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

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IIntroduction

Cigarette smoke contains hundreds of potentially toxic (or therapeutic) compounds, many of which have unknown action in the human body [1]. Ulcerative colitis (UC) and Crohn's disease (CD) show an inverse association with cigarette smoking exposure. Non- or ex-smokers have a higher risk for UC while smokers are more likely to suffer from CD. Anecdotal evidence suggested that smoking resumption may improve the clinical outcome of ex-smokers with refractory UC.

Cigarette smoking has a negative impact on most autoimmune disorders, being associated with a high risk of cardiovascular, lung and digestive diseases; notwithstanding of this, cigarette smoking appears to have beneficial effects in UC. Studies showed that carbon monoxide (CO) is one candidate that may concur to this helpful effect [3-4]. Nicotine could also be responsible for most of the immunoregulatory effects of cigarette smoke. Also it is worth mentioning that considering the bimodal distribution of UC [5-6], the second older-age peak (between 50 and 80 years of age) is characterized by higher rates of former smokers [7-9], thus suggesting that smoking suspends the onset of the UC rather than fully protecting it.

What is this paper about?

The program PURSUIT (The Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment) included a multicenter, randomized, double-blind, placebo-controlled, Phase 3 trial designed to evaluate the safety and efficacy of a subcutaneous monthly basis treatment regimen with Golimumab for the induction and the maintenance of remission in adults with moderate-to-severe UC. All patients recruited poorly responded or did not tolerate treatment with 6-mercaptopurine (6-MP), azathioprine (AZA), corticosteroids and / or 5-aminosalicylates (5-ASA), or were corticosteroid-dependent. Study participants were naïve to treatment with TNF inhibitors and had a Mayo score at baseline between 6 and 12 as well as an endoscopy sub-score equal to or greater than 2.

Responders to induction treatment with Golimumab were eligible to be randomized in the phase 3 study of maintenance PURSUIT (PURSUIT-M), which was conducted in 251 centers. The primary endpoint of this study was the maintenance of clinical response through week 54, while secondary endpoints included clinical remission and mucosal healing (Mayo endoscopy score of 0 or 1) at both weeks 30 and 54. Patients were randomized into three groups given placebo or 50mg or 100mg of Golimumab. The proportion of Golimumab induction responders who maintained clinical response through week 54 was significantly greater in both the 100mg and the 50 mg groups (respectively 50,6% and 47,1%) as compared to the placebo group (31,4%). The same trend was observed for the proportion of patients in clinical remission at both weeks 30 and 54 (with percentages equal to 28,6%, 23,5% and 15,4% respectively) and in the proportion with mucosal healing at both weeks 30 and 54 (43,5%, 41,8% and 26.9%). In the course of the PURSUIT-M study, also antibody levels against Golimumab were evaluated and their incidence through week 54 was only 2,9%. Accordingly, Golimumab concentrations remained stable in serum from weeks 8 through 44, with higher serum Golimumab concentrations at week 54 in the 100mg group. Sandborn WJ et al. showed that safety results were consistent with the known safety profile of the drug in rheumatologic indications and with that reported for other anti-TNF-α agents. Patients who received placebo, 50-mg and 100-mg Golimumab groups reported injection-site reactions in 1.9%, 1.9% and 7.1% respectively; infections in 28.2%, 39.0% and 39.0%; serious adverse events were report in 7.7%, 8.4% and 14.3% and serious infections were reported in 1.9%,3.2% and 3.2% respectively. No injection-site reaction was serious and no anaphylactic reactions were reported.

Through week 54, three deaths and three malignancies were reported in the 100mg Golimumab maintenance group, in patients with a previous history of disease. One case of breast cancer was reported in a patient who had received only placebo during induction and maintenance.

Conclusion

Low-dose smoking resumption in selected subgroups of ex-smokers with refractory UC represents an unconventional therapeutic approach that could ameliorate signs and symptoms of disease. Smoking risk factors should be considered and discussed with patients.

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