Supplement 1. Research Protocol

Review title
Use of Immune Checkpoint Inhibitor
s in the Treatment of Patients With Cancer and Preexisting Autoimmune Disease: A Systematic Review

Anticipated start date
May 2016

Review team members and their organizational affiliations

<table>
<thead>
<tr>
<th>Title</th>
<th>First Name</th>
<th>Last Name</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr.</td>
<td>Noha</td>
<td>Abdel-Wahab</td>
<td>Section of Rheumatology and Clinical Immunology, Department of General Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; Rheumatology and Rehabilitation Department, Assiut University Hospitals, Faculty of Medicine, Assiut, Egypt.</td>
</tr>
<tr>
<td>Dr.</td>
<td>Mohsin</td>
<td>Shah</td>
<td>Section of Rheumatology and Clinical Immunology, Department of General Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA</td>
</tr>
<tr>
<td>Dr.</td>
<td>Maria A.</td>
<td>Lopez-Olivo</td>
<td>Section of Rheumatology and Clinical Immunology, Department of General Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA</td>
</tr>
<tr>
<td>Dr.</td>
<td>Maria E.</td>
<td>Suarez-Almazor</td>
<td>Section of Rheumatology and Clinical Immunology, Department of General Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA</td>
</tr>
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Funding sources
None

Conflict of interest
None

Collaborators

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<th>Last Name</th>
<th>Affiliation</th>
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<tbody>
<tr>
<td>Dr.</td>
<td>Gregory F</td>
<td>Pratt</td>
<td>Research Medical Library at The University of Texas MD Anderson Cancer Center</td>
</tr>
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Background
The use of checkpoint inhibitor (CPI) therapy is rapidly expanding from its initial approval in melanoma to other solid and hematological malignancies, exponentially increasing the population of cancer patients that can potentially benefit from the immune antitumor effects of CPI. However, up to 80% of patients receiving these agents experience irAEs. Because of this high frequency, patients with preexisting autoimmune diseases have been excluded from the CPI clinical trials because of concerns of exacerbation of the underlying autoimmunity, and potential susceptibility to severe irAEs. As the use of CPI expands to more cancers, and becomes available to patients in the community at large, who may have increased
comorbidities compared to patients in trials, there will be an increased need to determine the risk-benefit ratio in cancer patients with preexisting autoimmune diseases.

**Review question(s)**
To summarize the evidence on adverse events reported in patients with cancer and a preexisting autoimmune disease treated with CPI therapy.

**Searches**
The following databases will be searched: Medline, EMBASE, Web of Science, PubMed ePubs, and the Cochrane Central Register of Controlled Trials (CENTRAL) with no language or any other restrictions. Reference lists of relevant studies will also be checked. Table 1 of Supplement 2 shows the Medline and EMBASE search strategies.

**Types of study to be included**
We will include original studies (case reports, case series, and observational studies), if they describe patients with cancer and an established diagnosis of autoimmune disease prior to receiving one of the CPI agents approved by the U.S. Food and Drug Administration (FDA) for treatment of cancer, and provide a detailed clinical description of each reported case. We will include studies written in languages other than English. We will also include cases published in abstract format. We will exclude studies reporting patients who fulfilled the diagnosis of an autoimmune disease after receiving the CPI therapy.

**Condition or domain being studied**
Any type of cancer.

**Participants/ population**
Patients of any age and gender

**Intervention(s), exposure(s)**
The exposure is treatment with any FDA approved CPI agents.

**Comparator(s)/ control**
Not applicable.

**Context**
We will include patients of any age and gender diagnosed with any type of cancer and any autoimmune disease as long as the autoimmune disease was diagnosed prior to starting the treatment with any FDA approved CPI agents.

**Outcome(s)**
**Primary outcomes**
Occurrence of adverse events related to the use of CPI in patients with preexisting autoimmune diseases, whether exacerbation of the underlying autoimmunity and/or de novo irAEs.

**Secondary outcomes**
Frequency of adverse events (autoimmune disease flare and/or de novo irAEs) per each individual autoimmune disease.
Synthesis of how the adverse events were managed.
Synthesis of the final clinical outcome and the tumor response to CPI treatment.

**Data extraction, (selection and coding)**
Titles and/or abstracts of studies retrieved will be screened independently by two review authors to identify studies that potentially meet the eligibility criteria. The full text of these potentially eligible studies will be retrieved and independently assessed for further eligibility by the same two review team members. Any disagreement between the two review members over study eligibility of particular studies will be resolved through discussion and adjudicated by a third reviewer (MLO).

A data extraction form will be created in an excel document to collect the following data for each eligible study: study characteristics (e.g. publication date, study design, number of patients reported), patient population characteristics (e.g. age, gender, type of cancer, preexisting autoimmune disease, and baseline treatment for the autoimmune diseases), exposure characteristics (e.g., duration since diagnosis of autoimmune disease till exposure to CPI, status and current treatment of the underlying autoimmune diseases at exposure to CPI, and type of CPI), and outcome characteristics (e.g. occurrence of any adverse events, management of adverse events including discontinuation of CPI if required, outcome of adverse events, tumor response to CPI, and number of deaths).

**Quality assessment**

To evaluate the quality of reporting, we will use the reporting guidelines from the International Society for Pharmacoepidemiology (ISPE) and the International Society of Pharmacovigilance (ISoP) for publishing adverse events reports. We will consider only the items reported by the guidelines as required information including: i) relevance of the title to the reported information, ii) adequate description of the patient (demographics, existing health condition, relevant past medical history, physical and laboratory abnormalities, and significant morbidity or mortality), iii) adequate description of the drug (identification of both the generic and trade names of the drug and the manufacturer, drug dosage, duration between drug administration and the reported adverse events, and concomitant therapy that could potentially contributes to the development of adverse events), iv) adequate description of the adverse events and their outcome, and v) discussion of the evidence supporting the causal association between the drug and the reported adverse events. Other items reported by the guideline as desirable or relevant information will not be considered for the quality assessment. Possible item ratings are yes, partially, or no.

The assessment will be carried out independently by two review team members (N.A. and M.S.) and any disagreement will be resolved through discussion until reaching consensus. When no consensus can be reached, we will ask a third party to adjudicate (M.L.O.).

**Strategy for data synthesis**

Data will be summarized using descriptive statistics, with median and ranges for continuous variables and frequencies and percentages for dichotomous variables. The results will be presented narratively and tabulated. The final report will follow the PRISMA statement.

**Analysis of subgroups or subsets**

We will compare the occurrence of adverse events (flare and/or de novo irAEs) between patients with active versus those with inactive autoimmune disease at baseline, patients on concomitant therapy with immunosuppressants at initiation of CPI versus those not on therapy, and patients receiving ipilimumab versus those receiving different class of CPI agents.

**Contact details for further information**

Maria E. Suarez-Almazor, Department of General Internal Medicine, Unit 1465, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA.
Tel: 713-745-4516; Fax: 713-563-4491.
Email: msalmazor@mdanderson.org