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Research Article

Peripheral Neuropathies in Checkpoint Inhibitor Therapy: An In-depth Investigation through Pharmacovigilance Data-driven Analysis

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Abstract

Background: In recent years, the advent of immunotherapeutic drugs, particularly checkpoint inhibitors (CIs), has revolutionized the landscape of cancer treatment, offering unprecedented hope and improved outcomes for patients. Given the increasing use of these immunotherapies, in addition to the impact on patient survival and quality of life, it is necessary to better understand adverse events related to CIs.

Objective: search and analyze data contained in an important pharmacovigilance database (FAERS), in order to understand the incidence of peripheral neuropathies, as an adverse event, in patients undergoing therapy with CIs in a real-world context.

Methods: This observational study analyzes post-marketing pharmacovigilance data on CIs, The study focuses on adverse events within the (FAERS) database and IQVIA Analytics databases supplied sales data from 2018 to 2022, with queries conducted in May 2023 for the evaluation period spanning January 1, 2018, to December 31, 2022.

Results: Atezolizumab displayed the highest reported neuropathy instances, succeeded by Ipilimumab. Pembrolizumab consistently maintained a low rate of neuropathies per 10,000 sales. The outcomes concerning "Peripheral neuropathies NEC," with Avelumab exhibiting the highest likelihood of reporting. Subsequent inferences ranked Atezolizumab as the second highest, followed by Pembrolizumab, Ipilimumab and Novolumab. Atezolizumab displayed the highest reporting odds ratio when contrasted with Ipilimumab, signifying a heightened likelihood of adverse event reporting associated with the former. The analysis revealed noteworthy RORs for Pembrolizumab versus Nivolumab, and Pembrolizumab versus Ipilimumab. The only drug that exhibited a reporting ROR surpassing the threshold of 2 was Avelumab.

Conclusion: Atezolizumab and Ipilimumab exhibited desproportionality in the neuropathy incidence, while Pembrolizumab showed consistent low rates.

Keywords: CTLA-4; Immune checkpoint blocker; Immune-related adverse events; Neuropathy; PD-1; PD-L1

Introduction

In recent years, the advent of immunotherapeutic drugs, particularly checkpoint inhibitors (CIs), has revolutionized the landscape of cancer treatment, offering unprecedented hope and improved outcomes for patients. By unleashing the body's immune system to combat malignancies, CIs have shown remarkable efficacy in numerous cancer types. However, as with any therapeutic intervention, their usage is not without potential side effects. With the increase in the prescription and administration of CIs, adverse events, including neurological events, have been reported all over the world. Although neurological adverse events are classified as uncommon, their impact on patient well-being and treatment management requires a comprehensive assessment of their incidence and clinical implications [1,2]. Peripheral neuropathy is a medical condition characterized by dysfunction or damage to one or more peripheral nerves. It typically results in a range of sensory, motor, or autonomic symptoms, depending on the specific nerves affected. Neuropathy can manifest as tingling, numbness, weakness, or pain in the affected areas of the body. It may have various causes, including diabetes, infections, toxins, autoimmune disorders, in addition to use of specific medications [3].

It is estimated that peripheral neuropathies affect approximately 3% of patients treated with the class of CIs. Such events can be classified from mild to moderate, where it is not necessary to discontinue therapy with CIs, but there are cases considered more serious that, in addition to discontinuation, require treatment with a specific immune modulator, such as corticoids [2]. Given the increasing use of these immunotherapies, in addition to the impact on patient survival and quality of life, it is necessary to better understand adverse events related to CIs. Therefore, the objective of this study was to search and analyze data contained in an important pharmacovigilance database (FAERS), to understand the incidence of peripheral neuropathies, as an adverse event, in patients undergoing therapy with CIs in a real-world context.

Methods

Data Sources

This observational study analyzes post-marketing pharmacovigilance data on CIs, sourced from patient, healthcare professional, and pharmaceutical company reports. The study focuses on adverse events within the Food and Drug Administration Adverse Event Reporting System (FAERS) database, utilizing the Medical Dictionary for Regulatory Activities (MedDRA) hierarchy. Specifically, the analysis centers on the "peripheral neuropathies NEC" High-Level Term (HLT). Additionally, IQVIA Analytics databases supplied sales data from 2018 to 2022, with queries conducted in May 2023 for the evaluation period spanning January 1, 2018, to December 31, 2022.

Data Analysis

The study examined CIs, namely pembrolizumab (anti-PD-1), ipilimumab (anti-CTLA-4), nivolumab (anti-PD-1), atezolizumab (anti-PD-L1), and avelumab (anti-PD-L1), representing distinct classes of immune CIs widely utilized in diverse cancer treatments. A dual-pronged evaluation approach is employed for a comprehensive safety profile assessment. This involves analyzing absolute adverse report numbers and relative frequencies from post-market surveillance (FAERS) between January 1st, 2018, and December 31st, 2022. Simultaneously, disproportionality analysis, utilizing Reporting Odds Ratio (ROR) with a 95% CI, explores Peripheral Neuropathies (PNs) reporting frequencies among Immune CIs. To analyze the impact of medication sales and adoption on reported adverse events, we conducted a five-year analysis of event frequencies. This aimed to unveil potential correlations between medication sales, usage, and reported events, providing insights into safety profiles and real-world medication impact. Given diverse indications and patient cohorts, data standardization challenges were addressed by quantifying adverse events per 10,000 units sold in North America, enabling meaningful comparisons despite varying incidences.

Results

A total of 1585 neuropathic adverse events were reported with the selected drugs. Table 1 illustrates the number of events found and units sold for each of the Immune CIs (Figure 1). When assessing the drugs with the highest incidence of adverse events reported in the FAERS, irrespective of the specific event or system involved, Ipilimumab emerged as having the highest incidence, closely followed by Atezolizumab. Notably, a downward trend was observed across all drugs (Figure 2).

The examination of the data reveals a relationship between the total number of reported adverse events and the corresponding occurrences of neuropathies. A predictable linear correlation emerges, as the total number of reported adverse events surges, so does the frequency of reported neuropathies. This association was validated by a robust Spearman coefficient of 0.92, underscoring a remarkable level of correlation between these phenomena.

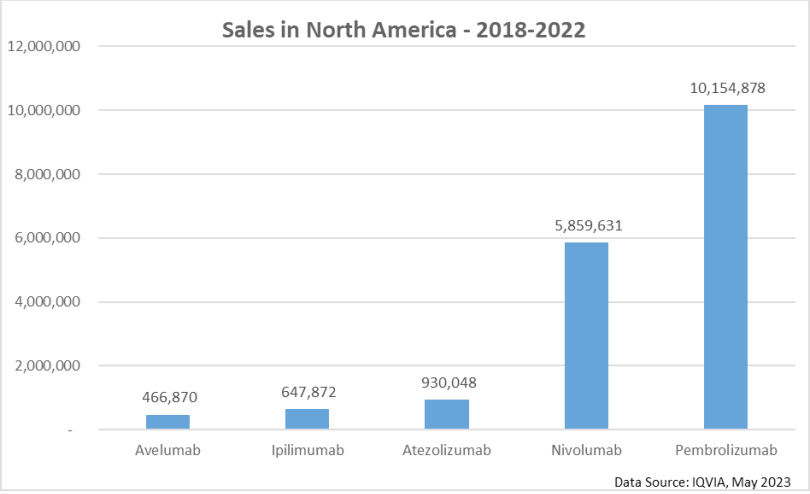

Figure 1: Total sales in North America between 2018 and 2022.

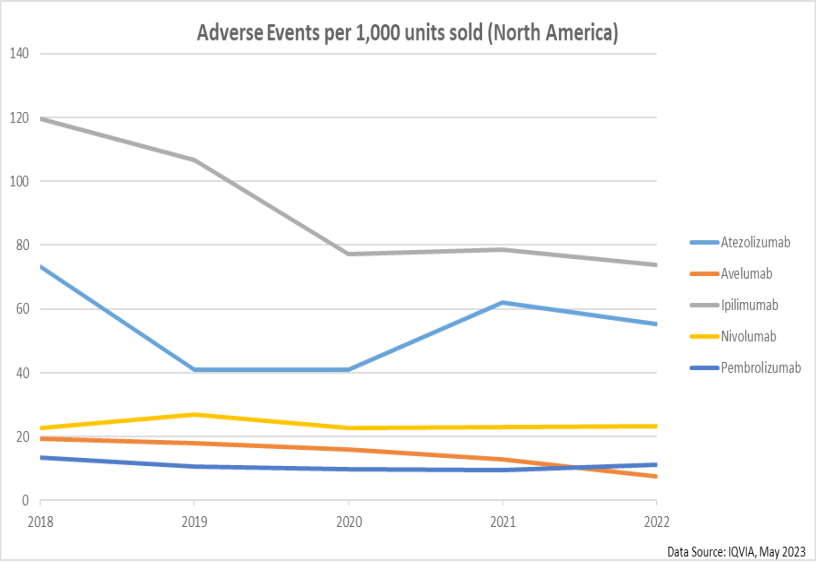

Figure 2: Adverse events per 1,000 units sold in North America.

The relative reported frequency per sales exhibited a low trend, necessitating normalization to a scale of 10,000 units sold. In the assessment of neuropathy reports, a prevailing downward trend was observed among most drugs. Atezolizumab displayed the highest reported neuropathy instances, succeeded by Ipilimumab. Conversely, Pembrolizumab consistently maintained a low rate of neuropathies per 10,000 sales (Figure 3). The initial disproportionality analysis was executed to compare the five drugs against the entire database, as per its intended methodology. This preliminary assessment unveiled statistically significant disproportionalities in adverse event reporting across all drugs. Particularly noteworthy were the outcomes concerning "Peripheral neuropathies NEC," with Avelumab exhibiting the highest likelihood of reporting (ROR 4.92, CI95% 3.62-6.70, $p<0.001$). Subsequent inferences ranked Atezolizumab as the second highest (ROR 3.60, CI95% 3.20-4.05, $p<0.001$), followed by Pembrolizumab (ROR 2.67, CI95% 2.45-2.91, $p<0.001$), Ipilimumab (ROR 2.16, CI95% 1.92-2.44, $p<0.001$), and, lastly, Novolumab (ROR 1.80, CI95% 1.64-.1.97, $p<0.001$) (Table 1; Figure 4).

Medication	Reported Peripheral Neuropathies (n)	Units Sold (2018-2022)
Avelumab	42	466.870
Ipilimumab	276	647.872
Atezolizumab	280	930.048
Nivolumab	462	5.859.631
Pembrolizumab	525	10.154.878

Table 1: Total reported adverse events related to peripheral neuropathy and units sold for each checkpoint inhibitor.

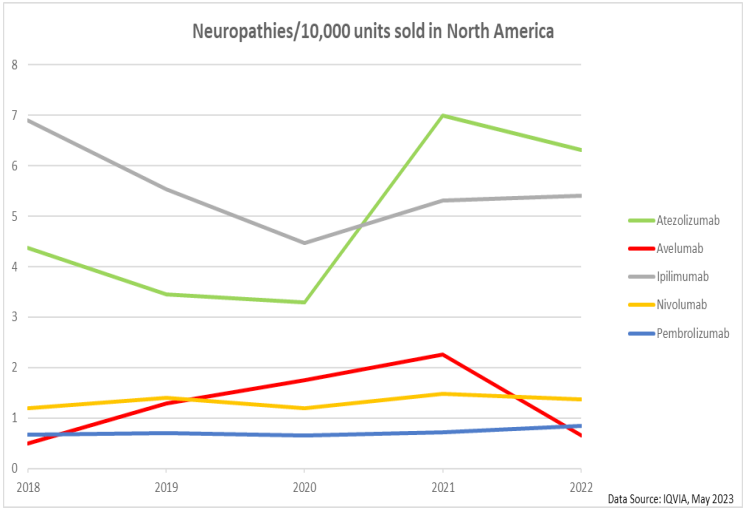

Figure 3: Neuropathies per 10,000 units sold in North America.

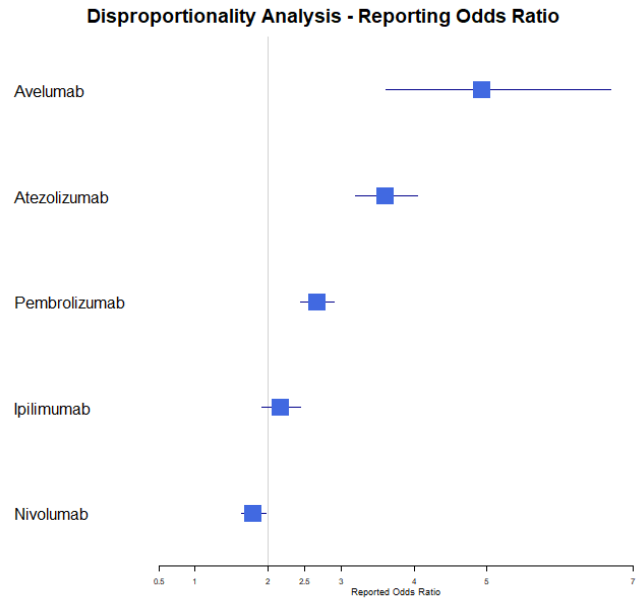

Figure 4: Disproportionality analysis by drug.

Upon conducting inter-drug comparisons, notable differences in reporting odds ratios (RORs) emerged, shedding light on distinct pharmacovigilance trends. Specifically, Atezolizumab displayed the highest reporting odds ratio when contrasted with Ipilimumab (ROR 1.66, CI95% 1.41-1.97, p<0.001), signifying a heightened likelihood of adverse event reporting associated with the former. Following suit, the analysis revealed noteworthy RORs for Pembrolizumab versus Nivolumab (ROR 1.48, CI95% 1.31-1.68, p<0.001), and Pembrolizumab versus Ipilimumab (ROR 1.23, CI95% 1.06-1.42, p<0.001). However, it is noteworthy to mention that none of the comparative analyses reached the predefined ROR threshold of 2, which was utilized as a determinant for identifying disproportional reporting (Table 2; Figure 5). In the final phase of our analysis, we pursued a comparative assessment of each individual drug against the collective group of five medications encompassed within this study. Notably, the only drug that exhibited a Reporting Odds Ratio (ROR) surpassing the threshold of 2 was Avelumab (ROR 2.11, CI95% 1.55-2.88, p<0.001). Conversely, each of the remaining drugs manifested RORs below the specified threshold, with Atezolizumab demonstrating an ROR of 1.63 (CI95% 1.43-1.86, p<0.001), Pembrolizumab registering an ROR of 1.18 (CI95% 1.07-1.32, p<0.001), Ipilimumab yielding an ROR of 0.89 (CI95% 0.78-1.02, p=0.02), and Nivolumab displaying an ROR of 0.66 (CI95% 0.59-0.73, p<0.001) (Table 2; Figure 6).

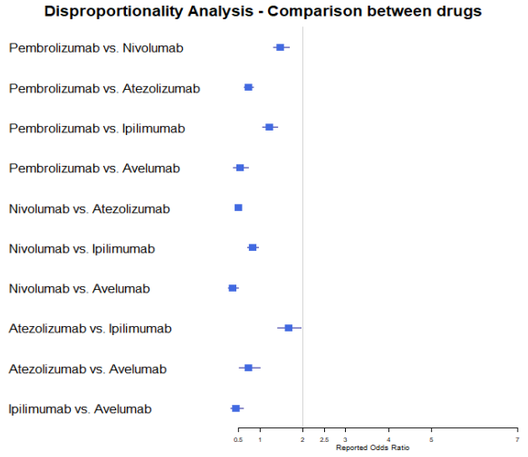

Figure 5: Disproportionality analysis, inter-drug comparisons.

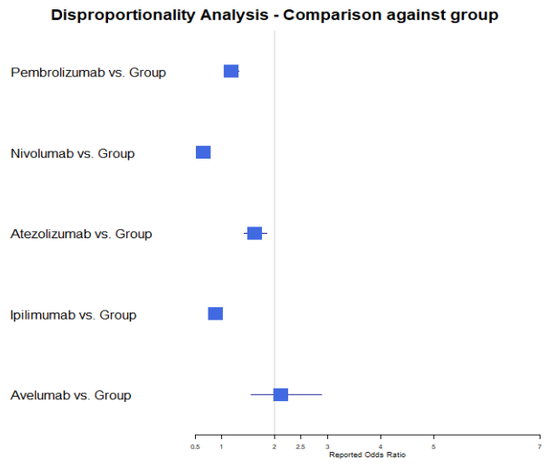

Figure 6: Disproportionality analysis, drug against group.

Comparison	ROR	Lower IC 95%	Upper IC 95%	P-Value
Each checkpoint inhibitor analysis				
Avelumab	4.92	3.62	6.70	<0.001
Atezolizumab	3.60	3.20	4.05	<0.001
Pembrolizumab	2.67	2.45	2.91	<0.001
Ipilimumab	2.16	1.92	2.44	<0.001
Nivolumab	1.80	1.64	1.97	<0.001
Inter-drug Analysis				
Pembrolizumab vs Nivolumab	1.48	1.31	1.68	<0.001
Pembrolizumab vs Atezolizumab	0.74	0.64	0.86	<0.001
Pembrolizumab vs Ipilimumab	1.23	1.06	1.42	<0.001
Pembrolizumab vs Avelumab	0.54	0.39	0.74	<0.001
Nivolumab vs Atezolizumab	0.50	0.43	0.58	<0.001
Nivolumab vs Ipilimumab	0.83	0.71	0.96	0.001
Nivolumab vs Avelumab	0.36	0.26	0.50	<0.001
Atezolizumab vs Ipilimumab	1.66	1.41	1.97	<0.001
Atezolizumab vs Avelumab	0.73	0.52	1.01	0.016
Ipilimumab vs Avelumab	0.44	0.32	0.61	<0.001

Table 2: Reporting odds ratio of “Peripheral neuropathies NEC” qnd confidence intervals for a 95% level of significance.

Discussion

This study assessed peripheral neuropathies linked to CIs within the FAERS database. Examination of adverse event curves, encompassing neuropathies and general adverse events, unveiled a noticeable declining trend, prompting scrutiny and potential elucidation. One interpretation posits that physicians' acclimatization to these drugs over time may lead to reduced reported adverse events. Professionals could be more adept at managing recognized side effects of CIs, thus decreasing reported occurrences. This aligns with the Weber effect in pharmacovigilance: in 1984, Weber postulated that adverse event reporting of a drug peaks in the second year after its approval and subsequently declines [4]. Alternatively, health practitioners might opt not to report anticipated adverse events perceived as inherent to the drug, given established safety profiles. Given peripheral neuropathies' rarity, precise calculation of events per 10,000 units sold was essential for meaningful pattern detection. This meticulous analysis revealed Atezolizumab and Ipilimumab as prominent, with around sixfold higher neuropathy incidence than the other three drugs, despite low overall incidence rates. This aligns with the finds of the study by Ruggiero et al [6], which analyzed European pharmacovigilance databases and observed elevated peripheral neuropathy reports with atezolizumab relative to other ICIs, evident in both monotherapy and combination therapy with ipilimumab/nivolumab.

Notably, Pembrolizumab consistently maintained a low neurological adverse event rate over the evaluation period, reflecting stability. Conversely, Avelumab's safety profile displayed a distinct pattern, featuring a notable peak in reported neurological adverse events in 2021. This observation prompts inquiries into temporal reporting patterns and the underlying factors driving this surge. The disproportionality analysis indicated RORs exceeding 2 for all drugs except Nivolumab. While Harpaz et al [5] set the threshold at 2, other authors propose 1.0. Irrespective of the threshold chosen, it's evident that most drugs exhibit a disproportional frequency of reported peripheral neuropathies. Atezolizumab exhibited the highest reported peripheral neuropathies per units sold and the second-highest disproportionality. Conversely, avelumab had the highest disproportionality but the lowest neuropathies per units sold in 2022. Potential reasons include indications, combinations, or the Weber effect, considering their launch years (atezolizumab in 2016, avelumab in 2017). This underscores the significance of comprehensive evaluation across multiple metrics or perspectives, regardless of the underlying cause.

ICI-associated neuropathies constitute a prevalent neurological complication, often reported within the European database [6]. While infrequent, their clinical significance demands vigilant consideration from edical practitioners due to potential severity. Other authors have described cases of acute sensorimotor neuropathy and polyneuropathy linked to ipilimumab treatment [7,8]. As with any retrospective study, this investigation has inherent limitations that warrant acknowledgment. Reliance on secondary data sources, such as FAERS database, may introduce biases, data inconsistencies [9], or incomplete reporting [10]. To establish a more robust understanding of the safety profiles of CIs, future prospective studies and real-world data analyses are warranted. Additionally, exploring potential factors contributing to the observed variation in neurological adverse events, including patient characteristics and concomitant medications, may yield valuable insights for further refining therapeutic strategies. A significant bias to note in conducting disproportionality analysis between groups and drugs arises from its non-application to the complete dataset. In inter-drug and group analyses, the comparison is limited to the data of the comparator drug or group, potentially resulting in shifts in disproportionality analysis weights. In conclusion, this study adds to the growing body of evidence concerning the safety profiles of CIs, particularly in the context of neurological adverse events. The findings underscore the importance of vigilant pharmacovigilance practices and continuous evaluation of drug safety in clinical settings. A comprehensive understanding of the dynamics of adverse event reporting and management for this therapeutics is indispensable to guide future regulatory decisions and optimize the landscape of precision medicine. Further research endeavors and collaborations between clinicians, researchers, and regulatory authorities will facilitate the progress toward safer and more effective therapeutic interventions in the realm of oncology and immunotherapy.

Conclusion

The evaluation of CI adverse event curves revealed a notable downward trend, possibly due to physician habituation or underreporting of expected outcomes. Atezolizumab and Ipilimumab exhibited higher neuropathy incidence, while Pembrolizumab showed consistent low rates. The decline in neurological adverse events is encouraging, likely driven by improved monitoring and clinical practices. However, further investigation is warranted. The study provides valuable insights for precision medicine, but acknowledges limitations. Future prospective studies and consideration of patient characteristics are essential. Vigilant pharmacovigilance practices are crucial in oncology to optimize drug safety and enhance therapeutic interventions.

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