ORIGINAL ARTICLE

Effects of Biochemically Confirmed Smoking Cessation on White Blood Cell Count

GREGORY A. ABEL, MD, MPH; J. TAYLOR HAYS, MD; PAUL A. DECKER, MS; GARY A. CROGHAN, MD, PHD; DAVID J. KUTER, MD, DPHIL; AND NANCY A. RIGOTTI, MD

OBJECTIVES: **To determine the relationship between white blood cell (WBC) indices and several baseline variables in a large cohort of healthy smokers and to assess whether these changed after biochemically confirmed smoking cessation.**

SUBJECTS AND METHODS: **The study consisted of 784 healthy smokers enrolled in a trial of sustained-release bupropion, 300 mg/d, for relapse prevention after smoking cessation from 1995 to 1998. Both WBC counts and absolute neutrophil counts (ANCs) were measured at baseline, week 7, and week 52. Smoking status was assessed at weeks 7 and 52 by self-report and biochemically confirmed with expired air carbon monoxide levels. Multivariate analyses compared changes in WBC count and ANC between smokers who did and did not stop smoking, adjusting for treatment group, age, sex, and body mass index.**

RESULTS: **Of 784 smokers enrolled, 461 had biochemically confirmed tobacco abstinence after 7 weeks of bupropion; 429 were randomly assigned to receive continued bupropion therapy or placebo until week 52. Between baseline and week 7, there was a significantly larger decrease in WBC count in continuously abstinent subjects compared with continuing smokers (adjusted *P*=.03). At 52 weeks, continuously abstinent subjects, compared with continuing smokers, had a greater decline from baseline in WBC count ($1.2\pm1.9 \times 10^9$/L vs $0.1\pm1.9 \times 10^9$/L; *P*<.001) and ANC ($1.0\pm1.6 \times 10^9$/L vs $0.2\pm1.5 \times 10^9$/L; *P*<.001).**

CONCLUSION: **Biochemically confirmed tobacco abstinence leads to a rapid and sustained decrease in WBC and ANC, possibly reflecting a decrease in an underlying state of tobacco-induced inflammation.**

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ANC = absolute neutrophil count; BMI = body mass index; WBC = white blood cell

Cigarette smoking is the leading preventable cause of mortality in the United States and was responsible for approximately 20% of all cardiovascular deaths in 1990.[1] Although the relationship between smoking and cardiovascular mortality is well established, the underlying mechanism remains largely elusive. Compared with nonsmokers, smokers have higher levels of cholesterol,[2] increased platelet reactivity,[3] and elevated levels of inflammatory markers such as C-reactive protein and fibrinogen.[4,5] This last finding provides evidence that inflammation may be an important mechanism by which smoking leads to cardiovascular disease; indeed, these same markers have been shown consistently to herald coronary artery disease.[6]

White blood cells (WBCs) are another essential element of inflammatory processes.[7] An association between cigarette smoking and increases in WBC counts[5,8-14] and absolute neutrophil counts (ANCs)[8,15] has been reported, but there have been few prospective studies of the impact of smoking cessation on these leukocyte indices.[16-20] The largest longitudinal study assessing the impact of smoking cessation on WBC counts was performed as part of a cohort study of human immunodeficiency virus infection in men who have sex with men.[20] White blood cell counts were higher in smokers than in nonsmokers, and they declined after 6 months of self-reported tobacco abstinence; however, this study, like most of the others, relied exclusively on subjects' self-reports of tobacco abstinence rather than requiring biochemical validation of smoking status, as is now standard in the smoking cessation literature.[21] The one published prospective study that used biochemical confirmation of smoking status had a low number of subjects, as few as 30 in the comparison group of those who continued to smoke.[22]

Our study goals were to characterize the relationship between WBC indices and several baseline variables in a large cohort of healthy smokers and to assess whether these changed after biochemically confirmed smoking cessation. We analyzed data from a randomized controlled trial of sustained-release bupropion for smoking cessation and relapse prevention.[23] We hypothesized that the WBC count and ANC of healthy smokers would increase with increased tobacco exposure. We additionally posited that these parameters would undergo significant,

From the Department of Medicine (G.A.A., D.J.K., N.A.R.) and Tobacco Research and Treatment Center (N.A.R.), Massachusetts General Hospital, Harvard Medical School, Boston, Mass; and Division of General Internal Medicine (J.T.H.), Division of Biostatistics (P.A.D.), Division of Medical Oncology (G.A.C.), and Nicotine Dependence Center (J.T.H., G.A.C.), Mayo Clinic College of Medicine, Rochester, Minn.

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Individual reprints of this article are not available. Address correspondence to J. Taylor Hays, MD, Division of General Internal Medicine, Mayo Clinic College of Medicine, 200 First St SW, Rochester, MN 55905 (e-mail: hays.taylor@mayo.edu).

sustained decreases after biochemically confirmed smoking cessation.

SUBJECTS AND METHODS

The study subjects were 784 healthy volunteers from 5 sites (Palo Alto, Calif; Rochester, Minn; Boston, Mass; Providence, RI; and Portland, Ore) who smoked at least 15 cigarettes per day, wanted to quit smoking, and had enrolled in a study of the efficacy of sustained-release bupropion for relapse prevention after smoking cessation from 1995 to 1998. All participants received open-label bupropion (300 mg/d) for 7 weeks (Figure 1). Those who had biochemically confirmed tobacco abstinence at week 7 were invited to enroll in a double-blind trial in which they were randomly assigned to receive bupropion, 300 mg/d, or placebo for 45 weeks and then be followed up for an additional year after the conclusion of the double-blind medication phase. Further study details have been published previously.[23]

MEASURES

WBC Parameters. All participants had blood withdrawn and analyzed for WBC count ($\times 10^9$/L), percent neutrophils, and cotinine level (μg/L) at baseline (before smoking cessation), 7 weeks (end of open-label bupropion course), and 52 weeks (end of double-blind phase, with half of subjects assigned to receive bupropion). Tests of subjects from all sites were performed at Corning SciCor Laboratory (now Covance, Inc) in Princeton, NJ.

Smoking Status. Point-prevalence tobacco abstinence was defined as self-report of not smoking during the previous 7 days, confirmed by an expired air carbon monoxide level of 10 ppm or lower. Participants were considered to have experienced smoking relapse if they reported any smoking after the quit date, had an expired air carbon monoxide level greater than 10 ppm, missed any visits during the open-label treatment phase (weeks 1 to 7), or missed more than 2 consecutive visits during the double-blind medication phase (weeks 8 to 52). All participants who met the point-prevalence abstinence criterion at every visit were considered continuously abstinent. For this study, subjects were classified as continuously abstinent, point-prevalence abstinent (ie, self-report of "not even a puff" for the 7 days preceding the visit of interest but failing to meet the continuous abstinence criterion), or smoking.

Other Measures. Baseline measures included age, sex, body mass index (BMI), number of cigarettes smoked per day during the past year, age at smoking initiation, years smoked, nicotine dependence based on the Fagerstrom Tolerance Questionnaire, serum cotinine (a nicotine metabolite), number of previous quit attempts, number of other smokers in the household, alcohol dependence based on the Self-Administered Alcoholism Screening Test, and history of depression based on the Structured Clinical Interview for Axis I depression, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.[24-27] Both alcohol and depression history were included because of evidence that these factors may also affect WBC parameters independently of smoking status.[8,10,27]

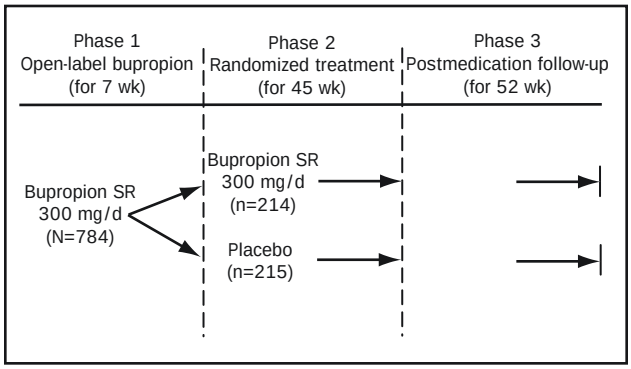

FIGURE 1. Study design. SR = sustained release.

STATISTICAL ANALYSES

Baseline characteristics of the subjects were summarized by frequency and percentage for all variables. The ANC was determined by multiplying the total WBC count by the percent neutrophils. To determine a reference range in healthy smokers for WBC count, ANC, and percent neutrophils, the mean, median, 90th, 95th, and 99th percentiles were calculated for each parameter by using data collected at baseline, when all subjects were smoking. Linear regression was used to determine the potential association of each hematologic parameter with subject baseline characteristics.

For each hematologic parameter, the change from baseline to week 7 and week 52 was calculated; the change between week 7 and week 52 was also calculated. These differences over time were then compared across the 3 smoking groups (continuously abstinent, point-prevalence abstinent, and smoking) using analysis of variance, with a separate analysis performed for each period. These analyses were performed univariately and multivariately adjusting for age, sex, BMI at baseline, and BMI change from baseline to week 7 or 52 (or between week 7 and 52). To control for the possible confounding effect of bupropion, treatment group was added as a covariate for analyses that compared baseline or week 7 with week 52. If the overall effect of membership in the smoking group was found to be statistically significant after adjusting for age, sex, baseline BMI, and change in BMI, linear contrasts were used to perform pairwise comparisons of the 3 smoking groups. To

supplement the aforementioned analysis, the change from baseline to each time point for each smoking group was compared to 0 using a 1-sample *t* test. In all cases, 2-tailed $P \leq .05$ was considered statistically significant.

RESULTS

Of 784 smokers enrolled at baseline, 461 had biochemically confirmed tobacco abstinence after 7 weeks of open-label bupropion therapy. Of these 461 subjects, 429 were randomized to receive either continued bupropion therapy (n=214) or placebo (n=215). The 32 abstinent subjects not randomized were discontinued from the study because of scheduling difficulty (n=20), adverse events (n=10), and protocol deviation (n=2).

Demographics and baseline characteristics of the 784 study subjects are given in Table 1. Their mean ± SD age was 45.4±9.8 years, and 54% were women. On average, subjects smoked 27.3±10.1 cigarettes per day during the year before entry into the study and had a mean smoking history of 28.3±10.0 years (range, 2-59 years).

The subject characteristics associated with each WBC parameter at baseline are shown in Table 1. White blood cell counts, ANCs, and percent neutrophils did not vary significantly based on the Self-Administered Alcoholism Screening Test or the Structured Clinical Interview for Axis I depression score. Higher WBC counts were independently associated with an increased BMI ($P<.001$), as well as several measures of tobacco exposure or degree of nicotine dependence (smoking more cigarettes per day, $P=.02$; higher Fagerstrom score, $P<.001$; and higher serum cotinine level, $P<.001$). A higher ANC was associated with a higher BMI ($P=.03$), higher Fagerstrom score ($P<.001$), and higher serum cotinine level ($P<.001$). Percent neutrophils was associated with a slight increase in serum cotinine level ($P=.02$).

The distribution for each hematologic parameter at baseline, with all subjects smoking, is summarized in Table 2. The mean ± SD WBC count was $8.4\pm2.3 \times 10^9$/L, and the mean ± SD ANC was $5.3\pm1.9 \times 10^9$/L. The 90th percentile for the WBC count was 11.4×10^9/L, and the 90th percentile for the ANC was 7.5×10^9/L.

The change from baseline to week 7 for each leukocyte parameter in the 3 smoking groups (continuously abstinent, point-prevalence abstinent at week 7, and smoking) is summarized in Table 3. During that time, all participants were assigned to take bupropion. The mean WBC count declined in all 3 groups between baseline and week 7 ($P<.001$ in each group), but the decrease was significantly larger in the 2 groups of subjects who were abstinent from tobacco at week 7 compared with the continuing smokers (continuously abstinent, 1.4±2.1; point-prevalence abstinent, 1.2±1.9; smoking, 0.8±2.0; $P=.02$). This difference remained significant ($P=.03$) after adjusting for age, sex, BMI at baseline, and change in BMI. The decline in WBC count was significantly greater among continuously abstinent participants at week 7 than among continuing smokers ($P=.009$) but not between point-prevalence abstinent smokers and continuing smokers. Declines between baseline and week 7 were also seen in ANCs and neutrophil percentages for each group, but the magnitude of each decline was not significantly different across the 3 groups at week 7.

The change in each WBC parameter from baseline to week 52 and from week 7 to week 52 across the 3 smoking groups is shown in Table 4. Half the sample was randomly assigned to take either bupropion or placebo between weeks 7 and 52. The decline in WBC count from baseline was significantly greater among the 2 groups of subjects who were abstinent at week 52 compared with continuing smokers (continuously abstinent, 1.2±1.9; point-prevalence abstinent, 1.7±2.4; smoking, 0.1±1.9; $P<.001$) in an analysis that controlled for treatment group assignment (bupropion vs placebo) for weeks 7 to 52. The decline in WBC count and ANC was not different between the continuously abstinent and point-prevalence abstinent groups between baseline and week 52, but both groups had greater declines in these parameters than continuing smokers. A similar result was observed for the decline in WBC count and ANC between weeks 7 and 52. There were no significant differences across smoking groups for change in percent neutrophils from baseline to week 52 or from week 7 to week 52.

DISCUSSION

We found a strongly positive relationship between cigarette smoking and both WBC count and ANC in a large cohort of healthy smokers. A causal role for smoking in these changes is supported by the dose-response relationship, with a larger effect seen in heavier smokers, as well as the fact that smokers' higher WBC counts reversed rapidly after smoking cessation. This reversal became apparent within 7 weeks of smoking cessation, and the decreased WBC count was sustained after 1 year of abstinence.

Taken alongside research of the association of smoking with other risk factors for cardiovascular disease, such as C-reactive protein, fibrinogen, and homocysteine,[4,5] our results provide another important clue for the possible mechanism by which smoking contributes to the development of atherosclerotic disease. Future studies that aim to assess the effect of smoking cessation on qualitative WBC characteristics, such as cytokine production, seem warranted. In addition, the fact that prior smokers had a decrease in total WBC count and ANC but a comparatively

TABLE 1. **Baseline Characteristics and Laboratory Values for the 784 Smokers***

Characteristic	No. (%) of subjects	White blood cells ($\times 10^9$/L)		Absolute neutrophil count ($\times 10^9$/L)		Neutrophils (%)	
		Mean ± SD	*P* value†	Mean ± SD	*P* value†	Mean ± SD	*P* value†
Age (y)			.19		.60		.40
18-29	43 (5)	7.9±2.7		5.0±2.2		61.3±8.1	
30-39	183 (23)	8.2±2.2		5.2±1.8		62.3±7.7	
40-49	322 (41)	8.5±2.4		5.3±2.1		62.1±8.3	
50-59	179 (23)	8.7±2.1		5.4±1.7		62.0±7.7	
≥60	57 (7)	8.3±1.8		5.1±1.3		61.6±5.8	
Sex			.60		.38		.17
Female	423 (54)	8.4±2.2		5.2±1.8		61.7±8.0	
Male	361 (46)	8.4±2.3		5.3±2.0		62.5±7.7	
Body mass index‡ (kg/m^2)			<.001		.03		.24
<25	302 (39)	8.2±2.4		5.3±2.1		62.9±8.6	
25-29.9	288 (37)	8.3±2.2		5.2±1.8		61.4±7.5	
≥30	192 (25)	8.8±2.2		5.4±1.7		61.6±7.1	
Cigarettes smoked per day during the past year			.02		.06		.82
15-20	351 (45)	8.2±2.2		5.1±1.8		61.8±7.9	
21-40	380 (48)	8.6±2.3		5.4±2.0		62.3±7.7	
≥41	53 (7)	8.5±2.3		5.3±1.9		61.2±9.0	
Age (y) at smoking initiation			.17		.34		.38
<18	472 (60)	8.5±2.4		5.3±2.0		61.8±8.2	
≥18	312 (40)	8.3±2.0		5.2±1.7		62.3±7.3	
Years smoked			.11		.45		.40
0-19	157 (20)	7.8±2.2		4.9±1.7		61.6±7.7	
20-25	169 (22)	8.6±2.2		5.4±1.9		62.4±7.9	
26-30	159 (20)	8.4±2.3		5.4±2.0		63.1±8.3	
31-35	135 (17)	8.7±2.6		5.5±2.2		61.6±8.0	
≥36	164 (21)	8.5±2.1		5.3±1.6		61.4±7.5	
Fagerstrom Tolerance Questionnaire			<.001		<.001		.07
<7	232 (30)	7.9±2.0		4.9±1.6		61.3±7.2	
≥7	549 (70)	8.6±2.4		5.5±2.0		62.4±8.1	
Serum cotinine‡ (μg/L)			<.001		<.001		.02
0-300	224 (29)	7.8±2.0		4.8±1.5		61.1±7.4	
301-400	243 (31)	8.5±2.3		5.3±1.9		62.0±8.1	
401-500	201 (26)	8.4±2.4		5.4±2.1		62.4±8.2	
≥501	114 (15)	9.2±2.3		5.9±2.0		63.2±7.5	
Other smokers in the household			.85		.74		.72
No	551 (70)	8.4±2.3		5.3±1.9		62.0±7.9	
Yes	233 (30)	8.4±2.3		5.3±1.9		62.2±7.8	
SAAST score			.39		.67		.41
<7	704 (90)	8.4±2.3		5.3±1.9		62.1±7.9	
≥7	80 (10)	8.6±2.4		5.4±2.0		61.4±7.4	
History of major depression‡			.09		.15		.84
No	636 (83)	8.5±2.3		5.3±1.9		62.0±7.9	
Yes	137 (18)	8.1±2.1		5.1±1.7		61.9±7.7	

*Because of rounding, not all percentages total 100%. SAAST = Self-Administered Alcoholism Screening Test.

†*P* value from linear regression with the hematologic parameter as the dependent variable and each characteristic as the independent variable. For this analysis age, body mass index, number of cigarettes smoked per day during the past year, years smoked, and serum cotinine level were treated as continuous variables and sex, age at smoking initiation, Fagerstrom Tolerance Questionnaire, other smokers in the household, SAAST score, and history of major depression were treated as categorical variables.

‡Total does not equal 784 because of missing data for some participants.

small change in percent neutrophils provides ancillary evidence that the hematologic effect of smoking on atherosclerosis is not achieved solely via increased neutrophil-mediated inflammation. Indeed, prior cross-sectional studies have shown that many WBC lines, not just neutrophils, are increased in smokers.[15,28]

In healthy smokers, we found a mean WBC count of 8.4×10^9/L in both men and women; this value compares to a mean WBC count of 7.2×10^9/L in men and 7.3×10^9/L in women (smokers and nonsmokers) in the second National Health and Nutrition Examination Survey.[29] Although smoking was known to be associated with higher WBC

TABLE 2. **Baseline Hematologic Parameters for the 784 Smokers**

Characteristic	Mean ± SD	Median	Percentile		
			90th	95th	99th
White blood cells ($\times 10^9$/L)	8.4±2.3	8.1	11.4	12.5	15.1
Absolute neutrophil count ($\times 10^9$/L)	5.3±1.9	4.9	7.5	8.8	11.3
Neutrophils (%)	62.0±7.9	62.4	72.1	74.9	80.3

counts in otherwise healthy persons, such quantitative data of the distribution of WBC counts in healthy smokers were hitherto lacking. Our WBC reference ranges may help physicians identify the statistically normal upper limit of WBC counts in smokers and may aid in decisions regarding further work-up or hematologic consultation when confronted with an elevated WBC count in a known smoker.

For example, should a smoker with a confirmed WBC count of 14.0×10^9/L on routine laboratory examination be evaluated further? This WBC count is between the 95th and 99th percentile for the healthy smokers in our study. In the absence of an obvious source of infection or inflammation, such a patient would likely warrant further work-up despite his or her smoking status. In contrast, a smoker with a WBC count of 12.4×10^9/L is within the statistically normal range of our subjects.

Our study has several strengths. First, as self-reported assessments of smoking status have been shown to be questionably reliable,[21,30] our design incorporated biochemical confirmation of smoking cessation alongside prospective measures of changes in WBC parameters. Second, our study population was heterogeneous with regard to race and sex, was drawn from diverse regions of the United States, and was specifically screened to be free of evidence of chronic illness.

Third, the changes in WBC counts and ANCs correlated well with previous population-based studies of the relationship between cigarette smoking and WBC parameters.[9,13,19,20] For example, Smith et al[9] published a cross-sectional analysis of differential WBC counts and smoking status using data from the European Prospective Investigation for Cancer Study. They found WBC counts of 7.8, 6.4, and 6.2×10^9/L for current, former, and never male smokers, respectively ($P<.001$). Our continuously abstinent group sustained a decrease in WBC count of 1.2×10^9/L, correlating well with the difference between the current and former smoker groups in the European Prospective Investigation for Cancer Study.

The major limitation of our study is the fact that some of our participants were taking sustained-release bupropion. All participants took the drug for the first 7 weeks, and a random half were assigned to take it for weeks 8 to 52. This factor did not influence our baseline analyses of

TABLE 3. **Change in Hematologic Parameters From Baseline to Week 7**

Characteristic	Continuously abstinent from quit date		Abstinent for ≥7 days at week 7 but not continuously abstinent since quit date		Smoking at week 7		*P* value*	Adjusted *P* value†
	No. of subjects	Mean ± SD	No. of subjects	Mean ± SD	No. of subjects	Mean ± SD		
White blood cells ($\times 10^9$/L)								
Baseline	276	8.4±2.4	169	8.1±2.1	136	8.5±2.2		
Week 7		7.0±1.7		6.9±1.9		7.7±1.9		
δ (week 7 minus baseline)		–1.4±2.1‡		–1.2±1.9‡		–0.8±2.0‡	.02	.03§
Absolute neutrophil count ($\times 10^9$/L)								
Baseline	276	5.3±2.1	169	5.1±1.6	136	5.4±1.7		
Week 7		4.2±1.3		4.1±1.4		4.7±1.4		
δ (week 7 minus baseline)		–1.1±1.9‡		–0.9±1.6‡		–0.7±1.7‡	.09	.15
Neutrophils (%)								
Baseline	276	62.1±8.4	169	61.8±7.3	136	62.6±7.2		
Week 7		59.8±6.8		59.2±7.9		60.5±7.0		
δ (week 7 minus baseline)		–2.3±8.7‡		–2.6±7.1‡		–2.1±7.1‡	.84	.71

*From analysis of variance with change (δ) in hematologic parameter as the dependent variable and smoking status as the independent variable.
†From analysis of variance with change (δ) in hematologic parameter as the dependent variable and smoking status as the independent variable. Covariates include age, sex, body mass index (BMI) at baseline, and δ BMI (week 7 BMI minus baseline BMI).
‡$P \leq .001$ from a 1-sample *t* test comparing δ to 0.
§Linear contrasts were used to perform pairwise comparisons among the 3 smoking groups to evaluate whether the groups were significantly different from each other. At week 7, the continuously abstinent group was significantly different ($P=.009$) from the smoking group, but the continuously abstinent group was not significantly different from the abstinent for ≥7 days group ($P=.24$), and the abstinent for ≥7 days group was not significantly different from the smoking group ($P=.16$).

TABLE 4. **Change From Baseline and Week 7 to Week 52 in Hematologic Parameters**

Characteristic	Continuously abstinent from week 7		Abstinent for ≥7 days at week 52 but not continuously abstinent since week 7		Smoking at week 52			
	No. of subjects	Mean ± SD	No. of subjects	Mean ± SD	No. of subjects	Mean ± SD	*P* value*	Adjusted *P* value†
White blood cells ($\times 10^9$/L)								
Baseline	126	8.1±2.0	57	8.4±2.7	90	7.9±2.4		
Week 7	123	6.8±1.6	56	6.8±1.4	89	6.8±1.9		
Week 52	126	6.9±1.6	57	6.8±1.6	90	7.8±2.4		
δ 1 (week 52 minus baseline)	126	–1.2±1.9‡	57	–1.7±2.4‡	90	–0.1±1.9	<.001	<.001§
δ 2 (week 52 minus week 7)	123	0.1±1.4	56	–0.1±1.6	89	0.9±1.9‡	<.001	<.001§
Absolute neutrophil count ($\times 10^9$/L)								
Baseline	126	5.0±1.7	57	5.3±2.3	90	5.0±2.0		
Week 7	123	4.0±1.1	56	4.1±1.0	89	4.2±1.5		
Week 52	126	4.1±1.2	57	4.0±1.2	90	4.8±1.9		
δ 1 (week 52 minus baseline)	126	–1.0±1.6‡	57	–1.4±2.2‡	90	–0.2±1.5	<.001	<.001//
δ 2 (week 52 minus week 7)	123	0.05±1.2	56	–0.2±1.3	89	0.6±1.7‡	.001	.001//
Neutrophils (%)								
Baseline	126	61.6±8.2	57	62.1±8.1	90	62.0±8.0		
Week 7	123	58.7±6.6	56	60.3±7.2	89	59.8±8.3		
Week 52	126	58.3±6.8	57	58.2±7.1	90	60.0±7.4		
δ 1 (week 52 minus baseline)	126	–3.3±8.3‡	57	–3.9±7.6‡	90	–2.0±7.2¶	.30	.16
δ 2 (week 52 minus week 7)	123	–0.4±7.0	56	–2.0±7.4¶	89	0.2±8.7	.13	.12

*From analysis of variance with change (δ) in hematologic parameter as the dependent variable and smoking status as the independent variable. Treatment group, bupropion vs placebo, was included as a covariate.

†From analysis of variance with change (δ) in hematologic parameter as the dependent variable and smoking status as the independent variable. For δ 1, covariates include age, sex, body mass index (BMI) at baseline, δ BMI (week 52 BMI minus baseline BMI), and treatment group, bupropion vs placebo. For δ 2, covariates include age, sex, BMI at week 7, δ BMI (week 52 BMI minus week 7 BMI), and treatment group, bupropion vs placebo.

‡$P \leq .001$ from a 1-sample *t* test comparing δ to 0.

§Linear contrasts were used to perform pairwise comparisons among the 3 smoking groups to evaluate whether the groups were significantly different from each other. For δ 1, the continuously abstinent group ($P=.001$) and the abstinent for ≥7 days group ($P<.001$) were both significantly different from the smoking group, but they were not significantly different from each other ($P=.14$). For δ 2, the continuously abstinent group ($P<.001$) and the abstinent for ≥7 days group ($P<.001$) were both significantly different from the smoking group, but they were not significantly different from each other ($P=.61$).

//Linear contrasts were used to perform pairwise comparisons among the 3 smoking groups to evaluate whether the groups were significantly different from each other. For δ 1, the continuously abstinent group ($P=.003$) and the abstinent at the end point group ($P<.001$) were both significantly different from the smoking group, but they were not significantly different from each other ($P=.21$). For δ 2, the continuously abstinent group ($P=.002$) and the abstinent at the end point group ($P<.001$) were both significantly different from the smoking group, but they were not significantly different from each other ($P=.38$).

¶$P \leq .05$ from a 1-sample *t* test comparing δ to 0.

WBC parameters because participants did not start bupropion until after the baseline assessment. Bupropion could potentially confound the effect of smoking cessation on WBC parameters, but this is unlikely because the effect remained significant after controlling for treatment group in a multivariate analysis. Additionally, a review of the original phase 1 and 2 trial data revealed that the WBC count was not significantly different between subjects taking bupropion or placebo.

We observed relatively small mean increases in WBC counts and ANCs; however, recent data have shown that even a modest increase in WBC counts is associated with deleterious cardiovascular remodeling and mortality.[30-33] For example, Elkind et al[31] showed that in a population of healthy subjects, even after adjustment for cardiovascular risk factors including smoking, an increase in the WBC count of just 1.0×10^9/L was associated with a sonographically visible increase in aortic arch plaque thickness. In addition, in a subanalysis of TACTICS-TIMI (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction) 18 data, Sabatine et al[32] reported that routine WBC counts that were elevated but still in the reference range were an excellent predictor of mortality among patients who subsequently experienced the acute coronary syndrome.

CONCLUSION

Our study indicates that WBC counts and ANCs are elevated in otherwise healthy smokers, that these parameters decline rapidly after biochemically confirmed smoking

cessation, and that the decrease is sustained, possibly reflecting a decrease in an underlying state of tobacco-induced inflammation. The implications of this relationship range from helping to guide the medical work-up in a healthy smoker with leukocytosis to broadening our understanding of how smoking leads to atherosclerosis.

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