PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Prescriber Preference for a Particular Tumor Necrosis Factor Antagonist Drug and Treatment Discontinuation: Population-based Cohort
AUTHORS	Fisher, Anat; Basset, Ken; Wright, James (Jim); Brookhart, M.; Freeman, Hugh; Dormuth, Colin

VERSION 1 - REVIEW

REVIEWER	Jeff Curtis UAB, Birmingham AL USA
REVIEW RETURNED	17-Aug-2014

GENERAL COMMENTS	These authors have described the physician preference for use of anti-TNF drugs on drug persistence using BC Canada data. The idea represented in the article is interesting and a useful contribution to the literature, and I have only a few comments: The outcome is a composite: patients could switch to a different biologic, or stop all biologics altogether. It seems like the main findings might be appreciably different if these two components of the outcome were examined separately. For example, what if patients were started on a non-preferred TNF inhibitor; were they more likely to be switched to a preferred TNF inhibitor? Performing subgroup analyses that separates the two outcomes (switching to another biologics, vs. discontinuing altogether) would help reassure readers that results are consistent regardless of whether one looked at switching biologics or stopping altogether. Besides use of concomitant MTX, please comment on what local and coverage-related factors, if any, might influence physicians to choose an infusion vs. injectable drugs. For example, is reimbursement preferable for one drug, or type of drug (injectable vs. infusion) vs. the other? Is access to infusion therapies like infliximab limited in some way? Please provide a clinical interpretation of, “Infliximab or adalimumab, on the other hand, were usually initiated by physicians with lower preference for these drugs (only 34% or 19% of courses were initiated by a physician with high preference for drug,respectively).” What is the authors’ explanation of this finding? A small point, but the ability to accurately classify disease duration assumes that people could be followed in the data from the time of disease onset. Please provide additional information that reassures the reader that they have indeed found new onset RA in their data.

REVIEWER	Ole Rintek Madsen Dept. of Rheumatology

	Copenhagen University Hospital Gentofte Denmark Advisory Board member and/or speaker: BMS, Pfizer, MSD, Abbvie, Roche.
REVIEW RETURNED	29-Aug-2014

GENERAL COMMENTS	A population based cohort study examining the effect of physician preference for a particular tumor necrosis factor alpha (TNF) antagonist on the risk of treatment discontinuation in rheumatoid arthritis. The study is nicely performed and presented. It demonstrates that drug survival may be dependent on physician preference for a particular drug and questions the effect of drug coverage policy. Specifically: Third line, introduction: A "l" is missing in "health". The second paragraph in the introduction should be moved to the discussion section. Is it possible that the physician preference was dependent on the geographic (urban versus rural)? A long travel time to the physician´s clinic may strengthen the preference for subcutaneous treatment. Was the drug coverage level for the different drugs independent of the physician? Subcutaneous treatment was most frequently prescribed. It should be mentioned that a previous study has shown that patients and rheumatology physicians nurses (and patients) have a strong preference for subcutaneous treatment (Huynh TK et al. Patient Prefer Adherence. 2014 Jan 20;8:93-9). It is also relevant to mention that patients preference in many cases is dependent on physican preference (Chilton F et al. Musculoskeletal Care. 2008 Mar; 6(1):1-14). These referencess should be added. It should be mentioned that the study indicates that the pharmaceutical industry may have a strong interest in influencing physicians despite administrative restrictions.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Jeff Curtis

(1) The outcome is a composite: patients could switch to a different biologic, or stop all biologics altogether. It seems like the main findings might be appreciably different if these two components of the outcome were examined separately. For example, what if patients were started on a non-preferred TNF inhibitor; were they more likely to be switched to a preferred TNF inhibitor? Performing subgroup analyses that separates the two outcomes (switching to another biologics, vs. discontinuing altogether) would help reassure readers that results are consistent regardless of whether one looked at switching biologics or stopping altogether.
Dr. Curtis referred to a significant point regarding the study outcome. He commented that the outcome could be regarded as a composite of switching (to a different drug from the same therapeutic

group), or discontinuing (all drugs from this group). Our approach in designing the study is to avoid use of composite outcome, since it may mask specific effect of the exposure. However, we view the current outcome as a single outcome. In the decision of prescribing drugs, switching should be considered a series of different decisions. The first decision would be deciding to discontinue the current drug. This decision is followed by a decision to start another drug, selecting a therapeutic group, selecting a specific new drug within this group, etc. Therefore, when combining patients who switched with patients who discontinued TNF antagonists altogether, we include patients in which the first decision of stopping the current drug was made.

The question Dr. Curtis asked, whether patients who had been started on a non-preferred TNF inhibitor were more likely to be switched to a preferred TNF antagonist is very interesting; however, we consider that a different research question. We certainly agree that this question, as well as others, require further search, and we added this as a direction in our revised manuscript as well (Discussion, Unanswered questions and future research).

(2) Besides use of concomitant MTX, please comment on what local and coverage-related factors, if any, might influence physicians to choose an infusion vs. injectable drugs. For example, is reimbursement preferable for one drug, or type of drug (injectable vs. infusion) vs. the other? Is access to infusion therapies like infliximab limited in some way?

Both reviewers asked for clarification on local and coverage-related factors that might influence prescribing decisions. Canada's publicly funded health care system is characterized by universal coverage for medically necessary health care services provided on the basis of need, rather than the ability to pay. The British Columbia Fair Pharmacare program is based on family annual income, and when families reach their deductible, their eligible medication costs are paid by the program. In British Columbia, there is no preferable TNF antagonist (please refer to British Columbia Ministry of Health. Special Authority request form, reference number 26 in the revised manuscript) and therefore, coverage is not a factor in determining which drug the patient is prescribed. We could not find any documentation of shortage of any of the study drugs in our province during the study period. Please note that even if some temporary factors existed, such as limited supply of one of the drugs, we allowed an adjustment of the physician preference to this factor by considering prescribing only in the year preceding each new prescribing. We mentioned in our method section that “By including a year of data … we minimized the effect of factors not related to preference that might have influenced a specific prescribing decision”.

(3) Please provide a clinical interpretation of, “Infliximab or adalimumab, on the other hand, were usually initiated by physicians with lower preference for these drugs (only 34% or 19% of courses were initiated by a physician with high preference for drug, respectively).” What is the authors’ explanation of this finding?

Since most new users were prescribed etanercept (63%) it is not surprising that based on the algorithm used to assign preference level, etanercept was also a commonly preferred drug. The survey conducted by Kamal et al 2006 as mentioned in our discussion (reference number 36), showed that physicians believed that etanercept is the most efficacious and the safest among the TNF antagonists (although there is no strong research evidence for this claim). Since infliximab and adalimumab were commonly of lower preference level, it is possible that when patients who were initiated infliximab and adalimumab, there were special considerations, such as patient request, other comorbidities (that were not captured in our analysis), compliance to self-injection, etc.

(4) A small point, but the ability to accurately classify disease duration assumes that people could be followed in the data from the time of disease onset. Please provide additional information that reassures the reader that they have indeed found new onset RA in their data.

Regarding Dr. Curtis comment on the accuracy of estimating disease duration from administrative databases, we would like to refer the reader to a Canadian study that found that “the mean ± SD disease duration estimated from administrative data (9.6 ± 6.6 years) was ~1 year shorter than the mean ± SD rheumatologist diagnosed disease duration … (10.8 ± 10.6 years), a difference that was not statistically significant on a paired t-test (P > 0.0544)” (Widdifield et al in Arthritis Care and Research. 65 (10) (pp 1582-1591), 2013). We added this observation in Table 1, where we described

estimates of disease duration.

Reviewer Name Ole Rintek Madsen

(1) Third line, introduction: A "l" is missing in "health".
We corrected typo pointed out.
(2) The second paragraph in the introduction should be moved to the discussion section.
Dr. Rintek Madsen suggested moving the second paragraph in the introduction to the discussion section. Since this paragraph explain the rationale for selecting TNF antagonists' treatment in rheumatoid arthritis to study physician preference, we think it is more appropriate to be included in the introduction and it leads the reader through our planning phase, as well as introduces background on relative effectiveness and safety of the drugs.
(3) Is it possible that the physician preference was dependent on the geographic (urban versus rural)? A long travel time to the physician´s clinic may strengthen the preference for subcutaneous treatment.
We agree with Dr. Rintek Madsen's comment that physician preference might have been dependent on the geographics. Therefore we included 5 categories of Geographical area in our model (please refer to table 1 in the manuscript). Three of them represent mainly large urban concentrations (Greater Vancouver, Greater Victoria and (mainland) urban areas). We used Greater Vancouver area, which offers most of the large health care facilities in our province, as our reference category.
(4) Was the drug coverage level for the different drugs independent of the physician?
Please refer to bullet (2) in our response to Dr. Curtis comments above.
(5) Subcutaneous treatment was most frequently prescribed. It should be mentioned that a previous study has shown that patients and rheumatology physicians nurses (and patients) have a strong preference for subcutaneous treatment (Huynh TK et al. Patient Prefer Adherence. 2014 Jan 20;8:93-9). It is also relevant to mention that patients' preference in many cases is dependent on physician preference (Chilton F et al. Musculoskeletal Care. 2008 Mar; 6(1):1-14). These references should be added.
We thank Dr. Rintek Madsen for the references quoted. While several studies showed that rheumatoid arthritis patients prefer subcutaneous TNF antagonists' treatment (Williams et al in Rheumatology 2006, 45(12):1575-6 and Huynh et al. Patient Prefer Adherence 2014, 20(8)93-9) we decided not to add it to our manuscript, since patient preference is outside the scope of our study. However, we did mention shortly the correlation between patients' preference and physicians' preference in our discussion (Explanations and interpretation).
(6) It should be mentioned that the study indicates that the pharmaceutical industry may have a strong interest in influencing physicians despite administrative restrictions.
We agree with this suggestion, and included it in the revised manuscript (Discussion, Explanations and interpretation).