Original article

Descriptive analysis of 179 German reports of melanoma reported to an adverse drug reaction database as a drug-related adverse effect, and comparison with melanoma cases contained in German cancer registries

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Summary

Background. Malignant melanoma (MM) is one of the most aggressive forms of skin cancer. The occurrence of MM associated with drug therapy has been described in the literature. However, there is no analysis of a substantial number of validated reports of drug-associated MM.

Aim. To analyse a substantial number of validated spontaneous reports of drug-associated MM with regard to the suspected drug and the reported characteristics, and to compare these analyses with those of MM cases occurring in the general population in Germany.

Methods. Spontaneous reports of MM associated with drug therapy in Germany were identified in a large adverse drug reaction database (EudraVigilance). These results were then compared with analyses of MMs in the pooled data from a population-based German cancer registry.

Results. The 10 most frequently suspected drugs in the MM reports all target the immune system, with 7 of these being immunosuppressants. The median time to onset to MM diagnosis was 2.0 years. Patients with drug-associated MM were 11 years (median) younger than patients with MM in the cancer registry, and this age difference was greater for female than for male patients.

Conclusions. Our results emphasize the importance of regular dermatological examinations of patients being treated with immunosuppressants. Physicians should be aware that in these patients, MM might be detected at younger ages and even within 2 years after initiating therapy.

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Introduction

Owing to its metastatic potential, malignant melanoma (MM) is one of the most aggressive forms of skin cancer and accounts for the majority of skin cancer-associated deaths.[1–3] In Germany, the age-standardized incidence in 2018 was 18.9 per 100 000 for females and 20.2 per 100 000 for males.[4]

The main environmental risk factor for MM is ultraviolet light radiation.[1] Further downstream, the elimination

of neoplastic melanocytes by the immune system is of importance.[5]

The occurrence of MM associated with drug therapy has been described for a few immunosuppressants and also for thiazides, and an increased risk either due to their immunosuppressive or photosensitizing potential has been hypothesized.[6–12] However, there is no analysis of a substantial number of validated reports of drug-associated MM, with regard to the suspected drugs or a comparison of the characteristics of these MMs with those of naturally occurring MMs. The aim of this study was therefore to analyse these reports and compare the results with those of MMs from a German cancer registry.

Methods

The study was approved by the local ethics committee of the Medical Faculty of the University Bonn (009/17 and 458/20).

Study design

This was a noninterventional pharmacoepidemiological study, performed in an adverse drug reaction (ADR) database and a population-based registry using descriptive analyses. All ADR reports from Germany are stored in EudraVigilance, the ADR database of the European Medicines Agency (ADR definition, seriousness criteria and reporting obligations have been described previously[13–15]). From here on, we refer to MM identified in the ADR database as 'reports', and those identified in the cancer registry as 'cases'.

Data access

Owing to data protection requirements and the EudraVigilance database access policy, the individual pseudonymized ADR reports are not freely accessible as different levels of access are granted for different user levels. However, even with the lowest level of access, it is possible to perform the same analysis in EudraVigilance with aggregated data (public access: www.adrreports.eu/en/index.html). Similar requirements exist for the individual data of cancer registries, which are accessible for scientific purposes upon request (https://search.datacite.org/works/10.18444/5.03.01.0005.0015.0002).

Databases

Adverse drug reaction database. A validated dataset of 179 reports referring to drug-associated MMs was identified for Germany between January 1978 and March 2019 (for detailed description of report identification see Fig. 1 and Data S1 and S2). These validated MM reports were analysed with regard to (i) the annual number of reports per 10 million inhabitants, (ii) demographic parameters, (iii) reported autoimmune diseases, (iv) MM characteristics, (v) drugs most frequently reported, and (vi) reporting rates (number of ADR reports per 100 000 drug prescriptions). Additionally, we performed sex- and age-stratified analyses (for further details, see Data S1).

Cancer registry data. The population-based cancer registration in Germany is organized and data transmitted annually by the federal states to the Centre for Cancer Registry at the Robert Koch Institute (RKI).[16,17] MM thickness is classified according to the currently applicable TNM (tumour, node, metastasis) classification.[18] The national incidence trends for skin MM during the period 1995–2018 (see Fig. 2) are based on estimates as it is expected that not all of the federal states will have complete coverage of cases. In contrast, the comparison of demographical parameters, MM locations and MM types and thickness with the MM reports (see Table 2 and Table S4) are based on all MM cases notified by the registries during the same period.

Results

Demographics

Of the MM reports, 52.0% referred to females and 46.4% to males. The overall median age was 53 years and the median age for females was around 10 years younger than that of males (48.5 vs. 60.0 years, respectively) (Tables 1 and 2).

Comorbidities

More than half of the patients (57.0%, 102 of 179) had at least one autoimmune disorder, with arthritis (all forms) (37.3%, 38 of 102), multiple sclerosis (32.4%, 33 of 102) and psoriasis (28.4%, 29 of 102) being the most frequently reported (the ranking differed between male and female patients). Almost 40% (69 of 179) of patients were currently taking or had in the past taken immunosuppressants, with a higher proportion in male (42.4%; 35 of 83) than female (34.4%; 32 of 93) patients (Table 1, Table S1).

Number of cases

Both the annual number of MM reports and the estimated crude incidence rates of MM cases increased
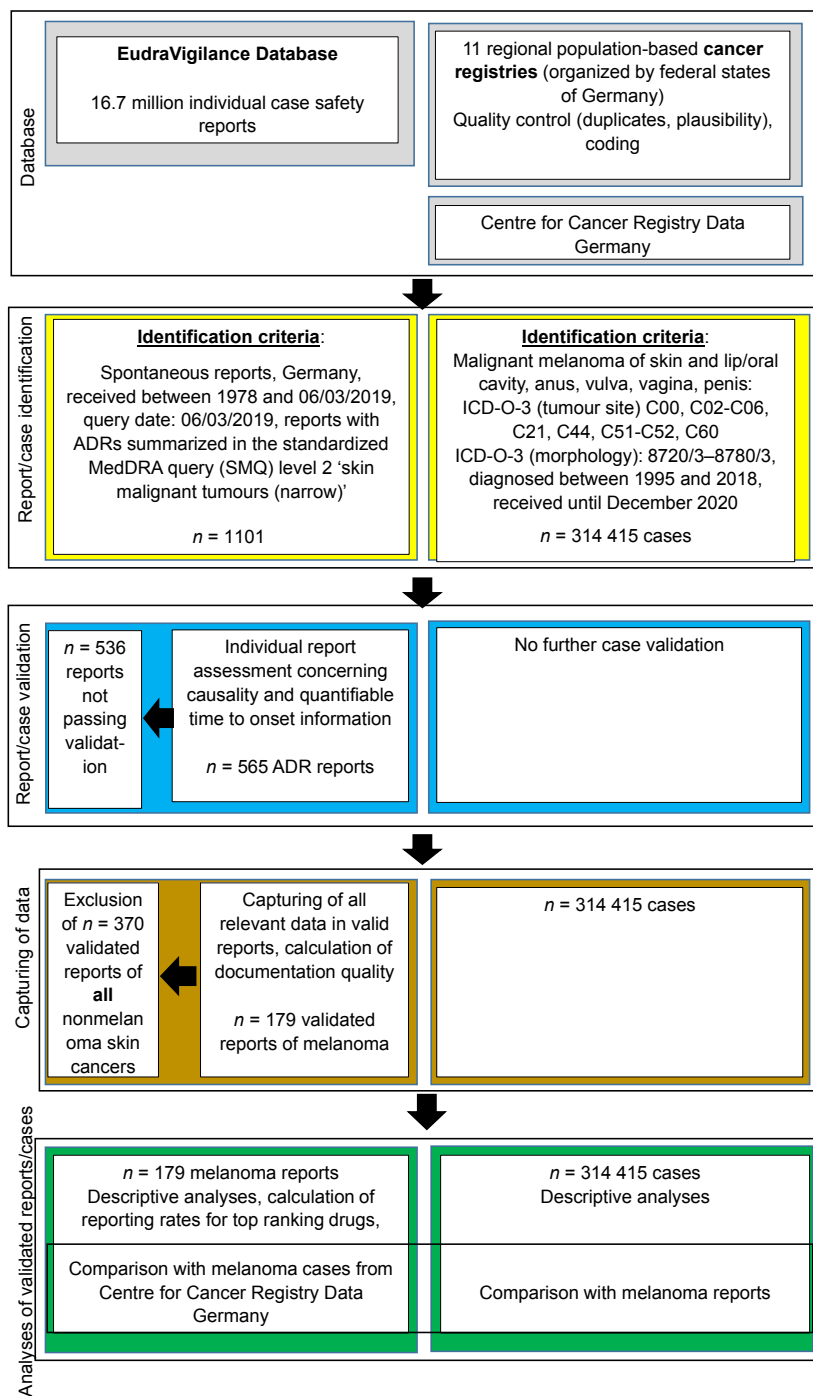
Figure 1 Flow chart report and case identification and validation. On the left-hand side, the workflow from the identification, validation and capturing of the melanoma reports from the adverse drug reaction (ADR) database to their analyses, while on the right-hand side, the identification and capturing of the melanoma cases from the cancer registry is depicted. The melanoma cases include $n = 7406$ cases (2.4%) identified by death certificate only. ICD, International Classification of Diseases; MedDRA, Medical Dictionary for Regulatory Activities.
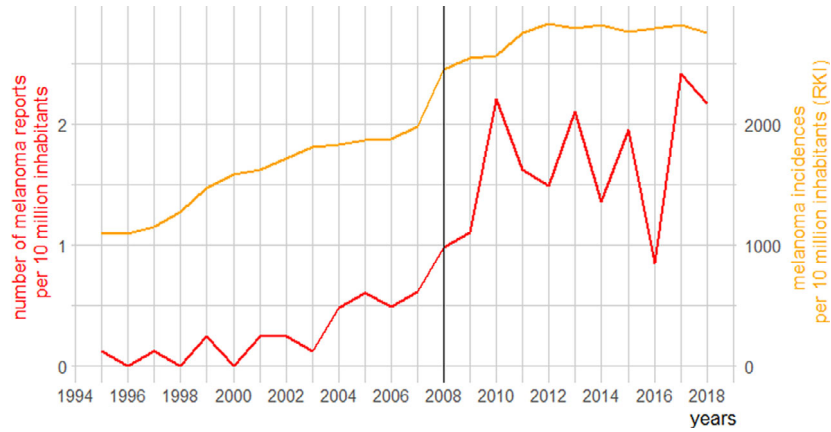
Figure 2 Annual number of adverse drug reaction reports per 10 million inhabitants and estimated incidence rates from the German cancer registry. In July 2008, a reimbursed skin screening for detection of skin cancer was introduced in Germany, which to some extent may account for the increase of melanoma reports and melanoma incidences around this time point (vertical line).

during the period investigated, with both curves showing similarities. A steeper increase was observed around July 2008 (Fig. 2).

Age differences

Patients in the reports were substantially younger than the patients in the cases (median: 53 and 63.0 years). The highest quotient of reports per 10 million inhabitants occurred in the age class 65–

69 years, whereas the highest incidence for the cases was observed in the age class 80–84 years (Fig. 3, Table 2).

Sex differences

In both datasets, female patients were younger than male patients, and patients of both sexes were younger in the reports than the cases (11 years younger for female patients (reports median 48.5 years vs. cases
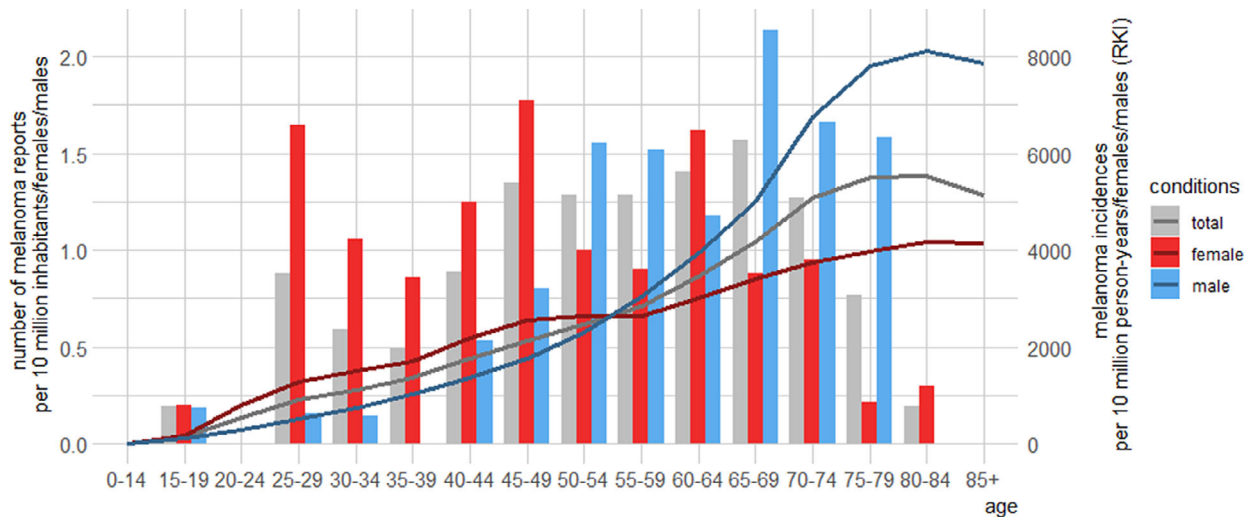

Figure 3 Age- and sex-stratified analysis of the mean number of reports of melanoma as adverse drug reaction (ADR) per 10 million inhabitants (bars) and the estimated melanoma incidence per 10 million person-years (lines) in Germany. In the melanoma reports, until the age class 45–49 years female patients accounted for most of the reports (except for the age class 60–64 years), whereas it was the reverse in the higher age classes. In the melanoma cases, the intersection of the curves for the female and male incidences was the age class 55–59 years. Notably, because not all melanoma reports included information about sex and/or age, the grey bars of all ADR reports may not lie exactly in the middle of the red and blue bars that are referring to female and male patients.

Table 1 Descriptive analysis of characteristics in melanoma reports.[a]

	Melanoma reports (n = 179)
Patient demographics	
Age, years; mean (median)	52.8 (53.0)[b]
Sex, n (%)	
Female	935 (2.0)
Male	83 (46.4)
Unknown	3 (1.7)
Most frequently reported autoimmune diseases[c]	
Reports with this information	102 (57.0)
Top 3 most frequently reported diseases, n (%)	
Arthritis (all forms)	38/102 (37.3)
Multiple sclerosis	33/102 (32.4)
Psoriasis (all forms)	29/102 (28.4)
Personal cancer history[d]	
Reports with this information	43 (24.0)
History of any cancer	32 (74.4)
Skin cancer	15/43 (34.9); MM 10/15 (73.3)
Skin and other cancer	2/4 (34.7); MM 1/2 (50.0)
Other cancer	14/43 (32.6)
No history of cancer	11/43 (25.6)
Top 5 most frequently reported drug classes (n = 179)[e]	
Immunosuppressants	104/179 (58.1)
Immunostimulants	20/179 (11.2)
Antineoplastic agents	10/179 (5.6)
Dopaminergic agents	7/179 (3.9)
Systemic drugs for obstructive airway diseases	6/179 (3.4)
Reports of drugs with PP (n = 179)[f]	76/179 (42.5)
Suspect drugs	
Total drugs, n[g]	211
Reports with this information, n (%)[g]	179 (100)
Top 10 most frequently reported suspect drugs[h,i]	
Adalimumab	37/179 (20.7); 30/179 (17.0)
Etanercept	16/179 (8.9); 13/179 (7.3)
Dimethyl fumarate	11/179 (6.1); 8/179 (4.5)
Glatiramer acetate	10/179 (5.6); 10/179 (5.6)
Fingolimod[i,i]	9/179 (5.0); 9/179 (5.0)
Interferon-β[i,i]	9/179 (5.0); 9/179 (5.0)
Azathioprine[i,i]	8/179 (4.5); 3/179 (1.7)
Infliximab[i,i]	8/179 (4.5); 6/179 (3.4)
Methotrexate[i,m]	5/179 (2.8); 2/179 (1.1)
Omalizumab[i,m]	5/179 (2.8); 5/179 (2.8)
TTO, days; median (IQR)	
All reports of MM	730 (401–1530)
Reports of MM with PP drugs	906 (587–1946)
Reports of MM without PP drugs	598 (297–1097)
Immunosuppressant use (past or current)	
Reports with this information	74 (41.3)
Past/current use	69/74 (93.2)
No past/current use	5/74 (6.8)
Most frequently reported immunosuppressants[n]	
Reports with this information	74 (41.3)
Top ranking drugs	

Table 1 continued

	Melanoma reports (n = 179)
(Methyl-)prednisolone	23/74 (31.1)
Methotrexate	21/74 (28.4)
Corticosteroid	10/74 (13.5)
Azathioprine	9/74 (12.2)
Ciclosporin[n]	8/74 (10.8)
Infliximab[n]	8/74 (10.8)
Seriousness of melanoma[p]	
Reports with this information	179 (100)
Serious	177/179 (98.9)
Death	9/179 (5.0)
Life-threatening	29/179 (16.2)
Hospitalization	65/179 (36.3)
Disabling	3/179 (1.7)
Primary reporting source[q]	
Reports with this information	178 (99.4)
Physician	127/178 (71.3)
Pharmacist	4/178 (2.2)
Other HCP	7/178 (3.9)
Consumer	24/178 (13.5)

ADR, adverse drug reaction; HCP, healthcare professional; IQR, interquartile range; MM, malignant melanoma; PP, photosensitizing potential; TTO, time to onset. [a]Data are n/N (%) unless otherwise stated. [b]No data available for 30 patients. [c]Patients with autoimmune diseases had to have one of the following diseases: Crohn disease, ulcerative colitis, psoriasis (all forms), multiple sclerosis, arthritis or ankylosing spondylitis. These diseases had to be coded in the patient history or as indication for drug therapy. [d]Information on patient's own cancer history was recorded within the individual report assessment, which includes a review of the free-text information (narrative) in each report. [e]Assignment of drugs was performed in accordance with Anatomical Therapeutic Chemical classification (see Data S3). [f]PP was based on the relevant information in the product information or literature (for list of drugs see Data S3). [g]179 ADR reports had information about 211 suspected drugs; > 1 drug was suspected in 21 ADR reports. [h]Two sets of numbers are given; the first was where the drug was suspect alone or in combination with another drug; the second was where the drug was the sole suspect drug. [i]Although 10 drug substances were identified, some drugs had equal ranking: [j]equal fifth; [k]equal sixth, [l]equal seventh. [m]Drug with PP according to literature. [n]Six drugs are listed because one ADR report could include more than one past or current immunosuppressant and [o]the bottom two shared fifth equal ranking. [p]An ADR report was classified as either serious or not serious. All cases included information about the seriousness of the melanoma; however, within the seriousness criteria, each ADR report could be assigned to more than one category. [q]The primary reporting source is the number of reports that exclusively listed only one of these reporting sources; reports in which more than one reporting source was listed (e.g. reported by both the physician and the patient) are not tabulated.

60.0 years) and 8 years younger (reports median 58 years vs. cases 66.0 years) for male patients (Table 2).

In the reports, the sex-specific quotient of ADR reports per 10 million inhabitants was higher for

Table 2 Patient demographics, location, type and thickness of melanoma in the melanoma reports and cases.[a]

	Reports of MM (n = 179)	Cases of MM in the German Cancer Registry (n = 314 415)
Patient demographics		
Age, years; mean (median)	52.8 (53)	60.1 (63.0)
Sex and age by sex		
Female, n (%)	93 (52.0)	157 189 (50.0)
Age, years; mean (median)	48.7 (48.5)	59.6 (60.0)
Male, n (%)	83 (46.4)	156 956 (50.0)
Age, years; mean (median)	58.1 (58.0)	63.7 (66.0)
Unknown sex	3 (1.7)	–
Location of MMs[b]		
Reports with this information, n (%)	86 (48.0)	281 030 (89.5)
Lips	0/86 (0.0)	456 (0.2)
Eye/eyelid	2/86 (2.3)	1285 (0.5)
Ear and auditory canal	1/86 (1.2)	5677 (2.0)
Other part of the face	11/86 (12.8)	25 119 (8.9)
Scalp and neck	1/86 (1.2)	12 943 (4.6)
Trunk	18/86 (20.9)	97 637 (34.7)
Upper extremities including shoulder	31/86 (36.0)	65 027 (23.1)
Lower extremities including hips	23/86 (26.7)	69 327 (24.7)
Overlapping cutaneous sites	–	487 (0.2)
Nasal and oral cavity	3/86 (3.5)	956 (0.3)
Anus	0/86 (0.0)	489 (0.2)
Vulva	0/86 (0.0)	1174 (0.4)
Vagina	–	328 (0.1)
Penis	0.0 (0/86)	125 (0.0)
Type of melanoma[b]		
Reports with this information, n (%)	43 (24.0)	214 102 (68.2)
Nodular	12/43 (27.9)	33 104 (15.5)
Amelanotic	0/43 (0.0)	4339 (2.0)
Lentigo maligna	5/43 (11.6)	25 756 (12.0)
Superficial	24/43 (55.8)	140 825 (65.8)
Acral lentigo	1/43 (2.3)	5708 (2.7)
Any other type	2/43 (4.7)	4370 (2.0)
Tumour thickness of melanomas[b]		
Reports with this information	41 (22.9)	233 554 (74.3)
T1	18/41 (43.9)	145 549 (62.3)
T2	12/41 (29.3)	38 388 (16.4)
T3	3/41 (7.3)	27 408 (11.7)
T4	9/41 (22.0)	22 209 (9.5)

[a]Data are n/N (%) unless otherwise stated. [b]For melanoma reports, there may be more than one assignment (for location, type and thickness) if more than one melanoma was reported. Classification of melanoma reports refers only to melanoma thickness, as information on ulceration was often not provided.

female than for male patients up to the age class 45–49 years, whereas from the age of 50 years onwards (except for the age class 60–64 years), this was reversed. A similar trend was seen for the cases, with the sex-specific incidence being higher for women than men up to the age class 50–54 and then higher for men from the age of 55 years onwards.

These results might be related to sex-specific differences of the underlying diseases requiring treatment. For example, 75% of patients with multiple sclerosis were female (median age 48.0 years), whereas 69.0% of patients with psoriasis were male (median age 56.0 years) (Table S2).

Associated drugs

Of the 179 reports, 104 (58.1%) had an immunosuppressant reported as the suspect drug, while 76 (42.5%) of the reports suspected a drug with photosensitizing potential (in 21 of the 179 reports, > 1 drug was suspected). However, all of the 10 most frequently suspected drugs in the reports act on the immune system: 7 immunosuppressants, 2 immunostimulants [interferon (IFN)-β, glatiramer], and an anti-IgE antibody (omalizumab). Adalimumab accounted for a fifth of all reports and ranked first irrespective of patient sex. Adalimumab also had the highest reporting rate (MM reports per 100 000 prescriptions), followed by fingolimod, etanercept, dimethyl fumarate, glatiramer and IFN-β (2.3, 1.7, 1.0, 0.7, 0.7 and 0.2, respectively). Reporting rates varied by age and sex (Table S3). For example, the highest reporting rate was for adalimumab in female patients, but for fingolimod in male patients.

Cancer characteristics

Time to onset to cancer diagnosis. The median time to onset (TTO) to MM diagnosis over all reports was 730 days (Table 1). It was shorter for etanercept and adalimumab (561 and 587 days, respectively) and longer for dimethyl fumarate, fingolimod, IFN-β, and glatiramer (915.0, 985.0, 1460.0 and 2387.5 days, respectively) (Table S3). The TTO was longer for drugs with photosensitizing potential (907 days) than for those without (600 days) (Table 1). In addition, the TTO was longer in patients with multiple sclerosis (980 days) and shorter in patients with psoriasis and arthritis (556 and 597 days, respectively) (Table S2).

Location. The most common site for MM in reports was the 'upper extremities including shoulder'

(36.0%), whereas it was the 'trunk' in the MM cases (34.7%). Sex-specific differences in locations were observed between reports and cases (Table 2, Table S4).

Type and thickness. A lower number of the reports recorded MM type or thickness (24.0% and 22.9%, respectively), compared with the cases (68.2% and 74.3%, respectively). Among the specified types, superficial MM was the most frequently reported in both reports (55.8%) and cases (65.8%), followed by nodular MM (27.9% and 15.5%, respectively). In the reports, nodular MM occurred more often in male (40.9%) than in female patients, but this was not seen in the cases (Table 2, Table S4). The relative share of T4- and T2-classified tumours was higher in the reports (T4: 22.0%; T2: 29.3%) than in the cases (9.5% and 16.4%, respectively). In the reports, the percentage of T1 and T2 MM was higher in female than in male patients, whereas the reverse was seen for T3 and T4. A similar pattern, except for the T2 designation, was noted for cases.

Discussion

In the present study, we analysed 179 spontaneous ADR reports about drug-associated MM and compared these with MM cases ($n = 314\,415$) in the German national cancer registry.

The number of MM reports increased in the period analysed.[15] However, the number of ADR reports without specifying any reaction also generally been increasing.[15] The reasons for this increase may include tightened reporting obligations, lowered reporting thresholds (e.g. online reporting making it easier to report),[15] and increases in frequency of MM diagnosis,[2] among others. The steeper incline observed around 2008 likely reflects the start of a nationwide skin cancer screening programme in Germany.[19]

The younger age of patients, especially female patients, in the reports (Fig. 3, Table 2) might be explained by (i) treatment with immunosuppressants or immunostimulants of specific diseases that are more prevalent in younger[20] or female[21] patients, (ii) the tumour-promoting effects of immunosuppressants, (iii) a detection bias due to increased medical surveillance, or (iv) younger women being more likely to visit a physician and to participate in preventive medical examinations.[22]

In the 179 reports, the suspect drug was considered to be an immunosuppressant in 58.1% and a drug with photosensitizing potential in 42.5% of the reports. Of the 10 top ranking drugs in the reports, 7 were

immunosuppressants and for 6 photosensitizing potential was mentioned in literature (it should be noted that the same drug can have both effects). It remains unclear whether it is the photosensitizing potential or the pharmacological immunosuppressive effect that might have the larger contribution in terms of a hypothesized impact on MM occurrence. Immunosuppression itself appears to be a plausible mechanism, as the immune system is critical for identifying and eliminating malignant cells and MM is a highly immunoactive tumour type.[5,23] The literature shows conflicting results with regard to immunosuppressant-associated MMs. Higher risks with higher cumulative doses of immunosuppressants and for anti-tumour necrosis factor (TNF)-α drugs such as adalimumab and etanercept (the two drugs with highest numbers in our analysis) were reported by studies from Norway[24] and Sweden.[25] However, for anti-TNF-α drugs, other studies did not confirm these associations.[26] Differences in the study populations with regard to ethnicity, risk factors (e.g. comorbidities, sun exposure), study designs and the rare frequency of drug-associated MMs may account for the conflicting results. In addition, we cannot exclude the possibility that other drugs used in the past or used concomitantly, apart from the suspected drugs, may also have impacted on drug-associated MM in our reports.

With regard to the drug product information, 5 out of the 10 most frequently reported drugs have MM explicitly listed as an ADR. In addition, for four of these drugs (adalimumab, etanercept, fingolimod, infliximab) skin cancer screening prior to start respectively during treatment is recommended, which may lead to more frequent or earlier detection of MMs in these patients. Similarly, the TTO was shorter for adalimumab and etanercept (1.6 and 1.5 years; Table S3) than over all reports (2 years; Table 1). Askling *et al.*[27] found a higher overall cancer occurrence within the first year of adalimumab treatment, but other authors did not. The TTO may vary between patient populations (e.g. depending on comorbidities), between individual drugs (e.g. photosensitizing potential of different immunosuppressive mechanisms). In a study from Denmark,[28] the median time to diagnosis of MM was 4.2, 3.1 and 2.8 years from onset of mild psoriasis, severe psoriasis and psoriatic arthritis respectively, and 2.3 years after initiation of biologic therapy compared with 1.5 years in our analysis. It may also be speculated that the longer TTO in reports of drugs with photosensitizing potential could be related to initiation of new tumours rather than to promotion of preclinical tumours already existing at the start of

therapy. Based on our reports, we could not assess if skin screening was actually performed before start of drug therapy, thus, promotion of extant preclinical tumours at therapy start might have led to the shorter TTO in some reports.[27]

As only 24% and 22.9% of MM reports provided information on type and thickness of MM, no firm conclusions could be drawn from the data, and the results are discussed only briefly. Superficial MM was the most frequently diagnosed MM type in the literature,[24] and our results concur with this. Previous reports suggested a higher occurrence of nodular MM in male than female patients[29] as seen in our reports, and nodular MM are more likely to be at a more advanced stage at diagnosis.[30] This might explain the higher share of T4 MMs in the reports compared with cases and in male compared with female patients. Additionally, male patients may not seek medical advice until the later stages of disease. In addition, selection bias cannot be excluded.

The strengths of our analysis include the high number of validated reports referring to drug-associated MM. In addition, we compared the data to a large number of cases contained in the national cancer registry. Concerning the analysis of the reports, the known method-inherent limitations of a spontaneous reporting system, such as under-reporting, apply.[15] There are also specific limitations to our study, including the limited information in the reports relating to risk factors such as phototherapy (e.g. in patients with psoriasis), excessive sunlight exposure and skin phototype.

Conclusion

As a clinical translation of our findings, physicians treating patients with immunosuppressants should be aware that MM might be detected at an earlier age than normal (and younger in female than in male patients) and even within 2 years after initiating therapy. Our results highlight the importance of regular dermatological examinations for patients being treated with immunosuppressants. In addition, physicians reporting MM as an ADR should be encouraged to provide all relevant information, particularly with regard to tumour type and thickness.

Acknowledgement

What's already known about this topic?

• The occurrence of MM associated with drug therapy has been described in the literature for a few immunosuppressants and for thiazides.
• An increased risk either due to their immunosuppressive or to their photosensitizing potential was hypothesized.
• However, there is no analysis of a substantial number of validated reports of drug-associated MM with regard to the suspected drugs or a comparison of their characteristics with those of naturally occurring MMs.

What does this study add?

• The 10 most often suspected drugs in the reports of drug-associated MM all target the immune system (7 immunosuppressants).
• Median time to onset to MM diagnosis over all reports was 2.0 years.
• Patients with drug-associated MM were 11 years younger than patients with MM from the cancer registry, with age differences being stronger for female than for male patients.
• The study findings emphasize the importance of regular dermatological examinations for patients receiving immunosuppressants.

References

1 Leonardi GC, Falzone L, Salemi R et al. Cutaneous melanoma: from pathogenesis to therapy (Review). Int J Oncol 2018; **52**: 1071–80.
2 Garbe C, Keim U, Eigentler TK et al. Time trends in incidence and mortality of cutaneous melanoma in Germany. J Eur Acad Dermatol Venereol 2019; **33**: 1272–80.
3 Matthews NH, Li WQ, Qureshi AA et al. Epidemiology of melanoma. In: Cutaneous Melanoma: Etiology and Therapy (Ward WH, Farma JM, eds). Brisbane, Australia: Cordon Publications, 2017; 3–23.

4 RKI. Zentrum für Krebsregisterdaten. Malignes Melanom der Haut. Available at: https://www.krebsdaten.de/Krebs/DE/Content/Krebsarten/Melanom/melanom_node.html (accessed 20 January 2022).

5 Speeckaert R, van Geel N, Vermaelen KV *et al.* Immune reactions in benign and malignant melanocytic lesions: lessons for immunotherapy. *Pigment Cell Melanoma Res* 2011; **24**: 334–44.

6 McKenna MR, Stobaugh DJ, Deepak P. Melanoma and non-melanoma skin cancer in inflammatory bowel disease patients following tumor necrosis factor-alpha inhibitor monotherapy and in combination with thiopurines: analysis of the Food and Drug Administration Adverse Event Reporting System. *J Gastrointestin Liver Dis* 2014; **23**: 267–71.

7 Nardone B, Hammel JA, Raisch DW *et al.* Melanoma associated with tumour necrosis factor-[alpha] inhibitors: a Research on Adverse Drug events And Reports (RADAR) project. *Br J Dermatol* 2014; **170**: 1170–2.

8 Robinson CL, Guo M. Fingolimod (Gilenya) and melanoma. *BMJ Case Rep* 2016; **2016**: bcr2016217885.

9 Michiels Y, Bugnon O, Michiels J-F *et al.* Detection of a new melanoma in a patient treated with fingolimod. *BMJ Case Rep* 2019; **12**: e227951.

10 Walker J, Smylie A, Smylie M. An association between glatiramer acetate and malignant melanoma. *J Immunother* 2016; **39**: 276–8.

11 Carbone ML, Lacal PM, Messinese S *et al.* Multiple sclerosis treatment and melanoma development. *Int J Mol Sci* 2020; **21**: 2950.

12 Nardone B, Majewski S, Kim AS *et al.* Melanoma and non-melanoma skin cancer associated with angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers and thiazides: a matched cohort study. *Drug Saf* 2017; **40**: 249–55.

13 European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module VI – collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2). 2017. Available at: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf (accessed 20 January 2022).

14 EMA. Guideline on good pharmacovigilance practices (GVP). Annex I – Definitions (Rev 4). 2017. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-4_en.pdf (accessed 20 January 2022)

15 Dubrall D, Schmid M, Alesik E *et al.* Frequent adverse drug reactions, and medication groups under suspicion. *Dtsch Arztebl Int* 2018; **115**: 393–400.

16 Robert Koch Institut. Centre for Cancer Registry Data. Available at: https://www.rki.de/EN/Content/Health_Monitoring/Cancer_Registry/cancer_registry_node.html; jsessionid=83BC7505D7E8E97AC6ECDAC1A368A84B.internet091 (accessed 20 January 2022).

17 Robert Koch Institut, Zentrum für Krebsregisterdaten. Available at: https://www.krebsdaten.de/Krebs/EN/Content/Methods/methods_node.html (accessed 20 January 2022).

18 Brierly JD, Gospodarowicz MK, Wittekind C. Skin tumours. Malignant melanoma of the skin. In: *TNM Classification of Malignant Tumours*, 8th edn Chichester: John Wiley & Sons, 2017; 131–50.

19 Hübner J, Eisemann N, Brunßen A *et al.* Skin cancer screening in Germany: review after ten years. *Bundesgesundheitsbl* 2018; **61**: 1536–43.

20 Amador-Patarroyo MJ, Rodriguez-Rodriguez A, Montoya-Ortiz G. How does age at onset influence the outcome of autoimmune diseases? *Autoimmune Dis* 2012; **2012**: 251730.

21 Angum F, Khan T, Klaer J *et al.* The prevalence of autoimmune disorders in women: a narrative review. *Cureus* 2020; **12**: e8094.

22 Deutsches Ärzteblatt. [Men are more likely to avoid going to the doctor] (in German). Available at: https://www.aerzteblatt.de/nachrichten/99929/Maenner-druecken-sich-haeufiger-vor-Arztbesuch (accessed 20 January 2022).

23 Olsen CM, Green AC. Risk of invasive melanoma in patients with rheumatoid arthritis treated with biologics: an updated meta-analysis. *Ann Rheum Dis* 2018; **77**: e49.

24 Berge LAM, Andreassen BK, Stenehjem JS *et al.* Use of immunomodulating drugs and risk of cutaneous melanoma: a nationwide nested case-control study. *Clin Epidemiol* 2020; **12**: 1389–401.

25 Raaschou P, Simard JF, Holmqvist M *et al.* Rheumatoid arthritis, anti-tumour necrosis factor therapy, and risk of malignant melanoma: nationwide population based prospective cohort study from Sweden. *BMJ* 2013; **346**: f1939.

26 Leombruno JP, Einarson TR, Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. *Ann Rheum Dis* 2009; **68**: 1136–45.

27 Askling J, van Vollenhoven RF, Granath F *et al.* Cancer risk in patients with rheumatoid arthritis treated with anti–tumor necrosis factor α therapies: does the risk change with the time since start of treatment? *Arthritis Rheum* 2009; **60**: 3180–9.

28 Egeberg A, Thyssen JP, Gislason GH *et al.* Skin cancer in patients with psoriasis. *J Eur Acad Dermatol Venereol* 2016; **30**: 1349–53.

29 Greenwald HS, Friedman EB, Osman I. Superficial spreading and nodular melanoma are distinct biological entities: a challenge to the linear progression model. *Melanoma Res* 2012; **22**: 1–8.

30 Sgouros D, Lallas A, Kittler H *et al.* Dermatoscopic features of thin (≤2 mm Breslow thickness) vs. thick (>2 mm Breslow thickness) nodular melanoma and

predictors of nodular melanoma versus nodular non-melanoma tumours: a multicentric collaborative study by the International Dermoscopy Society. *J Eur Acad Dermatol Venereol* 2020; **34**: 2541–7.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Identification, validation and analyses of melanoma reports.

Data S2. Overview analysis.

Data S3. List of drugs reported as suspected.

Table S1. Reported autoimmune diseases, most frequently suspected drugs, use of immunosuppressants and seriousness of ADR reports in the melanoma reports for females and males.

Table S2. Patient demographics and time to onset analyses of the most frequently reported autoimmune diseases.

Table S3. Descriptive analyses of the six most frequently suspected drugs in the melanoma reports.

Table S4. Stratified analyses of location, type and thickness of melanoma in reports and cases.