PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Adherence to guidelines in use of biological agents to treat psoriasis in Brazil
AUTHORS	Silveira, Miriam; de Camargo, Iara; Osorio-de-Castro, Claudia; Barberato-Filho, Silvio; Del Fiol, Fernando; Guyatt, Gordon; de Camargo, MaYARA; Lopes, Luciane

VERSION 1 - REVIEW

REVIEWER	Dr. Wayne Gulliver Canada CONFLICTS OF INTEREST (in past 2 years) as of September 2013 Dr. Gulliver has received honoraria for participation in Advisory Boards for Abbott/AbbVie, Janssen, Amgen and Bio-K. Dr. Gulliver has received honoraria for participation in Speaker engagements and consultative meetings for Abbott/AbbVie, Janssen, Amgen, Actellion, Roche, Novartis and LEO Pharma. As well Dr. Gulliver has acted as a clinical trial investigator for Abbott/AbbVie, Janssen, Amgen, Pfizer and Celgene. As well Dr. Gulliver as a Co-Author on the Canadian Psoriasis Guidelines
REVIEW RETURNED	24-Oct-2013

GENERAL COMMENTS	I thoroughly enjoyed reading this paper, and gained some insight into the practice of medicine and law in Brazil. The paper is certainly worthy of publication; but I believe it will need some further work in order to come to the conclusions that were made. Page 2 paragraph 2, line 5 under “methods” The Canadian guidelines, as well as other guidelines that I have reviewed, biologic agents are recommended in patients with moderate to severe psoriasis, who have failed topical and phototherapy, or have failed systemic therapies (e.g. Cyclosporine and Methotrexate), or have contraindication to these therapies). In terms of monitoring, this is often country specific, and guided by the monograph. It varies from biologic to biologic. Page 2 line 5 under “results” the authors state that 169 (83.2%) of patients failed to meet standards of prior use of topical or systemic medication. The authors did not indicate which patients were contraindicated, either through prior illness, In the case of Cyclosporine, which would include hypertension; or renal dysfunction; with Methotrexate, liver dysfunction, renal dysfunction; and for both medications that could potentially interact. This issue can be easily dealt with by the authors, as they did have access to patient’s comorbidities, stating 12.8% have cardiovascular disease, but not indicating which were hypertension, IHD, PVD or

	stroke. Authors would also have had access to patient's medications, and therefore, drug interactions with systemic therapies, which would make the patient eligible for biologics, would be important information for the readers. Another important comorbidity is psoriatic arthritis, in which Cyclosporine is ineffective, and Methotrexate is unable to prevent join damage. This comorbidity would be of great importance in determining the patients therapy. On page 8, table 2, description line 5. Phototherapy is infrequently used in 32% of Brazil. Being a tropical climate I would expect that most patients did have natural UV exposure. Again page 8, table 2, line 6, it stated that 71% of patients had used non biologic systemic therapy before lawsuit, whereas in the result, line 5, it said patients failed to meet standards of prior use of topical and systemic medications in 169 (83.2%) of patients. On page 11, first paragraph, with respect to contraindications listed (on line two and three), alcohol, uncontrolled infection, liver disease, pregnancy, hypertension, fatty liver, renal disease, and drug interactions are important, whereas pleural effusion, coagulopathy, MACE (major acute cardiovascular events) may not be relevant for Cyclosporine or Methotrexate. In the next sentence, comorbidities of the cardiovascular system are actually important indications in the use of biologics, and recent data in both the RA, and psoriasis literature suggests that biologics such as anti-TNF may decrease the risk of MACE. The only relevant contraindication is significant heart failure and the use of anti-TNFs. A limitation, of the study includes the fact that there is no control group of patients which have attained biologics through the usual health care approval. It certainly detracts somewhat from the impact of the data, as we have no insight into how these patients are managed within the Brazilian system. (Page 12, line 1), it should be noted that psoriasis patients on biologics other than, a slight increased risk of infection have no increased risk of malignancies or lymphoma. Long term data recently published, including five year ustekinumab data supports these findings. I believe with the addition of the data suggested, we have a better picture of how the clinical practice of dermatology and the judicial system are making decisions that are in the best interest of the patients.

REVIEWER	Alexander Nast Dpt of Dermatology, Charite University Hospital
REVIEW RETURNED	12-Nov-2013

GENERAL COMMENTS	The article presents interesting data on court based reimbursement decisions in Brasil. The article compares a) court decisions between 2004 and 2010 and guidelines recommendations from guidelines first published in 2005/2006 in Europe (referenced are later updates) and 2012 in Brasil. In addition, guidelines recommendations with respect to monitoring are compared to information derived from patient interviews. In my understanding, court decisions usually contain a reasoning, which does not seem to have been systematically analysed by the authors. It is difficult to ask judges to be aware of medical guidelines published in Europe, the whole process of court decisions is not

	made very clear. Is a mere prescription enough for the judge to assume a correct indication for a treatment? Where additional experts involved. Which solutions do the authors suggest to improve the current situation (e.g. at least two independent doctors given an assessment to the court?). Why was the time period of 2004 - 2010 selected. It is not valid to analyse guideline adherence to guidelines that were not even published at that time (2004). If I am not mistaken, the fist Brazilian guideline was published in 2012, so from that time on, a regional guidance was availlable whose implementation can be assessed. The only multinational guideline, the European guideline was not referenced. To ensure valid comparability, the original publication from 2005 onwards for the national guidelines should be referenced as well because they are the standard of care - although in different health care settings - at that time. Did you see any trends / improvement of guideline complient management over time (eg. comparison 2004-2007 vs. 2008 - 2010?) Minor points: 1) the publication need correction by a native speaker 2) Ref. 1 can be ommited, no need to support this with a ref. 3) Ref. 3 is suitable for QoL impact put not mortality, the phrase needs rephrasing, mortality due to what? 4) methods: the list of items in the questionaire does not mention comorbidity but results are presented for that, where is the data generated? 5) Results page 7 line 26, "four biologic drugs:" but only three stated! 6) Table 1, time of diagnosis: the category >1 does not make sense because it includes all of the above, adding up all the numbers does not total 100% 7) Page 8, line 46, please check numbers for uv therapy, I calculated 37% and also check line 51/52 not only 10 but only 37 patients? 8) Table 3: please consider removing the results of prior treatments in the group of patients still on treatement after 1 year, I dont see any additonal value 9) page 11, line 1 this statement cannot be made based on the presented data, you are referencing Table 1, but table 1 does not provide any information on the mentioned CI, instead it contains the group of "others" which may very well contain CI, in additional, cardiovascular disease is a contraindication to CYA, the list of contraindications provided does not make sense to me, why is alcohol (in which amount/do you mean alcohol induced liver disease?) a CI to immunosuppression, same applies to pregnancy (CyA is a treatment option for pregnant women). The whole section needs complete rewriting. Unclear assessment of possible CI to conventionals has to be considered as a weakness of this publication! 10) it is suprising, the the Brazilian GL do not recommend Biologics because of safety concerns, most of the other guidelines are limited by the label and financial limitations (line23, page 12, there is no evidence that conventionals are less toxic than biologics (page 13, line 17) 11) Please check ref. page 12 line 41 (22, 29 not matching/not found?) 12 Again as mentioned above, the courts can only judge based on medical advise, if no medical advice is seeked, this needs to be changed (page 12, line 26), doctors are responsible for their patients and the lack of monitoring is a disaster and it should be the task of

	the national dermatological society joined with the pharmaceutical industry to ensure that dermatologists are aware of monitoring necessities. 27) Ref. as mentioned above omit 1., add guidelines in their 2005-2007 versions, consider adding EU guidelines, correct 22 Razany - Rzany is correct, check for missing 29

VERSION 1 – AUTHOR RESPONSE

Reviewer Name: Dr. Wayne Gulliver Institution and Country Canada
Please state any competing interests or state 'None declared': CONFLICTS OF INTEREST (in past 2 years) as of September 2013 : Dr. Gulliver has received honoraria for participation in Advisory Boards for Abbott/AbbVie, Janssen, Amgen and Bio-K. Dr. Gulliver has received honoraria for participation in Speaker engagements and consultative meetings for Abbott/AbbVie, Janssen, Amgen, Actellion, Roche, Novartis and LEO Pharma. As well Dr. Gulliver has acted as a clinical trial investigator for Abbott/AbbVie, Janssen, Amgen, Pfizer and Celgene. As well Dr. Gulliver as a Co-Author on the Canadian Psoriasis Guidelines.
Comments:
I thoroughly enjoyed reading this paper, and gained some insight into the practice of medicine and law in Brazil. The paper is certainly worthy of publication; but I believe it will need some further work in order to come to the conclusions that were made.
Thank you for your suggestions.
Q1 - Page 2 paragraph 2, line 5 under "methods" The Canadian guidelines, as well as other guidelines that I have reviewed, biologic agents are recommended in patients with moderate to severe psoriasis, who have failed topical and phototherapy, or have failed systemic therapies (e.g. Cyclosporine and Methotrexate), or have contraindication to these therapies). In terms of monitoring, this is often country specific, and guided by the monograph. It varies from biologic to biologic.
Response 1 - The reviewer states that all guidelines require prior use of topical and systemic therapies which is a criterion we used. We reviewed all guidelines for recommendations regarding monitoring. We detail below the section of each guideline in which we found the monitoring recommendations. The one guideline in which we did not find monitoring recommendations was the Canadian guidelines. We have therefore modified our statement regarding monitoring to specify that 4 out of 5 guidelines recommended monitoring.
"We reviewed all recommendations in each guideline and chose as standards only those recommendations that for prior treatment were uniformly endorsed across all guidelines and for monitoring were endorsed by 4 of the 5 guidelines."
European guideline S3 - 2012: Monitoring recommendations, page 37 (summarized Table 28); page 49 (Table 35); page 55 (Table 42);
NHS (NICE) guideline 2012: Monitoring recommendations, page 3; page 9 (principle of care); page 25 (general recommendations).
British Association of Dermatologists 2009: monitoring recommendations, page 999-1002.
American Academy of Dermatology 2008: monitoring recommendations, page 838-842.
Brazilian Society of Dermatology 2012: monitoring recommendations, page 17.

Q2 - Page 2 line 5 under "results" the authors state that 169 (83.2%) of patients failed to meet standards of prior use of topical or systemic medication. The authors did not indicate which patients were contraindicated, either through prior illness, In the case of Cyclosporine, which would include hypertension; or renal dysfunction; with Methotrexate, liver dysfunction, renal dysfunction; and for both medications that could potentially interact.
This issue can be easily dealt with by the authors, as they did have access to patient's comorbidities, stating 12.8% have cardiovascular disease, but not indicating which were hypertension, IHD, PVD or stroke.

Response 2 - The reviewer makes the point that in some patients the guidelines may not have been violated because patients had contraindications to all systemic drugs. We found, however, that no patient had contraindications that would have prevented the use of all recommended systemic agents (cyclosporin, methotrexate, and acitretin). Moreover, we have found that no patient was taking other medication that interacted with all three candidate systemic therapies. We have stated this in the revised manuscript as follows:
" No, patients had contraindications, or were using drugs with problematic interactions, that would have prevented the use of all recommended systemic agents (cyclosporin, methotrexate, and acretinin)" .
Q3 - Authors would also have had access to patient's medications, and therefore, drug interactions with systemic therapies, which would make the patient eligible for biologics, would be important information for the readers. Another important comorbidity is psoriatic arthritis, in which Cyclosporine is ineffective, and Methotrexate is unable to prevent join damage. This comorbidity would be of great importance in determining the patien.ts therapy.
Response 3 - As stated in response to point Q2 above, there was no patient who was taking drugs with interactions that would have precluded the use of all three potential systemic therapies. The reviewer has an excellent point regarding patients with psoriatic arthritis. However, we excluded such patients, an exclusion we neglected to mention in the original manuscript, but have now included as follows: "We excluded patient with psoriatic arthritis".
Q4 - On page 8, table 2, description line 5. Phototherapy is infrequently used in 32% of Brazil. Being a tropical climate I would expect that most patients did have natural UV exposure.
Response 4 - Southern Brazil is in a moderate climate and there patients have limited sunlight exposure. Moreover, we know of no guideline that accepts sun exposure as an alternative to phototherapy.
Q5 - Again page 8, table 2, line 6, it stated that 71% of patients had used non biologic systemic therapy before lawsuit, whereas in the result, line 5, it said patients failed to meet standards of prior use of topical and systemic medications in 169 (83.2%) of patients.
Response 5 - Although 71% of the patients had used non biologic systemic therapy only 16.8% had used both systemic therapy and topical therapy. Use of both types of treatment was required to meet guideline standards of prior therapy.

Q6 - On page 11, first paragraph, with respect to contraindications listed (on line two and three), alcohol, uncontrolled infection, liver disease, pregnancy, hypertension, fatty liver, renal disease, and drug interactions are important, whereas pleural effusion, coagulopathy, MACE (major acute cardiovascular events) may not be relevant for Cyclosporine or Methotrexate.
In the next sentence, comorbidities of the cardiovascular system are actually important indications in the use of biologics, and recent data in both the RA, and psoriasis literature suggests that biologics such as anti-TNF may decrease the risk of MACE. The only relevant contraindication is significant heart failure and the use of anti-TNFs.
Response 6: There are disagreements in the literature regarding comorbidities that make the use of immunosuppressive drugs of biologics inadvisable or contraindicated. Given the controversies, we have deleted the paragraph referring to these issues.
Q7- A limitation, of the study includes the fact that there is no control group of patients which have attained biologics through the usual health care approval. It certainly detracts somewhat from the impact of the data, as we have no insight into how these patients are managed within the Brazilian system.
Response 7: We have added the following to the discussion, almost exactly borrowing the reviewer's wording:
" That we did not study the management of patients who have received biologics through the usual health care system (i.e. without recourse to the courts) represents another limitation of the study Thus, our study provides only indirect evidence regarding how these patients are managed within the Brazilian system".

Q8 - (Page 12, line 1), it should be noted that psoriasis patients on biologics other than, a slight increased risk of infection have no increased risk of malignancies or lymphoma. Long term data recently published, including five year ustekinumab data supports these findings. I believe with the addition of the data suggested, we have a better picture of how the clinical practice of dermatology and the judicial system are making decisions that are in the best interest of the patients.
Response 8 - We have tried to find the evidence to which the reviewer refers. What we have located is specific to the drug the reviewer mentions, as well as some other studies. Our interpretation of the literature is that there is some conflicting data. We have modified the relevant text as follows:
“Biologic agents may be associated with serious adverse effects, including opportunistic fungal infection, and a possible increase in the risk of malignancies and lymphoma, though data regarding malignancies and lymphoma is inconsistent”.
Reviewer Name Alexander Nast Institution and Country Dept. of Dermatology, Charite University Hospital lease state any competing interests or state ‘None declared’: none

The article presents interesting data on court based reimbursement decisions in Brasil.

The article compares a) court decisions between 2004 and 2010 and guidelines recommendations from guidelines first published in 2005/2006 in Europe (referenced are later updates) and 2012 in Brasil. In addition, guidelines recommendations with respect to monitoring are compared to information derived from patient interviews.

1. In my understanding, court decisions usually contain a reasoning, which does not seem to have been systematically analyzed by the authors.
Response 1 - Professor Nast is correct; we did not analyze the reasoning of the court. The reason we did not is that well-argued reasoning is of little help if guidelines are not followed, and poorly-argued reasoning is not problematic if guidelines are followed.
2. It is difficult to ask judges to be aware of medical guidelines published in Europe, the whole process of court decisions is not made very clear.
Response 2 - We agree and have added the following to the discussion, including citations:
"One could argue that it may be unreasonable to ask judges to be aware of medical guidelines, particularly those arising from other jurisdictions. A proposed solution to this problem would be to provide the court with high quality technical analyses. In this case, experts in psoriasis aware of the guidelines would provide the analyses. So far, such analyses are unavailable (Vieira FS, Zucchi P. [Distortions to national drug policy caused by lawsuits in Brazil]. Rev Saude Publica. 2007;41(2):214-22.; Biehl J, Amon JJ, Socal MP, Petryna A. Between the court and the clinic: lawsuits for medicines and the right to health in Brazil. Health Hum Rights. 2012;14(1):E36-52; Chieffi AL, Barata RB. ['Judicialization' of public health policy for distribution of medicines]. Cad Saude Publica. 2009;25(8):1839-49). Our results emphasize the need for technical analyses to guide court decisions, ideally considering two independent opinions."
3. Is a mere prescription enough for the judge to assume a correct indication for a treatment?
Response 3 - In the current system, the answer is yes.

4. Where additional experts involved.
Resonse 4 - Currently, typically, there are no experts to help the courts in their consideration of cases involving requests for medication.

5. Which solutions do the authors suggest to improve the current situation (e.g. at least two independent doctors given an assessment to the court?).
Response 5- We agree with the reviewer's suggestion for two independent expert opinions (see our response to Dr. Nast's point 2).

6. Why was the time period of 2004 - 2010 selected. It is not valid to analyses guideline adherence to

guidelines that were not even published at that time (2004). If I am not mistaken, the first Brazilian guideline was published in 2012, so from that time on, a regional guidance was available whose implementation can be assessed.
Response 6 - We started in 2004 because that is the first year in which data regarding the results of court cases with requests for biologics for psoriasis was collected systematically. We used 2010 as the end data because that was the time at which our research commenced. The Brazilian government issued its first guidance in 2004, but Brazilian dermatological societies issued guidelines in 2009. Our implicit position in this paper is that when international guidelines provide consistent recommendations, such recommendations should guide practice in Brazil.

7. The only multinational guideline, the European guideline was not referenced. To ensure valid comparability, the original publication from 2005 onwards for the national guidelines should be referenced as well because they are the standard of care - although in different health care settings - at that time.
Response 7 - We apologize, but we are not sure to the exact European guideline to which the reviewer is referring. We do not have access to the 2005 guidelines, but it is our understanding that the recommendations on which we have focused (i.e. the need for trying other agents before moving to biologic agents, and the need for regular follow-up and monitoring) have been in place since the first guideline for use of biologic agents in psoriasis was published.
8.Do you see any trends / improvement of guideline compliant management over time (eg. comparison 2004-2007 vs. 2008 - 2010?)
Response 8 - Unfortunately, in collecting the data we did not record the date for each case. Therefore, we are unable to address this issue.

MINOR POINTS:
1) the publication need correction by a native speaker
Dr. Guyatt, a coauthor and native English speaker, has carefully reviewed all the wording in the paper.
2) Ref. 1 can be omitted, no need to support this with a ref.
We omitted the reference as suggested.
3) Ref. 3 is suitable for QoL impact put not mortality, the phrase needs rephrasing, mortality due to what?
We have reviewed the relevant evidence and found that it is inconsistent with respect to mortality. Therefore, we have deleted the reference to an increase in mortality with psoriasis.
4) Methods: the list of items in the questionnaire does not mention comorbidity but results are presented for that, where is the data generated?
In the questionnaire we asked patients questions regarding comorbidity. We add this information in the methods:
“The questionnaire included the following: what drugs the patient was using for the treatment of psoriasis prior to the court judgment, the time of diagnosis of psoriasis, comorbidities and whether patients received at least annual review”.
5) Results page 7 line 26, "four biologic drugs:" but only three stated!
The fourth biologic drug that was used in the patients in our data set was efalizumab which has since been withdrawn from the market.
6) Table 1, time of diagnosis: the category >1 does not make sense because it includes all of the above, adding up all the numbers does not total 100%.
The reviewer is correct. This is ≤ 1 not ≥1. We have corrected in the manuscript.
7) Page 8, line 46, please check numbers for uv therapy, I calculated 37% and also check line 51/52 not only 10 but only 37 patients?
The reviewer is correct. We’ve corrected the error.
8) Table 3: please consider removing the results of prior treatments in the group of patients still on treatment after 1 year, I don’t see any additional value.

We apologize, but we do not clearly understand what Dr. Nast is asking. We do not see any reference to results of prior treatments in Table 3.

9) page 11, line 1 this statement cannot be made based on the presented data, you are referencing Table 1, but table 1 does not provide any information on the mentioned CI, instead it contains the group of "others" which may very well contain CI, in additional, cardiovascular disease is a contraindication to CYA, the list of contraindications provided does not make sense to me, why is alcohol (in which amount/do you mean alcohol induced liver disease?) a CI to immunosuppression, same applies to pregnancy (CyA is a treatment option for pregnant women). The whole section needs complete rewriting. Unclear assessment of possible CI to conventional has to be considered as a weakness of this publication!
We have revised the paper, eliminated the statements that Dr. Nast found problematic, and instead have stated:
"No patient had contraindications, or were using drugs with problematic interactions, that would have prevented the use of all recommended systemic agents (cyclosporine, methotrexate, and acitretin)."

10) it is surprising, the Brazilian GL do not recommend Biologics because of safety concerns, most of the other guidelines are limited by the label and financial limitations (line23, page 12, there is no evidence that conventional are less toxic than biologics (page 13, line 17).
The explanation of the Brazilian guidelines focus on toxicity is as surprising (and obscure) to us as it is to Dr. Nast.
11) Please check ref. page 12 line 41 (22, 29 not matching/not found?).
We've checked and include the correct reference.

12) Again as mentioned above, the courts can only judge based on medical advice, if no medical advice is seeked, this needs to be changed (page 12, line 26), doctors are responsible for their patients and the lack of monitoring is a disaster and it should be the task of the national dermatological society joined with the pharmaceutical industry to ensure that dermatologists are aware of monitoring necessities.
We have revised the discussion in keeping the Dr. Nast's viewpoint.
Explanations for inappropriate practice include inadequate training and knowledge of the physicians who prescribe the drugs[24]. Another possibility is that incentives from the pharmaceutical industry are influencing the prescription of biologic agents in psoriasis. Whatever the reason, our findings demonstrate that the court system is not functioning well. This is not necessarily the fault of the judges, but of a system that does not ensure that judges have the appropriate access to expert guidance. Independent review by disinterested experts would have led the court to insist on appropriate prior treatment before considering biologic agents. The health system also appears negligent in not ensuring optimal follow-up to patients who receive payment for their drugs from the government. The responsibility for informing practitioners of optimal management could rest with the pharmaceutical industry, the national dermatologic society, or the government.

13) Ref. as mentioned above
We have omitted the reference in question..
b) Add guidelines in their 2005-2007 versions,
See response 7 above.
c) consider adding EU guidelines,
We have added the guideline from the AAD..
d)correct 22 Razany - Rzany is correct, check for missing 29
We've made the necessary correction

VERSION 2 – REVIEW

REVIEWER	Alexander Nast Charite Berlin
REVIEW RETURNED	03-Jan-2014

GENERAL COMMENTS	Thank you for the well done revision. Few points remain 1) I disagree with the new sentence: The patients in this sample did not have heart failure, the only universally agreed upon any contraindication to the use of immunosuppressive dr ugs. You probably mean heart disease NYHA III / IV for TNFs? heart failure is no universally agreed upon contraindication for immunosupressive drugs. 2) Still misspelled ref.: 23 Rzany

VERSION 2 – AUTHOR RESPONSE

Thank you for your comments. Below you can see point by point response:
1- I disagree with the new sentence: "The patients in this sample did not have
heart failure, the only universally agreed upon any contraindication to the use of immunosuppressive drugs.
- We've change to : The patients in this sample did not have heart NYHA III / IV heart disease, a potential contraindication for TNFs (Table 1).

2) till misspelled ref.: 23 Rzany
We 've change to Rzany,