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The Effects of Biological Agents on Melanocytic Nevi: A Preliminary Report

Biyolojik Ajanların Melanositik Nevuslar Üzerine Etkileri: Ön Raporu

Abstract

Objective: The aim of our study was to evaluate the changes of the melanocytic nevi during the biological agent therapy.

Methods: For this purpose, 40 index nevi of 25 adult patients who were treated with infliximab, adalimumab, etanercept or rituximab were included in this study. All of the patients underwent clinical and dermoscopic evaluation before the beginning of the treatment, 6 months and 1 year after the beginning of the treatment. Among dermoscopic examination methods, pattern analysis, ABCD score system and three-point checklist were performed.

Results: In terms of the diameter of the index nevi, there was no statistically significant difference between the first examination and that of the sixth month, but differences was observed between the first examination and that of the twelfth month. There was also no statistically significant difference in total dermoscopy scores calculated by ABCD score system application on 31 nevi at the times of assessment. At the end of the study, we detected 24 new nevi formation in 7 patients, whom all of were over 35 years of age, however no eruptive nevi or melanoma formation were observed.

Conclusion: An increase in the diameters of the present nevi and formation of new nevi may be seen with biological agent therapy in one-year-follow-up.

Keywords: Biological agents, dermoscopy, melanocytic nevus

Öz

Amaç: Çalışmamızın amacı biyolojik ajan tedavisi süresince melanositik nevuslardaki değişiklikleri incelemektir.

Yöntemler: Bu amaçla, infliximab, adalimumab, etanercept veya rituksimab ile tedavi edilen 25 erişkin hastanın 40 indeks nevusunu çalışmada değerlendirildi. Bütün hastalara tedaviye başlamadan önce, tedavi başlangıcından altı ay ve bir yıl sonra dermatolojik muayene ve dermoskopik inceleme yapıldı. Dermoskopik muayene metodlarından; patern analizi, ABCD skorlama sistemi ve 3 nokta kontrol listesi kullanıldı.

Bulgular: İndeks nevus çapları açısından, altıncı ayda yapılan muayene ile ilk muayene arasında istatistiksel olarak anlamlı farklılık izlenmezken, ilk muayene ile on ikinci ayda ki muayene arasında izlendi. ABCD skorlama sistemi ile hesaplanan 31 nevusun toplam dermoskopi skorlarında da değerlendirme süreçlerinde istatistiksel olarak anlamlı fark yoktu. Çalışmanın sonunda, hepsi 35 yaşın üzerinde olan yedi hastada 24 yeni nevus (10 tanesi bir hastada) oluşumu saptadık, ancak erüptif nevus veya melanom oluşumu gözlenmedi.

Sonuç: Biyolojik ajan tedavisi ile bir yıllık takipte mevcut nevusların çapında artış ve yeni nevus oluşumu izlenebilir.

Anahtar kelimeler: Biyolojik ajanlar, dermoskopi, melanositik nevus

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Introduction

Biological immune modulators (biologic agents) such as infliximab, adalimumab, etanercept, cetuximab are widely used in anti-inflammatory and tumor therapy. They are highly efficient in certain diseases, but may cause a great variety of adverse side-effects. The best understood and to a certain extent expected adverse side-effect of certain biological agents is impaired function of the immune system resulting in a certain immunodeficiency (1). There is still controversy with respect to malignancies (2). However, a recent metaanalysis shows that patients treated with anti-tumor necrosis factor- α (anti-TNF- α) therapy have a significantly increased risk of non-melanoma skin cancer (NMSC) (3). But the occurrence of NMSC may be due to the previous use of phototherapy and immunosuppressive agents, even if a potential risk developing cancer after anti-TNF- α therapy cannot be excluded (4).

On the other hand a casual relationship between TNF- α inhibitors and reactivation of melanoma has not yet been described, but late recurrence of locoregional metastatic melanoma were reported in two cases (5). Bovenschen et al. (6) reported that treatment with the recently available biological agents might be associated with the formation of eruptive nevi. However, there are only a few case reports about the effect of biological agents on melanocytic nevi (6-8), but there is no study of wide series evaluating the changes in size and structure of the melanocytic nevi or the formation of new nevi, and also the potential risk of malignant transformation during the treatment with biological agents.

Therefore, the purpose of this study was to determine macroscopic and dermoscopic changes in melanocytic nevi during the treatment with biologic agents.

Methods

Forty-two adult patients referred to the Dermatology and Rheumatology Clinics of Kocaeli University Faculty of Medicine between February 2011 and November 2011 who were scheduled for a treatment with infliximab, adalimumab, etanercept or rituximab for various diseases, such as ankylosing spondylitis, rheumatoid arthritis and psoriasis-psoriatic arthritis.

The study was approved by the local ethics committee of our institution. Written informed consent was obtained from each patient. Then the following information about the patients were recorded: Age, weight, previous medical history including former use of other medication and treatment, the age which the nevi appeared first, the presence of uncountable nevi ($n > 50$), a history of blistering sunburn in childhood, phototherapy and tanning lamps and a family history of multiple nevi and melanoma. Skin types of the patients were recorded according to the Fitzpatrick's skin types.

Dermatological examination of the patients were performed to disclose the presence of 1 or 2 nevi larger than 2 mm in the head and neck, chest, back, upper and lower extremities and gluteal-genital areas which were recorded as index nevi. Patients without nevus or with nevus smaller than 2 mm were also followed for a new nevus formation or an increase

in the diameter of the present nevus. The selected nevi were evaluated in terms of diameter, location, macroscopic features such as elevation, shape and color. The locations of the nevi were also marked on the body diagrams. Dermoscopic examination was performed for the nevi with a diameter of 2 mm or larger with Dermlite II Fluid Dermoscope (3Gen LLC, USA). Pattern analysis, ABCD score system and three-point checklists were performed among dermoscopic examination methods. Nevi were also viewed with a digital camera, which was attached to the dermoscope. Digital images of dermoscopic views were re-evaluated also by a second experienced trainer.

The patients were re-evaluated at the 6th (first follow-up) and 12th months (second follow-up) for the treatment with biological agents for the macroscopic and dermoscopic changes of the index nevi. Patients with new nevus formation also underwent a clinical and dermoscopic examination. Photographs were retaken at the 6th and 12th months for the nevi that were previously photographed in the beginning of the treatment.

Statistical Analysis

Data were analyzed with SPSS version 21.0 for Windows. Friedman test with Bonferroni correction was used to compare the mean diameters of the 40 nevi at the first examination and the follow up at the 6th and 12th months. The statistical significance level in this analysis was accepted as 0.017 with Bonferroni correction.

Also, repeated measures of variance analysis were used to test differences between the total dermoscopy score (TDS) values in the first examination and 6th-12th months of follow-up. P value < 0.05 was considered statistically significant.

Results

Forty-two adult patients initially enrolled in this study. Six patients were excluded from the study before the 6th month of the biological agent therapy because of various side effects which is not associated with skin. The study was completed with 36 patients, 20 (55.5%) males and 16 (44.4%) females. The age of the study group ranged from 23-70 (mean 42 ± 12.48).

Of the study group, 18 (50.0%), 9 (25.0%), 7 (19.4%) and 2 (5.6%) patients were scheduled for a treatment with infliximab, adalimumab, etanercept and rituximab, respectively. The indications of treatment with biological agents were ankylosing spondylitis ($n=16$), rheumatoid arthritis ($n=9$), psoriasis and/or psoriatic arthritis ($n=9$), adult Still's disease ($n=1$) and SLE ($n=1$).

A total of 42 index nevi in 25 patients in the study group were planned for follow-up. The remaining 11 patients were also followed-up for new nevus formation. Of the 42 index nevi, 8 (19.05%) were localized on the head and neck, 15 (35.72%) on the frontal trunk, 10 (23.81%) on the back, 4 (9.52%) on the upper extremities, 4 (9.52%) on the lower extremities and 1 (2.38%) on the gluteal region. Two suspicious nevi were excised in the beginning of the study. The rest 40 nevi underwent clinical and dermoscopic evaluation in the beginning, at the 6th and 12th months of the treatment.

When the patients evaluated according to the skin types; it was seen that type 4 in 18 (50.0%), type 3 in 15 (41.7%), type 2 in 2 (5.6%) and type 1 in 1 (2.8%) of the patients. The patients' previous treatment agents were sulphasalazine (n=9) acitretin (n=5), methotrexate (n=7), cyclosporine (n=4), systemic corticosteroids (n=1), leflunomide (n=1), cyclophosphamide (n=1) and biological agents different from going to be use. In addition some of the patient had systemic photochemotherapy (PUVA) history in 3 patients, narrow-band ultraviolet B (UVB) in 1 patient and local PUVA in 2 patients. The cases in study group were receiving methotrexate (n=12), colchicine (n=3), antimalarials (n=6), corticosteroids (n=12) and isoniazid (n=8) in combination with biological agents.

The mean diameters of the 40 nevi were 4.33 ± 1.58 mm, and 4.42 ± 1.61 mm, 4.54 ± 1.70 mm at the first examination and 6th and 12th months follow-up, respectively. The increase in the diameter at three different stages was statistically significant ($p < 0.001$). The difference was not statistically significant between the first examination and the first follow-up ($p = 0.026$), and between the two follow-up examinations ($p = 0.039$). However, the difference between the first examination and the second follow-up was statistically significant ($p < 0.001$) (Table 1).

According to the dermoscopic analyses in total of 40 nevi, pattern analyses at the follow-up examination did not show any difference except new globule development in one nevus. The features of clinical and dermoscopic examination of the 40 nevi was consistent with dermal nevus (n=6), blue nevus (n=2), acral nevus (n=1), dysplastic nevus (n=1) and benign melanocytic nevus (n=30).

ABCD scoring system could apply to 31 nevi. The mean TDS values calculated according to the ABCD scoring system in 31 nevi were 2.81 ± 1.07 , 2.92 ± 1.12 , 2.92 ± 1.03 in the first examination and 6th and 12th months of the follow-up examinations, respectively. The difference between the mean TDS values in the first examination and first, second follow-ups were not statistically significant ($p = 0.117$) (Table 2).

In terms of three-point check-list, 2 of the 3 criteria were present in only 2 nevi in the first examination and follow-up examinations. There was no statistical significance in the follow-up period ($p = 0.368$). It was recommended the excision of two nevi (one of the nevi had 5.1 TDS score), but the patient accepted at the second follow-up, one of them was reported as benign melanocytic nevus, and the other one was solar lentigo in histopathological examination.

At the end of the study, there were 24 (10 were in one patient who was taken infliximab for ankylosing spondylitis) (Figure 1) new nevus formation in 7 patients older than 35 years of

age. These nevi were evaluated as benign melanocytic nevi with clinical and dermoscopic examination. There was no statistically significant difference in these nevi, in terms of the used treatment agent or location of the new nevus. There was no case developing eruptive nevi or malignant melanoma. There was no phototherapy history in any patients with change on nevi.

Discussion

It was reported that the cases with new nevus formation during treatment with biological agents such as infliximab, alefacept, etanercept and this effect probably related with immunosuppressive actions of these agents (6,7). In addition, an increased risk of development of dysplastic nevus (atypical nevus) and development and reactivation of melanoma was also reported during the treatment with biological agents (5,6,9).

To the best of our knowledge, 3 patients developing new melanocytic nevus (6,7), 2 patients with late recurrence of locoregional metastatic melanoma (5) and 2 patients with primary melanoma development (9) were reported after treatment with biological agents. Bovenschen et al. (6) reported development of eruptive nevi with a mean diameter of 2 mm especially in palms of two patients with Crohn's disease who were treated with azathioprine and infliximab. Katsanos et al. (7) reported a case of multiple new nevi developing during treatment with infliximab in a patient with



Figure 1. Multiple and scattered new nevi formation in a patient who was taken infliximab for ankylosing spondylitis at the 12th month of the therapy

Table 1. The mean diameters of the index nevi at the first examination and the follow-up at the 6th month and 12th month

Diameter of the nevi	n	mean (mm) ± SD	p value
First examination	40	4.33 ± 1.58	0.001*
6 th month	40	4.42 ± 1.61	
12 th month**	40	4.54 ± 1.70	

*Friedman test with Bonferroni correction, SD: Standard deviation, ** $p < 0.001$

Table 2. The mean total dermoscopy score values in the first examination, and at 6th and 12th months of follow-up

TDS**	n	Mean ± SD	p value
First examination	31	2.81 ± 1.07	0.117*
6 th month	31	2.92 ± 1.12	
12 th month	31	2.92 ± 1.03	

*Repeated measures of variance analysis, **TDS: Total dermoscopy score, SD: Standard deviation

Crohn's disease. Like Bovenschen et al. (6) and Katsanos et al. (7), we detected 24 new nevi formation in 7 patients at the end of our study, also. All new nevi were benign melanocytic type according to the clinical and dermoscopic examination. The locations of the newly formed nevus were frontal trunk and extremities. There was no significant difference in these patients in terms of the used biological agent or localization of the new nevi. All patients with new nevi were over 35 years old. Since new nevus formation is unusual for this age group, the authors think that this is a remarkable finding. One of the patients with new nevus formation had 10 nevi with a diameter approximately 2-3 mm on the fore-arms which were detected in a patient with ankylosing spondylitis who were treated with infliximab at the 12 months examination. In the literature, there is no reported criterion concerning the number of nevus for eruptive nevi. However, since the development of nevi was not as many in our case, so we did not accept them as "eruptive nevi".

To the best of our knowledge, there is no case series in the literature about the effects of biological agents on melanocytic nevi. According to a yet unpublished study in Paediatric Haematology-Oncology Department of Kocaeli University, 9 of the 19 nevi showed statistically significant increase in diameter at the 18th month follow-up of chemotherapy in children. But it was not clear for the authors if this finding was a result of chemotherapy or a natural result of the growth process in children. However, it was not observed statistically significant increase in the diameters of the existing nevi in adult patients in the same study (10). We detected an enlargement in the diameters of the present nevi and the difference between the increase in the mean diameter of the nevi in the first and 12 months examinations was statistically significant in our study group ($p>0.05$). Since the patients were adults and did not report a difference in body weight in the follow-up period, we think that the increase in the diameter is a remarkable finding.

According to the ABCD scoring system of the 31 nevi in our study, the difference between the mean TDS values in the first examination and first, second follow-ups were not statistically significant. Similarly according to the unpublished study of Öztürk et al. (10), there was no significant difference in TDS values of the present nevi of the children and adults, undergoing chemotherapy because of their hematologic malignancies (10). The dermoscopic examination of the 40 nevi in our study group showed no significant difference according to the criteria of three-point checklist method.

From the present study, we can conclude two important result; the first one is an enlargement in the diameters of the existing nevi and second one is formation of new nevi can be seen during biological agent therapy. However, we did not observe any differentiation in the structural components of the nevi. Also we didn't detect any suspicious lesion for melanoma with clinical or dermoscopic examination in our study group. The relatively short period of the 1-year-follow-up is a limitation of our study, but the findings are still important since this is the first study of dermoscopic examination of nevi during treatment with biological agents. In the literature, the reported cases of new nevi and eruptive

nevi formation were noticed between 3 weeks and 4 years after the use of TNF- α inhibitors (6,7). So the 1-year-follow-up period may be quite sufficient.

The hypothesis for the development of eruptive nevi associated with immunosuppression involves melanoma growth stimulatory activity; endogenous growth factor for normal melanocytes, nevocytes and malignant melanocytes which is produced by melanocytes (11). In another literature, Greene et al. (12) postulated that in systemic immunosuppression, destruction of tumor-specific lymphocytes by cytotoxic or immunosuppressive agents may lead to the formation of atypical nevi or melanoma. It is plausible that also for biological agents, eruptive nevi are the results of the immunosuppressive action of these agents (13).

As a conclusion an increase in the diameters of the existing nevi and formation of new nevi can be seen with biological agent therapy in 1-year-follow-up. We think that the exact role of biological agents in melanocytic proliferation either benign or malignant is difficult to determine because these patients often have a history of treatment with various immunosuppressives and there may also be other risk factors like phototherapy for carcinogenesis. In the mean time, complete skin examination in the beginning of the therapy, regular close follow-ups, especially in high risk patients, avoiding exposure to UV and informing the patients about the possible changes in the nevi are strongly recommended. Certainly, further studies on long-term data are needed to determine the relative risk of immune suppression with respect to nevi and possible malignant melanoma.

Ethics

Ethics Committee Approval: The study were approved by the Kocaeli University of Local Ethics Committee, Informed Consent: Consent form was filled out by all participants, Peer-review: Internal peer-reviewed.

Authorship Contributions

Concept: Nurşah Doğan, Nilgün Bilen, Design: Nurşah Doğan, Nilgün Bilen, Data Collection or Processing: Nurşah Doğan, Nilgün Bilen, Aysun Şikar Aktürk, Ayşe Cefle, Analysis or Interpretation: Nurşah Doğan, Çiğdem Çağlayan, Literature Search: Nurşah Doğan, Nilgün Bilen, Writing: Nurşah Doğan, Nilgün Bilen, Aysun Şikar Aktürk, Conflict of Interest: No conflict of interest was declared by the authors, Financial Disclosure: The authors declared that this study has received no financial support.

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