   | 8    | 4    | 4    | 5    | 4    |
| Dose    | 8      | 8     | 8   | 8    | 8    | 8    | 8    | 8    |
| P4      | 2.6    | 1.42  | 1.34| 1.94 | 1.05 | 1.12 | 3.35 | 1.49 |
| RTI     | 4      | 6     | 8   | 8    | 4    | 5    | 5    | 5    |
| Dose    | 8      | 8     | 8   | 8    | 8    | 8    | 8    | 8    |
| P5      | 2.58   | 2.6   | 1.61| 2.11 | 2.23 | 2.22 | 2.03 | 0.91 |
| RTI     | 4      | 6     | 6   | 7    | 8    | 8    | 9    | 9    |
| Dose    | 8      | 8     | 8   | 8    | 8    | 8    | 8    | 8    |
| P6      | 0.48   | NA    | 0.76| 1.37 | 0.28 | 0.28 | 2.22 | 1.84 |
| RTI     | 4      | 6     | 7   | 6    | 6    | 6    | 8    | 9    |
| Dose    | 8      | 8     | 8   | 8    | 8    | 8    | 8    | 8    |
| P7      | 1.61   | NA    | 2.57| 1.34 | 1.94 | 3.28 | 2    | 2.5  |
| RTI     | 4      | 5     | 8   | 8    | 8    | 8    | 8    | 8    |
| Dose    | 6      | 8     | 8   | 6    | 6    | 6    | 8    | 8    |
| P8      | 1.98   | 2.26  | 1.68| 2.14 | NA   | 1.81 | 2.42 |  | Secondary failure Switch to infliximab |
| RTI     | 4      | 6     | 6   | 8    | 8    | 8    | 4    | 4    |
| Dose    | 8      | 8     | 8   | 8    | 8    | 8    | 4    | 4    |
| P9      | 0.07   | 1.45  | 1.89| 1.89 | 1.12 | 0.76 | 0.76 | 1.12 |
| RTI     | 4      | 6     | 6   | 7    | 7    | 8    | 9    | 10   |
| Dose    | 8      | 8     | 8   | 8    | 8    | 8    | 8    | 8    |
| P10     | 1.38   | 3.2   | NA  | 2.85 | 2.45 | 3.71 |  | Secondary failure Switch to abatacept |
| RTI     | 4      | 6     | 4   | 4    | 4    | 4    | 4    | 4    |
| Dose    | 8      | 8     | 8   | 8    | 8    | 8    | 8    | 8    |
| P11     | 2.31   | 2.31  | 3.48| 0.85 |  |  | Neutropenia Switch to abatacept |
| RTI     | 4      | 5     | 6   | 4    | 4    | 4    | 4    | 4    |
| Dose    | 8      | 8     | 8   | 8    | 8    | 8    | 8    | 8    |
| P12     | 2.56   | 1.03  | 4.08| 3.51 |  |  | Secondary failure Switch to abatacept |
| RTI     | 4      | 6     | 6   | 4    | 4    | 4    | 4    | 4    |
| Dose    | 8      | 8     | 8   | 8    | 8    | 8    | 8    | 8    |
| P13     | 0      | 1.03  | 1.55| 2.57 | 5.35 |  |  | Secondary failure Switch to abatacept |
| RTI     | 4      | 6     | 6   | 8    | 6    | 6    | 6    | 6    |
| Dose    | 6      | 6     | 6   | 6    | 6    | 6    | 6    | 6    |

Dose: mg/kg, W: week, M: month, P: Patient, RTI: Retreatment interval, NA: not available

Table 3: Comparison between “successful long-term maintenance” group vs. “Secondary failure” group’s characteristics at baseline.
|                                | Secondary failure (n=4) | Patients with successful long-term maintenance (n=6) |
|--------------------------------|-------------------------|-----------------------------------------------|
| Age, mean (SD), years          | 60.75± 6.7              | 41.8 ± 15.23                                  |
| Female, n (%)                  | 2 (50%)                 | 4 (66.7%)                                     |
| Disease duration, mean (SD), years | 15±14.07               | 7.8 ± 4.35                                    |
| TCZ exposure before tapering, months (SD) | 19.5±7.23               | 14.8 ± 7.5                                    |
| Remission achievement delay, months (SD) | 3.5±3.4               | 2.16 ± 2.4                                    |
| Remission duration, months (SD) | 8 ± 5.7                 | 4.8 ± 2.13                                    |
| RF positive, n (%)             | 3 (75%)                 | 2 (33.3%)                                     |
| ACPA positive, n (%)           | 3 (75%)                 | 2 (33.3%)                                     |
| Erosive status, n (%)          | 4 (100%)                | 4 (66.7%)                                     |
| Previous number of sDMARDs     | 2.75±1.25               | 2 ± 0.63                                      |
| Previous number of bDMARDs     | 1.5±1.73                | 1.66 ± 1.21                                   |
| Swollen joint count            | 0                       | 0.166 ±0.4                                    |
| Tender joint count             | 2.25±2.6                | 3.16±4.57                                     |
| Hyperemia at Doppler           | 1 (25%)                 | 1 (16.7%)                                     |
| Number of patients with active synovitis | 1 (25%)             | 4 (66.7%)                                     |
| Number of active synovitis     |                         |                                               |
| Hands                          | 8                       | 4                                              |
| Feet                           | 0                       | 5                                              |
| Concomitant therapy            |                         |                                               |
| MTX, n (%)                     | 2(50%)                  | 2(33.3%)                                      |
| LEF, n (%)                     | 0(0%)                   | 2 (33.3%)                                     |
| DAS28; mean (SD)               | 1.48±1.1                | 1.51 ± 1.05                                   |
| ESR, mm/h; mean (SD)           | 7.5±11                  | 6.66±10.1                                     |
| CRP, mg/L, mean (SD)           | 2.55±3.3                | 3 ±1.87                                       |
| TCZ plasma level, mg/L; mean (SD) | 7.12±7.7               | 7.35 ± 6.41                                   |
| ADAb positivity                | 0                       | 0                                              |
| Flare, mean (SD)               | 2±0                     | 1±0.9                                          |

SD: standard deviation, n: number, TCZ: tocilizumab, RF: rheumatoid factor, ACPA: anti-citrullinated peptide antibodies, MTX: methotrexate, LEF: leflunomide, DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, ADAb: antidrug antibodies, NS: non
Table 4: Comparison between patients with one flare or less vs. patients with more than a flare.

|                                      | Patients with one flare or less (n=5) | Patients with more than a flare (n=8) | p-value |
|--------------------------------------|---------------------------------------|---------------------------------------|---------|
| Age, mean (SD), years                | 40.8 ±15.7                            | 52.9±12.5                             | NS:     |
| Female, n (%)                        | 3 (60%)                               | 6 (75%)                               | NS:     |
| Disease duration, mean (SD), years   | 12.4 ±8.7                             | 10.9±10.4                             | NS:     |
| TCZ exposure before tapering, months (SD) | 16.4±8.8                         | 20.4±5.7                               | NS:     |
| Remission achievement delay, months (SD) | 3 ±2.4                             | 2±2.8                                 | NS:     |
| Remission duration, months (SD)      | 5.6±2.8                               | 8.8±7.5                               | NS:     |
| RF positive, n (%)                   | 0 (0%)                                | 7 (87.5%)                             | 0.0     |
| ACPA positive, n (%)                 | 0 (0%)                                | 7 (87.5%)                             | 0.0     |
| Erosive status, n (%)                | 3 (60%)                               | 7(87.5%)                              | NS:     |
| Previous number of sDMARDs           | 1.8±0.8                               | 2.4±1                                 | NS:     |
| Previous number of bDMARDs           | 1.6±1.1                               | 1.75±1.3                              | NS:     |
| Swollen joint count                  | 0                                     | 0.125 ±0.3                             | NS:     |
| Tender joint count                   | 2.4±4.3                               | 3.6±2.97                              | NS:     |
| Hyperemia at Doppler                 | 0 (0%)                                | (37.5%)                               | NS:     |
| Number of patients with active synovitis | 3 (60%)                         | 4(50%)                                 | NS:     |
| Number of active synovitis           |                                       |                                       |         |
| Hands                                | 3                                     | 11                                    | N.S:    |
| Feet                                 | 2                                     | 3                                     | N.S:    |
| Concomitant therapy                  |                                       |                                       |         |
| MTX, n (%)                           | 3 (60%)                               | 3 (37.5%)                             | N.S:    |
| LEF, n (%)                           | 1 (20%)                               | 2 (25%)                               | N.S:    |
| Flare, mean (SD)                     | 0.6±0.5                               | 2.13±0.35                             | 0.0     |

SD: standard deviation, n: number, TCZ: tocilizumab, RF: rheumatoid factor, ACPA: anti-citrullinated peptide antibodies, MTX: methotrexate, LEF: leflunomide, NS: non significant