Myasthenia Gravis Related to Cancer Treatment with Anti-PD-1 Monoclonal Antibodies: Systematic Review and Meta-analysis

(Protocol)

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1. BACKGROUND

Neurological adverse events following cancer treatment with the new group of immune checkpoint inhibitor antibodies are rare, yet potentially fatal complications (Antonia et al. 2016; Hottinger 2016; Zimmer et al. 2016). Nivolumab and pembrolizumab, two human IgG4 anti-PD-1 (Programmed cell death protein 1) monoclonal antibodies, were approved for treatment of unresectable melanoma by the US Food and Drug Administration in 2014 and by the European Medicines Agency in 2015. Both drugs have since then been approved for treatment of other types of cancer. By binding to PD-1, an inhibitory cell surface receptor found on T-cells, nivolumab and pembrolizumab stimulate T-cells to engage in an immune response against cancer cells (Fessas et al. 2017; Pardoll 2012).

Immune checkpoint receptors play an important role in balancing immune reactivity between a relevant response to pathogens while preserving self-tolerability (Pardoll 2012). Inherent in the mechanism of action lies a potential risk for off-target effects related to reactivity against healthy tissue, i.e. immune-related adverse events such as myasthenia gravis. An increasing number of case report of myasthenia gravis related to nivolumab and pembrolizumab treatment have been published within the last few years; and Japanese study reported an incidence of myasthenia gravis of 0.12% among patients treated with nivolumab (Suzuki et al. 2017). Of note, several authors found evidence of concurrent or isolated myositis.

Diagnosing myasthenia gravis is usually straightforward as symptoms are quite characteristic, including fluctuation of ocular or bulbar symptoms and/or weakness of neck and proximal limb muscles (Gilhus 2016; Gilhus and Verschuuren 2015). The documentation of autoantibodies against neuromuscular junction proteins such as the acetylcholine receptor (AChR) or muscle-specific kinase (MuSK) strongly supports the diagnosis. In case of negative antibody titers, neurophysiological work-up and a positive response to treatment may be needed to verify the diagnosis. However, as outlined above, myasthenia gravis following treatment with immune checkpoint inhibitor antibodies is considered an immune-related adverse event; and hence its phenotype might differ from classical myasthenia gravis with respect to e.g. clinical presentation, neuromuscular junction antibodies, treatment response and prognosis. Further, the immunological response may not be limited to the neuromuscular junction; other components of the neuromuscular system might also be affected to varying degrees. This could complicate and prolong the diagnostic process, and in turn delay therapy.

Due to the rapidly increasing application of anti-PD-1 monoclonal antibodies (ref. needed), neurologists and other clinicians will encounter more and more oncological patients with neuromuscular symptoms suggestive of immune-related myasthenia gravis. Yet, up to this date no attempt has been made to summarize the literature on the salient features of this new neurological entity. We will therefore perform a systematic review, the first of its kind, in order to characterize the symptoms, clinical findings and laboratory results of presumed anti-PD-1 monoclonal antibodies associated myasthenia gravis, focusing on how to distinguish this disorder from other neuromuscular diseases (e.g. concurrent myositis).

1.1 Target condition

The target condition is signs of neuromuscular junction failure compatible with myasthenia gravis in patients treated with nivolumab or pembrolizumab monotherapy or one of these in combination with other immunological agents, e.g. the CTLA-4 inhibitor ipilimumab. We will investigate the potential overlap with other neuromuscular disease entities, such as myopathies or neuropathies, with regards to clinical and laboratory findings.

We consider the diagnosis of myasthenia gravis *likely* based on typical symptoms of ocular, bulbar and/or proximal weakness that fluctuate and/or intensify with repeated muscle activity. We consider the diagnosis *highly likely* if, in addition, autoantibodies against neuromuscular junction components are found in plasma samples and/or neurophysiological tests, i.e. single nerve fiber or repetitive nerve stimulation, show increased jitter or decrement, respectively. The diagnosis will be considered *possible* if laboratory test are inconclusive, and *unlikely* if distal muscle weakness is the only finding and/or laboratory findings point to axonal, demyelinating or muscular injury.

1.2 Index tests

The following will be considered as index tests: Clinical testing (Jolly's Test, Ice pack-test), pharmacological testing (Edrophonium test), blood plasma analyses (AChR-ab, MuSK-ab, CPK-level), neurophysiology testing (EMG, ENG, single nerve fiber stimulation, repetitive nerve stimulation), nerve or muscle biopsy.

1.3 Rationale

The rationale for conducting a systematic review on the presumed autoimmune neuromuscular adverse events related to treatment with anti-PD-1 monoclonal antibodies is based on a growing number of cases reported, which show overlapping symptomatology and laboratory tests indicating both neuromuscular dysfunction as well as myopathy. Investigating whether this heterogeneous group can be meaningfully classified into distinct subgroups (myasthenia gravis, myopathy, neuropathy etc.), or if the conditions are multifaceted with overlapping pathophysiology, is an important first step for developing and evaluating an optimal treatment strategy.

2. OBJECTIVES

2.1 Primary objective

Using the PICO approach, we have phrased the following primary research question:

In patients treated with an anti-PD-1 monoclonal antibody for disseminated cancer or melanoma, who develop neuromuscular symptoms or who have pre-existing neuromuscular symptoms that become more pronounced following anti-PD-1 monoclonal antibody therapy (P), do neurological examination and laboratory workup, including neurophysiology and antibody titers, (I) sufficiently discriminate between neuropathies and myopathies, including myositis, on one hand (C) and neuromuscular junction failure compatible with myasthenia gravis on the other (O)?

2.2 Secondary objectives

In addition, we have phrased the following secondary research questions:

- Do patients treated with an anti-PD-1 monoclonal antibody for disseminated cancer or melanoma (P), who fulfill clinical and laboratory criteria for anti-PD-1 monoclonal antibody-associated myasthenia gravis (I), respond better, similar or worse to treatment with pyridostigmine and immunomodulation (C) than patients with myasthenia gravis in general (O)?

- Do patients treated with an anti-PD-1 monoclonal antibody for disseminated cancer or melanoma (P), who fulfill clinical and laboratory criteria for anti-PD-1 monoclonal antibody-associated myasthenia gravis (I), have a better, similar or worse prognosis with respect to their myasthenia (C) than patients with myasthenia gravis in general (O)?

3. METHODS

3.1 Criteria for considering studies for this review

3.1.1 Types of studies

We will evaluate all case reports, cross-sectional or longitudinal, retrospective or prospective observational studies as well as interventional trials, and, if available, meta-analyses and reviews, reporting on patient history of neuromuscular symptoms following treatment with anti-PD-1 monoclonal antibodies.

We will include only articles that allow assessment of patient data at the single-subject level. We will exclude articles that concern patients already used in another article by the same authors (or the same institution). We will include studies published in English and listed in Medline (PubMed), Cochrane Central Register of Controlled Trials (The Cochrane Library), and ClinicalTrials.gov without any date limit.

3.1.2 Participants

Adults (age ≥ 18 years) who have received anti-PD-1 monoclonal antibody therapy for disseminated cancer or melanoma, regardless of prior or concomitant therapy, presenting in health care facilities with neuromuscular symptoms, i.e. of peripheral nervous system (PNS) etiology, will be included. We will include patients irrespective of co-morbidities and previous history of neuromuscular diseases.

3.1.3 Index tests

See above (1.2).

3.1.4 Target conditions

See above (1.1).

3.2 Search methods for identification of studies

3.2.1 Electronic searches

We will search the following databases for relevant English literature with no date limit, and the search will be updated shortly before submission of the planned manuscript in order to include the newest references: Medline (PubMed), Cochrane Central Register of Controlled Trials (The Cochrane Library), and ClinicalTrials.gov.

We will use the following search terms: (”Nivolumab” or “Pembrolizumab” or “PD-1 inhibitor” or ”checkpoint inhibitor”) and (”myasthenia” or ”myositis” or ”myopathy” or ”neuromuscular” or ”neuropathy” or ”neuritis” or ”weakness” or ”AChR” or ”anti-MuSK” or ”EMG” or “ENG” or ”single nerve fiber”). Non-English literature will be included only if an English abstract is available and a reliable translation of the manuscript into English is possible. The references of relevant articles will be manually searched to identify additional articles. Further, articles will be cross-referenced using the ‘cited by’ function on PubMed.

The search strategies (including MeSH headings for searches in PubMed) will be saved and recorded in an appendix.

3.3 Data collection and analysis

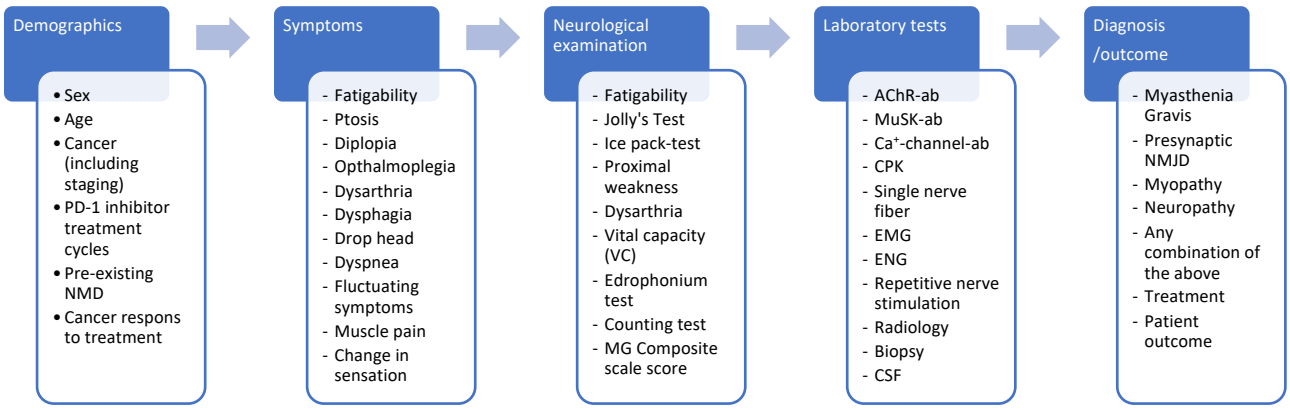
3.3.1 Selection of studies

A comprehensive literature search will be performed as outline above. Titles will be reviewed first, followed by evaluation of the abstracts with titles suggesting that a study might be of relevance. Then eligible studies will be identified on the basis of their full text. Of note, we will only include studies that provide data on the single subject level (i.e. individual patients); thus, studies reporting solely on group level data will be excluded. Studies reporting on myocarditis only will not be included. The initial selection and further review will be performed by SJC and AJ. Disagreement on whether to include a study will be settled by DK. We will use proprietary reference manager software to manage the large number of studies, and we will document the study selection in a detailed flow chart.

3.3.2 Data extraction and management

Following identification of relevant studies, AJ and SJC will independently extract the relevant information from each study. We will record 1) journal name and Vancouver-style reference, 2) study

design (e.g. systematic review, cross-sectional study, case report, cohort study), 3) method of recruitment (e.g. prospective or retrospective), 4) study setting, 5) characteristics of the patient population (e.g. age, gender, co-morbidities, cancer diagnosis, PD-1 inhibitor therapy regime and cycles). More specifically, we will extract information related to the following categories; demographics, symptoms, neurological examination, laboratory tests, diagnosis and outcome (details outlined in figure below). This information will be stored in a dedicated database. The review will be reported following the PRISMA criteria.



3.3.3 Assessment of methodological quality

We will assess the relevance and timing of the clinical and laboratory workup, as well as the conclusions that the authors arrive at. Also, we will assess whether the authors provide relevant discussions on differential diagnoses. Further, we will assess whether the studies declare the level of expertise of the physicians responsible for the diagnostic workup; were neurologist specialized in neuromuscular junction disorders consulted or in charge of the diagnostic workup?

3.3.4 Statistical analysis and data synthesis

Depending on the results of the literature search and review, we will propose to conduct a meta-analysis on available numerical data. If possible, odds ratios for laboratory tests on patients diagnosed with myasthenia gravis will be performed.

3.4 Funding

None.

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