Pharmacoepidemiology and Drug Safety

WILEY

ORIGINAL ARTICLE

Titel: Risk of Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis Among Patients Treated With Immune Checkpoint Inhibitors Compared to Other Antineoplastic Medications: A Nationwide Study

Ida M. Heerfordt[1,2] | Magnus Middelboe[1] | Christian Kjer Heerfordt[3] | Henrik Horwitz[1,4] | Rasmus Huan Olsen[1,4]

[1]Department of Clinical Pharmacology, Copenhagen University Hospital—Bispebjerg and Frederiksberg, Copenhagen, Denmark | [2]Department of Geriatric and Palliative Medicine, Copenhagen University Hospital - Bispebjerg and Frederiksberg, Copenhagen, Denmark | [3]Department of Respiratory Medicine and Infectious Diseases, Copenhagen University Hospital - Bispebjerg and Frederiksberg, Copenhagen, Denmark | [4]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Correspondence: Ida M. Heerfordt (ida.marie.heerfordt@regionh.dk)

Received: 10 April 2025 | **Revised:** 28 October 2025 | **Accepted:** 11 November 2025

Funding: Henrik Horwitz received a grant from Kongelig Hofbuntmager Aage Bangs Fond.

Keywords: adverse drug reactions | immunotherapy | oncology | pharmacovigilance | real-world data | Stevens–Johnson syndrome | toxic epidermal necrolysis

ABSTRACT

Purpose: This study aimed to assess the risk of Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) among patients treated with immune checkpoint inhibitors (ICIs), compared to those receiving molecularly targeted therapies or conventional chemotherapy, using real-world data.

Methods: We conducted a nationwide study involving all patients treated with antineoplastic agents in Denmark from May 2018 to December 2024, identified through the Danish National Hospital Medication Registry. SJS/TEN cases were identified within 3 months of each administration using the International Classification of Diseases, 10th Revision codes L51.1 and L51.2, as recorded in the Danish National Patient Register. Incidence rates of SJS/TEN were calculated per 10 000 patients treated, and incidence rate ratios (IRRs) were estimated to compare treatment modalities.

Results: Among 91 424 patients treated with antineoplastic agents, 19 developed SJS/TEN. The incidence rates per 10 000 patients treated were 6.89 for ICIs, 1.79 for molecularly targeted therapies, and 1.51 for conventional chemotherapy. Patients receiving ICIs had a higher risk of developing SJS/TEN compared with those receiving molecularly targeted therapies (IRR 3.84, 95% CI 1.39–10.60, $p = 0.009$) or conventional chemotherapy (IRR 4.57, 95% CI 1.52–11.57, $p = 0.001$).

Conclusion: While the risk of SJS/TEN is higher among patients treated with ICIs compared to those receiving other types of antineoplastic agents, the overall incidence in the real-world setting remains low.

1 | Introduction

Immune checkpoint inhibitors (ICIs) have significantly improved treatment for advanced and metastatic cancers, including melanoma, non-small cell lung cancer, and renal cell carcinoma [1]. These therapies enhance patient outcomes but can also lead to immune-related adverse events such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [1, 2].

Summary

- Randomized studies have found a risk of Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) of about 30 cases per 10 000 cancer patients treated with immune checkpoint inhibitors (ICIs), compared to 4 cases per 10 000 controls.
- Our study analyzes real-world data from Danish national health databases over six years.
- We investigated the rates of SJS/TEN in patients treated with ICIs versus those given molecularly targeted therapies or conventional chemotherapy.
- In clinical settings, we found a risk of SJS/TEN of 6.89 per 10 000 patients treated with ICIs, compared to 1.79 for molecularly targeted therapies and 1.51 for conventional chemotherapy.

SJS and TEN are rare but potentially fatal cutaneous adverse reactions characterized by extensive epidermal necrosis and detachment [3–5]. The underlying pathophysiology involves a complex immune-mediated response, most often triggered by medications [3, 4, 6]. In addition to the associated mortality risk, these conditions significantly impair the quality of life for patients and lead to medications ceasing [3, 4]. In most drug-related cases, the causative medication was initiated within weeks before symptom onset [4, 7]. To increase sensitivity, we applied a broader 3-month exposure window in this study.

A review of randomized clinical trials (RCTs) reported approximately 3 cases of SJS/TEN per 1000 cancer patients treated with ICIs, compared to only 0.4 cases per 1000 in the control groups [2]. The control groups consisted of patients receiving placebo or an active comparator, depending on the individual trial design [2]. This data suggests a significant increase in risk associated with these immunotherapies. Additionally, SJS and TEN associated with ICIs have been documented in case reports and through spontaneous reporting systems [2, 8], though these are not ideal for determining true incidence rates [9, 10]. The risk of SJS and TEN with ICIs in real-world settings remains under-investigated.

With the widespread and increasing use of ICIs in clinical settings [1], and the potential risks of SJS and TEN [2], our study aims to compare the risks associated with ICIs to those of molecularly targeted therapies or conventional chemotherapy using real-world data.

2 | Methods

This study employed a nationwide design, examining all Danish citizens systematically registered in the Danish Civil Registration System with a unique personal identification number [11]. This facilitates accurate linkage across various national health registries. In Denmark, antineoplastic agents are administered in public hospitals as part of the tax-funded healthcare system. The Danish National Hospital Medication Register contains nationwide data on hospital-administered medications, including information on drug type classified under the Anatomical Therapeutic Chemical classification system (ATC) and administration time, recorded via an electronic prescribing system [12, 13].

Through the Danish National Hospital Medication Registry, we identified and included all patients residing in Denmark from May 2018 to the end of December 2024 who had been treated with antineoplastic agents, classified under the ATC group L01. Patients were included at the time of the first administration of an antineoplastic agent during the study period. From this point, a follow-up period of 3 months was initiated. If a patient received a new administration of an antineoplastic agent at any time after inclusion, a new 3-month follow-up period was initiated from the date of that administration. A patient could therefore contribute multiple nonoverlapping observation periods, and in the case of continuous treatment, be under prolonged or repeated follow-up.

The antineoplastic agents were categorized into three different cancer treatment modalities: ICIs, molecularly targeted therapies, and conventional chemotherapy. Patients were allowed to contribute to multiple exposure groups simultaneously. Events were attributed to all treatment categories to which the patient was exposed at the time of event onset. Table 1 provides an overview of the included treatment modalities and example drugs. A complete list of included medications and ATC codes is available in Table S1.

Patients were included regardless of cancer type or cancer stage (i.e., both primary and secondary malignancies). For all patients included in the study, we extracted the following baseline

TABLE 1 | Overview of included antineoplastic agents by treatment modality. Full list of Anatomical Therapeutic Chemical classification system codes is available in Table S1.

Treatment modality	Example drug classes	Representative agents
Immune checkpoint inhibitors	PD-1 inhibitors, PD-L1 inhibitors, CTLA-4 inhibitors	Nivolumab, Pembrolizumab, Ipilimumab
Molecularly targeted therapies	Tyrosine kinase inhibitors, HER2 inhibitors, proteasome inhibitors	Imatinib, Trastuzumab, Bortezomib
Conventional chemotherapy	Alkylating agents, antimetabolites, taxanes	Cisplatin, Methotrexate, Paclitaxel

Abbreviations: CTLA-4 = cytotoxic T-lymphocyte-associated protein 4, HER2 = human epidermal growth factor receptor 2, PD-1 = programmed cell death protein 1, PD-L1 = programmed death-ligand 1.

TABLE 2 | Baseline characteristics.

Treatment group	Patients, *n*	Age in years, mean (SD)	Female, *n* (%)	Top 3 cancers (patients, *n*)
Immune checkpoint inhibitors	11 608	67 (11)	5295 (46)	Lung (4854) Melanoma (2141) Renal (1024)
Molecularly targeted therapies	39 040	65 (16)	21 801 (56)	Breast (6142) Non-follicular lymphoma (3342) Myeloma (2723)
Conventional chemotherapy	66 261	64 (18)	35 435 (53)	Breast (11 762) Lung (9457) Colon (4724)

characteristics: age, sex, and cancer diagnosis. We identified cases of SJS and TEN occurring during the observation periods, defined as the 3-month interval following each administration of an antineoplastic agent. Diagnoses were ascertained using the International Classification of Diseases, 10th revision (ICD-10) codes L51.1 (erythema multiforme bullosum/SJS) and L51.2 (TEN), as recorded in the Danish National Patient Register [14]. This register includes diagnosis data from all hospital contacts in Denmark, allowing systematic identification of outcome events within the predefined risk window after drug exposure.

The incidence rate was then calculated per 10 000 patients treated, separately for each treatment modality: ICIs, conventional chemotherapy, and molecularly targeted therapies. Incidence rate ratios (IRRs) were subsequently estimated to compare the relative risk of SJS/TEN between treatment modalities. Pairwise comparisons were performed using either molecularly targeted therapies or conventional chemotherapy as the reference group. Statistics were applied for the Poisson distribution, and all statistics were calculated in SAS version 9.4 (SAS Institute Inc., Cary, NC).

This research was approved by the Danish Data Protection Agency (p-2024-15 764) and the Danish National Board of Health (FSEID-00007077). All data were anonymized. Danish data regulations precluded reporting of the specific numbers of patients between 1 and 4 or exact *p* values or IRRs which would unveil these numbers.

3 | Results

From May 2018 to December 2024, a total of 91 424 patients received treatment with antineoplastic agents and were included in the study. For further details see Table 2.

During follow-up 19 patients developed SJS/TEN. The average age of these 19 patients was 63.5 years, with a standard deviation of 17.8 years. Twelve of the patients were male. Six had received antineoplastic agents from two different subgroups within the 3 months prior to the onset of SJS/TEN. Due to the small number of cases, further details cannot be disclosed in accordance with Danish general data protection regulations.

TABLE 3 | Incidence of Steven–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) following treatment administration.

Treatment group	SJS/TEN cases (number of patients treated)	Incidence rate per 10 000
Immune checkpoint inhibitors	8 (11 608)	6.89
Molecularly targeted therapies	7 (39 040)	1.79
Conventional chemotherapy	10 (66 261)	1.51

The incidence rates of SJS/TEN per 10 000 patients treated were as follows: 6.89 for ICIs, 1.79 for molecularly targeted therapies, and 1.51 for conventional chemotherapy (Table 3).

TABLE 4 | Incidence rate ratios (IRR) for Stevens–Johnson syndrome/toxic epidermal necrolysis by treatment modality.

Comparison	IRR (95% CI)	*p*
Molecularly targeted therapies vs. conventional chemotherapy (reference)	1.18 (0.45–3.12)	0.73
Immune checkpoint inhibitors vs. conventional chemotherapy (reference)	4.57 (1.52–11.57)	0.001
Immune checkpoint inhibitors vs. molecularly targeted therapies (reference)	3.84 (1.39–10.60)	0.009

Table 4 shows the IRRs comparing the treatment modalities. Patients treated with ICIs had a significantly higher risk of developing SJS/TEN compared with those receiving molecularly targeted therapies (IRR 3.84, 95% CI 1.39–10.60, $p = 0.009$) or conventional chemotherapy (IRR 4.57, 95% CI 1.52–11.57, $p = 0.001$).

4 | Discussion

Conventional chemotherapy consists of cytotoxic agents that broadly target proliferating cells [15]. Molecularly targeted therapies inhibit specific oncogenic signaling pathways within cancer cells, such as those mediated by tyrosine kinases or proteasomes [16]. ICIs enhance antitumor immunity by blocking inhibitory receptors on T-cells, thereby modulating immune, rather than tumor-intrinsic, pathways [1, 15].

ICIs and molecularly targeted therapies have substantially improved clinical outcomes in several cancer types [15]. For instance, ICIs have extended median overall survival by several months compared to chemotherapy in advanced non-small cell lung cancer, and 5-year survival rates exceeding 50% have been reported in metastatic melanoma [17, 18]. These advances highlight the transformative efficacy of these agents, while also reinforcing the importance of monitoring for rare but serious adverse events such as SJS/TEN.

This nationwide study highlights variability in the risk of developing SJS/TEN across different antineoplastic treatment modalities. Notably, the incidence of SJS/TEN among patients treated with ICIs is higher compared to those receiving molecularly targeted therapies or conventional chemotherapy. This may be due to the broad activation of the immune system by ICIs, which can trigger severe immune-related skin reactions.

This study has several limitations. Patients across the different treatment groups experiencing varying risks for SJS/TEN did not only differ in terms of antineoplastic treatment modalities but also in age, sex, and type of cancer. These factors could potentially influence the risk of developing SJS/TEN and introduce bias when assessing risk differences between treatment modalities [19]. Due to the limited number of events ($n = 19$), we were unable to adjust for these factors in the analysis. In addition, data on ethnicity were not available, although certain genetic risk factors, such as specific human leukocyte antigen alleles, are known to vary across populations [4]. Differences in diagnostic surveillance intensity between treatment groups may also have influenced the likelihood of outcome detection. Lastly, although the ICD-10 codes for SJS/TEN have been validated in the Danish National Patient Register with a high positive predictive value [20], the register only captures events assessed in hospital settings. This limitation may lead to underreporting of milder cases of SJS [14].

In real-world settings in Denmark, the observed risk associated with ICIs (7 per 10000 treated) is lower than that reported in RCTs, which document an incidence of about 30 per 10000 treated [2]. Several factors may contribute to this discrepancy. Underreporting of milder cases is more likely in observational data, while RCTs often involve systematic monitoring. In addition, greater clinical awareness of immune-related skin reactions, shaped by prior RCT findings, may have improved early recognition and management in practice. Differences in patient selection, cancer stage, comorbidities, or genetic susceptibility may also play a role.

In conclusion, the absolute number of SJS/TEN cases remains low, highlighting the infrequency of these severe reactions. This study contributes to the existing literature on the safety profiles of ICIs by providing insights into real-world outcomes.

4.1 | Plain Language Summary

This study looked at how often a rare but serious skin reaction, called SJS or TEN, occurs in patients receiving different types of cancer treatment. SJS/TEN can be life-threatening and is usually caused by medications. We used nationwide health data from Denmark to track all patients treated with cancer treatments in Danish hospitals between 2018 and 2024. We compared the risk of SJS/TEN among patients who received ICIs, a modern type of cancer immunotherapy, to those receiving more traditional cancer medicines, such as chemotherapy or molecularly targeted therapies. Out of 91424 patients treated with cancer treatments, only 19 developed SJS or TEN. We found that patients treated with ICIs had a higher risk (about 7 in 10000) than those treated with other types of cancer treatments, whose risk was about 2 in 10000. However, even in the ICI group, these reactions were very rare. This research helps patients and doctors better understand the safety of different cancer treatments and shows that while ICIs carry a slightly higher risk of severe skin reactions, the overall likelihood remains low.

Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** pds70272-sup-0001-TableS1.docx.