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Smoking and Early Infliximab Response in Crohn's Disease: a Meta-analysis

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Abstract

Background: Infliximab is used to treat moderate to severe Crohn's disease (CD), but its efficacy varies. Although cigarette smoking worsens CD, its impact on the infliximab response is unknown. We conducted a systematic review and meta-analysis of clinical trials to determine the effect of smoking on the induction response to infliximab.

Methods: A systematic search was performed of MEDLINE, EMBASE, CINAHL, the Cochrane central register of controlled trials, the Cochrane IBD Group Specialized Trials Register for publications, and abstracts from major conferences from January 1996 to December 2010. Random effects meta-analysis using the Mantel–Haenszel method was conducted. Heterogeneity across studies was assessed using the Q statistic, the I^2 statistic, and τ^2.

Results: We identified 12 articles; four were excluded due to use of non-validated scoring systems. The remaining eight included a total of 1658 patients, with 649 active smokers. Luminal response was assessed by the Crohn's Disease Activity Index in four studies (three of which included fistula response) and the Harvey–Bradshaw index in two (both including fistula response), and two studies examined only the fistula response. The relative risk for response to infliximab among smokers was 0.99 (95% CI 0.88–1.11) (τ^2 = 0.0143). Analyses of the five studies examining both inflammatory and fistulizing CD were similar to the analysis of all eight studies. The pooled relative risk was 0.92 (95% CI 0.80–1.06) (τ^2 = 0.0154).

Conclusion: Though smoking worsens CD, this meta-analysis does not show a negative effect of smoking on initial response to infliximab. This must be viewed in the proper context, as long-term maintenance of response may yet be influenced by smoking status.

Keywords: Infliximab; smoking; Crohn's disease

1. Introduction

Inflammatory bowel disease (IBD), generally classified as either Crohn's disease (CD) or ulcerative colitis (UC), is a disorder of the immune system resulting in chronic inflammation of the gastrointestinal tract. Currently, an estimated 1.4 million persons in the USA carry a diagnosis of IBD.[1] Although much remains unknown about the exact pathogenesis of these diseases, our knowledge has greatly evolved over the past decades. IBD appears to be the result of a disordered immune response to an environmental exposure, mainly to native bowel bacteria.

Treatment of CD remains challenging, even with the availability of newer biologic therapies, used either as an alternative to or in combination with traditional therapies, such as mesalamine derivatives, corticosteroids, and immune modulators (6-mercaptopurine

[6MP]/azathioprine [AZA] or methotrexate). Infliximab (Remicade) was FDA-approved in 1998 as the first of these biologic therapies for CD and is a chimeric monoclonal antibody that targets the signaling of inflammation by tumor necrosis factor (TNF)-α, a key pro-inflammatory cytokine responsible for bowel mucosal inflammation. Studies have consistently shown the benefits of infliximab for the induction and maintenance of response and remission, both for luminal CD and the treatment of perianal fistulas.[2–6] Despite this proven efficacy, current evidence suggests that about 30% of patients will not exhibit any initial response to infliximab, while a further 20% will demonstrate a response without achieving full remission.[7] While these rates may be improved with concurrent 6MP/AZA treatment,[8] it is vital to look for other modifiable factors that may influence this response.

Currently only one environmental/lifestyle exposure, smoking, has consistently been shown to affect IBD activity. Paradoxically, while smoking has been shown to be less common in UC and to lessen the severity of UC, it has consistently been found to be more common in those with CD and to worsen the severity of CD.[9–12] The recent large meta-analysis by Mahid et al.[13] found an association between current smoking and CD (odds ratio 1.76, 95% CI 1.40–2.22), similar to the findings of the population-based studies by Bernstein et al.[9] and Lakatos et al.[14] Smokers with CD have also been observed to undergo earlier and more frequent surgery,[15] develop quicker recurrence of clinical and endoscopic disease after surgery,[16] have more severe disease activity with a higher reliance on immune modulating medications,[15] and a greater overall mortality rate.[17]

Although smoking clearly worsens CD, its impact on the efficacy of medical therapy for CD is largely unknown. The recent systematic review by Narula and Fedorak[18] was unable to identify any significant association between smoking status and the response to infliximab. Given the continuing uncertainty, we continued the work of Narula and Fedorak[18] by updating their systematic review and performing a meta-analysis of clinical trials to quantify the effect of smoking on the induction response to infliximab.

2. Methods

2.1 Literature search

We performed a medical literature search of MEDLINE, EMBASE, CINAHL, the Cochrane central register of controlled trials, and the Cochrane IBD Group Specialized Trials Register for articles published from January 1996 to December 2010. We used PubMed, Ovid and EMBASE to perform the searches, which did not have any language restriction. The search was performed using the following keywords and MeSH terms: 'smoke', 'smoking', 'inflammatory bowel disease', 'Crohn's disease', 'Crohn's', 'biological agents', 'Remicade', and 'infliximab'. Boolean operators ('not', 'and', 'or') were also used in succession to narrow and widen the search. We also used the 'explode' and 'related article' function in the Ovid search to increase the breadth of the articles we collected. We also reviewed abstracts from major conferences for studies not available as published manuscripts. We also went through the references of the articles that we collected to find other literature that we might have missed during the search. Finally, one of the co-authors (SK), an expert in the field of IBD, was consulted to investigate for studies not identified by the literature search and for any unpublished data.

2.2 Inclusion and exclusion criteria

We used the Patients, Intervention, Comparator, Outcomes, Study design (PICOS) criteria for inclusion and exclusion of studies in the meta-analysis. The studies included in the meta-analysis had to meet the following criteria: (1) cohort study among patients with CD (study design); (2) CD diagnosis according to well-defined criteria (patients); (3) inclusion of adults (>90% of patients aged >16 years) with CD (patients); (4) minimum follow-up period for assessment of response after induction of 4 weeks for luminal disease, 10 weeks for perianal fistulizing disease, with response to either one or both classified as a response to induction (outcomes); (5) assessment of luminal disease severity by either the Crohn's Disease Activity Index (CDAI) or the Harvey–Bradshaw Index (HBI) (outcomes); (6) assessment of the fistula response limited to perianal fistulas, Montreal behavior subtype 'p' (patients); and (7) assessment of smoking status (present smokers and former smokers were both included) (comparator: smokers versus non smokers) among patients who received infliximab therapy (intervention).

We excluded studies that (1) combined both UC and CD response to infliximab; (2) were review articles, case reports, editorials, or letters to the editor; or (3) did not assess smoking status separately for responders and nonresponders to infliximab therapy.

We rated the methodological quality of the selected studies using the Newcastle–Ottawa Quality Assessment Scale for nonrandomized studies. This scale uses a starring system to assess each study. Three categories are used to grade the studies: (1) selection of the studied cohort, which includes fours items; (2) outcome assessment, with three items; and (3) comparability between the studied cohort and controls, with two items.

2.3 Data collection

Two independent investigators (SI and AV) identified articles that met the predetermined inclusion and exclusion criteria as stated above. Of the total of 2157 papers that were identified, only eight met the inclusion and exclusion criteria and were included in the meta-analysis (Figure 1). Both the investigators used a standardized data collection form to increase uniformity and reduce bias in reporting. In the case of discrepancy, the investigators resolved the disagreement by discussion with a senior investigator (KS). The papers included in our meta-analysis were reviewed in detail for data extraction on first author, year of publication, journal, study design, duration of follow-up, type of Crohn's disease (luminal, fistulous, or both), severity score for assessment of Crohn's disease, number of patients studied, and response of smokers and nonsmokers to infliximab therapy.

2.4 Statistical analyses

This meta-analysis was performed using the guidelines of the Quality of Reporting of Meta-analysis, the Meta-analysis of Observational Studies in Epidemiology guidelines for observational studies, and the recommendations of the Cochrane Collaboration. All statistical analysis was conducted in R version 2.12.2 (R Foundation for Statistical Computing, 2011).

A random effects meta-analysis using the Mantel–Haenszel method was conducted. Random effects were chosen rather than fixed effects due to variability between studies with respect to definitions of smoking status and response, as well as the time of response assessment after the start of infliximab. Pooled estimates of the relative risk (RR) were reported.

Heterogeneity across studies was evaluated with the Q statistic, which uses the χ^2 test to assess heterogeneity. The degree of heterogeneity was reported using the I^2 statistic. Between-study variability was measured using τ^2. Sensitivity analyses were conducted to ensure that the findings were not unduly influenced by a single study by (1) excluding any study that appeared to be an outlier and (2) excluding the largest study. Due to the relatively small number of studies (eight), we were unable to use a funnel plot to assess publication bias.

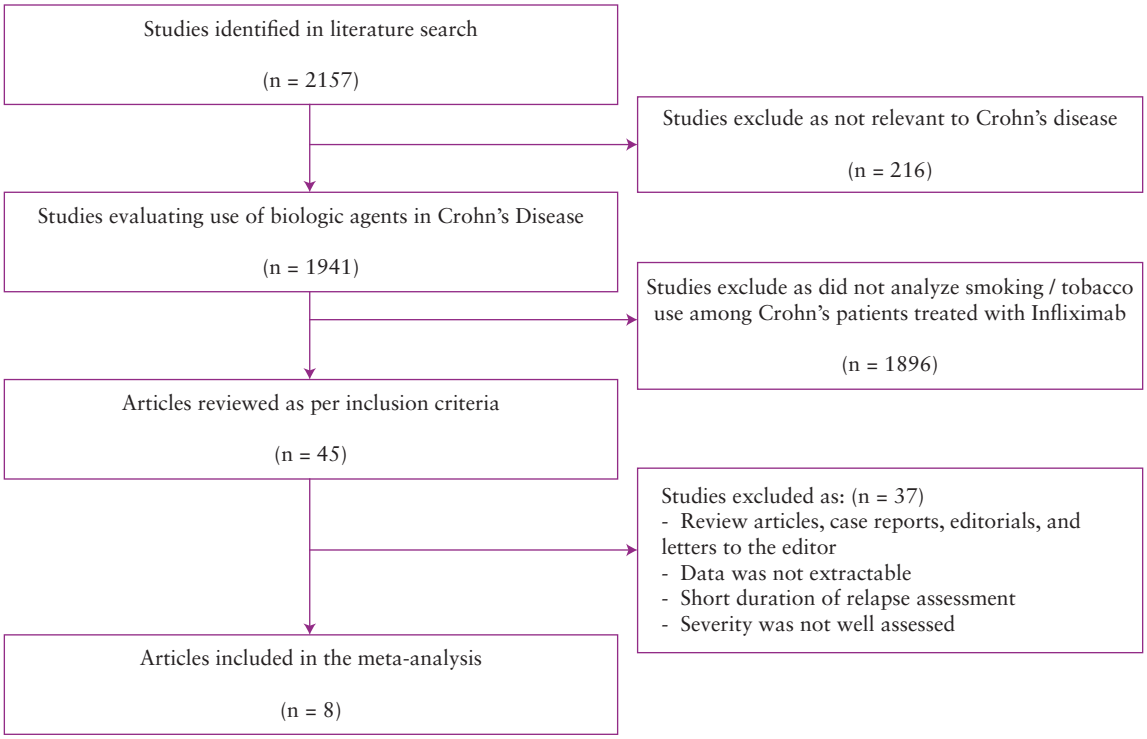

Figure 1. PRISMA flow diagram of assessment of studies identified in the meta-analysis.

3. Results

In total, eight studies, including 1726 patients, satisfied the study criteria[4,7,19–24] (Figure 1). Of these patients, 629 (36%), were active smokers. None of the studies reported patient demographic data divided between smokers and nonsmokers. None of the studies addressed smoking duration. Mean or median age of patients enrolled across all the studies ranged between 31 and 38 years, with duration of disease (when reported) at study enrollment ranging between 7.9 and 13 years. Most of the studies included were prospective cohort studies (5/8), while one of the studies was a multicenter, double-blind, randomized, placebo-controlled trial, and the remaining two were retrospective cohort studies. Six of the eight studies included in our analysis were rated as high-quality studies, and the other two were medium-quality studies (Table 1).

Five of the studies assessed both luminal and fistula response, one only luminal response, and two only fistula response. Luminal response was assessed with the CDAI in four studies (three of which included fistula response) and the HBI in two (both including fistula response), while two studies examined only fistula response (Table 1). The five studies assessing both luminal disease and fistula response reported these results together, without subdividing by phenotype. All studies dosed infliximab at 5 mg/kg of body weight. All studies assessing for fistula response followed the standard regimen of three infusions at weeks 0, 2, and 6. Most patients assessed for luminal response were given a single infliximab infusion.

The initial meta-analysis was conducted on all eight studies. A large degree of heterogeneity (Q = 19.02, p < 0.0081) was noted. The percentage of variability attributable to heterogeneity was 63.2% (I^2 = 63.2%). The estimate of the average effect (RR) was 0.99 (95% CI 0.88–1.11) (τ^2 = 0.0143, between-study variance) (Figure 2). The high degree of heterogeneity further supports the use of the random effects model. An additional analysis of the five studies that examined both inflammatory and fistulizing CD was similar to the analysis of all eight studies. The pooled RR was 0.92 (95% CI 0.80–1.06) (τ^2 = 0.0154). There was a high degree of heterogeneity among the five studies (Q = 11.29, p < 0.0235).

Two of the studies were distinct in their assessment of inflammatory luminal disease, with the infliximab response assessed using the HBI in these two studies. The other studies assessing luminal CD used the CDAI. Due to the differences in luminal CD assessment, studies using the CDAI and those only analyzing the fistula response were then analyzed separately from the two HBI studies (Figure 3). All studies used the same or a comparable method for assessing the infliximab response in subjects with fistulizing CD (Table 1).

The forest plot (Figure 3) displays the results of our subgroup meta-analyses classified by assessment of responses (HBI versus CDAI). The pooled relative risk for the two studies that used HBI for assessment of response was 0.63 (95% CI 0.48–0.83). The pooled relative risk among the six studies remaining was 1.04 (95% CI 0.97–1.13) (τ^2 = 0.0028, between-study variance). These studies showed no association between smoking and the response to infliximab treatment. Of the six studies not using the HBI, there was one potential outlier,[4] since it was the only study with positive results (i.e., the lower confidence limit of the RR was >1). When this study was removed, the pooled estimates remained nonsignificant, indicating that it did not have a major effect on the findings. When this was followed by additionally removing the largest study to examine whether it had undue influence,[20] the results were unchanged. Thus, the sensitivity analyses support the use of all six studies in the meta-analysis.

4. Discussion

Since its approval, researchers have aimed to identify factors that may predict and/or improve infliximab response rates. Several patient-associated factors that are known to predict a better initial response include younger age, shorter duration of disease, Crohn's colitis,[25] high serum C-reactive protein, and low serum TNF-α levels.[26] The

Table 1. Patients with Crohn's disease treated with infliximab: studies comparing smokers and initial response to infliximab.

Study	Year	Number of patients	Definition of luminal response	Definition of fistula response	Definition of smoking	No. of active smokers	Quality of study
Vermeire et al.[25]	2002	234	CDAI decreased by 70 points at week 4	At least 50% decrease in the number of draining fistulae at week 10	Not defined	106	High
Orlando et al.[20]	2005	573	CDAI decreased by 70 points at week 12	At least 50% reduction of the number of fistulae at week 12	>7 cigarettes/week	211	High
Sands et al.[4]	2004	306	NA	At least 50% reduction in the number of fistulae at weeks 10 and 14	Not defined	106	High
Hlavaty et. al.[21]	2005	287	CDAI decreased by 70 points at week 4	At least 50% reduction of the number of fistulae at week 10	Not defined	75†	Medium
Laharie et. al. [22]	2005	44	CDAI decreased by 100 points by week 8	NA	>5 cigarettes/day	21	High
Luna-Chadid et. al. [23]	2004	108	NA	At least 50% reduction in the number of fistulae for at least 4 consecutive weeks after week 6 of therapy	>5 cigarettes/day	54	Medium
Arnott et. al. [7]	2003	74	HBI decreased by 3 points after 4 weeks	At least 50% reduction in the number of fistulae at week 10	>5 cigarettes/day for >6 months	21	High
Parsi et. al. [24]	2002	100	HBI decreased by 3 points 4–6 weeks after infusion	Closure of at least 50% of fistulae by 10–12 weeks	>5 cigarettes/day for >6 months	35	High

NA, not applicable.
†Data not available in 72 patients.

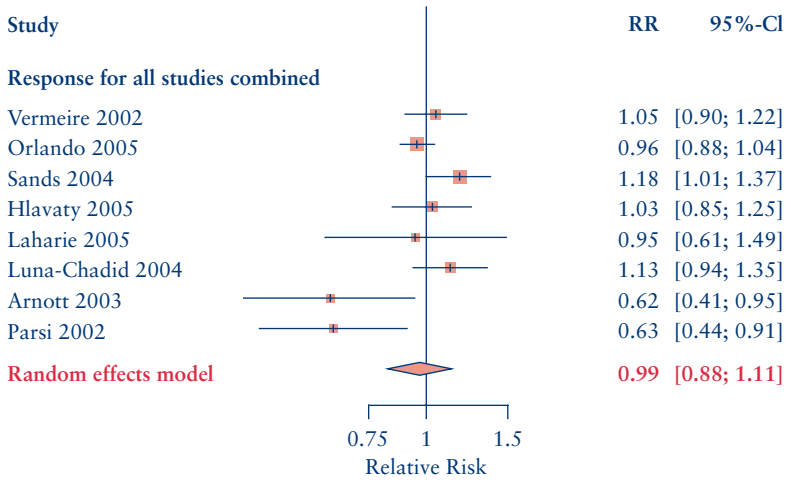

Figure 2. Relative risk of smoking and initial response to infliximab for all the studies included in the meta-analysis.

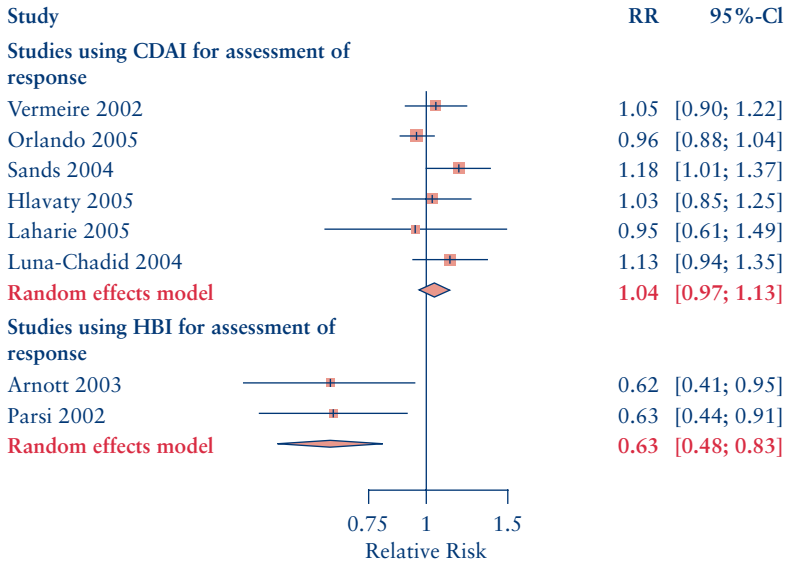

Figure 3. Relative risk of smoking and initial response to infliximab: subgroup meta-analysis of the studies classified by assessment of response.

recent SONIC trial has shown remission rates to infliximab to be increased with concurrent AZA usage.[8] While early findings suggest no short-term increased risk of complications with this approach,[27] many practitioners still express concern regarding the safety of dual immune suppression. Even if we accept the safety of dual therapy, there is still room for improvement, with almost half of the SONIC patients still failing to achieve the primary endpoint of steroid-free remission with combination therapy.[8]

Given the established association of smoking not just with CD but with worse CD-related outcomes,[28] it would be natural to assume that a treatment approach that involves smoking cessation would achieve improved initial infliximab response rates. The results of our meta-analysis suggest otherwise. As with the earlier systematic review, we found no association between smoking status and infliximab response. Our findings relied on many of the same studies included in the prior systematic review, but, unlike Narula and Fedorak,[18] we limited our evaluation to induction/early response and quantified this result with the formal meta-analysis. While smoking may not in fact impact the initial response to infliximab, limitations of our analysis, as well as limitations of the studies included in the analysis, need to be taken into account.

The first significant issue is the unclear nature of the degree of smoking that places the CD patient at risk. In the context of CD there is no universally accepted cutoff for the amount of smoking that may negatively impact the CD patient. Studies examining the epidemiology of smoking and CD have used various definitions of smoking, in terms of both the number of cigarettes per day and the length of time the individual has smoked. Within our own meta-analysis, three out of the eight studies notably did not specifically define smoking at all, with the lower cutoff in the remaining studies ranging from more than one cigarette a day to a minimum of six per day (Table 1). The type of cigarette used may also be important, but again this was not addressed by any of the included studies. These limitations are unfortunate, but not surprising as none of the studies was designed to specifically address the impact of smoking on infliximab response. Also, since smoking status in these studies was self-reported, there is always the chance that the true incidence of smoking may be higher.

The second, and more pressing, limitation of our analysis is the different method that was used for assessing luminal CD activity. The inclusion of the two studies assessing the response with the HBI, with the associated heterogeneity, does weaken the strength of the larger analysis. While the meta-analysis results were unchanged when excluding the HBI studies, it is hard to ignore that both of these studies, distinct from the other six, showed a diminished response to infliximab among smokers. Generally, the patients in the two HBI studies appeared to be similar to those in the other six studies, though the 60 patients assessed for luminal disease with the HBI by Arnott et al.[7] were at the younger end of the age spectrum for the studies as a whole, with a mean age of 31.5 years, without defining the duration of disease. The 14 patients with fistulizing disease had a mean age of 35.5 years. The patients in the other HBI study, by Parsi et al.,[24] reported a median age of 36 years and duration of disease of 10 years for the entire group, more typical of the eight studies as a whole. While the HBI has been validated against the CDAI and is commonly used in CD studies, the whole notion of using clinical indices to assess disease activity has continued to be a subject of intense debate.[19] More and more studies have added endoscopic assessment of disease activity as an endpoint for both CD and UC therapy, given the frequent discordance between clinical indices and endoscopic findings.[29,30] Looking at the forest plot (Figure 2), one is left to wonder how the results may have differed if the other six studies used the HBI rather than the CDAI.

The specific mechanism by which smoking affects CD is still largely unknown. Speculation has included possible effects on barrier function and the vascular system of the gastrointestinal tract, as well as its effect on the nervous system; smoking may also have a direct effect of on the immune system. A recent report has noted a direct effect of smoking on the function of blood mononuclear cells, with a divergent effect between CD and UC patients,[31] but it remains unclear whether nicotine is the key factor or whether other tobacco components play a role in its effects on CD.[7,24] However, very little is known about what effect smoking specifically has on TNF-α production and signaling, so there is currently no current biochemical rationale for why smoking should interfere with the benefits of anti-TNF therapy.

Though smoking clearly leads to worse CD outcomes, and we should continue to strongly recommend smoking cessation to our patients, our meta-analysis does not support a negative effect of smoking on the initial response of CD patients to infliximab. While this is a surprising result, this must be viewed in the proper context. The studies included in this meta-analysis were all conducted to assess induction, not maintenance. CD is a lifelong illness, and the effects of smoking are seen over years rather than weeks. Thus, a lack of short-term effect should not imply the same over a longer period of time. However, based on this study we can conclude that a patient's smoking status should not influence a provider's decision to initiate biologic therapy with infliximab. It is hoped that, as further study data accumulate, additional information about long-term response and remission rates related to smoking status will become available.

Conflict of Interest

None to declare.

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Specific author contributions: SI, study concept and design, data extraction and analysis, and drafting of the manuscript; AV, SI, data extraction and analysis, and drafting of the manuscript; LR, data extraction and analysis; SS, data extraction and analysis; SK, revision of the manuscript; KS, study concept and design, data extraction and analysis, drafting of the manuscript, and revision of the manuscript. All authors approved the final version of the manuscript.
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