Identification of Outcome Domains in Immune Checkpoint Inhibitor-Induced Inflammatory Arthritis and Polymyalgia Rheumatica: A Scoping Review by the OMERACT irAE working group

Abstract

Introduction: Immune checkpoint inhibitors (ICI), increasingly used cancer therapeutics, can cause off-target rheumatic inflammatory effects, including inflammatory arthritis (ICI-IA) and polymyalgia rheumatica (ICI-PMR). There are no validated classification criteria or outcome measures for rheumatic irAEs, and adaptation of treatment recommendations from their corresponding rheumatic diseases may not be appropriatesince pathogenesis may not be similar and interference with ICI efficacy may play a role.. We summarized clinical descriptors of ICI-IA and ICI-PMR and aggregated domains used for these conditions, in order to supportthe development of a core set of domains.

Methods: We searched through 4 electronic databases through March 2021 to identify all studies that provide both clinical descriptions and domains relevant to ICI-IA and ICI-PMR. Domains were mapped to core areas, such as pathophysiological manifestations, life impact, resource use and longevity/survival, as suggested by the OMERACT 2.1 Filter.

Results: We identified 69 publications, over a third of which utilized non-specific diagnoses of “arthritis,” “arthralgia,” and/or “PMR”. Other publications provided the number, the distribution and/or names of specific joints affected, while others labeled the irAE as the corresponding rheumatic disease, such as rheumatoid arthritis or spondyloarthritis. Most distinct domains

mapped to the pathophysiology/manifestations core area (24 domains), such as signs/symptoms (12 domains), labs (6 domains) and imaging (5 domains) with one harm domain of adverse effects from irAE treatment. Forty-three publications also referenced irAE treatment, 35 subsequent response, and 32 tumor response.

Conclusion: There were several domains mapped to the pathophysiologic manifestations core area, although most publications highlighted domains evenly distributed among the other core areas of life impact, longevity/survival and resource use.

Introduction

Immune checkpoint inhibitors (ICI) have been revolutionary for the treatment of cancer by enhancing Tcell-mediated anti-tumor responses[1]. However, in doing so, they can cause off-target inflammation of various organ systems, which are termed immune-related adverse events (irAE). Many irAE resemble *de novo* autoimmune diseases, such as inflammatory arthritis presenting like rheumatoid arthritis (RA) and spondyloarthritis[2–4], or sicca syndrome similar to primary Sjogren's syndrome[5,6]. These rheumatic irAE can be associated with significant morbidity, lower quality of life and can impact the ability of patients to continue their ICI therapy. Treatment of such irAE often follows treatment recommendations of *de novo* rheumatic diseases. It is not fully known, however, how closely the pathogenesis of irAE corresponds to *de novo* rheumatic disease, as some publications have identified notable differences[7–9]. Furthermore, clinical characteristics and response to immunosuppression in ICI-inflammatory arthritis (ICI-IA) are different than in RA, with the majority of ICI-IA patients having seronegative disease, higher prevalence of tenosynovitis, and often require higher glucocorticoid doses[10]. Thus, it is unclear if the domains used to evaluate disease and guide treatment of *de novo* rheumatic diseases, including RA could be adapted to the treatment of irAE such as ICI-IA. Furthermore, the patient population used to derive the "treat-to-target" strategy in RA is vastly different than those who develop ICI-IA, as the latter are actively being treated for a malignancy. To conduct high quality observational studies or clinical trials, it is critical to have well-characterized disease definitions and identify relevant domains that should be measured longitudinally[11]. As a first step towards this end, we reviewed the literature to identify diagnostic features and domains that have been described for ICI-IA and ICI-PMR, the most frequent rheumatic presentations observed in ICI-treated patients. Therefore, in this study, we aimed to: 1)

describe how ICI-IA and ICI-PMR have been categorized in the literature, and 2) identify relevant domains in ICI-IA/PMR that have been reported in prior clinical studies to inform the development of a core set of domains for future ICI-IA trials.

Methods

This scoping review was performed in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Review guidelines. The study protocol was pre-specified and registered in advance with the Open Science Framework (DOI 10.17605/OSF.IO/G68PE).

Eligibility criteria

We included studies describing adults (aged 18 years or older) with arthralgia, inflammatory arthritis, and/or polymyalgia rheumatica attributable to ICI that also reported at least one domain. All published peer-reviewed, full-length, randomized-controlled trials and both prospective and retrospective observational studies involving patients with either ICI-IA and/or ICI-PMR were included. Given the relative novelty of this disease entity, we also included qualitative studies and case series of at least three patients, which we felt was an adequate number of patients to provide meaningful data for domain selection. We excluded studies reporting on patients with rheumatic irAE that was not classified as ICI-IA or ICI-PMR, as well as those with preexisting autoimmune diseases. We also excluded case reports or case series with <3 patients, editorials, guidelines, reviews without original patient data, oncologic clinical trials, and pharmacovigilance studies.

Information Sources

To identify all available literature relevant to our aims, we performed a search in Medline (using PubMed), EMBASE, Cochrane and CINHL databases through an end date of March 19, 2021.

Search Strategy

The search protocol (see Supplementary Material for full protocol) was developed by the OMERACT (Outcome Measures in Rheumatology) irAE working group, which included clinicians, researchers, and representatives from OMERACT. Major search terms included "PD-1/PDL-1," "CTLA-4," "checkpoint inhibitor," "immunotherapy," drug names, AND "arthritis," "arthralgia," "polymyalgia rheumatica," "rheumatic," and "musculoskeletal." Our search was restricted to humans and the English language.

Study selection

Using Covidence software, all search results were screened, and duplicates were removed. Prior to screening, the study protocol was discussed amongst members of the OMERACT irAE working group. Using the eligibility criteria, 4 screeners (NG, NC, SW, WvB) independently screened a random sample of the total search results to ensure accurate screening protocol and understanding of eligible studies. Queries were discussed prior to moving forward with review of all studies. Two of the four reviewers screened each title/abstract, and a third reviewer was responsible for resolving conflicts.

Data charting process

Two different reviewers extracted the above data from each study, and disagreements in the extracted data were resolved by discussion. One reviewer (NG) did a final review of all extractions for accuracy and completeness.

Data items

Data extracted from the selected studies included study characteristics (author, year of publication, journal, country of first author, and study design), a rheumatology co-author (yes/no), number of patients with *de novo* irAE, number of patients in study with pre-existing rheumatic conditions to be excluded, and patient demographics (mean age, sex distribution, race/ethnicity, cancer type/stage), ICI treatment regimen, other past therapies for cancer, information about the rheumatic irAE such as onset (weeks) and characterization, duration of follow-up, treatments, and all reported domains, both specific to the rheumatic irAE or not. Oncologic domains, if available, were also included. Instruments used to measure domains were extracted separately for future use.

Synthesis

Clinical characteristics of ICI-IA and ICI-PMR were grouped into thematic categories. The number of included publications utilizing each characterization category to describe the irAE was tabulated. Clinical descriptions not fitting one of these categories were also collected, and the number of publications using those descriptors was tallied. Domains identified from the selected publications were mapped to core areas in accordance with the OMERACT 2.1 Filter[12] with some additional core areas relevant to this patient population. Some core areas were

subdivided into domains such as symptoms/signs, laboratory findings, imaging, etc. The number of included publications for each reported domain was tabulated.

Results

Search Results

Our search strategy identified 6,324 references, and 1,326 duplicate references were removed by the software (**Figure 1**). Of the 4,998 titles and abstracts that were screened, 4,811 were excluded due to lack of relevance. Of the 186 publications that were assessed for full-text eligibility, 117 publications were excluded. The primary causes of ineligibility were lack of description of ICI-IA and ICI-PMR (41 publications), inappropriate article type (39 publications), <3 relevant patients (19 publications), and no outcome reported (9 publications) (**Figure 1**). Four publications were excluded for reporting only patients with pre-existing rheumatic disease. Overall, 69 were included in data synthesis (see **Supplement** for full list).

Characteristics of publications and participants

The included publications were published between 2011 and 2021 from several countries: United States of America (31 publications), France (9 publications), Canada (6 publications), Australia (5 publications), Netherlands (4 publications), Spain (4 publications), Italy (3 publications), Germany (2 publications), China (2 publications), Greece (1 study), Japan (1 study), and the United Kingdom (1 study). Most studies were retrospective (12 case series and 45 retrospective observational studies), and 12 studies were prospective cohorts. A rheumatology co-author was present in 41 (59%) publications. There was one qualitative study[13]. Twenty publications included patients with pre-existing rheumatic disease along with patients developing

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de novo irAE and those reporting on patients with pre-existing disease exclusively were excluded.

The sample sizes per publication ranged from 3 to 216, and there were 1,107 different patient descriptions, though not all patients are unique due to being included in multiple cohorts. Of the 38 publications where age could be determined, the mean age was 63.3 years (SD 6.1). Of the 33 publications where sex could be ascertained, 54% of patients were male. The three most common malignancies were melanoma (48 publications), lung cancer (42 publications), and renal/urothelial cancer (40 publications), and treatment of both stage III and IV were reported. Specific treatments could be extracted from 54 publications and included anti-PD-1/PD-L1 monotherapy (22 publications), anti-CTLA-4 only (1 publication) or any combination of monotherapy, combination ICI therapy and/or sequential therapy (31 publications). No publications described patients receiving only combination therapy, and 22 publications described other cancer therapeutics including targeted agents, chemotherapies, radiation and/or surgery, either previously or concurrently with ICI. Onset of irAE ranged from 3 to 38 weeks (median 12 weeks) after ICI initiation. Duration of follow-up ranged from 1 week to almost 5 years.

Clinical presentations

Publications were placed in one of 7 groups based on their characterization of the ICI-IA and/or ICI-PMR (**Table 1**). Several publications (27/69, 39%) used nonspecific terms of "arthritis", "arthralgia'', "arthritis/arthralgia", "arthralgia/myalgia" with or without the term "polymyalgia rheumatica" without further descriptors. Of these 27 publications, 23 (85%) did

not appear to involve rheumatologists as (co-)authors. Four publications used a more specific term of "inflammatory arthritis," and three of these (75%) involved a rheumatology co-author. Twelve publications (17%) described arthritis based on the number of joints involved - monoarticular, oligoarticular and polyarticular as well as a separate descriptor for PMR. Definitions for what constituted oligoarticular and polyarticular were not always provided. Seven publications (10%) listed the specific joints that were involved (i.e. involvement of the metacarpophalangeal (MCP) joints, wrist joints, and bilateral shoulder joints). Three publications (4%) used both number of joints and specific joints (i.e. monoarthritis of the left knee, polyarthritis of the MCPs, oligoarthritis of the knee/wrist/shoulder). Seven publications (10%) described joint involvement based on size – small, large, small and large, as well as gave the ICI-PMR diagnosis. Nine publications (13%) described irAE based on the traditional corresponding rheumatic disease (i.e. rheumatoid arthritis, RA-like; Spondyloarthritis (SpA), SpA-like; PMR or PMR-like). Of these 9 publications, 4 publications only described PMR and PMR-like syndromes.

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Some publications had clinical descriptions in addition to these 7 descriptive categories of arthritis. Five publications had an additional or separate characterization of tenosynovitis or enthesopathy, 3 described an "activated osteoarthritis" phenotype, and 6 publications utilized classification criteria for RA or PMR to aid in their diagnosis.

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Domains

Figure 2 displays the reported domains for all included publications mapped to core areas suggested by the OMERACT Filter 2.1, adjusted for this specific patient population.

Pathophysiologic Manifestations

Domains mapped to this core area included signs/symptoms, laboratory results, and imaging findings. Within signs and symptoms, the most described domains were joint pain (12 publications), joint swelling (10 publications), joint stiffness (8 publications) and synovitis (6 publications). Fifteen publications also mentioned the presence or absence of symptoms that may be associated with inflammatory arthritis, such as tenosynovitis, enthesitis, and/or dactylitis. The most common laboratory results reported were serologic investigation of anti-nuclear antibody (ANA), rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (CCP) (22 publications), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (19 publications), followed by synovial fluid analysis (7 publications) and HLA genetic testing (5 publications). Imaging results were reported for ultrasound (12 publications), MRI (10 publications), PET scan (10 publications), and X-ray (8 publications).

Life impact

Response to specific rheumatic irAE treatment, either positive or negative, was the most common domain described in 35 publications, and two publications went further to describe patients as glucocorticoid-refractory. Examples of response to treatment included terms such "improvement," "worsening," and "resolution," although these terms were inconsistent. Eight publications described the persistence of arthritis event after ICI therapy was discontinued, and six discussed the impact that tapering or stopping immunosuppression had on the arthritis. Other life impacts published included mobility problems (4 publications), disability (3 publications), and fear of potential decreased ICI efficacy from immunosuppression for the irAE (3

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publications). One qualitative study[13] also described thematic domains relating to diagnostic delay and misattribution, fear of dependency on others/lack of social support, and unpredictability of the irAE.

Oncologic domains/longevity

Thirty-two publications described tumor response to the ICI, which encompassed clinical responses by the oncologist (complete response, partial response, stable, progression) as influenced by oncologic criteria, such as RECIST/iRECIST[14]. Overall survival (OS), the duration of patient survival from treatment initiation, and/or progression-free survival (PFS), the time from treatment imitation until cancer worsening, was utilized in 8 publications. Death was mentioned in 4 publications. One paper discussed the status of the malignancy at the time of the irAE[15]. Other oncologic-related domains include other non-arthritis irAEs described (32 publications) and the use of ICI after irAE (31 publications), such as continued, temporarily held, or discontinued.

Societal/resource use

The most commonly used resource was specific irAE treatments (43 publications). Thirteen publications explicitly stated a consultation from a specialty service like rheumatology or orthopedics, and 3 publications described the hospitalization of a patient for their irAE. Seven publications described harms that were attributable to specific treatments used to treat the irAE, such as steroids, disease-modifying agents, or biologics.

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CTCAE

Instruments used for outcome measures in rheumatologic conditions, such as rheumatoid arthritis, that were adapted for irAE were not the focus of our current investigation. However, given that irAE are adverse events from oncologic treatments, it should be noted that 31 publications utilized the Common Terminology for Cancer Adverse Events (CTCAE v5.0)[16] to describe irAE severity from grade 1 to 3 with 1 - mild pain with inflammation, erythema or joint swelling, 2 - moderate pain associated with signs of inflammation, erythema, or joint swelling limiting instrumental activities of daily living (ADL) and 3 - severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; limiting self-care ADL.

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Non-specific domains

Several domains were also noted in publications that were not specific to the irAE of interest (ICI-IA/PMR) but rather to larger cohorts including other irAE. These have been listed with the number of publications for each in **Supplementary Table**.

Discussion

This is the first literature review to aggregate and characterize both clinical descriptors and outcomes for the increasingly recognized conditions of ICI-IA and ICI-PMR. This study demonstrates the heterogeneity present in clinical descriptions of ICI-IA/PMR. The most common description (39%) was non-specific arthritis, arthralgia +/- PMR grouped together. Most of the publications utilizing these descriptors did not include a rheumatologist as a co-author, which could explain the lack of clinical details regarding musculoskeletal manifestations.

In categories describing more detailed information regarding joint involvement, the most commonly described included number of joints (17%), the specific list of joints (10%), the differentiation of small vs. large joints (10%), or any combination of the three. Similar to the relationship between traditional, or *de novo,* RA and PMR, the distinction between ICI-IA and ICI-PMR can be difficult to ascertain. As such, several publications describe an inflammatory arthritis with or without features of PMR, or as primarily ICI-PMR with the presence of peripheral arthritis. Six publications utilized ACR/EULAR classification criteria to provide a diagnosis of ICI-RA or ICI-PMR. The heterogeneity in descriptions highlights a need for a more systematic way of reporting these irAE, or classification criteria specific to ICI-IA, that would assist in better studying these disorders in the future.

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Domains used in the included publications were mapped to concepts of pathophysiology, resource (treatment), and impact of health condition, and the one included qualitative study provided several life impact domains for consideration. While some instruments that are validated in other diseases, such as those used for RA (e.g. CDAI), were reported as outcome measures for these patients, it is not clear if they would be appropriate for use in a consistent and universal way across all ICI-IA and ICI-PMR patients, as they may not adequately reflect the heterogeneity of joint and structures involved such as enthesitis or tenosynovitis, or distribution of joints in the lower extremities. Further endpoint development is likely to be required.

Given that this is a unique population with both an inflammatory disease and a malignancy, an adjustment to the OMERACT 2.1 Filter is proposed by adding oncologic domains to the longevity core area since cancer status and tumor response are heavily linked to longevity. Another proposal would be to add oncologic domains as a whole separate concept or core area. Regardless, the results of this aggregation of domains can help inform the

development of an OMERACT Core Domain set for ICI-IA and ICI-PMR. This unique population also lends itself to the blurring of intended effects and harms within concept areas, as an intended benefit domain, such as treatment of irAE, can have harms attributed to that specific immunosuppressive treatment as well as potential harms of reversing efficacy of the ICI.

One reason for the heterogeneity in both clinical descriptions and outcome measures may relate to the primary specialty involved in the included publication. Rheumatologists are more experienced in providing specific characterization of irAE, whereas other specialties are more likely to describe arthralgia, arthritis, and myalgia interchangeably. Musculoskeletal adverse events from oncologic therapies often follow terminology used in the CTCAE dictionary, which is limited in the assessment of joint and muscle pain[16]. In addition, oncologists may focus more on oncologic domains, such as overall survival or progression-free survival as it relates to oncologic therapies, whereas rheumatologists tend to focus more on irAE treatment and quality of life. Thus, there is an unmet need for the input from both specialties as well as the widespread adoption and inclusion of patient-reported domains to develop specific domains within this area to more accurately reflect the manifestations and impacts of disease to improve classification and follow patients prospectively.

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A strength of this study is the broad inclusion of observational studies, including case series to cohorts, from multiple databases to determine how ICI-IA and ICI-PMR have been described and what outcome measures have been used. We excluded oncologic randomized clinical trials, which are generally of the highest quality study; however, studies of these trials demonstrate the poor characterization of musculoskeletal adverse events[24] and limited relevant outcome measures, again highlighting a deficiency of the CTCAE dictionary for rheumatic irAE. Given the novelty of these diseases, there have been no clinical trials focusing on ICI-IA and

ICI-PMR patients. We did not analyze or grade the quality of the included publications, as we were aiming to be as inclusive as possible to collect all reported outcome measures. We limited this query to include patients without any pre-existing autoimmune disease (AID) in order to distinguish patients who experience a flare of their disease as a result of ICI from a *de novo* irAE. Patients with pre-existing AID differ from ICI-inflammatory arthritis pathologically[7,9], and they may have different tumor responses as well depending on the use of baseline immunosuppression prior to ICI therapy[25,26]. Limitations of this study are the inclusion of English-only publications and the exclusion of abstracts and conference proceedings.

Conclusion

There is notable heterogeneity in the clinical descriptions of ICI-IA and ICI-PMR in the literature, and it is still unclear how best to describe these entities. The outcome measures reported appear to be evenly mapped across the primary core domains. However, given that a main goal for these patients is optimal treatment of the underlying cancer, we recommend the addition of oncologic domains in this specific setting to better accommodate this patient population.

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