**Resposta às notas do editor do estudo AWARE 2 anos**

Comentário 1: Com o objectivo de optimizar a legibilidade do seu artigo e assim
incrementar potencialmente as citações do mesmo, recomendamos que os
conteúdos redigidos em inglês sejam revistos por  um "native speaker",
tradutor qualificado ou empresa especializada em serviços de "language
polishing".

Resposta: O artigo foi revisto por um “native speaker”.

Comentário 2: O resumo e o Abstract deve ser estruturado de forma paralela ao texto,
isto é deve incluir a discussão e a conclusão em separado.

Resposta: o resumo e abstract foram alterados por forma a incluir a discussão e conclusão em separado.

Comentário 3: Não devem ser utilizadas abreviaturas no abstract e no resumo.

Resposta: as abreviaturas foram eliminadas do resumo e abstract.

**Resposta aos revisores do estudo AWARE 2 anos**

Revisor A comentário 1: Na tabela 1 ao testar a associação entre a utilização de recursos
medicos e o tempo da intervenção por vezes não estavam cumpridas as
regras de cochran pelo que em vez do teste do qui-quadrado devia ter sido
usado um teste exato como por exemplo o teste de fischer.

Resposta: A Tabela foi corrigida apresentando agora os valores de p do teste de Cochran’s Q, que foi o utilizado por ser emparelhado.

Revisor A comentário 2: O termo correlação não é o mais correcto para se referir á eventual
relação de UAS7 e presença de angioedema.

Resposta: O termo correlação foi substituído pelo termo associação que é o termo correcto neste contexto.

Revisor A comentário 3: Na fig 2 e 3 a legenda não é muito intuitiva para se perceber a que
diferenças o autor se refere com \*, \*\* e \*\*\*.

Resposta: A legenda da fig. 2 foi corrigida por forma a clarificar as diferenças entre \*, \*\* e \*\*\*. A legenda da fig. 3 apenas tem \*.

Revisor B

Todas as sugestões feitas pelo revisor ao longo do texto do artigo foram incorporadas e as referências corrigidas.

Comentários pág 11:

1- Como explica a utilização de corticoides orais neste grupo de doentes (10,8% baseline)?

2- Como explica o aumento de corticoides orais (8,2%) no 2º ano de tratamento, quando no 1º ano de tratamento tinha ocorrido um descrécimo (1,8%) ?

Resposta: De acordo com as recomendações, é lícito fazer em SOS um ciclo curto de corticóides, em qualquer que seja o degrau de terapêutica em que o doente esteja. Sendo a urticária uma doença flutuante, com exacerbações e remissões, muitas vezes sem factores desencadeantes aparentes, poderá ter coincido que tanto na baseline com no 2º ano de tratamento os doentes estavam em exacerbação aquando da visita em causa. Estes dados foram acrescentados ao artigo, na página 10 – “Approximately 11% of patients were under corticosteroid therapy at baseline, 1.8% at year 1 and 8.2% at year 2.” – e a justificação foi acrescentada na discussão, na página 13 – “Regarding corticosteroid therapy, and according to current recommendations, a short course of corticosteroids can be prescribed as relief therapy, regardless of the line of therapy the patient is under. Since urticaria is not a stable pathology, oscilating between exacerbations and remissions, often without apparent triggering factors, the percentage of patients on this therapy at baseline, 1 year and 2 years may reflect the different exacerbation or remission phase the patient was experiencing when the visit occurred.”

Reviewer C, commentary 1: Acknowledgments: Is any financial support declared?

Answer: Yes. The financial support is declared under “Funding”.

Reviewer C, commentary 2: Are any conflicts of interest declared? It is a Pharma sponsered study. Only two authors from a numerous group of investigators.

Answer: The Conflicts of interests section stated that “The authors declare collaborating and receiving fees from Novartis and other pharmaceutical companies either through participation in advisory board or consultancy, congress symposia, clinical trial conduct, investigator-initiated trials or grants.”

However, since two of the reviewers considered this declaration insufficient, we have asked all authors to specify their individual conflicts of interest. These are still not completely reflected on the paper since we are waiting for some authors to answer.

Reviewer D

1. **In the Portuguese abstract** is stated:
	1. “Material e Métodos: Coorte não intervencional, prospectiva,…”

I think it would be more correct to state: “Estudo de coorte, observacional, prospectivo,…”

Answer: the abstract was changed accordingly.

* 1. “A gravidade dos sintomas de urticária, …. embora o DLQI apenas tenha sido significativo aos 2 anos.”

I think it would be more correct to state: “A gravidade dos sintomas de urticária, …. embora a diminuição no DLQI apenas tenha atingido significado estatístico no 2º ano.”

Answer: the abstract was changed accordingly.

* 1. “A UC ainda demonstrou ter impacto no DLQI, mostrando que a terapêutica pode ser optimizada”

I think it would be more accurate to state: “Ainda poderá ser optimizada”

Answer: the abstract was changed accordingly.

1. **In the section Materials and Methods**, subsection Setting and participants we can read:
	1. “The AWARE study was a worldwide non-interventional international multicenter study conducted in 36 countries.”

In my opinion this statement should be made in the subsection “Study design”

Answer: According to the STROBE guidelines it is our understanding that this statement should be in this subsection, similar to the AWARE baseline publication[1](#_ENREF_1).

“Inclusion criteria were: written informed consent of the patient to participate in the study; age 18 years or more; medically confirmed diagnosis of CU present for more than 2 months; refractory to treatment with standard dose of H1-AH. Exclusion criteria were: anticipated difficulties of follow-up during at least two years; participating in any other clinical urticaria study.

Grammatically we should read: “Inclusion criteria were: written informed consent of the patient to participate in the study; age 18 years or more; medically confirmed diagnosis of CU present for more than 2 months; refractility ~~refractory~~ to treatment with standard dose of H1-AH. Exclusion criteria were: anticipated difficulties of follow-up during at least two years; participation ~~participating~~ in any other clinical urticaria study.

Answer: the text was changed accordingly.

1. **In the section Materials and Methods**, subsection Methods of assessment we can read:

Patient Reported Outcomes (PROs) – UAS72-7 and DLQI5,8,9 ­– were filled by patients weekly during the consultation

I would like to ask if the patients were weekly observed during the two years?

Answer: No. In this cohort, study variables were collected at baseline, 1 year and 2 years, during a follow-up period of two years. Text was changed to: “[…] were filled by patients daily on the week before the consultation (UAS7), DLQI was filled during the consultation and scores were introduced on the eCRF.”

1. **In the section Results**:
	1. Subsection –participants- we read: “Of the 5,237 patients included worldwide in the AWARE study, the 76 patients included in the study in Portugal were analyzed. Not all data were available for every patient. All tables and figures state the number of patients with data available for each analyzed variable. Missing data were considered to be Missing Completely at Random (MCAR).”

Substitute: the 76 patients included in the study in Portugal were analysed” for “the 76 patients included in the Portuguese cohort were analysed”

Answer: the text was changed accordingly.

Comment: It would be important to state here how many patients were enrolled in the study, how many were lost for follow-up and how many had all the data available

Answer: This information was included in this subsection.

* 1. Subsection -The percentage of patients with omalizumab therapy almost duplicated after 2 years of the AWARE study– we read:

“According to the guidelines at the time of the study, third line therapies included omalizumab, montelukast or ciclosporin2-4,7,8,10-13, although the 2017 revision of the EAACI/GALEN guidelines have changed the recommendation of third line therapy to include only omalizumab14.”

This has already been said so you may cut it and it doesn’t belong to the results.

Answer: this sentence has been deleted.

* 1. Subsection -Medical resources utilization and absenteeism decreased after 2 years of the AWARE study– we read:

“Over the 2 years of this study, there was a significant decrease of all the resources used from baseline to years one and two, with…”

You should standardize. Either you write everything in numbers or you spell them

Answer: the whole paper has been standardized regarding this issue. The authors have chosen to keep the numbers.

“There were no changes from year 1 to year 2.”

Suggestion: “There were no significant changes between year 1 to year 2.”

Answer: the text was changed accordingly.

* 1. Subsection -Urticaria symptoms decreased after 1 year and impact on QoL decreased after 2 years: UAS7 and DLQI evaluation– we read:

“..-compared to baseline and year 1. UAS7 did not … At the end of 2 years, 79.0% of patients …”

Suggestion: “..-compared to baseline and ~~year 1~~ to year 1. UAS7 did not … At the end of the second year ~~2 years~~, 79.0% of patients …”

Answer: the text was changed accordingly.

1. **In the section Discussion:**

“Although CU is a relatively common pathology,….of the AWARE Portuguese Cohort patients patients, in a real-world context and It reflects reflects the resources allocated …”

Suggestion: “Although CU is a relatively common pathology,….of the AWARE Portuguese Cohort patients, in a real-world context and It reflects the resources allocated …”

Answer: the text was changed accordingly.

The percentage of patients treated with this monoclonal antibody at baseline was 28.9% and almost duplicated at year 2 to 55.1%. The percentage of patients under omalizumab at baseline was similar to the percentage reported in the AWARE baseline of German patients (21.4%); however it seems to be different at year 1 and year 2 where the reported percentages were 27.6% and 31.4%, respectively15,16.

This Sentence is not clear, you should rewrite it

Answer: the sentence was rewritten and now reads: “In the Portuguese cohort, the percentage of patients treated with omalizumab at baseline was 28.9% and almost duplicated at year 2 to 55.1%. The percentage of patients under omalizumab at baseline was similar to the percentage reported in the AWARE German cohort (21.4%). However, it seems to be higher in our cohort at year 2: 55.1% vs 31.4%.”

* 1. It is expected that about 40-70% of the CU patients attending urticaria specialized centers will become symptom free with first line therapy (H1-AH once daily).

But in your case the patients were mainly referred to specialized centers and you state that this is the most probable reason for the high percentage of patients treated with omalizumab (55%). How do you explain this contradictory conclusion?

Answer: The sentence has been changed and now reads: “Although the current standard therapy with standard doses of H1-AH is still the mainstay of treatment for CSU, it only leads to an absence of symptoms in <50% of patients, and even increasing the dose still leaves approximately 30% of patients symptomatic. Omalizumab has been a major breakthrough in the care of these patients[2](#_ENREF_2)”.

* 1. At year 2 the mean UAS7 further decreased to the level of *well controlled disease*, statistically different from baseline and year 1.

It would be interesting to compare your results with the results from the other groups as you did for other variables.

Answer: Comparisons have been added: “These results are in line with other AWARE reports that show a decrease in total mean UAS7 score in CSU patients from baseline to year 2, suggesting an improvement in disease control[3-5](#_ENREF_3), and reaching the level of *well controlled disease* at year 2[4](#_ENREF_4),[5](#_ENREF_5).”

Revisor F:

This is a very interesting study on real-life patients with chronic
urticaria (CU), in a certain way the continuation of the previous study
referring to the demographics of patients recruited to this study (Ref 26).
Nevertheless, there are some aspects that need clearing and some repetitions
could be removed (it is at least twice referred that Omalizumab if the 3rd
line and ciclosporin the 4th line therapy, and refeed what is measured by
UAS7)

Answer: the repetitions have been removed when they did not change the context of the sentence.

It might be important to refer how many of the 76 patients were lost to
follow-up and how many were evaluated after 1 year and after 2 years. It is
possible that some parameters are missing as for UAS7 (only 41) and DLQI
(only 30), but certainly some patients were completely lost.

Answer: This information was included in the Results section.

It is important to refer to the period evaluated (1 week / 1 month/ 2 months before evaluation) when considering the working days lost/ healthcare resources. How is it possible that after 1 and 2 years "Our results revealed that over this study, at year 1 and year 2 no patients lost work-days due to CU."- Not even to attend medical consultations? Or for administrations of omalizumab that at this period had to be performed at the Hospital?

Answer: The sentence has been change to clarify this issue: "Our results
revealed that over this study, at year 1 and year 2 no patients lost work-days due to CU, except to attend medical consultations or for administrations of omalizumab, but not due to disease severity."

If the improvement is so evident and DLQI does not change so significantly
it might be a reason to refer to the most specific PRO that measures QoL in
urticaria (CuQ2oL) that is better to measure the impact of CU control on
HRQoL.

Answer: CuQ2oL is indeed more specific for urticaria. However, at the time of the study, it could not be used because it was not validated for the Portuguese population. The following sentence was added: Neither UCT (Urticaria Control test) nor CuQ2oL were used because, at the time of the study, they were not validated for the Portuguese population[6](#_ENREF_6),[7](#_ENREF_7).”

In the methods (pg 11) it is important to refer that UAS7 measures urticaria
activity not urticaria symptoms (wheals are not symptoms).

Answer: symptoms were replaced by disease activity.

In the discussion it may not be correct to report that UAS7 is not correlated with angioedema or CIndU as this is not at all adequate to measure neither activity of angioedema nor CIndU.

Answer: the word “correlation” was replaced by “association”, which is the correct term in this context.

When referring to the factors that impact on Health-related QoL apart from itch and unpredictability of disease it is important to refer angioedema and concomitant CIndU.

Answer: The sentence was changed to refer angioedema and concomitante CIndU.

When comparing Portuguese AWARE data with those from other european
countries it might be important to include France, even though they have
only initial data published.

Answer: several comparisons with other AWARE cohorts have been introduced.

COIs need to be more clear and specified for each author – "The authors
declare collaborating and receiving fees from Novartis and other pharmaceutical companies (which ones?) either through participation in advisory board or consultancy, congress symposia, clinical trial conduct, investigator-initiated trials or grants"

Answer: Since two of the reviewers considered this declaration insufficient, we have asked all authors to specify their individual conflicts of interest. These are still not completely reflected on the paper since we are waiting for some authors to answer.

In the abstract please refer that what is significant is the reduction of
DLQI, not DLQI  – "... o impacto na Qualidade de Vida, avaliado pelo DLQI, diminuíram após um ano e continuaram a diminuir aos dois anos, embora REDUÇÃO Do DLQI apenas tenha sido significativo aos 2 anos."

Answer: the abstract was changed accordingly.

In the introduction it is not very clear what the authors mean by
"existing international guidelines show disparities regarding the tests
and exams that should be applied to investigate possible etiologies or
factors that could lead to CU worsening1-8."

Answer: this sentence has been removed.

When referring to the changes in International guidelines from 2014 to 2018
the removal of montelukast should also be referred.

Answer: the sentence was changed to incorporate the removal of montelukast.

When referring to the baseline it is better to clear that "Only 29.3% of
patients had a well-controlled urticaria at enrollment, measured by UAS7.”

Answer: The sentence has been changed accordingly.

In page 10/11 I would remove: . According to the guidelines at the time of
the study, third line therapies included omalizumab, montelukast or
ciclosporin2,4,5,7,8,10,11,13,14, although the 2017 revision of the EAACI/GALEN guidelines have changed the recommendation of third line therapy to include only omalizumab1. – Also it is not clear why there are so many references in this sentence following ciclosporin.

Answer: References have been removed and only the 2014 EAACI/GA2LEN guideline[8](#_ENREF_8) was maintained.

Use always the same spelling for cyclosporin/ciclosporine (!!!)

Answer: this has been corrected.

Please clear in the limitations: "If patients were not previously diagnosed with CU or were followed only in the private setting they have not been included**."**

Answer: Given the inclusion criteria, this sentence was redundant. Sentence was changed.

Revisor G:

1. (page 9, line 2) How many questions does the questionnaire have?

Answer: UAS has two items. UAS7 is a registry of these 2 items throughout 7 consecutive days.

2. (page 9, line 3)Which category did you put e.g. 0.5, since UAS7 outcome is continuous?

(page 9, line 7) Which category did you put e.g. 1.5, since DLQI outcome is continuous?

Answer: Both UAS7 and DLQI can only assume integer numbers. However, both variables are considered continuous and statistical analyzed as such. Some examples are[1-5](#_ENREF_1),[9-22](#_ENREF_9).

3. (page 10, line 6) Put "variables" instead of "data". (page 10, line 12) Put "23.6%" instead of

"23.7%". (page 11, line 6) Put 30.8% instead of 28.9% (vide Figure 1).

Answer: These corrections have been made.

4. (pages 11, lines 8-18) These results from Table 1 (page 25) were obtained by employing

Pearson's chi-squared test to compare two "independent" groups. However, that assumption

of independence does not happen here since e.g. the 56 individuals observed at 1st year are

the same ones previously observed at baseline time. So, the authors must remove these

inferential results.

Answer: The table legend was incorrect and one of the p-values was also incorrect. Both have been corrected.

5. (page 11, line 23) I suspect that the previous comment also covers the comparison of two

means in Figures 2 and 3. But for that it would be necessary for the authors to make it clear

which tests, mentioned previously (page 9, lines 20-22), were used in obtaining each of these

results. For instance, the Kruskal–Wallis test is used for comparing two or more independent

samples, while the Mann-Whitney U test is often used when the assumptions of the

independent samples t-test are violated.

Answer: We have clarified in the figure legends that the Friedman test with correction for multiplicity has been used.

6. (page 14, line 23) Display the p-values when it is concluded that there is statistical significance. By the way, it would be better to put these results in the Results section.

Answer: p-values have been added throughout the text.

7. (page 15, line 9) What does joint analysis mean? I did not see the related explanation in the

Methods section.

Answer: Joint analysis means that all types of CU were assessed together, not separating CSU from CIndU. Since when separated analyses were done this is clearly indicated, we have removed the term “joint” for clarity.

8. For the continuous outcomes, a multivariate analysis of variance (independent samples) or

an equivalent method for dependent samples is the most appropriate statistical analysis for

these longitudinal data instead of testing two groups at a time.

Answer: the statistical analysis section has been changed and is now more clear.

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