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Review Article

Evaluation of Neurological Safety Profile in the Use of Checkpoint Inhibitors: A Real-World Evidence Approach Based on Pharmacovigilance Data

Abrahao A[1], Tenorio PHM[2], Rodrigues M[2], Osvaldo J. M. do Nascimento[1*]

[1]Department of Neurology, Fluminense Federal University (UFF), Niteroi, Rio de Janeiro, Brazil

[2]Campinas State University (FCM-UNICAMP), Campinas, São Paulo, Brazil

*Corresponding author: Osvaldo J. M. do Nascimento, Department of Neurology, Fluminense Federal University (UFF), Niteroi, RJ, Brazil

Abstract

The use of immunotherapies based on the concept of checkpoint inhibitors is increasingly becoming a medical practice in oncology. These therapies target some specific factors, inhibiting them, blocking them to stop the multiplication of these altered cells and consequently the tumor. This study focused on the neurological safety profile of the most prescribed checkpoint inhibitors and traced a correlation between the use of these agents and the increase in neurological adverse events in the main indications. Examining pharmacovigilance databases and medication sales, the analysis found a correlation between reported neurological adverse events and medication usage. As the total number of adverse events increased, the number of neurological adverse events also rose linearly, emphasizing the importance of monitoring potential neurological effects. For the analysis of adverse event data, the databases of FDA (FAERS) and EMA (VigiAccess) were consulted, while sales data between 2018 and 2022 were extracted from the IQVIA Analytics databases. Among the studied checkpoint inhibitors (pembrolizumab, ipilimumab, nivolumab, atezolizumab, and avelumab), pembrolizumab had the lowest ratio of reported adverse events, suggesting a relatively safer profile.

Introduction

The evolution of science and therapeutic armamentarium in recent years has significantly modified the average life expectancy as well as the quality of life. In the Western world, and especially in the more developed world, cancer has become the leading cause of death, surpassing cardiovascular events. It is expected that by 2040 almost 30 million people worldwide will develop some type of cancer and that the number of cancer deaths will exceed 17 million [1]. Oncology has been, therefore, one of the areas of greatest investment in research and development. In the last decade there has been a significant advance in the treatment of numerous types of cancer, through the use of drugs based on immunotherapy. Several innovative molecules, the use of monoclonal antibodies, or blockers of immune co-receptors, have been a frequent part of the therapeutic arsenal, which is increasingly used. All of this has become possible through the study of an important function of the immune system, consisting of its ability to attack normal and abnormal cells in the body, that is, to act as a defense against external biological agents, as well as internal ones, as in the case of a cell. altered, or cancerous. Apparently, cancer cells use checkpoints to try to outwit the immune system. In this sense, more modern

immunotherapeutic drugs were designed and developed. These are the checkpoint inhibitors, whose most common denomination in the scientific literature, preserves the origin in English, regardless of the researched language, as "checkpoint inhibitors". Due to this prevalence of citation of the term in the world literature, the present work maintained the use of the term originally coined in English. These checkpoint inhibitors [2] target some specific factors, inhibiting them, blocking them to stop the multiplication of these altered cells and consequently the tumor.

In recent years, oncology has been the main target of investments in clinical research, consequently of the pharmaceutical industry, in the search for more agents that can exert some type of activity in the immune system. The phase 3 pipeline of these drugs has grown by more than 60% over the last 7 years, focusing on approximately 450 immunotherapies in more than 60 different types of mechanism of action. Therefore, the use of immunotherapies based on the concept of checkpoint inhibitors is increasingly becoming a medical practice in oncology [3]. The targeted immune activation, particularly the activation of T lymphocytes, leads to the risk of developing responses also directed towards healthy tissues. Knowing the safety profile of these drugs well to calculate the risk-benefit is essential. With this, it is necessary to understand the representativeness of these agents not only in the benefits brought in fighting cancer, prolonging life, improving the lives of patients and even the cure, but also the adverse events brought by this practice and the burden that this entails. can represent, mainly in our country, in its public and private representation.

The benefit and effectiveness of using checkpoint inhibitors, especially in oncology, is well established. Proven fact in the incorporation of them in the public and private sectors all over the world. In Brazil, so far these drugs are restricted to the complementary health system, most of them approved for several indications by the National Health Agency – ANS [4]. The use of these agents has been growing and with it the need to evaluate the possible adverse events arising from their use. Specifically, the present work aimed to research the most important databases in the world and in Brazil to show the neurological safety profile of the main checkpoint inhibitors sold worldwide [5-8]. Trace a correlation between the use of these agents and the increase in adverse events in the main indications. The difficulty still lies in the fact that although these drugs have a similar mechanism of action, the cancer to be treated varies greatly. Caveats need to be made, as the databases do not bring the clinical history of each patient, specific tumor staging, prognosis, comorbidities, concomitance of other treatments. For the present, the most prescribed and most sold checkpoint inhibitors worldwide were analyzed. Consequently, when analyzing the most important pharmacovigilance databases in the world, it is expected to find the reflection of the most prevalent adverse events. A more accurate analysis allows assessing the pattern of the five main most prescribed agents and whether any of these drugs could have a higher safety profile.

Mechanism of Action of Checkpoint Inhibitors

It is known that the immune system can recognize and react early against the development of tumors through an active process that basically has three phases: elimination, equilibrium, and escape [9,10]. However, even with this antitumor mechanism, some cells can circumvent this process by different mechanisms, among them through proteins present on the surface of T cells, generically called checkpoints [11]. Immunological checkpoints act as inhibitory signals that regulate inflammatory processes after T cell activation. Monoclonal antibodies capable of blocking such regulatory immunological targets as CTLA-4, PD-1 and PD-L1 have positive evidence in cancer immunotherapy and are called immune Checkpoint Inhibitors (ICIs) [12]. In 1987, the CTLA-4 checkpoint was described for the first time [13], where its expression was observed mainly on the surface of CD4+ and CD8+ lymphocytes [10]. CTLA-4 blockade by ICIs - such as ipilimumab - interferes with the initial stimulation of regulatory T cell proliferation and increases the amount of effector T cells, stimulating the immune response against the tumor, favoring tumor cell death [14]. PD-1 is a receptor expressed on the surface of multiple immune cells [15] and its ligand, PD-L1, is present on different types of tumor cells and/or immune cells [16]. ICIs with action on PD-1, prevent the binding of PD-L1 to its receptor, making the immune system capable of recognizing tumor cells [16-18]. Some examples of monoclonal antibodies that act in this pathway are Atezolizumab, Avelumab, Nivolumab and Pembrolizumab.

Data Analysis

For the analysis of adverse event data, the FAERS (FDA) and VigiAccess (EMA) databases were consulted, while sales data between 2018 and 2022 were extracted from the IQVIA Analytics databases. These consultations were carried out in May 2023, and the periods evaluated were from January 1, 2018, to December 31, 2022. A five-year analysis was then carried out because of the different launches of checkpoint inhibitors and consequently their prescription, sales and report of adverse events to the platforms. Five checkpoint inhibitors were selected: pembrolizumab, ipilimumab, nivolumab, atezolizumab and avelumab.

When comparing the events reported in the FAERS and VigiAccess databases, it was possible to observe, in a first analysis, that there is a greater number of events reported in FAERS. It was also observed that there is a correlation between the number of adverse events reported in FAERS and VigiAccess, with a Pearson coefficient of 0.95, indicating a strong correlation (Figure 1).
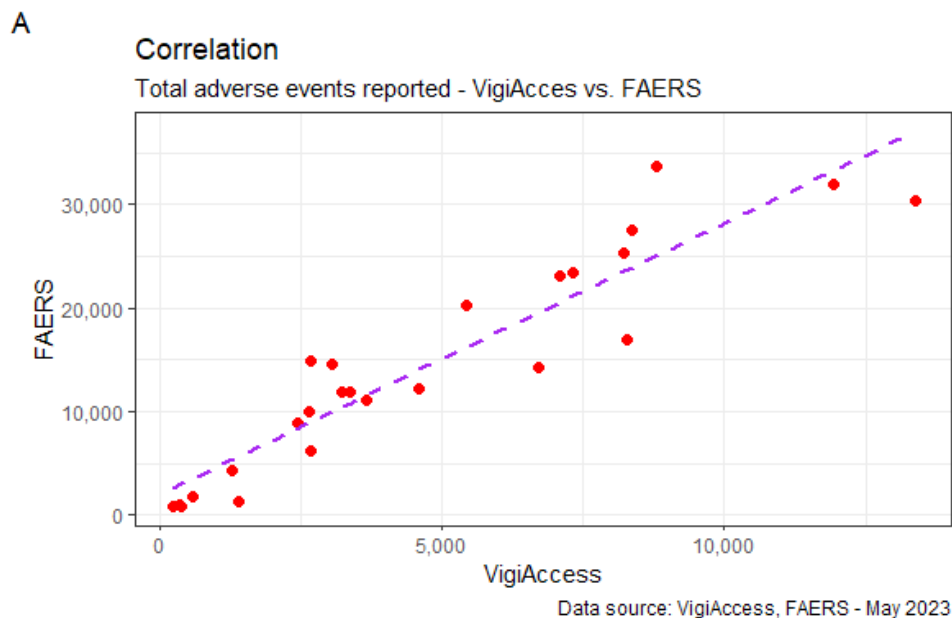
Figure 1: Correlation between reported events in FAERS and VigiAccess database.

It was also observed that, despite not being a linear increase, the number of adverse events reported increased along with the number of units sold in North America (Pearson=0.86) (Figure 2).
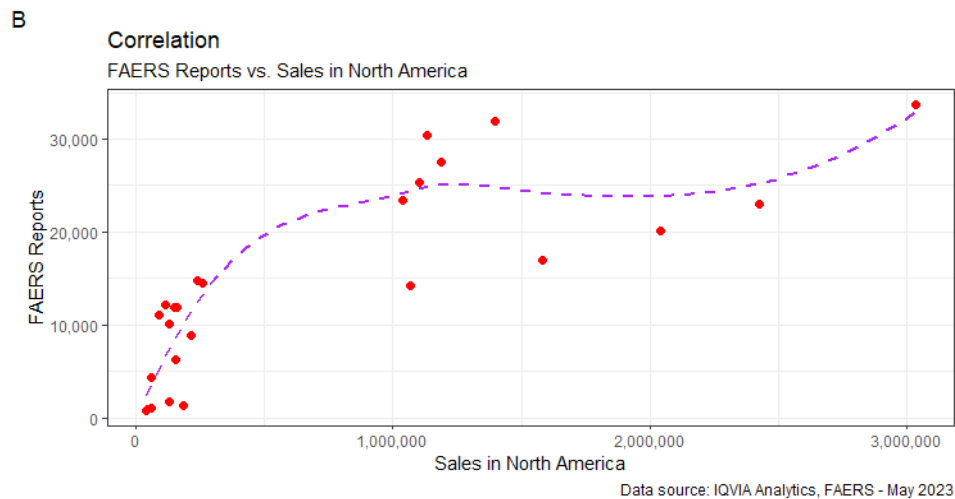

Figure 2: Correlation between reported events in FAERS and sales.

Finally, it was observed that as the total number of reported adverse events increases, the number of reported neurological adverse events increases, in a linear relationship with a Pearson coefficient equals to 0.99 (Figure 3).
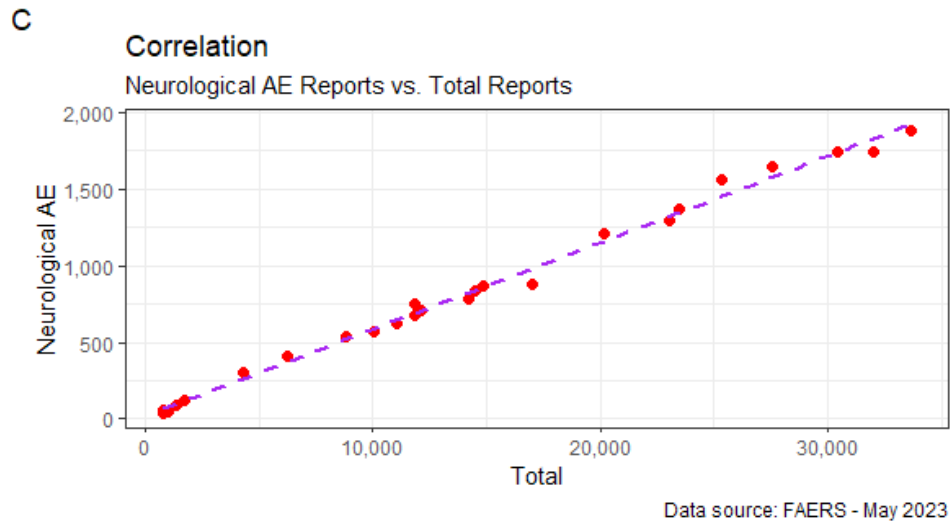
Figure 3: Correlation between reported neurological adverse events and total adverse events reported.

Between 2018 and 2022, the top-selling drug was Pembrolizumab, followed by Nivolumab. A possible justification for these numbers is that, in addition to more indications for use, these drugs are used in diseases with a higher incidence of adverse events (Figure 4).
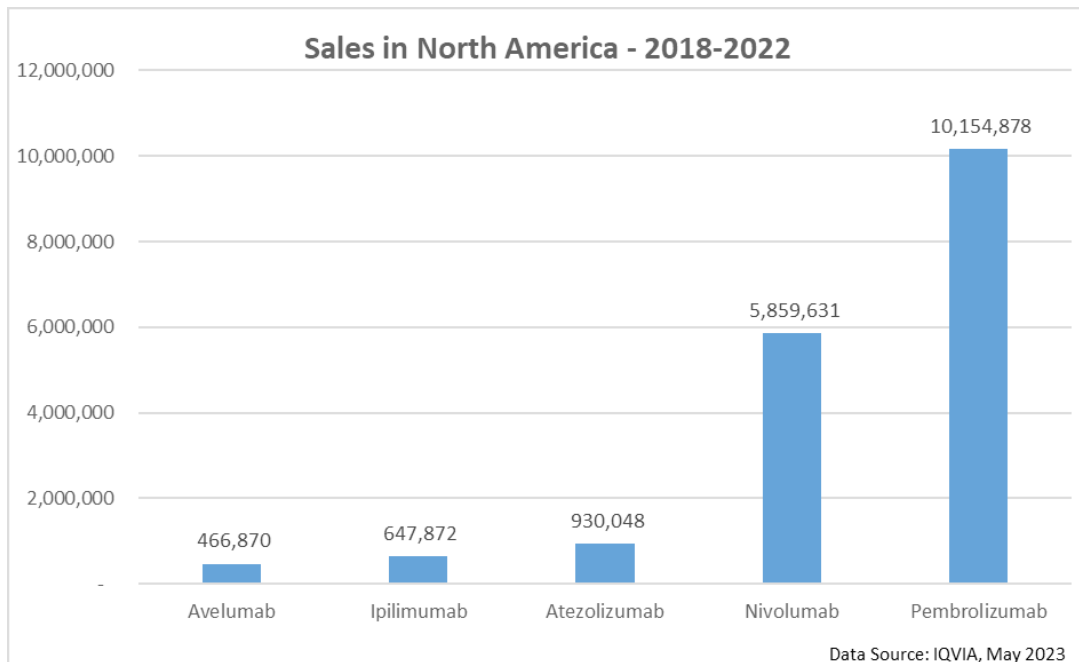

Figure 4: Total sales in North America between 2018 and 2022.

Since these drugs have multiple indications and different therapeutic schemes, heterogeneous patient pool and diseases covered with different incidences, the only possible measure of data standardization was the number of adverse events per unit sold. As the incidence of adverse events was rare, the number of adverse events per 1000 units sold in North America was chosen as the measure.

When evaluating which drugs have the most adverse events reported in the FAERS, regardless of the type of event or system involved, Ipilimumab has the highest incidence, followed by Atezolizumab. It was observed a downward trend for all drugs (Figure 5).
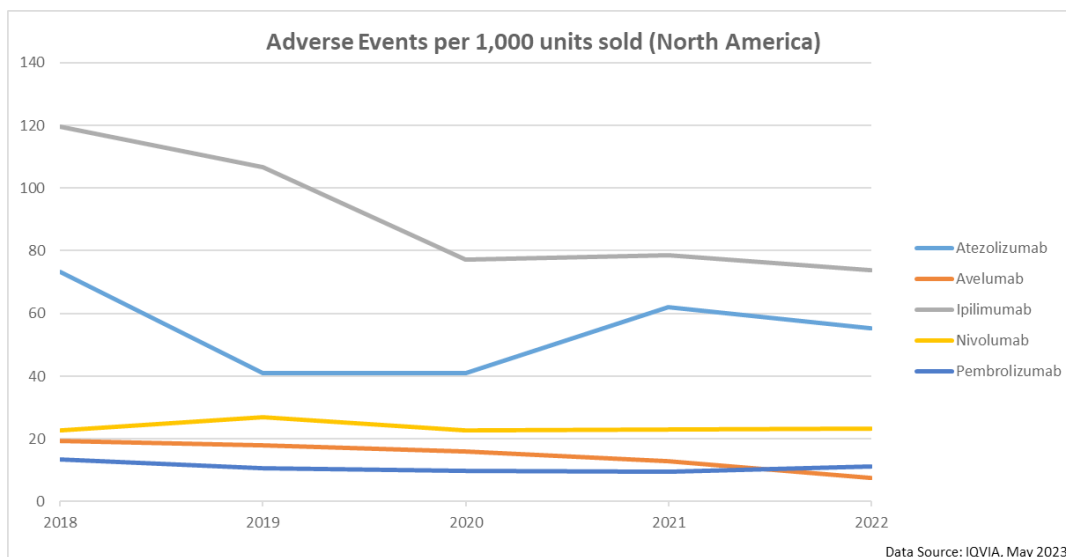

Figure 5: Adverse events per 1,000 units sold in North America.

When evaluating the incidence of neurological adverse events for every 1000 units sold, it was also observed that the drug with the most reported events was Ipilimumab, followed by Atezolizumab and Nivolumab. The drug with the lowest number of reported adverse events (both general and nervous system) was Pembrolizumab. A downward trend was also observed in this evaluation for almost all drugs (Figure 6).
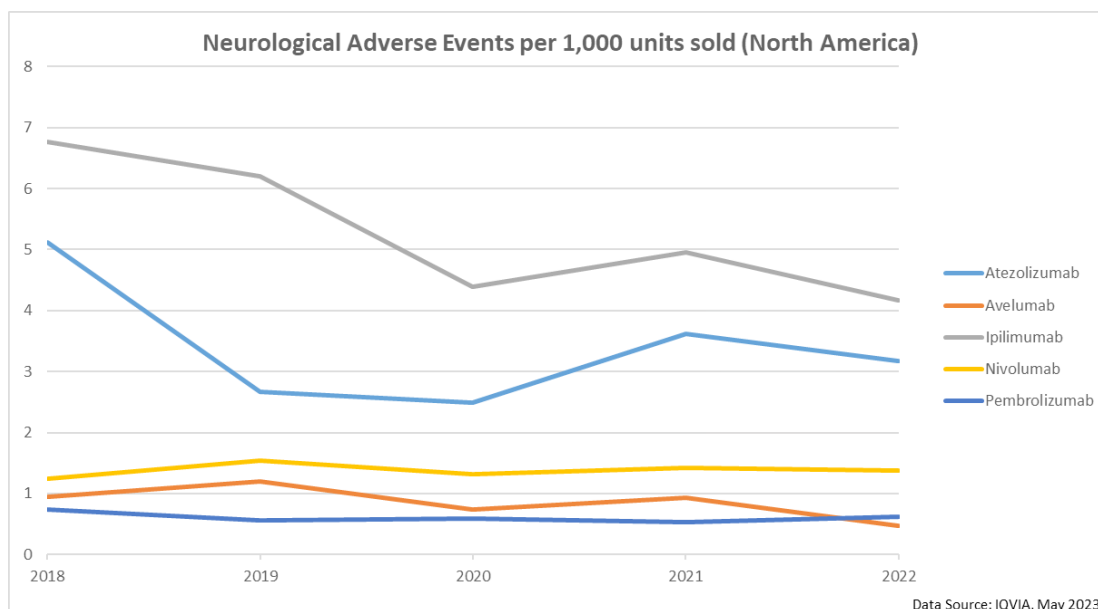

Figure 6: Neurological adverse events per 1,000 units sold in North America.

Discussion

Evaluating the curves for both general and neurological adverse events, it can be observed that there was a downward trend, possibly explained by the habituation of physicians to these drugs. Fewer adverse events may be occurring, but it may also be that health professionals have stopped reporting adverse events that they consider to be expected from the drug.

Although the number of reported adverse events was higher in 2018, it was still necessary to calculate them for every 1000 units sold. When evaluating the drug and the year in which more neurological adverse events occurred (Ipilimumab in 2018), the number was still less than 7 events per 1000 units sold, which suggests that these events are rare. When comparing the curve of general adverse events and adverse neurological events, an extremely similar curve is observed, which was expected, since its Pearson correlation coefficient was 0.99. Despite being the drug with the most units sold, Pembrolizumab was the one that had the fewest adverse events, both general and neurological. This suggests that this drug is, among checkpoint inhibitors, one of the safest. However, some considerations are necessary: in the present study, we did not evaluate the indications for the use of the studied medications. Thus, drugs that are used in more severe, more advanced diseases or that require association with other drug therapy may present these indications as a confounding factor. Nivolumab is cited as an example, which, in most cases, is used in combination. It should also be noted that Ipilimumab has a different mechanism of action from other drugs.

This study has, as a limitation, the fact that it does not separate the indications for use, underlying pathologies, total treatment time, severity of the initial disease, associated use of other drugs and topography of the disease. Furthermore, only a 5-year window was observed. It is important to emphasize that this analysis was based on physician reports of adverse events and this practice and education should be reinforced. It is mandatory there is and not country specific. But the lack of serious mechanisms of control and a severe regulatory endorsement could deny an important source of drug safety. Since oncology market analysis indicates a trend to increase the use of checkpoint inhibitors and the advent of new formulations with the same mechanism of action, future studies are needed to assess the trend of adverse event reporting curves. To determine the full safety pattern of checkpoint inhibitors other pharmacovigilance databases that were not the aim of the current analysis should be accessed, including country specific ones.

Conclusion

Checkpoint inhibitors have revolutionized oncology by enhancing the immune response against tumor cells. While their efficacy is well established, evaluating their safety profiles is crucial. This study focused on the neurological safety profile of the most prescribed checkpoint inhibitors. Examining pharmacovigilance databases and sales data, the analysis found a correlation between reported adverse events and medication usage. As the total number of adverse events increased, the number of neurological adverse events also rose linearly, emphasizing the importance of monitoring potential neurological effects. Among the studied checkpoint inhibitors (pembrolizumab, ipilimumab, nivolumab, atezolizumab, and avelumab), pembrolizumab had the lowest ratio of reported adverse events, suggesting a relatively safer profile. However, considering specific indications, therapeutic schemes, and patient characteristics is essential when interpreting these results. The study acknowledges limitations such as not evaluating specific indications, disease severity, and concomitant medications. Further research is needed to track the trend of adverse event reporting over time and address these limitations.

Prompt reporting of adverse events by healthcare professionals is crucial for ongoing drug safety monitoring. The study highlights the need for robust control mechanisms and rigorous regulatory oversight to ensure the safety of checkpoint inhibitors. With the projected increase in their use and the development of new formulations, continuous monitoring and assessment of adverse events are paramount. By conducting diligent surveillance, healthcare professionals can make informed decisions, refine treatment strategies, and maximize patient safety and therapeutic outcomes in the field of oncology. The integration of artificial intelligence (AI) can significantly enhance the process of adverse event reporting in healthcare, however, despite the potential of AI, medical reports remain essential in the process of drug safety monitoring. Healthcare professionals should receive continuous training for detecting and reporting adverse events. Without these reports, a trusty database of adverse events can never be structured.

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