Dear Reviewers, you will find below our responses.

Best regards.

The authors.

Reviewer(s)’ Comments to Author:

Reviewer: 1

Comments to the Author
The authors have examined the reasons influencing the choice to use tocilizumab (TCZ) as monotherapy and compared the effectiveness of monotherapy and combination with csDMARDs in a prospective, open-labeled clinical trial including several centers in France. They found that age, disease activity, previous infections, and absence of use of MTX during the past 2 years influenced the use of TCZ as monotherapy. The effectiveness and safety was similar when using TCZ as monotherapy or in combination with csDMARDs, which mostly included MTX. The study is well performed and the results are clearly presented. The topic is not original and confirms previous results from clinical trials and cohort studies. The other weakness is the limited duration of follow-up. I have a few suggestions to improve the manuscript:

In the abstract it is important to mention the year when the study was conducted. Indeed, one of the factors influencing the use of TCZ as monotherapy is the calendar year.
The text was modified as follow:
“Amongst the 577 analyzed patients recruited from January 2012 to August 2013..”

Page 7. What is the meaning of “by physicians’ characteristics”? It would be useful to provide some details here.
The text was modified as follow:
“…physicians’ characteristics (i.e. sociodemographic, type and year of practice start, geographic location),”

Table 1. I was surprised to see that naive patients were included in the monotherapy group. Does it mean that these 2 patients were completely naive of any DMARD and received TCZ as a first therapy alone? This seems pretty awkward.
These 2 patients have been double checked and were really naïve of csDMARD. We think it is probably a patient’s choice or a contraindication.

Page 10. the reviewer does not understand why the authors suddenly use median values to describe RA duration whereas all other results including in Table 1 are presented as mean ± SD. Either the authors found that the distribution of values is not normal and thus should present all their results as median (IQR), including in Table 1, or if values are normally distributed they should use mean ± SD.

The median RA duration previously mentioned in the text was to give a supplemental precision.
The text was modified as follow:
“RA duration was longer in the MONO group when compared to the COMBO group with 45 % and 41% of patients presented with RA for more than 10 years.”
HAQ-DI is numerically higher in the MONO group. The authors do not describe this point in the results; why?

The text was modified as follow:

“At baseline, MONO patients presented with higher disease activity than COMBO patients (DAS28-ESR: 5.4±1.3 versus 5.0±1.2; CDAI: 29.3±13.7 versus 25.7±11.4; SDAI: 31.9±14.9 versus 27.2±12.1; HAQ-DI 1.66±0.63 versus 1.49±0.64; worsening of structural damage over the past 2 years: 51.4% versus 46.6%)”

Page 11. The heading: “Efficacy” is misplaced since the authors describe in the following paragraphs the factors influencing the use of TCZ as monotherapy

Efficacy is replaced by: “Explicative factors of the tocilizumab strategy (MONO or COMBO)”

Page 11. It would be useful to show the results of the Univariate analysis too.

The text was modified as follow:

In Study size and statistical methods: “Univariate analyses were used to select (p-value ≤ 0.10) the explanatory variables to include in the multivariate model then statistical significant (p≤0.05) or medically relevant parameters were retained for the multivariate model.”

In Explicative factors of the tocilizumab strategy (MONO or COMBO):

“Univariate Analyses
Univariate analyses conducted on observed data showed nine significant and medically relevant predictor parameters for the initiation of tocilizumab as monotherapy: patient’s age (±65 years: p=0.0026), RA duration (±15 years: p=0.0422), MTX within the two last years (p<0.0001), arterial hypertension (p=0.0560), pulmonary disease (p=0.0163), gastrointestinal disease (p=0.0626), past infectious disease (p=0.0817), dyslipidemia (p=0.0018), mean CRP or mean DAS28-ESR values (p=0.0024 and p=0.0018).”

Table 2. The results presented in parenthesis are sometimes confusing. It is better to always present the percentage for the whole group.

Table 2 has been modified

Page 13. To be consistent with Table 2, use 8.8% rather than 9% when describing the number of patients in whom a csDMARD was added.

The text has been modified.

Regarding changes in the use and dosage of glucocorticoids it would be useful to provide the results of the statistical analysis.

The results of the propensity score is included in the text. No other analyses have been performed.

Page 14. How did the authors handle the results in case of a change in csDMARDs. For example, in patients initially treated with TCZ as monotherapy was the introduction of a csDMARD considered as a treatment failure? It would seem logical to do so.

- Non-evaluable responses were considered as failure. Addition and/or change of csDMARD were not considered as treatment failure either in MONO nor in COMBO groups. Additional analyses for sub-groups of patients with or without csDMARD intensification are shown below:

Table: Clinical DAS28-ESR remission at M12 [Analysis population - Sub-population of patients without DMARD intensification (N=540)]

|                | Monotherapy N=208 | DMARD association N=332 | Total N=540 |
|----------------|-------------------|------------------------|-------------|
|                |                   |                        |             |
|                |                   |                        |             |
|                |                   |                        |             |
Monotherapy
N=208
DMARD
association
N=332
Total
N=540

DAS28-ESR remission (<2.6) N (completed patients)

|            | Monotherapy | DMARD association | Total |
|------------|-------------|-------------------|-------|
|            | N=208       | N=332             | N=540 |
| Missing data| 95          | 144               | 239   |
| No         | 44 (38.9%)  | 69 (36.7%)        | 113 (37.5%) |
| Yes        | 69 (61.1%)  | 119 (63.3%)       | 188 (62.5%) |

DAS28-ESR remission (<2.6) N (non assessable response = non response)

|            | Monotherapy | DMARD association | Total |
|------------|-------------|-------------------|-------|
|            | N=208       | N=332             | N=540 |
| Missing data| 0           | 0                 | 0     |
| No         | 139 (66.8%) | 213 (64.2%)       | 352 (65.2%) |
| Yes        | 69 (33.2%)  | 119 (35.8%)       | 188 (34.8%) |

Table : Clinical DAS28-ESR remission at M12 [Analysis population - Sub-population of patients with DMARD intensification (N=37)]

|            | Monotherapy | DMARD association | Total |
|------------|-------------|-------------------|-------|
|            | N=20        | N=17              | N=37  |
| DAS28-ESR remission (<2.6) N (completed patients)
|            | N=20        | N=17              | N=37  |
| Missing data| 8           | 6                 | 14    |
| No         | 2 (16.7%)   | 6 (54.5%)         | 8 (34.8%) |
| Yes        | 10 (83.3%)  | 5 (45.5%)         | 15 (65.2%) |

|            | Monotherapy | DMARD association | Total |
|------------|-------------|-------------------|-------|
|            | N=20        | N=17              | N=37  |
| DAS28-ESR remission (<2.6) N (non assessable response = non response)
|            | N=20        | N=17              | N=37  |
| Missing data| 0           | 0                 | 0     |
| No         | 10 (50.0%)  | 12 (70.6%)        | 22 (59.5%) |
| Yes        | 10 (50.0%)  | 5 (29.4%)         | 15 (40.5%) |

Maintenance rate which reflects both efficacy and safety was defined in 3 ways:

1. Using the Kaplan-Meier method, the rate of the maintenance at M12 of the initial therapeutic strategy (proportion of patients with no changes from initial treatment: tocilizumab used as monotherapy with no dose changes OR tocilizumab combined with a csDMARD with no modification of the csDMARD and without RoActemra® dose change) was 39% (CI 95%=[34;43]) and the associated median time until modification was 6.5 months (CI 95%=[5.6;7.9]). No differences were observed between MONO and COMBO patients.
When the rate of treatment maintenance at M12 was defined:

2. as the proportion of patients with no change in initial TCZ treatment until M12 (with no dose modification or discontinuation of TCZ), this rate was 50%, CI 95%=[46;54] (45%, CI 95%=[39;52] if TCZ monotherapy at inclusion and 53%, CI 95%=[48;58] if TCZ in combination). The median time until change was 12.1 months, CI 95%=[8.8;-] (8.4 months, CI 95%=[6.2;-] if RoActemra® monotherapy at inclusion and the median was not reached if RoActemra® in combination)

3. as the proportion of patients still treated with TCZ at M12, this rate was 69% [CI 95%=[65;73] (67%, CI 95%=[60;73] if TCZ monotherapy at inclusion and 71%, CI 95%=[65;76] if RoActemra® in combination). The median time until treatment discontinuation was not reached.
It is this last definition which has been chosen in the article as the most common. Eventually at M12, 16 patients of the Mono group had an associated csDMARD and 25 patients of the Combo group were receiving TCZ as monotherapy.

In order to make it clearer the text has been modified.

In **Study size and statistical methods**: “The rate of the maintenance of tocilizumab treatment (proportion of patients still treated with at M12, addition or intensification of csDMARD not taken into account) until M12.”

In **Efficacy**: “Using the Kaplan-Meier method, the median rate of retention in tocilizumab treatment until M12 (proportion of patients still treated with tocilizumab at M12 without csDMARD changes imputation) was 69%.”

**Page 15. Table 3**: ACR520 should read ACR50

The table has been modified.

Page 16. First paragraph: the authors should be more precise in their description. Were the results only numerically different or statistically different?

The text has been modified.

The ACT-RAY study showed that ALT and AST elevations were more frequent in patients treated with TCZ in combination as compared to as monotherapy. It would be interesting for the reader to know if this was also the case in ACT-SOLO? If the results are different this point should be discussed.

The text has been modified as follow:

In **Safety**: “At least one serious and/or medically significant hepatic event was reported in 24 patients (4%) without differences between MONO (3.8%) and COMBO (4.1%) patients.”

In **Discussion**: “Laboratory values were not systematically assessed during the study, and only reported when linked to an adverse event. This might explain the absence of difference between MONO and COMBO patients in reported hepatic events in contrast of what was shown in the ACT-RAY study. [32]”

**Reviewer: 2**

Comments to the Author

Idier and colleagues describe factors associated with choice of TCZ monotherapy using a large cohort of TCZ treated patients. They also show efficacy, drug attrition and safety data for MONO vs. COMBO treated TCZ patients. Patients with higher age, severe infections, intolerance to MTX and higher disease activity were more likely to receive monotherapy. Efficacy and safety was similar between MONO vs. COMBO treated TCZ patients. The paper is solid and the results interesting although not
entirely new.

Some points need further consideration:

- **P8** The text „At inclusion, RA and patients’ characteristics were generally less favourable...” is vague and should be rephrased.
  The text has been modified: “At inclusion, RA and patients’ characteristics were generally numerically less favourable in the MONO group (Table 1).

- When looking at the baseline differences between the two groups they seem to be rather minor, for instance with respect to DAS28 score (both slightly over 5 units). Do the authors think that these differences are clinically meaningful?
  Multivariate analyses showed a difference between the two groups. No other statistical tests were done for disease activity at inclusion between groups.

- Regarding MTX it is not quiet easy to understand: in the table it shows that virtually all patients in both groups received MTX (>90%), while in the text it is stated that only 52% received MTX during the last two years in the later MONO group, while almost 90% took MTX in the later combo group. Does it mean that the other 40% in the later MONO group were exposed to MTX more than two years before inclusion?
  Yes, the text has been modified to make it clearer: “Within the two last years, among the 543 patients having received MTX at least once, only 52% of MONO patients were treated with MTX while COMBO patients were 89% in this case”

- How do the authors explain that 8% of patients started csDMARDs in the MONO arm?
  The text has been modified as follow : “In the MONO group, 20 patients (8.8%) subsequently received csDMARDs at least once for insufficient response.”

- While 3 out 4 parameters associated with the use of MONO are conceivable the higher DAS28 being associated with preferential MONO seems a little counterintuitive. What is the explanation for this finding?
  This was described by Gabay et coll 2015, with Mono patients being older, more co-morbid, with longer disease duration, lower BMI, more active disease, and more previous bDMARDs and saying that “Patients treated initially in monotherapy may, thus, represent a subgroup of patients that is more difficult to manage”. And despite the age, comorbidities...or because of them, these patients may be the ones who less respond to MTX, which explains the higher disease activity.

- It is not entirely clear why the authors term this study „non-interventional study“. While I understand that patients were treated according to standards and TCZ was used as part of the clinical routine, the methods mention a sample size calculation, which intends that the study be planned a priori. I guess no randomization has been done and the decision which group was chosen was up to the treating rheumatologist. This should be mentioned more explicitly.
  The followed precision has been added: “non- interventional (i.e. observational)”

- The discussion could be streamlined.
  Some changes were done.