Methotrexate in psoriatic patients with melanoma
-A case-control study

Master thesis in Medicine

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Abstract

Introduction: Malignant melanoma is the sixth most common tumour in Sweden with a 5% annual increase in incidence the last ten years and an increase in mortality-rate. Psoriasis is a common disease effecting 1.5-2% of the population in Western countries. Methotrexate has been used to treat moderate to severe psoriasis since the 1950s. Whether Methotrexate increases the risk of developing melanoma is still under debate.

Aim: The aim of the study was to evaluate if Methotrexate increases the risk of melanoma in patients with psoriasis.

Method: An explorative case-control study was preformed to evaluate if there was a difference in exposure to Methotrexate in psoriatic patients with melanoma compared to psoriatic patients without melanoma. Subjects were enrolled and data was collected from medical records from the Department of Dermatology at Sahlgrenska University Hospital. A case-group of 52 subject with psoriasis and melanoma was compared to a control-group of 503 subject with psoriasis without melanoma. Fischer's exact test was used to analyze the difference of proportion in Methotrexate treatment.

Results: There was a higher tendency of Methotrexate treatment in the case-group, OR=1.39. The result was not statistically significant (p= 0.35, 95% CI 0.64-2.85)

Discussion and Conclusion: The analytic result in our study indicated that there was a higher risk of being exposed to Methotrexate for the case-subjects compared to the control-subjects but the result was not statistically significant. The study failed to show a statistically significant association between Methotrexate treatment and the risk of melanoma in psoriatic patients. Further research in the area is needed.

Key words: Malignant melanoma, Psoriasis, Methotrexate

Introduction

Melanoma

Malignant melanoma is the sixth most common tumour in Sweden with a 5% annual increase in incidence during the last ten years and an increase in mortality-rate (1).

Risk factors

Exposure to UV-radiation is considered the most important environmental factor for developing melanoma (1). Skin susceptibility to solar damage, history of sunburn episodes and great amounts of solar exposure are risk factors for developing melanoma (2). Family or personal history of melanoma is another major risk factor (2).

Histopathology

Melanomas originate from melanocytes at the epidermal-dermal junction of the skin (2). Depending on which parts of the cutaneous layer they affect the melanoma is either invasive or non-invasive. In the non-invasive form, melanoma in situ, the lesion is entirely located to the epidermal part of the skin and the basal membrane is intact (2). If the lesion extends into the dermis the melanoma is classified as invasive (2).

Depending on the capacity for expansive growth in the dermis the melanoma can be classified as either tumorigenic or non-tumorigenic (2). The major histological feature that distinguishes tumorigenic melanomas from non-tumorigenic melanoma is the ability of melanoma cells to proliferate in the dermis and created an expansive mass in the dermal part of the skin (2).

Types of melanoma

Melanomas can be differentiated into subtypes according to clinical, histopathological and epidemiological variations (1).

Superficial spreading melanoma is the most common subtype (1) and most often occur in relatively young to middle aged patients (2). In Sweden it represent 81-84% of the melanoma affecting patients under the age of 50 and 60-63% of the melanoma found in patients over 50 years old (1). Superficial spreading melanoma is commonly found in skin that has been intermittent exposed to UV-radiation (1). The melanoma has a superficial spreading, with a radial growth phase, it enables early diagnosis of the tumour (1).

Nodular melanoma often arise *de novo,* without a pre-existing or adjacent in situ component (2). Nodular melanoma are often fast growing (1) and are often at more advanced stage at the time of diagnosis and therefore it has a poorer outcome compared to superficial spreading melanoma (2).

Lentigo maligna melanoma is typically found in elderly patients, on skin that has been chronically exposed to UV-radiation (1). Lentigo maligna melanoma arise from Lentigo maligna, the in situ phase of the tumour (1) and it is a melanoma that typically evolves slowly (2).

Acral lentiginous melanomas are located in palms, feet and soles or under the nails. Acral lentiginous melanoma accounts for 1,5% of all melanomas in Sweden (1).

Amelanotic melanoma are devoid of pigment and tend to be aggressive (2).

Clinical staging of Melanoma

The treatment of and prognosis for melanoma is based on TNM-classification (1). In order to evaluate the primary tumour (T), potential spread to regional lymph nodes (N) and distant metastasis (M) the following variables must be assessed; tumour thickness according to Breslow, occurrence of ulceration and mitosis, Clark level of invasion and Sentinel Node Biopsy (1).

The thickness of the melanoma is measured in Breslow and is the most important factor in predicting survival (2). The depth of the melanoma is measured in millimetres from the top of the granular layer to the deepest extension of the tumour (2). Most melanoma thinner than 0.75 mm is non-tumorigenic and metastasis from tumours less than 0.76 mm is rare (2). Melanoma less than 1.0 mm thick is considered curable with a 95-98% survival rate (1).

Ulceration is classified as the loss of continuity of the epithelium over the surface of the tumour and is used in staging melanoma (2). Regardless of the tumour thickness a presence of ulceration always deteriorate the prognosis (1). The presence of mitoses in the dermis indicates that that melanoma has the propensity to metastasize (2).

Clark levels of invasion are used to classify how deep into the different cutaneous layers the melanoma has penetrated (2). When the tumour is in situ and has not invaded through the basal membrane it is classified as Clark I. In Clark II the tumour is micro-invasive. When a tumour is invasive in the dermis it is classified as either level III or IV depending on depth of invasion. In Clark V the tumour invades the subcutaneous fat (2).

For all invasive melanomas there is a risk of metastatic spread (1). Melanomas can metastasize regionally in the skin or distant via lymphatic or haematogenous routes (2). The sentinel node is the first regional lymph node to which the skin region, that contains the melanoma, is initially drained (1). The risk of metastatic spread directly correlates to the thickness of the melanoma (1). Regional lymph node involvement is rare for melanomas less than 0.76 mm thick (2). If distant metastases occur the prognosis is very poor (2) the 10 year survival rate is 4.1% (1).

Psoriasis

Psoriasis is a common disease, affecting 1.5-2% of the population in Western countries. It is a chronic inflammatory disorder characterized by variable sized lesions in the skin (2). The primary nature of psoriasis is unknown (3) but it is a well-established theory that it is the combination of predisposing genetic factors and environmental components that leads to clinical manifestation of the disease (4).

Histopathology

Though the precise course of action is not fully understood it is known that the alternation in the skin emerge from a T cell response (5). The activated T cell secrete pro-inflammatory cytokines,-including interleukins, interferon γ and TNFα in the dermis and the epidermis (5) which result in four pathological reactions in the skin; inflammation, epidermal hyper-proliferation, abnormal maturation of the keratinocytes and vascular changes (6).

Clinical manifestations

The disease has several clinical variations (4) and varies in severity (5). Psoriasis vulgaris is the most common form, affecting 70-80% of the patients (4). 20 % of the psoriatic patients have guttate psoriasis, an acute variant of psoriasis vulgaris, often affecting young people (2)(4). Generalized erythroderma and generalized pustular psoriasis are more uncommon clinical variations of psoriasis (4). Generalized erythroderma is a severe form of psoriasis vulgaris where the entire skin is affected (5). Localized pustular psoriasis, most commonly called pustulosis palmaris et plantaris (PPP), is a pustular form of the disease where pustules occur on the palms, soles or both (2). Psoriatic arthritis can be considered a clinical variation as well as a comorbidity of psoriasis (4). Psoriasis arthritis varies from a mild joint disease to a severe and erosive form of arthritis (7). In the majority of cases the disease starts in the skin prior to the joints (7).

Psoriasis alters in severity both between different individuals and can alter over time from mild to severe in the same patient. The disease severity is most commonly measured in the Psoriasis Area and Severity Index (PASI) where a higher number indicates a more severe form of the disease (8)

Treatment

There is no cure for psoriasis. The goal is to control the disease and maintain long-term remission (9). As figure 1 illustrates, the first line of treatment is topical therapy with corticoids and vitamin D analogues. The second line of treatment is phototherapy or systemic non-biological therapy. The third line of treatment is systemic biological therapy (10). If not control or long-term remission is achieved with topical treatment the second or third line of treatment is used. Patients with psoriasis vulgaris or guttate pattern psoriasis are offered narrow band UVB treatment. If more than 10% of the body surface is affected, the disease is classified as moderate to severe and if phototherapy is not suitable or has been ineffective the patient is offered systemic therapy (10).

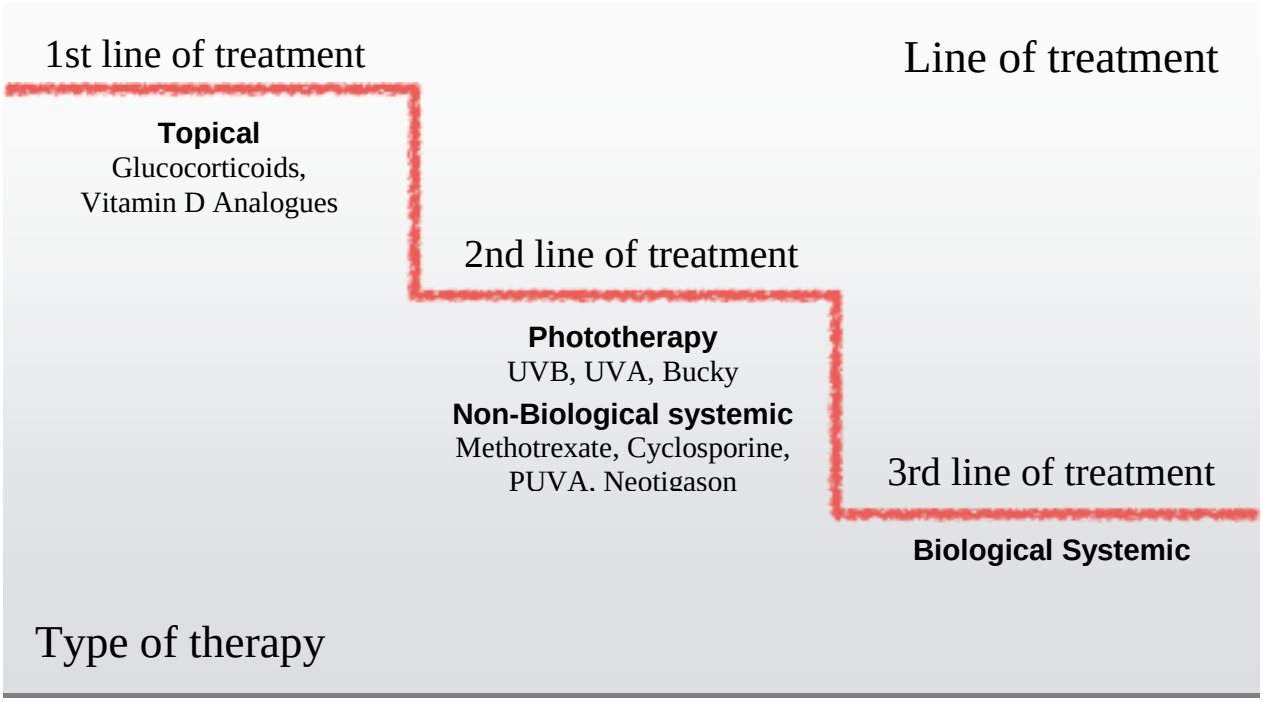

Figure 1. Treatment for psoriasis.

Methotrexate is the most commonly prescribed systemic drug for the treatment of moderate to severe psoriasis (9). Methotrexate is indicated when topical treatment and phototherapy has failed to improve the patients symptoms (11). PUVA, Psoralen + UVA, is a therapy that was once widely used but because of its carcinogenic effects, increasing the risk of skin cancer, it is currently used with restriction (12)(13). Biological drugs are relatively new and expensive drugs that target key-elements of the immune system that generates and maintain the histopathological alterations seen in psoriasis (14). Because Methotrexate is cheap and cost-effective compared to the newer biological drugs it remains the most commonly prescribed drug for psoriasis (9). In 2010 58.8% of the patients that received systemic treatment in Sweden were prescribed Methotrexate and 26% were prescribed biological drugs (15).

Methotrexate

Methotrexate is a folic acid analogue that was first used in the treatment of psoriasis in the 1950s (11)(12). Though used for treating psoriasis for more than 50 years the precise mechanism of action remains unclear (16).

Mechanism of action

Methotrexate is known to have anti-inflammatory, anti-proliferative and immunosuppressive effects (11). Methotrexate interferes with the synthesis of components necessary for DNA synthesis and therefore inhibits cell division in rapidly proliferating cells (16). The drug therefore has an inhibiting effect on the epithelial hyper-proliferation present in psoriasis (11). It also has an anti-inflammatory effect because it inhibits lymphocyte proliferation (16). Recent studies have shown that Methotrexate has a wide range of anti-inflammatory actions including suppression of pro-inflammatory cytokines that promote keratinocyte proliferation and dermal inflammation in psoriasis (9).

Methotrexate used in the treatment of psoriasis

Methotrexate is considered the golden standard for the treatment of moderate to severe psoriasis (9). Methotrexate is indicated when topical treatment and phototherapy has failed to improve the patient's symptoms or when such treatment is contraindicated (11). The drug is also used to treat psoriasis arthritis (11). Methotrexate can be used in combination therapy with phototherapy, PUVA, Cyclosporine and biological drugs (17).

Side effects and toxicity

Methotrexate is a teratogenic drug (11). It is contraindicated for patients with severe liver or kidney disease, severe anaemia and tuberculosis (9). When using Methotrexate there is a risk of myelosupression, hepatotoxicity and pulmonary fibrosis (17). It has been suggested that Methotrexate may increase the risk of malignancy but scientific studies up to this date is inconclusive (9).

Previous research in the area

It is an on-going controversy whether there is a link between psoriasis and an increased risk of malignancies. Excessive tobacco use, alcohol abuse and unhealthy lifestyle are risk factors commonly seen in psoriatic patients and have been proposed as a reason for the elevated risk of cancer (18). Psoriasis has been linked to a higher risk of lymphoma (19). Gelfand et al. has showed that psoriatic patients, over the age of 65 have an increased risk of developing lymphoma compared to the general population (20) and that the relative risk is higher for those patients that have received systemic therapy (19). In a study from 2011 Chen et al. found a higher risk of cancer in young psoriatic patients in Taiwan compared to a control group of the same age. The study showed that young males with psoriasis had an elevated risk in developing certain malignancies, one of them being malignant melanoma (18).

Because of the association between the severity of psoriasis and elevation of cancer risk it has been suggested that the increased incidence of cancer is due to the treatment rather than the disease (18). It should be noted that systemic treatment with PUVA, Methotrexate and Cyclosporine is only given to patients with moderate to severe forms of psoriasis (13). It has been established that high-dose exposure to PUVA, that is more that 250 treatments, is associated with increased risk of developing melanoma and squamous cell carcinoma (6).

Whether Methotrexate gives an increased risk for malignancies is still under debate (9). Research in this field has showed debatable and opposite results. A study from 1975 showed no increased rate of internal malignancies for psoriatic patients with Methotrexate treatment (21). In a study from 1982, Stern found no association between treatment with Methotrexate in psoriasis and the development of non-melanoma skin cancer or non-cutaneous malignancies (22). A study from 1983 of 248 long-termed Methotrexate-treated psoriatic patients reported only 10 malignancies, none of them a malignant melanoma, in a mean follow-up-period of 7 years. This was a smaller number than expected and the study therefore concluded that long-term Methotrexate treatment did not contribute to the development of malignant neoplasms (23).

There are several case reports of patients that have developed lymphoma after been given Methotrexate in treatment for psoriasis (24)(25) or rheumatoid arthritis (26)(27). Up to this date there is only one study that shows an increased risk of malignant melanoma in patients treated with Methotrexate (28). In an Australian cohort study among 459 patients with rheumatoid arthritis exposed to Methotrexate Buchbinder et al. showed a 3-fold increased risk of melanoma relative to the general population. The study also reported a 5-fold increase of Non-Hodgkin lymphoma and almost a 3-fold increase of lung-cancer for patients with rheumatoid arthritis exposed to Methotrexate (28). No comparison to patients with rheumatoid arthritis that had not been exposed to Methotrexate was made. To our knowledge there are no studies up to date that have investigated the

risk of developing melanoma in patients with psoriasis that is treated with Methotrexate compared to psoriatic patients that have not been treated with Methotrexate. Psoriasis is a common disease and Methotrexate continues to be the most commonly prescribed systemic drug for its treatment. It is therefore important to determine if Methotrexate enhances the risk of melanoma.

Aim

The aim of the study was to evaluate if Methotrexate increases the risk of melanoma by investigating if there was a difference in exposure to Methotrexate in psoriatic patients that have had a melanoma compared to psoriatic patients that have not had a melanoma.

Material and Methods

Study design

The study was an explorative case-control study to evaluate the risk of having a history of Methotrexate treatment in patients with psoriasis and melanoma and melanoma in situ. The study was a pilot study which investigated if there is a difference in exposure to Methotrexate in a group of psoriatic patients with melanoma compared to a group of psoriatic patients without melanoma.

Study population

Subjects were enrolled from medical records at the Department of Dermatology at Sahlgrenska University Hospital in Gothenburg, Sweden. All data collection was made between 2015-01-26 and 2015-03-13.

To enroll patients with psoriasis all patients with a psoriasis diagnosis that had a visit to the Department of Dermatology at Sahlgrenska University Hospital between 1997-01-01 and 2006-12-31 with the ICD10 codes L40.0 to L40.9 for psoriasis were sought out. A psoriasis diagnosis was defined as all ICD10 codes starting with"L40". This yielded a total of 7131 unique patients of which 6714 was at least 18 years old at the time of visit.

To enroll patients with melanoma and melanoma in situ all patients that had a medical record with a diagnosis of malignant melanoma from the Department of Dermatology at Sahlgrenska University Hospital between 1997-01-01 and 2014-12-02 were sought out. An intermission between being exposed to Methotrexate and developing a melanoma was estimated, therefore the last date for melanoma was set to 2014-02-02. A melanoma or a melanoma in situ diagnosis was defined as an ICD10 code starting with "C439" for malignant melanoma or "D03" for melanoma in situ or a code that equals "Z089C" for post-treatment examination of melanoma in the skin. This yielded a total of 3560 unique patients of which 3559 was at least 18 years old at the time of visit.

Cases (n=67) were selected by cross-referencing the 3559 patients with malignant melanoma with the 6714 patients with psoriasis. This yielded 67 unique patients with both a malignant melanoma and psoriasis diagnosis. Controls (n= 709) were randomized from the 6714 patients with psoriasis diagnosis. 709 subjects was selected to enter the study because that number represent a value of 10% of the 7131 psoriasis patients that had visit the Department of Dermatology at Sahlgrenska University Hospital between 1997-01-01 and 2006-12-31. The flowchart shown in figure 2 outlines the process of enrolling subjects to the study.

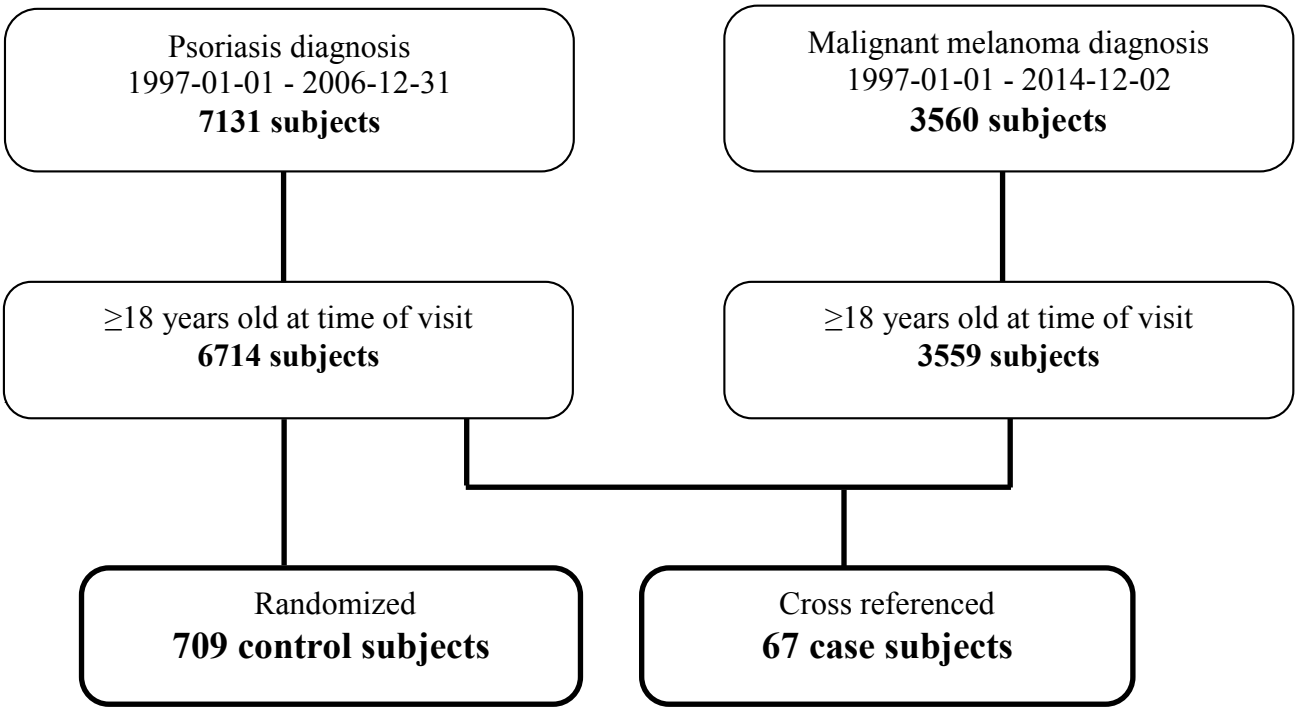

Figure 2. Flowchart of patients enrolled in the study.

Data collection

For all 776 patients, (i.e. 67 cases and 709 controls) the complete medical records at the Department of Dermatology at Sahlgrenska University Hospital were reviewed. If a patient's medical record was not found in the Melior electronic medical record system the data was sought out from archived copies of medical records in the Central Archive at Sahlgrenska University Hospital. If a melanoma was diagnosed at the Department of Dermatology at Sahlgrenska University Hospital data was extracted from an appended histopathological report in the medical record. If a melanoma was

diagnosed at the Department of Plastic Surgery at Sahlgrenska University Hospital the information was sought out in a likewise manner from their medical records. Data were extracted and recorded on a standardized data collection form that was designed for this study. The demographic characteristics of age and sex were recorded for all 776 patients.

The clinical characteristics recorded for psoriasis is presented in table 1. If available, the clinical characteristics for psoriasis were recorded for all the 67 cases and the 709 controls; age of onset, type or types of psoriasis and PASI score. If several PASI scores were mentioned in the medical record the highest was chosen. The following topical treatment was recorded; glucocorticoids and vitamin D analogues. Treatment with salicylic acid, Protopic® and Allphosyl® was recorded as"other topical treatment".

Phototherapy treatment with UVB, PUVA and bath-PUVA were recorded, and if available, number of treatments. For those patients where the exact number of treatments for UVB or PUVA was not noted in the medical records a number was estimated based upon the available information. For patients where the medical record only stated a number of treatment schemes prescribed for UVB or PUVA it was estimated to be 30 treatments each time. For patients that had undergone a number of UVB therapies but where the exact number of treatment was not stated it was estimated to either 10 or 20 sets of 30 treatments each time. Depending largely on what was stated in the medical records the amount of UVB treatments given was estimated to be either 300 or 600 when patients had a history of several years of UVB therapy. For patients where the medical record only stated that the patient had a history of the maximum amount of PUVA therapy it was estimated to be 200 treatments. If a patient had been subscribed Re-PUVA or a portable UVB light unit for home use it was recorded. If a patient had been subscribed"Climate therapy", a subsidized rehabilitation trip to a warmer climate in order to get UV-exposure, it was recorded.

Treatment with Methotrexate was recorded. If treated with Methotrexate the first day of treatment and the last day of treatment were recorded. If a patient had been given several episodes of Methotrexate treatment the first day of the initial/earliest treatment regime and that last day of the latest treatment regime was recorded. If the treatment was ongoing last date of treatment was set to 2014-12-31. Duration of Methotrexate treatment was recorded in months. Methotrexate treatment prescribed for the treatment of psoriasis arthritis from the department of rheumatology was included. Treatment with Neotigason was recorded. If systemic biological treatment was used it was recorded which type of drug and the year it was first given.

Table 1. Clinical characteristics recorded for psoriasis

	Type of Data /Treatment recorded as
Age of onset	
Type of Pso	ICD10 code
PASI- score	Highest documented
Topical treatment	
Glucocorticoids	Yes/No
Vit-D Analogues	Yes/No
Other topical treatment	Yes/No
Phototherapy	
UVB	Yes/No – Number of treatments
PUVA	Yes/No – Number of treatments
Bath-PUVA	Yes/No – Number of treatments
Re-PUVA	Yes/No
Portable UVB light unit for home use	Yes/No
Climate therapy	Yes/No
Systemic therapy	
Neotigason	Yes/No
Methotrexate	Yes/No - Date of treatment period - Duration in months
Biological treatment	Yes/No - Type of drug - Year it was first given

The clinical characteristics recorded for the melanomas are presented in table 2. If available, the clinical characteristics for melanomas were recorded; heredity, date of diagnosis and the histopathological characteristics: type of melanoma, Clark level of invasion, thickness in Breslow, occurrence of mitosis and ulceration. It was recorded if a Sentinel Node biopsy was done and its result. The occurrence of metastasis was recorded.

Table 2. Clinical characteristics measured for melanoma

	Characteristics recorded as
Heredity*	Yes/No
Date of diagnosis	
Histopathological features	
Type of melanoma	-Melanoma in situ -Lentigo maligna -Lentigo maligna melanoma -Superficial spreading melanoma -Nodular melanoma -Acral malignant melanoma -Amelanotic malignant melanoma
Clark level of invasion	I-V
Breslow	In millimetres
Mitosis	Yes/No
Ulceration	Yes/No
Disease severity	
Sentinel Node biopsy	Yes/No - Result
Metastasis	Yes/No

**Heredity; Defined as a family history of malignant melanoma*

Predefined inclusion and exclusion criteria were used. The inclusion and exclusion criteria used for the case-group are presented in table 3. The inclusion and exclusion criteria used for the control-group are presented in table 4. All patients with a psoriasis diagnosis made at the Department of Dermatology at Sahlgrenska University Hospital between 1997-01-01 and 2006-12-31 were included. Patients with no medical record from the Department of Dermatology at Sahlgrenska University Hospital between 1997-01-01 and 2006-12-31 in the Melior electronic medical record system or in the Central Archive of Sahlgrenska University Hospital were excluded. Misclassified patients and patients with no psoriasis diagnosis between 1997-01-01 and 2006-12-31 were excluded. Patients where the psoriasis diagnosis was uncertain or altered to another diagnosis were excluded. Patients with only a medical record of a consulting examination by a physician from the

Department of Dermatology, but no patient visit to the Department of Dermatology, were excluded.

Patients in the case group with an incorrect or no melanoma diagnosis were excluded.

Table 3. Inclusion and exclusion criteria for the case-group

Inclusion
Psoriasis diagnosis at the Department of Dermatology between 1997-01-01 and 2006-12-31
Melanoma or melanoma in situ diagnosis
≥ 18 years old at time of visit
Exclusion
No psoriasis diagnosis between 1997-01-01 and 2006-12-31
Incorrect or no melanoma diagnosis
Psoriasis diagnosis uncertain or altered to another diagnosis
No medical record in Melior or in the Central Archive
Patients with only a medical record of a consulting examination by a physician from the Department of Dermatology, but no patient visit to the Department of Dermatology

Table 4. Inclusion and exclusion criteria for the control-group

Inclusion
Psoriasis diagnosis at the Department of Dermatology between 1997-01-01 and 2006-12-31
≥ 18 years old at time of visit
Exclusion
No psoriasis diagnosis between 1997-01-01 and 2006-12-31
Psoriasis diagnosis uncertain or altered to another diagnosis
No medical record in Melior or in the Central Archive
Patients with only a medical record of a consulting examination by a physician from the Department of Dermatology, but no patient visit to the Department of Dermatology

Statistical methods

The study was a pilot and due to its explorative design no power calculation and no sample size was estimated. Fischer's exact test was used to analyze the difference of proportion in Methotrexate treatment. The statistical analysis was two-sided and a p-value < 0.05 was considered statistically significant. The analysis was performed in the statistical computing program"R" version 3.0.3.

The result from the pilot study was used to calculate the sample size for further studies in the research area. A post-hoc analysis was performed to calculate the number of patients required to get significance by multiplying the number of patients in each group (patients with Methotrexate and melanoma, patients with no Methotrexate and with melanoma, patients with Methotrexate and no melanoma, patients with no Methotrexate and no melanoma) with integers (2,3,4, ...) and testing with Fisher's exact test for significance.

Ethics

Since the study was a student project an approval from the Ethical Review Board was not needed according to the Swedish regulations. The ethical aspect of the study was taken into consideration and was evaluated by the researchers involved in the project in conjunction with the board of the Department of Dermatology at Sahlgrenska University Hospital. Permission to review the subjects' medical records was given by the Head of Department of Dermatology Helena Gustafsson and the Head of Department of Plastic Surgery Anna Elander at Sahlgrenska University Hospital. The study was conducted in agreement with the Declaration of Helsinki as revised in the latest version.

According to the Declaration of Helsinki all research involving human subjects require informed consent. Due to the large number of subjects and the necessity to extract data from old medical records an informed consent was considered unobtainable. According to §32 in the Declaration of Helsinki an informed consent is not needed when it is impossible or impracticable to obtain. Therefore it was assessed that we did not need an individual informed consent from the subjects involved in the study.

The risk of violating the integrity of the individual patient when reviewing medical records was taken into consideration. The potential benefits of the study and the necessity of evaluating the risk of developing melanoma when treated with Methotrexate was considered to outweigh the risk of violating the integrity of the subjects.

Results

Of the 67 case-subjects enrolled in the study 52 subjects were included and 16 subjects were excluded. Of the 709 control-subjects 503 subjects were included and 205 subjects were excluded. 6 subjects were excluded from the case-group because they did not have a melanoma diagnosis. 10 case-subjects and 205 control-subjects were excluded because they did not have a psoriasis diagnosis at the Department of Dermatology at Sahlgrenska between 1997-01-01 and 2006-12-31 or because no medical record was found in the Melior electronic medical record system or in the Central Archive at Sahlgrenska University Hospital. 1 subject from the control group (n=709) had a melanoma and was therefore included in the case group. The flowchart shown in figure 3 outlines the process of enrolling subjects to the study and the number of subjects that were included and excluded.

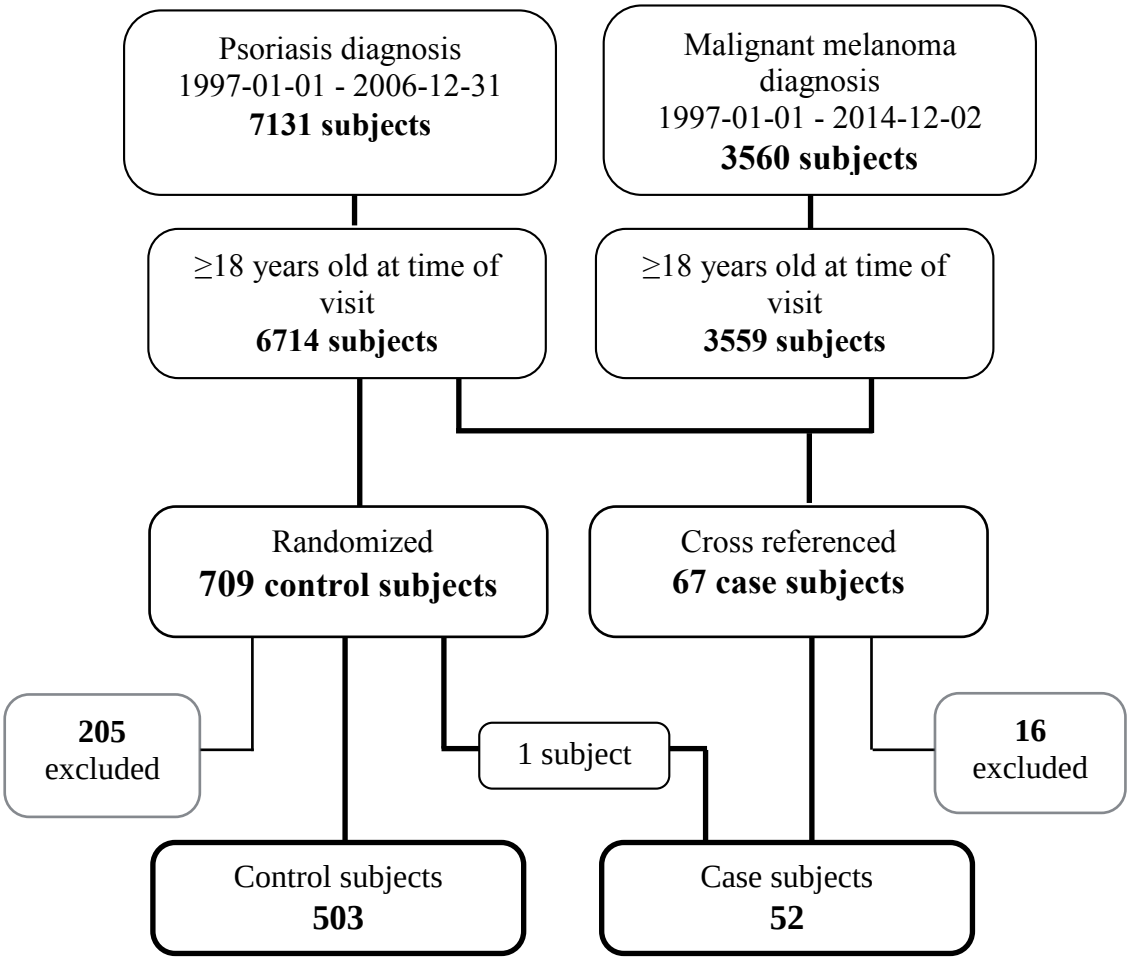

Figure 3. Flowchart of patients in the study.

Demographic result

The case-group (n=52) had a majority of male subjects, consisting of 69.3% (n=36) men and 30.7% (n=16) women. The control-group (n=503) had a more equal distribution with 48.3% (n=243) men and 51.7% (n=260) women. The mean age was higher for the case-subjects. The mean age of the study subject in 2015 was 73 (±16.1) years in the case-group and 63 (± 6.5) years in the control-group, as showed in table 5.

Table 5. Demographic characteristics of the 52 case-subjects and the 503 control-subjects

		Case-subjects n=52 N(%) or Mean ± SD	Control-subjects n= 503 N(%) or Mean ± SD
Sex			
	Female	16 (30.7%)	260 (51.7%)
	Male	36 (69.3%)	243 (48.3%)
Age (years)			
	*Mean**	73 ±16.1	63 ±16.5
	Range	36-98	29-106
	Mean year of birth	1941	1951

** The estimated age of the subjects in 2015*

Descriptive result

The ICD-10 code for"Psoriasis unspecified", L40.9, was the most common psoriasis diagnosis in both groups. 53.8% (n=28) of the case-subjects and 58.2% (n=293) of the control-subjects had one unique L40.9 diagnosis. The second most common ICD-10 code was L40.0 for"Psoriasis vulgaris". 13.4% (n=7) of the case-group and 10.5% (n=53) of the control-group had more than one unique L40 code, i.e. more than one psoriasis diagnosis. The table that shows the complete distribution of ICD-10 codes is presented in the appendix.

As table 6 shows there was a PASI scored noted in as few as 7 subjects (13.4%) in the case-group and in 63 subjects (12.5%) in the control-group.

The number of subjects that had been treated with topical therapy, phototherapy and systemic therapy are presented in table 6. The exposure to topical therapy was similar in the case-group and in the control-group. Almost all subjects in the study had been exposed to glucocorticoids, i.e. 94.2% (n=49) of the cases and 93.4% (n=470) of the controls.

The number of subjects treated with UVB was similar in both groups. 51.9% (n=27) of the cases and 47.9% (n=241) of the controls had been treated with UVB. The mean numbers of UVB treatments was significantly higher in the case-group, 396 ± 347 treatments, compared to the control-group, 125 ± 190 treatments. Exposure to PUVA was similar in both groups. None of the cases-subjects had been exposed to more than 200 PUVA-treatments.

The numbers treated with Methotrexate was 23% (n=12) in the case-group and 17.6% (n=89) in the control-group. The mean treatment of Methotrexate, measured in months, was higher in the control-group. The control-group had a mean exposure of 60 ± 54 months of Methotrexate treatment compared to the case-group that had a mean exposure of 28 ± 40 months of Methotrexate treatment.

Table 6. Clinical characteristics for psoriasis of the 52 case-subjects and the 503 control-subjects

	Case-subjects n=52 (*n1*)* N(%) or Mean ± SD (Range)	Control-subjects n= 503 (*n2*)* N(%) or Mean ± SD (Range)
*PASI (n1=7 / n2=63)**	11.2 ±5.3 (5-18.3)	10.5 ±6.9 (1.4-32.7)
Topical therapy		
Glucocorticoids	49 (94.2%)	470 (93.4%)
Vit-D analogues	34 (65.3%)	325 (64.8%)
Other topical treatment	9 (17.3%)	153 (30.4%)
Phototherapy		
UVB	27 (51.9%)	241 (47.9%)
*Numbers of UVB treatments (n1=18 / n2=193)**	396 ± 347 (10-1495)	125 ± 190 (2-1427)
> 300 UVB treatments	11 (20.7%)	22 (4.3%)
PUVA	8 (15,3%)	46 (9.1%)
*Numbers of PUVA treatments (n1=6 / n2=30)**	102 ± 51.5 (46-200)	105 ± 124.9 (4-491)
> 200 PUVA treatments	0	4 (0.7%)
Bath- PUVA	4 (7.6%)	30 (5.9%)
*Numbers of Bath-PUVA treatments (n1=3 / n2=21)**	42 ± 23.7 (28-69)	75.3 ± 141.4 (4-641)
Re- PUVA	1 (1.9%)	7 (1.4%)
Portable UVB for home use	4 (7.6%)	25 (4.9%)
Climate therapy	1 (1.9%)	22 (4.5%)
Systemic therapy		
Neotigason	5 (9.6%)	43 (8.5%)
Methotrexate	12 (23.0%)	89 (17.6%)
*Methotrexate treatment in months (n1=11 / n2=82)**	28 ± 40.1 (1-132)	60 ± 54 (0.5-218)
Biological treatment	3 (5.7%)	30 (5.9%)

** Subjects it was noted for in the case-group (n1) and in the control-group (n2)*

The clinical characteristic of the melanomas in the case-group (n=52) is presented in table 7. The melanomas in subjects exposed to Methotrexate (n=12) were in most aspects similar to the subjects not been exposed to Methotrexate (n=40). The majority of melanomas in the study-population (71.1%) were non-invasive. There were 6 different types of Melanoma in the group exposed to Methotrexate (n=12) but only 4 different types of melanoma in the group not exposed to Methotrexate (n=40). There was a higher incidence of ulceration and mitosis in the group exposed to Methotrexate. Metastasis occurred in 25% (n=3) of the subjects exposed to Methotrexate. There were no metastases among the 40 subjects that had not been exposed to Methotrexate.

Table 7. Clinical characteristics of the melanoma in the 52 case-subjects. Categorized as subjects exposed to Methotrexate (n= 12) and subjects not exposed to Methotrexate (n=40)

	Case-subjects exposed to Methotrexate n=12 (*n1*)* N(%) or Mean ± SD (Range)	Case-subjects not exposed to Methotrexate n= 40 (*n2*)* N(%) or Mean ± SD (Range)
*Heredity***	0	1(2.5%)
Type of Melanoma		
Melanoma in situ	2 (16.6%)	5 (12.5%)
Lentigo Maligna	2 (16.6%)	12 (30%)
Lentigo Maligna Melanoma	0	0
Superficial spreading melanoma	2 (16.6%)	16 (40%)
Nodular Melanoma	3 (25%)	4 (10%)
Acral malignant melanoma	1 (8.3%)	0
Amelanotic malignant melanoma	1 (8.3%)	0
Type of Melanoma not specified	1 (8.3%)	3 (7.5%)
*Breslow in mm (n1=8/ n2=23)**	2.07 ± 1.5 (0.55-4.7)	1.4 ± 2.1 (0.21-10.3)
*Clark level (n1=8/ n2=23)**		
Level II	1 (8.3%)	7 (17.5%)
Level III	3 (25%)	13 (32.5%)
Level IV	2 (16.6%)	3 (7.5%)
Level V	2 (16.6%)	0
Ulceration	2 (16.6%)	2 (5%)
Mitosis	3 (25%)	4 (10%)
Sentinel Node Biopsi	1 (8.3%)	5 (12.5%)
Metastasis	3 (25%)	0

** Subjects it was noted for in the case-group (n1) and in the control-group (n2)*
*** Heredity; Defined as a family history of malignant melanoma*

Analytic result

Fischer's exact test showed higher tendency of Methotrexate exposure in the case-group, OR=1.39. The difference between the groups was not statistically significant (p =0.35, 95% CI 0.64-2.85). Figure 4 presents the number and the percentage of subject in the case-group and the control-group with and without Methotrexate treatment.

	Methotrexate	
	Yes	**No**
Case-group n=52	12	40
Control-group n=503	89	414

	Methotrexate		
	Yes	**No**	**OR= 1.39**
Case-group n=52	23.1 %	76.9 %	**P= 0.35**
Control-group n=503	17.7%	82.3%	**95% Confidence interval 0.64-2.85**

Figure 4. The analytic result of the study.

A post-hoc analysis was performed to calculate the number of subjects required in future studies to get a statistically significant result. It showed that a study including 3366 subjects is needed to get a p-value = 0.032. All 3366 subjects would have a psoriasis diagnosis. A study of 3366 subjects would have to include 312 case-subjects with melanoma and 3056 control-subjects without melanoma.

Discussion

The analytic result in the study indicates that there was a higher risk of being exposed to Methotrexate for the case-subjects compared to the control-subjects. The result was not statistically significant and it is therefore not possible to conclude whether psoriatic patients with melanoma have a higher risk of being exposed to Methotrexate. The study did not take into consideration whether the patient had been exposed to Methotrexate before or after the melanoma was diagnosed. This is important to consider when evaluating the result.

In a cohort-study from 2008 Buchbinder et al. showed a 3-fold increased risk of melanoma in patients with rheumatoid arthritis that had been exposed to Methotrexate relative to the general population. No comparison was made to patients with rheumatoid arthritis that had not been exposed to Methotrexate. It is therefore not possible to determine how much of the observed risk of melanoma was due to the exposure to Methotrexate (28).

The main focus of this case-control-study was to evaluate whether there is a higher risk of having been exposed to Methotrexate in psoriatic patients with melanoma compared to psoriatic patients without melanoma. The study was designed in this way trying to avoid the difficulties in not being able to conclude whether the elevated risk of developing melanoma was caused by Methotrexate or due to other aspects of the disease or treatments. Previous research in the area concludes that there is an elevated risk of developing melanoma when exposed to a larger amount of PUVA (29). Doing research on relations between melanoma in psoriatic patients and the use of Methotrexate it would be preferable to be able to determine if a history of PUVA treatment has an impact on the study's results. The obtained data of the study-subjects exposure of PUVA was in many aspects uncertain. It is therefore hard to estimate the effect it may have had on the study-subjects risk of developing melanoma.

Prior studies have shown an association between disease severity and elevated risk of cancer in psoriasis (30) but it has not been established whether this is due to the disease or the treatment (18). The majority of the patients in our study had an unspecified diagnosis for psoriasis (L40.9) and as few as 12.6% (n=70) subjects had a noted PASI score. It is therefore difficult to draw any conclusion whether disease severity may influence the outcome of the study.

The majority of the subjects, 69.3%, in the case-group (n=52) were male. Our data are in line with the study from 2011 by Chen et al. that showed an increased risk of developing melanoma in young males with psoriasis (18). Chen et al. proposed that this elevated risk among male psoriasis patients could be explained by a more frequent exposure to common risk factors for malignancies, i.e. excessive tobacco intake, alcohol abuse and an unhealthy lifestyle (18). Our study does not include data regarding exposure to risk factors such as tobacco, alcohol or unhealthy lifestyle choices. Therefore it is not possible to determine whether this have had an influence on the uneven distribution of male subject in the case-group.

Further research is needed to evaluate whether Methotrexate has in impact on developing melanoma in psoriatic patients. In order to do so properly the study must be modified. A larger sample size is needed to get statistically significant results. Future studies should modify how patients are sought out to reduce the number of subjects being excluded. The data for melanomas should be sought from the cancer register to identify melanomas that has been diagnosed and treated by a general physician or at another hospital. The study can be improved by enrolling more accurate data concerning the subjects age at the time of visit and register the time of death for those subjects that has deceased. The study would be improved by more extensive and detailed data concerning the subjects' type of psoriasis and the PASI score. Another improvement would be to have more precise data of the exposure to phototherapy. Future studies would be improved by recording the dose of Methotrexate that was prescribed. If the mean dose and cumulative dose of Methotrexate

can be estimated future studies could evaluate whether it is the duration of treatment or mean dose of exposure that has the most impact on risk of melanoma, if an increased risk of melanoma is identified for Methotrexate exposed patients.

To further investigate the relation between psoriasis, melanoma and Methotrexate it would be interesting to design a study to examine if there is a difference in risk of developing melanoma in psoriatic patients compared to patients that are prescribed Methotrexate for other diseases. Such a study could reveal if the risk of developing melanoma in psoriatic patients is different compared to rheumatic patients that have been exposed to Methotrexate.

Based on the result from the study it is not possible to conclude whether psoriatic patients with melanoma have been exposed to Methotrexate to a greater extent than psoriatic patients with no melanoma. The question remains - does Methotrexate treatment increase the risk of melanoma? Another question that remains unsolved is to what extent disease severity affects the risk of malignancies in psoriasis. It is noteworthy that metastasis occurred in 25% (n=3) of the subjects exposed to Methotrexate and in none of the subjects not exposed to Methotrexate in our study. Therefore a new question arises from the research - could Methotrexate have an impact on melanomas ability to metastasize?

Methodological considerations

The generalizability of the results is limited by the relatively small sample size of our study. The study was retrospective and in many aspects based on anamnestic information available in medical records which makes the data uncertain.

The study has several limitations that have a potential for selection bias. It only includes patients treated at the Department of Dermatology and is therefore favoring patients with higher disease

activity and more severe forms of psoriasis. With a higher frequency of severe forms of psoriasis one could presume that second and third line of therapy is more frequently used in our study population than in psoriatic patients in general.

Almost a third (28.4%, n=221) of the 776 subjects enrolled in the study were excluded, a part of them due to the fact that no medical record was found in the Melior electronic medical record system or in the Central Archive at Sahlgrenska University Hospital. A possible reason that no medical record could be found is that the patients were treated at other dermatology clinics, previously part of the Department of Dermatology at Sahlgrenska University Hospital. The medical records from these clinics are kept in the Regional Archive of Västra Götaland located in Värnersborg. This results in a selection bias where patients that were treated at other dermatology clinics of Sahlgrenska University Hospital are excluded from the study.

Another limitation that has a potential for selection bias is that the study only includes melanoma that has been diagnosed and treated at the Department of Dermatology and the Department of Plastic Surgery at Sahlgrenska University Hospital. It does not include melanoma that has been diagnosed and treated by a general physician or at another hospital. A melanoma is in the majority of the cases thinner if it is detected by a physician rather than the patient (1). Assuming that psoriatic patients treated at the Department of Dermatology gets full body exam by a physician more frequently than patients with milder forms of psoriasis it is possible that their melanoma is found and removed in an earlier stage.

A limitation of the study is how the mean age of the study population was estimated. To determine the age of the subjects we used data of their time of birth and calculated their age in 2015. Doing so we assumed that all subjects were alive in 2015 which is very unlike when some of the subjects

were born before 1920. Further we do not know if subjects have deceased or their time of death which means that the mean age of the study population is most likely inaccurate.

There are limitations in the data concerning the study-subjects exposure to phototherapy. In the majority of the cases the number of treatments was estimated. It is therefore hard to draw any conclusions concerning the patients' exposure to phototherapy. Moreover, the data of the study-subjects exposure to Methotrexate has limitations. No estimation of mean dose or cumulative dose of Methotrexate can be calculated because we did not record the dose of the drug that was prescribed.

We did not include data on risk factors for developing malignancies such as alcohol consumption, tobacco use, unhealthy lifestyle choices, skin type and exposure to UV-radiation. In retrospective studies this type of data are uncertain and difficult to obtain. This is an expected bias in the study.

Conclusion

It is a controversy whether Methotrexate increases the risk of malignancies. A previous cohort-study has show an increased risk of malignant melanoma in rheumatic patients treated with Methotrexate. The analytic result in this case-control-study indicated that there was a higher risk of being exposed to Methotrexate for the case-subjects compared to the control-subjects but the result was not statistically significant. It is therefore not possible to conclude if there is a significant association between Methotrexate treatment and melanoma in psoriatic patients based on the results from the study. Further research in the area is needed. The result from the study and the methodological considerations can be used to improve the study-design, materials and methods in future studies. It would be meaningful for both psoriatic patients as well as other patients treated with Methotrexate to determine whether the drug gives an increased risk of melanoma or not. If there is an elevated risk there are other drugs or treatments available. If there is no elevated risk there is no need to alter the treatment for the patients that respond well to Methotrexate therapy.

Populärvetenskaplig sammanfattning

Psoriasis är en hudsjukdom som drabbar 3 % av befolkningen i Sverige. Sjukdomen kan variera i svårighetsgrad från lätta besvär som kan behandlas med salvor utskriva av en läkare på vårdcentralen till svåra besvär som behöver behandlas av en hudläkare. Det läkemedlet som oftast används i behandling för medelsvår till svår psoriasis är Metotrexat. Trots att Metotrexat har använts i mer än 50 år för att behandla psoriasis är det ännu inte helt klarlagt hur läkemedlet verkar. Medicinska forskare har länge diskuterat om det finns en ökad risk för att utveckla cancer när man behandlas med Metotrexat. Trots att många olika studier gjorts kring ämnet har ingen hittills kunnat avgöra om så är fallet. Under senare år har forskningen delvis inriktat sig på huruvida behandling med Metotrexat ger ökad risk för maligna melanom.

Malignt melanom är en cancer som utgår ifrån de bruna, pigmenterade cellerna i huden. Det är en cancer som blir allt vanligare i Sverige och under de senaste åren har både antalet som drabbas av sjukdomen och antalet som dör av den ökat. Risken att drabbas av malignt melanom ökar om man utsatts för stora mängder UV-strålning från solen men också om man har en ljus hudtyp som lätt bränns. Avgörande för behandling av maligna melanom är att cancern hittas och opereras bort i ett tidigt stadium när sjukdomen bara finns i huden. Om det maligna melanomet tas bort i tid så kan man bli helt botad från sin cancer. Ett malignt melanom som fått växa kan sprida sig från huden till resten av kroppen. Patienten har då en spridd cancersjukdom där dödligheten är mycket hög.

I vår studie ville vi undersöka sambandet mellan malignt melanom och Metotrexat-behandling hos personer med psoriasis. Vi har gjort en studie där vi undersöker om det finns en skillnad i Metotrexat-behandling hos de psoriatriker som haft malignt melanom jämfört med de psoriatriker som inte haft malignt melanom. Genom att jämföra dessa två grupper med varandra ville vi se om vi kunde hitta ett samband mellan att ha blivit behandlad med Metotrexat och utveckla ett malignt melanom. I vår studie kunde vi inte visa att det finns ett statistisk signifikant samband mellan

Metotrexat-behandling och malignt melanom hos psoriatriker. Vår analys visade att de psoriatriker som haft ett melanom var behandlade med Metotrexat i större utsträckning än psoriatriker som inte haft melanom. Resultatet i vår studie var dock inte statistiskt signifikant och därför kan man inte dra några slutsatser utifrån det. Fler studier behöver göras för att klargöra om det finns ett samband mellan Metotrexat-behandling och maligna melanom hos psoriatriker.

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Appendix

Distribution of ICD-10 codes for Psoriasis in the case-group (n=52) and -control-group (n=503)

	Case n=52	**Control n=503**
	N (%)	**N (%)**
L40.0	15 (28.8%)	67 (13.3%)
+L40.3		4
+L40.4	1	1
+L40.8		3
+L40.9		1
+L40.5 L40.8		1
Total	**16**	**77**
L40.1		**1**
L40.3	1	58 (11.5%)
+L40.9	1	9
Total	**2**	**67**
L40.4		19
+L40.9		2
Total		**21**
L40.5	1	6
+L40.0	2	6
+ L40.3		2
+40.9	3	21
Total	**6** (11.5%)	**35** (6.9%)
L40.8		5
+L40.9		3
Total		**8**
L40.9	**28** (53.8%)	**293** (58.2%)
NA		1