Impact of smoking on the effectiveness of TNF-α inhibitors in patients with rheumatoid arthritis or Crohn’s disease

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Cigarette smoking may be associated with the augmentation of pro-inflammatory cytokines including Tumor Necrosis Factor-alpha (TNF-α), which may affect the outcomes of pharmacological agents such as TNF-α inhibitors. The purpose of this study was to investigate the impact of smoking on the effectiveness of TNF-α inhibitors in patients with rheumatoid arthritis (RA) or Crohn’s disease (CD). We used systematic literature review methods. A total of 1,147 articles were selected after exclusion of duplicates through a database search. Among them, 28 articles were finally selected through a review of titles and abstracts and a subsequent review of full articles. The effectiveness of TNF-α inhibitors in patients with RA or CD among the selected articles was summarized by their smoking status. Meta-analysis was performed with random effect model. When current smokers were compared with non-smokers for response after adjustments through meta-analysis among patients with RA, current smokers had 59% less response than non-smokers with statistical significance (Pooled adjusted OR=0.41, 95% CI=0.17-0.95). In patients with CD, current smokers tended to have lower clinical response than non-smokers, but statistical significance was not shown. In subgroup analyses for luminar CD or fistulizing CD, current smokers tended to have a lower response in luminar CD (Pooled OR=0.62, 95% CI=0.34-1.14), but smoking status was not associated with drug response in fistulizing CD. This study raises awareness of the adverse effects of smoking in terms of clinical response in patients treated with TNF-α inhibitors.

Introduction

Cigarette smoking is an important environmental risk factor for many diseases and affects outcomes of pharmacological agents. Cytochrome P-450 (CYP) 1A1, 1A2, and 2E1 enzymes are induced by smoking, which can lower drug concentrations in the body via the effects of drug clearance.[1] Nicotine can also lower the effect of anti-hypertensive medication and be associated with increases in adverse effects when a medicine has a cardiovascular adverse drug reaction through the activation of the sympathetic nervous system.[1] Therefore, smokers who take certain medications are recommended to quit smoking or to receive dosage adjustments.

The hazards to immunity, inflammation, and autoimmunity by cigarette smoking have been studied. Cigarette smoking may be associated with the augmentation of pro-inflammatory cytokines including Tumor Necrosis Factor-alpha (TNF-α).[2] Many epidemiology studies show evidence that smoking is a risk factor for several autoimmune diseases such as rheumatoid arthritis (RA) and Crohn’s disease (CD).[3,4] In addition, smok-
ing can affect the outcomes of pharmacological agents such as TNF-α inhibitors including infliximab, adalimumab, and etanercept, which are used for the treatment of RA or CD. TNF-α inhibitors produce excellent clinical responses for patients with these diseases, but there are limited therapeutic alternatives for patients who fail to respond to TNF-α inhibitors.[5] Therefore, practical guidance to achieve optimal drug responses in patients who use TNF-α inhibitors is very important. But, there is not sufficient information on the effect of smoking on the therapeutic outcome of TNF-α inhibitors. There are still controversies about whether smoking affects the response in patients treated with TNF-α inhibitors.[6] Thus, the purpose of this systematic review study was to investigate the pooled results for the impact of smoking on the effectiveness of TNF-α inhibitors in patients with RA or CD.

**Methods**

**Literature search**

We employed the population, intervention, comparison, outcome, time, setting, and study design (PICOTS-SD) strategy for published literature searches. Population was defined as patients with RA or CD under the treatment of TNF-α inhibitors. Disease severity and patients' demographics such as age and gender were not limited. TNF-α inhibitors included etanercept, adalimumab, infliximab, certolizumab pegol, and golimumab. Intervention was smoking and control was non-smoking or smoking cessation group. Outcomes, time points of outcome measurement, and clinical settings were not imposed as a restriction. Types of literature included pharmacokinetic studies, randomized control trials, and prospective or retrospective observational studies. Published articles were searched before June 15, 2013 using the following 4 electronic databases: Pubmed (www.pubmed.gov), Ovid-Medline (http://gateway.ovid.com/autologin.html), Ovid-Embase (http://gateway.ovid.com/autologin.html), and Cochrane Library (http://www.thecochranelibrary.com/view/0/index.html). Search terms based on defined PICOTS-SD were extracted using the mesh or emtree thesaurus, and field codes such as [TW], [Mesh], and mp. for exact searching were applied. Articles were limited to human studies. A detailed search strategy is presented in supplementary table1.

**Literature selection, data extraction and quality assessment**

Appropriate studies from searched articles were selected by two independent reviewers using the predefined inclusion and exclusion criteria in the protocol. Eligible articles were studies of the association between smoking and TNF-α in patients with RA or CD. Studies that did not provide sufficient information to evaluate the clinical association between smoking and TNF-α, such as non-clinical studies, case reports and abstracts, and non-English studies were excluded. For effective selection of appropriate studies, the first selection was performed using the title and abstract and the final selection was done after reviewing the full article. Consensus was achieved by discussion between the two reviewers in case of disagreement in the study selection. If consensus was not reached between them, the decision was made by majority rule after involvement of a third party. Pre-defined summary format was used in extracting data from the final literature selections.

**Data analysis**

Final literature selections were summarized for study design, smoking definition, sample size, and outcomes by smoking status. Response rates were synthesized from studies that showed homogeneity in terms of smoking status and outcomes using a meta-analysis technique. Revman version 5.2 (Cochran IMS) was used for meta-analysis. The discrete outcomes extracted from individual studies (i.e., response rate of TNF-α inhibitors) were synthesized and presented as pooled odds ratio (OR) and 95% confidence interval (CI). If a study reported only adjusted OR, natural log of OR and standard error calculated through statistical equations were used to calculate pooled OR. Heterogeneity across all the pooled studies was visually...
expressed in a forest plot, and the degree of heterogeneity was estimated by Cochran’s Q statistic and the I^2 statistic. Random effect model was applied conservatively, and sensitivity analyses for subgroups, such as specific indication, were performed.

**Results**

**Literature selection**

From PubMed, Ovid MEDLINE, Ovid EMBASE, and Cochrane Library, 194, 380, 894, and 5 articles were searched, respectively. A total of 1,147 articles were identified after exclusion of duplicate articles. Through independent reviews of the study titles and abstracts, 118 articles were selected after exclusion of non-clinical trials and non-interaction studies between TNF-inhibitors and smoking. The review of the full text of these 118 articles identified 25 articles after applying exclusion criteria. In addition, 3 articles were identified from the references of selected articles. A total of 28 articles were finally selected. Among them, 6 articles were for RA[7-12] and 22 articles were for CD.[13-34] Figure 1 shows the literature selection flows.

**Impact of smoking on drug response in patients with RA**

Six RA-relevant articles are summarized in Table 1. They were all observational studies and reported outcomes using

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Age Mean (SD)</th>
<th>Drug Treatment period</th>
<th>Smoking Status</th>
<th>Outcome (EULAR criteria)</th>
<th>Results</th>
<th>Included studies in Meta-Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canhao et al., 2012</td>
<td>PCS</td>
<td>52.6</td>
<td>ADA, ETA, INF</td>
<td>≥1Y</td>
<td>Ever-S (n=132), Never-S (n=485)</td>
<td>GR</td>
<td>Ever-S vs. Never-S</td>
</tr>
<tr>
<td>Saevarsdottir et al., 2011</td>
<td>PCS</td>
<td>53</td>
<td>ADA, ETA, INF</td>
<td>3.6M</td>
<td>C-S (n=98), Ex-S (n=90), Non-S (n=113)</td>
<td>GR</td>
<td>C-S vs. Ex-S vs. Non-S (3M)</td>
</tr>
<tr>
<td>Abhishek et al., 2010</td>
<td>RCS</td>
<td>-</td>
<td>ADA, ETA, INF</td>
<td>3M</td>
<td>C-S (n=71), Ex-S (n=173), Non-S (n=133)</td>
<td>GR+R</td>
<td>C-S vs. Non-S (3M)</td>
</tr>
<tr>
<td>Hyrich et al., 2006</td>
<td>PCS</td>
<td>55 (12)</td>
<td>INF, ETA</td>
<td>6M</td>
<td>C-S (n=601), Non-S (n=1,535)</td>
<td>GR+R</td>
<td>C-S vs. Non-S (6M)</td>
</tr>
<tr>
<td>Mattey et al., 2009</td>
<td>PCS</td>
<td>56.3</td>
<td>ADA, ETA, INF</td>
<td>3,12M</td>
<td>Ever-S (n=103), Never-S (n=51)</td>
<td>GR+R</td>
<td>Ever-S vs. Never-S (3M)</td>
</tr>
<tr>
<td>Soderlin et al., 2012</td>
<td>PCS</td>
<td>55.5</td>
<td>ADA, ETA, INF</td>
<td>3,6,12M</td>
<td>C-S (n=216), Ex-S (n=345), Non-S (n=373)</td>
<td>GR+R</td>
<td>C-S vs. Non-S (3M)</td>
</tr>
</tbody>
</table>

PCS=Prospective Cohort Study; RCS=Retrospective Cohort Study; ETA=Etanercept; INF=Infliximab; ADA=Adalimumab; OR=Odds Ratio; AOR=Adjusted Odds Ratio; GR=Good Response; R=Response; Current-Smoker=C-S; Ex-Smoker=Ex-S; Non-Smoker=Non-S.
the same European League Against Rheumatism (EULAR) response as good response, response and non-response: Good response was defined as disease activity score (DAS) 28 below 3.2 and additional improvement >1.2; Non-response was DAS >5.1 and additional improvement <0.6. Response was between good response and non-response. On the other hand, these six articles used different definitions for smoking. Whereas some articles classified patients into current smoker, ex-smoker, and non-smoker at the starting point of treatment, others classified patients into ever-smoker (i.e., current smoker plus ex-smoker) and never-smoker. In a meta-analysis, clinical outcomes of TNF-α inhibitors (response and good response vs. non-response) were compared by smoking status at the prescription time point (current smokers vs. non-smokers; ex-smokers vs. non-smokers). In all studies, smokers showed lower response rates even though some articles did not show statistical significance. For consistency in the outcome definition, meta-analysis was conducted using the four articles categorizing outcomes as responders and non-responders (Abhishek, Hyrich, Mattey, Soderlin),[7,9,10,12] without the other two articles (Canhao and Saevarsdottir)[8,11] categorizing outcomes as good responders and non-responders. Results of meta-analyses based on the smoking status and outcome presentation methods (i.e., ORs or percentage) are shown in Fig. 2A, Fig. 2B, and Fig. 2C. Their heterogeneities examined by $I^2$ (75%, 32%, and 40%) were moderate, but p-values were $\geq 0.05$ in chi-square test. Lower response trends in smoker groups than non-smoker groups were shown in forest plots.

In a meta-analysis comparing response rates depending on smoking status, smokers had 36% less response than non-smokers (Pooled OR=0.64, 95% CI=0.26-1.52) (Fig. 2A), and ever-smokers showed less response than never-smokers (Pooled OR=0.44, 95% CI=0.19-1.03) (Fig. 2C), without statistical significance. For the meta-analysis of two studies that had adjusted ORs as clinical outcomes, current smokers had 59% less response than non-smokers with statistical significance (Pooled

Figure 2. Meta-analysis of clinical response to TNF-α inhibitors in patients with rheumatoid arthritis. A. current smokers vs. non-smokers, B. current smokers vs. non-smokers after adjustment, C. ever-smokers vs. never-smokers
## Table 2. Summary of clinical response to TNF-alpha inhibitors in patients with Crohn’s disease

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Age Mean (Y±SD)</th>
<th>Drug</th>
<th>Indication</th>
<th>Outcome measure time</th>
<th>Definition of smoking (unit: cigarette)</th>
<th>Definition of outcome</th>
<th>Outcome Smoker vs. Non-smoker</th>
<th>Included studies in Meta-Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaparro et al., 2011</td>
<td>RCS</td>
<td>39±12</td>
<td>INF LCD, FCD, Perianal CD</td>
<td>Patients with ≥3 administrations, mean follow-up=41M</td>
<td>≥1/day</td>
<td>LCD: Decrease of ≥3 in HBI FCD: Decrease of ≥50% in the number of draining fistulae</td>
<td>AHR=2.05 (p=0.019)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Parsi et al., 2004</td>
<td>RCS</td>
<td>40</td>
<td>INF FCD</td>
<td>FCD: at 4 wks from 3 administrations (0.2,6 wk)</td>
<td>≥5/day within 6M from drug administration</td>
<td>Partial: Decrease of ≥50% in the number of draining fistulae Complete: closure of fistulae or cessation of fistulae drainage</td>
<td>Relapse from complete responders AOR=1.8 (0.8-4.02)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Zorzi et al., 2012</td>
<td>PCS</td>
<td>35,36 (Median)</td>
<td>ADA INF CD</td>
<td>54 wks</td>
<td>-</td>
<td>Remission: CDAI&lt;150 with no use of steroid</td>
<td>AOR=0.49 (0.26-0.92)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Aguas et al., 2012</td>
<td>PCS</td>
<td>42.3</td>
<td>ADA</td>
<td>Intestinal resection for ileal or ileocolonic CD</td>
<td>Every other wk during 12M after surgery</td>
<td>-</td>
<td>No relapse during 12M after surgery</td>
<td>50% (2/4) vs. 84% (21/25)</td>
<td>O</td>
</tr>
<tr>
<td>Arnott et al., 2003</td>
<td>PCS</td>
<td>34</td>
<td>INF LCD, FCD</td>
<td>LCD: at 4 wks from 1 administration, FCD: at 4 weeks from 3 administrations (0.2,6 wk)</td>
<td>≥5/day within 6M from drug administration</td>
<td>LCD: Decrease of ≥3 in HBI FCD: Decrease of ≥50% in the number of draining fistulae</td>
<td>52.4% (11/21) vs. 84.0% (42/50) AOR=0.24 (0.06-0.91)</td>
<td>O</td>
<td></td>
</tr>
<tr>
<td>Fefferman et al., 2004</td>
<td>PCS</td>
<td>40</td>
<td>INF LCD, FCD</td>
<td>LCD: at 4wks from 1 administration, FCD: at 4weeks from 3 administrations (0.2,6 wk)</td>
<td>≥7/wk at drug administration</td>
<td>Symptom improvement</td>
<td>69.6% (32/46) vs. 79.9% (123/154)</td>
<td>O</td>
<td></td>
</tr>
<tr>
<td>Hlavaty et al., 2005</td>
<td>PCS</td>
<td>(34.6±12.1) FCD (38.9±14.5)</td>
<td>INF LCD, FCD</td>
<td>LCD: at 4 weeks from 1 administration, FCD: at 5 weeks from 3 administrations (0.2,6 wk)</td>
<td>-</td>
<td>LCD: Decrease of ≥70 CDAI FCD: Decrease of ≥50% in the number of draining fistulae</td>
<td>60.0% (45/75) vs. 60.6% (83/137)</td>
<td>O</td>
<td></td>
</tr>
<tr>
<td>Katz et al., 2012</td>
<td>RCS</td>
<td>25 ±13</td>
<td>INF CD</td>
<td>Over 1 Y</td>
<td>-</td>
<td>Symptom improvement and continuous treatment</td>
<td>27.3% (9/33) vs. 51.1% (69/135)</td>
<td>O</td>
<td></td>
</tr>
<tr>
<td>Kevans et al., 2006</td>
<td>PCS</td>
<td>29</td>
<td>INF LCD, FCD</td>
<td>LCD: after 1 administration, FCD: after 3 administrations (0.2,6 wk)</td>
<td>Presence of smoking at drug administration</td>
<td>Symptom improvement</td>
<td>73.3% (33/45) vs. 70.8% (34/48)</td>
<td>O</td>
<td></td>
</tr>
<tr>
<td>Kong et al., 2013</td>
<td>-</td>
<td>34</td>
<td>INF CD, Ulcerative colitis:</td>
<td>Smoker: 86 wks Non-smoker: 59 wks</td>
<td>-</td>
<td>Complete response: cure of diarrhea and stomach cramp, closure of all fistulae</td>
<td>37.5% (3/8) vs. 59.1% (13/22)</td>
<td>O</td>
<td></td>
</tr>
<tr>
<td>Laharie et al., 2005</td>
<td>RCS</td>
<td>35±14</td>
<td>INF LCD (35±14Y)</td>
<td>8 wk-response</td>
<td>≥5 / Day within 6M from drug administration</td>
<td>Decrease of ≥100 in CDAI</td>
<td>61.9% (13/21) vs. 65.2% (15/23)</td>
<td>O</td>
<td></td>
</tr>
<tr>
<td>Lin et al., 2012</td>
<td>RCS</td>
<td>39.9</td>
<td>INF LCD</td>
<td>Lost-responders after INF injection per 8 wks during ≥6 M</td>
<td>Over 3 times per 6 wks</td>
<td>-</td>
<td>Symptom improvement</td>
<td>66.7% (2/3) vs. 81.5% (22/27)</td>
<td>O</td>
</tr>
<tr>
<td>Luna-Chadid et al., 2004</td>
<td>PCS</td>
<td>38</td>
<td>INF FCD</td>
<td>FCD: at 4 weeks from 3 administrations (0,2,6 wk)</td>
<td>≥5 / Day within 6M from drug administration</td>
<td>Decrease of ≥50% in fistulae</td>
<td>85.2% (46/54) vs. 75.9% (41/54)</td>
<td>O</td>
<td></td>
</tr>
</tbody>
</table>
adjusted OR=0.41, 95% CI=0.17-0.95) (Fig. 2B).

Impact of smoking on drug response in patients with CD

Table 2 shows the summaries of 22 articles that reported associations of smoking and clinical response to TNF-α inhibitors in patients with CD. They were all observational studies, and the definitions of clinical response as a final endpoint varied. In general, Crohn’s Disease Activity Index (CDAI) of ≥70% decrease or Harvey-Bradshaw index (HBI) of ≥3 decreases was used for luminal CD, and a decrease of ≥50% in the number of draining fistulae was used for fistulizing CD. Smoking status was classified into current smoker and non-smoker at the time of treatment initiation.
of drug prescription. Among 22 articles, 3 were excluded due to different presentation of clinical outcomes (i.e., clinical response in 19 articles vs. adjusted hazard ratio in Chaparro, adjusted odds ratio for relapse in Parsi, and adjusted odds ratio in Zorzi). Reported drug responses by smoking status were inconsistent in those studies. 13 studies showed better drug response (lower OR) in current smokers than in non-smokers, whereas 6 studies (Kevans, Lunnarchild, Molnar, Rudolph, Vermeier, Triantafillidis) showed worsened drug response (higher OR) in current smokers than in non-smokers. Pooled OR for 19 studies was 0.76 (95% CI=0.55-1.04) (Fig. 3). Current smokers had lower responses in luminar CD (Pooled OR=0.62, 95% CI=0.34-
1.14) (Fig. 4A) and higher responses in fistulizing CD (Pooled OR=1.04, 95% CI=0.61-1.76) (Fig. 4B), but these results had no statistical significance.

Discussion

In this study, clinical response to TNF-α inhibitors in patients with CD or RA seemed to be lower among smokers than non-smokers. Drug interaction with smoking was reported in previous articles. Smoking interacted with drug metabolism and elimination through induction of CYP enzymes such as CYP1A1, 1A2, and 2E1.[1] Therefore, to achieve the treatment effects for drugs that interact with smoking, dose adjustments would be required for smokers. When patients stop or start smoking, dose increase or decrease would be also required.[1]

Moreover, smoking is related to disease deterioration, chronic inflammation, increase of adverse drug reactions, and reduction of drug response.[2,35] In addition, cigarette smoke contains thousands of toxic chemicals including carcinogens that lead to unknown adverse effects on the disease or drug treatments.[1]

Smoking may be a negative predictor of response to TNF-α inhibitors as observed in our study, even though no biologically plausible reason was clearly elucidated. Meanwhile, smoking is a well-recognized risk factor for the development of RA or CD [3,4] with an association with more severe disease state such as higher levels of disability and extra-articular manifestations.

The proposed mechanisms for this phenomenon are as follows. A complex alteration in immune cell function is reported in smokers. The effect of smoking includes induction of inflammatory response, immune suppression, alteration of cytokine balance, and DNA damage.[38] For example, smoking patients with RA or CD exhibit increased TNF-α release and stimulated T lymphocytes.[39] An increase in TNF-α could lead to greater consumption of TNF-α inhibitors, thereby reducing circulating drug levels. Kong et al. reported that smoking patients administered infliximab for CD had a median trough level of 0.34 mg/L versus 13.3 mg/L for non-smoking patients.[22] Furthermore, the level of antibodies against infliximab was significantly higher in smokers than in non-smokers, which is associated with a negative response to infliximab in CD.[22]

Both smoking-induced systemic inflammation, including cytokine levels, and smoking-elevated basal metabolic rate[7] may interact to reduce the response of anti-rheumatoid drugs.[40,41]

The study findings were not statistically significant, although the smoking group was more likely to show lower response to TNF-α inhibitors than the non-smoking group. This study could not confirm the potential association for the following reason: It was very difficult to obtain information on the distinct history of smoking. (i.e., changes in smoking habits after initiation of therapy, duration and amount of smoking, and duration of smoking cessation). Other confounding parameters such as disease severity, disease duration, previously tried drugs, and concomitant therapy may not be comparable between smoking and non-smoking groups due to the nature of the observational study. In addition, a statistical approach for publication bias may not be appropriate in this study. But, for reference, bias was assessed by graphical funnel plotting and Begg and Mazumdar's rank correlation (Begg's test) and Egger's linear regression asymmetry test of the intercept (Egger's test). We did not see publication bias in the graphical approach or through statistical testing.

This study has limitations. First, all the studies we included in this review study were observational studies. We knew that a randomized controlled trial study design to investigate a negative impact of smoking on drug response would not be feasible for ethical reasons. The best way to increase validity of observational studies may be to analyze the association between drug and smoking while controlling confounding variables such as disease severity, TNF-α inhibitor compliance, and concomitant drugs. However, most articles we enrolled simply reported clinical response results in smokers and non-smokers. Only a few articles reported adjusted odds ratios in patients with RA, showing a significantly lower response in smokers. We expect further studies to more clearly prove an association between smoking and drug effect after controlling for confounders. Second, definitions of smoking differed in each study in terms of time point and amount of exposure to cigarettes. A majority of studies classified smoker or non-smoker by smoking status at the time of drug initiation, but some studies considered ex-smoking status. [7,8,10-12] Some studies defined the amount of smoking as more than 5 cigarettes per day within 6 months from initiation of drug administration,[16,19,20,28,29] more than 7 cigarettes per week,[18,26] more than 1 cigarette per day,[17] or the presence of smoking without considering cigarette numbers.[13-15,22-25,27,31-34] These variable smoking definitions could contribute to the discrepancy in the study results. Third, we could not separately report individual TNF-α inhibitor drugs due to the small number of studies we analyzed. Further studies are required to define the interference of smoking with individual TNF-α inhibitors in terms of pharmacokinetic and pharmacodynamics profiles.

Conclusion

Despite the above limitations, our study suggests a potential smoking effect on TNF-α inhibitors used in patients with RA or CD. Potential reduction of clinical response to these drugs in smokers could raise awareness of smoking cessation in order for these patients to achieve optimal drug response and to ultimately reach the treatment goal for the diseases. The study findings support that smoking behaviors may be considered an additional risk factor in the treatment with TNF-α inhibitors.

Acknowledgments

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Conflict of Interest

None of the authors has any conflicts of interest regarding this study.

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