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Original Research

Prevalence of immune-related systemic adverse events in patients treated with anti-Programmed cell Death 1/anti-Programmed cell Death-Ligand 1 agents: A single-centre pharmacovigilance database analysis

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Abstract ***Aim:*** The growing use of immune checkpoint inhibitors (ICIs) is associated with the occurrence of immune-related adverse events (irAEs). Few data are published on systemic, immunohaematological and rheumatic irAEs. In a pharmacovigilance database analysis, we screened for these irAEs and calculated their prevalence.
Patients and methods: Participants were recruited via *Registre des Effets Indésirables Sévères des Anticorps Monoclonaux Immunomodulateurs en Cancérologie* (REISAMIC)[1] a French registry of grade ≥2 irAEs occurring in ICI-treated patients. The pathologies of interest were systemic autoimmune and inflammatory diseases, rheumatic diseases and immune cytopenia.
Results: Out of 908 patients treated with anti-Programmed cell Death 1 (PD1)/anti-Programmed cell Death-Ligand 1 (PD-L1) agents (together with an anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) agent in 40 cases) between December 2012 and December 2016 at a single centre, 21 patients experienced systemic irAEs. The types and the prevalence of irAEs were as follows: immune thrombocytopenia (0.2%), Sjögren syndrome (0.3%), rheumatoid arthritis (0.2%), polymyalgia rheumatica (0.2%), psoriatic arthritis (0.2%), seronegative polyarthritis (0.7%) and sarcoidosis (0.2%). Patients with Sjögren syndrome or seronegative polyarthritis were more likely to have received combination therapy with ipilimumab (2.5% for both).
We described these 21 cases, together with nine additional cases from five other centres. Most irAE were moderately severe (grade 2, 63%). The median time to onset was 57°days (interquartile range (IQR) 24–117). The ICI was withdrawn in 12 cases, 25 patients (83%) received corticosteroids, and five patients (17%) received immunosuppressant/immunomodulatory agents. The irAEs resolved fully or partially in 28 cases (93%).
Conclusion: Although systemic, immunohaematological and rheumatic diseases are rarely associated with ICI use, the prevalence is higher when two ICIs are combined. Corticosteroids are often effective and may enable the continued administration of ICIs. Studies designed to identify at-risk patients are warranted.

1. Introduction

Immune checkpoint inhibitors (ICIs), such as antagonistic monoclonal antibodies against cytotoxic T-lymphocyte antigen 4 (CTLA-4) such as ipilimumab, programmed death-1 (PD1) such as nivolumab and pembrolizumab and programmed death ligand-1 (PD-L1) such as atezolizumab, durvalumab, and avelumab are effective treatments for a growing list of cancers (initially in advanced melanoma, followed by non-small cell lung carcinoma, renal cell carcinoma and Hodgkin's lymphoma). However, ICI use is associated with the development of immune-related adverse events (irAEs). This type of toxicity is expected, because immune checkpoints: (1) have an important role in immune self-tolerance and (2) are involved in the pathophysiology of autoimmune diseases [1,2]. Grade 3–4 irAEs occur in 10–15% of patients treated with an anti-PD1 agent alone, 20–30% of patients treated with an anti-CTLA-4 agent alone and 55% of patients treated with both at the same time [3]. Anti-PD-L1 agents seem to be tolerated at least as well as anti-PD1 agents. The most frequent irAEs (10–15% of events) are skin disorders (pruritus, rash and vitiligo), digestive tract disorders (colitis and hepatitis) and endocrine disorders (hypophysitis and thyroiditis). Less frequently (<5%), irAEs may affect the lungs, the kidneys or the nervous system [4].

Although detailed descriptions of organ-specific irAEs are now becoming available, there are very limited data ascertainable on systemic, haematological and rheumatic irAEs – especially in patients treated with anti-PD1/anti-PD-L1 agents. Our current knowledge is mainly based on case reports and literature reviews. We took advantage of the implementation of a pharmacovigilance database at the Gustave Roussy (GR) cancer centre to collect data on systemic irAEs and thus to calculate their prevalence (which was previously unavailable for most of these types of events).

2. Patients and methods

The *Registre des Effets Indésirables Sévères des Anticorps Monoclonaux Immunomodulateurs en Cancérologie* (REISAMIC) is a French registry of grade ≥2 irAEs in ICI-treated patients set up at Gustave Roussy (GR) cancer centre (Villejuif, France). REISAMIC is based on two cohorts: a retrospective cohort (initiated in December 2012) of patients included in clinical trials,

[1] Registre des Effets Indésirables Sévères des Anticorps Monoclonaux Immunomodulateurs en Cancérologie, managed by the Gustave Roussy cancer centre (Villejuif, France).