

# Investigation of photosensitivity side effect of systemic doxycycline used in the treatment of acne vulgaris

Sabir Hasanbeyzade, Elif Demirci Saadet\*

Department of Dermatology and Venereology, Medicana International Hospital, Ankara, Turkey.

\* Department of Dermatology, Atilim University, Medicana International Ankara Hospital, Ankara, Turkey.

## Abstract

**Objective** In this study, photosensitivity and other side effects due to the usage of systemic doxycycline in summer during acne treatment and whether these side effects were related to the demographic and clinical properties of the patients were investigated.

**Methods** Before conducting the study, approval of the ethics committee of the hospital was obtained. 251 patients who applied to the dermatology outpatient clinic between 01.05.2021-30.09.2021 and were diagnosed with moderate-severe acne were included in the study. Demographic characteristic of the patients, clinical and treatment features, and development of photosensitivity or other side effects during or after the treatment were examined.

**Results** Side effects were seen in 9 out of a total of 251 patients (3.6%). Among these patients, 5 patients (2%) had erythematous papules or plaque-like lesions on the face, and 4 patients (1.6%) had erythematous papules on the forearms. A statistically significant difference for age, sex, the severity of the disease, and treatment dose was not detected between groups classified according to the side effects (p values were respectively: 0.67, 0.058, 0.343, and 0.858). Statistically, a significant difference was found between these groups for the treatment period and usage of sun protection (p values were respectively: 0.011 and 0.003).

**Conclusion** In patients who have erythematous papules and plaques on the face, these findings regressed with topical treatment. Therefore these findings were considered to be due to the usage of the topical acne agent. However, most patients having erythematous papules on their forearms were not using sunscreens and had personal and/or familial history of atopy. Because side effects did not require cessation of the systemic treatment and regressed with administered treatment; in the case of regular usage of sunscreen and utilization of benzoyl peroxide in combination, the photosensitivity side effect was thought to be minimal.

## Key words

Acne vulgaris; Doxycycline; Photosensitivity; Acne treatment.

## Introduction

Although acne vulgaris can be seen in all age groups, it is a chronic inflammatory disease of the pilosebaceous unit that is frequently seen during adolescence having many factors in its etiology. While it affects 9.4% of the whole population; its severe forms are more frequently seen in males.<sup>1</sup> In Turkey, its prevalence is around 60.7% in adolescents between the ages of 13-19. While acne is seen more frequently in

females at the ages of 13-14; it is seen more in males at the age group of 15-18.<sup>2</sup> In the pathogenesis of acne, an increase in sebum

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## Address for correspondence

Dr. Sabir Hasanbeyzade, MD,  
Dermatovenerologist, Dermatology and Venereology  
Department, Medicana International Hospital,  
Ankara, Turkey.  
Garantievler 15. sokak, 1/8, Ulukavak mahallesi,  
Çorum Merkez, Türkiye.  
Ph: 00905526372939  
Email: dr.sabir.hasanov@gmail.com

production, *propionibacterium acnes* colonization, hyperkeratinization, and inflammatory processes are present.<sup>3</sup> Factors like stress; hormonal irregularities, some administered medications, daily care or make-up products used, and nutrition are the ones that affect the development of acne indirectly.

The treatment of acne is generally determined according to the severity of the disease. While topical agents (retinoids, benzoyl peroxide, or their combinations) are generally used in mild acne, topical agents +/- systemic antibiotics are used in moderate acne; systemic isotretinoin is used in severe/very severe acne. Doxycycline among systemic antibiotics might lead to photosensitivity reactions, especially in the summer; thus, its usage should be avoided.

In our study, we examined the photosensitivity developed due to the usage of systemic doxycycline in the summer for the treatment of acne vulgaris. Also, we investigated the relationship with factors such as age, sex, the dosage of the medication, administration period of the medication, type of accompanying topical treatment and usage of sunscreen, and whether usage of systemic doxycycline is safe during summer, or not.

## Material and Method

For the study, ethics consent was obtained from the non-clinical research ethics committee of our hospital.

Patients between the ages of 12-45 who had applied to our dermatology outpatient clinic between the dates of 01.05.2021-30.09.2021 and were diagnosed with acne were included in the study. The files of the patients were examined retrospectively and among the patients matching these criteria, patients having moderate and severe acne according to *global acne grading*

*system* (GAGS) scoring and being initiated treatment of systemic doxycycline were selected.<sup>4</sup> Patients diagnosed with another disease and patients using medications having a high risk for photosensitivity (retinoids, psoralens, fluoroquinolones, etc.), and patients having a history of these medications for a period of 6 months before acne treatment were excluded from the study. Patients were using 10% benzoyl peroxide (BPO) topically in addition to systemic doxycycline treatment. A total of 251 patients were included in the study. Initial examination, severity scoring, arrangement of the treatment, following up of the treatment, and evaluation of the observed side effects were performed by the same physician.

Demographic characteristics of the patients, data related to the severity of the diseases, treatment durations and doses, the development of photosensitivity or other side effects during or after the treatment and, if developed, then the used medication and the time of healing, usage of sunscreens were entered into SPSS statistics 25 (IBM© Corp., Armonk, NY, USA) program and their statistical analyses were performed. Continuous variables were expressed as the mean and standard deviation, discrete variables were expressed as numbers and percentages. Concerning continuous variables, while the intergroup statistical difference was investigated, the Kolmogorov-Smirnov test was used to examine whether they conformed to normal distribution or not. The presence of a statistically significant difference between two independent groups that do not conform to a normal distribution concerning continuous variables was examined with Mann Whitney U test, which is a non-parametric test, the presence of a statistically significant difference among 3 or more independent groups was examined with Kruskal-Wallis test, the presence of difference among 3 or more independent groups

conforming to normal distribution was examined with ANOVA test and the presence of statistically significant difference among independent groups compared for discrete variables was examined with chi-square test.

**Results**

9 (3.6%) out of a total of 251 (100%) patients included in the study were determined to have side effects. Among these patients, 5 patients (2%) had erythematous papules or plaque-like lesions on the face, and 4 (1.6%) had erythematous papules on the forearms. The mean age of patients included in the study was 23.58±7.62 and 46 (18.3%) of these were male, 205 (81.7%) of them were female; the mean age of patients with side effects was 25.22±8.74, and 3 (18.3%) of them were male, 6 (66.7%) of them were female. While 209 (88.3%) out of 251 patients had the disease in moderate severity, 42 (16.7%) patients had severe disease. 8 (88.9%) out of 9 patients who had developed side effects had disease of moderate severity, and 1 (11.1%) had severe disease. 194 (77.3%) of the patients were using sunscreens regularly, and 57 (22.7%)

of them were not using them. General statistical information of all patients, patients with side effects, and types of side effects are provided in **Table 1**.

Statistically, a significant difference was not found between patient groups with or without side effects due to systemic doxycycline treatment for age, sex, the severity of the disease, treatment dose, and usage of sunscreen (p values were as: 0.508, 0.236, 0.645, 0.91, 0.113, respectively). Between these two groups, a statistically significant difference was found for treatment periods (p=0.03). The ratio of developing side effects was found to be higher in the group having treatment duration of one month compared to other groups.

Statistically, a significant difference was not determined among patients with side effects, divided into groups according to the type of side effects for age, sex, the severity of the disease, and treatment dose (p values were as: 0.67, 0.058, 0.343, 0.858, respectively). Statistically, a significant difference was found between these groups for the treatment period and usage of sun

**Table 1** General statistical data.

	<i>General</i>	<i>Having no side effects</i>	<i>With side effects</i>	<i>Erythematous papules/ plaques on the face</i>	<i>Erythematous papules on forearms</i>
Number/percentage	251 / 100%	242 / 96.4%	9 / 3.6%	5 / 2%	4 / 1.6%
Age	23.58±7.62	23.52±7.59	25.22±8.74	24±10.65	26.75±6.85
Sex					
Male	46 (18.3%)	43 (17.8%)	3 (33.3%)	3 (60%)	0 (0%)
Female	205 (81.7%)	199 (82.2%)	6 (66.7%)	2 (40%)	4 (100%)
The severity of the disease					
Moderate	209 (83.3%)	201 (83.1%)	8 (88.9%)	4 (80%)	4 (100%)
Severe	42 (16.7%)	41 (16.9%)	1 (11.1%)	1 (20%)	0 (0%)
Treatment dose (mg)					
100	199 (79.3%)	192 (79.3)	7 (77.8%)	4 (80%)	3 (75%)
200	52 (20.7%)	50 (20.7%)	2 (22.2%)	1 (20%)	1 (25%)
Duration of treatment					
1 month	37 (14.7%)	33 (13.6%)	4 (44.4%)	0 (0%)	4 (100%)
2 months	82 (32.7%)	81 (33.5%)	1 (11.1%)	1 (20%)	0 (0%)
3 months	132 (52.6%)	128 (52.9%)	4 (44.4%)	4 (80%)	0 (0%)
Sunscreen					
Using	194 (77.3%)	189 (78.1%)	5 (55.6%)	5 (100%)	0 (0%)
Not using	57 (22.7%)	53 (21.9%)	4 (44.4%)	0 (0%)	4 (100%)

**Table 2** Time of developing side effects, treatment options, and time of healing data in patients with side effects.

	<i>With side effects</i>	<i>Erythematous papules/plaques on the face</i>	<i>Erythematous papules on forearms</i>
Time of formation of side effects (day)	12.33±5.64	8.2±1.79	17.50±4.04
Treatment of side effects			
Topical. cs. <sup>1</sup>	4 (44.4%)	2 (40%)	2 (50%)
Oral ah. <sup>2</sup>	2 (22.2%)	2 (40%)	0 (0%)
Topical. cs. + oral ah. <sup>3</sup>	3 (33.3%)	1 (20%)	2 (50%)
Time of healing of the side effect (day)	3.78±0.97	3.8±1.1	3.75±0.96

<sup>1</sup> Topical corticosteroid, <sup>2</sup> Oral antihistamine, <sup>3</sup> Topical corticosteroid and oral antihistamine combination.

protection (p values were respectively: 0.011 and 0.003). Side effects were found to be less frequent in patients having treatment duration of 2 months. Most of the erythematous papules found on the face were seen in patients with treatment duration of 3 months, and erythematous papules found on the forearms were seen in patients with treatment duration of 1 month. None of the patients having erythematous papules on the forearms were using sunscreens. However, all patients with erythematous papules on the face were using sunscreens.

The mean time of development of side effects in the patients was 12.33±5.64 days following the treatment of acne treatment, and the mean healing time after treatment for side effects was initiated or topical drug is discontinued was 3.78±0.97 days. In the side effect treatment of these patients, 4 of them (34.8%) were administered topical corticosteroids, 2 patients (22.2%) were administered systemic antihistamines, 3 patients (33.3%) were administered a combination of topical steroids and oral antihistamines. These durations and treatments in subgroups divided according to the type of side effects are given in **Table 2** in detail. While a statistically significant difference was found in the time of the development of side effects in patient groups displaying side effects (p= 0.002), no statistically significant difference was found for the time of healing of these side effects (p>0.10). Erythematous papules seen on

the forearms developed at a later stage.

Treatment was not terminated in any of the patients due to side effects; systemic doxycycline treatment was discontinued only when acne improved. An increase in pigmentation, onycholysis, widespread erythema or burning, and stinging sensation in sun-exposed areas was not observed in any of the patients.

## Discussion

There is a tendency to avoid systemic usage of the tetracycline group of antibiotics during summer due to their effects like photosensitivity and the formation of hyperpigmentation. When the Pubmed database was searched for photosensitivity side effects of systemic usage of doxycycline among tetracycline group antibiotics (search was performed by using keywords like doxycycline photosensitivity, doxycycline phototoxicity), case-based data were found to be present in general. The basic side effect was seen to be onycholysis in most of the cases.<sup>5-14</sup> In their placebo-controlled double-blind studies performed on volunteers, Blank *et al.* observed phototoxic reactions in 2 out of 10 patients who were exposed to the sun on a ship for 5 hours following the administration of 200 mg/day doxycycline for a period of 1 week. Frost *et al.* observed sunburn-like reactions in 6 out of 15 volunteers who had been using 200 mg/day doxycycline for 1 week following sun

exposure in their placebo-controlled double-blind studies.<sup>16</sup> Bjellerup *et al.* stated that doxycycline had a high risk for phototoxicity (observed in 4 out of 8 patients) in their double-blind study performed with fluorescence exposure.<sup>17</sup> In 1 out of 10 patients using 200 mg doxycycline, phototoxic effects were seen following the exposure to a high-density UV lamp.<sup>18</sup> In addition to these studies performed on a limited number of volunteers, there are studies carried out on acne patients using doxycycline, as well. Layton *et al.*<sup>19</sup> observed phototoxic reactions in 38 out of 106 patients using 150-200 mg/day doxycycline in their prospective cohort study, Kus *et al.*<sup>20</sup> observed photosensitivity reactions in 2 out of 26 acne vulgaris patients using 200 mg/day doxycycline for the first month, then 100 mg/day for 2 months in their study in which they had measured the efficacy of systemic doxycycline and azithromycin in the treatment of acne vulgaris. Sanchez *et al.* explained that they have not encountered photosensitivity in any of their 20 rosacea patients using 20 mg doxycycline and topical metronidazole in the randomized, double-blind placebo-controlled study that they performed.<sup>21</sup> Tuyet Nguyen *et al.* described bilateral erythematous and "heart-shaped" rash in the dorsal thenar region of the hands of 3 patients using doxycycline for acne.<sup>22</sup> Kristen *et al.* defined subacute cutaneous lupus erythematosus in a patient using doxycycline for dental treatment of 3 days.<sup>23</sup> Alexander *et al.* reported a case of photoallergic erythroderma developing on the 5th day of treatment with 200 mg/day doxycycline for erythema chronicum migrans.<sup>24</sup> Stupica *et al.* compared the usage of 200 mg/day doxycycline for a period of 10 and 15 days in the treatment of erythema migrans and did not observe photosensitivity in any of the 108 patients, however side effect was seen in 7 out of 117 patients (6%) using the drug for 15 days.<sup>25</sup> In some of the studies related to the usage of doxycycline in the treatment of

erythema migrans, a high ratio of phototoxicity/photosensitivity side effects reaching up to 15% was reported.<sup>26,27</sup> In some of these studies, although a high dose of doxycycline was used such as 300 mg/day, studies stating that a high ratio of photosensitivity was observed following the usage of low doses and for a short period are also present.<sup>28</sup> The authors attributed these differences in photosensitivity/ phototoxicity ratios to the fact that the studies were carried out in different seasons and different geographical locations.

In our study, we analyzed moderate and severe acne patients diagnosed with acne vulgaris during summer retrospectively and examined the side effects that developed during the treatment period and in the following 3 months, and the time of the development of these side effects. We examined the relationship of side effects with the severity of the disease, dose, and duration of acne treatment, the medications used in the treatment of side effects, and the duration of treatment.

Patients included in the study were mostly female, only 18.3% of the patients consisted of male patients. We thought that this was related to the fact that women cared for their outer appearances more compared to men and applied to a hospital more frequently. Studies are reporting higher photosensitivity to doxycycline is present in females. Masa *et al.* found a photosensitivity finding ratio of 2.7% in females and 0.8% in males.<sup>29</sup> However, sex difference was not present in our study concerning side effects. In addition, sex difference was not determined in previous studies.<sup>29</sup>

The ratio of side effects was found to be 3.6% in the patients. 2% of the patients had erythematous papules/plaques, and 1.6% had erythematous papules on the forearms. Statistically, a significant difference was not

found between groups developing and not developing side effects concerning doxycycline dose between groups when patients developing side effects were grouped according to the type of side effects, as well. Therefore, the treatment dose was considered to be ineffective for the development of side effects. Photosensitivity was specified to develop at low doses and early stages in some studies; and at high doses in others.<sup>29,30</sup>

The side effect ratio was higher in patients having a treatment period of 1 month. This situation can be interpreted as treatment was discontinued in a short time in patients who developed side effects; however, systemic treatment was not discontinued in any of the patients of our study due to side effects. Systemic treatment was discontinued only when clinical improvement was observed. In addition, a study showing that photosensitivity side effect due to doxycycline is not related to the treatment period is also present.<sup>19</sup>

Erythematous papules on the face were more in patients having 3 month period of treatment with doxycycline and benzoyl peroxide used in the treatment combination. All of these patients were using sunscreens. Since rash was not present in other sun-exposed areas, this side effect was attributed to the temporary irritant effect of benzoyl peroxide and regressed with administered treatments. Therefore, if BPO is to be used with doxycycline in summer, it should not be forgotten that side effects in the type of erythematous papules might develop on the face despite sunscreen usage.

None of the patients having erythematous papules and plaques on the forearms were using sunscreens. A history of allergic asthma, allergic conjunctivitis, allergic rhinitis, and/or allergic contact dermatitis was found to be present in the personal and/ or familial history of these

patients. Therefore, if doxycycline is to be used during summer, if an atopy history is present in the patient or the patient's family, then erythematous, pruritic papules and plaques may form in uncovered areas. Besides, since this side effect developed at a later stage compared to other side effects (mean 11-23 days, **Table 2**), patients have to be informed on this matter verbally. If atopy was present in personal and/or familial history, then these patients should be informed to use sunscreen and moisturizers. The formation of this type of side effect on the forearms of patients who did not use sunscreen; then subsiding of the side effect after the patient started using sunscreens and not recurring led to the consideration that it could be photosensitivity due to doxycycline treatment; however, remission of it with topical treatment and not being observed in other areas such as the neck, and the face made us think that it could be photosensitivity forming based on atopy rather than being a mere photosensitivity reaction. Moreover, most of the patients observed to have photosensitivity reactions were not using sunscreens and were exposed to the sun for short periods per day in other studies.<sup>29</sup>

Although literature cases are presenting the development of hyperpigmentation with the usage of tetracycline group antibiotics,<sup>31,32</sup> none of the patients in our study had hyperpigmentation.

In our study, all side effects were curable within a short time without requiring the discontinuation of the medication and were of mild intensity, and also no sequellae were present during the follow-up period of 3 months after the treatment. In light of all these data, we think that doxycycline treatment might be administered in the summer as well, especially for patients requiring systemic treatment, on the condition that sunscreens are used and taking individual and/or familial history of atopy into

consideration.

**Limitations of the study** Since the number of patients was limited, it should be performed with a larger case series and in comparison with the control group to demonstrate that usage of systemic doxycycline is safe in the summer. Since the patients included in the study were selected among patients applying to the dermatology outpatient clinic of a single hospital in a single country and since daily sun exposure periods and the intensity of sun exposure is geographically different in countries found in different latitudes throughout the world, the result of the study cannot be generalized for countries in different latitudes.

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