**Responses to Referee´s comments**

**Title: Biosimilar agents for psoriasis treatment: perspectives of Portuguese patients**

**Título:** Agentes biossimilares no tratamento da psoríase: perspetiva dos doentes portugueses

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First of all, the authors would like to thank the opportunity to clarify some points of the aforementioned manuscript, which led to some revisions, which in the authors´ opinion contributed to the improvement of the manuscript’ quality.

In the following pages the authors tried to respond in a detailed and itemized fashion to each of the referee´s comments.

**Reviewer A**

**Comment 1**

The new manuscript version is clearly structured, in many parts well written and accessible. Most of the issues raised in my first review were answered in a clear and satisfactory manner. In particular with regard to, the identification of the research design; the sampling technique; the inclusion and exclusion criteria; issues related with informed consent and approval by the ethics committee. The authors also provided the questionnaire as supplementary material, and applied the one sample chi-squared test as suggested. However, there are important issues which remain to be clarified with regard to statistical analysis and sample size determination.

As to the minimum size of the sample to be used, which should have been determined before starting the study, how was it calculated? It is not acceptable, in a study of this size, only to state in the manuscript that the sample is sufficient. Where are the calculations that underlie this statement?

* The target population of the questionnaire is “patients treated with biologic agents in our department (nearly 130)”. For a Population size of 130, a confidence level of 95% and a margin of error of 5% we need to interview 98 patients to get results representative of the target population. If we considered all Portuguese patients treated with biologic agents, the target population would not be enough. However, our department is a reference center for the treatment of psoriasis in Portugal, thus in our opinion may represent the Portuguese reality of the treatment of psoriasis with biologic therapies.

Even though, in the limitations section, we state that the patient sample is small and for that reason, generalization of findings warrants caution

The authors understand the reviewer comment but clearly feel that the results and conclusion this study are very interesting, represent the Portuguese reality in this issue and are of great importance for the scientific community that treat immune-mediated diseases, such as psoriasis.

**Comment 2**

Regarding the internal validation of the questionnaire, it might be important to provide Cronbach's alpha that allows us to evaluate the internal consistency of the responses given by the patients. Considering that the most important questions were five to nine, it is important that this coefficient be provided in the manuscript.

* We appreciate the comment of the reviewer about the internal validation of the questionnaire and Cronbach's alpha was calculated to evaluate the internal consistency of the responses given by the patients in questions five to nine.

Because Cronbach's alpha was 0.812, greater than 0.7, we can assume that these responses have relatively good internal reliability.

**Comment 3**

It remains unclear how the logistic regression models were adjusted. In this case, all results were omitted and no details were provided on how the statistical analysis was conducted to obtain them.

The sample size raises serious doubts about the possibility of regressions, especially when Enter method is used for selecting variables to enter the final model. In my opinion, the appropriate statistical methodology to make a regression, taking into account this sample size, is the following:

first, perform a univariate analysis, which in this case is an analysis of the association between the response variable and each of the variables demographic. This analysis can be performed using the exact chi-square test or through a univariate logistic regression.

Only then, a multivariate logistic regression model should be fitted, considering only the variables in whose univariate analysis was obtained p <0.250, and using the stepwise forward variable selection method instead of the enter method.

By adjusting a multivariate regression using the enter method, without first performing a univariate analysis, the final model will include variables without any interest, which reduces the accuracy of the results obtained, visible in the amplitude of the Odds Ratio confidence intervals.

If, in the univariate analysis, there are no associations whose p <0.250, then the multivariable logistic regression should not be performed at all.

Another important issue has to do with how the dependent variable was defined. The authors report that the dependent variable refers to the response of the patients, but several questions have been asked, for example, from five to nine, whose possible answers are five rather than two. I put this question because the logistic regression only allows considering the dependent variable as binary. How were the five possible values grouped, in order to transform the dependent variable into binary? Have lines (a) and (b) been grouped together, and then lines (c), (d) and (e)?

It is mentioned that only a logistic regression was performed, on which question, 5, 6, 7, 8 or 9? If all were considered then five logistic regressions were performed? This question was not clear in the article.

What about the independent variables, how categorical variables (questions 1, 2 and 3) were included in the regression? If more than two different values were considered, what was the reference class considered for each one? For example, as for education, four classes were considered or classes were grouped?

The fact that we have categorical variables with more than two classes, associated to the use of the Enter method, in a sample of this size, makes the results of a multivariate logistic regression very unreliable. It is very probable that we will have confidence intervals of infinite amplitude, which makes the use of this statistical methodology unfeasible. Without reference to univariate logistic regressions or chi-square association tests, I assume that the univariate analysis was not done, which should have been the appropriate analysis, before considering a logistic regression model in the first place.

* We take in to account the opinion of the reviewer about the appropriate statistical methodology and the definition of variables. We included the detail of the analysis in the article.

**Comment 4**

Finally, in the methods section, it was not stated that the tests were performed at a significance level of 5%.

* We included a statement in the methods section “Tests were performed at a significance level of 0.05”

As long as these questions are not clarified, I think the article still does not meet the conditions for publication.

Your sincerely

Tiago Torres