The ION-Ghent guidelines for the management of immune related adverse events (irAE's)

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SUMMARY

Checkpoint inhibitors targeting CTLA4, PD1 and PD-L1 have become a part of the daily clinical practice in the management of stage IV melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC) and Hodgkin-lymphoma patients. While these agents can elicit strong anti-tumour immune responses, they can also generate immune related adverse events, which can become life threatening if not detected and managed promptly. At the University Hospital Ghent, we created a working group of organ specialists with specific experience in dealing with immune related adverse events. This initiative is part of ION (Immuno-Oncology-Network) Ghent. In this paper we would like to share our institutional guidelines for the clinical care of patients treated with checkpoint-inhibitors with the Belgian Oncology Community.

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INTRODUCTION

Checkpoint inhibitors are becoming part of the daily oncology practice. Ipilimumab (anti-CTLA4 antibody) was the first checkpoint inhibitor to be reimbursed for the treatment of metastatic melanoma (June 2012). Since April 2016 nivolumab and pembrolizumab (both anti-PD1 antibodies) have also become available in Belgium for this indication. By January 2017 the reimbursement criteria for nivolumab were expanded to include patients with stage IV RCC, NSCLC and Hodgkin Lymphoma. As in melanoma, pembrolizumab will also be available for first line treatment of metastatic NSCLC, albeit in a biomarker-selected population. Additionally, the combination treatment of ipilimumab plus nivolumab has become available for the treatment of metastatic melanoma. These antibodies have resulted in impressive results in patients who had no other treatment options.

However, checkpoint inhibitors can cause a wide range of immune-related adverse events (irAEs). Grade 3/4 treatment-related adverse events are observed in 22-24% of ipilimumab-treated patients, in 5-10% of nivolumab- or pembrolizumab-treated patients and in 55% of patients treated with the combination of ipilimumab plus nivolum-

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Keywords: checkpoint inhibitors, immune related adverse events, irAE's, management, toxicity.

FIGURE 1A.

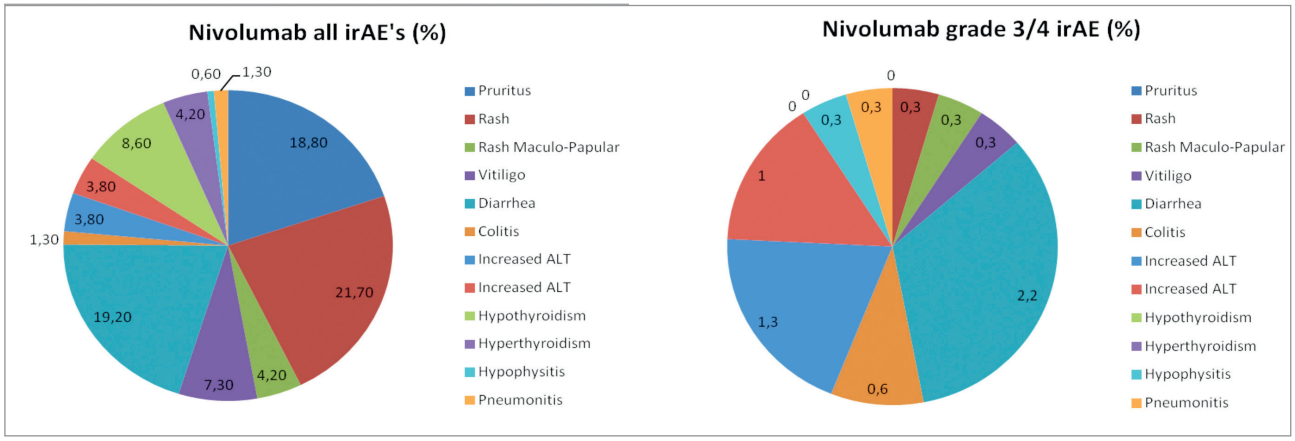
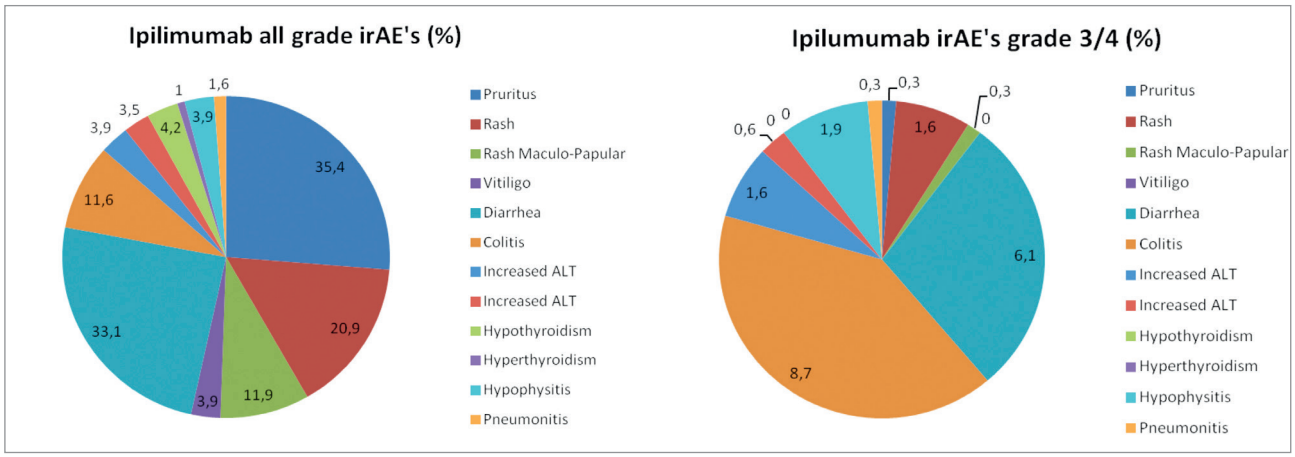


FIGURE 1B.



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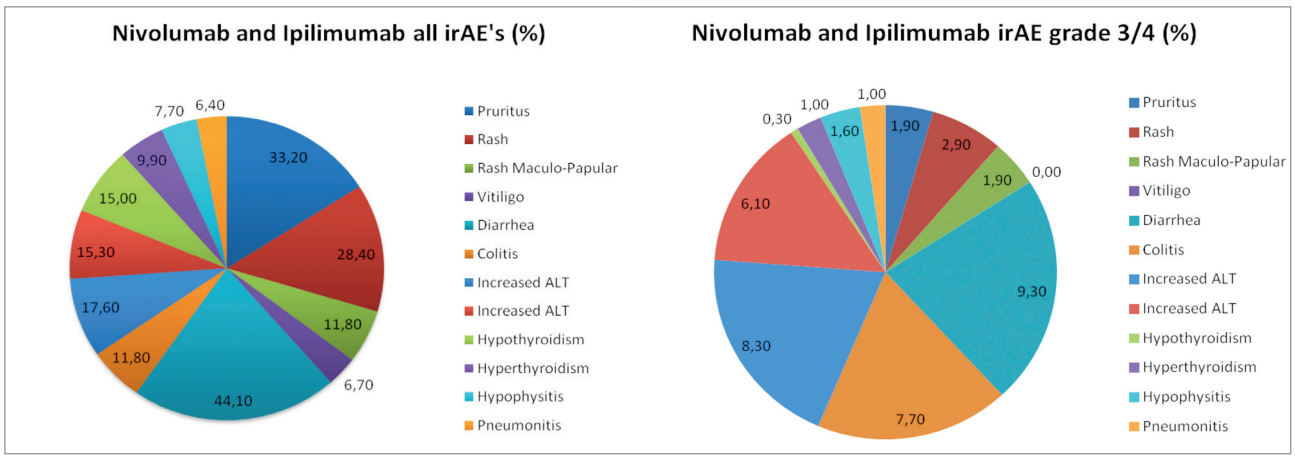

FIGURE 1. Distribution of irAE's per treatment (nivolumab, ipilimumab or the combination) based on data from the CheckMate 067, investigating these drugs in metastatic melanoma-patients (Larkin et al., NEJM 2015, supplementary index, table S3).[4] The clinician should be aware that the risk of a certain immune-related adverse event may depend on the type of cancer, e.g. pneumonitis induced by treatment with anti-PD1 has been more frequently described in patients with NSCLC.[1]

Table 1. Basic evaluations, that have to be done, by treatment initiation and during follow up, for asymptomatic patients.

	At baseline (2w before start treatment)	Before every administration	Every 6 w during treatment	Every 3m after stop treatment for 1y	Every 6m >1y after stop treatment
Physical Examination - Performance status - Body weight - HR (heart rate) and blood pressure - History of Fever/infection - Particular attention to the symptoms mentioned in *Table 2*	x	X	X	X	X
ECG	X				
Pulmonary Function Test*	X				
Laboratory test - Complete blood count - Electrolytes: Na, K, HCO3, Ca, Phosphorus, urea, creatinine with estimated GFR - Glycemia - AST, ALT, GGT, bilirubine - Albuminemia, CRP	X	X	X	X	X
Hormonal status - TSH, T4 - Cortisol, ACTH - LH, FSH, estradiol, testosterone	X	X	X	X	X

* to be considered, depending on medical history of the patient, primary cancer diagnosis, co-morbidity and symptoms.

ab.[1-3] Prompt diagnosis and adequate management are of utmost importance to reduce morbidity and to enable treatment continuation.

To address these safety issues, we have created an immunotherapy working group of organ specialists at the Ghent University Hospital, experienced in dealing with irAEs. This working group wrote institutional guidelines for the clinical care of patients treated with checkpoint-inhibitors. In this manuscript we share these guidelines with the Belgian Oncology Community.

THE PATHOPHYSIOLOGY OF IRAES IN BRIEF

After recognition of cancer cells by the host's immune system, the amplitude of the anti-tumour immune response is the result of a balance between co-stimulatory and inhibitory signals, the latter being the immune checkpoints. In normal circumstances, these immune checkpoints maintain self-tolerance and protect the host tissues from damage by an immune response (e.g. during infections). Administration of antibodies that block the CTLA4 and PD-1 co-inhibitory immune checkpoint molecules increases the antigen-specific T-cell immune responses. Hereby the immune system is turned against the tumour. As a consequence, self-tolerance can be disrupted, resulting in an uncontrolled immune response. This can cause autoimmune or inflammatory side effects with a risk of collateral damage to normal organ systems and tissues (most frequently affecting skin, gastrointestinal, hepatic, pulmonary, and endocrine systems).[4,5]

SAFE ADMINISTRATION OF CHECKPOINT – INHIBITORS

CLINICAL PRESENTATION OF IRAE'S – WHAT TO EXPECT?

Nearly all organs can be affected by immune related adverse events. Some patients experience mild toxicities without any impact on daily life, while other patients develop severe life-threatening irAEs requiring urgent medical care. So far, the incidence rates of the latter have been relatively low, but with an increasing number of patients treated with immunotherapy, the number of clinical cases will rise. The distributions of the most irAEs per treatment are illustrated in *Figure 1*.[4]

TIMING OF ONSET OF IRAES

Immune related adverse events can occur at any time during treatment: at the beginning, during or after treatment discontinuation.

Before immunotherapy initiation, an extended evaluation should be performed. A detailed patient medical history is essential, as existing autoimmune conditions can flare up during immunotherapy. Patients and their healthcare providers, including their general practitioner, should always be informed of the specific side effects of checkpoint inhibitors before treatment initiation. Self-management should strongly discouraged.[5]

Identification and early treatment of immune related AEs are essential to limit their duration and severity. Therefore, occurrence or worsening of new symptoms should be rapidly reported without delay.

Depending on the type of checkpoint inhibitor, specific timing of certain irAEs can be observed. irAEs related to the prescription of ipilimumab occur in a well-defined pattern. Skin toxicities develop between the 2nd and the 10th week after treatment initiation. Digestive system AEs usually occur between week 5 and 10, and hepatic AE's between week 6 to 14. Endocrine AE's have a median time to onset of 7-20 weeks.[6]

Endocrinopathies induced by pembrolizumab and nivolumab have a median time to onset of 10 and 11 weeks respectively.[7] Skin toxicities have a median time to onset of 5 weeks after initiating treatment with nivolumab. Median time to onset for renal AEs has been described to be approximately 15 weeks.[8]

Immune related adverse events can also occur after treatment termination. Therefore we recommend that surveillance should be continued for at least one year, with a clinical evaluation and a blood sample every 3 months. From the second year on, the interval can be prolonged up to every 6 months.[5]

All evaluations (history taking, clinical exam, blood tests and investigations, such as ECG of pulmonary function test/PFT) and their recommended timing are presented in *Table 1.*

TREATMENT PRINCIPLES

Depending on the grade of the irAE, the immunotherapy treatment may be continued or interrupted and/or corticosteroids can be administered. Corticosteroids should be tapered slowly, starting at least 1 month after the resolution of symptoms. Otherwise, relapse or worsening of adverse events can occur. If prolonged immune suppression with corticosteroids is necessary, antibiotic prophylaxis to prevent opportunistic infections should be considered.[5]

GENERAL ADVERSE EVENTS

FATIGUE

The most common adverse event across clinical studies with checkpoint inhibitors is fatigue, with an incidence of 16-37% in single-agent studies. The mechanism behind this AE is not fully understood.[9] In some cases, treatment-related fatigue may be an early symptom of hypothyroidism or eventually caused by a treatment-related anaemia.

FEVER

Fever and chills are considered to be the result of cytokine release and a nonspecific activation of an immune response. These AEs can be managed supportively with antipyretics such as nonsteroidal anti-inflammatory drugs. In case of grade 3 infusion reactions, patients may also receive antihistamines and corticosteroids intravenously. However, infusion reactions with anti-PD1/anti-PDL1 agents are very rare (<1%). In case of persistent fever, the necessary investigations should always be done to exclude an underlying infection.[9]

HAEMATOLOGICAL TOXICITIES

Haematological toxicities occur in less than 1% of patients with a solid tumour treated with anti-CTLA4 or anti-PD1. Patients with anaemia usually present with classical symptoms as fatigue, shortness of breath, a pale skin colour and/or palpitations. Leukopenia results in an increased risk for serious infections. Thrombocytopenia leads to petechiae, ecchymoses and spontaneous mucosal bleedings. The biochemical evaluation should include haptoglobine, schizocytes, CMV PCR, serology (CMV, EBV and other, depending on the clinical presentation). From haematological toxicity grade 2 (Hb < 10g/dL, WBC < 3000/mm3 or trombocytes < 50.000/mm3) on, haematology consultation is recommended to manage these toxicities safely (interruption of immunotherapy and low dose methylprednisolone 0.5mg/kg/d) and to perform a bone marrow evaluation (aspirate and trephine biopsy) if necessary.[10,11]

ORGAN-SPECIFIC ADVERSE EVENTS

MUSCULOSKELETAL ADVERSE EVENTS

Musculoskeletal AEs, such as arthralgia, myalgia and muscle spasms, are quite common during treatment with ipilimumab.[12] More rare events such as polymyalgia rheumatica, myositis and arthritis have also been reported. Arthralgia is one of the most common AEs under treatment with anti-PD1, occurring in 9-20% of patients treated with pembrolizumab and in 5-13% of patients treated with nivolumab.[4,13,14] However, grade 3-5 arthralgia occurs in less than 1%. Normally, a symptomatic therapy with anti-inflammatory drugs is sufficient, but some cases may require low doses of corticosteroids (i.e. prednisolone 5-10mg/d orally).[1]

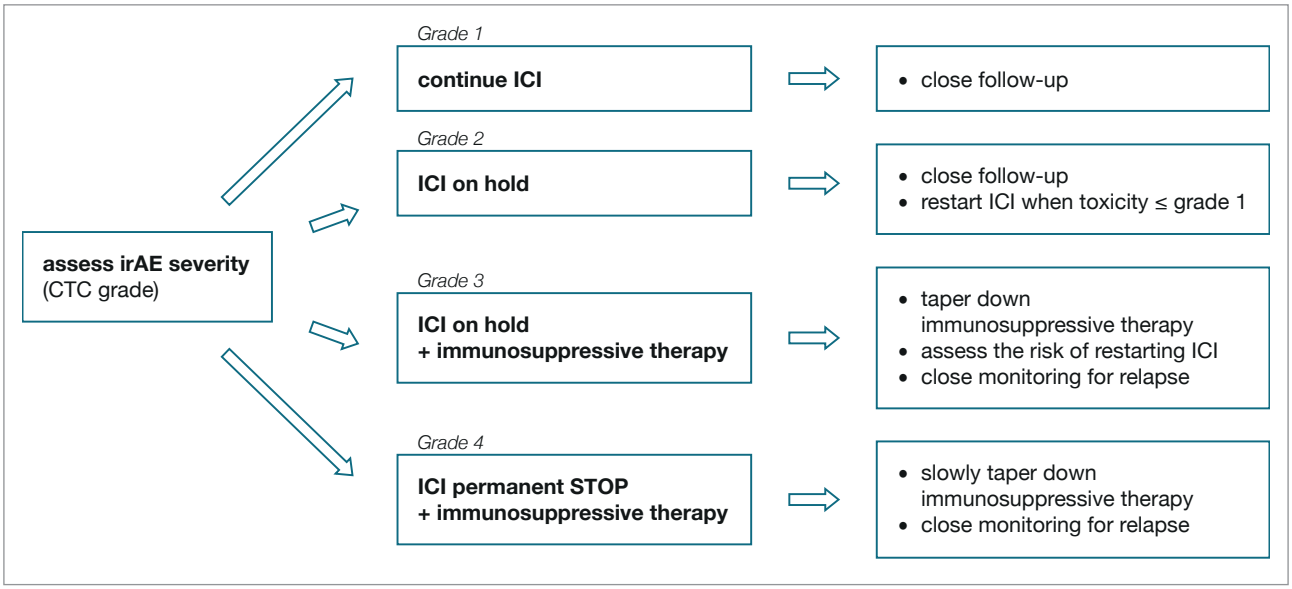

FIGURE 2. Treatment principles of irAE management.

HEPATITIS

The hepatic toxicities related to the treatment with checkpoint-inhibitors typically consist of asymptomatic elevations of AST and ALT levels. Anti-CTLA4 antibodies are associated with elevated AST and ALT levels in 10% of the patients, while 5% or less of the patients treated with anti-PD1/anti-PDL1 experience this AE. Higher rates of AST/ALT elevations of approximately 20% have been reported when anti-CTLA4 and anti-PD1 blocking antibodies are administered together or when anti-PD1 antibodies in monotherapy are administered to patients with HCC. Hepatitis with anti-CTLA4 therapy occurs approximately 8-12 weeks after the initiation of therapy. To our knowledge, this has not been reported in the context of anti-PD1/anti-PDL1 therapy.[8] Treatment of immune-related hepatitis involves a corticosteroid taper for a minimum of 3 weeks. In case of grade 2 toxicity, it should be considered to interrupt treatment depending on the clinical presentation. In case of grade 3/4 toxicity, interruption is recommended, especially if the elevated liver parameters persist. Immune suppression with mycophenolate mofetil or antithymocyte globulin, which has been used successfully in one case, can be considered for patients with a steroid-resistant immune-mediated hepatitis.[15] In one case report, ipilimumab induced hepatitis resolved with a combination of tacrolimus and prednisolone. Still, the experience with these drugs in terms of irAE-management is rather limited, and they should only be used in consultation with a hepatologist.[16] The role of infliximab in these patients is unclear (*Figure 3*).

COLITIS

Diarrhoea and colitis are typical immune related events associated with the use of checkpoint inhibitors. Diarrhoea is defined as an increased stool frequency, while colitis involves abdominal pain and either clinical or radiological evidence of chronic inflammation. The cornerstone of effective management is early intervention. Colitis/diarrhoea occurs more frequently in patients treated with a CTLA4-inhibitor (grade 3-4 toxicities in about 5%) compared to an incidence of 1-3% in patients treated with anti-PD1/anti-PD-L1 inhibitors. Diarrhoea/colitis usually occurs 6-8 weeks after initiation of anti-CTLA4-therapy.[9]

If a patient presents with diarrhoea, and if the same symptoms persist for more than 3 days or if the symptoms worsen within a shorter period of time, measurements should be taken to exclude an infectious cause (including coproculture). Furthermore, from grade 2 on the checkpoint inhibitor should usually be interrupted, the diagnosis should be confirmed with endoscopy and biopsies and radiographic evaluation and treatment oral corticosteroids should be initiated (*Figure 3*). In case of insufficient response to the interventions mentioned above, the patient should be hospitalised for intravenous corticosteroids (methyldprednisolone 1-2mg/kg total daily dose). If the symptoms do not ameliorate within the first 3 days of intravenous corticosteroids, additional immune suppression with infliximab should be considered (dosing 5 mg/kg). Administration of infliximab can be repeated after 2 weeks if symptoms persist. It concerns off-label use of this drug and the indication should be discussed with a gastroenterologist before drug initiation (*Figure 4*). A few reports also propose the administration of budesonide for patients with a grade 1-2 colitis. Budesonide is a corticosteroid analogue that is released in the terminal ileum where it is locally effective

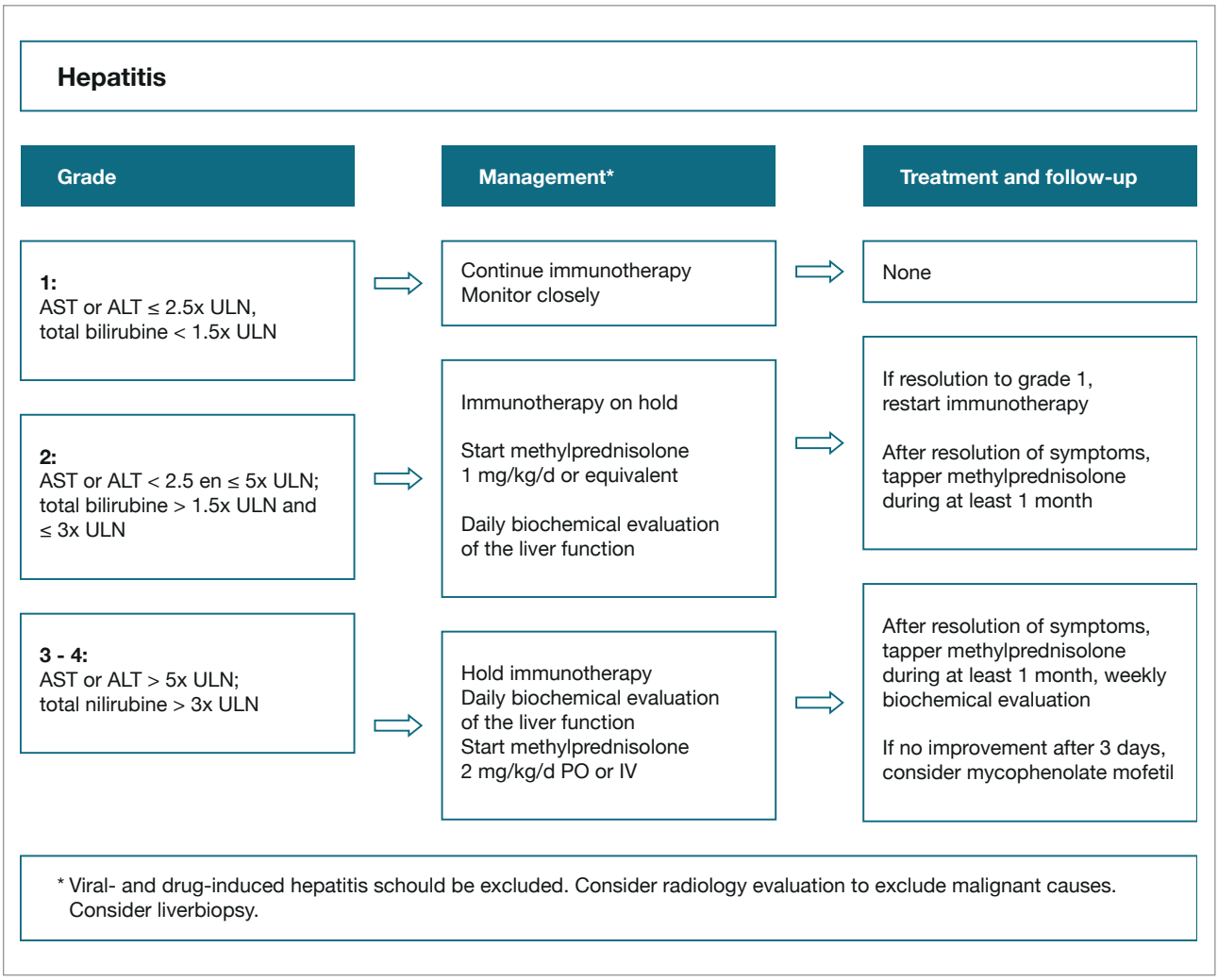

FIGURE 3. Management of hepatitis.

on the mucosa and is rapidly transported to the liver where more than 90% of the corticosteroid agent is metabolized by the liver ('first pass effect'). This guarantees a local effect combined with reduced corticoid side effects. Budesonide could be an alternative for treatment with prednisolone. However, in accordance with the most international guidelines, we recommend the use of conventional steroids given the greater efficacy and the lack of supporting data.

ENDOCRINE ADVERSE EVENTS

Immune related toxicities affecting the endocrine glands occur more frequently with anti-CTLA4 antibodies compared with anti-PD1/anti-PDL1 antibodies. Typical endocrine events associated with anti-CTLA4 therapy include: hypophysitis, hypothyroidism, thyrotoxicosis and thyroiditis.[9] Rare cases of diabetes mellitus type 1 have also been described.[17] The endocrine AEs mostly present with nonspecific symptoms such as fatigue and headache. In rare cases, patients may present with an adrenal crisis that requires hospitalization, endocrinology consultation, intravenous corticosteroid replacement therapy and aggressive fluid and electrolyte replacement. If hypophysitis or thyrotoxicosis is suspected we always recommend endocrinologist consultation. Obviously, this should also be the case for patients who present with rare endocrinopathies, such as diabetes mellitus.

Hypophysitis has demonstrated to be the most frequent grade 3/4 and dose-limiting endocrine AE of ipilimumab.[7] The diagnose is made by means of biochemical testing of prolactin, FT4, TSH, LH and FSH, ACTH and cortisol as well as radiological evidence of pituitary inflammation. Pituitary MRI is the recommended imaging modality in this context.[17] In case of symptoms (headache, mass effects), acute treatment is based on high-dose glucocorticoids. A suggested regimen is methylprednisolone 1-2 mg/kg per day for 3-5 days, followed by prednisone 1-2 mg/kg per day, gradually tapered over 4 weeks. Slow tapering is recommended as early reduction of glucocorticoids may induce a relapse, or trigger an adrenal crisis. Hormone replacement therapy should be started

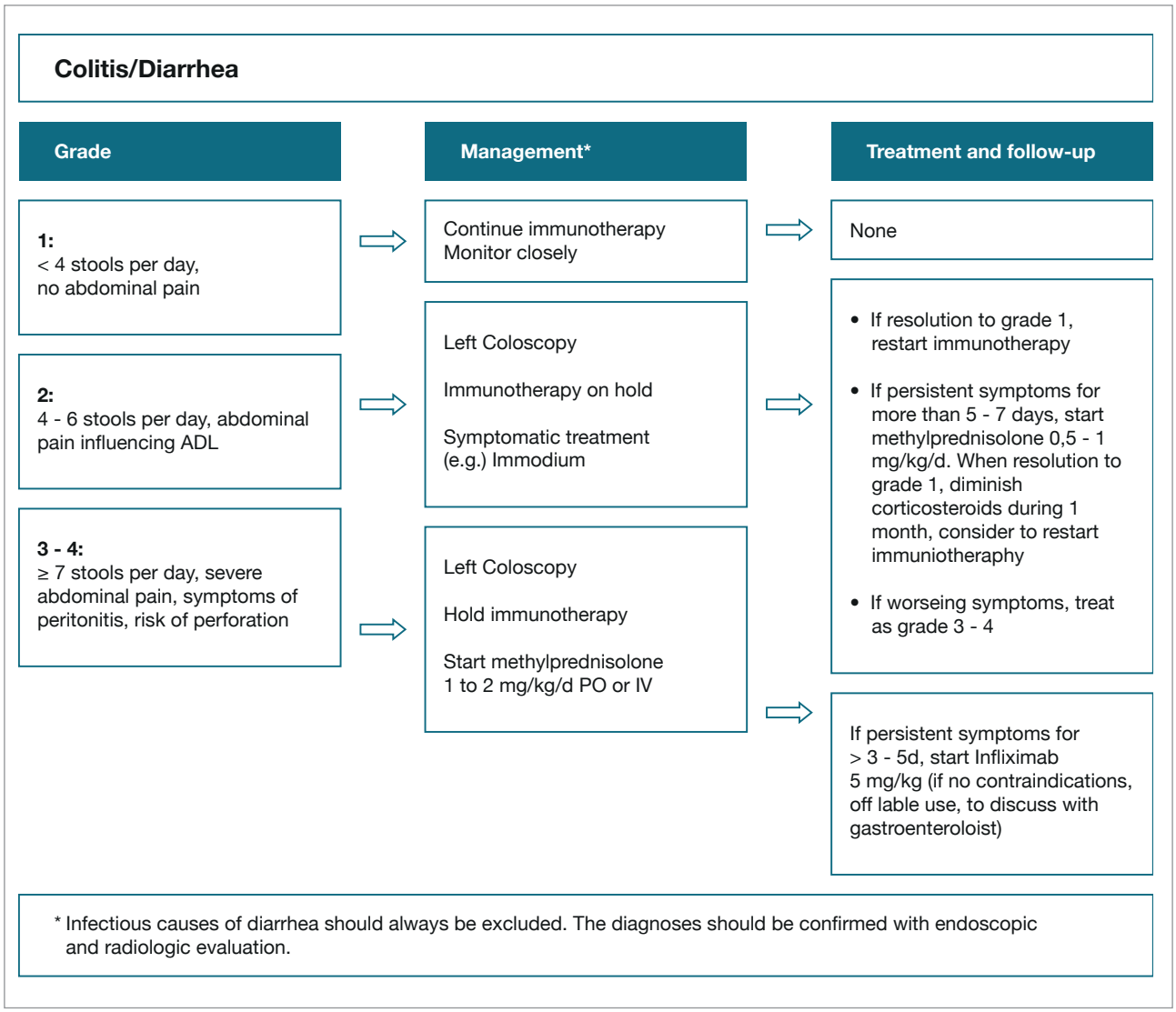

FIGURE 4. Management of colitis.

when deficiencies are documented: cortisol, thyroxine, testosterone/estradiol should be replaced. Hormone deficiencies frequently recover over time, especially for the thyrotrophic and gonadotropic axes. Glucocorticoid replacement therapy may be needed lifelong.[18]

Thyroid dysfunction occurs more frequently with anti-PD1 (~10%) than with anti-CTLA4 therapy (<5%). Antithyreoglobulin or antithyroid peroxidate antibodies might cause the development of this AE. Cases of Graves' disease have been described, due to development of anti-TSH-receptor antibodies. TSI *(thyroid stimulating immunoglobulin)* and anti-TPO *(thyroid-peroxidase)* antibodies should be evaluated in patients with thyrotoxicosis, and anti-TPO should be measured for patients with hypothyroidism. However, antibodies are not present in all cases.[9]

Hypothyroidism is managed with thyroid hormone replacement (e.g. Levothyroxine 50 – 125 µg per day, depending on grade and body weight). Symptoms may need several weeks to resolve and TSH level usually takes even longer. Subclinical hypothyroidism usually does not need treatment, unless the patient becomes symptomatic, or the patient has a history of cardiovascular disease. Measurement of TSH level is recommended 6 after treatment initiation.[7]

Thyrotoxicosis is managed depending on the underlying pathophysiologic mechanism. As most cases of thyrotoxicosis result from cytolysis during the early phase of thyroiditis leading to thyroid hormone leakage in the general circulation, only supportive treatment (physical rest, beta-blockade e.g. propranolol 10-40 qid) is warranted during this self-limiting period. Hereafter, patients should be monitored for evolution towards hypothyroidism or restoration of euthyroidism. If hyperthyroidism is suspected (i.e. true hyperfunctioning of the thyroid gland, e.g. in case of Graves' disease), standard anti-thyroid therapy (thiamazol or propylthiouracil) should be initiated

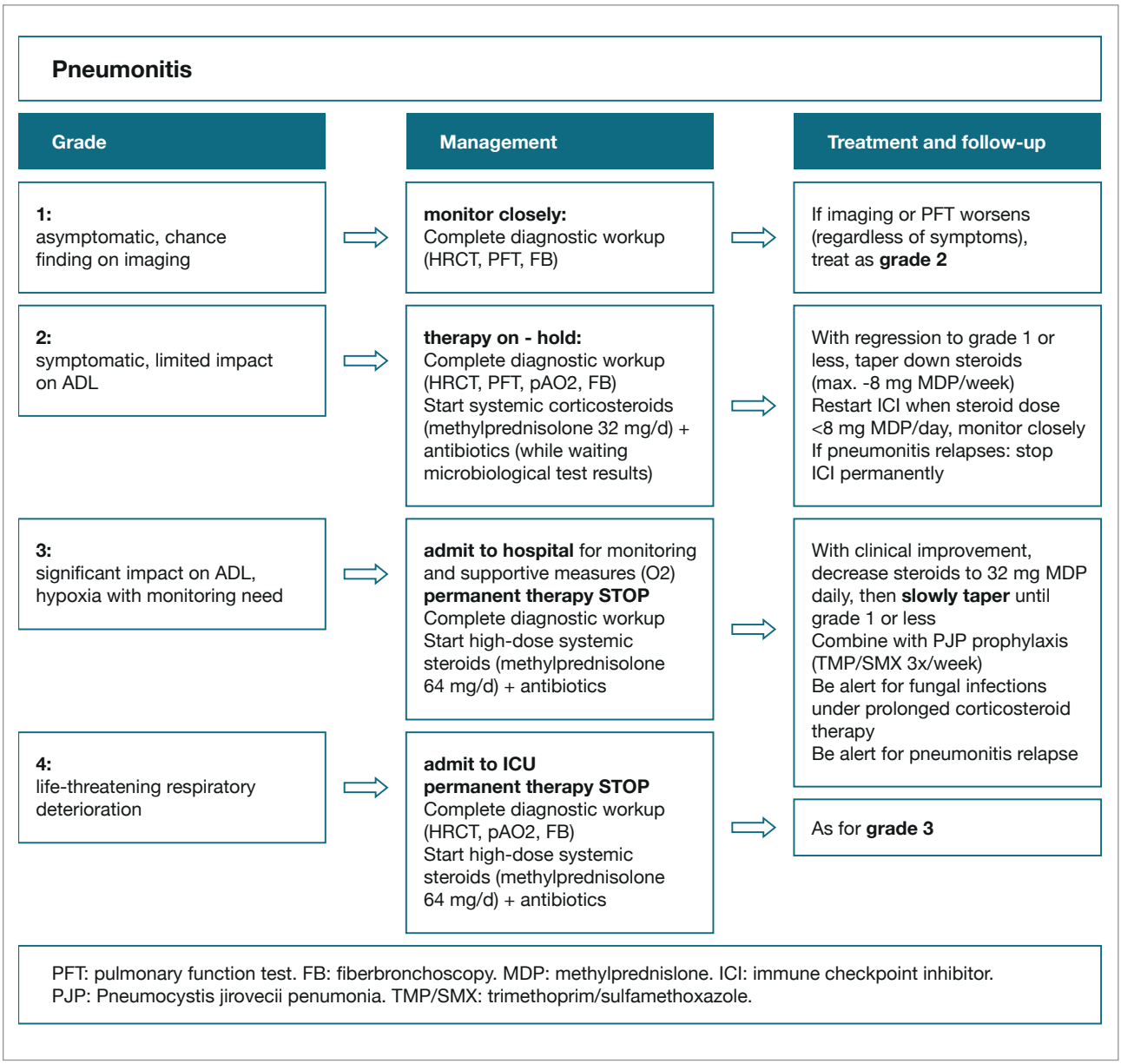

FIGURE 5. Management of pneumonitis.

along with the before mentioned supportive measures.[7] Development of a hypophysitis usually results in stopping the immune checkpoint inhibitor. On the other hand, if hypo- and hyperthyroidism is treated successfully with replacement therapy, the checkpoint inhibitor can usually be continued with close monitoring.[9]

PNEUMONITIS

Pneumonitis has been observed with any PD-1 or PD-L1-targeted inhibitor, more than in the setting of CTLA-4 monotherapy. The incidence reported in trials is 1-7% all-grade toxicities, with only 1% severe (grade 3-4) toxicity. Very few patients with death due to respiratory failure have been reported. Pneumonitis is more prevalent in NSCLC and RCC patients then in melanoma treated with anti-PD1, and combination with anti-CTLA4 seems to increase this risk.[19] Pre-existing lung conditions, such as COPD/emphysema or predisposing factors such as a history of thoracic irradiation, may also increase the risk for the development of pneumonitis. There are no data regarding patients with known interstitial lung disease (usually excluded from trials). Interestingly, a recent report indicates significantly higher tumour response rates in anti-PD-1 or anti-PD-L1-treated patients who develop pneumonitis.[20]

The time-to-onset of pneumonitis induced by an immune-checkpoint inhibitor is highly variable, with a peak incidence around the 12th week on therapy. Typical clinical manifestations include increase in dyspnoea and cough (dry

Table 2. Symptoms requiring prompt referral to an organ specialist experienced in treating irAE's.

Diarrhea, abdominal pain, extreme fatigue, weight loss, nausea, vomiting, polyuria, extensive rash or pruritus, shortness of breath, coughing, jaundice, headache, confusion, vision disturbances, muscle weakness, numbness, arthralgia or swollen joints, myalgia or fever.

or productive), with variable levels of hypoxia and inspiratory crackles on auscultation. Standard work-up includes oxygen saturation check, chest X-ray, high-resolution CT scan, pulmonary function testing (we recommend baseline PFT for each patient started on a PD1/PDL1 inhibitor) and fiberbronchoscopy to exclude infection. The radiographic distribution can be diffuse or very localized, with patterns reminiscent of cryptogenic organizing pneumonia (COP), non-specific interstitial pneumonitis, or even full ARDS. The differential diagnosis includes infectious pneumonia, COPD exacerbation, pulmonary embolism, radiation pneumonitis or oncological progression (e.g. carcinomatous lymphangitis or retro-obstructive pneumonia).

The cornerstone of the management is foremost awareness and interruption of therapy at first signs of pneumonitis. A flowchart for the management is given in *Figure 5*. A few points should be emphasized: we recommend a treatment pause, full diagnostic workup and close follow-up at first radiological signs of pneumonitis in patients with significant pulmonary comorbidity regardless of symptoms (i.e. with grade 1), with reinstatement of therapy if the condition remains stable. We feel that this level of caution should be exercised in this patient group where respiratory reserves are limited. Corticosteroids for grade 3 pneumonitis should be tapered down slowly to avoid flare-up (by analogy to the management of cryptogenic organising pneumonia). A prolonged course of corticosteroids implies prophylactic antibiotic treatment against Pneumocystis infection. We recommend against the use of infliximab or other TNF-blockers in so-called "steroid-resistant" severe pneumonitis. Besides the absence of evidence, the combination of TNF-blockade and a prolonged course of high-dose steroids has been associated with a higher mortality due to overwhelming Pneumocystis infection. Moreover, TNF blockade by itself can induce interstitial lung disease. Do not withhold ICU admission and full ventilatory support in metastatic patients with severe pneumonitis and objective tumour response under immune checkpoint blockade. Discuss oncological prognosis in this specific setting with the ICU staff. Beware of pneumonitis relapse after corticosteroid tapering, even after permanent discontinuation of immune checkpoint blockade.

DERMATOLOGICAL TOXICITIES

Cutaneous side effects during immunotherapy are frequent, but are mainly limited to grade 1 to 2 in severity.[21] Reported skin toxicity is higher in anti-CTLA4 agents than in anti-PD1 agents. A maculo-papular rash involving varying percentages of body surface is most of often observed. In grade 1 to 2 skin toxicity treatment with a topical corticosteroid is advised. Supportive treatment with oral antihistamines in case of itch can be added. In grade 3 to 4 systemic corticotherapy will be needed and referral to a dermatologist for evaluation and eventual skin biopsy is advised.

The occurrence of vitiligo (depigmentation) is less frequent but can be a bystander effect of an efficient anti-melanocytic cytotoxic T cell response. Several studies indicate a higher response and a survival benefit when depigmentation occurs during immunotherapy in melanoma.[22-24]

Several other cutaneous manifestations have been reported during immunotherapy amongst which the induction of and/or aggravation of existing autoimmune skin disorders. Urgent dermatological advice needs to be considered in extensive skin toxicity not reacting on topical corticotherapy and/or associated with systemic symptoms (e.g. fever) and/or in case of blisters or tenderness/pain of the skin.

RARE TOXICITIES WITH IMMUNE CHECKPOINT INHIBITORS

Single agent ipilimumab has been associated with a number of neurological symptoms, such as a transverse myelitis, PRES (posterior reversible encephalopathy syndrome), autoimmune encephalitis, enteric neuropathy, aseptic meningitis and a few cases of Guillain-Barré-syndrome. Patients with symptoms that could mimic a neurological event should be referred to a neurologist promptly. High dose corticosteroids, intravenous immunoglobulins and plasmapheresis are possible treatment options.[1,5,25]

A few ophthalmological side effects have also been associated with checkpoint inhibitors in monotherapy and with the combination of nivolumab plus ipilimumab. Immune-related uveitis can normally be treated with topical corticosteroids, while oral corticosteroids can be consid-

ered for patients who experience grade 3-4 toxicity. Treatment of ophthalmological side effects should always be done in consultation with an ophthalmologist.[1,5]

Pancreatitis has been reported infrequently in clinical trials with checkpoint inhibitors. Routine assessment of these enzymes is not recommended, though clinical suspicion should result in prompt evaluation of these markers. Asymptomatic elevations in lipase should not be followed nor treated.[9]

Isolated cases of nephritis have also been reported in the clinical trials. The clinical course is usually an asymptomatic, gradually rising creatinine, and most patients improved with the use of corticosteroids. Whenever an immune-related nephritis is suspected, it is recommended to perform an extended blood analysis (incl. sodium, potassium, chlorine, calcium, phosphorous, bicarbonate) beside the standard tests (*Table 2*), collect a urine sediment (creatinine, ureum, sodium and protein) and perform a 24h urine collection. In case of a grade 2 toxicity (creatinine > 1.5x baseline) or severe electrolyte disturbances we advice to request a nephrology consultation.[9]

Isolated cases of cardiac AEs have been reported in patients treated with ipilimumab. Myocarditis, pericardial effusion, cardiomyopathy, arrhythmias and atrial fibrillation have been described. Cardiac events under treatment with nivolumab and pembrolizumab are very rare.[1]

SPECIAL SUBGROUPS

AUTO-IMMUNE DISEASE

Patients with a history of autoimmune disease have been excluded from clinical trials. As such, the experience with checkpoint inhibitors in patients with a history of autoimmune disease is limited and based on case reports. Theoretically checkpoint inhibitors could result in an exacerbation of the underlying disease. However, case reports have also been published where disease activity remained stable and occasionally signs of improvement have even been observed. The prescribing clinician should consider the risk of additional irAEs in patients with organ-specific autoimmunity. If immunotherapy is prescribed, a multidisciplinary approach is necessary in case of a pre-existing autoimmune disease. However, in this patient population these agents should be used with caution and alternative treatment options should be considered first. In patients with endocrine deficiencies checkpoint inhibitors can be prescribed with close monitoring and adaptation of the substitutive therapies if necessary.[5]

CHRONIC INFECTIONS (HBV,HCV,HIV)

Patients with a history of chronic viral infections such as HBV, HCV and HIV have always been excluded from clinical trials. Administration of anti-CTLA4 or anti-PD1 in patients with a hepatocellular carcinoma due to HBV or HCV patients seems to have a good safety profile. However, hepatic toxicity seems to be more frequent in these patients.[9] The experience with checkpoint inhibitors in patients with HIV is limited to a few case reports. One case report describes that a stable HIV viral load remained undetectable.[26]

TRANSPLANT PATIENTS

A limited number of case reports exist describing the use of checkpoint inhibitors in patients who have undergone kidney transplantation. One case report describes a patient with a renal transplant from a living donor who was treated with nivolumab. Immunosuppressive treatment with glucocorticoid and sirolimus prevented an adverse immune response of the kidney.[27] Another case report describes the safe administration of anti-CTLA4, followed by anti-PD1 to a patient with a renal transplant, receiving immunosuppressive treatment with prednisolone and tacrolimus without inducing rejection of the xenograft.[28] However, the experience with checkpoint inhibitors in this patient population is limited. Before drug administration the patient should be offered a detailed explanation of the potential risk of allograft rejection and the treatment should be administered with close monitoring of vital organ functions. Also in allogeneic stem cell transplant recipients, checkpoint inhibitors might lead to an increased risk of graft-versus-host disease, but data are lacking.

FUTURE TREATMENT OF PATIENTS AFTER DEVELOPMENT OF AN IRAE – CAN IMMUNOTHERAPY BE REINTRODUCED?

The literature on this topic is very limited. We have some personal experience in treating melanoma patients with anti-PD1, after development of serious irAEs on anti-CTLA4. Patients with unresolved endocrinopathies, induced by treatment with anti-CTLA4, can be safely treated with anti-PD1. However, this may require adjustment of the substitution therapy during anti-PD1-treatment. Patients, who develop one AE during treatment with anti-CTLA4, do not necessarily develop the same AE during treatment with anti-PD1. It is also possible that anti-PD1-therapy does not cause any side effects, while the patient developed a dose-limiting toxicity on anti-CTLA4. The optimal treatment strategy should be defined and discussed with the patient on an individual basis, considering the possible benefits and risks of the various options.

KEY MESSAGES FOR CLINICAL PRACTICE

1. **Nearly all organs can be affected by immune related adverse events (irAEs).**
2. **irAEs events can occur at any time during treatment.**
3. **Identification and early treatment of irAEs are essential to limit duration and severity.**

CONCLUSIONS

With the increasing use of checkpoint inhibitors, the number of irAEs will grow, as well the experience in dealing with them. The management of mild and frequent toxicities will quickly become a part of the routine clinical practice of oncologists and haematologists. However, the diversity of less frequent irAEs, which can be life threatening, necessitates a local network of organ specialists to support the irAE management. Early recognition and management of possible irAEs are of great importance to guarantee safety and reduce morbidity of these drugs. This manuscript describes the guidelines that resulted from such collaboration at the Ghent University Hospital.

REFERENCES

1. Zimmer L, Goldinger SM, Hofmann L, et al. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. Eur J Cancer. 2016;60:210-25.
2. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015;372(26):2521-32.
3. Robert C, Long GV, Brady B, et al Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372(4):320-30.
4. Larkin J, Hodi FS, Wolchok JD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015;373:1270-1.
5. Champiat S, Lambotte O, Barreau E, et al. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. Ann Oncol. 2016;27(4):559-74.
6. Weber JS, Dummer R, de Pril V, et al. MDX010-20 Investigators. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: detailed safety analysis from a phase 3 trial in patients with advanced melanoma. Cancer. 2013;119(9):1675-82.
7. González-Rodríguez E, Rodríguez-Abreu D, Spanish Group for Cancer Immuno-Biotherapy (GETICA). Immune Checkpoint Inhibitors: Review and Management of Endocrine Adverse Events. Oncologist. 2016;21(7):804-16.
8. Weber JS, Hodi FS, Wolchok JD, et al. Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma. J Clin Oncol. 2017;35(7):785-792.
9. Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol. 2015;26(12):2375-91.
10. Weber JS, Yang JC, Atkins MB, et al. Toxicities of Immunotherapy for the Practitioner. J Clin Oncol. 2015;33(18):2092-9.
11. Villadolid J, Amin A. Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. Transl Lung Cancer Res. 2015;4(5):560-75.
12. Yervoy prescribing information http://packageinserts.bms.com/pi/pi_yervoy.pdf
13. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016;375(19):1823-33.
14. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015;373:1627-39.
15. Chmiel KD, Suan D, Liddle C, et al. Resolution of Severe Ipilimumab-Induced Hepatitis after Anti-Myocyte Globulin Therapy. J Clin Oncol. 2011;29(9):e237-40.
16. Cheng R, Cooper A, Kench J, et al. Ipilimumab-induced toxicities and the gastroenterologist. J Gastroenterol Hepatol. 2015;30(4):657-66.
17. Marrone KA, Ying W, Naidoo J. Immune-related Adverse Events from Immune Checkpoint Inhibitors. Clin Pharmacol Ther. 2016;100(3):242-51.
18. Albarel F, Gaudy C, Castinetti F, et al. Long-term follow-up of ipilimumab-induced hypophysitis, a common adverse event of the anti-CTLA-4 antibody in melanoma. Eur J Endocrinol. 2015;172(2):195-204.
19. Nishino M, Giobbie-Hurder A, Hatabu H, et al. Incidence of Programmed Cell Death 1 Inhibitor–Related Pneumonitis in Patients With Advanced Cancer. A Systematic Review and Meta-analysis. JAMA Oncol. 2016;2(12):1607-16.
20. Gettinger S, Shepherd F, Antonia SJ, et al. First-line nivolumab (anti-PD-1; BMS-936558, ONO-4538) monotherapy in advanced NSCLC: Safety, efficacy, and correlation of outcomes with PD-L1 status. Abstract #9030, ASCO 2016.
21. Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer. 2016;54:139-48.
22. Teulings HE, Limpens J, Jansen SN, et al. Vitiligo-like depigmentation in patients with stage III-IV melanoma receiving immunotherapy and its association with survival: a systematic review and meta-analysis. J Clin Oncol. 2015;33(7):773-81.
23. Nakamura Y, Tanaka R, Asami Y, et al. Correlation between vitiligo occurrence and clinical benefit in advanced melanoma patients treated with nivolum-

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ab: A multi-institutional retrospective study. J Dermatol. 2017;44(2):117-122.

24. Hua C, Boussemart L, Mateus C, et al. Association of Vitiligo With Tumor Response in Patients With Metastatic Melanoma Treated With Pembrolizumab. JAMA Dermatol. 2016;152(1):45-51.

25. Williams TJ, Benavides DR, Patrice KA, et al. Association of Autoimmune Encephalitis With Combined Immune Checkpoint Inhibitor Treatment for Metastatic Cancer. JAMA Neurol. 2016;73(8):928-33.

26. Davar D, Wilson M, Pruckner C, et al. PD-1. Blockade in Advanced Melanoma in Patients with Hepatitis C and/or HIV. Case Rep Oncol Med. 2015;2015:737389.

27. Barnett R, Barta VS, Jhaveri KD. Preserved Renal-Allograft Function and the PD-1 Pathway Inhibitor Nivolumab. N Engl J Med. 2017;376(2):191-2.

28. Herz S, Höfer T, Papapanagiotou M, et al. Checkpoint inhibitors in chronic kidney failure and an organ transplant recipient. Eur J Cancer. 2016;67:66-72.