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Management of Rheumatologic Immune-Related Adverse Events (Rh-irAEs) – An Overview of Immunosuppressive Therapies

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Introduction

Cancer treatment has entered a new era with the expanding role of immunotherapy, in particular immune checkpoint inhibitors (ICIs). ICIs, including those that target cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed death protein-1 (PD-1), and programmed death ligand-1 (PD-L1), work by blocking the intrinsic down-regulators of the immune system, leading to sustained activation of effector T-cells to enhance endogenous anti-tumour immune responses.

The potential downside of sustained immune activation is the risk of breaking immune tolerance, which can lead to immune-related adverse events (irAE). These have been reported in up to 80% of patients who receive ICI monotherapy and in 95% of those who receive ICI combination therapy.[1] The most common irAEs include skin rashes, gastrointestinal inflammation, and endocrinopathies, but they can essentially involve any major organ in the body, and multiple organs simultaneously.[1,2] They can occur anytime during treatment and sometimes after cessation of immunotherapy. The severity can vary from mild to severe, sometimes requiring hospitalization, and even rarely leading to death. The severity of irAEs has traditionally been graded on a scale of 1 to 5 based on the Common Terminology Criteria for Adverse Events (CTCAE), which can also be used help determine appropriate management.[3-5] Grades 1 and 2 are considered mild, Grades 3 and 4 include severe adverse events, and Grade 5 toxicities are those that are fatal.[3] Management ranges from clinical monitoring, temporarily holding the ICI, symptomatic support, and the use of immunosuppressive agents, either short or long term.[1,2] While many irAEs are transient, others require chronic immunosuppression, and often lead to permanent discontinuation of ICI therapy.

Rheumatologic irAEs (Rh-irAEs) have increasingly been reported and include ICI-associated arthralgias (ICI-arthralgias), myalgias (ICI-myalgias), inflammatory arthritis (ICI-IA), PMR-like presentation (ICI-PMR), myositis (ICI-myositis), vasculitis (ICI-vasculitis), and sarcoid like reactions (ICI-SLR). Rheumatologists have a key role in the diagnosis and management of Rh-irAEs, in collaboration with the patient and their oncologist, and should aim to support the oncologist to maintain effective cancer care.[6]

While there are currently no large-scale clinical trials that provide a guide for the optimal management of Rh-irAEs, recommendations and guidelines are available from organizations such as the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the Society for Immunotherapy of Cancer (SITC).[2,4,5] In general, CTCAE Grade 1 toxicities can often be managed conservatively, those that are classified as Grade 2 can be managed with non-steroidal anti-inflammatory therapies, intra-articular injections, and low dose prednisone, while Grade 3-4 toxicities often require more aggressive immunosuppressive therapy with the temporary or permanent discontinuation of immunotherapy.[7]

With the delicate balance of immune activation for enhancement of anti-tumour responses, and immune suppression for management of irAEs, there is a concern that high dose and long-term immunosuppression, may “undo” the anti-tumour response to ICIs. In this article, we will review the available evidence on efficacy and safety of corticosteroids, conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs), and biologic disease modifying anti-rheumatic drugs (bDMARDs) in the management of Rh-irAEs.

Corticosteroids

Corticosteroids are the most commonly used immune-modulators across the majority of irAEs, including Rh-irAEs, and have been used intra-articularly, orally, and intravenously, at various doses, with good success. They are considered the standard of care first-line intervention in most cases.[5] Recommended starting doses should be guided by type and severity of irAE. Although the majority of irAE respond to systemic corticosteroids, there is a proportion that may be refractory or relapse with steroid taper.[8]

Oral prednisone has been effectively used across all Rh-irAEs, including ICI-associated IA, PMR, myositis, and SLR. A reasonable starting dose of prednisone is 10–20 mg daily for patients with mild-to-moderate symptoms and up to 1 mg/kg daily for those with severe symptoms, significantly impacting daily function or involving a major organ.[2,9] Intra-articular corticosteroid injection can be considered in cases of mono-or oligoarthritis, particularly involving large joints,[2,4,9] and high dose intravenous corticosteroids may be required for severe ICI-myositis, especially when respiratory muscles are affected.

As with corticosteroid use in general, corticosteroids for treatment of irAEs should be used for the shortest duration and at the lowest dose possible. Patients should be monitored for common side effects, including infections, mood changes, gastrointestinal intolerance, hyperglycemia, hypertension, and bone loss and treated with concomitant prophylaxis as indicated including gastrointestinal and bone protection.

The data on safety of steroids to treat irAEs is conflicting. In pre-clinical studies, even low dose steroids were shown to markedly alter the anti-tumour activity of T-cells.[10] In a pooled meta-analysis of retrospective studies, there was no significant impact of steroids used for the management of irAEs on progression free survival (PFS) or overall survival (OS).[11] However, visual inspection of the forest plots showed tremendous heterogeneity, with some studies suggesting harm and others indicating a benefit. Some of the inconsistencies in the existing data have been attributed to steroid dose, timing of steroid initiation, and type of irAE. In a retrospective study comparing prednisone dosing for the management of ICI-hypophysitis in melanoma patients, high dose prednisone (> 7.5 mg daily average) was associated with a lower OS.[12] In another retrospective analysis of over 500 melanoma patients treated with a PD1 inhibitor, those who experienced early onset irAEs (within 8 weeks) and were treated with high dose prednisone (> 60 mg/d) had a lower PFS and OS.[13] Finally, a recent study by Gente et al. observed strong trends toward worse PFS and OS at prednisone equivalent doses of > 10 mg, and this trend was even more pronounced at doses of > 1 mg/kg, in patients with Rh-irAEs, but not in patients with other irAEs.[14]

All of the currently available data on the safety of steroids is limited by confounding and bias. Other confounding factors include the underlying tumour type, duration of steroid exposure, and other underlying patient factors.[15] Until there are well designed randomized trials, corticosteroids should be used at the lowest effective dose and tapered as soon as possible to optimize tumour outcomes.

Conventional Synthetic Disease-modifying Antirheumatic Drugs

There are no prospective, randomized trials on the optimal use of systemic immunosuppression in patients with irAEs. CsDMARDs, including methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), azathioprine (AZA) and mycophenolate mofetil (MMF) have been successfully used in numerous case reports and case series of patients with a variety of irAEs, including Rh-irAEs.[1,16-18] In these limited studies, without control groups, there have been varying clinical responses and no apparent negative impact on ICI efficacy. Of 177 patients in the multicentre CanRIO cohort, the majority of whom had ICI-IA, 42 were treated with csDMARDs, including HCQ (62%), followed by MTX (40%).[19] Of those treated with HCQ and MTX, 65% and 82% respectively had a complete or partial response to their ICI-IA.

In a recent systematic review, Barron et al found that Rh-irAEs accounted for 20% of patients with chronic irAEs, of which ICI-IA was most common.[20] This is consistent with Canadian data which showed 83% had chronic inflammatory arthritis persisting for at least three months after stopping ICI therapy.[21] In the majority of cases, csDMARDs are reserved for patients with steroid-refractory, steroid-dependent or life-threatening presentations. In some instances, particularly in patients with mild symptoms, agents such as HCQ, MTX, and SSZ can be used instead of corticosteroids.

The choice of immunosuppression often mirrors the agents commonly used to treat idiopathic diseases with similar manifestations. For example, ICI-hepatitis and ICI-pneumonitis are often treated with MMF, while ICI-IA is often treated with MTX, HCQ, and SSZ, and ICI-myositis with AZA and MMF.[22,23] There are no large-scale clinical trials that comparatively demonstrate effectiveness of one csDMARD versus another in any given irAE. As such, treatment decisions are left to the rheumatologist, or other specialists involved. Other considerations when choosing an immunosuppressant agent include the severity of symptoms, overlapping comorbidities, expected tolerance, and patient preference.

While csDMARDs have been reported to be effective steroid sparing agents for treating Rh-irAEs, their impact on the efficacy of ICIs is unclear. Due to limited sample size in most studies, immunosuppressive drugs, including glucocorticoids, csDMARDs and bDMARDs, are often grouped together for examining outcomes related to immunosuppression. A recent cohort study of patients with advanced melanoma treated with ICIs showed that immunosuppressive drugs, including glucocorticoids, infliximab, and MTX, negatively impacted the efficacy of ICIs if started before the initiation of ICI therapy, but had no impact if started after ICI initiation.[24] Another cohort study observed that the use of glucocorticoids with and without other immunosuppressive agents was actually associated with a longer OS.[25] Clinical studies examining the isolated impact of csDMARDs on ICI efficacy are lacking. Mouse studies have found contradictory results with HCQ.[15] Nonetheless, clinical trials evaluating cancer treatment regimens that include combination csDMARDs with ICI are underway.[15] At this time, most evidence points to no definite negative impact of csDMARDs on ICI efficacy when started for irAE treatment.

Biologic and Targeted Synthetic Disease-Modifying Anti-Rheumatic Drugs

Biologic and targeted synthetic DMARDs (tsDMARDS), including tumour necrosis factor alpha inhibitors (TNFi), interleukin 6 inhibitors (IL-6i) and Janus kinase inhibitors (JAKi) have become standard of care for many auto-immune diseases including inflammatory arthritis and colitis. They have been increasingly used to treat a variety of irAEs, particularly those that are refractory to other immunosuppression, and with life-threatening presentations. In certain cases, they are used in early disease, for short duration, in order to induce remission of irAE and minimize steroid exposure.

Infliximab, a TNFi, has been a cornerstone for the treatment of ICI-colitis, particularly in patients who flare with steroid taper, or require high doses of steroids to control inflammation. Preclinical studies suggest less negative effect on antitumour activity compared to corticosteroids.[10] TNFi have been used successfully in many case series and case reports of patients with ICI-IA, ICI-SLR, and ICI-myocarditis.[6]

Tocilizumab is a promising option for treating ICI-IA.[26] It has also been used for refractory ICI-myositis and ICI-myocarditis. Preclinical data suggest that blocking IL-6 may reduce immunotherapy toxicity and promote tumour immunity,[27] making it an ideal agent. However, clinical data is still lacking with most experience based on case reports or case series.

Similarly, there is increasing interest in the use of JAKi for refractory disease, including ICI-myocarditis and myositis.[28,29] The JAK/STAT signaling pathway may play a role in tumorigenesis and tumour evasion, and blocking this pathway could have a synergistic anti-tumour effect on ICI therapy. However, JAK/STAT signalling may be important for the upregulation of immune checkpoints (e.g. PD-L1), and some experts argue that JAK inhibition could potentially reduce the expression of ICI targets and interfere with the effectiveness of ICI therapy.[30,31] Further clinical experience is needed to define the role of JAKi for the treatment of irAE.

Finally, there is limited experience with other biologic agents such as IL-17 inhibitors (e.g. secukinumab), T cell modulators (e.g. abatacept, alemtuzumab), and rituximab, all of which have been used in refractory and life-threatening cases, however, due to their mechanism of action, they are not considered first-line agents of choice.[6]

As with csDMARDs, there are no well-designed prospective clinical trials that compare the use of b/tsDMARDs with the standard of care or that comparatively demonstrate the effectiveness of one b/tsDMARD versus another for treating any given irAE. The data on the impact of b/tsDMARD use and tumour outcomes is mixed, and predominantly includes patients who have received TNFi used to treat ICI-colitis. In colitis, doses of TNFi are usually given for short duration (1–3 months), whereas ICI-IA may require longer duration of treatment, the impact of which is not

yet known. In a recently published retrospective multicentre observational study of patients with ICI-IA treated with either MTX, TNFi or IL-6i, those treated with a bDMARD experienced more rapid arthritis control, but also had a shorter time to cancer progression.[26] At present, given the lack of definitive safety evidence, we recommend use of b/tsDMARDs only in csDMARD-refractory cases or for the induction of remission, and for as short a duration as tolerated.

Conclusion

With the increasing use of ICIs for cancer, rheumatologists and other specialists will increasingly be relied upon to help guide management of the resulting auto-immune toxicities. Much of what we do now has been guided by clinical experience, case reports, and case series, and extrapolated from idiopathic diseases that manifest with similar phenotypes. We urgently need well-designed, prospective clinical trials to guide treatment decisions. In the interim, early consultation and strong collaboration is needed between rheumatologists, oncologists, patients, and other health care providers to optimize patient outcomes. It is important for us all to remain current with the changing landscape of data emerging in this field.

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