REVISOR A:

 [1]nas IL-12 e 23  
  
 [2]PSOLAR ?  
  
… limitada entre nós.  
  
 [3]Portugueses (maiúscula)  
  
 [4]Substituir ou por “nem” (> fluidez e compreensão do texto)  
  
 [5]Utilizado em simultâneo MTX  
  
 [6]Suprimir doentes (repetição)  
  
 [7]Suprimir the use of  
  
 [8]Incluir formalmente o design do study “retrospective…)  
  
 [9]Irrespective of height? O peso como medida absoluta e não o BMI ? Não  
seria possível trabalhar esse dado?  
  
 [10]Suprimir a 2ª ref a IL  
  
 [11]Suprimir the  
  
 [12]Parece-me texto mais perceptível e fluido…  
  
 [13]Colocar n=, processo de recolha, caracterizar os centros privado e  
publico, grande centros populacionais…)  
  
 [14]Suprimir “a”  
  
 [15]Não repetir regarding (supra)  
  
 [16]Redundante: adjuvante therapy…  
  
 [17]Esta frase não seria mais justificada no capítulo da discussão?  
Aqui, parece colocada “a martelo”…  
  
 [18]Não repetir inícios de frases ou parágrafos…  
  
 [19]Parece-me mais coloquial e fluido assim  
  
Os autores gostariam de agradecer as sugestões propostas pelo revisor, tendo sido todos os pontos sugeridos tidos em consideração e modificados. As modificações sugeridas (entre outras melhorias e reestruturações ao manuscrito) estão realçadas a amarelo na versão revista.

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Revisor B:  
  
-  
"Não foram observaram eventos..."  -> Não foram observados eventos...  
 (na pag 2, em "Resultados", linha 4)  
  
Os autores gostariam de agradecer a análise e os comentários do revisor. O erro assinalado foi corrigido na nova versão.  
  
  
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Revisor C:

The authors would like to thank the comments adressed by the reviewer.  
  
- The manuscript is well-written, requiring a minor English review (namely,  
the use of  decimal dot instead of a comma in decimals).

Decimal dots were inserted in all numeric data along the revised version of the manuscript.  
  
- Part of the discussion is interspersed within the results.

In the revised version of the paper, only a small consideration on the role of metotrexate in adjuvant therapy was left in the “results” section to help improve understanding, importance and relevance of immunomodulation association and data analysis.

- A reference to a previous Portuguese study may be included: Eur J  
Dermatol. 2018 Feb 1;28(1):89-91. Ustekinumab in patients previously  
treated with TNFa inhibitors: a real-life study.  
  
 A reference to this study was added in the revised version of the manuscript.  
  
  
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Revisor D:

Acho que faltaria fazer referência ao Estudo Phoenix II no parágrafo em  
que se reporta a importãncia dos protocolos de Intensificação e  
Optimização dos regimes terapêuticos, em doentes sob terapêutica  
biotecnológica com Ustecinumab. Sobretudo em "partial responders", com  
percentuais de melhoria PASI entre 50 e 75%.( 6).

Os autores gostariam de agradecer a análise e os comentários do revisor. A referencia assinalada foi introduzida na nova versão.

Considero ainda haver pouca informação sobre os hábitos de vida destes  
doentes( dieta? exercicio fisico diário?, tabagismo?  dificuldades  
económicas?), que são fáceis de conseguir e ajudariam a compreender  
eventuais e pontuais casos de perda de resposta ao longo do tempo, e mesmo  
falhas de compliance e persistência (adesão).  
  
   
Os autores compreendem e concordam com o comentário do revisor. No entanto, devido à natureza retrospetiva do estudo, parte dessa informação não estava disponível. Contudo, no manuscripto, é feita uma breve referência às comorbilidades cardiovasculares desta população de doentes, na qual, (para além do peso), não foi encontrada diferença ou significância de relação entre a sua presença e a falência terapêutica, motivo pelo qual informação mais alongada ou discussão não foi incluída.  
  
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Revisor E:

The authors would like to thank the comments adressed by the reviewer.  
  
-        Minor formatting changes  are needed. For instance in the  
third line of 3.1 there’s space between the sign and the numerical value  
 (± 15,2, range 2-71), while on line 4 of the same section, there is no  
spacing (±12,8, range 4-62). The same applies to PASI75 and PASI 75  
throughout the text.

Formating changes were made in the revised version of the manuscript.  
  
   
  
-        “The TRANSIT study demonstrated the benefit of dose  
escalation from 45 to 90 mg in patients weighting <100 kg who did not reach  
PASI 75 at week 28.16 Despite the low number of patients in each of the  
weight categories in our cohort of patients, it seems that the  
dosage-adjustment threshold may be set too high. The significance of weight  
in treatment efficacy underlines the importance of regular weight  
measurements in medical appointments in these patients, as previously  
suggested.9 “ – this is not a direct result of the study, but rather a  
point for discussion. I would suggest this to be moved to “Discussion and  
Conclusions” instead.

The authors agree with the suggestion made by the reviewer, and therefore changed this topic to discussion.

-        Two different notations are used throughout the paper n:  
…. /p: …. And n= …./ p=…  
  
I advise on harmonization to n=…/p=…. For instance on the 7th paragraph  
of 3.2 it should be read p=0.035 instead of p:0.035.  
  
 Formating changes were made in the revised version of the manuscript.  
  
-        In legend of figure 2, where it reads “standart”, it  
should read “standard” instead.  
  
Typo was corrected in the revised version of the manuscript.  
  
-        In figure 2, the scale of the y axis may be somewhat  
misleading as it starts on 75%. The visual difference between groups is too  
much for the absolute difference in magnitude.  
  
 The scale used in Figure 1 was intended to emphasize the differences between the groups, indicating with an asterisk when the difference is statistically significant. The authors, however, accept if the reviewer considers it important to graph the same data with the y-axis starting at zero.

-        In figure 1, there should be no Portuguese in the legend, as  
the paper is written in English. Therefore “Não naïve” should be  
replaced by “non-naïve).  
  
 Typo was corrected in the revised version of the manuscript.  
  
-        The vast majority of paragraphs of  the Results section  
begin with either “Regarding” or “Considering”. I suggest minor  
rewording of some of these to avoid becoming too repetitive.  
  
 Formating and typographical changes were made in the revised version of the manuscript.  
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Revisor F:  
  
  
 The authors would like to thank the comments adressed by the reviewer.  
  
Major comments:  
  
1) Sample characterization should include information concerning where the  
patients come from, ie, were all the patients coming from the northern  
region of Portugal, or from different parts of the country (in this last  
case, the number of patient from each region should be reported; e.g.,  
dividing them between northern, center, south). If the authors do not have  
access to this information, a statement disclosing that should be included.

The present work represents a retrospective analysis of the data collected from patients treated in Dermatology departments of Centro Hosp Porto and Laser Clinic of Belém. Because both centers receive patients from several geographic areas of the country, and since data from primary residence were not always available, nor considered important by the authors in the conception of “materials and methods”, such data has not been collected and is therefore not available for evaluation.

2) The answer to the previous comment (item 1) affects our considerations  
concerning sample size: the sample size presented herein is adequate for a  
simple centre or a two centre study; but if the study was performed in a  
large number of centres, the number of patients enrolled may not be  
adequate.

This represents a two centre study. A sentence highlighting this information was introduced in the revised version of the manuscript.

3) Also concerning sample characterization, the authors do not provide any  
information concerning the trial centre(s); was this a single centre study,  
or a multicentre study? Were all the patients treated within Centro  
Hospitalar do Porto, or some of them also treated in Lisboa (Centro Laser),  
etc? This information should be included and the number of patients from  
each centre should also be provided.

This represents a two centre study. A sentence highlighting this information was introduced in the revised version of the manuscript.

4) In the therapeutic response analysis section, the authors state that "The  
therapeutic response (defined as PASI75 or more) at week 4, 12, 24 and 52  
was recorded." But they report results concerning a 60-weeks group. Either  
correct the previous sentence or clarify.  
5) Figure 1 is missing the 60-weeks treatment duration. This data should be  
included.

The weeks chosen for data analysis are guided by weeks used in the analysis of therapeutic response in various experimental and observational clinical trials in psoriasis. Study data collected pointed to week 0, 4, 12, 24 and 52 because they represent weeks of frequent clinical evaluation in real life practice.

In addition to this, it was also collected the week at which the patient remained in therapy, whether that week was 60 or 180 weeks (as an observational study not all patients initiated treatment at the same time), allowing a perception of a protracted decline in efficacy, although it did not mean that this week was an important point of analysis or evaluation. Due to the fact that at week 60 there was no difference compared to week 52, and also because it was not the subject of the initial analysis, this week was only mentioned to demonstrate the persistence of therapy of the main cohort.

6) In the same section, the authors state that "Considering the treatment  
response according to patients’ weight (Fig. 2), a tendency to inferior  
clinical response was observed in patients weighting 90-100 kg. When  
patients under standard dose of ustekinumab were analysed, this difference  
was statistically significant at week 24 (p: 0.035)."  This is an  
interesting observation. However, the authors do not present data to support  
it. Thus, a simple correlation between body weight (x axis) and absolute  
PASI scores (y axis), for each treatment durations (4, 12, 24, 52 and 60  
weeks), should be provided to support this statement. Concerning this, the  
authors refer to the TRANSIT study, which was performed in french patients  
receiving also methotrexate, which clearly constitutes a confounding factor.  
Moreover, such correlation study constitutes e real novelty that will  
emphasize this manuscript's relevance.

Figure 2 displays the data supporting the mentioned observation.

7) Was there a statistical difference  concerning the number of patients  
achieving PASI75 score between different treatment durations? Again, data  
interpretation could benefit from comparison of absolute PASI score indexes  
between the treatment durations. Furthermore, from the authors data  
described in the text and depicted in figure 1, there seem to be a maximal  
effect achieved by 24 weeks, with no significant increase afterwards, in the  
majority of patients. This constitutes a major finding; therefore, should be  
included and discussed. If not, please clarify why.

Due to the fact that at week 60 there was no difference compared to week 52, and also because it was not the subject of the initial analysis, this week was only mentioned to demonstrate the persistence of therapy of the main cohort. As an intention to treat analysis, it would be incorrect to analyse and compare results of a small group of subjects that were on week 180 of treatment versus the main 116 patient cohort.

A maximal effect in the first weeks of treatment is established in literature, after which it plateaus, an effect common to all biologic drugs.

8) Concerning the itens 6) and 7), authors should rephrase Discussion and  
Conclusions Section.  
  
9) The authors report PASI75 response only up to the 60th week of treatment;  
however, they also mention some side effects on patients after 120 and 180  
weeks of treatment. Why the data concerning the 120th and 180th weeks of  
treatment were not reported?

The weeks chosen for data analysis are guided by weeks used in the analysis of therapeutic response in various experimental and observational clinical trials in psoriasis. Study data collected pointed to week 0, 4, 12, 24 and 52 because they represent weeks of habitual clinical evaluation in real life practice. In addition to this, it was also collected the week at which the patient remained in therapy, whether that week was 60 or 180 weeks (as an observational study not all patients initiated treatment at the same time), allowing a perception of a protacted decline in efficacy, but it did not mean that this week was an important point of analysis or evaluation. Due to the fact that at week 60 there was no difference compared to week 52, and also because it was not the subject of the initial analysis, this week was only mentioned to demonstrate the persistence of therapy of the main cohort. As an intention to treat analysis, it would be incorrect to analyse and compare results of a small group of subjects that were on week 180 of treatment versus the main 116 patient cohort that only achieved week 60.

10) A short sentence should be included to describe the statistical aspects  
of the work, i.e., which software was used, which statistical methods were  
applied and how results are presented (e.g., mean +/- SEM or mean +/-  
standard deviation).  
  
 Statistical aspects of the work were described in the revised version of the manuscript.  
  
Minor comments:  
  
1) Abstract in portuguese, Results, line 4: where one reads " Não foram  
observaram eventos cardiovasculares" it should read "Não se observaram  
eventos cardiovasculares". 

Typo was corrected.

2) All variables should be presented as mean +/- SEM or mean +/- standard  
deviation (as applicable), including body weight, BMI, drugs washout period,  
etc.

 Statistical aspects of the work were described in the revised version of the manuscript.