

# Impact of smoking on the effectiveness of TNF- $\alpha$ inhibitors in patients with rheumatoid arthritis or Crohn's disease

Im-Sook Song<sup>1#</sup>, Hyun Soon Sohn<sup>2#</sup>, Hyunah Kim<sup>3</sup>, Eunjeong Lim<sup>1</sup>, Mihwa Kwon<sup>1</sup>, Ji-Hye Ha<sup>4</sup> and Jin-Won Kwon<sup>1\*</sup>

<sup>1</sup>College of Pharmacy and Research Institute of Pharmaceutical Sciences, Kyungpook National University, Daegu 700-721, South Korea, <sup>2</sup>Graduate School of Clinical Pharmacy, CHA University, Gyeonggi-do 463-836, South Korea, <sup>3</sup>College of Pharmacy, Sookmyung University, Seoul 140-742, South Korea, <sup>4</sup>Clinical Research Division, National Institute of Food and Drug Safety Evaluation (NIFDS) Chungcheongbuk-do 363-700, South Korea

\*Correspondence: J. W. Kwon; Tel: +82-53-950-8557, Fax: +82-53-950-8580, E-mail: jwkwon@knu.ac.kr

#These authors contributed equally as co-first authors

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Cigarette smoking may be associated with the augmentation of pro-inflammatory cytokines including Tumor Necrosis Factor-alpha (TNF- $\alpha$ ), which may affect the outcomes of pharmacological agents such as TNF- $\alpha$  inhibitors. The purpose of this study was to investigate the impact of smoking on the effectiveness of TNF- $\alpha$  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- $\alpha$  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 luminal CD or fistulizing CD, current smokers tended to have a lower response in luminal 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- $\alpha$  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 as-

sociated 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- $\alpha$ ).[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-

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ing can affect the outcomes of pharmacological agents such as TNF- $\alpha$  inhibitors including infliximab, adalimumab, and etanercept, which are used for the treatment of RA or CD. TNF- $\alpha$  inhibitors produce excellent clinical responses for patients with these diseases, but there are limited therapeutic alternatives for patients who fail to respond to TNF- $\alpha$  inhibitors.[5] Therefore, practical guidance to achieve optimal drug responses in patients who use TNF- $\alpha$  inhibitors is very important. But, there is not sufficient information on the effect of smoking on the therapeutic outcome of TNF- $\alpha$  inhibitors. There are still controversies about whether smoking affects the response in patients treated with TNF- $\alpha$  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- $\alpha$  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- $\alpha$  inhibitors. Disease severity and patients' demographics such as age and gender were not limited. TNF- $\alpha$  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](http://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- $\alpha$  in patients with RA or CD. Studies that did not provide sufficient information to evaluate the clinical association between smoking and TNF- $\alpha$ , 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- $\alpha$  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

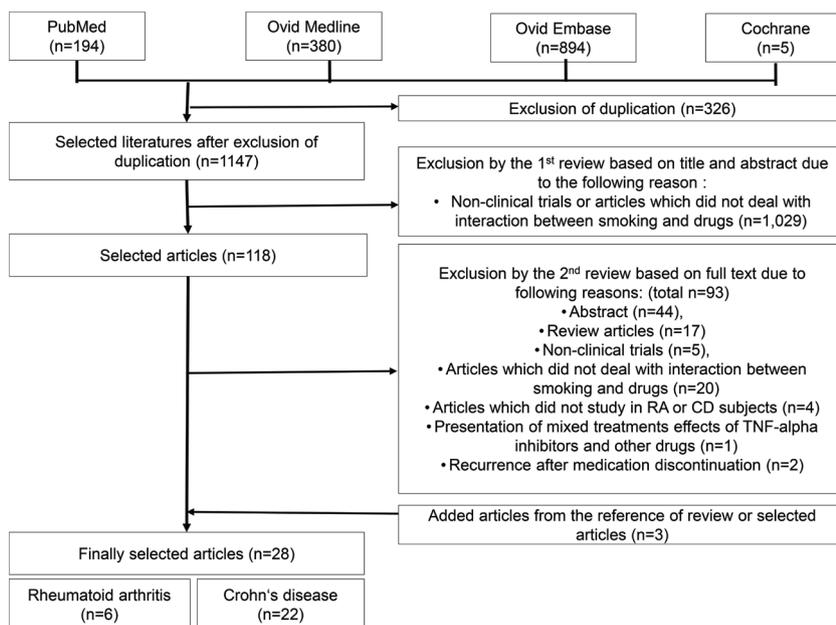


Figure 1. Flow chart of article selection

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 1.** Summary of clinical response to TNF-alpha inhibitors in patients with rheumatoid arthritis

Reference	De-sign	Age Mean (SD)	Drug	Treat-ment period	Smoking Status	Out-come (EULAR criteria)	Results	Included studies in Meta-Analysis	
Canhao et al., 2012	PCS	52.6	ADA, ETA, INF	$\geq 1Y$	Ever-S (n=132), Never-S (n=485)	GR	Ever-S vs. Never-S AOR=0.98 (0.97-0.99)	X	
Saevarsdottir et al., 2011	PCS	53	ADA, ETA, INF	3,6M	C-S (n=98), Ex-S (n=90), Non-S (n=113)	GR	C-S vs. Ex-S vs. Non-S (3M)	28% (28/98) vs. 39% (35/90) vs. 43% (49/113)	X
							C-S vs. Non-S (3M)	AOR=0.52 (0.29-0.96)	
							C-S vs. Non-S (6M)	AOR=0.55 (0.31-0.96)	
Abhishek et al., 2010	RCS	-	ADA, ETA, INF	3M	C-S (n=71), Ex-S (n=173), Non-S (n=133)	GR+R	C-S vs. Ex-S vs. Non-S (3M)	81.6% (58/71) vs. 90.8% (157/173) vs. 92.5% (123/133)	O
							Ever-S vs Never-S (3M)	88.1% (215/244) vs. 92.5% (123/133)	
							C-S vs. Non-S (3M)	AOR=0.20 (0.05-0.83)	
							C-S vs. (Ex-S+Non-S) (3M)	AOR=0.30 (0.11-0.81)	
Hyrich et al., 2006	PCS	55 (12)	INF, ETA	6M	C-S (n=601), Non-S (n=1,535)	GR+R	C-S vs. Non-S (6M)	74.5% (448/601) vs. 76.2% (1738/2278)	O
								INF: AOR=0.77 (0.60-0.99)	
								ETA: AOR=1.06 (0.80-1.41)	
Mattey et al., 2009	PCS	56.3	ADA, ETA, INF	3,12M	Ever-S (n=103), Never-S (n=51)	GR+R	Ever-S vs. Never-S (3M)	79.6% (82/103) vs. 94.1% (48/51)	O
								AOR=1.98 (1.34-3.13)	
							Ever-S vs. Never-S (12M)	46.6% (48/103) vs. 64.7% (33/51)	
		AOR=1.65 (1.18-2.30)							
Soderlin et al., 2012	PCS	55.5	ADA, ETA, INF	3,6,12M	C-S (n=216), Ex-S (n=345), Non-S (n=373)	GR+R	C-S vs. Non-S (3M)	AOR=0.53 (0.32-0.87)	O
							C-S vs. Non-S (6M)	OR=0.92 (0.55-1.54)	
							C-S vs. Non-S (12M)	OR=1.12 (0.60-2.12)	

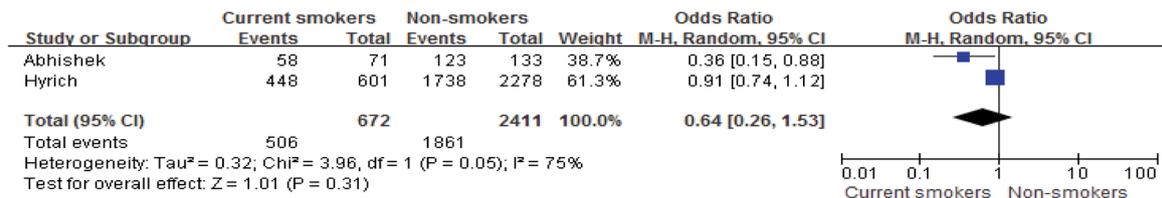
PCS=Prospective Cohort Study; RCS=Retrospective Cohort Study; ETA=Etanercept; INF=Infliximab; ADA=Adalimumab; OR=Odds Ratio; AOR=Adjusted Odds Ratio; GR=Good Response; R=Response; Current-Smoker=C-S; Ex-Smoker=Ex-S; Non-Smoker=Non-S.

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- $\alpha$  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

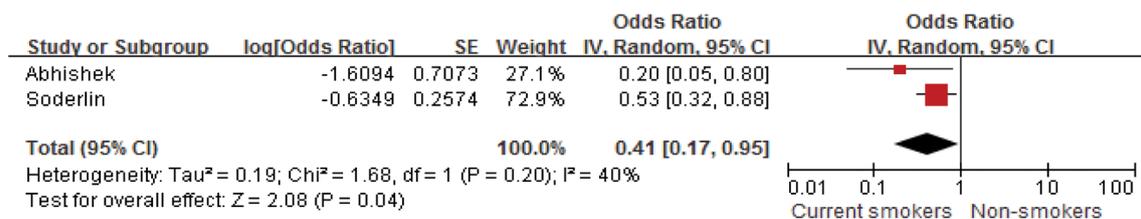
as responders and non-responders (Abhishek, Hyrich, Matthey, Soderlin), [7,9,10,12] without the other two articles (Canhao and Saevarsdottir) [8,11] categorizing outcomes as good responders and non-responders. Results of meta-analyses based on the smoking status and outcome presentation methods (i.e., 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

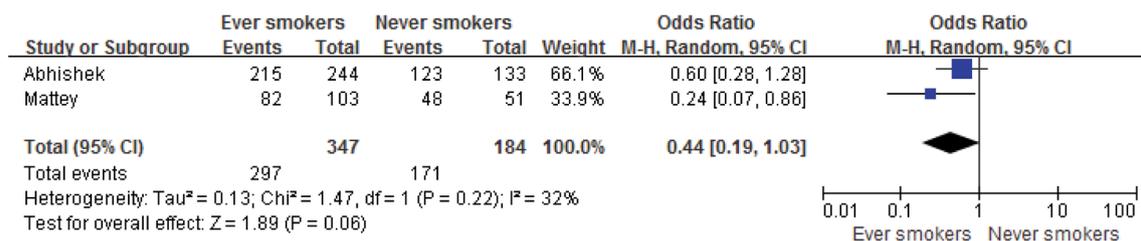
A



B



C



**Figure 2.** Meta-analysis of clinical response to TNF- $\alpha$  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

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

Table 2. Continued

Reference	Design	Age Mean (Y±SD)	Drug	Indication	Outcome measure time	Definition of smoking (unit: cigarette)	Definition of outcome	Outcome Smoker vs. Non-smoker	Included studies in Meta-Analysis
Molnar et al., 2012	RCS	25.9	ADA, INF	Active CD refractory (n=44), FCD (n=4), LCD (n=13)	1 Y (administration per 4-8 wks)	-	Non-response : Dose increase, Change treatment, Surgery required, Continuous steroid treatment	80% (16/20) vs. 56% (23/41)	○
Nichita et al., 2010	RCS	38±11	ADA	CD	At 4-6 wks after injection (every other wk)	-	Decrease of ≥ 3 in HBI	79.3% (23/29) vs. 88.5% (23/26)	○
Orlando et al., 2005	PCS	30.1	INF	LCD, FCD	LCD: at 12 wks after 1 <sup>st</sup> injection (1-3 injections) FCD: at 12 wks after 1 <sup>st</sup> injection (0,2,6 wk)	≥7/wk at drug administration	LCD: Decrease of ≥ 70 in CDAI, FCD: Decrease of ≥50% in the number of draining fistulae	77.2% (187/242) vs. 80.7% (322/399)	○
Papamichael et al., 2012	PCS	32 (Median)	ADA	FCD (n=10) Penetrating CD (n=5)	24M	-	Endoscopic relapse	50.0% (4/8) vs. 71.4% (5/7)	○
Parsi et al., 2002	RCS	36	INF	LCD, FCD	LCD : at 4 weeks from 1 administration, FCD : at 4 weeks from 3 administrations (0,2,6 wk)	≥5/day within 6M from drug administration	LCD : Decrease of ≥ 3 in HBI FCD: Decrease of ≥ 50% in the number of draining fistulae	48.6% (17/35) vs. 76.9% (50/65) LCD: AOR=0.09 (0.02-0.38) FCD: AOR=0.42 (0.06-2.82)	○
Rudolph et al., 2008	RCS	37	INF	CD	After 3 administrations (0,2,6 wk)	Smoking within 6M from drug administration	Improvement of initial clinical response	92.1% (35/38) vs. 86.9% (139/160) Smokers among initial responders (n=174) had lower response duration (HR=2.63, p=0.005)	○
Sakuraba et al., 2012	PCS	34.1	INF	CD patients who had surgeries of ≥ 2 and no adverse reaction	24M	-	Clinical remission (patients did not show increase of >50 in CDAI)	66.7% (2/3) vs. 57.1% (4/7)	○
Triantafyllidis et al., 2010	PCS	39±14	ADA	CD	At 4 wks	-	Decrease of >70 in CDAI	100% (11/11) vs. 89.5% (17/19)	○
Vermeire et al., 2002	PCS	-	INF	LCD (n=137) FCD (n=103)	LCD: at 4 weeks from 1 administration, FCD: at 4 weeks from 3 administrations	-	LCD: Decrease of >70 in CDAI FCD: Decrease of ≥50% in the number of draining fistulae	75.5% (80/106) vs. 69.5% (89/128) AOR=1.38 (0.647-2.8)	○

PCS=Prospective Cohort Study; RCS=Retrospective Cohort Study; Wks=weeks; INF=Infliximab; ADA=Adalimumab; CDAI=Crohn's Disease Activity Index; HBI=Harvey-Bradshaw index; FCD=Fistulizing Crohn's Disease; LCD=Lumina Crohn's Disease; AHR=Adjusted Hazard Ratio; AOR=Adjusted Odds Ratio

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

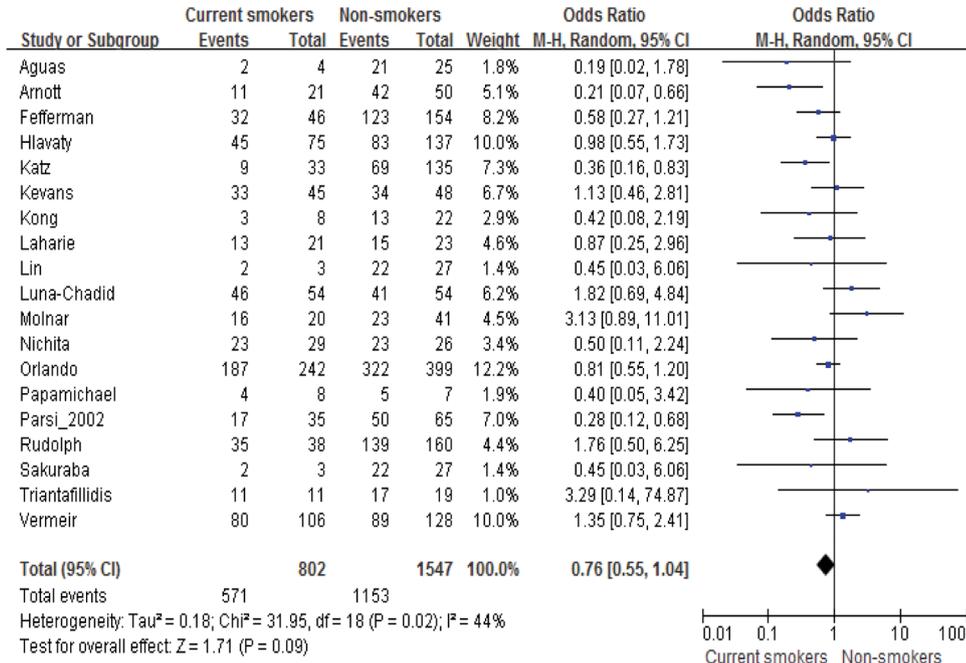


Figure 3. Meta-analysis of clinical response to TNF- $\alpha$  inhibitors between current smokers and non-smokers in patients with Crohn's disease

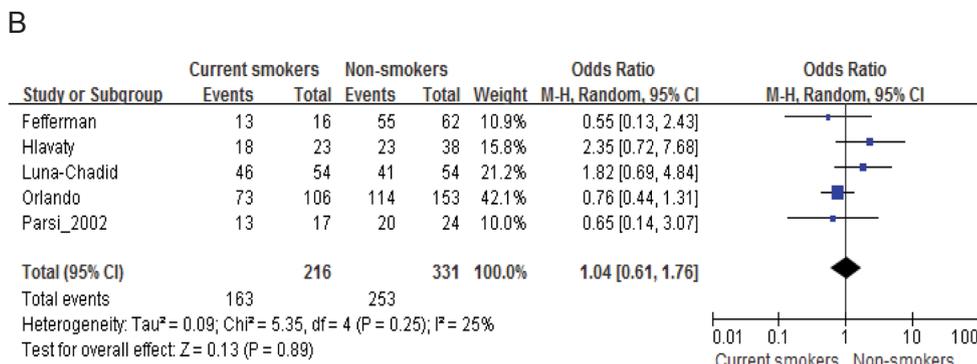
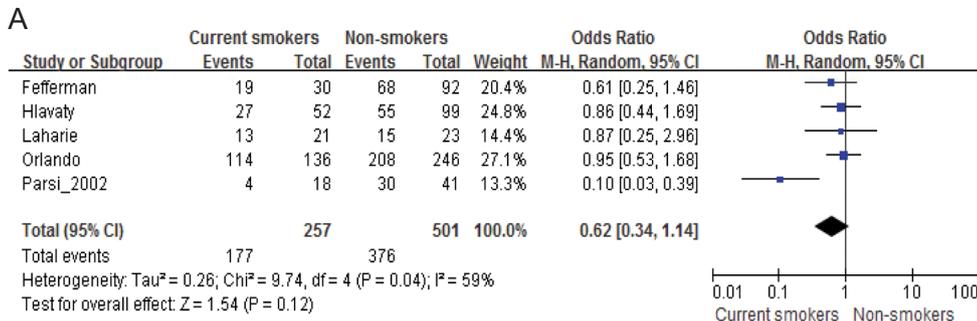


Figure 4. Meta-analysis of clinical response to TNF- $\alpha$  inhibitors in patients with luminal or fistulizing Crohn's disease. A. current smokers vs. non-smokers in patients with luminal Crohn's disease. B. current smokers vs. non-smokers in patients with fistulizing Crohn's disease

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, Triantafyllidis) 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 luminal 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- $\alpha$  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- $\alpha$  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. [36,37] 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- $\alpha$  release and stimulated T lymphocytes.[39] An increase in TNF- $\alpha$  could lead to greater consumption of TNF- $\alpha$  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- $\alpha$  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- $\alpha$  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- $\alpha$  inhibitor drugs due to the small number of studies we analyzed. Further studies are required to define the interference of smoking with individual TNF- $\alpha$  inhibitors in terms of pharmacokinetic and pharmacodynamics profiles.

## Conclusion

Despite the above limitations, our study suggests a potential smoking effect on TNF- $\alpha$  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- $\alpha$  inhibitors.

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## Conflict of Interest

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

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