PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Hymenoptera venom allergy: work disability and occupational impact of venom immunotherapy
AUTHORS	Paolocci, Giulia; Folletti, Ilenia; Torén, Kjell; Muzi, Giacomo; Murgia, Nicola

VERSION 1 - REVIEW

REVIEWER	giovanni passalacqua Allergy and Respiratory Diseases University of Genoa, ITALY
REVIEW RETURNED	28-May-2014

GENERAL COMMENTS	In this paper, the Authors explored a special and poorly quantified aspect of hymenoptera venom allergy, that is the impact on working condition, including working disability, and the possible effects of venom immunotherapy on this aspect. 81 subjects with a history of HVA were included and evaluated by an occupation-oriented questionnaire. They were also stratified according to risk level. MAJOR COMMENTS In general, it is not clear what this study aimed to demonstrate. Either the epidemiological distribution of hymenoptera allergy within at-risk workers, or the efficacy of VIT, or the combined effect. I would like to see a more well detailed description of aims, outcomes, and results. Methods. Was the diagnostic procedure the same, and with the same reagents, throughout the spanned period? Please provide at least some details on reagents and VIT extracts. Was the same extract used in all patients for a given insect? Methods. The desensitization protocol is vaguely described. For instance, how many weeks for the induction phase? Same extract for all patients? Also, it is not clear if the study was designed to assess the occurrence of work disability, or the effect of VIT. This should be clearly stated in methods. It is not clear to me how were the questionnaire items selected? Panel of experts? Literature? Both. This must be specified, since the quetionnaire is neither validated nor previously described at all. Page 5, row 8-9. How was a “financial loss” defined? Table 2 is hard to interpret. Also, 183 patients are mentioned in the first row, whereas the sum (44+44+93) is 181. MINOR COMMENTS What this paper adds, 3rd point. There is no evidence that adherence to VIT must be improved. In this regard also ref 5 quoted in the introduction is misleading, since it concerns a guideline, not to an experimental trial on adherence. The discussion is overlong, and often not pertinent to the results of

	the study.

REVIEWER	Patrizia Bonadonna Allergy Unit AOUI Verona
REVIEW RETURNED	29-May-2014

GENERAL COMMENTS	The idea of this study could be good but there are some mistakes and inaccuracies: 1) Is not very clear how the patients has been enrolled 2) The survey used is very poor with very few questions and thhese questions are not clear 3) The final message is not very clear 4) There is a very important bias: the survey are adminsitered also in patients who already started the immunotherapy

VERSION 1 – AUTHOR RESPONSE

Reviewer 1.

ANSWER TO MAJOR COMMENTS:

Q1.1 In general, it is not clear what this study aimed to demonstrate. Either the epidemiological distribution of hymenoptera allergy within at-risk workers, or the efficacy of VIT, or the combined effect. I would like to see a more well detailed description of aims, outcomes, and results.
A1.1 The primary aim of this study is to evaluate the prevalence and predictors of work-disability in a group of patient treated with Venom Immunotherapy (VIT). The secondary outcome was to assess the effects of VIT on occupational functioning. We not aimed to have an epidemiological distribution within at risk workers, because this has been already studied previously. Anyway we have changed our aims section to be more clear and straightforward as the reviewer rightly suggested.
Q1.2.Was the diagnostic procedure the same and with the same reagents throughout the spanned period? Please provide at least some details on reagents and VIT extracts. Was the same extract used in all patients for a given insect?
A1.2. We absolutely agree that this is an important point to clarify. We have added information regarding diagnostic procedure and VIT extract in the method section. Moreover we have added the distribution of subjects with work disability according to type of extract used for VIT (aqueous or depot) in table 1. In detail the diagnostic procedure used to identify a patient with hymenoptera venom allergy was the same for all our subjects (included patients that have concluded VIT), following the EAACI statement on diagnosis of Hymenoptera Venom Allergy. The extract used for the diagnostic procedure was from Stallergenes (Antony, France), while the extract used for VIT were from Stallergenes (Antony, France), Alk-Abello (Hørsholm
Denmark), Anallergo (Firenze, Italy).
Q1.3 The desensitization protocol is vaguely described. For instance, how many weeks for the induction phase? Same extract for all patient?
A1.3 This point is right, we appreciate very much this comment and we have added more information about desensitization protocol in the methods section.
Q1.4 Also, it is not clear if the study was designed to assess the occurrence of work disability, or the effect of VIT. This should be clearly stated in methods.
A1.4 Please refer to answer 1.1
Q1.5 How were the questionnaire items selected? Panel of experts? Literature?
A1.5 The definition of work disability was formulated on the basis of previous surveys about work disability, widely available in the literature. Questions about VIT impact on work were discussed

among a panel of allergologists and occupational physicians. We have added this description in the methods section.
Q1.6 How was a financial loss defined?
A1.6 We agree that the term of “finanacial loss” could be misleading, so we change financial loss in economic loss, which was the original definition, based on the questionnaire answer “Did you suffer economic loss because of Hymenoptera sting reaction?”. Furthermore we also asked for the amount of economic loss in euro/year. Anyway we did not add this information on the paper because it is strongly related to the patient occupation.
Q1.7 Table 2 is hard to interprete.
A1.7 We agree, so we decide to remove the table. 183 is a typo error.
MINOR COMMENTS
Q1.8 There is no evidence that adherence to VIT must be improved. In this regard also ref 5 quoted in the introduction is misleading, since it concerns a guideline, not to an experimental trial on adherence.
A1.8 We agree on this remark, so we have changed conclusions and removed it from the section “ what this paper add”.
Q1.9 The discussion is overlong, and often not pertinent to the results of the study.
A1.9 We have reviewed the discussion section trying to make more concise and pertinent.
Reviewer 2
Q2.1 Is not very clear how the patients has been enrolled
A2.1 We have considered first all the 364 patients treated with immunotherapy for hymenoptera venom allergy from 1997 to 2011 at the Perugia University Hospital, Italy. After excluding patients retired at the time of insect sting or VIT, students and housewives, we reached the final number of 181 patient actively working at the time of insect sting and during VIT.
Q2.2 The survey used is very poor with very few questions and thhese questions are not clear
A2.2 The question reported in the methods section are just the “key questions” and they do not represent all the questionnaire. In any case, the aim of this study was just to assess work disability among patients treated with VIT for hymenoptera venom allergy, and as a secondary outcome the impact of VIT on work. The questions about work disability were taken from previous surveys, as it is stated in the method section.
Q2.3 The final message is not very clear
A2.3 in the revised form of the manuscript we try to make the final message more clear and straightforward.
Q2.4 There is a very important bias: the survey are administered also in patients who already started the immunotherapy
Q2.4 The aim of this study was to assess work disability due to hymenoptera venom allergy in patient in treatment or treated with VIT, therefore the questionnaire is administered only in patients undergoing or that have been previously treated with VIT. We agree that a longitudinal study on work disability with a questionnaire administered prior to VIT, during VIT and at the end of VIT could be more informative, but the number of new subject treated in our centre did not allowed this type of longitudinal study. We are very open to any kind of further scientific collaboration, especially in a multicentre survey, which could increase the number of subjects, allowing also this kind of longitudinal approach.

VERSION 2 – REVIEW

REVIEWER	giovanni passalacqua allergy and respiratory diseases university of genoa italy
REVIEW RETURNED	02-Jul-2014

GENERAL COMMENTS	The Authors have satisfactorily addressed my technical questions , adding information on extracts, diagnostic procedures, and desensitization protocols. This is in line with current clinical practice and guidelines, and can be accepted in a real-life setting. The changes have of course improved the quality of the article. In addition table 1 has been improved and one table removed. Nonetheless, the objective of the study as expressed remains partially unclear. As described, it seems that there is a correlation between VIT and financial loss and a work-disability, and this would sound strange since VIT exerts a well demonstrated protective effect. Probably, the Authors should better specify that patients receiving VIT were chosen because they had had important reactions to hymenoptera (indication to VIT) The statement that a quantification of the economical impact is not ethical, is not reasonable. In fact there is no need to have absolute figures in euros, but a % of loss (after/before) would be an indicative parameter.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1.

ANSWER TO FURTHER COMMENTS:

Q1.1 As described, it seems that there is a correlation between VIT and financial loss and a work-disability, and this would sound strange since VIT exerts a well demonstrated protective effect. Probably, the Authors should better specify that patients receiving VIT were chosen because they had had important reactions to hymenoptera (indication to VIT)
A1.1 We agree with the reviewer that this finding would sound strange, but, as we added now in the discussion section, the awareness about the risk of severe systemic reaction was not homogenous in our group of patient. This condition would create a room for further improvement, making more widespread in our patients the knowledge of severe reaction and the role of VIT in prevent this risk and improve the quality of life

Q1.2. The statement that a quantification of the economical impact is not ethical, is not reasonable. In fact there is no need to have absolute figures in euros, but a % of loss (after/before) would be an indicative parameter.
A1.2. We thank the reviewer for this important suggestion and we agree that the percentage change would a better indicator than the absolute loss in euro, but unfortunately we have not this data. This was another reason to not present the data about absolute loss in this final version of the manuscript.