Use of immune checkpoint inhibitors in patients with solid tumors and pre-existing autoimmune or inflammatory disease: real-world data

Virginia Calvo*, Marta Andrés Fernández, Ana Collazo-Lorduy, Fernando Franco, Beatriz Núñez & Mariano Provencio

1Servicio de Oncología Médica, Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, 28222, Spain
2Estudiante de Medicina, Universidad Autónoma de Madrid, Calle Francisco Tomás y Valiente 1, Cantoblanco, Madrid, 28049, Spain

*Author for correspondence: vircalvo@hotmail.com

Aim: Immune checkpoint inhibitors (ICIs) are a cornerstone in cancer treatment but they can induce immune-related adverse events (irAEs). Furthermore, patients with pre-existing autoimmune and/or inflammatory disease (AID) have been excluded from clinical trials. The objective of this study is to evaluate the efficacy and safety of ICIs in patients with cancer and AID. Materials & methods: This is an observational, retrospective study carried out at the Medical Oncology Department of Hospital Universitario Puerta de Hierro, Majadahonda, Madrid between January 2016 and December 2018. Results: A total of 202 cancer patients treated with ICIs were included, 15 (7.4%) of them had pre-existing autoimmune diseases. The most frequent pre-existing AID were thyroid diseases (33.3%): autoimmune hypothyroidism, Graves–Basedow disease and Hashimoto’s thyroiditis. Three patients had psoriasis, two antinuclear antibodies + polyarthritis, one rheumatoid arthritis, another latent autoimmune diabetes in adults, another systemic lupus erythematosus and the last one, a polymyalgia rheumatica. In this series, the majority of patients (73.33%) did not experience any flare up of their autoimmune disease. In patients who had AID flare up, this was treated with corticosteroids. The most frequent cause of immunotherapy discontinuation was tumor progression (40%). A total of 20% of patients had to discontinue immunotherapy due to toxicity. Conclusion: In our series, AID flare ups or irAEs in patients with pre-existing AID who receive immunotherapy are not very common and can often be controlled without interrupting treatment. Prospective studies are needed to establish the incidence of irAEs in patients with pre-existing autoimmune conditions, evaluate risk–benefit and elaborate management clinical guidelines in this population.

Keywords: cancer • discontinuation • flare-ups • immune-related adverse events • immune checkpoint inhibitors • immunotherapy • real-world data • risk–benefit • toxicity

Background
Immune checkpoint inhibitors (ICIs) have dramatically changed cancer treatment and have become standard of care in different types of cancer. ICIs include anti-programmed cell death 1 (anti-PD-1) agents (nivolumab and pembrolizumab), anti-programmed cell death-ligand 1 (anti-PD-L1) agents (atezolizumab, durvalumab and avelumab) and cytotoxic T lymphocyte-associated protein 4 inhibitors (anti-CTLA-4) like ipilimumab and tremelimumab. ICIs have been approved for the treatment of multiple advanced solid tumors, including melanoma, non-small-cell lung cancer (NSCLC) and urothelial cancer. In many other pathologies, these drugs are under investigation in other settings such as neoadjuvant and adjuvant treatments.

Ipilimumab, an anti-CTLA-4 antibody, was the first ICI approved by health authorities as a treatment for metastatic melanoma in patients without prior treatment, in 2011 [1]. After this, it has been studied in NSCLC or renal cell carcinoma. Ipilimumab was followed by antibodies that block PD-1 and PD-L1; the first of these was...
pembrolizumab, an anti-PD-1 antibody approved in 2014 for the treatment of metastatic melanoma [2] that was later also approved for NSCLC [3,4]. Nivolumab, another anti-PD-1, was initially approved for the treatment of melanoma [5], NSCLC [6,7] and renal cell carcinoma [8]. Atezolizumab is the only anti-PD-L1 and was approved in 2016 for the treatment of urothelial carcinoma [9]. Later, these PD-1/PD-L1 blocking antibodies have been shown to be effective in other types of tumors, such as head and neck cancer [10], Hodgkin lymphoma [11], hepatocellular carcinoma [12] or gastric cancer [13].

Since the mechanism of action is different, its combination has been studied and shown to have a synergistic effect, obtaining better results than monotherapy in melanoma. The combination of ipilimumab with nivolumab was approved by the US FDA in 2015 for the treatment of advanced melanoma [14] and has also been studied in the treatment of NSCLC with promising results [15]. The development of ICIs as a cancer treatment has brought with it the appearance of new toxicities, related to the activation of the immune system. These toxicities are known as immune-related adverse events (irAEs). The most frequent adverse effects are cutaneous, gastrointestinal, respiratory and endocrine (especially affecting the thyroid gland). These inflammatory and/or autoimmune manifestations are frequent, up to 70% for anti PD-1 and up to 90% for anti-CTLA-4. A recent meta-analysis has found that anti-CTLA-4 treatment causes high-grade irAEs in approximately 20–30% of patients [16]. Meanwhile, anti PD-1 treatment causes high-grade irAEs in less than 5% [17]. Due to the appearance of these irAEs, patients with autoimmune diseases (ADs) have been excluded from clinical trials with ICIs. For this reason, there is very little evidence about the impact that having a pre-existing AD can have on the selection, toxicity or efficacy of immunotherapy treatment.

Despite this, some studies show that although these patients often have exacerbations of their pre-existing AD, they can be easily managed, benefiting from the anti-tumor effect of ICIs. These studies, therefore, suggest that by balancing the overall risk–benefit, patients with pre-existing ADs can benefit from immunotherapy treatment.

The objective of this study is to evaluate the efficacy and safety of ICIs in patients with cancer and pre-existing autoimmune and/or inflammatory disease (AID).

Material & methods

Study design

This is an observational, retrospective and single-center study, carried out at the Medical Oncology Department of Hospital Universitario Puerta de Hierro, Majadahonda, Madrid. The list of patients was obtained through the HUPHM Pharmacy Service and it included all patients treated with immunotherapy (nivolumab, pembrolizumab, atezolizumab or ipilimumab) at the Medical Oncology Service of this hospital, between January 2016 and December 2018, inclusive. Inclusion criteria include all patients over 18 years old with a cancer diagnosis treated with immunotherapy according to assistential protocol or within a clinical trial.

Patients treated with different treatments (chemotherapy, tyrosin-kinase oral inhibitors) were excluded from our study. A total of 206 were reviewed (electronic medical record). Four had to be excluded because they did not meet the inclusion criteria.

Variables

Different variables were collected: age, sex, type of cancer, tumor stage, date of diagnosis, previous treatments, immunotherapy treatment, start date, end date, reason for discontinuation, immune-related adverse effects, date of last follow up or date of exitus.

Regarding the history of AD, the following data have been collected: type of AD, date of diagnosis, treatment and evolution of AD after treatment with immunotherapy.

Analysis

Statistical analysis was carried out using SPSS v25.

Results

A total of 206 medical records of patients treated with immunotherapy (nivolumab, pembrolizumab, atezolizumab or ipilimumab) were reviewed in the Medical Oncology Service, of the HUPHM, between January 2016 and December 2018, both years included. Of these, four were excluded because they did not meet the inclusion criteria, they had been treated with several immunotherapy drugs during the course of the disease and this could confound our results. Of the 202 patients diagnosed with cancer and treated with immunotherapy (monotherapy or in
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**Table 1. Characteristics of patients with previous autoimmune disease.**

| Patient | AID | Tumor | ICI | Line of treatment | Treatment duration | Discontinuation | Evolution AID | Exitus |
|---------|-----|-------|-----|-------------------|-------------------|----------------|---------------|--------|
| 1       | Autoimmune hypothyroidism | Renal cell carcinoma | Atezolizumab | 2 | 9 weeks | Toxicity | Exacerbation | No |
| 2       | Autoimmune hypothyroidism | Hepatocarcinoma | Nivolumab | 1 | 4 weeks | Toxicity | No changes | Yes |
| 3       | Graves-Basedow disease | Lung cancer: adenocarcinoma | Pembrolizumab | 1 | 6 weeks | Progression | No changes | No |
| 4       | Graves-Basedow disease | Hepatocarcinoma | Nivolumab | 2 | 15 weeks | Exitus | Exacerbation | Yes |
| 5       | Hashimoto thyroidis | Melanoma | Nivolumab + ipilimumab | 1 | 33 months | No changes | No |
| 6       | Psoriasis | Lung cancer: adenocarcinoma | Nivolumab | 1 | 12 months | Toxicity | Exacerbation | No |
| 7       | Psoriasis | Lung cancer: adenocarcinoma | Nivolumab + carboplatin/paclitaxel | 1 | 14 months | No changes | No |
| 8       | Psoriasis | Lung cancer: squamous cell carcinoma | Nivolumab | 1 | 12 months | Progression | No changes | No |
| 9       | ANA + polyarthritis | Lung cancer: adenocarcinoma | Pembrolizumab | 1 | 6 weeks | Exacerbation | No |
| 10      | ANA + polyarthritis | Timoma | Pembrolizumab | 2 | 3 weeks | Progression | No changes | Yes |
| 11      | Rheumatoid arthritis | Lung cancer: adenocarcinoma | Nivolumab | 2 | 14 months | Exitus | No changes | Yes |
| 12      | LADA | Melanoma | Nivolumab + ipilimumab | 5 | 13 weeks | Progression | No changes | No |
| 13      | Systemic lupus erythematosus | Renal cell carcinoma | Nivolumab | 2 | 7 months | Progression | No changes | No |
| 14      | Polymyalgia rheumatica | Hepatocarcinoma | Nivolumab | 1 | 18 months | No changes | No |
| 15      | Antinuclear antibodies (+ ENA, DNA) | Hepatocarcinoma | Nivolumab | 1 | 8 months | Progression | No changes | Yes |

AID: Autoinflammatory disease; ANA: Antinuclear antibody; ENA: Extractable nuclear antigen; ICI: Immune checkpoint inhibitor; LADA: Latent autoimmune diabetes in adult.

combination) at a certain point in the course of their disease, 15 were found to have a history of AD (7.4%). The characteristics of these 15 patients are described in Table 1.

A broad spectrum of pre-existing AD was reported. A total of five patients (33%) had a history of autoimmune thyroid disease, two (13%) patients had a history of autoimmune hypothyroidism, two (13%) of Graves Basedow disease and one (7%) of Hashimoto thyroiditis. A total of three (20%) patients had psoriasis, two (13%) antinuclear antibodies (ANAs) + polyarthritis, one (7%) rheumatoid arthritis, one (7%) latent autoimmune diabetes in adults Type diabetes, another systemic lupus erythematosus and another, polymyalgia rheumatica. The last case was a patient with positive ANAs but without established diagnosis.

Most of the patients (73.33%), did not experience any change or exacerbation of their AD during immunotherapy treatment, four (27%) of them had a worsening of prior manifestations.

The most frequent cause of discontinuation of immunotherapy treatment was the progression of tumor disease (40%), five patients of them died (33.3%). Only three of the 15 patients (20%) had to discontinue immunotherapy due to toxicity. In two of these patients, the toxicity was related to a worsening of prior manifestations of the pre-existing AD (psoriasis in one case and autoimmune hypothyroidism in another), while the toxicity of the third patient, hepatotoxicity, was not related to his underlying AD (autoimmune hypothyroidism).

Finally, it is important to note that five of the 15 patients (33.3%) did not present any immune-related adverse reaction, although two of these five patients experienced a worsening of their underlying disease.

Of the 202 patients, 114 (56.4%) experienced some irAE. Of those, 58 (50.9%) experienced only one, 33 (28.9%) experienced two and 23 (20.2%) experienced three or more (up to six).

Because, the degree of toxicity was not well recorded in the medical records in all cases, we considered serious irAEs those requiring hospital admission and/or interruption of immunotherapy treatment. Of the 114 patients
Table 2. Immune-related adverse events.

| irAEs                       | Nivolumab (n = 124) | Pembrolizumab (n = 26) | Atezolizumab (n = 10) | Ipilimumab (n = 5) | Nivolumab + ipilimumab (n = 24) | Nivolumab + daratumumab (n = 6) | Nivolumab + carboplatin/paclitaxel (n = 7) |
|-----------------------------|---------------------|------------------------|-----------------------|-------------------|-------------------------------|-----------------------------------|-------------------------------------------|
| Asthenia                    | 22 (17.7%)          | 12 (46.2%)             | 0                     | 0                 | 2 (8.3%)                      | 1 (16.7%)                         | 3 (42.9%)                                 |
| Hyporexia                   | 1 (0.8%)            | 3 (11.5%)              | 0                     | 0                 | 0                             | 0                                 | 0                                         |
| Rash                        | 4 (3.2%)            | 2 (7.7%)               | 1 (10%)               | 2 (40%)           | 5 (20.8%)                     | 0                                 | 2 (28.6%)                                |
| Pruritus                    | 6 (4.8%)            | 4 (15.4%)              | 0                     | 0                 | 6 (25%)                       | 1 (16.7%)                         | 2 (28.6%)                                |
| Vitiligo                    | 1 (0.8%)            | 0                      | 0                     | 0                 | 1 (4.2%)                      | 0                                 | 0                                         |
| Psoriasis                   | 1 (0.8%)            | 0                      | 0                     | 0                 | 1 (4.2%)                      | 0                                 | 1 (14.3%)                                |
| Infusional reaction         | 1 (0.8%)            | 0                      | 0                     | 0                 | 1 (4.2%)                      | 0                                 | 0                                         |
| Diarrhea/vomiting           | 3 (2.4%)            | 4 (15.4%)              | 0                     | 0                 | 4 (16.7%)                     | 0                                 | 0                                         |
| Liver toxicity              | 9 (7.3%)            | 2 (7.7%)               | 1 (10%)               | 0                 | 6 (25%)                       | 0                                 | 0                                         |
| Pancreatic toxicity         | 3 (2.4%)            | 0                      | 0                     | 0                 | 1 (4.2%)                      | 0                                 | 0                                         |
| Pneumonitis                 | 7 (5.6%)            | 2 (7.7%)               | 0                     | 0                 | 5 (20.8%)                     | 0                                 | 0                                         |
| Arthritis                   | 5 (4%)              | 3 (11.5%)              | 1 (10%)               | 0                 | 0                             | 0                                 | 1 (14.3%)                                |
| Neurotoxicity               | 5 (5%)              | 1 (3.8%)               | 0                     | 0                 | 0                             | 0                                 | 0                                         |
| Anemia                      | 2 (1.6%)            | 1 (3.8%)               | 0                     | 0                 | 0                             | 0                                 | 0                                         |
| Neutropenia                 | 3 (2.4%)            | 2 (7.7%)               | 0                     | 0                 | 0                             | 0                                 | 0                                         |
| Thrombocytopenia            | 1 (0.8%)            | 1 (3.8%)               | 0                     | 0                 | 0                             | 0                                 | 0                                         |
| Renal toxicity              | 1 (0.8%)            | 1 (3.8%)               | 0                     | 0                 | 2 (8.3%)                      | 1 (16.7%)                         | 0                                         |
| Thyroid toxicity            | 16 (12.9%)          | 2 (7.7%)               | 1 (10%)               | 0                 | 3 (12.5%)                     | 1 (16.7%)                         | 1 (14.3%)                                |
| Parathyroid toxicity        | 1 (0.8%)            | 0                      | 0                     | 0                 | 0                             | 0                                 | 0                                         |
| Mellitus diabetes           | 0                   | 1 (3.8%)               | 0                     | 0                 | 2 (8.3%)                      | 0                                 | 0                                         |
| Suprarrenal insufficiency   | 1 (0.8%)            | 0                      | 0                     | 0                 | 1 (4.2%)                      | 0                                 | 0                                         |
| Others                      | 3 (2.4%)            | 0                      | 0                     | 0                 | 2 (8.3%)                      | 0                                 | 1 (14.3%)                                |

irAE: Immune-related adverse event.

who presented any irAEs, 24 had to discontinue immunotherapy (11.9%). Of these 24 patients who had severe irAEs, 12 were receiving nivolumab as monotherapy and seven nivolumab + ipilimumab.

Table 2 shows the different irAEs that appeared with the different treatment schedules.

Discussion

ICIs represent an important new treatment modality for cancer patients. Despite the important clinical benefits of ICI therapy, these treatments can also cause a variety of irAEs. The mechanisms leading to irAEs are unclear, although irAEs caused by ICIs resemble AD. That is the reason why all the clinical trials leading to the approval of ICI therapy actively excluded patients with pre-existing active AD because of apprehension that these individuals might be at risk for treatment-induced irAEs.

The management of irAES according to the European Society for Medical Oncology guidelines depends on the grade. For grades 3 and 4, immunotherapy has to be permanently discontinued. Treatment with high-dose corticosteroids should be started promptly and other immunosuppressive treatments such as infliximab, micofenolato or ciclofosfamide should be considered, in case of deterioration under steroids. In grade 1 toxicity, immunotherapy can be continued adding other treatments for the toxicity. In grade 2, treatment is usually discontinued, corticosteroids can be started and treatment can be resumed, if toxicity improves under treatment [18].

Combination immunotherapy has only been approved for patients with metastatic melanoma. Treatment-related AEs were observed in 95% of patients. In 55% of patients, these AEs were of grade 3 or higher [19] The onset of grade 3–4 toxicities for either monotherapy with nivolumab or combination immunotherapy differs, as irAEs not only may develop earlier in combination therapy but also may start over a prolonged period of time.

The objective of this observational study of patients with cancer and pre-existing AD is to evaluate the efficacy and safety of ICIs.
Many patients who are diagnosed with cancer have a pre-existing AD, for example, approximately 14–25% of patients with lung cancer also have an AID [20]. However, in our series only 7.4% of patients with cancer treated with ICIs had a pre-existing AID. This low prevalence in our sample may be due to several factors. First, the use of immunotherapy in patients with pre-existing AD is not very widespread due to the lack of experience. The increased risk of irAEs, which can be unpredictable and potentially very serious, and the risk of AID symptom exacerbation (flare-ups) in patients with pre-existing AID has led these patients to be frequently excluded from immunotherapy clinical trials. For this reason, there is very little evidence and very little clinical experience in the use of immunotherapy in these patients. Second, our sample includes patients receiving immunotherapy within a clinical trial, whose exclusion criteria include suffering or having some autoimmune-based pathology.

In our study, we found that four of the 15 patients (26.67%) with pre-existing AID had autoimmune exacerbations. This percentage was lower to that observed in other series. Johnson et al. [21] retrospectively evaluated 30 patients with pre-existing autoimmune disease and metastatic melanoma. Of the 30 patients who received ipilimumab, 15 (50%) experienced irAEs or flare ups of their underlying AD. Leonardi et al. [20] retrospectively analyzed the safety of anti-PD-1 and PD-L1 antibodies (nivolumab, pembrolizumab or atezolizumab) in 56 patients with NSCLC and pre-existing AD. A total of 55% of patients developed a flare up and/or irAEs. Danlos et al. [22] compared 45 patients with underlying AD to 352 patients without AD who were treated with anti-PD-1 agents in the Registry of Severe Adverse Reactions to Immunomodulatory Antibodies Used in Oncology between 2014 and 2016. About 47.1% of the patients with AD experienced an AD flare up, 65.9% experienced an irAEs and 9.4% developed a grade 3/4 irAEs. In a recent review of 41 case reports published to date, in 65.6% of patient immunotherapy resulted in a flare up of the baseline disease; being severe and very severe in 22.7% of patients [23].

Of the four patients in our study with pre-existing AID that had flare ups, one was treated with atezolizumab, two with nivolumab and one with pembrolizumab, so we cannot think that a certain drug could interfere with previous AID more than another.

The most frequent cause of discontinuation of immunotherapy was not irAEs, as we might expect from patients with pre-existing AD, it was progression of tumor disease (40%). Only three of the 15 patients (20%) had to discontinue immunotherapy for toxicity. Despite the fact that five patients died during our follow-up period, no deaths occurred as a consequence of treatment.

On the other hand, although it is true that irAEs occurred (not related to pre-existing AID) in ten of the 15 patients (66.7%), most were mild and easy to control. Of the five patients (33.3%) who did not have any irAEs, two experienced worsening of their disease. Three patients (20%) did not present any irAE or not to their pre-existing AID. The incidence of irAEs observed in Johnson et al. did not exceed the incidence of irAEs found by other studies in a population without AID. In our study, 66.7% of patients with AID present irAEs.

Despite the limited information in this regard, some studies have concluded that ICIs can be used in patients with previous AID, since the potential risks do not seem to outweigh the benefit of these treatments. Khan et al. [24] observed that AID were relevant in NSCLC, 14% of patients with NSCLC had a concurrent AID and they could be treated with ICIs, since they observed that patients with AID present a mortality from cancer and from any cause similar to patients who do not have AID. In patients with melanoma and AID, Johnson et al. [21] concluded that ipilimumab treatment can be considered, always leading to close surveillance and monitoring of the patient, and the Menzies et al. study obtained a similar conclusion regarding anti-PD1 therapy [25].

This is a complex topic and our series is very heterogeneous with different types of tumors and different types of immunotherapy treatments described. Complex interactions could happen between all the conditions presented. Great caution must be taken before drawing conclusions as some combinations of cancer with AID may respond remarkably well and other subsets of patients may only accrue harm.

Conclusion

In our series, exacerbations or irAEs in patients with prior AD receiving immunotherapy treatment are not very common and can often be controlled without interruption of treatment. Administration of immunotherapy in cancer patients with a pre-existing controlled autoimmune condition seems safe with an adequate follow up and early onset of treatment once flare ups or irAES happen.

Prospective studies are needed to establish the incidence of irAEs in patients with pre-existing autoimmune conditions, evaluate the risk–benefit indexes and elaborate management clinical guidelines in this population.
Immune checkpoint inhibitor have dramatically changed cancer treatment and have become standard of care in different types of cancer.

The development of immune checkpoint inhibitors as a cancer treatment has brought with it the appearance of new toxicities, immune-related adverse events.

The most frequent adverse effects are cutaneous, gastrointestinal, respiratory and endocrine (especially affecting the thyroid gland).

There is very little evidence about the impact that having a pre-existing autoimmune disease (AD) can have on the selection, toxicity or efficacy of immunotherapy treatment.

By balancing the overall risk–benefit, patients with pre-existing ADs can benefit from immunotherapy treatment.

Most of the patients (73.33%), did not experience any change or exacerbation of their AD during immunotherapy treatment, four (27%) of them had a worsening of prior manifestations.

The most frequent cause of discontinuation of immunotherapy treatment was the progression of tumor disease.

Administration of immunotherapy in cancer patients with a pre-existing controlled autoimmune condition seems safe with an adequate follow up and early onset of treatment once flare ups or immune-related adverse events happen.

Author contributions
V Calvo analyzed and interpreted the patient data regarding the autoimmune diseases and the adverse events and wrote the article. MA Fernández collected all the data. A Collazo-Lorduy was a major contributor in writing the manuscript. F Franco contributed to the clinical interpretation of data. B Núñez collected data and helped with the writing. M Provencio contributed to the design and final interpretation. All authors read and approved the final manuscript.

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Ethical conduct of research
The authors state that both data collection and analysis have been carried out anonymously at all times, taking appropriate precautions to maintain patient confidentiality. When patients entered the Medical Oncology Department (Hospital Universitario Puerta de Hierro, Majadahonda, Madrid) they signed a document allowing us to use their electronic medical records for research purposes. This work has been classified by the Spanish Agency of Medicines and Health Products (AEMPS) as a postauthorization study with other designs different from the prospective follow up (abbreviated as EPA-OD), and has the favorable opinion of the Ethical Committee for Research with Medicines of the HUPHM and the Ethics Subcommittee of the Autonomous University of Madrid. Institutional consent for publication was obtained.

Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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