PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Knowledge, attitude and practice of healthcare professionals towards infliximab and insulin glargine biosimilars: Result of a UK web-based survey
AUTHORS	Chapman, Stephen; Fitzpatrick, Raymond; Aladul, Mohammed

VERSION 1 - REVIEW

REVIEWER	Kimme Hyrich The University of Manchester, UK
REVIEW RETURNED	23-Mar-2017

GENERAL COMMENTS	This is an interesting and timely survey as the introduction of biosimilars is rapidly changing practice, particularly in the specialities included in this survey and also highlights areas where more research is needed. I have a few comments on the report: Introduction: I would argue that at the time of license of biosimilars there was not a “wealth of clinical and scientific literature”, at least for infliximab for which there had been clinical trials in new users but no data on originator to biosimilar switchers and the EMA approval was based primarily on data from new users only. Similarly, the drugs do not require trials in all indications and a blanket indication mapping the originator product is often granted. These factors may contribute to the concerns raised by the survey respondents and should be highlighted. The sentence stating that branded monoclonals such as adalimumab, rituximab and trastazumab now have competition is confusing as at the time of this paper, not all of these drugs are off patent and rituximab has a licensed biosimilar. Please clarify. Methods: Would be good to map the survey dates in direct relation to when these drugs were licensed and available for use. Results: Your survey response is very low. Even though you don’t know the direct number of possible respondents, it is estimated there are around 500 rheumatology consultants and ~1000 Gastro consultants in the UK, so your survey, which also includes registrars, will have maybe tapped into <10% of these. This should be discussed further as a limitation. What does daily or weekly biosimilar prescribing mean? Is this writing a prescription every day or seeing patients receiving biosimilars every day, for example.

	Your description of Figure 4 doesn't match with the data, which suggests that rheumatologists had concerns about safety and efficacy of switching, but if I understand this did not necessarily inhibit their use, which was a different choice of answer. Please clarify. Discussion: One of the challenges of this survey is that fact that it is being published during a period of active increase in biosimilar use, particularly in rheumatology and dermatology. The survey took place over the same period when the etanercept biosimilar was being introduced and prescribed for the first time. Rheumatology is not a big user of infliximab, unlike gastroenterology so most rheumatologists may have had limited or their first experience with biosimilars at the time of this survey and opinions will change once physicians gain more experience. Therefore there is some limitation in directly comparing the results of this survey with other similar surveys which may have been done at different times, some even before the introduction of biosimilars for some specialties. Perhaps this could be helped by dating some of the comparisons made in the discussion and also stressing the need to repeat this survey in even 1-2 years' time to see if regular use of drug changes attitudes. You comment that the BSG position statement was quite encouraging towards biosimilar use. Did this differ from say the BSR or BAD statement. I agree with your postulate that more pharmacovigilance data may help alleviate concerns, but this is difficult as the physicians need to prescribe the drugs to generate these data, so at the time of this survey, it is almost not possible to yet have these data to publish, but with time these may increase. However, results from some studies could also heighten concerns as your postulate assumes that these drugs will be found to be equally safe and effective (which they very well could be) when used in routine clinical practice. Perhaps instead of "alleviating concerns" it could lead to more informed prescribing.

REVIEWER	Satoru Yamada Kitasato Institute Hospital, Japan
REVIEW RETURNED	04-Apr-2017

GENERAL COMMENTS	In this study, authors tried to investigate knowledge and attitude toward biosimilars. Although it is a very interesting and important issue, I think authors must rule out sampling error. Authors should clarify several points below; Major points (1) a. How many gastroenterologists are belonging to the British Society of Gastroenterology? b. Among members of the British Society of Gastroenterology, only 54 gastroenterologists seemed to response to this survey. Comparing with whole members of the British Society of Gastroenterology, did 54 responders have similar characteristics (age, sex, ethnicity…)? c. Can 54 participants represent whole members? (2) How about the British Society of Medical Dermatology and 61

	responders? (3) How about the Association of British Clinical Diabetologists and 58 responders? (4) How about the British Society for Rheumatology and 61 responders? (5) Why did authors use web-survey only? (6) In my personal opinion, to avoid sampling error, authors may pay reward to participants and authors should be funded by certain organization(s). How do authors think about reward and/or funding? Minor points (1) I cannot see 11 question questionnaire. (p3, line 3 from bottom) (2) Figure 3 must be figure 1, because it is first figure. (p4, line 9)

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Kimme Hyrich
Institution and Country: The University of Manchester, UK
Please state any competing interests: None declared

Please leave your comments for the authors below

This is an interesting and timely survey as the introduction of biosimilars is rapidly changing practice, particularly in the specialities included in this survey and also highlights areas where more research is needed. I have a few comments on the report:

Introduction:
I would argue that at the time of license of biosimilars there was not a “wealth of clinical and scientific literature”, at least for infliximab for which there had been clinical trials in new users but no data on originator to biosimilar switchers and the EMA approval was based primarily on data from new users only. Similarly, the drugs do not require trials in all indications and a blanket indication mapping the originator product is often granted. These factors may contribute to the concerns raised by the survey respondents and should be highlighted.
• Response to reviewer: This a good point and we have amended this paragraph for clarification that wealth of clinical and scientific literature on early approved biosimilars (somatropin, epoetins and filgrastim), while, more clinical and non-clinical studies are required for infliximab and insulin glargine switching. Page 3 line 12-15.

The sentence stating that branded monoclonals such as adalimumab, rituximab and trastazumab now have competition is confusing as at the time of this paper, not all of these drugs are off patent and rituximab has a licensed biosimilar. Please clarify.
• Response to reviewer: This a good point and we have revised and updated the narrative as the EMA approved two adalimumab biosimilars in addition to rituximab biosimilar and we have updated the information in the former paragraph. Page 3 line 7-9

Methods:
Would be good to map the survey dates in direct relation to when these drugs were licensed and available for use.
• Response to reviewer: We have added Figure 1 which shows the date of the surveys with the time of patent expiry of infliximab and insulin glargine and the time of introduction of infliximab and insulin glargine biosimilars. Appended

Results:
Your survey response is very low. Even though you don't know the direct number of possible respondents, it is estimated there are around 500 rheumatology consultants and ~1000 Gastro consultants in the UK, so your survey, which also includes registrars, will have maybe tapped into <10% of these. This should be discussed further as a limitation.
• Response to reviewer: We have added this point to the limitations. Page 7 line 7-8

What does daily or weekly biosimilar prescribing mean? Is this writing a prescription every day or seeing patients receiving biosimilars every day, for example.
• Response to reviewer: Participants were asked "how often do you prescribe biosimilars?" We assume respondents meant writing prescription, therefore we have amended the narrative. Page 5 line 6-8

Your description of Figure 4 doesn't match with the data, which suggests that rheumatologists had concerns about safety and efficacy of switching, but if I understand this did not necessarily inhibit their use, which was a different choice of answer. Please clarify.
• Response to reviewer: We have revised the narrative and added the figure number where we have quoted percentage response. Furthermore, we have included a sentence highlighting that concerns only stopped a small proportion of rheumatologists from switching. Page 5 line 21-27

Discussion:
One of the challenges of this survey is that fact that it is being published during a period of active increase in biosimilar use, particularly in rheumatology and dermatology. The survey took place over the same period when the etanercept biosimilar was being introduced and prescribed for the first time. Rheumatology is not a big user of infliximab, unlike gastroenterology so most rheumatologists may have had limited or their first experience with biosimilars at the time of this survey and opinions will change once physicians gain more experience. Therefore there is some limitation in directly comparing the results of this survey with other similar surveys which may have been done at different times, some even before the introduction of biosimilars for some specialties. Perhaps this could be helped by dating some of the comparisons made in the discussion and also stressing the need to repeat this survey in even 1-2 years' time to see if regular use of drug changes attitudes.
You comment that the BSG position statement was quite encouraging towards biosimilar use. Did this differ from say the BSR or BAD statement.
I agree with your postulate that more pharmacovigilance data may help alleviate concerns, but this is difficult as the physicians need to prescribe the drugs to generate these data, so at the time of this survey, it is almost not possible to yet have these data to publish, but with time these may increase. However, results from some studies could also heighten concerns as your postulate assumes that these drugs will be found to be equally safe and effective (which they very well could be) when used in routine clinical practice. Perhaps instead of "alleviating concerns" it could lead to more informed prescribing.

• Response to reviewer: We have revised and amended the narrative taking in account the proportions of infliximab utilisation by gastroenterologists, rheumatologists and dermatologists. We have added the BSR and BAD position statements about biosimilars. In addition to the needs of repeating this survey in the next 1-2 years to compare attitudes following more utilisation of these new biosimilars and more published data.

Reviewer: 2
Reviewer Name: Satoru Yamada
Institution and Country: Kitasato Institute Hospital, Japan
Please state any competing interests: None declared

Please leave your comments for the authors below

In this study, authors tried to investigate knowledge and attitude toward biosimilars. Although it is a very interesting and important issue, I think authors must rule out sampling error. Authors should clarify several points below;

Major points
(1) a. How many gastroenterologists are belonging to the British Society of Gastroenterology?
b. Among members of the British Society of Gastroenterology, only 54 gastroenterologists seemed to response to this survey. Comparing with whole members of the British Society of Gastroenterology, did 54 responders have similar characteristics (age, sex, ethnicity…)?
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(5) Why did authors use web-survey only?
(6) In my personal opinion, to avoid sampling error, authors may pay reward to participants and authors should be funded by certain organization(s). How do authors think about reward and/or funding?
Minor points
(1) I cannot see 11 question questionnaire. (p3, line 3 from bottom)
(2) Figure 3 must be figure 1, because it is first figure. (p4, line 9)

Response to reviewer:
• This survey is a part of a larger PhD project which will involve face to face interviews with HCPs in a variety of specialties. NHS research approval has been given for this phase and interviews will commence shortly. These results will be presented in due course.
• We don't know the detailed characteristics of respondents since it was an anonymised survey. Furthermore, the total membership of the professional associations is unknown, but we have estimated the response rate based on previous workforce data and amended the discussion and added this point as a limitation to the study.
• As this part of a PhD project, we did not have sufficient resources to reward HCPs for participation in the study.
• Survey questionnaire appended below
• Figures have been renumber and additional figure included

Questionnaire:
1. Are you
• Consultant/ registrar
• General Practitioner
• Pharmacist
• Nurse

2. What is your speciality?

3. What is your work setting?

4. Which statement best describes what you understand a biosimilar to be.... (Please select only one)
• A new biological medicine
• A generic biological medicine
• A counterfeit copy of a biological medicine
• A similar copy of a biological medicine

• I have heard about biosimilars but I do not know what they are
• I have never heard about biosimilars

5. Are biosimilars on your local formulary?
• Yes
• No
• I do not know
• Not applicable

6. How important are the following factors when considering prescribing a biosimilar?
Not at all important important Slightly Moderately important Very important Extremely important N/A

• Important to stimulate innovation of biological medicine
• Important to stimulate competition in the biological medicine market
• Important to save costs for the NHS
• Important to offer alternatives in case of drug shortage
• Important to increase the overall use of biologics

7. How often do you prescribe biosimilars?
• Never
• Once a year
• Once a month
• Once a week
• Every day
• N/A

8. When considering starting a new patient on a biosimilar, how concerned are you about safety and effectiveness?
No concerns Minor concerns Major concerns This stops me prescribing a biosimilar
• Safety
• Effectiveness

9. When considering switching a patient to a biosimilar, how concerned are you about safety and effectiveness?
No concerns Minor concerns Major concerns This stops me prescribing a biosimilar
• Safety
• Effectiveness

10. How likely are the following factors to increase your use in biosimilars?
Extremely unlikely Unlikely Likely Extremely likely
• Guidance from NICE or other reputable national body
• Local policy, such as inclusion in formulary
• Potential cost saving to my organisation
• Any cost saving from using biosimilars being invested in my services
• Increased patient acceptability
• Robust cost effectiveness data of biosimilars versus branded biological medicines
• Robust pharmacovigilance studies on biosimilars

11. How often are patients on biosimilars entered onto audit or registry-compatible databases?
• Never
• Rarely

• Sometimes
• Always

VERSION 2 – REVIEW

REVIEWER	Kimme Hyrich University of manchester, UK Honoria from Abbvie and Pfizer >12 months ago
REVIEW RETURNED	28-Apr-2017

GENERAL COMMENTS	No further queries - all prior queries addressed adequately.