CLINICAL REPORT

Risk of Non-melanoma Skin Cancer in Patients with Atopic Dermatitis Treated with Oral Immunosuppressive Drugs

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There is uncertainty about the risk of developing non-melanoma skin cancer (NMSC), including basal cell carcinoma and squamous cell carcinoma (SCC), in patients with atopic dermatitis (AD) treated with oral immunosuppressive drugs. A total of 557 patients with AD treated with these drugs in the University Medical Center Utrecht and Groningen, the Netherlands, were analysed. NMSC after oral immunosuppressive treatment was reported in 18 patients (3.2%). The standardized incidence ratio for developing SCC was 13.1 (95% confidence interval (CI) 6.5–19.7). Patients developing NMSC were older at the start of therapy ($p < 0.001$) and data lock ($p < 0.001$) compared with patients without NMSC. No significant differences were found in sex, cumulative days of oral immunosuppressive drugs and follow-up between these groups ($p = 0.42$, $p = 0.88$, and $p = 0.34$, respectively). In interpreting these results it is important to include other factors, such as lack of association between treatment duration and tumour development and the long interval between treatment discontinuation and tumour development in some patients.

Key words: atopic dermatitis; oral immunosuppressive drugs; non-melanoma skin cancer.

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Atopic dermatitis (AD) is a chronic inflammatory skin disease with a prevalence of 1–3% in adults (1). Although AD can be controlled adequately with topical treatment and/or ultraviolet (UV) light therapy in the majority of patients, a subgroup of severe and difficult-to-treat patients remains. Furthermore, in some patients it is impossible to taper topical corticosteroid treatment to a safe maintenance scheme. Oral immunosuppressive drugs are indicated in all of these patients.

Oral immunosuppressive drugs that are regularly used in the management of AD are cyclosporin A (CsA), azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF), enteric-coated mycophenolate sodium (EC-MPS), (extended-release) tacrolimus and systemic glucocorticosteroids.

Clinical efficacy and safety have been proven in clinical trials for most of these drugs (2–5). However, treatment duration in clinical trials is limited. Due to the chronic nature of AD, long-term treatment with oral immunosuppressive drugs is often necessary to maintain adequate disease control. Recent drug survival studies demonstrate that oral immunosuppressive drugs are regularly used for many years in daily practice (6–8).

An important barrier to long-term use of oral immunosuppressive drugs in patients with AD is the possible increased risk of development of malignancies, especially non-melanoma skin cancer (NMSC), including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).

Most data on the risk of developing malignancies in patients treated with oral immunosuppressive drugs are derived from transplant patients (9, 10). Immunosuppressive agents may increase the risk of cancer development by causing DNA damage and diminishing DNA repair mechanisms. Tumour angiogenesis may be promoted and the susceptibility to viral infections may be increased. Finally, immune surveillance, which normally prevents the growth and development of malignancies, may be inhibited by immunosuppressive drugs (9, 11, 12). Recent studies also report an increased risk of NMSC and lymphoma in patients using AZA for autoimmune diseases, such as inflammatory bowel disease (IBD) and other non-rheumatic autoimmune diseases (13–15).

To date, there has been a lack of data regarding the risk of NMSC in patients with AD using oral immunosuppressive drugs.

The aim of this study was to estimate the incidence of NMSC in a large cohort of patients with AD treated with oral immunosuppressive drugs in the Netherlands and to compare these findings with those for the Dutch general population.

MATERIALS AND METHODS

Design

This retrospective cohort study was approved by the Medical Ethics Committee of the University Medical Center Utrecht, The Netherlands. Data were collected from the Departments of Dermatology of the University Medical Center Utrecht and the University Medical Center Groningen, The Netherlands, in the period from 1989 to 1 January 2014.

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Study population

All adult patients with AD receiving oral immunosuppressive drugs (CsA, AZA, MTX, MMF, EC-MPS and (extended-release) tacrolimus) for more than 2 months were included.

For all patients, the follow-up period ended on 1 January 2014, independent of whether the treatment had already discontinued. AD should have been the primary indication for the treatment with oral immunosuppressive drugs. Patients aged <18 years at the start of the treatment were excluded.

Medical records were screened for the following patient and treatment characteristics: sex, age at start of use of oral immunosuppressive drug treatment, age at data lock, duration of follow-up calculated from the first starting date of oral immunosuppressive treatment until data lock, type of medication and cumulative days of oral immunosuppressive drug use.

Outcome

All patient files in the histopathology register (Pathologisch Anatomisch Landelijk Geautomatiseerd Archiefsysteem; PALGA), a nationwide database for pathology reports in the Netherlands with national coverage, were screened for NMSC until 16 May 2014 (16). Tumours that developed within 6 months after the start of the treatment were considered as not related to drug treatment and were excluded from analysis.

In patients with a diagnosis of NMSC, the following additional information was collected: type of malignancy, age at time of NMSC diagnosis, cumulative days of oral immunosuppressive drug use until diagnosis, time between start of oral immunosuppressive drug use and diagnosis, time between cessation of oral immunosuppressive drug use and diagnosis, history of UV light therapy and history of malignancies before treatment with oral immunosuppressive drugs.

Statistical analysis

All statistical analyses were performed using SPSS statistics 21. Subgroup analyses for patients with and without NMSC were performed. The Mann–Whitney U test and the χ^2 test were used to calculate whether there was a statistically significant difference between the subgroups in terms of sex, age at data lock, age at start of treatment, the total duration of treatment and the duration of follow-up. The incidence of NMSC (including both BCC and SCC) was compared between patients treated for ≤2 years and >2 years and patients treated ≤5 years and >5 years. Separated analyzes for the incidence of only SCC were performed as well. Dependent on the number of patients treated with monotherapy with a specific oral immunosuppressive drug (without a history of other oral immunosuppressive drugs), subgroup analyses of the individual treatment groups were carried out.

The standardized incidence ratio (SIR) of SCC in our cohort was calculated by dividing the number of observed cases (number of newly diagnosed malignancies) by the number of expected cases in the general Dutch population in the same period, corrected for age (17). The 95% confidence interval (CI) of the SIR was calculated using the indirect method (18). This method was described previously by van den Reek et al. (13). Due to the fact that BCCs are not systematically registered in the Netherlands, no SIR could be determined for BCCs.

RESULTS

Characteristics of the total group

A total of 557 patients with AD (299 male patients, 53.7%) with one or more treatment episodes with oral immunosuppressive drugs from 1 January 1989 until 1 January 2014 were included in this study (**Table I**).

CsA was prescribed most frequently (770 episodes), followed by EC-MPS (157 episodes), AZA (139 episodes), MTX (69 episodes), MMF (15 episodes), tacrolimus (24 episodes) and extended-release tacrolimus (13 episodes). There was a wide variation in treatment duration (**Fig. 1**).

Results from the histopathology database (PALGA)

NMSC during or after oral immunosuppressive treatments was reported in 18 patients (3.2%) **(Fig. 2)**. The individual results are shown in **Table II**.

SCCs after oral immunosuppressive treatment were found in 10 patients (1.8%). Two of these patients had more than 1 SCC and 3 of these patients were already diagnosed with an SCC before the start of oral immunosuppressive treatment. One of the 10 patients also developed a BCC.

BCCs after oral immunosuppressive treatment were found in 9 patients (1.6%). One of these patients also developed an SCC. One of these 9 patients developed 3 BCCs and 2 patients were already diagnosed with a BCC before the start of oral immunosuppressive treatment.

Patients with a malignancy vs. patients without a malignancy

Patients who developed NMSC were significantly older compared with patients without a malignancy at the start of therapy ($p<0.001$) and at data lock ($p<0.001$) (**Table III**).

Sex, cumulative days of oral immunosuppressive drugs use until data lock and duration of follow-up were not statistically significantly different between the groups ($p=0.42$, $p=0.88$, and $p=0.34$, respectively). There was no significant difference in the incidence of NMSC be-

Table I. Patient characteristics

	All patients ($n=557$)
Patient characteristics	
Male, *n* (%)	299 (53.7)
Age at data lock, median [IQR]	44.7 [33.4–55.2]
Age at inclusion[a], median [IQR]	37.1 [25.5–48.7]
Duration of follow-up in year[b], median [IQR]	6.0 [3.0–10.2]
Total patients years of follow-up	3,855.5
Treatment characteristics	
Cyclosporine A only, *n* (%)	281 (50.4)
Azathioprine only, *n* (%)	13 (2.3)
Enteric-coated mycophenolate sodium only, *n* (%)	8 (1.4)
Methotrexate only, *n* (%)	15 (2.7)
>1 oral immunosuppressive drug, *n* (%)	240 (43.1)
2 different drugs, *n* (%)	164 (29.4)
3 different drugs, *n* (%)	55 (9.9)
4 different drugs, *n* (%)	20 (3.6)
5 different drugs, *n* (%)	1 (0.2)

[a]Age at start of treatment with oral immunosuppressive drugs. [b]From start of oral immunosuppressive drugs until data lock.
IQR: interquartile range.

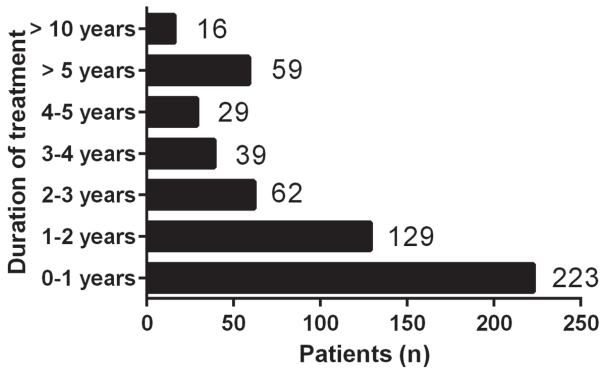

Fig. 1. Duration of treatment with oral immunosuppressive drugs ($n = 557$).

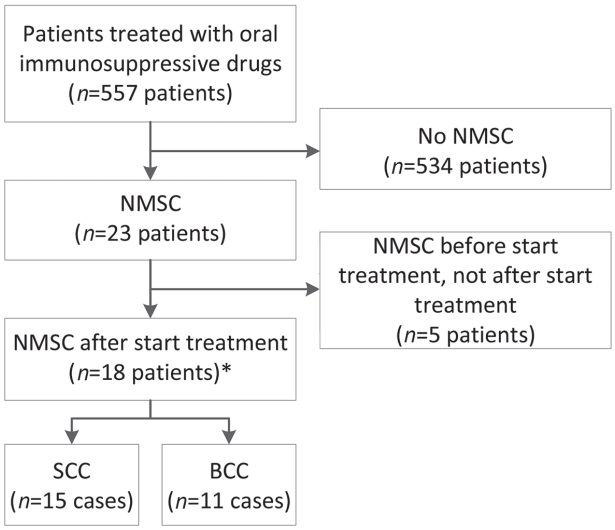

Fig. 2. Study flow-chart. BCC: basal cell carcinoma; NMSC: non-melanoma skin cancer; SCC: squamous cell carcinoma. *Some patients had more than one malignancy.

Table II. Characteristics of patients with non-melanoma skin cancer

Pat. No.	Sex	Tumour	Treatment	Age at diagnosis, years	Cumulative days of oral immunosuppressive drug use from start until diagnosis	Time between start of oral immuno-suppressive drug use and diagnosis (days)	Time between stop of oral immuno-suppressive drug use and diagnosis (days)	History of UV light therapy	History of malignancy
1	F	SCC	CsA	51	554	3,961	<3,407[a]	Unknown	No
2	F	SCC	CsA	55	227	3,278	3,051	No	No
3	F	SCC	CsA	56	489	808	319	Unknown	No
4	M	SCC	AZA	40	185	185	Still on treatment at diagnosis	No	SCC, dysplastic papilloma frenulum, non-Hodgkin's lymphoma
5	F	SCC (5×)	CsA	68 (SCC 1) 69 (SCC 2 and 3) 70 (SCC 4 and 5)	344 (SCC 1) 370 (SCC 2) 441 (SCC 3,4 and 5)	3,380 (SCC 1) 3,644 (SCC 2) 3,715 (SCC 3) 4,038 (SCC 4) 4,101 (SCC 5)	Still on treatment at diagnosis (SCC 1 and 2) 62 (SCC 3) 385 (SCC 4) 448 (SCC 5)	Unknown	No
6	M	SCC	EC-MPS, CsA	68	2,705	4,855	1331	UVB	SCC
7	M	SCC	CsA	48	2,166	6,286	4,120	UVB and PUVA	No
8	M	SCC (2×)	CsA	64 (SCC 1 and 2)	632 (SCC 1 and 2)	2,792 (SCC 1) 2,957 (SCC 2)	1,267 (SCC 1) 1,432 (SCC 2)	UVB	No
9	F	SCC	MTX, CsA	59	385	406	Still on treatment at diagnosis	UVB	No
10	F	SCC and BCC	MTX, CsA	70 (SCC and BCC)	249 (SCC) 452 (BCC)	328 (SCC) 528 (BCC)	Still on treatment at diagnosis (SCC and BCC)	No	SCC, breast cancer
11	M	BCC	CsA	44	210	1,460	<1,250[a]	PUVA	No
12	M	BCC	CsA	59	281	3,094	2,813	No	No
13	F	BCC	CsA, EC-MPS	31	243	1,574	1,331	UVB	No
14	F	BCC	CsA, MMF, EC-MPS, Advagraf (tacrolimus)	65	437	611	Still on treatment at diagnosis	UVB	No
15	M	BCC	CsA	66	280	280	Still on treatment at diagnosis	No	BCC
16	F	BCC	CsA	41	259	350	61	UVB	No
17	F	BCC (3×)	AZA, CsA, MTX	72 (BCC 1, 2 and 3)	462 (BCC 1) 560 (BCC 2 and 3)	462 (BCC 1) 560 (BCC 2 and 3)	Still on treatment at diagnosis	UVB	No
18	M	BCC	CsA	74	218	1,128	910	UVB and PUVA	8× BCC, SCC, adenocarcinoma oesophagus

[a]Loss to follow-up.
AZA: azathioprine; BCC: basal cell carcinoma; CsA: cyclosporin A; EC-MPS: enteric-coated mycophenolate sodium; MMF: mycophenolate mofetil; NMSC: non-melanoma skin cancer; PUVA: psoralen and ultraviolet A; SCC: squamous cell carcinoma; UVA: ultraviolet A; UVB: ultraviolet B; UV: ultraviolet.

Table III. Patient characteristics of the total group ($n=557$). Non melanoma skin cancer (NMSC) and specified for squamous cell carcinoma (SCC)

	NMSC during or after treatment ($n=18$)	No NMSC during or after treatment ($n=539$)	p-value differences	SCC during or after treatment ($n=10$)	No SCC during or after treatment ($n=547$)	p-value differences
Male, *n* (%)	8 (44.4%)	291 (54.0%)	0.424	4 (40.0)	295 (53.9)	0.381
Age at data lock, years, median [IQR]	61.8 [51.7–70.5]	44.1 [32.7–53.8]	<0.001	61.2 [52.2–70.5]	44.3 [33.0–54.7]	0.001
Age at start, years, median [IQR][a]	54.7 [40.4–64.2]	36.4 [25.0–48.1]	<0.001	54.7 [40.5–58.3]	36.9 [25.1–48.3]	0.004
Cumulative days of oral immunosuppressive drug use until last day of follow-up, median [IQR]	499.0 [255.0–1,087.0]	505.0 [252.0–1,123.0]	0.879	531.5 [438.3–1,663.5]	498.0 [252.0–1,117.0]	0.351
Durations of follow-up, years, median [IQR][b]	6.9 [3.9–12.5]	6.0 [2.9–10.1]	0.343	11.7 [4.6–13.3]	6.0 [2.9–10.1]	0.087

[a]Age at start of treatment with oral immunosuppressive drugs. [b]From start of oral immunosuppressive drugs until data lock.
IQR: interquartile range; NMSC: non-melanoma skin cancer; SCC: squamous cell carcinoma.

tween patients treated ≤2 years ($n=352$, incidence 3.4%) and patients treated >2 years ($n=205$, incidence 2.9%) ($p=0.76$) and no significant difference between patients treated ≤5 years ($n=482$, incidence 3.3%) and patients treated >5 years ($n=75$, incidence 2.7%) ($p=0.77$).

Patients who developed an SCC were compared with those who did not develop an SCC (Table III). Patients developing an SCC were significantly older at data lock and start of treatment compared with those who did not develop an SCC ($p=0.001$ and $p=0.004$, respectively). Sex, cumulative days of oral immunosuppressive drugs until data lock and duration of follow-up were not statistically significantly different between the groups ($p=0.38$, $p=0.35$, and $p=0.09$, respectively). There was no significant difference in the incidence of SCC between patients treated ≤2 years ($n=352$, incidence 2.0%) and those treated >2 years ($n=205$, incidence 1.5%) ($p=0.65$) and no significant difference between patients treated ≤5 years ($n=482$, incidence 1.7%) and those treated >5 years ($n=75$, incidence 2.7%) ($p=0.54$).

Due to the small number of events multivariate analysis to evaluate the effect of multiple influences on the risk of development of NMSC could not be performed.

Subgroup analysis: CsA monotherapy

CsA monotherapy was used in 281 patients (**Table IV**). Patients with CsA monotherapy who developed NMSC were statistically significantly older at the start of therapy ($p=0.001$) and at data lock ($p<0.001$) compared with patients with CsA monotherapy without malignancy. Sex, cumulative days of oral immunosuppressive drugs until data lock and duration of follow-up were not statistically significantly different between the groups ($p=0.96$, $p=0.79$, and $p=0.10$, respectively).

Patients with CsA monotherapy who developed SCC were compared with patients who did not develop SCC (Table IV). Patients developing SCC were significantly older at data lock and start of treatment compared with patients who did not develop SCC ($p=0.003$ and $p=0.02$, respectively). Duration of follow-up was longer in patients who developed an SCC ($p=0.01$) vs. patients who did not develop an SCC. Sex and the cumulative days of oral immunosuppressive drugs until data lock were not significantly different ($p=0.31$ and $p=0.30$) between patients with and without an SCC.

Subgroup analyses of the other treatment groups were not performed due to the small number of patients in these groups.

Comparison with the Dutch population

The SIR for the risk of development of an SCC in this study population was 13.1 (95% CI 6.5–19.7). One patient developed 5 SCCs; thereby increasing the SIR value. The calculated SIR for the development of an SCC, without this outlier, was 8.8 (95% CI 3.4–14.3).

In addition, 3 of the 10 patients already had a SCC before the start of treatment and probably were more prone to develop another SCC. The calculated SIR for the development of an SCC, without these 3 patients, was 10.7 (95% 4.6–16.7).

The SIR for the risk of development of an SCC in patients with CsA monotherapy was 25.3 (95% CI 10.3–40.2). The calculated SIR for the development of SCC in patients with CsA monotherapy, without the

Table IV. Patient characteristics of cyclosporine A (CsA) monotherapy ($n=281$). Non melanoma skin cancer (NMSC) and specified for squamous cell carcinoma (SCC)

	CsA monotherapy with NMSC during or after treatment ($n=11$)	CsA monotherapy without NMSC during or after treatment ($n=270$)	p-value differences	CsA monotherapy with SCC during or after treatment ($n=6$)	CsA monotherapy without SCC during or after treatment ($n=275$)	p-value differences
Male, *n* (%)	6 (54.5%)	145 (53.7 %)	0.956	2 (33.3)	149 (54.2)	0.311
Age at data lock, years, median [IQR]	59.0 [52.3–69.5]	40.1 [28.8–51.0]	<0.001	58.7 [52.2–68.8]	40.3 [29.1–51.8]	0.003
Age at start, years, median [IQR][a]	51.0 [40.2–59.7]	32.1 [23.6–45.1]	0.001	50.3 [38.3–57.5]	32.4 [23.7–45.3]	0.022
Cumulative days of oral immunosuppressive use until last day of follow-up, median [IQR]	379.0 [227.0–632.0]	350.5 [210.8–772.3]	0.785	521.5 [341.0–1015.5]	345.0 [212.0–765.0]	0.304
Durations of follow-up, years, median [IQR][b]	11.0 [4.0–12.5]	5.4 [2.5–9.7]	0.095	12.5 [9.3–14.0]	5.3 [2.6–9.7]	0.012

[a]Age at moment of start of treatment with oral immunosuppressive drugs. [b]From start of oral immunosuppressive drugs until data lock.
IQR: interquartile range; NMSC: non-melanoma skin cancer.

aforementioned outlier who developed 5 SCCs, was 14.3 (95% CI 2.9–25.7).

DISCUSSION

This is the first study investigating the occurrence of NMSC in a large group of patients with AD treated with oral immunosuppressive drugs. NMSC during or after oral immunosuppressive treatments were reported in 18 out of 557 patients (3.2%). The patients who developed NMSC were significantly older than those who did not develop these malignancies. Follow-up did not differ significantly between these groups. However, it is noteworthy that in 4 out of the 18 patients the malignancy was detected under the age of 45 years, which is relatively young.

Literature concerning the risk of developing NMSC during or after oral immunosuppressive treatment in patients with AD are scarce. In a retrospective cohort study, Väkevä et al. (19) evaluated 272 patients with various skin diseases treated with CsA, with a median follow-up time of 10.9 years. No NMSC or lymphoma was found in the patients with AD. Berth-Jones et al. (20) evaluated the use of CsA in 100 patients with AD (mean follow-up time 8 weeks). They reported one BCC, which developed in a sebaceous naevus; no SCC was reported. Furthermore, there are some case reports describing (cutaneous) lymphoma in patients with AD using oral immunosuppressive drugs (21–23).

Most information on the development of NMSC after oral immunosuppressive treatment is derived from organ transplant studies. These patients have a markedly increased risk of NMSC (12, 24). The cumulative incidence of malignancies is reported to increase in relation to the number of years since transplantation (25). A mean interval between transplantation and tumour diagnosis is reported in the literature: 8 years for patients who receive transplants at approximately 40 years of age and approximately 3 years for those who receive transplants after the age of 60 years (24, 26, 27). These results are not entirely applicable to patients with AD, because organ transplant patients often use more than one oral immunosuppressive drug simultaneously and they more often have prolonged treatment, resulting in more long-term data.

More recently, data relating oral immunosuppressive treatment to the risk of developing malignancies in other chronic inflammatory diseases have become available. Lymphomas are reported in patients with rheumatoid arthritis treated with methotrexate (28, 29). In patients with IBD, various studies have shown that patients treated with thiopurines had an increased risk of development of NMSC or lymphoproliferative disorders (30–32). In patients with psoriasis, different studies have shown an increased risk of NMSC (33–35). However, most of these patients were also treated with UV light for longer periods, which might have made a major contribution to the increased risk of SCC.

Since AD and NMSC are both common diseases, it can be expected that patients with AD will develop NMSC, irrespective of the immunosuppressive treatment. Confounding factors, such as other therapeutic interventions, lifestyle factors and occupation (indoors or outdoors) are difficult to eliminate and causal relationships are difficult to affirm. Two meta-analyses were found in literature. Deckert et al. (36) included 6 systematic reviews on the risk of cancer in patients with AD. They concluded that there are no data suggesting that AD itself is associated with an increased risk of NMSC. A more recent meta-analysis performed by Gandini et al. (37) included 18 studies (9 on NMSC). They concluded that patients with AD may be at increased risk of BCC, but methodological limitations prevented them from drawing a definitive conclusion.

In the present study, we compared our data concerning SCC with the general Dutch population with a correction for age and found an increased SIR for development of an SCC. These findings were corrected for external, time-dependent influences, by comparing our patients with a patient cohort of the same age in the same time period. The SIR for the risk of development of SCC in the patients included in this study was 13.1 (95% CI 6.5–19.7) (8.8 without outlier with 5 SCCs). Earlier studies in organ transplantation (2,561 patients) and autoimmune hepatitis (45 patients) reported an SIR of 65 (95% CI 53–79) and 28.5 (95% CI 9.9–43.1), respectively (38, 39).

The SIR of 13.1 suggests that patients with AD treated with oral immunosuppressive drugs are at risk of developing an SCC. For interpretation of the results it is important to realize that the numbers of SCCs were low. No significant association was found between the cumulative days of treatment and the risk of development of SCC ($p = 0.35$). In a recent study investigating the incidence of SCC in 59 patients with auto-immune inflammatory rheumatic diseases treated with AZA, a higher cumulative dose and a treatment duration of at least 11 years were qualified as risk factors for the development of SCC (13). In our study only 16 patients had a treatment duration of >10 years. None of the patients developed an SCC. In addition, no significant differences were seen in the SCC incidence between patients treated ≤ 5 years and patients treated >5 years with oral immunosuppressive drugs.

For dermatologists prescribing oral immunosuppressive drugs in daily practice, it is important to know the risk of developing NMSC in individual drugs. A subgroup analysis in our study was only possible for CsA. The SIR for 281 patients treated with CsA monotherapy for development of an SCC was 25.3 (95% CI 10.3–40.2), suggesting an increased risk of developing an SCC during or after CsA treatment. However, one patient developed 5

SCCs; thereby exerting much influence on the SIR value. The calculated SIR for the development of SCC, without this outlier, was 14.3 (95% CI 2.9–25.7).

Also in this group, lack of association with treatment duration and the sometimes long intervals between CsA discontinuation and the development of an SCC makes the relationship doubtful in some patients.

For interpretation of the results it is important to realize that 5 out of 18 patients with NMSC during or after oral immunosuppressive treatment had a previous similar type of tumour before the start of treatment. These patients are probably more prone to develop the tumour; it is not clear what the contribution of the immunosuppressive treatment was to the development of new tumours. Robsahm et al. (40) showed that patients with a history of SCC were more at risk of developing another SCC (SIR of 9.88 in women and 10.1 in men). In our study, the calculated SIR for the development of an SCC, without these 3 patients who had already had an SCC, was 10.7 (95% CI 4.6–16.7).

Study limitations

The median duration of follow-up in this study was 6.0 years (IQR 3.0–10.2), which is relatively short. However, the incidence of NMSC was comparable in the patients with follow-up ≤5 years (n=245) compared with the group with a follow-up >5 years (n=312) (data not shown).

Data concerning BCCs were collected with utmost care, but there will probably be an underestimation of the real incidence. This might be attributed to the fact that BCCs are regularly treated without histological confirmation.

Data on a history of UV light therapy were not available for all evaluated patients, thus the influence of UV light therapy on the development of NMSC is unclear. However, it is common in the Netherlands to prescribe UV light therapy only in short courses of up to 4 months. Psoralen combined with UV A light (PUVA), which is associated with NMSC, is rarely prescribed in patients with AD in the Netherlands. In addition, data on skin type, phototype, naevi, hair and eye colour and history of sunburns were lacking. Data on tumour aggressivity were not available.

Finally, the data for the general population that were used to calculate the SIR for SCC matched our cohort on age and calendar year, but not on sex.

Conclusion

NMSC during or after long-term treatment with oral immunosuppressive drugs was found in 18 out of 557 (3.2%) patients with AD, with an SIR of 13.1 for SCC. For interpretation of the results it is important to include other factors: in this study we found a lack of association between treatment duration and the risk of developing a tumour, a history of a malignancy before treatment in 5 out of 18 patients, and a long interval between treatment discontinuation and the development of the tumour in some patients.

It is always important to balance the benefit of treatment against the potential risks in each individual patient. Patients treated with oral immunosuppressive drugs should regularly visit the dermatologist for monitoring treatment effect and safety laboratory tests. Thorough inspection of the skin during each visit enables early detection and treatment of NMSC. As the occurrence of NMSC in our study was independent of treatment duration, skin inspection should start within the first year during treatment.

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