Low-dose smoking resumption in ex-smokers with refractory ulcerative colitis

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Abstract

Background and aim: Ulcerative colitis (UC) is primarily a disease of non-smokers. Ex-smokers may have a more refractory disease course and anecdotal evidence in non-controlled clinical trials have suggested that smoking resumption, or the administration of nicotine, may ameliorate signs and symptoms of UC in ex-smokers. We report outcomes of ex-smokers with refractory UC who resumed low-dose cigarette smoking.

Methods: 17 ex-smokers with refractory UC were identified. Clinical remission was defined as a disease activity index score of 0.

Results: Two out of 17 patients refused the recommendation to resume smoking. Of the 15 patients who resumed smoking, the mean daily number of cigarettes was 8.6. Fourteen out of those 15 patients who resumed smoking were able to maintain prolonged clinical remission off steroids. One out of the 15 patients failed to improve and required oral steroids. Another patient was compelled to quit smoking since he became addicted. His disease flared after maintaining a prolonged remission of 3 years and he eventually underwent surgery. Three out of these 15 patients switched from cigarettes smoking to nicotine compounds and continued to maintain remission.

Conclusion: Resumption of low dose smoking in a selected group of ex-smokers with refractory UC may ameliorate signs and symptoms. Quality of life, medication side effects, and smoking risk factors should all be considered and discussed with patients. Smokers should be meticulously followed for compliance with “low-dose” regimen and all associated smoking risks.

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1. Introduction

The etiology of inflammatory bowel disease (IBD) remains unknown despite evidence for both genetic and environmental contributing factors. Furthermore, while Crohn’s disease (CD) and ulcerative colitis (UC) share many epidemiological and clinical features, one striking distinction is an inverse association with cigarette smoking exposure. Patients with UC tend to be non-, or ex-smokers while those with CD tend to be smokers. Additionally, former smokers with UC tend to have poorer outcomes while current smokers with CD tend to have higher complication and post-operative relapse rates. Cigarette smoke contains hundreds of potentially toxic (or therapeutic) compounds, many of which have unknown action in the human body. Unfortunately, the identity of a well-defined cause-and-effect relationship among the numerous tobacco smoke agents remains elusive. Furthermore, the definitions of smokers and former smokers in terms of number of cigarettes and the relative timing for development of UC after smoking cessation has varied. Finally, for obvious reasons, a prospective study of the effect of cigarette smoking on UC would be of questionable ethics due to the recognized harmful impact of cigarette smoking.

Herein, we conducted an observational study assessing the effect of smoking resumption on a small cohort of refractory UC former smokers treated in a dedicated IBD clinic.

2. Methods

We conducted a retrospective descriptive study, reviewing medical records of UC patients who were recommended moderate smoking resumption (3–5 cigarettes per day) from clinic practice (SBH, DTR) at our institution. No systematic strategy was used to identify all patients who were UC former smokers, current smokers, or those who were recommended smoking resumption. All those patients identified had refractory disease and/or were steroid dependent. In all the cases, this recommendation was one of several other alternatives, mainly surgery or experimental therapy. Medical records were electronically searched to identify patients. Inclusion criteria were: evidence of current or ex-smoking, alternative nicotine consumption, and availability of long term follow up data. UC patients or patients with history of total proctocolectomy for UC who were refractory to conventional therapy were included. Exclusion criteria were: the diagnosis of CD or indeterminate colitis. In our study, smoking was defined as regular smoking of any amount of tobacco for at least a year, and former smoking required quitting tobacco consumption for at least three months prior to the onset of UC. Non-smoking was defined as never having smoked or having only occasional rare experiences with smoking. All patients included in the analysis had provided authorization for medical record review for research purposes, and the study was approved by the University of Chicago Institutional Review Board. Information was obtained from all enrollees by reviewing relevant medical records and personal or telephone interviews. Comprehensive general medical history and particular details relevant to the diagnosis of UC, history of cigarette smoking prior to disease onset (duration of smoking, amount, and temporal relationship to the disease onset), current smoking status, indication for smoking resumption, risk factors for smoking related diseases, concomitant therapies, and quality of life were all considered. Retrospective assessment of the effects of smoking as a therapeutic measure was defined according to clinical response judged by the treating physician and reported in the medical charts using a pre-defined clinical criteria — simple colitis clinical activity index (SCCAI).

3. Results

We were able to identify 17 former smokers who had been primarily diagnosed with UC and presented to our clinic with refractory disease and/or were steroid dependent. In all the cases conventional therapies were exhausted (aminosalicylates, thiopurines, anti-TNF biologics). Fifteen patients had refractory or steroid dependent UC, one patient had a permanent ileostomy with relapsing aphthous stomatitis and one patient had an ileal pouch anal anastomosis (IPAA) with chronic refractory pouchitis. Median patient age at evaluation was 57 years (range 36–77). At diagnosis most patients were younger than 50 years of age with a median age of 35 years (18–56). Nine patients were females and 8 were males. Median disease duration was 16 years (range 2–43). Fourteen patients quit smoking prior to diagnosis. Three patients presented with UC while they were actively smoking. However, these patients perceived a strong temporal association between smoking cessation and worsening of UC symptoms and were thus eligible for this small cohort. The average smoking load of the 14 patients who were ex-smokers at disease onset was 22 pack years, median load was 10.9 pack years, ranging between 2 and 96 pack years. Information regarding the interval between quitting and disease onset was available for only 12 patients. The mean interval period was 66 months, median interval was 36 months, and the range was 5–192 months (Table 1). Nine patients were steroid dependent, two patients were allergic to 5-ASA of whom one was reluctant to initiate immunosuppressants, one patient was intolerant to azathioprine and two others refused colectomy despite failure of cyclosporine and infliximab. These patients were offered several treatment options: anti-TNFα in certain cases, experimental therapies obtainable through clinical trials, colectomy, and smoking resumption in moderation (3–5 cigarettes per day) or an alternative equivalent nicotine compound.

Fifteen patients chose to resume smoking while two patients (#16 and #17) were reluctant and declined this recommendation. One patient (#16) who was steroid dependent was able to achieve remission with 5-ASA resumption. The other patient had refractory colitis and was intolerant to thiopurines and underwent proctocolectomy. Fourteen out of those 15 patients who commenced smoking demonstrated improvement in symptoms and signs. One patient (#14) failed to improve and required oral steroids to control inflammation. Throughout follow up, twelve patients continued active smoking and three patients switched to alternative nicotine compounds. For those who continued active smoking, the median daily number of cigarettes was 5, range 0–30. Of note, three patients increased their smoking dose up to 20–30 cigarettes per day. Fourteen patients were able to maintain clinical remission (SCCAI=0) through a median period of 23 months (range 3–120). Nine patients maintained remission with smoking or nicotine compounds alone. Five patients maintained remission on conventional...
regimen (5-ASA, immunomodulators, low dose prednisone and tapering of cyclosporine) combined with concomitant smoking or alternative nicotine consumption (Table 2).

All eight steroid dependent patients who had commenced smoking/nicotine were able to wean off steroids. One patient who was able to maintain remission with smoking alone became gradually addicted to cigarettes and was eventually compelled to quit smoking. Despite switching to nicotine compounds (transdermal patch and then nicotine gum), his disease flared and became refractory to steroids and immunosuppressants, leading to surgery. Currently, eleven patients still in remission are light smokers or require reasonably low dose nicotine supplements. Two patients are heavy smokers. All the patients presented are continuing periodic follow up.

### 4. Discussion

Cigarette smoking is a well known health hazard and one of the leading avoidable causes of mortality and morbidity. Cigarette smoke represents a mixture of four thousand toxic substances including nicotine, carcinogens (polycyclic aromatic hydrocarbons), organic compounds (unsaturated aldehydes such as acrolein), solvents, gas substances (carbon monoxide), and free radicals. Cigarette smoking is associated with a risk of serious chronic disorders including cardiovascular disorders, lung disease, and cancers. Most immune mediated diseases such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, primary biliary cirrhosis and Crohn’s disease are negatively impacted by smoking.13,14

Unexpectedly, cigarette smoking appears to have beneficial effects in UC, Parkinson’s disease,15 autoimmune thyroiditis16 and perhaps Alzheimer’s disease.17 In particular, the relationship of smoking and IBD is intriguing. Smoking appears to protect against the development of UC but has a deleterious effect on CD. In CD, smoking is associated with an increased risk for complications and ileal post surgical recurrence.1–4,17

Further, smoking accounts for much of the discord between UC and CD, and in families afflicted with IBD, cigarette smoking plays a protective role against UC.18,17 Similarly, smoking has a dichotomous effect on thyroid disease and also some neurological diseases: on one hand protective against chronic
autoimmune thyroiditis and Parkinson’s disease, and on the other hand, noxious for Grave’s disease and multiple sclerosis.\textsuperscript{20}

UC affects predominantly non-smokers and former smokers.\textsuperscript{2} It appears that current smokers suffer lower rates of UC when compared with the general population matched for sex and age thus suggesting a protective role for smoking.\textsuperscript{3} For current smokers compared with lifetime non-smokers, the meta-analysis by Calkins yielded a pooled odd ratio (OR) of 1.64\textsuperscript{21} and the Mayo Clinic meta-analysis yielded an OR of 1.79,\textsuperscript{21} respectively. It should be noted that these findings are based on heterogeneous studies utilizing observational data which lacks consistent and strict definitions for current, former, and nonsmoker. These limitations mainly stem from the obvious ethical constraints that prevent conducting a high quality, methodological, prospective trial. Finally, these odds ratios which suggest a protective effect of smoking merely represent a suspension effect, as the relative risk of UC is not decreased in former smokers. The concept of suspension is clarified by Motley et al. who showed that on average, lifelong non smoker males develop UC 15 years prior to ex-smoker males\textsuperscript{10} and Abraham et al. who showed that the lack of history of smoking suspends the onset of the UC rather than completely protects against it.

UC does, however, run a more amiable course in smokers than non-smokers. Some have even described a lower colectomy rate in smokers,\textsuperscript{7,28,29,31} but this was not shown by others.\textsuperscript{6,30,32} van der Heide et al. demonstrated a dose-dependent beneficial effect of smoking.\textsuperscript{29} In smokers, inflammation appears to be more limited and appears to have lower retrograde extension rates.\textsuperscript{29,33} Anecdotally, smoking may be associated with a decreased risk of colonic carcinoma in UC.\textsuperscript{34} Primary sclerosing cholangitis is observed almost exclusively in non-smokers.\textsuperscript{29,35} Smokers were described to have a lower incidence of pouchitis after protocolecotomy with IPAA by some,\textsuperscript{9} but not by all.\textsuperscript{38} Finally, smoking cessation has a detrimental impact on the course of the disease and “quitters” require more therapy escalation (steroids and immunomodulators).\textsuperscript{29,30}

Unfortunately, the identity of a causal relationship among the multitude of substances in cigarettes is elusive. Recent studies showed that the gaseous molecule carbon monoxide (CO) is one candidate that may contribute to the beneficial association between smoking and UC.\textsuperscript{39,40} Hegazi et al. demonstrated CO exposure at low concentrations ameliorated Th-1 mediated chronic murine colitis. The anti-inflammatory effects of CO are attributed to the induction of heme-oxygenase-1 (HO-1) and the broad impact of these pathways in intestinal inflammation. HO-1 induction correlated with effects of CO are attributed to the induction of heme-oxygenase-1 (HO-1) and the broad impact of these pathways in intestinal inflammation. HO-1 induction correlated with the increased IL-10 and IL-22 expressions in vivo, which may be relevant anti-inflammatory mechanisms of this pathway, because both cytokines were determined to have a protective role in colonic inflammation in mice.\textsuperscript{45}

Significant attempts to isolate potential therapeutic substances in cigarettes other than nicotine as valuable therapeutic agents in UC have not been performed. Nicotine is one of the most pharmacologically active substances in tobacco smoke, thus it seems logical to hypothesize that it responsible for most of the immunoregulatory effects of cigarette smoke. Nicotine is associated with alterations in rectal blood flow, intestinal permeability, colonic mucous production, colonic

### Table 2  Outcomes of smoking/nicotine resumption.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cigarette/nicotine compounds per day</th>
<th>Concomitant medication</th>
<th>Duration of remission (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20 cigarettes</td>
<td>None</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>4 cigarettes</td>
<td>AZA</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>5 cigarettes</td>
<td>None</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>5 cigarettes</td>
<td>None</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>10–12 mints \textsuperscript{a}</td>
<td>None</td>
<td>120</td>
</tr>
<tr>
<td>6</td>
<td>10 cigarettes</td>
<td>None</td>
<td>72</td>
</tr>
<tr>
<td>7</td>
<td>5 cigarettes</td>
<td>None</td>
<td>12</td>
</tr>
<tr>
<td>8</td>
<td>25 cigarettes</td>
<td>None</td>
<td>46</td>
</tr>
<tr>
<td>9</td>
<td>4 cigarettes</td>
<td>Cys/AZA/prednisone/topical 5-ASA</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>3 cigarettes</td>
<td>5-ASA/prednisone</td>
<td>5</td>
</tr>
<tr>
<td>11</td>
<td>2 cigarettes</td>
<td>AZA/5-ASA/topical 5-ASA</td>
<td>3</td>
</tr>
<tr>
<td>12</td>
<td>7 cigarettes plus 2 lozenges \textsuperscript{b}</td>
<td>AZA/5-ASA</td>
<td>120</td>
</tr>
<tr>
<td>13</td>
<td>30 cigarettes</td>
<td>None</td>
<td>72</td>
</tr>
<tr>
<td>14</td>
<td>3–10 cigarettes</td>
<td>None</td>
<td>Failed to attain remission</td>
</tr>
<tr>
<td>15</td>
<td>3 lozenges \textsuperscript{c}</td>
<td>None</td>
<td>28</td>
</tr>
</tbody>
</table>

Abbreviations: AZA – azathioprine, Cys – Cyclosporine.

\textsuperscript{a} Nicotine mints, each contains 4 mg of nicotine.

\textsuperscript{b} Nicotine lozenges, each contains 2 mg.

\textsuperscript{c} Nicotine lozenges, each contains 4 mg.
mucosal eicosanoid levels, and cell mediated and humoral immunity in smokers. Several randomized controlled trials studied the effects of nicotine patches for induction and maintenance of remission. Although most studies were limited by small numbers, they still demonstrated benefit for nicotine patches (15–25 mg/day) as an inductive agent but not as an effective maintenance agent. Patients treated with nicotine were significantly more likely than placebo or standard therapy patients to withdraw due to adverse events. One might postulate that topical rectal nicotine would be better tolerated due to a lower rate of side effects; however, a placebo control trail failed to demonstrate such benefit. Lashner et al. specifically tested the potential therapeutic effect of nicotine gums in titrated doses according to symptom control and tolerance versus placebo. This study tested only 7 patients and demonstrated that 3 who were former smokers benefited from this intervention. Only observational retrospective studies (case reports and series) describe the effects of actual smoking resumption in UC. All these studies show beneficial effect on the course of the disease. Rudra et al. demonstrated that almost 50% of a small cohort achieved and maintained remission for at least six weeks while smoking. Green et al. identified 51 UC patients who were current smokers and maintained remission. Most of these patients had benefit from ongoing smoking or smoking resumption. To the best of our knowledge, there was no study that directly addressed the issue of initiating smoking in lifelong nonsmokers. However, our experience suggests that neither nicotine nor smoking is as effective for the aforementioned patients as for former smokers. Moreover, lifelong nonsmokers would be less likely to tolerate nicotine and be reluctant to acquire a hazardous habit like smoking.

Since the optimal therapeutic approach to UC ex-smokers is still unresolved we have decided to describe our real life experience. Our study describes a small series of UC former smokers who have failed most conventional therapeutic measures and eventually improved once they have resumed smoking. A recent retrospective study demonstrated a favorable clinical outcome for UC patients with later onset. This study demonstrated that patients with early-onset UC were more likely to be non-smokers and had a family history of IBD compared to late-onset UC patients who were more likely to be former smokers. However, stratifying to the different smoking categories (former, current or non-smokers) did not reveal significant differences in clinical patterns. Older data suggests that ex-smokers, in contrast to lifelong nonsmokers, suffer a less favorable outcome. Our patients had both an early presentation of disease onset and additionally previous exposure to tobacco. Perhaps this combination is distinctive in posing an additive risk (synergism) that eventually contributes to disease refractoriness.

All patients were recommended smoking resumption in moderation (low dose), fearing the obvious harmful effects of smoking. As this approach would appear bold and unconventional, it was taken after careful evaluation of all risks and benefits. In each case, background risk factors that might have been associated with smoking were assessed. In addition, the consequences of implementing the available alternatives versus the expected risks of low dose smoking resumption were thoroughly considered. Finally, after appropriately informing the patients of their personal options, their individual preferences were considered as well. With regard to clear risk factors that may be ascribed to tobacco exposure, none of the patients in our small series had cardiovascular disease, hypertension, diabetes mellitus, chronic lung disease, obstructive sleep apnea, thyroid disorder, upper gastrointestinal disorders, or oropharyngeal and laryngeal disorders. One patient had been previously diagnosed with cervical cancer for which she was operated. In each of these cases, alternatives such as long term steroid therapy, long term immunosuppression, long term anti TNFα therapy and surgery were considered. Each of these options confers potential significant side effects as well as known and unknown long term complications, for instance increased risk for neoplasia and/or opportunistic infections. In particular, surgery with permanent ileostomy or IPAA may significantly impact patients’ quality of life. Furthermore, the potential "cure" of proctectomy and IPAA is diminished in ex-smokers who would more often require therapy for pouch complications.

The hazards of active smoking are both immediate and cumulative. Likewise, smoking cessation has instant benefits; however, the most discernable impact of smoking cessation would occur after an extended period of time. For example, after one year of quitting, the excess risk of coronary heart disease is half that of an active smoker’s, five years after quitting the risk for stroke risk is reduced to that of a non-smoker, and 10 years after quitting, lung cancer death rate is only about half that of a smoker (U.S. Surgeon General’s Report, 1990). Unfortunately, there is lack of clear definitions of the “dose needed to harm”. Thus, it is reasonable to believe that in patients who have been exposed to substantial “pack years” and lack risk factors directly attributed to tobacco, smoking resumption in moderation may not confer additional significant risk. Moreover, since elderly patients suffer from co-morbidities and immune dysregulation that may lead to differential response to therapy or contribute to the development of malignancies and susceptibility to infections. immnosuppressant may raise a variety of safety concerns that may outweigh the concerns with smoking resumption in low dose.

This study describes the real life successful experience with a unique group of refractory UC patients. In our small series 15 out of 17 ex-smokers with UC who had been offered to consider smoking resumption elected to do so while refusing the alternative interventions. Of those, 14 were able to maintain prolonged remission. Eleven of these patients were older than 50 years, however, most these patients developed UC at an earlier age, and do not represent the subgroup of pure late-onset UC. All the patients in this series that were steroid dependent were able to wean off steroids. Furthermore, all the patients that maintained remission attributed it to the beneficial effect of the smoking or the nicotine compounds. Unfortunately, but as expected, one patient became addicted and thus was obligated to quit. Unsurprisingly this patient’s disease was refractory and thus, he underwent surgery. Presently, none of the other patients has developed any of the expected complications. However, two patients are considered heavy smokers, for whom we strongly suggest a gradual taper. It might be that an ensuing substitution with nicotine compounds (if tolerable) should be considered for those who benefit from smoking resumption. Our approach requires an honest and detailed patient discussion emphasizing all expected risks conjointly with a vigilant
dedicated proactive monitoring for potential detrimental effects and addiction.

There are several limitations to this study. Regrettably, we were unable to trace the entire cohort of former smokers in our practice and thus, we have described only a small series of patients and we cannot present an actual rate of former UC smokers and their characteristics. Perhaps we miss a distinctive feature that could define this subgroup of patients and direct a more suitable approach. Additionally, it is difficult to ascertain clear benefit for tobacco exposure in patients who were getting concomitant therapies and the lack of endoscopic criteria to corroborate clinical remission (mucosal healing) is another drawback. Finally, facing the retrospective nature of this study and recall bias, we are unable to demonstrate or rebut a “dose effect” both prior to the disease onset and also after intervention. Notwithstanding, this is the first case series to report that directed smoking resumption appears to improve the clinical course in a unique subset of UC patients.

5. Conclusions

Low-dose smoking resumption in refractory UC patients who are ex-smokers may ameliorate signs and symptoms of inflammation and have a safety profile that is at least comparable with long term corticosteroids, immunosuppressants, and biologics. This approach represents an unconventional therapeutic intervention that seems suitable only for a specific subgroup of patients. Quality of life, medication side effects and smoking risk factors should all be considered and discussed with patients. Such individualized medicine should be handled with caution and converging with meticulous follow-up for latent tobacco risks.

Identifying the substance(s) in tobacco/smoking that most profoundly impact(s) the immune system and, developing a non-smoking and relatively safe therapy is needed.

Conflict of interest

None.

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