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Updated Brazilian guidelines for the management of immune-related adverse events associated with checkpoint inhibitors - edition 2.0

Diretrizes brasileiras atualizadas para o manejo de eventos adversos relacionados ao sistema imunológico associados aos inibidores de checkpoint - edição 2.0

*Brazilian Society of Clinical Oncology Task Force

ABSTRACT

Immunotherapy (IT) in the form of monoclonal antibodies targeting coreceptors involved in the modulation of the immune synapse represents a standard of care for patients with distinct malignancies. Over the past years, evidences supporting the clinical use of IT both in monotherapy, as well as in combinatorial regimens, grew dramatically, leading to multiple regulatory approvals. With the expanding clinical incorporation of IT, understanding the mechanisms and management of the adverse events (AE) associated with this class of drugs is of utmost importance for professionals involved in patient care. In 2017, the Brazilian Society of Clinical Oncology (SBOC) issued the initial version of the "Brazilian guidelines for the management of immune-related toxicities associated with checkpoint inhibitors". In this article, we aimed to update general and specific aspects related to immune-related AEs associated with the use of immune-checkpoint inhibitors, including emerging evidences and updated algorithms for the most frequent clinical manifestations.

Headings: Immunotherapy; Practice guideline; Adverse effects; Immune-checkpoint inhibitors.

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RESUMO

A imunoterapia (IT) na forma de anticorpos monoclonais direcionados a correceptores envolvidos na modulação da sinapse imune, representa um padrão de tratamento para pacientes com neoplasias distintas. Nos últimos anos, as evidências que apoiam o uso clínico da TI tanto em monoterapia quanto em regimes combinatórios cresceram dramaticamente, levando a várias aprovações regulatórias. Com a crescente incorporação clínica da TI, entender os mecanismos e o manejo dos eventos adversos (EA) associados a essa classe de medicamentos é de extrema importância para os profissionais envolvidos no cuidado ao paciente. Em 2017, a Sociedade Brasileira de Oncologia Clínica (SBOC) publicou a versão inicial das "Diretrizes brasileiras para o manejo de toxicidades imunorrelacionadas associadas a inibidores de *checkpoint*". Neste artigo, buscamos atualizar aspectos gerais e específicos relacionados aos EAs relacionados ao sistema imunológico associados ao uso de inibidores de *checkpoint* imunológico, incluindo evidências emergentes e algoritmos atualizados para as manifestações clínicas mais frequentes.

Descritores: Imunoterapia; Orientação prática; Efeitos adversos; Inibidores de *checkpoint* imunológico.

INTRODUCTION

Over the past decade, immunotherapy consolidated its role as one of the cornerstones of cancer treatment, with unprecedented efficacy demonstrated across various clinical settings. Distinct monoclonal antibodies targeting inhibitory coreceptors involved in the modulation of the immune synapse have been approved by Brazilian health authorities, including the anti-*cytotoxic T-lymphocyte associated protein 4* (CTLA-4) agent, ipilimumab; anti-*programmed cell death receptor-1* (PD-1) agents, nivolumab, pembrolizumab, and cemiplimab; and anti-*programmed- death ligand-1* (PD-L1) agents, atezolizumab, durvalumab, and avelumab. Clinical applications of immunotherapy have significantly expanded as a result of the incorporation of these agents into the management of patients with melanoma and other skin tumors, lung, kidney, bladder, head and neck, breast, esophagus, and hematological malignancies, among others. In addition, the use of these agents is no longer restricted to the advanced/metastatic scenario, as recent approvals in the adjuvant setting have led to the inclusion of these agents also at earlier stages. Besides the increased number of available agents and indications, the enormous potential for combinatorial approaches paved the way for an even greater expansion of indications in the coming years, with some already incorporated into clinical practice, including ipilimumab/nivolumab, atezolizumab/bevacizumab, pembrolizumab/axitinib, anti-PD-1 and anti-PD-L1/chemotherapy. Along with response rates ranging from 10% to more than 50% in different indications, the use of immune-checkpoint blockade yields the possibility of lasting responses and long-term benefits.[1-5]

In this context, knowledge of adverse events (AE) associated with this class of drugs, their pathophysiological mechanisms and, above all, the proper management of these AEs represent an essential skill for the oncologist, as well as for the team involved in the care of patients with cancer.

In 2017, the "Brazilian guidelines for the management of immune-related toxicities associated with checkpoint inhibitors" were issued by the Brazilian Society of Clinical Oncology (SBOC), in its initial version.[6] In this article, we aimed to update general and specific aspects related to immune-related adverse events (irAEs) associated with the use of immune-checkpoint inhibitors (ICIs), including emerging evidences and updated algorithms for the most frequent clinical manifestations. The purpose of this update is to review the evidence made available since the original guideline was released, as well as to provide updated recommendations for the management of irAE, thus promoting greater safety and increased chances of therapeutic success for patients with cancer under treatment with ICIs.

Key aspects of the update

- **Objective:** to update the "Brazilian guidelines for the management of immune-related toxicities associated with checkpoint inhibitors" based upon a comprehensive literature review encompassing the main studies addressing irAEs.
- **Incidence and presentation of irAEs:** with the expansion of indications of ICIs, there has been an increasing number of studies that aimed to determine the frequency of irAEs effects. Data from several clinical trials and meta-analyses were included in order to better characterize the incidence of irAEs, including emerging data on fatal and uncommon irAEs.

- **High-risk subgroups:** evidence regarding the use of ICIs in groups of patients considered to be at increased risk of irAEs has been updated, including patients with autoimmune disorders, those receiving corticosteroids prior to the initiation of ICIs, patients with chronic viral infections, older adults, and solid organ transplant recipients.
- **Re-exposure to immunotherapy:** with greater understanding of adverse effects and their appropriate management, emerging evidence has become available regarding the safety and efficacy of rechallenge following treatment interruptions. Updated recommendations were defined to provide evidence on treatment discontinuation and re-exposure to ICIs.
- **Specific adverse effects:** recommendations for the management of frequent and relevant have been updated, with new treatment algorithms for rare toxicities, including as cardiac, renal, hematological, musculoskeletal/rheumatic, and neurological irAEs.

Overview of immune-related toxicities and pathophysiological mechanisms

General aspects and pathophysiological mechanisms of irAEs were previously published in the first edition of the "Brazilian guidelines for the management of immune-related toxicities associated with checkpoint inhibitors".[6] Although the specific mechanisms underlying irAEs are not yet fully understood, accumulated evidence suggests that the development of irAES is associated with the disruption of immune coreceptors' role in the maintenance of immune homeostasis and self-tolerance. Different manifestations of irAEs reflect different pathophysiological mechanisms including: 1. exacerbation of a subclinical autoimmune condition or upregulation of pre-existing autoantibodies; 2. triggering of a new inflammatory or immune-related condition resulting from the aberrant activation of autoreactive lymphocytes; 3. imbalance in the local and systemic levels of cytokines, leading to an inflammatory and self-reactive state; and 4. cytotoxic responses mediated by the interaction of monoclonal antibodies with their target receptors (e.g., cytotoxic T-lymphocyte-associated protein 4 [CTLA-4] expressed by healthy tissues).[7] Data from translational studies suggest that irAEs usually develop through a combination of these factors involving autoreactive T-lymphocytes, autoantibodies, and cytokine production.[8] However, the magnitude to which each of these components contribute to the development of irAEs remains poorly understood and may vary depending on the severity and profile of the irAEs.

Incidence and presentation of irAEs

The incidence and kinetics of onset of irAE may be influenced by the type of monoclonal antibodies used and regimen (combination vs monotherapy), the underlying malignancy and patient's intrinsic risk factors. Immune-related AEs may occur at any time during treatment, including the period after treatment discontinuation, and may range in severity from mild to severe, and even life-threatening events. Available data on irAEs are based primarily on toxicities documented in clinical trials and, more recently, on the results of several meta-analyses dedicated to the study of such events and real-life cohorts. Considering all grades and agents, the most common irAEs were fatigue (18.26%), pruritus (10.61%), and diarrhea (9.47%). The most common grade ≥3 irAEs are fatigue (0.89%), anemia (0.78%), and elevated aspartate aminotransferase (AST) (0.75%). No statistically significant relationship between irAE rates and primary cancer type has been identified to date, although the highest incidence of irAEs has been described in patients with melanoma and the lowest in patients with lung cancer.[9] However, it is important acknowledge that the available evidence on the incidence of such events may be limited by variations in the screening protocols used to detect irAEs in each study and also in clinical practice, as such protocols dynamically evolve with increasing knowledge about irAEs. In general, the rates of any grade and grade ≥3 irAEs associated with monotherapy with anti-PD-1/PD-L1 agents (60-75% and 10-15%, respectively) are lower than those associated with ipilimumab monotherapy, whose expected rates of any grade and grade ≥3 irAEs, usually reported in the ranges of 75-80% and 20-25%, depending on the dose of anti-CTLA-4 used.[9,10]

Possible exceptions include specific endocrinopathies, such as thyroiditis/thyroid dysfunction, which have been more frequently reported with anti-PD-1/PD-L1 administration. A meta-analysis including patients from 19 randomized clinical trials compared the rates of AEs related to anti-PD-1 versus anti-PD-L1 monoclonal antibodies. The incidence of irAEs was similar between with anti-PD-1 and anti-PD-L1 agents (relative risk = 1.24; 95% confidence interval [CI] = 0.79-1.93), as was the incidence of irAEs leading to death (relative risk = 1.38; 95% CI = 0.11-16.89).[11] On the other hand, combinatorial strategies such as nivolumab/ipilimumab are associated with a significant increase in the incidence of toxicities (any grade: 95%; grade 3 or higher: 55%) and higher treatment discontinuation rates.[12-15] Combinations of ICI with other classes of antineoplastic agents, such as anti-angiogenic drugs and/or chemotherapy, do not significantly increase the incidence of irAEs but are associated with increased overall toxicity due to the addition of AEs from each treatment class. Chemo-immunotherapy combinations, when compared to immunotherapy alone, have a higher incidence of grade 3-4 AEs (relative risk = 1.32; 95% CI = 1.12-1.55), with no significant impact on mortality rates.[16]

Regarding the time to onset of irAEs, patients treated with ipilimumab usually experience a new AE within the first 12 weeks of treatment and resolution in 6-8 weeks (approximately 7 weeks for grade 3-4 AEs), but 5-15% of patients may experience persistent irAEs after 24 months, most of which grades 1-2.[17]

Similarly, most irAEs associated with the use of anti-PD-1/PD-L1 agents occur within the first 4 months after initiating therapy; however, the interval to onset tends to be shorter for combinations of anti-CTLA-4 and anti-PD-1/PD-L1 drugs.[18] Combination treatments with chemotherapy or anti-angiogenic agents do not appear to impact the onset, duration, or resolution of irAEs.[16,19]

The frequency of fatal irAEs was evaluated in a meta-analysis including more than 19,000 patients, which demonstrated a mortality rate of 0.36% with anti-PD-1 therapy, 0.38% with anti-PD-L1, 1.08% with anti-CTLA-4, and 1.23% with the combination of anti-PD-1/PD-L1 and anti- CTLA-4. Colitis is the most frequent cause of death following anti-CTLA-4 therapy. Pneumonitis, hepatitis, and neurological events are the main causes of death associated with anti-PD-1/PD-L1 therapy. Colitis and myocarditis are the most frequent causes of death due to irAEs in combination regimens, although we must acknowledge that there may be an overlap of severe and potentially fatal AE from both types of agents.[20] The onset of fatal AEs also appears to be early in most cases, with a median for onset of 40 days with anti-PD-1/PD-L1 agents in monotherapy and less than 15 days for those treated with the combination of ipilimumab and nivolumab.

A possible association between the development of irAEs and better treatment outcomes in patients treated with ICI has been documented in different studies. Two recent meta-analyses demonstrated a positive association between the development of low-grade irAEs and response rates (RRs), progression-free survival (PFS), and overall survival (OS) in patients treated with immunotherapy regardless of the primary site, immunotherapy used, and irAEs. High-grade irAEs (grade 3 or higher) were associated with higher RR but lower OS.[21,22] One of the challenges in confirming this association is the fact that patients who achieve greater benefit from immunotherapy may eventually be exposed to therapies for a longer period, inducing a bias related to the duration of exposure. However, evidence of a true association between irAEs and better treatment outcomes is suggested by the fact that, as previously mentioned, irAEs tend to occur in the first few months of treatment and that this association persists after applying statistical methods to minimize this bias.

Recommendations for irAEs screening

Before initiating therapy with ICIs, all patients should be assessed for susceptibility to developing irAEs, as toxicity can potentially involve any organ or tissue. Subclinical manifestations can make the diagnosis of irAE especially challenging for physicians.[23,24] Therefore, both patients and the multidisciplinary team must be aware of the potential risks, thus allowing early identification of irAEs (Figure 1).[25,26]

It is recommended that all patients receiving ICIs be followed closely and carefully, and undergo periodic evaluations, including detailed anamnesis and a physical examination performed before each treatment administration. It is also recommended that laboratory tests be performed before the initiation of treatment and repeated throughout treatment as summarized in Table 1.[27] The frequency of tests can be modified based on individual assessments, the occurrence of AEs, and clinical suspicion. Nonetheless, no ideal screening strategy is unanimously accepted as a standard of care and, consequently, many of the current routines have been adapted from the clinical research protocols that led to the approval of these agents.

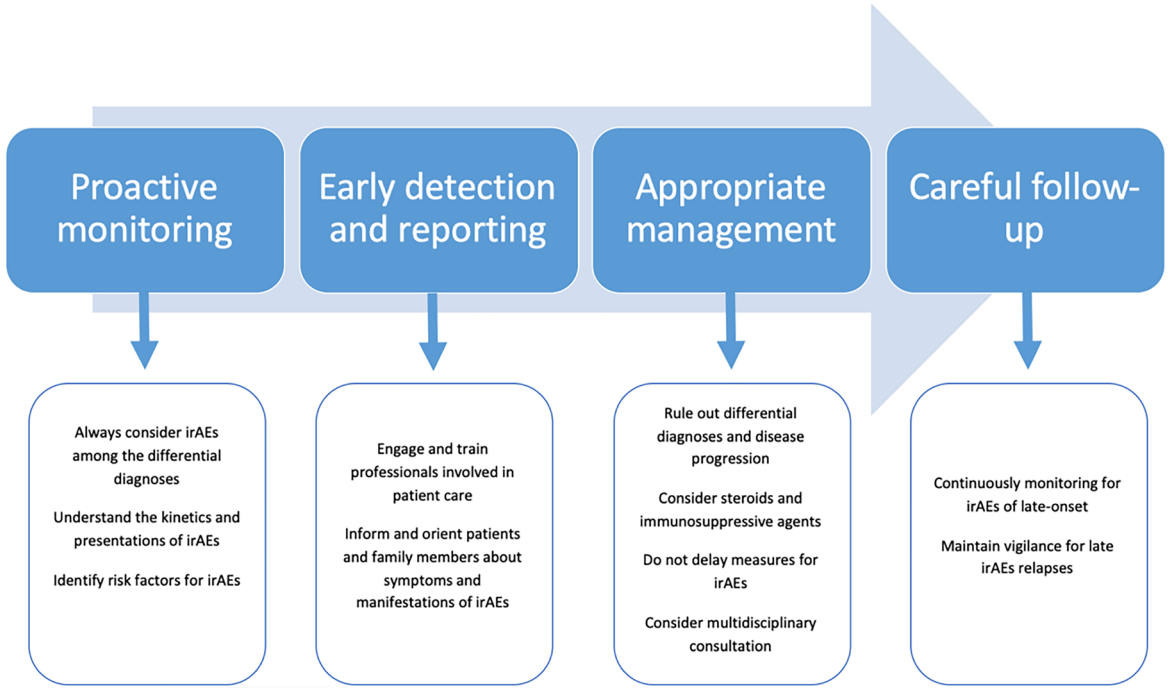

Figure 1. General approaches to minimize the impact of immune-related adverse events.

Table 1. Laboratory testing recommended at baseline and during immune-checkpoint inhibitor therapy (anti-CTLA-4 and/or anti-PD-1/PD-L1).

Frequency	Complete blood count (CBC/ blood clotting tests	Urea/ creatinine	Urinalysis/ urine protein test	Electrolyte tests (Na/K/Mg Ca)	AST ALT Bilirubin Alkaline phosphatase	Blood glucose	Amylase Lipase	TSH T4L	T3L	ACTH Basal cortisol test	FSH LH Testosterone (men)	HIV serology Hepatitis B and C serology#
Before treatment	X	X	X**	X	X	X	X**	X	-	-	-	X
Each cycle	X	X	-	X	X	X	X**	X*	-	-	-	-
Special situations	-	-	If clinically indicated	-	-	-	If clinically indicated	-	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated

*Every 3 to 6 weeks (alternating cycles, if the drug is administered every other week, is acceptable), and less frequently after the 6th month of treatment; **Optional testing (there are no precise recommendations on the best interval to perform the test); #: Despite evidence suggesting the safety of treatment with ICIs in patients with viral hepatitis or HIV infection, screening can be useful for patient monitoring, evaluation of adverse events and differential diagnoses; CBC: Complete blood count; ICIs: Immune-checkpoint inhibitors.

Recommendations for high-risk subgroups

Patients with a history of autoimmune disease are at increased risk of developing an irAE or a "flare" of the underlying autoimmune condition, therefore requiring greater attention and closer monitoring. As this is a very heterogeneous group, encompassing a wide range of pathologies and severity of manifestations, individualizing treatment is essential in the therapeutic decision-making process, and the benefit of each intervention should be considered along with the risk of toxicity and exacerbation of the autoimmune condition. Data showing the safety and efficacy of ICIs in patients with autoimmune diseases are limited. Retrospective data suggest that patients with stable autoimmune diseases may receive anti-PD-1 therapy. Although the risk of irAEs is higher in this population and that patients with preexisting autoimmune diseases may experience flares when treated with both anti-CTLA-4 and anti-PD-1 agents, such exacerbations occur at a rate of approximately 20 to 40%, and tend to be manageable, provided they are immediately recognized and managed appropriately. In addition, the RRs in this subgroup appear to be similar to those achieved in the general population.[28-31] However, the use of ICIs should be avoided in patients with severe active autoimmune disease or those using high-dose corticosteroids or immunosuppressants since any additional immune activation can be potentially life-threatening. Two ongoing clinical trials, one on lung cancer (NCT03656627) and the other on several tumor types (NCT03816345), are prospectively evaluating the use of ICIs in patients with underlying autoimmune disease.

Regarding the use of corticosteroids, retrospective studies suggest that the use of prednisone ≥10mg/day or equivalent when initiating therapy with anti-PD-1/PD-L1 is associated with lower RR, PFS, and OS. A multivariate analysis adjusted for Eastern Cooperative Oncology Group performance status, smoking, and presence of brain metastases showed that corticosteroids were associated with worse survival.[32,33] Thus, caution is recommended when using corticosteroid therapy before the initiation of ICIs until more robust evidence is available. Importantly, the use of corticosteroids or immunosuppressants for the management of irAEs after the beginning of treatment does not seem to affect the outcomes of patients receiving ICIs, although this is still controversial. In an analysis of efficacy and safety of patients with advanced melanoma and lung cancer who discontinued immunotherapy due to irAEs, the use of corticosteroids was not associated with worse RR, PFS, or OS.[34-37]

Patients with chronic viral infections were excluded from most clinical trials to date. However, the safety of ICI in patients with hepatitis B or C has been suggested by an increasing number of case series demonstrating hepatotoxicity rates similar to those seen in the general population.[38] Similarly, a phase I/II study evaluating the safety and efficacy of nivolumab in patients with hepatocellular carcinoma showed an acceptable safety profile in patients with chronic viral infection.[39] Regarding patients with HIV infection, a systematic review identified 73 patients treated with ICIs. In patients with melanoma and lung cancer the effectiveness was similar between patients with or without HIV infection, with RRs of 27% and 30%, respectively. Patients living with HIV did not show an increased incidence of AEs, and the viral load remained undetectable in 93% (26 of 28) of the patients who did not have a detectable viral load prior to treatment initiation.[40] Thus, treatment of patients with chronic viral infection with ICI appears to be safe, although close and multidisciplinary follow-up are of paramount importance.

Multidisciplinary management is also important in the complex setting of patients with a history of solid organ transplantation being considered for treatment with ICI. Safety and efficacy data are even more scarce in this population and limited to a small number of case reports or case series. Despite reports about safe administration of these agents in selected cases, recent case series suggested that the risk of rejection can exceed 40%, leading to mortality rates as high as 40-50%, depending on the organ transplanted.[41,42] Thus, therapeutic decisions involving the use of ICIs in solid organ transplant recipients should always be shared with the patients and other teams involved in their care and take into consideration the risk of transplant rejection, potential benefits from ICI therapy, and available therapeutic alternatives.

Regarding the indication of ICI for elderly patients, age alone should not be a contraindication to this therapeutic approach. Despite being underrepresented in randomized controlled trials, subgroups analyses in prospective and retrospective studies suggested that the efficacy and safety of immunotherapy in the older adults are similar to that of general population.[43,44] Importantly, factors such as comorbidities and potential drug interactions should be carefully considered in this population. Geriatric and frailty assessments are important predictors of irAEs and worsening quality of life, and both are recommended in this subgroup.[45]

Early approach to irAEs: overview

Early symptom recognition and rapid intervention remain critical factors in the management irAEs. In the initial evaluation, the exclusion of differential diagnoses (such as infections) is essential. Invasive procedures for obtaining tissue samples (bronchoscopy, endoscopy, skin biopsies, etc.) are frequently indicated. The temporary discontinuation of ICIs is often necessary, and the use of corticosteroids and symptomatic therapy remain the pillars of irAEs management. The use of corticosteroids to control irAEs does not seem to affect the efficacy of cancer treatment,[13,24,34] and the definitive discontinuation of immunotherapy is still indicated in severe cases.

Permanent discontinuation is usually not required for endocrine toxicities such as glandular dysfunction (even grade 4) provided that adequate hormonal replacement is initiated and the patient's clinical condition is stable. For patients with severe AEs that are refractory to oral or intravenous corticosteroid therapy, subsequent lines of treatment include monoclonal antibodies such as infliximab, rituximab, or tocilizumab (among others), mycophenolate mofetil, or other immunosuppressants (such as azathioprine and cyclosporine), particularly if no improvement is seen after 3-5 days of intravenous corticosteroid therapy. In selected cases, particularly those with neurological or hematological complications, plasmapheresis or intravenous immunoglobulin are therapeutic alternatives. It should be noted that the early recognition of refractory cases and the timely introduction of the appropriate therapy (corticosteroids, usually in addition to other treatments, when indicated) are crucial to the management of irAEs. In these situations, or even in cases of lower grade events, an evaluation by a specialist (such as endocrinologist or gastroenterologist) is encouraged, preferably a specialist who is familiar with the management of irAEs. Corticosteroids should be slowly tapered after adequate improvement of the irAE is achieved, usually over 4 weeks, with the possibility of extension for 6-8 weeks or longer in cases of pulmonary or hepatic irAEs. Patients treated with corticosteroids and/or immunosuppressive agents are at risk for opportunistic infections and tuberculosis reactivation, and, when appropriate, should receive antimicrobial prophylaxis as well as be monitored for signs of infectious conditions. The initial approach and management of irAEs are summarized in Figure 2. The doses of the drugs more commonly used in this clinical setting are described in Appendix 1.

Evaluation after discontinuation and rechallenging of immunotherapy

With greater access to immunotherapy and better understanding and management of irAEs, the possibility of rechallenging with new exposure to ICI after temporary discontinuation is increasingly frequent. Prospective data from randomized controlled trials supporting this strategy are scarce because most prospective studies used management algorithms that established permanent discontinuation of treatment for severe irAEs. In a cohort of 93 patients treated with anti-PD-1/PD-L1 who had grade 2 or higher irAEs, 40 were re-exposed to the same agent, 55% of which had a recurrence of one or more irAEs. There was no increase in irAE severity on re-exposure, and approximately 20% of patients developed different types of irAE from the previous ones.[46] These data are in line with those of other previously published cohorts[47] and suggest that rechallenge with anti-PD-1/PD-L1 agents can be considered with proper monitoring.

Toxicity	General approach (following the exclusion of differential diagnoses/always consider specialist interconsultation)		
Grade*	Immunotherapy	Directed approach	Follow up
Grade 1	Continue treatment	Symptomatics / topical steroids.	Continuous surveillance.
Grade 2#	Consider temporary interruption. §	Symptomatics / topical steroids. Considerer oral prednisone 0,5-1,0mg/kg/day if persistent.	Intensified surveillance. Consider rechallenge if improvement to grade 1 toxicity or complete resolution.
Grade 3	Withhold; consider rechallenge in select situations.	Oral prednisone 1,0-2,0mg/kg/day or IV methylprednisolone 1-2,0mg/kg/day.	Intensified surveillance. Consider immunosuppressants if steroid-refractory irAEs. Monitor for late recurrences
Grade 4	Permanent discontinuation	IV methylprednisolone 1-2,0mg/kg/dia. Consider immunosuppressants	Continuous surveillance. Monitor for late recurrences.

Figure 2. Simplified algorithm: initial approach and management of immune- related adverse events.
irAEs: Imune-related adverse events; *According to CTCAE v. 4; #: Persistent grade 2 toxicities may require approaches similar to grade 3-4 irAEs; §: If cutaneous or endocrine irAES, treatment may be continued.

Recommendations regarding the discontinuation of immunotherapy and rechallenging are summarized in Table 2. It should be noted that irAEs may have late onset, even after the discontinuation of the immunotherapy; therefore, monitoring for these adverse effects should be continuous,[48] and re-evaluations of toxicity (anamnesis, physical examination, and laboratory tests) after the discontinuation of treatment are suggested every 3-4 months in the first year and every 6 months thereafter.[12,48,49]

Selected AEs

Gastrointestinal irAEs

Gastrointestinal events may present as diarrhea, abdominal cramps, hemorrhage, and urgency. Other manifestations include pancreatitis, cholangitis, and enteritis. Although the time for the onset of diarrhea/colitis varies, this toxicity usually arises from the sixth to the eighth week after the beginning of ipilimumab (or its combinations) or 3-6 months after the initiation of anti-PD-1/PD-L1 agents.[50,51] The incidence of diarrhea appears to be dose-dependent in patients receiving anti-CTLA-4 therapy. Patients receiving a combination of anti-CTLA-4 and anti-PD-1/PD-L1 are at a higher risk of developing this adverse event.[15]

Clinical management is based on symptom severity (Appendix 1, Supplementary Material). For patients who do not respond to corticosteroid therapy within 3-5 days, the use of infliximab or vedolizumab is indicated. Early use of immunosuppressants is associated with better clinical outcomes in patients developing colitis. It is important to emphasize that infliximab should not be used in cases of sepsis or in patients with a suspected or confirmed intestinal perforation; thus, laboratory tests and stool tests (culture, stool ova and parasite test, *Clostridium difficile*, cytomegalovirus, or other viral etiologies) must be performed. Improvement in symptoms following infliximab usually occurs within 1-3 days, and its administration may be repeated after 2 weeks if necessary.[52,53] Vedolizumab, an anti-integrin agent, was recently compared to infliximab in a single-center retrospective cohort including 150 patients. Vedolizumab was associated with clinical rates of diarrhea remission similar to those obtained with infliximab but with a lower rate of gastrointestinal AE recurrence. Interestingly, patients who received vedolizumab also had better cancer outcomes, with higher PFS and OS than those who received infliximab.[54] Despite the limitation of being a retrospective study and requiring prospective validation, the use of vedolizumab in this clinical setting should be considered.

Colonoscopy is recommended for patients with persistent grade 2 or severe diarrhea. Endoscopic findings such as ulcerations or pancolitis are associated with a lower likelihood of response to corticosteroids alone, so the addition of immunosuppressants such as infliximab, vedolizumab, or mycophenolate is often required.[52,55] No prophylactic treatment for diarrhea induced by these ICI is currently validated.

The clinical impact of elevations in lipase and amylase levels remains uncertain, and ordering laboratory tests to determine their levels in asymptomatic patients is questionable because a discontinuation of therapy is not usually recommended based on these laboratory findings alone.[56] However, in symptomatic patients with elevated pancreatic enzymes, additional laboratory and radiologic workup are recommended in addition to a thorough clinical examination to exclude pancreatitis.[24]

Hepatic irAEs

The estimated incidence of hepatic irAEs is low, occurring in about 2-7% of patients treated with anti-PD-1/PD-L1 or anti-CTLA-4 alone, and the most common presentation is asymptomatic elevation of liver tests, such as aspartate aminotransferase, alanine aminotransferase, gamma- glutamyl transferase, or bilirubin.[14,15,17,57] However, there is a significant increase in the risk of hepatic AEs when dual immune checkpoint blockade is used (any grade, 15-30%; grades 3/4, 6.0-18.8%).[15,57] The initial presentation with acute liver failure is rare and the onset of symptoms typically occurs between 4-12 weeks.[58] Treatment-related liver toxicity is usually the diagnosis of exclusion, and viral and cancer- related causes for liver abnormalities should be ruled out. Unlike autoimmune hepatitis, hepatotoxicity caused by immunotherapy is not predominant in women. Antinuclear antibody (ANA) may be present in up to 50% of patients, usually at low titers (1:80), whereas anti-smooth muscle antibody (SMA) test results are rarely positive. Liver biopsy shows no or few plasma cells and fewer CD20+ and CD4+ lymphocytes when compared with autoimmune hepatitis.[58]

The management of hepatotoxicity includes the use of systemic corticosteroids and, in more severe cases, other immunosuppressants such as mycophenolate mofetil (Appendix 2, Supplementary Material).

Table 2. Recommendations for treatment discontinuation and rechallenge.

Permanent discontinuation	ICI rechallenge
Grade 4 toxicity (potentially fatal)* Recurrent grade 3 toxicity. Specific grade 3 toxicity (pneumonitis, hepatitis, nephritis). Grade 2 toxicity without resolution after 3 months of proper treatment. Specific grade 2 toxicity (cardiac, neurological)	Previous toxicity, currently if recover to Grade 1 or less Corticosteroid <10mg/day of prednisone or equivalent. No other immunosuppressant is needed.

*Exception to grade 4 endocrine toxicity adequately controlled with hormone replacement alone.

Infliximab is contraindicated because of the intrinsic potential for hepatic toxicity. The added value of performing liver biopsy remains controversial, and is based on expert recommendations. Liver biopsy can be considered in patients with low risk of bleeding and in corticosteroid-refractory cases, concomitant use of other hepatotoxic medications or suspected liver metastases. The main limitation of liver biopsy, in addition to its cost and being an invasive procedure, is the fact that there are no pathognomonic histological findings and that, in most cases, the biopsy does not change the management of this irAE.[59]

Pulmonary irAEs

Although pulmonary toxicity is relatively uncommon, it is a potentially life-threatening event and should be considered in patients with new onset of respiratory symptoms.[12,49] Of note, real-world data suggest that the incidence of pneumonitis is higher than that reported in clinical trials, and as high as 8-19% in patients with non-small cell lung cancer (NSCLC) treated with anti-PD-1/PD-L1 agents.[60,61] Also, pneumonitis is the most common fatal irAE, representing about 35% of the causes of death due to the use of anti-PD-1/PD-L1.[20]

Retrospective and post hoc analyses suggest that patients previously exposed to chest radiotherapy may be at increased risk for pneumonitis and radiation recall and, therefore, require closer surveillance. In KEYNOTE-001 trial evaluating pembrolizumab in patients with NSCLC, the incidence of pneumonitis was numerically higher in the patients who had received previous thoracic radiotherapy versus those with no previous thoracic radiotherapy (8% vs. 1%; p=0.15).[62] However, in the PACIFIC study, which evaluated the addition of durvalumab after chemoradiotherapy in patients with stage III NSCLC, the use of immunotherapy numerically increased the risk of pneumonitis, radiotherapy- induced pneumonitis, or any grade pneumonia but did not increase the risk of grade 3-4 pneumonitis (3.4% vs. 2.6%, respectively).[63]

Pneumonitis treatment must be adapted to the severity of the condition (Appendix 3, Supplementary Material). In this population, the concomitant use of empirical antibiotic therapy is frequent. Nevertheless, the exclusion of differential diagnoses using tests such as bronchoscopy or lung biopsy should be considered when the diagnosis is uncertain.

Cutaneous irAEs

Dermatologic toxicities, including pruritus, xeroderma, rash, psoriasiform lesions, and lichenoids, are the most common irAEs in patients treated with ICIs. They are more common in patients treated with anti-CTLA-4 agents and combination regimens. Although most cases are grade 1 or 2, serious events may occur, such as toxic epidermal necrolysis or Stevens-Johnson syndrome. Psoriasiform lesions and maculopapular eruptions are often the irAEs of earliest onset, with a median manifestation of 2-5 weeks after the initiation of therapy.[64] On the other hand, lichenoid dermatoses, bullous (bullous pemphigoid), and hypopigmentation/ depigmentation vitiligo-like lesions tend to have later onset.[64] A higher incidence of cutaneous irAEs is observed in patients with advanced melanoma than other neoplasms, particularly vitiligo-like changes, which are strongly associated with higher PFS and OS.[13,48]

The management of cutaneous irAEs follows the same principles recommended for other irAEs. Consultation with a dermatologist is often recommended, with a low threshold for skin biopsies (Appendix 4, Supplementary Material). Most cases can be managed using topical steroids combined or not with antihistamines, and ICI treatment usually does not need to be discontinued. For patients with pruritus, the use of GABA receptor agonists, such as pregabalin or gabapentin, or the NK-1 receptor antagonist aprepitant may be considered. In refractory or severe cases, a skin biopsy is crucial, and strategies such as systemic corticosteroid therapy, immunosuppressants, or monoclonal antibodies may also be necessary for therapeutic management.[65]

Endocrine irAEs

Endocrine irAEs are diagnosed in up to 10% of patients treated with ICIs. A high level of suspicion is recommended, since the symptoms may be nonspecific.[66] The onset of endocrine irAEs usually occurs at between the 4th and the 18th weeks of treatment (median: 11 weeks), but late manifestations can also occur.[67] A meta-analysis of 38 randomized controlled trials compared the incidence of endocrine irAEs resulting from different immunotherapies. Patients who received a combination of anti-PD-1/ PD-L1 and anti-CTLA-4 had a higher incidence of thyroid dysfunction than those who treated only with ipilimumab. Comparisons between anti-PD-1 and ipilimumab as monotherapies demonstrated that the use of anti-PD-1 was more likely to induce hypothyroidism, while the use of ipilimumab was associated with a higher incidence of hypophysitis. Other endocrine irAEs, including primary adrenal insufficiency and insulin-dependent diabetes mellitus, were uncommon and occurred in 0.7% and 0.2% of patients, respectively.[66] In patients receiving ICIs and presenting with hypotension/shock, nausea, vomiting, and mental confusion, the possibility of an adrenal crisis must be ruled out, although it is an extremely unusual event. The approach and management of the most common endocrine irAEs are summarized in Appendix 5 (Supplementary Material). It is worth mentioning that the use of corticosteroids, except for hormone replacement, is controversial in cases of endocrine toxicity and usually not recommended (except for the control of local symptoms/mass effects).

Conditions affecting the thyroid, such as hypothyroidism, hyperthyroidism, or symptomatic thyroiditis can occur, although the latter presentation is uncommon. Hypothyroidism with the use of ICIs occurs in approximately 6.6% of patients, with the lowest incidence (3.8%) reported with ipilimumab and the highest incidence (13.2%) reported with combination therapies.

The risk of hyperthyroidism, but not hypothyroidism, appears to be greater with the use of anti-PD-1 than with anti-PD-L1 (odds ratio [OR] = 5.36; *p*=0.002), and it is often temporary.[66] Thyroid function tests should be monitored before each dose or monthly and then every 6-12 weeks for 6 months after the completion of treatment. The median onset of thyroid dysfunction was 4 weeks after the initiation of immunotherapy.[68] The recommended treatment is the standard: hormone replacement or antithyroid drugs in selected cases.

Pituitary dysfunction is among the most commonly reported endocrine irAEs. The greatest incidence occurs with anti-CTLA-4 agents and combined regimens. The incidence is dose-dependent (1.0-4.0% with ipilimumab 3mg/kg and 16% with ipilimumab 10mg/kg). It is a rare event with the use of anti-PD-1 monotherapy (0.4%).[66]

Adrenal insufficiency is usually permanent and requires continuous hormone replacement. It presents as high levels of adrenocorticotropin hormone in the presence of low cortisol, differentiating it from hypophysitis. If adrenal insufficiency and hypothyroidism are both present, corticosteroids should be started before thyroid hormone replacement is administered due to the risk of adrenal crisis. Sepsis, for which broad-spectrum empirical antibiotic therapy is usually required, should always be investigated.[69]

Autoimmune (type 1) diabetes is a rare event reported in approximately 0.4-0.9% of patients using anti-PD-1 agents. Fasting blood glucose is the preferred test for patient follow-up and surveillance. Importantly, the use of high-dose corticosteroids for the treatment of other irAEs can induce or exacerbate hyperglycemia. Diabetic ketoacidosis may occur, even in patients with a previous diagnosis of type 2 diabetes and may present with symptoms such as increased thirst, pollakiuria, nausea, vomiting, mental confusion, abdominal pain, and dehydration. Corticosteroid therapy is not recommended for the treatment of type 1 diabetes since there is no evidence to support its use and it may further worsen glycemic control.[69,70]

Regardless of the presentation of endocrine irAEs, the permanent discontinuation of treatment is rarely recommended if hormone replacement therapy is initiated and the symptoms resolve. Follow-up by an endocrinologist is recommended.

Uncommon irAEs

As previously discussed, irAEs presentations are extremely heterogeneous and any organ/tissue could theoretically be the target of an immune-mediated injury. With the expansion of the use of immune coreceptor blockers, greater knowledge about rare irAEs has been acquired.

Cardiac irAEs

Cardiac irAEs, including myocarditis, pericarditis, cardiac fibrosis, arrhythmias, and heart failure, can occur even in patients without significant risk factors, and are associated a high mortality rate. The time to onset of these events is variable, and may occur after a single dose of immunotherapy. Patients receiving combination therapies appear to be at an increased risk for these AEs, followed by patients receiving anti-PD- 1 monotherapy.[71] The role of cardiac enzymes monitoring remains uncertain, despite being included in more recent research protocols in addition to periodic echocardiography or other imaging tests. The treatment of cardiac irAEs should be adapted according to the severity of the clinical presentation (Appendix 6, Supplementary Material). Permanent discontinuation of therapy is recommended, with the initiation of high-dose corticosteroids (prednisone 1-2mg/kg). The timing of the initiation of corticosteroid therapy in mild cases should be individualized considering the lack of data in this setting. In refractory patients, doses of corticosteroids similar to those used in cases of heart transplant rejection are usually indicated (1g of methylprednisolone per day, for 3 to 5 days) in addition to the addition of mycophenolate or infliximab.[72]

Hematologic irAEs

Hematological irAEs are rare, although a myriad of manifestations has been described. An analysis of the World Health Organization pharmacovigilance database identified 168 cases of hematological irAEs. The most common cases were immune thrombocytopenic purpura (68 cases) and hemolytic anemia (57 cases), including four cases in which both conditions occurred concurrently.[73] The incidence of anemia and thrombocytopenia appears to be higher in patients treated with ICIs for refractory Hodgkin's disease, which may be partly related to the previous use of myelotoxic therapies.[74] The treatment of hematological irAEs must be adapted to the condition's severity (Appendix 7, Supplementary Material). In steroid-refractory presentations, a bone marrow biopsy should be considered. In addition to the usual approaches, management of hematological irAEs may also include transfusion support, rituximab, and plasmapheresis. Ruling out alternative diagnoses for hematological conditions is of paramount importance, and possible causes include disease progression, bone marrow infiltration, bleeding, and AEs of other drugs.

Neurologic irAEs

Approximately 14% of patients using ipilimumab plus nivolumab may develop neurological irAEs, a significantly higher incidence than with anti-CTLA-4 or anti-PD-1 monotherapy, which have an incidence of 1% and 3%, respectively. Guillain-Barré syndrome, myasthenia gravis, aseptic meningitis, limbic encephalitis, transverse myelitis, reversible posterior encephalopathy syndrome, enteric neuropathy, granulomatous inflammation of the central nervous system, and Tolosa-Hunt syndrome have been reported. Severe cases of limbic encephalitis were reported in patients with small cell lung cancer.

Neurological paraneoplastic syndromes or autoimmune encephalitis can be exacerbated or revealed by the immune stimuli triggered by immunotherapy. Thus, tumors with a greater propensity to develop neurological paraneoplastic syndromes, such as small cell lung carcinoma and Merkel carcinoma, must be monitored with special attention to the possibility of neurological irAEs.[75-77]

The management of neurologic irAEs is similar to that for other irAEs (Appendix 8, Supplementary Material). In patients whose symptoms are suggestive of neurological irAEs, corticosteroid therapy and discontinuation of immunotherapy should be considered, even in mild presentations. Intravenous immunoglobulin and plasmapheresis may be considered in addition to corticosteroids and immunosuppressants. Pyridostigmine may be considered for patients with myasthenia gravis. Approximately one-third of patients with neurological irAEs have residual sequelae.[77] Pre-existing neurological conditions should not contraindicate treatment; however, individual risks should be evaluated before the use of ICIs.[78]

Rheumatic irAEs

The most common musculoskeletal and rheumatological symptoms are arthritis and polymyalgia, but their incidence has not been precisely established, which reflects the difficulty distinguishing between irAEs and musculoskeletal symptoms caused by other factors. Arthralgias without clear inflammatory signs can also significantly impact quality of life and require specific procedures. A meta-analysis that included clinical trials, observational studies, and case reports or case series reported an incidence of arthralgia of 1.0-43% and myalgia of 2.0-20%, showing a significant variability between reported symptoms and diagnosed rheumatological irAEs. Anti-PD-1 therapy is more commonly associated with rheumatologic irAEs. Myositis, although rare, can be fatal and present as a reactivation of preexisting paraneoplastic polymyositis or dermatomyositis.

Depending upon the clinical manifestation, mild cases can be managed with anti-inflammatory drugs, and in case of treatment failure, corticosteroids should be initiated. Disease-modifying antirheumatic drugs (DMARDs) and even plasmapheresis may be used in steroid-refractory patients, in addition to other rheumatological monoclonal antibodies commonly used for autoimmune conditions.[79-82] The approach to rheumatological irAEs must be adapted according with the event's severity (Appendix 9, Supplementary Material). In a cohort of 65 patients, predominantly composed of patients with lung cancer and melanoma who developed musculoskeletal symptoms, an algorithm for the management of irAEs led to symptom control in 54.4% of patients using prednisone 10 mg associated or not with non-steroidal anti-inflammatories (NSAIDs), and 12.3% required the use of DMARDs. Treatment was discontinued in 8.8% of cases and, as demonstrated in other immune-mediated toxicities, complete disease remission in patients with melanoma was observed in 39% of patients with rheumatologic irAEs, compared to 4% of patients without irAEs.[83]

Renal irAEs

Although initially characterized as rare (3.0-5.0% of patients), any renal grade irAEs may occur in 15-20% of patients treated with ICIs. Acute interstitial nephritis is the most common finding in renal biopsies. Renal toxicities have an earlier onset with combined regimens (2-3 months) than with anti-PD-1 monotherapy (3-10 months). In particular, patients being treated with platinum, pemetrexed, and pembrolizumab combination regimen should be closely monitored due to an increased risk of renal toxicity. The treatment of renal AEs should be tailored to the severity of the irAE (Appendix 10, Supplementary Material).

Ophthalmic irAEs

Ocular irAEs include uveitis, episcleritis, and conjunctivitis.[84] In a pharmacovigilance database, ophthalmic events were rare, representing up to 3% of all irAEs reported, with visual disorders (30.8%) and uveitis (15%) being the most common events. The combination of anti-CTLA-4 and anti-PD-1 results in the greatest risk for the development of uveitis (OR=4.77; 95%CI=3.835.94). Regarding tumor types, patients diagnosed with melanoma (OR=14.7; 95%CI=10.7-20.2) appear to be at higher risk of developing uveitis than those with lung cancer (OR=2.67; 95%CI=1.68-4.23).[85]

CONCLUSION

Despite the unequivocal clinical benefits resulting from ICIs, the mechanism of action of these agents implies an intrinsic risk of immune responses directed to healthy tissues, clinically manifesting as irAEs. Thus, a better understanding of their toxicities and the adequate management of AEs are crucial for therapeutic success. In addition to effective communication, the early diagnosis and timely initiation of measures to treat irAEs and the identification of irAE biomarkers are critical in determining the risks and benefits of these agents. Data suggest that the diversity of T-cell receptors[71] and the tumor mutational burden[86] may be associated with a higher incidence of irAEs; however, larger studies are needed to confirm this correlation. More recently, integrated drug-surveillance and multiomic evaluations have identified a possible correlation between gene mutations in LCP1 and ADPGK as predictive factors for irAEs; however, validation of this hypothesis in larger cohorts is necessary.[87]

Currently, a major limitation in the treatment of irAEs is the lack of anatomopathological correlation and a better definition of the mechanisms involved in each irAE, which translates into approaches that are still unspecific, and largely based on the use of steroids.

In current clinical practice, most treatments are still empirical and based on therapies extrapolated from correlate autoimmune diseases. Expanding the knowledge about pathophysiological mechanisms are likely to result in optimized and more specific therapeutic approaches. Immune-related dermatitis, for example, may be associated with an increase in interleukin-6, immunoglobulin E, and eosinophilic infiltrate, and each of these pathophysiological factors could be treated individually with different therapies.

Increasing and continuous development of immune-checkpoint modulators, combination therapies, and other immunotherapies are expected in the near future, making the recognition and proper management of irAEs even more challenging. Thus, the education of patients and healthcare providers involved in cancer care (nutritionists, physiotherapists, nursing professionals, and caregivers), continuing medical education, and continuously updating of guidelines, and encouragement of a multidisciplinary approach in collaboration with other experts (such as dermatologists, rheumatologists, gastroenterologists, and pulmonologists), are crucial for therapeutic success and for reducing the impact of these toxicities. Finally, continuous efforts to elucidate the pathophysiological mechanisms and develop national and international multicentric registries should be encouraged, as they are fundamental tools for increasing our understanding and improving the management of irAEs and for a safe treatment of cancer patients.

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SUPPLEMENTARY MATERIAL

Appendix 1A. Approach and management: colitis/diarrhea.

Colitis/diarrhea			
Grade*	**Management**	**Treatment**	**Observation**
1 Less than 4 bowel movements/day	Outpatient Continue treatment with immunotherapy	Monitoring/symptomatic (loperamide). Rehydration.	Monitoring. Laboratory tests in each administration.
2 4-6 bowel movements/day Abdominal pain or blood/mucus in stool	Outpatient Discontinue/delay administration of immunotherapy Consider colonoscopy in refractory cases	Rehydration/management of electrolyte disorders. If it lasts for more than 2-3 days or worsening: prednisone PO 0.5-1.0mg/kg/day (or equivalent).	Clinical reevaluation every 3-5 days, until improvement. If it gets worse, adjust treatment according to its severity. After improvement, corticosteroid tapering over at least 4 - 6 weeks. Consider prophylaxis for opportunistic and parasitic infections. Consider rechallenge if prednisone dose <10 mg/day, grade 1 toxicity, or complete resolution. If using a combination of anti-CTLA-4 and anti-PD-1/PD-L1, continue only anti-PD-1/PD-L1.
3-4 7 or more bowel movements/day/ incontinence Hemodynamic instability/severe pain/peritonitis/ fever	Inpatient Discontinue immunotherapy Consider colonoscopy Consider specialist evaluation	Consider intensive care support. Rehydration/management of electrolytic disorders. Methylprednisolone IV 1.0-2.0mg/kg/day (or equivalent). Consider prophylaxis. Consider infliximab or vedolizumab if there is no improvement in 3 days; Vedolizumab may be an alternative in refractory cases or contraindication to infliximab, as well as other immunosuppressants (example: mycophenolate). Empirical antibiotic therapy if fever/ hemodynamic instability or suspected co-infection.	Intravenous corticosteroids can be switched for oral if clinical improvement/stabilization. After improvement, corticosteroid tapering over at least 6 weeks. Consider prophylaxis for opportunistic and parasitic infections. Grade 3: consider rechallenge if prednisone dose <10mg/day, grade 1 toxicity or complete resolution. If using a combination containing anti-CTLA-4 and anti-PD-1/PD-L1, consider continuing only anti-PD-1/PD-L1 agent. Grade 4: definitive discontinuation of immunotherapy.

*According to CTCAE v.4; In any grade, exclude differential diagnoses, particularly infectious diarrhea (ex: *Clostridium difficile*); #: Do not use infliximab if intestinal perforation or sepsis is suspected - in these situations, consider mycophenolate or another immunosuppressant.

Appendix 2A. Approach and management: hepatitis and/or elevation of alanine aminotransferase/aspartate aminotransferase.

Hepatitis and/or elevated AST/ALT			
Grade*	**Management**	**Treatment**	**Observation**
1 AST or ALT <3 times upper limit of normal (ULN) and/or bilirubin >1.5 times the ULN	Outpatient Continue treatment with immunotherapy.	Monitoring.	Monitoring (laboratory test 1-2 times a week). Laboratory tests each administration. If it is worsening, adjust treatment according to severity/grade.
2 AST or ALT >3-5 times ULN or bilirubin >1.5-3.0 ULN	Outpatient. Discontinue/delay the administration of immunotherapy.	If it lasts more than 5-7 days or worsening: prednisone PO 0,5-1,0mg/day (or equivalent) .	Clinical/laboratory reassessment every 3 days until improvement. If it is worsening, adjust treatment according to severity/grade. After improvement, corticosteroid tapering over at least 4-6 weeks. Consider prophylaxis for opportunistic and parasitic infections. Consider rechallenge if prednisone dose <10mg/day, toxicity grade 1 or complete resolution.
3-4 AST or ALT >5 times ULN or bilirubin >3 times ULN	Inpatient. Discontinue immunotherapy. Liver biopsy not routinely recommended, but it may be considered in selected patients. Consider specialist evaluation.	Methylprednisolone IV 1.0-2.0mg/kg/day (or equivalent). Consider prophylaxis. Consider immunosuppressant (mycophenolate mofetil 500-1000mg 12/12h) if it is not improving in 3-5 days. Empirical antibiotic therapy if fever/ hemodynamic instability. Do not use infliximab.	Monitoring every 24-48h. Intravenous corticosteroids can be switched for oral if clinical improvement/stabilization. After improvement, corticosteroid tapering over at least 4-6 weeks. Consider prophylaxis for opportunistic and parasitic infections. Definitive discontinuation of immunotherapy.**

*According to CTCAE v.4; To any grade, exclude differential diagnoses particularly viral hepatitis and use of other drugs (statins, antibiotics); #: If hepatitis grade 4, the recommended dose of methylprednisolone IV is 2mg/kg/day; **Consider, in selected patients, delay of immunotherapy, and not definitive discontinuation, if AST/ALT up to 8x ULN and/or bilirubin up to 5x ULN; ULN: Upper limit of normal.

Appendix 3. Approach and management: pulmonary adverse events/pneumonitis.

Pulmonary adverse events/pneumonitis			
Grade*	**Management**	**Treatment**	**Observation**
1 Asymptomatic (only radiological changes)	Outpatient. Consider discontinuation/delay administration of immunotherapy.	Monitoring.	Clinical reassessment every 2-3 days; imaging test in 2-3 weeks. Consider rechallenge if improvement or resolution of radiological changes. If it is worsening, adjust treatment according to severity/grade.
2 Symptoms (daily living limitations)	Outpatient. Discontinue/delay administration of immunotherapy. Consider specialist evaluation.	Prednisone 1.0mg/kg/day (or equivalent).	Clinical reassessment every 1-2 days; imaging test in 3 days. After improvement, corticosteroid tapering over at least 4-6 weeks. Consider prophylaxis for opportunistic and parasitic infections. Consider empiric antibiotics. Consider reintroducing treatment if toxicity grade 1 or complete resolution. If persistent toxicity after 2 weeks or recurrent toxicity, consider definitive discontinuation of treatment as grade 3-4.
3-4 Symptoms (self-care limitations) or potentially fatal/ hypoxemia	Inpatient. Discontinue immunotherapy. Consider bronchoscopy/lung biopsy. Considerer specialist evaluation.	Consider intensive care/oxygen. Methylprednisolone IV 2.0-4.0mg/kg/day (or equivalent). Consider prophylaxis. Consider infliximab, mycophenolate mofetil or cyclophosphamide if there is no improvement within 48 hours. Empiric antibiotics.	IV corticosteroids can be switched for oral if clinical improvement/stabilization. Consider empirical antibiotic. After improvement, corticosteroid tapering over at least 6-8 weeks. Consider prophylaxis for opportunistic and parasitic infections. Grade 3: consider rechallenge in selected patients after resolution of the condition. Definitive discontinuation of immunotherapy.

*According to CTCAE v.4; In any grade, exclude differential diagnoses, particularly respiratory infections.

Appendix 4. Approach and management of rash or pruritus.

Management of maculopapular rash and/or pruritus				
Grade*	**Management**	**Local treatment**	**Systemic treatment**	**Observation**
1 (<10% BSA) ou 2 (10-30% BSA) tolerable	Outpatient. Continue immunotherapy therapy.	Low to medium potency corticosteroid 2x/day. (mometasone, budesonide)	Antihistamine PO (if associated pruritus).	Clinical reevaluation every 1-2 weeks. If it is worsening/persistence, step treatment and consider discontinue/ delay administration.
2 (unbearable) 10-30% BSA	Outpatient. Consider discontinue/delay administration. Consider skin biopsy. Consider specialist evaluation.	Medium/high potency corticosteroid 2x/day. (0.1% betamethasone cream, valerate)	Antihistamine PO (if associated pruritus). Consider GABA receptor agonists (pregabalin, gabapentin) (if associated pruritus). Prednisone 0.5-1.0mg/kg/day (or equivalent).	Clinical reevaluation every 1-2 weeks. After improvement, corticosteroid tapering over at least 4 weeks. Consider prophylaxis. Consider rechallenge if toxicity grade 1 or complete resolution. If worsening/persistence or if it recurs, increase treatment.
3 >30% BSA	Inpatient Discontinue / delay administration of immunotherapy Specialist evaluation and skin biopsy recommended	High potency corticosteroid 2x/day (betamethasone, dipropionate)	Antihistamine PO Consider GABA receptor agonists (pregabalin, gabapentin), or NK-1 receptor antagonist, aprepitant (if associated pruritus) Methylprednisolone EV 1.0-2.0mg/ kg/day (or equivalent) or Prednisone 1.0-2.0mg/kg/day (or equivalent). Consider prophylaxis.	Consider IV to oral corticosteroids switch if clinical improvement/stabilization. After improvement, corticosteroid tapering over at least 4 weeks. Consider prophylaxis for opportunistic and parasitic infections. Consider rechallenge if toxicity grade 1 or complete resolution. Consider definitive discontinuation if recurrence.
4 (Papules a/ or pustules, TEN, SJS)	Inpatient. Discontinue immunotherapy. Specialist evaluation and skin biopsy recommended.	Supportive measures and restoring the skin barrier.	Consider intensive care. Methylprednisolone EV 1.0-2.0mg/kg/day (or equivalent). Consider GABA receptor agonists (pregabalin, gabapentin), or the NK-1 receptor antagonist, aprepitant (if associated pruritus). Empirical antibiotic.	Consider IV to oral corticosteroids switch if clinical improvement/stabilization. After improvement, corticosteroid tapering over at least 4 weeks. Consider prophylaxis for opportunistic and parasitic infections. Definitive discontinuation of immunotherapy.

*According to CTCAE v.4; To any grade, exclude differential diagnoses and recommend hydration and photoprotection care; BSA: Body surface area; TEN: Toxic epidermal necrolysis; SJS: Stevens-Johnson syndrome.

Appendix 5. Approach and management: endocrine diseases.

Endocrine disorders			
Description*	**Management**	**Treatment**	**Observation****
Asymptomatic TSH elevation	Outpatient. Continue immunotherapy treatment. Consider specialist evaluation.	Monitoring.	Monitoring. Laboratories test each application. If it is worsening, adjust treatment according to severity/grade.
Hyperthyroidism	Outpatient if asymptomatic. Consider hospitalization in. symptomatic patients. Specialist evaluation recommended.	Consider discontinuation/delay immunotherapy if symptomatic. If symptoms, evaluate the initiation of beta-blockers and other measures, such as antithyroid agents.	Monitoring and consider the possibility of hypothyroidism after resolution of hyperthyroidism. If persistent hyperthyroidism, assess Graves' disease and the need for treatment. Consider rechallenge.**
Systemic endocrine disease	Outpatient. Consider discontinuation/delay administration Consider pituitary MRI. Specialist evaluation recommended.	Initiate hormone replacement. Prednisone 1.0-2.0mg/kg PO or methylprednisolone 1.0-2.0mg/kg IV (or equivalent) in patients with hypophysitis with mass effect. In patients with hypophysitis, always initiate corticosteroids some days before thyroid hormone replacement due to the risk of adrenal crisis.	Reassessment every 1-3 weeks. After improvement, corticosteroid tapering over at least 4 weeks. Consider prophylaxis for opportunistic and parasitic infections. Consider rechallenge.**
Adrenal crisis suspected	Inpatient. Discontinue/delay administration. Specialist evaluation recommended. Rule out sepsis.	Intensive care. Rehydration/correction of electrolytic disorders. Glucocorticoid and mineralocorticoid replacement. Consider empiric antibiotics.	Monitoring every 24-48h. Hormone replacement administration route can be changed after improvement. Consider rechallenge.**

*To any grade, exclude differential diagnoses; **It is acceptable to rechallenge if endocrine disease, even if grade 3 or higher, provided that it is adequately controlled with hormonal replacement, the patient is asymptomatic, and there is no mass effect.

Appendix 6. Approach and management: cardiac adverse events.

Cardiac adverse events			
Grade*	**Management**	**Treatment**	**Observation**
1 Elevation of myocardial injury markers and/or ECG	Discontinue immunotherapy. Consider specialist evaluation.	Transfer patients to coronary care unit if elevated troponin or ECG changes. Optimization of heart disease control (example: atrial fibrillation, heart failure, high blood pressure) . Consider early administration of prednisone 1.0-2.0mg/kg/day (or equivalent) depending on changes in tests.	Consider definitive discontinuation even in toxicity grade 1. If it is worsening, adjust treatment according to severity/grade.
2 Alteration of tests with mild symptoms	Discontinue immunotherapy Consider specialist evaluation	Transfer patients to coronary care unit if elevated troponin or ECG changes. Optimization of heart disease control (example: atrial fibrillation, heart failure, high blood pressure). Prednisone 1.0-2.0mg/kg/day (or equivalent).	Consider definitive discontinuation. After improvement, corticosteroid tapering over at least 4-6 weeks. Consider prophylaxis for opportunistic and parasitic infections. If it is worsening, adjust treatment according to severity/grade.
3-4 Moderate/ severe cardiac decompensation	Inpatient. Discontinue immunotherapy. Consider specialist evaluation.	Consider intensive care. Methylprednisolone EV 2.0-4.0mg/kg/day (or equivalent). Consider prophylaxis. Consider infliximab, mycophenolate mofetil, or tacrolimus if there is no improvement within 48 hours.	IV corticosteroids can be replaced for oral if clinical improvement/stabilization. After improvement, corticosteroid tapering over at least 6-8 weeks. Consider prophylaxis for opportunistic and parasitic infections. Definitive discontinuation of immunotherapy.

*According to CTCAE v.4; In any grade, exclude differential diagnosis.

Appendix 7. Approach and management: hematologic adverse events.

Hematologic adverse events			
Grade*	**Management**	**Treatment**	**Observation**
1 Hemoglobin >10g/d; Platelets >75,000/mm^3	Continue immunotherapy treatment. Considerer specialist evaluation.	Monitoring. Consider early initiating of prednisone 1.0-2.0mg/kg/day (or equivalent) depending on symptoms and speed of alterations.	Monitoring. Laboratory test for each application. If it is worsening, adjust treatment according to severity/grade.
2 Hemoglobin: 8-10g/dL; Platelets: 50,000 to 75,000/mm^3	Discontinue/delay immunotherapy administration. Considerer specialist evaluation.	Prednisone 1.0-2.0mg/kg/day (or equivalent).	Consider definitive discontinuation. After improvement, corticosteroid tapering over at least 4-6 weeks. Consider prophylaxis for opportunistic and parasitic infections. If it is worsening, adjust treatment according to severity/grade.
3-4 Hemoglobin <8g/dL; Platelets <50,000/mm^3	Inpatient. Discontinue immunotherapy. Considerer specialist evaluation. Consider bone marrow biopsy.	Consider intensive care. Transfusion support Consider rituximab, mycophenolate mofetil, immunoglobulin IV or plasmapheresis if there is no improvement within 48 hours	After improvement, corticosteroid tapering over at least 6-8 weeks. Consider prophylaxis for opportunistic and parasitic infections. Definitive discontinuation of immunotherapy.

*According to CTCAE v.4; In any grade, exclude differential diagnosis.

Appendix 8. Approach and management: neurological adverse events.

Neurological adverse events			
Grade*	**Management**	**Treatment**	**Observations**
1 Mild (No functional change)	Low threshold for discontinuation of immunotherapy. Consider specialist evaluation.	Monitoring. Consider early initiating of Prednisone 1.0-2.0mg/kg/day (or equivalent) depending on tests alteration.	Consider screening for diabetes mellitus, folate/B12, HIV, TSH, vasculitis, history of alcoholism. If it is worsening, adjust treatment according to severity/grade.
2 Moderate (symptoms cause some functional limitation)	Discontinue immunotherapy. Consider specialist evaluation.	Prednisone 1.0-2.0mg/kg/day (or equivalent).	Consider pulmonary function test and CSF analysis. Consider definitive discontinuation if refractoriness or absence of improvement of the condition. After improvement, corticosteroid tapering over at least 4-6 weeks. Consider prophylaxis for opportunistic and parasitic infections. If it is worsening, adjust treatment according to severity/grade.
3-4 Severe Functional limitation/respiratory symptoms	Inpatient. Discontinue immunotherapy. Consider specialist evaluation.	Consider intensive care. Methylprednisolone EV 2.0-4.0 mg/kg/day (or equivalent). Consider prophylaxis. Consider IV immunoglobulin or plasmapheresis if there is no improvement within 48 hours pyridostigmine may be beneficial in patients with myasthenia gravis.	Consider IV to oral corticosteroids if clinical improvement/stabilization. After improvement, corticosteroid tapering over at least 6-8 weeks. Consider prophylaxis. Definitive discontinuation of immunotherapy.

*According to CTCAE v.4; In any grade, exclude differential diagnosis.

Appendix 9. Approach and management: rheumatic and musculoskeletal adverse events.

Rheumatic adverse events			
Grade*	**Management**	**Treatment**	**Observation**
1 Mild pain with inflammatory symptoms	Continue immunotherapy.	Analgesia: Non-steroidal anti-inflammatory, metamizole, acetaminophen.	Monitoring Consider X-ray of the affected joint to exclude metastasis If it is worsening, adjust treatment according to severity / grade
2 Moderate pain with inflammatory symptoms; some functional limitation	Discontinue/delay administration of immunotherapy. Consider specialist evaluation.	Step analgesia. Consider intra-articular corticosteroids. Prednisone 10-20mg/day (or equivalent).	Consider Ultrasonography or MRI of most affected joints Consider reintroducing treatment if toxicity grade 1 or complete resolution If it is worsening, adjust treatment according to severity / grade
3-4 Severe pain with inflammatory symptoms and important functional limitation	Inpatient. Discontinue immunotherapy. Consider specialist evaluation. Consider bone marrow biopsy.	Prednisone 1.0-2.0mg/kg/day (or equivalent). Methylprednisolone EV 2.0-4.0mg/kg/day (or equivalent), if there is no improvement. Consider prophylaxis. Consider infliximab or disease-modifying antirheumatic drugs (DMARDs) if there is no improvement within 48 hours, as well as immunosuppressants.	After improvement, corticosteroid tapering over at least 6-8 weeks. Consider prophylaxis for opportunistic and parasitic infections. Consider definitive discontinuation of immunotherapy.

**According to CTCAE v.4; In any grade, exclude differential diagnosis.

Appendix 10. Approach and management: renal adverse events.

Renal adverse events			
Grade*	**Management**	**reatment**	**Observation**
1 Creatinine >1.5x ULN	Continue immunotherapy.	Monitoring. *According to CTCAE v.4; In any grade, exclude differential diagnosis.	Monitoring with kidney function test every week. Review hydration, medications, urinalysis. If it is worsening, adjust treatment according to severity/ grade.
2 Creatinine:1.5x e 3x ULN	Discontinue/delay administration of immunotherapy Consider renal biopsy. Consider specialist evaluation.	Consider hydration. Prednisone 1.0-2.0mg/kg (or equivalent).	Re-evaluate creatinine in 48-72h. Consider renal ultrasonography. Consider rechallenge if toxicity grade 1 or complete resolution. If it is worsening, adjust treatment according to severity/ grade.
3-4 *Creatinine >3x ULN*	Inpatient. Discontinue immunotherapy. Renal biopsy. Consider referral.	Methylprednisolone EV 2.0-4.0mg/kg/day (or equivalent), if there is no improvement. Consider prophylaxis.Consider infliximab, cyclosporine, mycophenolate mofetil if there is no improvement within 48 hours.	After improvement, corticosteroid tapering over at least 6-8 weeks. Consider prophylaxis for opportunistic and parasitic infections. Consider definitive discontinuation of immunotherapy.

*According to CTCAE v.4; In any grade, exclude differential diagnosis.

Appendix 1B. Drugs and doses most commonly used to manage immune-related adverse events.

Drug	Dose	Observation
Prednisone	0,5-2,0mg/kg/day PO	A long interval is recommended for complete discontinuation, usually 4-6 weeks. Consider prophylaxis for opportunistic infections.
Methylprednisolone	1,0-4,0mg/kg/day IV	Switching to oral corticosteroids should be considered after the condition has stabilized. A long interval is recommended for complete discontinuation, usually 4-6 weeks. Consider prophylaxis for opportunistic infections.
Mycophenolate mofetil	500-1000mg bid	Once initiated, discontinue if adverse event improves and prednisone dose ≤10mg/day.
Infliximab	5,0mg/kg IV every other week	Do not use if sepsis, suspected intestinal perforation or liver toxicity.
Vedolizumab	300mg IV (may be repeated after 2 weeks)	Contraindicated if sepsis or serious active infections, such as tuberculosis, cytomegalovirus, or other opportunistic infections.
Immunoglobulin IV	2,0g/kg per 5 days (0,4g/kg/day)	Maintenance therapy may be necessary depending on irAE and severity. Monitoring renal function in patients with nephropathy.
Rituximab	375mg/m^2 weekly for 4 weeks or 500mg/m^2 every other week (perform 2 doses)	Risk of hepatitis B virus reactivation - serology is recommended before initiating the treatment.
Cyclosporine	2-5mg/kg/day IV or PO bid	Dose depending on toxicity and grade.

Appendix 2B. Potential conflicts of interest of the authors of the drafting of the guidelines in the 12 months prior to submission.

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Alberto Julius Wainstein	BMS, MSD.	BMS, MSD, Roche, Sanofi.	MSD, Roche, Sanofi.	--	
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Rodrigo R. Munhoz	Bayer, Daiichi-Sankyo, BMS, MSD, Sanofi.	Bayer, Daiichi-Sankyo, BMS, MSD, Novartis, Merck, Sanofi.	BMS.	Bayer, BMS, Merck, MSD, Novartis, Roche.	Hospital Sírio Libanês e ICESP – São Paulo.
Romualdo Barroso-Souza	AstraZeneca, Eli Lilly, Libbs, MSD, Roche.	BMS, Bard Access, Eli Lilly, Libbs, Novartis, Pfizer, MSD, Roche.	Roche, Eli Lilly, Daiichi-Sankyo, MSD.	Roche, BMS.	Hospital Sírio-Libanês e Instituto Hospital de Base – Brasília.
Sergio J. Azevedo	--	--	--	--	Oncoclínicas – Porto Alegre.
Vladmir C. C. de Lima	BMS, Amgen, Merck-Serono, Janssen, AstraZeneca, MSD, Novartis.	Amgen, AstraZeneca, BMS, GSK, Novartis, MDHealth, MSD.	BMS, AstraZeneca, Eli Lilly, MSD.	BMS (institutional designations).	A C Camargo Cancer Center.
William William	AstraZeneca, Roche, BMS, Sanofi, Janssen, Pfizer, Novartis, MSD, Takeda.	Boehringer Ingelhein, Eli Lilly, Merck, AstraZeneca, Roche, BMS, Sanofi, Janssen, Pfizer, Novartis, MSD, Takeda.	AstraZeneca, Roche, BMS, Eli Lilly, MSD, Takeda.	AstraZeneca, Roche, BMS, MSD.	A Benefiência Portuguesa – São Paulo.