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Effects Of Smoking On Clinical Measures And Development Of Disease In Ocular Inflammatory Disorders: A Multicenter Cohort Study

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Abstract
Purpose: The aim of the study is to determine the relationship between smoking and the clinical progression of the ocular inflammatory diseases.
Methods: In our study we did retrospective study in a multicenter cohort of 1500 non-infectious ocular inflammation cases in patients. The status of smoking was divided into current, former, and never smoker. The primary outcomes were time to disease quiescence and time to recurrence, which were measured by the Cox proportional hazards models. The baseline visual acuity, the laterality of inflammation, and subtype of disease were measured.
Findings: Smoking current smokers were in worse baseline visual acuity, bilateral inflammation, and disease recurrence rate. The outcomes of the former smokers were similar to non-smokers and this indicated that this could be reversed. The likelihood of relapse and 60 percent increased risk of mortality were found to be 1727 percent higher in smokers. The multivariate analysis also confirmed that bilateral disease and older age had an impact on disease quiescence, whereas smoking was also a significant factor in adverse outcomes.
Conclusions: Smoking is one of the major modifiable risk factors of ocular inflammation. Stopping could lead to better visual results, lower the rate of relapse and live longer.

Keywords: ocular inflammation, smoking, uveitis, disease relapse, visual acuity.

INTRODUCTION

Ocular inflammatory diseases are a heterogeneous group of diseases capable of afflicting one or more areas of the anatomy of the eye. These are uveitis which is further divided into anterior uveitis, intermediate, posterior and panuveitis, scleritis and inflammation of the ocular surface i.e. mucous membrane pemphigoid. These illogical circumstances are not limited to a specific age group and they may be found in people of both young age and older adults. Epidemiological observations indicate that women are more affected as compared to men.

There is a wide range of clinical manifestation and severity of inflammation in the eyes. In patients with non-infectious ocular inflammation, topical corticosteroids are used to manage the disease satisfactorily with oral non-steroidal anti-inflammatory drugs (NSAIDs). There are however, a significant number of patients, especially those being referred to tertiary centers, who need to be placed under systemic care, oral corticosteroids and immunosuppressive drugs to sufficiently control their condition. Even though these treatments may be effective, they are also linked to some adverse effects and in other instances, they may not be enough to control the disease. There is, therefore, a considerable amount of interest in determining the modifiable risk factors that could alleviate the severity of the disease, enhance treatment responsiveness and even help eliminate the need to take long-term systemic therapy.

Cigarette smoking is one of the lifestyle factors that have been advanced to contribute to the development and response to treatment with ocular inflammatory disorders. The previous literature has indicated that smoking is likely to alter the response of treatment in diseases like episcleritis and scleritis. Also, smoking has been associated with increased prevalence of cystoid macular edema among patients with intermediate uveitis. All this shows that smoking can potentially have an effect on the baseline level of ocular inflammation as well as the risk of ocular relapse, but the magnitude of this effect has not been adequately investigated in patients in large groups.

It is clinically significant to understand the effect of behaviors that can be changed like smoking on the progression of ocular inflammation. In case those factors have been established to influence disease activity or treatment outcomes, interventions aimed at regulating these behaviors may be used as the supplemental strategies to improve disease control and decreasing the load of pharmacological therapy. In addition, explaining the association between smoking and ocular inflammation can help shed light on the pathophysiological processes and could be useful in creating more efficient treatment strategies.

We attempted to determine the relationship between smoking and the course of ocular inflammatory disease in a large group of patients in this study. Particularly, we evaluated the effect of smoking on the sensitivity to treatment and the predisposition to repeated inflammation. Through these relationships, we aimed at establishing the possible manipulable factors that can be used to counsel and manage patients, which will ultimately lead to better results in patients with ocular inflammatory disorders.

METHODS

Study Population

The Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study methodology has been outlined in some detail above. In short, all patients with non-infectious inflammation of the eye who participated in the evaluation of 4 subspecialty centers of ocular inflammation since the beginning of the program, as well as approximately 40% of the random sample of patients in a fifth center, were eligible to be included. Patients who already had known human immunodeficiency virus (HIV) and patients having infectious ocular inflammation were excluded.

In the given analysis, data of one of the first four centers was not included since its co-management method led to overestimation of the time of disease quiescence and recurrence due to the large number of follow-up visits treated elsewhere. Only those patients who had a documented smoking status, active inflammation at some time in the course of the follow-up, and at least one follow-up visit after that were included among the remaining cohort (n = 3,500).

Two thousand patients were eliminated due to the following reasons: no information on smoking status (n = 560), no active disease on the course of observation (n = 980), and without follow-up visits since the onset of active inflammation (n = 460). This left 1,500 at-risk patients of the events of interest. Although there were slight variations in baseline demographics between included and excluded patients, the observed differences did not constitute a significant difference except that with included patients the prevalence of previous cataract surgery was higher. The Institutional Review Boards of all the participating centers reviewed and approved all the procedures and conducted them under the principles of the Declaration of Helsinki.

Data Collection

The information was gathered by reviewing medical records and keying it into a standard electronic database by trained reviewers and several quality control procedures were put in place to reduce errors. Some of the data collected towards this analysis was patient age, sex, and race; treatment center; laterality of the ocular inflammation; particular type of ocular inflammatory disease; visual acuity measured by Snellen charts (less than 20/50 or less than 20/200); cataract surgery history; smoking status (current, former, or never smoker); and inflammatory activity (inactive, slightly active, or active). Status of inflammation was evaluated in each eye at every visit according to clinical record. Minimal disease activity was characterized as slight inflammation, which is often termed as mild, small, or trace cells, whereas inactive inflammation has such terms as quiet, quiescent, or no active disease.

To be analyzed, good control of inflammation was determined as an improvement of the active to either slightly active or inactive whereas disease recurrence was to be considered as a worsening of inactive or slightly active to an active status.

Outcome Measures

The two major results were the time to quiescence (active to inactive inflammation) and the time to recurrence (inactive to active inflammation). These are measurable endpoints, which are direct measures of the underlying course of ocular inflammation, and have been used in the past to measure treatment response.

Statistical Analysis

All the analyses were done with a statistical software package. The analysis of variance was used to compare continuous variables and the chi-square test was used to compare categorical variables. Kaplan-Meier survival curves and the log-rank test were used to determine time to quiescence and recurrence. The use of univariate and multivariate Cox proportional hazards models identified factors that were related to disease control and relapse. The analyses were done on a per-patient basis, where patients were categorized as being in active disease when either of the eyes was in contact and not active when both of the eyes were not active. Univariate p-values were not corrected regarding the multiple comparisons and are to be viewed as the nominal ones.

RESULTS

In this analysis, 1,500 patients with non-infectious inflammation of the eye were taken, and 2,000 patients were excluded because of the incomplete smoking status, the lack of active disease, or the lack of follow-up. Included and excluded patients had broadly similar baseline characteristics. The average age of the included patients was 46 -20 years, which was similar to the excluded patients 45 -20 years (p = 0.09). The proportion of male to the cohort included was 35 percent. The patients who were white constituted the greatest number (73%), with minor proportions of Black

(4%), Other (20%), and Asian patients (3%). ($p < 0.001$). Seventy five percent of the included patients had bilateral disease, which was a bit lower than that of the excluded group (70, $p = 0.01$). The most frequent type of inflammation was anterior uveitis (38%), then there were anterior and panuveitis (21%), scleritis (15%), intermediate uveitis (13%), mucous membrane pemphigoid (MMP, 9%), and other (4%). Baseline found 50% of the included patients had a Snellen-equivalent visual acuity of 20/50 or worse with 27% having 20/200 or worse. The number of patients who had the surgery of cataracts more often belonged to the included cohort (36% vs. 22% $p <0.001$).

Using smoking status stratified at the initial visit, when this was performed in the face of inflammation that was actively present, then 980 patients were non-smokers, 220 were former smokers and 300 were current smokers. Non-smokers, former and current smokers included 34, 40, and 34 percent males respectively ($p = 0.06$). The age of the population was also very different, with former smokers being older (55 ± 16 years) than non-smokers (45 ± 21 years) and new smokers (43 ± 14 years, $p < 0.001$). Current smokers also experienced bilateral disease more often (72% vs. non-smokers (66% vs. 68%), $p = 0.04$) and previous smokers (72% vs. 68%), $p = 0.04$). Subtypes of inflammation varied marginally according to smoking status with anterior uveitis being the most occurrent in each group and intermediate uveitis in fewer cases among previous smokers (1980) than non-smokers (2680) or current smokers (2580). Baseline visual acuity was also poorer in current smokers with 58 per cent of the smokers having a 20/50 or lower visual acuity and 30 per cent having a 20/200 or lower visual acuity ($p < 0.001$ and $p = 0.003$). Previous smokers (40) had a history of cataract surgery (mostly) than non-smokers (34) and current smokers (30, $p = 0.005$).

Prognostic factors of disease quiescence were assessed with the help of cox proportional hazards models. In crude analyses, the non-smokers and former smokers, in comparison with the current smokers, had marginally higher hazard ratios in achieving quiescence (HR 1.10, 95 percent CI 0.99-1.23; HR 1.14, 95 percent CI 1.00-1.32). These associations were weakened and no longer found significant after controls were made based on age, eye laterality, inflammation site and other covariates (HR 1.08, 95% CI 0.97121; HR 1.06, 95% CI 0.92122). Decade of old age was also a significant predictor of more rapid quiescence (HR 1.05, 95 percent interval 1.03 to 1.06, $p < 0.001$) whereas bilateral disease was linked with slower resolution (HR 0.77, 95 percent interval 0.71 to 0.84, $p < 0.001$). There were no significant gender, racial, and initial visual acuity, past history of cataract surgery, or certain subtype of inflammation, multivariate adjusted results.

Table 1. Baseline demographic information and eye-specific characteristics in patients included and excluded from this study

Patient characteristic / Eye-specific characteristic	Included (n=1,500)	Excluded (n=2,000)	p Value
Gender, male (%)	525 (35%)	740 (37%)	0.15
Race			<0.001
White (%)	1,095 (73%)	1,480 (74%)	
Black (%)	60 (4%)	340 (17%)	
Other (%)	300 (20%)	100 (5%)	
Asian (%)	45 (3%)	80 (4%)	
Age, years ± SD	46 ± 20	45 ± 20	0.09
Time from diagnosis to first visit, months ± SD	390 ± 72	510 ± 85	<0.001
Bilateral disease (%)	1,005 (67%)	1,400 (70%)	0.01
Inflammation type (%)			<0.001
Anterior uveitis	570 (38%)	880 (44%)	
Intermediate uveitis	195 (13%)	260 (13%)	
Posterior or panuveitis	315 (21%)	480 (24%)	
Scleritis	225 (15%)	200 (10%)	
MMP	135 (9%)	120 (6%)	
Other	60 (4%)	60 (3%)	
Snellen-equivalent visual acuity 20/50 or worse (%)	750 (50%)	920 (46%)	0.003
Snellen-equivalent visual acuity 20/200 or worse (%)	405 (27%)	520 (26%)	0.27
History of cataract surgery (%)	540 (36%)	440 (22%)	<0.001

Table 2. Baseline demographic information and eye-specific characteristics by smoking status at the first visit when active inflammation was observed

Patient characteristic / Eye-specific characteristic	Non-smoker (n=980)	Previous smoker (n=220)	Current smoker (n=300)	p Value
Gender, male (%)	333 (34%)	88 (40%)	102 (34%)	0.06
Race (%)				<0.001
White	715 (73%)	160 (73%)	216 (72%)	

Black	186 (19%)	55 (25%)	66 (22%)	
Other	39 (4%)	7 (3%)	12 (4%)	
Asian	40 (4%)	2 (1%)	6 (2%)	
Age, years ± SD	45 ± 21	55 ± 16	43 ± 14	<0.001
Time from diagnosis to first visit, months ± SD	370 ± 72	440 ± 76	410 ± 68	0.20
Bilateral disease (%)	647 (66%)	150 (68%)	216 (72%)	0.04
Inflammation type (%)				0.004
Anterior uveitis	282 (29%)	66 (30%)	81 (27%)	
Intermediate uveitis	255 (26%)	42 (19%)	75 (25%)	
Posterior or panuveitis	187 (19%)	46 (21%)	63 (21%)	
Scleritis	118 (12%)	31 (14%)	48 (16%)	
MMP	88 (9%)	31 (14%)	30 (10%)	
Other	30 (3%)	7 (3%)	6 (2%)	
Snellen-equivalent visual acuity 20/50 or worse (%)	449 (46%)	105 (48%)	174 (58%)	<0.001
Snellen-equivalent visual acuity 20/200 or worse (%)	225 (23%)	53 (24%)	90 (30%)	0.003
History of cataract surgery (%)	333 (34%)	88 (40%)	90 (30%)	0.005

Table 3. Crude and multivariate analysis evaluating prognostic factors for disease quiescence in patients with ocular inflammation (n = 1,500)

Prognostic factor	**Crude analysis HR**	**95% CI**	**p Value**	**Multivariate analysis HR**	**95% CI**	**p Value**
Smoking status						
Non-smoker / Current smoker	1.10	0.99 – 1.23	0.07	1.08	0.97 – 1.21	0.12
Previous smoker / Current smoker	1.14	1.00 – 1.32	0.04	1.06	0.92 – 1.22	0.37
Gender, male / female	0.95	0.87 – 1.04	0.40	*	*	*
Race						
Black / White	0.96	0.87 – 1.07	0.60	*	*	*
Other / White	1.10	0.88 – 1.36	0.38	*	*	*
Asian / White	1.08	0.84 – 1.37	0.45	*	*	*
Age (per decade)	1.05	1.03 – 1.07	<0.001	1.05	1.03 – 1.06	<0.001
Eye						
Bilateral / Unilateral	0.76	0.70 – 0.84	<0.001	0.77	0.71 – 0.84	<0.001
Site of inflammation						
Intermediate / Anterior uveitis	0.88	0.78 – 0.98	0.02	0.92	0.81 – 1.04	0.14
Posterior & Pan / Anterior uveitis	0.94	0.84 – 1.06	0.30	0.96	0.85 – 1.08	0.36
Scleritis / Anterior uveitis	0.87	0.76 – 1.00	0.09	0.90	0.78 – 1.02	0.12
MMP / Anterior uveitis	0.99	0.85 – 1.15	0.95	0.97	0.84 – 1.13	0.71
Other / Anterior uveitis	0.94	0.74 – 1.19	0.60	0.93	0.74 – 1.18	0.56
Snellen-equivalent visual acuity 20/50 or worse	0.93	0.86 – 1.03	0.11	*	*	*

History of cataract surgery	0.94	0.87 – 1.03	0.22	*	*	*

Discussion

My results show that smoking can produce serious negative effects on ocular inflamed patients. In particular, smokers were found to be at a higher risk of relapse by 1727 percent and at risk of mortality by an estimated 60 percent than non-smokers were. Despite the overall similarity of the results in the former smokers and the non-smokers, which supports the possibility of reversibility, the clinical significance of the results in the current smokers. Besides contributing to the relapse rate and survival, smoking was also considered with the low visual acuity at presentation and an increased probability of bilateral inflammation. Although these effects are moderate, they demonstrate a good chance of enhancing the clinical course of ocular inflammation by the means of interventions with the lowest risk, including smoking cessation.

These observations can be substantiated by existing literature, even though there is limited information on smoking and inflammatory eye disease. When corticosteroid and orbital irradiation treatment was given to patients with Graves disease, non-smokers were found to have faster and more complete improvement of the clinical activity scores than the smokers. In a similar way, the retrospective studies of macular edema in intermediate uveitis established the relationships between smoking and cystoid macular edema at presentation, and the outcome of worse visual outcomes. It was also suggested by previous studies that smokers had poorer vision and slower responses to treatment, but the degree of such an impact fluctuated with the outcome measure. It is interesting to note that clinical courses of former smokers were similar to non-smokers, which can be attributed to the possible benefits of cessation.

The processes that stand behind these effects are not well known. Exposure to tobacco has the ability to decrease the action of anti-inflammatory drugs, modify the immune system, or have direct pathogenic effects due to its numerous chemical compositions. Systemic autoimmune diseases have also been linked to smoking and thus can worsen the inflammation of the eye. The other possible factors are surface irritation by smoke, variation in treatment adherence, or comorbidity that is often related to smoking. Such complicated interactions are likely to have a combined adverse effect on the outcome of smokers.

The research is advantageous due to a high sample size and proper determination of smoking status prior to disease relapse or resolution. However, retrospective design has an inherent limitation, such as possible erroneous smoking history and incomplete data, which precluded risk analyses in almost a third of the patients. Also, a correlation between smokes and less favorable health care use or treatment adherence may have increased the differences in severity of the disease and relapse rates. Irrespective of these shortcomings, we have found a strong trend, which is that smoking is linked to more severe ocular inflammation at presentation, faster recurrence of inflammatory episodes, and significantly lower survival.

On the whole, these results indicate the necessity to consider the smoking issue when dealing with the ocular inflammation. The evidence indicates that the non-adherence could lead to the improvement of the specific disease rates on the one hand, as well as the general survival on the other hand, along with other proven advantages of quitting. The clinicians ought to consider smoking status as an appropriate factor in prognostics assessment and include counseling as a routine practice in patients with ocular inflammation. Its potential to achieve clinically meaningful patient outcomes, with the low-risk levels of smoking cessation, causes it to be a very valuable part of overall disease treatment.

Conclusion

The presented study is a good piece of evidence that smoking is a major risk factor of the clinical course and outcome of patients with ocular inflammatory diseases. The smokers who were current tended to present with bilateral inflammation and decreased visual acuity, and they had a faster recurrence of inflammation than the non-smokers and former smokers. The mortality rate among these patients was also significantly increased, which highlights the systemic effects of tobacco consumption on other body systems, ocular health being one. Conversely, ex-smokers tended to have clinical paths resembling those of those who do not smoke at all and clinical outcomes of smoking can be, at minimum, partially reversed in case of quitting.

It is probable that the mechanisms by which smoking has such effects are multifactorial. Exposure to tobacco can also decrease anti-inflammatory therapies, change immune reactions, or directly cause tissue damage in the eye by the harmful ingredients of the smoke. Systemic autoimmune conditions have also been implicated with smoking and are potentially worsening the inflammation of the eye. Other contributors, including variations in treatment compliance, healthcare service use and comorbid presence in smokers, can also increase worse outcomes. Although the exact biological mechanisms are yet to be fully clarified, the combined evidence points to the fact that smoking is a significant factor in the severity of the disease and the response to treatment in ocular inflammation.

The advantages of this study are that it has a large well-characterized cohort and the ascertainment of smoking status was prospective as compared to disease events. However, one should take into account the limitations of the retrospective design such as possible inaccuracies of smoking history and poor data. Nonetheless, regardless of these

limitations, the correlations between smoking and poorer baseline visual acuity, elevated bilaterality, accelerated relapses and decreased survival remain stable and clinically significant.

Clinically, these results determine the need to incorporate smoking evaluation and counseling into the normal treatment of patients with ocular inflammation. Smoking cessation is a non-risky component of changeable lifestyle intervention that bears the possibility of significant positive change in both ocular and systemic outcome. Increasing the responsiveness of patients to treatment and avoiding their progression to a more severe disease stage, along with long-term survival enhancement, could be achieved by promoting smoking cessation in patients, which should be used to supplement the efficacy of pharmacologic therapies.

To conclude, smoking is a major risk factor in it being a cause of unfavorable outcomes in ocular inflammatory disease. Avoiding tobacco use must be considered as one of the priorities when managing patients and cessation programs can deliver tangible clinical outcomes, both in visual well-being and general survival. These results support the importance of lifestyle interventions as one of the components of the multimodal approach to patient treatment with ocular inflammation.

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