

Does smoking reduce infliximab's effectiveness against Crohn's disease?

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Crohn's disease (CD) is an idiopathic inflammatory bowel disease and has no known cure. CD symptoms are treated using an array of medicines, including biological agents such as infliximab. However, infliximab therapy is expensive; therefore, identifying variables that can help predict response to infliximab is worthwhile. The present article reviews the impact of tobacco smoking on the efficacy of infliximab in CD. Earlier studies have speculated that smoking has a negative effect on the response to infliximab in CD, but the current literature is largely unable to identify a significant relationship between the two. Although smoking is known to have a negative effect on the course of CD, as well as other organ systems, presently, a CD patient's smoking status should not influence treatment decisions regarding infliximab therapy.

Key Words: *Crohn's disease; Inflammatory bowel diseases; Infliximab therapy; Ulcerative colitis; Smoking*

The inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), affect approximately 0.5% of Canadians (1). The generally accepted theory of causation is that a combination of environmental agents and a dysfunctional mucosal immune system in genetically susceptible individuals leads to the development of either CD or UC (2,3). Tobacco smoking seems to be the environmental agent with the largest impact on susceptibility to, and behaviour of, CD. While it is well-known that smoking is associated with health conditions such as cardiovascular disease, respiratory ailments and many forms of cancer, including colorectal, esophageal, gastric, small intestinal and pancreatic gastrointestinal cancers (4,5), studies have also shown that smoking predisposes people to the development of CD (6). The initial observation that smoking increases the risk of CD was made shortly after the association between smoking and UC was established in the early 1980s (7). Subsequent studies have shown a greater risk for CD in smokers than in nonsmokers (8,9), and several studies have demonstrated the adverse effects smoking has on the clinical course of disease. These adverse effects include earlier and more frequent surgery (10,11), quicker recurrence of clinical and endoscopic disease postsurgery (12,13), higher reliance on immunomodulating medications (10) and a greater overall mortality rate (14). Furthermore, selected studies in the literature have suggested that smoking cessation can improve the clinical course of disease and that patients with CD should be encouraged to quit (15).

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Le tabagisme réduit-il l'efficacité de l'infliximab contre la maladie de Crohn ?

La maladie de Crohn (MC) est une maladie inflammatoire de l'intestin idiopathique sans thérapie curative connue. Les symptômes de la MC sont traités au moyen de toute une série de médicaments, y compris des agents biologiques comme l'infliximab. Cependant, puisque la thérapie à l'infliximab est coûteuse, il est intéressant de déterminer les variables qui peuvent contribuer à prédire la réponse à l'infliximab. Le présent article vise à analyser les répercussions du tabagisme sur l'efficacité de l'infliximab contre la MC. Des études antérieures ont postulé que le tabagisme a un effet négatif sur la réponse de l'infliximab contre la MC, mais les publications à jour sont largement incapables d'établir une relation significative entre les deux. Même si on sait que le tabagisme a un effet négatif sur l'évolution de la MC, ainsi que sur d'autres systèmes organiques, le tabagisme d'un patient atteint de MC ne devrait pas influencer sur la décision thérapeutique de prescrire de l'infliximab.

To date, there is no known cure for CD, and symptoms are usually managed with 5-aminosalicylic acid compounds, corticosteroids, immunomodulators and biological agents such as infliximab (2,3). Infliximab therapy, introduced in 1998, is treatment with a monoclonal antibody that modifies CD activity by binding to and inhibiting the action of tumour necrosis factor-alpha (16). The drug has proven successful in the induction and maintenance of remission in patients with active luminal CD that has not responded to conventional anti-inflammatory drugs; it is also used for patients who cannot tolerate conventional therapy or for whom such therapy is contraindicated (17). Infliximab has also proven useful in the treatment of fistulizing in CD for patients whose disease has failed to respond to conventional treatment such as antibiotics and surgical drainage. Despite its effectiveness against both luminal and fistulizing CD, infliximab's use is limited by cost in most areas of the world. In 2007, a single infusion of infliximab at 5 mg/kg for a 70 kg patient cost US \$2,796.00 (18). This cost, along with the fact that approximately 30% of patients do not seem to benefit from the treatment, makes it important for researchers to identify predictive response factors, particularly those that are modifiable (19). Because tobacco smoking is the modifiable environmental factor with the largest impact on CD, a review of the currently available literature regarding the impact of smoking on the efficacy of infliximab was undertaken.

SYSTEMATIC LITERATURE SEARCH

A systematic search was conducted to retrieve high-quality, peer-reviewed infliximab studies that investigated the association between tobacco smoking and any facet of IBD. Potential English-language studies from the MEDLINE and PubMed databases from 1998 to 2008 were identified using medical subject heading terms "infliximab and Crohn's" combined with "smoking", "tobacco" and "inflammatory bowel disease". All titles and abstracts of the 487 articles retrieved from the search were reviewed, and if an article was assessed as potentially useful, it was reviewed for content. If the article considered tobacco smoking as a prognostic factor for response to infliximab, it was reviewed for quality. Studies that met level 2b (or higher) criteria proposed by the Oxford Centre for Evidence-Based Medicine levels of evidence (20) were included in the present review. Ten studies met the above criteria and had a total of 1779 participants.

SMOKING AND ITS IMPACT ON THE EFFICACY OF INFLIXIMAB

The 10 studies in our search included randomized controlled trials and retrospective cohort studies that examined prognostic variables for using infliximab in CD (Table 1). Two of these studies found that smoking had a significant impact on response to infliximab. In their retrospective cohort study of 100 CD patients treated with infliximab for 18 months in the United States, Parsi et al (19) demonstrated that nonsmokers had a higher response rate than smokers. This association was primarily noted in the case of patients with luminal disease, in which nonsmokers had a response rate of 73%, compared with a response rate of 22% for smokers ($P < 0.001$), as well as a higher rate of duration of response: 59% of nonsmokers were in remission for a duration of two months, compared with just 6% of the smokers ($P < 0.001$). This difference in the response rate was not observed for patients with fistulizing disease, but nonsmokers with fistulizing CD did have a longer duration of response than did smokers ($P = 0.046$). These findings were similar to those of Arnott et al (21), who also found that smokers were less likely to respond to infliximab in a prospective cohort study of 74 patients with CD in the United Kingdom. Smokers had only a 52% response rate compared with 84% among nonsmokers ($P = 0.005$). In this study, smokers' CD relapsed more frequently than that of nonsmoking patients (RR 3.2; $P = 0.0026$). Both of these trials enrolled patients who were using concurrent immunosuppressive therapy, which may have lessened the impact of their smoking on their disease courses; however, multivariate analyses in both studies confirmed that smoking had a negative, independent correlation with the response to infliximab (19,21).

Other studies in the review group did not confirm smoking to be a predictor of poor response to infliximab. In a prospective study of 240 patients with CD, Vermeire et al (22) found that smoking did not significantly influence the response to infliximab, with 75.5% of smokers and 69.5% of nonsmokers responding to the therapy ($P = 0.38$). For luminal disease, nonsmokers and smokers had similar response rates (74% versus 64%, respectively; $P = 0.5$); they also had similar durations of response (9.4 weeks compared with 8.4 weeks, respectively; $P = 0.6$). Smokers who were concurrently taking immunomodulators had similar response rates to those not taking immunomodulators (74% versus 71%, respectively; $P = 0.9$) as well as

similar durations of response (10.4 weeks versus 10.6 weeks; $P = 0.9$). For fistulous disease, response rates (89% versus 83%; $P = 0.9$) and duration of response (16.9 weeks versus 10.1 weeks; $P = 0.10$) were similar between nonsmokers and smokers, respectively, and concurrent immunomodulators had no effect on response (89% versus 86%; $P = 0.9$) or duration of response (19.8 weeks versus 15.4 weeks, respectively; $P = 0.46$). Multivariate analysis confirmed that smoking did not significantly influence the response rates or duration of response in this patient cohort. There were no significant differences between luminal and fistulizing CD, or between smokers using immunosuppressive therapy and those not taking such therapy; however, concomitant immunosuppressive therapy was identified as an independent predictor of positive response to infliximab (22).

In another prospective study, Fefferman et al (23) assessed for clinical predictors of infliximab response in a cohort of 200 patients with luminal and fistulizing CD. Response rates to infliximab in patients with luminal CD were similar for nonsmokers and smokers (74% compared with 64%, respectively; $P = 0.5$) and so were durations of response (9.4 versus 8.4 weeks, respectively; $P = 0.6$). Response rates for fistulizing CD were also similar (89% for nonsmokers versus 83% for smokers; $P = 0.9$); however, duration of response was greater for nonsmokers, but the result was not significant (23). As with Vermeire et al (22), this group of researchers found that response rates and duration of response were similar for smokers and nonsmokers, regardless of concomitant immunosuppressive therapy use.

Orlando et al (24) enrolled 573 patients with luminal and fistulizing CD in the largest CD study to date to examine demographic and clinical parameters influencing response to infliximab. Their results were similar for smokers and nonsmokers. In the case of luminal CD, 83.8% of smokers, compared with 84.6% of nonsmokers, responded ($P = 0.51$), while in the case of fistulizing CD, 68.9% of smokers and 74.5% of nonsmokers responded ($P = 0.45$). In Bordeaux, France, Laharie et al (25) also did not find significant differences in responses to infliximab in a group of 44 patients with luminal CD. They did not find that smoking was predictive of an immediate response to infliximab because 91.3% of nonsmokers and 85.7% of smokers had responded at two weeks ($P = 0.66$), and 65.2% of nonsmokers and 61.9% of smokers had responded at eight weeks ($P = 1.00$).

In 2005, Hlavaty et al (26) searched for human genetic polymorphisms and serological markers that might help predict responses to infliximab treatment for luminal and fistulizing CD. As part of their study, they included clinical variables, such as smoking status, because they believed the current literature regarding clinical predictors was inconsistent. Their results detailed similar response rates for nonsmokers and smokers; in the luminal population, 55.6% and 51.9%, respectively, responded ($P = 0.69$) and, in the fistulizing CD population, 73.7% and 78.3%, respectively, had cessation of drainage ($P = 0.19$).

In 2006, Kevans et al (27) explored the effectiveness of infliximab as a maintenance therapy in 93 patients with CD who were steroid-resistant or steroid-dependent. Response rates to infliximab in patients with luminal CD were similar for nonsmokers and smokers (71% compared with 73%, respectively; $P = 0.79$), and were also comparable among patients with fistulizing CD. They speculated that active smoking may affect disease severity but likely did not modify a patient's response to treatment.

TABLE 1
Overview of interventional studies examining the efficacy of infliximab in Crohn's disease (CD)

Author (reference)	Study design (duration)	n	Interventions	Outcomes measured	Results
Vermeire et al (22)	Prospective (four weeks for luminal CD, 10 weeks for fistulizing CD)	240	Treatment with infliximab in refractory luminal (57%) and fistulizing (43%) CD	Clinical response	Smoking did not significantly influence the response to infliximab, with 75.5% of smokers and 69.5% of nonsmokers responding (P=0.38).
Parsi et al (19)	Retrospective (18 months)	100	Treatment with infliximab in luminal (59%) and fistulizing (41%) CD	Clinical response and duration of response	73% of nonsmokers, compared with 22% of smokers, responded to infliximab (P<0.001). Prolonged response (duration more than months) was achieved in 59% of nonsmokers compared with 6% of smokers (P<0.001). For fistulous disease, overall response rates were not different between nonsmokers and smokers, but nonsmokers had a longer duration of response (P=0.046).
Arnott et al (21)	Prospective (12 months)	74	Treatment with infliximab in refractory luminal (81%) and fistulizing (19%) CD	Short-term response at four weeks and remission at one year	Those who smoked (52%) were less likely to respond to infliximab than those who did not (84%) (P=0.005); smoking patients relapsed more frequently than nonsmoking patients (P=0.0026; RR 3.2)
Fefferman et al (23)	Prospective (six months)	200	Treatment with infliximab in luminal (61%) and fistulizing (39%) CD	Clinical response and duration of response	For luminal disease, nonsmokers and smokers had similar response rates (74% versus 64%, respectively; P=0.5) and similar durations of response (9.4 weeks versus 8.4 weeks; P=0.6). For fistulous disease, response rates were similar between nonsmokers and smokers (89% versus 83%, respectively; P=0.9) and duration of response (16.9 weeks versus 10.1 weeks, respectively; P=0.10)
Luna-Chadid et al (29)	Prospective (10 weeks)	108	Treatment with infliximab in fistulizing CD	Cessation of drainage from fistula	Smoking did not affect the rate of response (86.8% of smokers responded versus 78.8% of nonsmokers; P not significant)
Parsi et al (28)	Retrospective (38 months)	60	Treatment with infliximab in fistulizing CD	Cessation of drainage from fistula site	Relapse for smokers who achieved complete response was nearly twice that of nonsmokers; this difference did not reach statistical significance (adjusted OR 1.8; 95% CI 0.8–4.02; P=0.16)
Orlando et al (24)	Prospective (40 months)	573	Treatment with infliximab in refractory luminal CD (54%), fistulizing CD (33%) or both (13%)	Clinical response and clinical remission	In luminal CD, 83.8% of smokers versus 84.6% of nonsmokers responded (P=0.51); in fistulizing CD, 68.9% of smokers versus 74.5% of nonsmokers responded (P=0.45)
Laharie et al (25)	Retrospective (56 weeks)	44	Treatment with infliximab in luminal CD	Response to infliximab (CDAI decline by >100) and long-term remission (CDAI <150)	Smoking was not a predictor of immediate response to infliximab because 91.3% of nonsmokers versus 85.7% of smokers responded at two weeks (P=0.66), and 65.2% of nonsmokers versus 61.9% of smokers responded at 8 weeks (P=1.00)
Hlavaty et al (26)	Prospective (four weeks for luminal CD, 10 weeks for fistulizing CD)	287	Treatment with infliximab in refractory luminal (71%) and fistulizing (29%) CD	Decline in CDAI to <150 or by >70 points for luminal CD, and cessation of drainage for fistulizing CD	Nonsmokers and smokers had similar responses to infliximab in both the luminal CD population (55.6% and 51.9%, respectively; P=0.69) and in the fistulizing CD population (73.7% and 78.3%, respectively; P=0.19)
Kevans et al (27)	Prospective (66 weeks)	93	Treatment with infliximab in refractory luminal (78%) and fistulizing (22%) CD	Complete resolution of CD symptoms or closure of all fistulae	Nonsmokers and smokers had similar responses overall (71% and 73%, respectively; P=0.79) in the initial response to infliximab. The two groups also had similar relapse rates

CDAI Crohn's Disease Activity Index

Although some of the above literature included discussions of fistulous CD, mainly perianal, two papers specifically focused on predictors of response in the case of fistulous disease. Parsi et al (28) examined responses to infliximab in a cohort of 60 CD patients with perianal, enterocutaneous, recto-vaginal and mixed fistulae. This study found that smokers were almost twice as likely to experience a relapse as nonsmokers were; however, this difference did not reach statistical significance (adjusted OR 1.8; 95% CI 0.8 to 4.02; $P=0.16$). Luna-Chadid et al (29), however, enrolled a somewhat larger sample size of 108 CD patients with various types of fistulae, and their study did not show significant differences in the response rates between smokers and nonsmokers.

DISCUSSION

The scholarly literature currently available reports mixed results for investigations of whether smoking affects the efficacy of infliximab. Of the 10 papers examined, two reported significant differences in the response rates between smokers and nonsmokers. Other studies either found no difference or had mixed results. One possible explanation for this apparent discrepancy involves the varying definitions of smoking used in these studies. Laharie et al (25), Arnott et al (21) and both Parsi et al (19,28) studies defined smoking as smoking more than five cigarettes per day for six months. Luna-Chadid et al (29) included any patients smoking more than five cigarettes per day, regardless of duration. However, other authors defined smoking as more than seven cigarettes per week at the time of a patient's first infliximab infusion (23,24). The studies by Hlavaty et al (26) and Kevans et al (27), based a 'smoking' definition on the patient being identified as smoking at the time of the first infusion, a definition which suggests that even a quantity of one cigarette per week classified someone as a smoker. The report by Vermeire et al (22) did not define what was meant by 'smoking', so it is possible their data was also confounded by a number of relatively light or intermittent smokers. Alternately, the data from authors whose results suggest smoking makes a difference in disease response could conceivably have been influenced by the enrollment of relatively heavy smokers. In any case, none of the available studies have adequately or consistently quantified smoking rates in their subjects, nor have they identified responses to infliximab according to the varying levels of smoking among their participants.

The different methods of collecting data (retrospective and prospective) may also explain some differences in the results because it is difficult to quantify consumption data based on recollection alone. Other complicating factors might include the different types of cigarettes that were smoked, the fact that some patients conceivably smoked only filtered cigarettes and some did not, and the fact that patients might have been those who only smoke a few puffs from each cigarette, while others may have smoked entire cigarettes. The randomized controlled trials examining infliximab, should ideally have subdivided the smokers' group, to account for the intensity and duration of smoking; however, the choice to categorize smokers into one group was most likely the result of limited sample sizes.

There is also some inherent difficulty in assessing the impact of smoking using short-term studies. For one thing, Crohn's disease affects many people at a young age, and these patients, even if smokers, would have had relatively little overall exposure to tobacco. However, smoking causes slow tissue damage over a long period of time, and smoking's effects on the efficacy of infliximab would have to be acutely profound

to be identified in short prospective studies. The longest study duration identified in the present report was 40 months, but some studies were conducted for only four to 10 weeks, depending on the location and type of CD. Clearly, higher quality long-term studies that examine responses in relation to both the duration and the doses of smoking involved are necessary.

The impact of smoking on the efficacy of other medications used to treat IBD has not been well studied. When Hinojosa et al (30) treated 50 CD patients with adalimumab (because patients had lost response to, or were intolerant to infliximab), and examined factors that predicted response in these patients, their data led them to the conclusion that although smokers had higher baseline CD activity index scores than nonsmokers, there was no significant difference in response between the two groups. Most of the other trials evaluating nonbiological medical treatments that are used for IBD were conducted before the wide publication of the knowledge that smoking adversely affects the course of CD (6). As a result, most of the randomized controlled trials that compare medications such as 5-aminosalicylates and azathioprine to placebo have not evaluated smoking as a variable that may have affected the response. For instance, the National Cooperative Crohn's Disease study (31), published in 1979, examined more than 25 possible variables that may have an impact on the efficacy of azathioprine, but smoking was not one of them. There was, however, one 1995 controlled double-blinded study (32) of the response to azathioprine treatment of CD that considered smoking as a potential predictive factor. This study did not show smoking to be an effect-modifier in determining the response to azathioprine. Similarly, two of the studies assessed in the present review (22,23) found that response rates and duration of responses were similar in smokers and nonsmokers regardless of concomitant immunosuppressive therapy use. These results, taken as a whole, suggest that there may be no relationship between smoking and immunosuppressive therapy for CD patients. Although there is a paucity of literature examining the role smoking may play in relation to other medications used to treat IBD, existing studies do not reliably show that it negatively affects the efficacy of these medications.

In addition to its use for CD, infliximab has been validated for use against other autoimmune disease states, such as rheumatoid arthritis (RA). Cigarette smoking is a well-recognized risk factor for the development of RA (33,34). As is the case with CD, smoking has been shown to have a negative impact on the course of RA, including associations with higher levels of disability (35) and extra-articular manifestations such as nodules (36). However, there is a scarcity of literature that examines whether smoking is a predictive factor for response to infliximab treatment of RA. One large study from the United Kingdom (37) has shown smoking to be a negative predictor of response to infliximab, but not to etanercept, nor did smoking affect infliximab's ability to help the patient stay in remission. This finding may suggest that nicotine and/or other substances or compounds related to cigarette smoking may interfere with the absorption or metabolism of certain drugs and may also interact with the disease state itself, such that smoking's role varies, leading to variant evaluations of smoking as a predictive factor for responses to infliximab treatment of different disease states. More studies would need to evaluate smoking as a predictive factor for response to infliximab for RA before it will be clear whether there is a consistent pattern or whether results are due to chance.

The current data regarding the influence of smoking status on the response to infliximab are conflicting and there is some possibility the influence may be minimal; however, patients with CD should be discouraged from smoking, given the negative effect it has on the course of disease and on cardiovascular and respiratory organ systems. However, at this point, a CD patient's smoking status should not influence the treatment decision regarding infliximab therapy. Only long-term prospective studies in which the timing and dosing of smoking are considered, can help conclusively determine the impact of smoking on the efficacy of infliximab treatment for CD.

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