New therapeutic perspectives to manage refractory immune checkpoint-related toxicities

Filipe Martins, Gerasimos P Sykiotis, Michel Maillard, Montserrat Fraga, Camillo Ribi, Thierry Kuntzer, Olivier Michielin, Solange Peters, Georges Coukos, Francois Spertini, John A Thompson, Michel Obeid

Immune checkpoint inhibitors are reshaping the prognosis of many cancer and are progressively becoming the standard of care in the treatment of many tumour types. Immunotherapy is bringing new hope to patients, but also a whole new spectrum of toxicities for healthcare practitioners to manage. Oncologists and specialists involved in the pluridisciplinary management of patients with cancer are increasingly confronted with the therapeutic challenge of treating patients with severe and refractory immune-related adverse events. In this Personal View, we summarise the therapeutic strategies that have been used to manage such toxicities resulting from immune checkpoint inhibitor treatment. On the basis of current knowledge about their pathogenesis, we discuss the use of new biological and non-biological immunosuppressive drugs to treat severe and steroid refractory immune-related adverse events. Depending on the immune infiltrate type that is predominant, we propose a treatment algorithm for personalised management that goes beyond typical corticosteroid use. We propose a so-called shut-off strategy that aims at inhibiting key inflammatory components involved in the pathophysiological processes of immune-related adverse events, and limits potential adverse effects of drug immunosuppression on tumour response. This approach develops on current guidelines and challenges the step-by-step increase approach to drug immunosuppression.

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Département d'Oncologie (F Martins MD, Prof O Michielin MD, Prof S Peters MD, Prof G Coukos MD)**, Service d'Endocrinologie, Diabétologie, et Métabolisme** (G P Sykiotis MD)**, Service de Gastro-entérologie et Hépatologie** (M Maillard MD, M Fraga MD)**, Service Immunologie et Allergie** (C Ribi MD, Prof F Spertini MD, M Obeid MD)**, Service de Neurologie** (Prof T Kuntzer MD)**, Centre d'Immunothérapie et de Vaccinologie** (M Obeid)**, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland** (F Martins)**; Crohn's and Colitis Center, Lausanne, Switzerland** (M Maillard)**; Ludwig Institute for Cancer Research, Epalinges, Switzerland** (Prof G Coukos)**; Fred Hutchinson Cancer Research Center, Seattle, WA, USA** (Prof J A Thompson MD)**; National Cancer Institute, Bethesda, MA, USA** (Prof J A Thompson)**; and Faculté Médecine Paris Descartes, Université Paris Descartes, Paris, France** (M Obeid)

Correspondence to : Dr Michel Obeid, Centre d'Immunothérapie et de Vaccinologie, Centre Hospitalier Universitaire Vaudois, Lausanne 1011, Switzerland **michel.obeid@chuv.ch**

Introduction

Monoclonal antibodies (mAbs) that block immune checkpoints, such as the cytotoxic T-lymphocyte antigen-4 (CTLA-4)-CD28 and programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) axes, are the main immunotherapies prescribed in current oncological practice. During the last decade, clinicians have been confronted with the management of immune-related adverse events (irAEs) resulting from immune checkpoint inhibitors (ICIs). Because of the increasingly widespread use of ICIs in oncology, new data on toxicities from these therapies are continuously reported, in addition to data documented in prospective clinical trials.[1,2] The advent of double checkpoint inhibition constitutes a new challenge because related toxicities often involve multiple organs and occur at higher frequencies than do those with monotherapy. For example, the Checkmate 067 trial[3] that used the ipilimumab–nivolumab combination in patients with advanced melanoma reported high-grade irAEs in 184 (59%) of 313 patients. The spectrum of organ systems affected by irAEs is broad and their management often requires expertise outside the specialty of oncology, and they often vary in frequency and severity depending on the drugs and the affected systems. Consequently, their optimal management requires experienced multidisciplinary teams. Extensive knowledge in the field of clinical immunology and immunosuppressive therapy, which is beyond the remit of current oncology guidelines, is often required of such teams. Another crucial challenge is the need for early recognition and prompt treatment of irAEs to avoid adverse outcomes due to delayed patient care. Like most treatment-related toxicities in oncology, irAEs are managed according to severity grading systems. Nevertheless, the limitations of these current systems should not be overlooked, and they should not be a substitute for clinical judgment, especially in frail patients and those that have rapidly evolving irAEs.

High-quality guidelines regarding the management of irAEs were released by the European Society of Medical Oncology,[4] the National Comprehensive Cancer Network,[5] and the Society for Immunotherapy of Cancer Toxicity Management Working Group.[6] These organisations provide comprehensive treatment algorithms for the most frequent irAEs and detail their recommendation regarding the use of immunosuppressive drugs according to irAE severity and duration. They also emphasise the importance of avoiding delays in work-up to rule out other differential diagnoses (eg, because of infectious complications or tumour progression) before starting effective immunosuppressive therapy. However, these guidelines do not include information about the management of severe and refractory irAEs, with which clinicians are frequently confronted. Retrospective data from a large cohort study, in which patients with cancer were administered ipilimumab, reported that 103 (35%) of 298 received corticosteroids to manage an irAE, and 29 (10%) of 298 required additional immunosuppressive drugs.[7] New forms of rare and sometimes life-threatening irAEs are constantly reported. These types of irAEs present a diagnostic and therapeutic challenge because there is a scarcity of data on which to base recommendations on management. Some experts are already adopting a first instance cytokine-directed therapy, such as tocilizumab (a humanised mAb that is an antagonist to the interleukin-6 [IL-6] receptor), in patients with steroid-refractory disease.[8]

New therapeutic perspectives to manage ICI-induced toxicities

Because of the scarcity of prospective trials on drug immunosuppression in the setting of high-grade irAEs, clinicians can only seek information from small series

	irAE indications	Protocols
Anti-IL-1 blockade	Severe irAE during acute phase; severe or refractory arthritis; chronic inflammatory; demyelinating polyradiculoneuritis; psoriasis-like reactions; psoriasis exacerbation; severe and anti-TNFα refractory colitis; myasthenia gravis; encephalitis; aseptic meningitis; myocarditis; pneumonitis	Anakinra 100 mg once per day, or canakinumab 300–600 mg once every 8 weeks
Anti-IL-6 blockade	Severe irAE during acute phase; severe or refractory arthritis; large vessel vasculitis; uveitis; myocarditis; pneumonitis; myasthenia gravis	Tocilizumab 8 mg/kg intravenously once per month or subcutaneous 162 mg once per week
Intravenous immunoglobulins	Guillain-Barré syndrome; subacute and chronic inflammatory demyelinating polyradiculoneuritis; subacute and chronic inflammatory neuropathies; immune neutropenia; immune thrombocytopenia; facial nerve palsy; myasthenia gravis; transverse myelitis; enteric neuropathy; encephalitis; aseptic meningitis	Intravenous immunoglobulins 400 mg/kg per day for 5 days, or once per month for a total of 3–4 courses
Anti-CD20 depletion	Systemic lupus erythematosus; severe Sjögren's syndrome; ANCA-associated vasculitis; cutaneous vasculitis; autoimmune autonomic ganglionopathy; sensory ganglionopathy; nephritis; myasthenia gravis; transverse myelitis; enteric neuropathy; encephalitis; aseptic meningitis; hepatitis	Rituximab 1 g every 2 weeks for 2 courses or 375 mg/m² once per week for 4 courses; ofatumumab 300 mg on the first day and 1000 mg on the second day; obinutuzumab 1000 mg on the first day; ocrelizumab 300 mg on the first and fourth day
Anti-IL-17 blockade	Severe colitis and anti-TNFα refractory colitis; severe or refractory arthritis; anti-IL-6 refractory irAEs	Ixekizumab 80 mg subcutaneous once every 2 weeks; brodalumab 210 mg subcutaneous once every 2 weeks; secukinumab 150 mg subcutaneous once every 2 weeks
Anti-TNFα blockade	Severe colitis; hepatitis; severe or refractory arthritis; nephritis; uveitis; pneumonitis; myocarditis	Infliximab 5 mg/kg once every 2 weeks; adalimumab 40 mg once every 2 weeks; golimumab 50 mg once per month; etanercept 50 mg once a week; certolizumab 400 mg once a month
Anti-integrin 4 blockade	Limbic encephalitis	Natalizumab 300 mg once per month
Anti-IL-23 and anti-IL-12 blockade	Acute phase, severe, or anti-TNFα refractory colitis; severe or anti-TNFα refractory psoriasis; severe or refractory arthritis	Ustekinumab initial dose 40 mg then 45 mg after 4 weeks and then 45 mg every 12 weeks
Janus kinase inhibitor	Severe or refractory arthritis	Tofacatinib 5 mg twice per day

irAE=immune-related adverse event; IL=interleukin type; ANCA=antineutrophil cytoplasmic antibody.

Table: **New therapeutic perspectives for the management of immune-related adverse events**

studies, case reports, and expert opinions on how to handle these challenging cases. Current guidelines promote a step-by-step approach, starting with high-dose steroids in the first instance and then increasing drug immunosuppression as needed. On the one hand, this consensus will probably be maintained in the absence of validated clinical or biological biomarkers that are predictive of steroid-refractory disease. On the other hand, clinicians who manage patients with severe irAEs should not discard the possibility of adding a cytokine-directed mAb from the start of a severe irAE (table). This approach has the putative advantage of shutting off a rapidly evolving immuno-pathophysiological process early on in the treatment process, and therefore prevents patient exposure to extended courses of immunosuppression.

A good example for aggressive drug immunosuppression in the first instance is ICI-related myocarditis. In this case, better efficacy of rapid immunosuppression is presumed because of its fulminant clinical presentation, the high associated morbidity and mortality rate, and the documented increased risk of adverse outcomes with lower steroid doses compared with high-dose therapy.[9] A meta-analysis in 2018 showed fatalities in 122 (0·6%) of 19 217 patients treated with ICIs.[10] These severe irAEs tended to occur soon after treatment initiation with monotherapy (median of 40 days) and even earlier with ICI combination (median of 2 weeks). Unusual clinical presentations with diagnosis delays were noted as mortality-contributing factors.

Biomarker-based approaches are being studied and will probably help to make therapeutic decisions on the management of irAEs from ICIs. For example, in ICI-related colitis ulcerative endoscopic findings have recently been suggested as surrogate markers for predicting steroid-refractory disease.[11] In this study, 90 colic biopsies from patients with ICI-related colitis showed different profiles of immune infiltrates in the epithelial layer: 27% of patients had predominant intraepithelial lymphocyte infiltration, whereas 73% of patients had predominant monocyte and neutrophil infiltration.[11]

The application of therapeutic knowledge from primary autoimmune disorders to irAEs is also hampered by their differences in disease phenotype, response to treatment, and pathophysiological mechanisms. For example, a histological analysis of liver biopsies from patients with ICI-related hepatitis showed a more diffuse, cytotoxic T-cell predominant, and lobular infiltrate pattern, with fewer CD4 T cells and plasma cells in the parenchyma than the infiltrate pattern from patients with primary autoimmune hepatitis.[12] The rareness of steroid efficacy in autoimmune hepatitis compared with most ICI-related hepatitis which is steroid sensitive is another difference.[13] Patients with multidrug-refractory severe hepatitis have been successfully treated with antithymocyte antiglobulin; this shows the relative resistance to non-selective immunosuppression of this irAE.[14,15] Furthermore, for patients with ICI-related myasthenia gravis, there is a higher risk of myasthenia

crisis and a particular association with myositis compared with their primary autoimmune counterparts.[16–18]

ICI-related colitis shows some common features with inflammatory bowel disease. Both disorders show sensitivity to anti-tumour necrosis factor (anti-TNFα) mAb and share some histological and pathophysiological features. The pathophysiological features are shown by the link between inflammatory bowel disease and some CTLA-4 polymorphisms in the general population.[19] Even though the chronic nature of inflammatory bowel disease tends to disrupt the epithelial layer and shows granulomatous lesions as characteristic features, the presence of a lymphocytic-neutrophilic infiltrate is a histological feature also seen in ICI-related colitis.

Because of the absence of validated biomarkers, immunopathological patterns could be considered as rational target tools to personalise a shut-off strategy (figure 1). For a predominant T-cell infiltrate, a T-cell-directed therapy, preferably anti-IL-6, and if not available, anti-IL-1 receptor, or anti-IL-12 and anti-IL-23 blockade, could be an optimal approach. A prominent B-cell and plasma cell infiltrate might be optimally targeted by an anti-B-cell strategy (anti-CD20 and anti-B-cell activating factor blockade). An infiltrate with a predominant neutrophilic and monocytic pattern with or without granulomas could be optimally targeted by an anti-TNFα strategy. Lastly, it has been recognised that biopsies are sometimes difficult to obtain depending on the clinical contexts and the organs involved, as in the case of neurological, rheumatological, and ocular irAEs. Therefore, the use of a cytokine-directed mAb that either targets the IL-6, TNFα, or IL-1 pathway is still the most upfront treatment option for patients with severe and steroid refractory conditions.

The safety profile of administrating the same biological and non-biological drugs for patients who have primary autoimmune disorders and patients with cancer is still not clear. Some of these drugs are considered to have a low likelihood of adverse effects on cancer response, although others could adversely affect T-cell anti-tumour response and consequently cancer prognosis. The use of these drugs outside of clinical trials should be advised and monitored by specialists in clinical immunology, and discussed in light of a cancer prognosis, anticipated time of onset of the chosen drugs, and their respective side-effect profiles.

Data from patients who had solid organ transplantation and were treated with ICIs show a significant negative effect of calcineurin inhibitors and mycophenolate mofetil on the T-cell response. Mycophenolate mofetil is already advised as a second-line immunosuppressive drug in current guidelines. However, in our opinion, they should be avoided in patients with immunogenic tumours, especially if there is curative intent, such as in patients with advanced melanoma. A therapeutic strategy that targets the IL-6 pathway is a robust substitute for older immunosuppressive drugs because IL-6 is a major mediator of the acute inflammatory phase in cytotoxic T-cell differentiation, has pro-tumour properties, and does not compromise the efficacy of immunotherapy.[20,21]

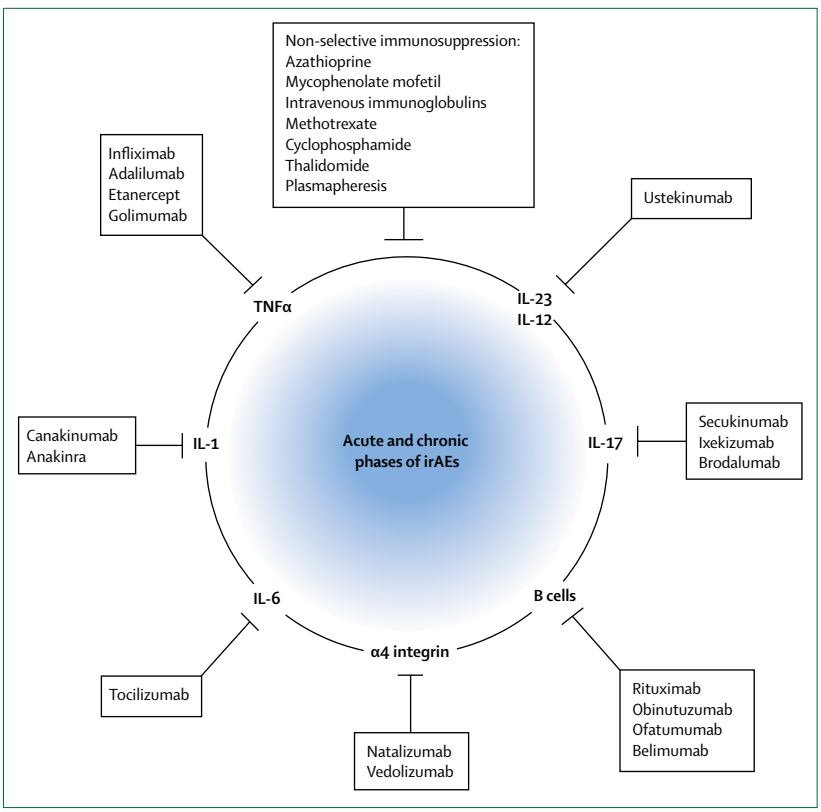

Figure 1: **Immunosuppressive drugs that can be used to treat immune-related adverse events and their targets**
In response to the acute inflammatory phase, many cytokines are continuously secreted, notably IL (interleukin)-1, IL-6, and human tumour necrosis factor α (TNFα). By analogy with inflammatory bowel disease treatment, blocking TNFα by infliximab has been proposed to treat immune-related adverse event (irAE) colitis. New humanised anti-TNFα antibodies, such as adalimumab and golimumab, could be alternatives to infliximab, likely exhibiting similar efficiency with fewer allergic side-effects. IL-1 and IL-6 are also acute phase targets; blocking these cytokines would impair their stimulatory effect on helper T cells, B cells, natural killer cells, macrophages, plasma cells, and haemopoietic stem cells, as well as their endothelial activation properties. This could be more efficient than classically advocated anti-TNFα strategies. Using a shut-off interruption strategy by applying preferentially an anti-IL-6 (tocilizumab) or anti-IL-1 (anakinra or canakinumab) drug if tocilizumab is not available could have additional advantages because of the pro-tumour and pro-metastatic activities of IL-6 and IL-1. Anti-IL-1 therapy could also be a useful adjunctive treatment in cases of immune-checkpoint inhibitors (ICIs)-induced encephalitis in which the inflammatory response is mainly driven by an IL-1 increase. B cell depletion (with rituximab, obinutuzumab, ofatumumab, or belimumab) could be helpful for neurological or haematological complications of ICIs, and in ICI-induced connective tissue diseases, severe Stevens-Johnson syndrome, and vasculitis-related irAEs. Additionally, IL-12/23 targeting could suppress the acute inflammation phase by impairing the positive stimulatory effect of IL-23 on TNFα secretion, which could be indicated in irAE cases refractory to anti-TNFα drugs. Anti-IL-17 strategy could be a good alternative after the failure of an anti-IL-6 therapy or in case of anti-TNFα-refractory psoriasis-like reactions.

Other aspects to consider with the use of these therapeutic strategies is the cost and their financial effects on health-care systems. Nevertheless, if the strategy is effective in managing severe and refractory irAEs, these costs might be amortised by decreases in patient morbidity. Clinical trials that provide data on toxicities of ICIs are urgently needed because of the rapid rate at which cancer immunotherapy is growing as an effective treatment option. However, most of these toxicities are so rare that clinical trials that evaluate

management are almost inconceivable. Therefore, irAEs must be reported to competent national regulators and published alongside empirically treated cases and case series.

Corticosteroids

Corticosteroids are considered first-line treatment for severe irAEs because of their rapid action and convenient use. Commonly used regimens comprise oral prednisone (1–2 mg/kg) or parenteral methylprednisolone (bolus range 125–1000 mg). High-dose corticosteroids have an inherent risk of infectious complications and metabolic disturbances (eg, iatrogenic Cushing's syndrome), and therefore corticosteroid weaning should be started at early signs of patient recovery. However, a tapering period of 4–6 weeks is advised to avoid flare phenomena relative to the long half-life of ICI mAbs.[6]

Calcineurin inhibitors, azathioprine, mycophenolate mofetil, and anti-TNFα therapies

By extrapolation, treatments used for inflammatory bowel disease and autoimmune hepatitis have been used to treat ICI-related colitis and hepatitis. Colitis due to severe and refractory irAE can be treated with a single dose of 5 mg/kg of infliximab (a chimeric monoclonal anti-TNFα antibody), much like treatment of Crohn's disease.[22] This treatment has been shown to be highly effective for corticosteroid-refractory colitis, with rapid responses occurring in 1–3 days . In some patients who relapse or do not have symptomatic improvement, a second dose is necessary after 2 weeks. Maintenance treatment should be reserved for chronic and relapsing cases. Infliximab is also advocated in steroid-refractory pneumonitis, although very little success has been reported because there have not been many studies that have shown a benefit with this drug.[23] Nevertheless, anti-TNFα therapy seems to be a better alternative than older immunosuppressive drugs for patients with steroid-refractory pneumonitis. Although this disorder is one of the most frequent irAEs with anti-PD-1/PD-L1 therapies, there is a scarcity of evidence-based treatment options to help manage this irAE. This frail population is also frequently subjected to long courses of steroids because pneumonitis often results in steroid dependency. Etanercept, adalimumab, certolizumab, and golimumab are also available and could be alternatives to infliximab. A published case of ICI-induced polyarthritis that was corticosteroid and methotrexate refractory treated with adalimumab showed excellent symptomatic improvement and clinical regression of joint inflammation.[24] Infliximab is also a rescue treatment option for steroid-refractory autoimmune hepatitis, which suggests that this is another reasonable indication for the use of other anti-TNFα drugs.[25] However, caution should be taken when using anti-TNFα mAbs to treat irAEs because rare cases of paradoxical adverse events—in which these drugs exacerbate the irAE they are meant to treat—have been reported during treatments. These encompass mostly the emergence or aggravation of psoriasis, inflammatory bowel disease, lung granulomatous disease, and uveitis; however, the full spectrum of these AEs is even wider.[26,27] Consequently, clinicians should always consider paradoxical AEs in their differential diagnosis of refractory irAEs, especially if these tend to change tissue or organ involvement and phenotype during treatment with biological drugs. Possible protocols could be adalimumab 40 mg every 2 weeks, golimumab 50 mg once per month, etanercept 50 mg once per week, or certolizumab 400 mg once per month.

Mycophenolate mofetil is considered a second-line treatment for ICI-induced hepatitis and is also advocated by most current guidelines as a second-line therapy on the basis of a relatively low level of evidence; by analogy with autoimmune hepatitis, azathioprine could also be a reasonable treatment option.[22] Calcineurin inhibitors have also been used as adjunct treatment for corticosteroid-refractory colitis and hepatitis, although evidence supporting their use in this setting is scarce because there is not a lot of literature about them.[28] A case of infliximab-refractory enterocolitis has also shown a rapid improvement after 2 weeks of ciclosporin. Clinicians should be made aware of this drug's ability to potentially prevent myocardial fibrosis and should be discussed in surviving cohorts of ICI-induced myocarditis.[29] Plasma dosing and level-based scheduling of mycophenolate mofetil and calcineurin inhibitors administration should be done to confirm safe therapeutic doses and avoid toxicity.

Beyond the aforementioned tested immunosuppressive and immunomodulatory drugs to treat severe and refractory irAEs, additional options may be available by extrapolating knowledge from the treatment of other primary automimmune disorders (figure 2).

Anti-IL-1 blockade

IL-1 is one of the main cytokines present during the acute phase of inflammation. Preclinical data have shown that the IL-1β pathway is an important promoter of tumour progression through stimulation of tumour-associated macrophages, myeloid suppressive cells, and up-regulation of PD-L1 in tumour cells.[30] Additionally, CNS injury leads to an inflammatory response that is partly mediated by an increase in IL-1 levels through tissue infiltration by neutrophils.[28] As shown in several animal models,[31] IL-1 receptor antagonists possess CNS-protective properties. A preclinical study[32] has pointed out the central role of IL-1 in autoimmune encephalitis, through its effect on the differentiation of IL-17-producing T cells. It was also a mediator of T-cell adhesion to the brain microvasculature in some blood–brain barrier preclinical models.[33] Anakinra, a recombinant IL-1 receptor antagonist, is approved for the treatment of rheumatoid arthritis; and is also used to treat other autoinflammatory disorders.[34] IL-1 blockade is accepted as having no detrimental effect on cancer response.[35] An anti-IL-1

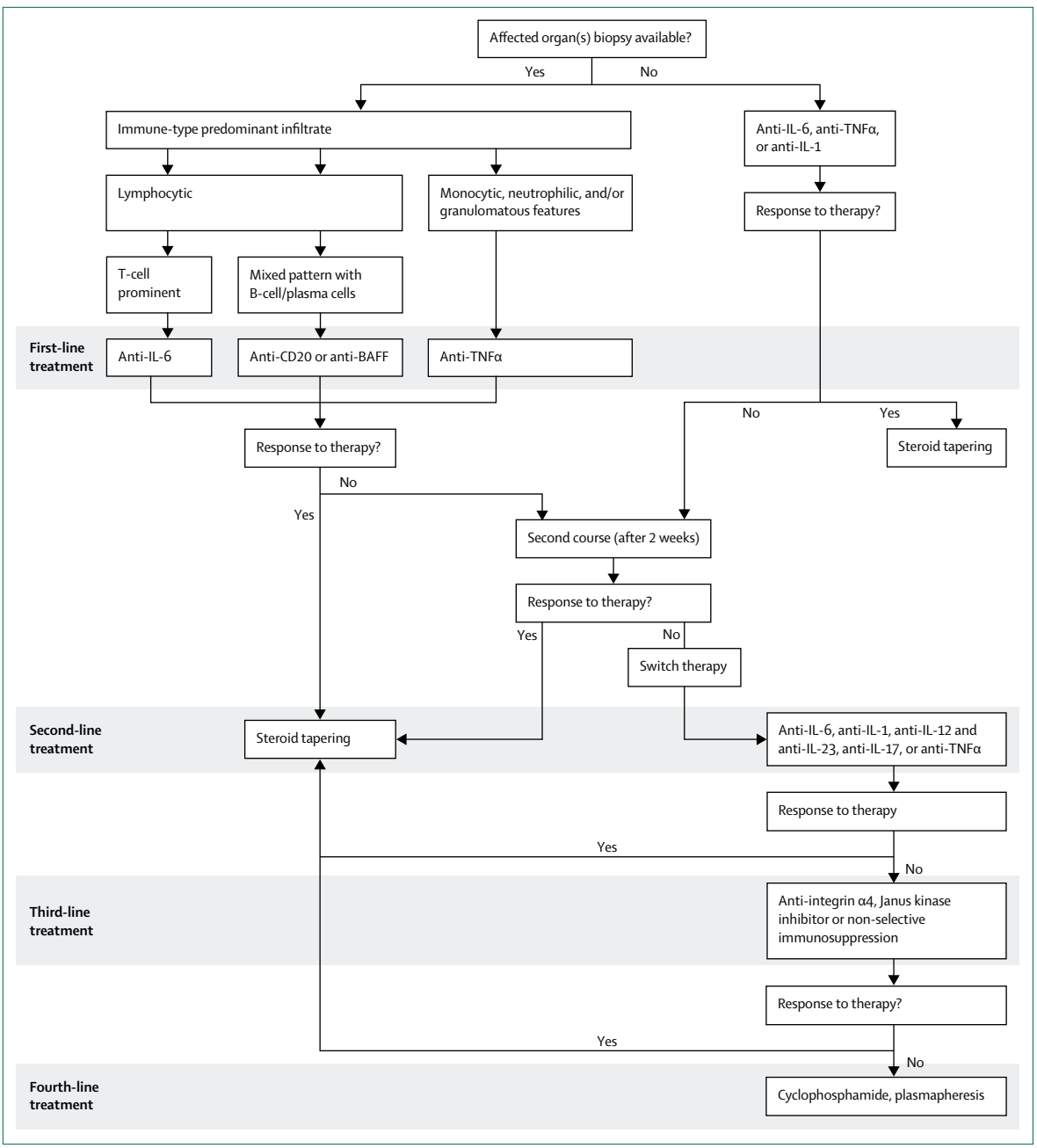

Figure 2: **Algorithms for personalised shut-off treatment of steroid-refractory or rapidly evolving immune-related adverse events**
For a predominant T-cell infiltrate, an anti-interleukin (IL)-6 blockade could be considered, whereas for a prominent B and plasma cell infiltrate component, an anti-B-cell strategy (anti-CD20 and anti-B-cell activating factor [BAFF] blockade) could be considered. Regarding an infiltrate with predominant neutrophilic and monocytic features with or without granulomatous features, an anti-tumour necrosis factor α (TNFα) strategy would be an option. In case of a clinical and biological improvement, another administration could be performed 2 weeks later if the initial response is not considered sufficient. Also, in case of response, steroid tapering should be initiated and done over a 4–6 week period. If a tissue biopsy is not available, an anti-IL-6 could be considered; however, if not available an anti-IL-1 or anti-TNFα strategy are reasonable options. As second-line treatment, an anti-IL-1 drug is preferable, but if not available an anti-IL-12/23 or anti-IL-17 drug could be considered after a first line with an anti-IL-6 therapy; if not available, then an anti-TNFα strategy could be an option. If no improvement is observed after the second administration repeated after 2 weeks, a third line should be considered. For that, we propose an anti-integrin α4 monoclonal antibody (natalizumab) as a first choice; if not available, then a non-selective immunosuppressive drug or a Janus kinase inhibitor could also be considered. If no improvement is observed after the second administration repeated after 2 weeks, a fourth line could be considered, such as cyclophosphamide 10–15 mg/kg and plasmapheresis. The fourth line could be repeated more than twice until immune-related adverse events resolution. The administration of intravenous immunoglobulin could be considered for syndromes with features similar to Guillain-Barré and chronic inflammatory demyelinating polyneuropathy at any moment.

strategy that uses anakinra or canakinumab could be a primary therapy option for some irAEs, such as acute phase myasthenia gravis, encephalitis, aseptic meningitis, severe arthritis, chronic inflammatory demyelinating polyradiculoneuritis, psoriasis, auto-inflammatory diseases, severe anti-TNFα-refractory colitis, pneumonitis, and myocarditis. A possible protocol could be anakinra 100 mg once a day or canakinumab 300–600 mg every 8 weeks.

Anti-IL-6 blockade

Together with IL-1 and TNFα, one of the main cytokines in the acute inflammation phase is IL-6. Additionally, IL-6 has been reported to promote cancer development and metastasis, and to function as a main cytokine in the generation of a systemic inflammatory response and the expansion of cancer-related symptoms, which can lead to the deterioration of physical performance and quality of life.[36] Furthermore, anti-IL-6 therapy appears to be very effective for severe inflammatory bowel disease that does not respond well to traditional therapy, which targets TNFα.[37]

Consequently, the use of anti-IL-6 therapy as an upfront treatment option could be an excellent alternative to anti-TNFα or anti-IL-1 drugs for many irAE indications, without compromising the efficacy of immunotherapy. Serum IL-6 has proven to be a useful marker for the activity of rheumatoid arthritis.[38] However, elevated serum levels of IL-6 are frequent in patients with cancer.[39] Nevertheless, an assessment of baseline IL-6 level assessment before ICI therapy followed by repeated measurements in case of irAE emergence could still be a useful biomarker. A serious caution is advocated in interpreting these results as they can also be indicative of tumour progression or an infectious complication. The elevation of serum IL-6 should not be considered a decisive factor in the introduction of anti-IL-6 therapy, as it has not been validated in dedicated clinical trials. A clinical trial (NCT03601611) plans to assess the efficacy of first-line tocilizumab treatment in patients with ICI-induced colitis and arthritis. Among other measurements, the levels of IL-6 and C-reactive protein will be taken to validate theses serum markers as irAE activity biomarkers and evaluate their usefulness in therapeutic decisions. A retrospective trial[8] showed a statistically significant correlation between C-reactive protein levels (an indirect surrogate of IL-1, IL-6, and TNFα serum levels) and irAE emergence as well as response to tocilizumab therapy in a cohort that was mainly represented by patients with lung cancer. Clinical improvement (defined as symptoms resolution or hospital discharge within 7 days) was observed in 27 (79·4%) of 34 patients, with 52·9% of the patients requiring only a single dose of tocilizumab for symptomatic response. Possible indications for anti-IL-6 therapy include severe irAEs in their acute phase, severe arthritis, uveitis, Graves' orbitopathy, myocarditis, large-vessel vasculitis, severe pneumonitis and myasthenia gravis.[40–45] A possible protocol might be 8 mg/kg tocilizumab administered via intravenous therapy once per month or 162 mg administered subcutaneously once per week. However, it should be used carefully in patients with refractory ICI-induced enterocolitis because of a potential increased risk of lower gastrointestinal tract perforation, as reported in patients with rheumatoid arthritis.[46,47]

Anti-IL-17 therapy

High IL-17 serum levels have been reported during ipilimumab-induced colitis.[48] Blockade through monoclonal antibodies such as secukinumab could constitute an interesting strategy to manage this toxicity. However, contradictory evidence regarding IL-17 blockade and its implications in promoting tumour growth and metastasis has raised concern.[49] For example, a patient with metastatic colon cancer (with a mismatch repair-deficient tumour) who initially responded to PD-1 blockade showed tumour progression after treatment with secukinumab for a psoriatic rash.[50] Because of the heterogeneous microenvironment in different tumour types and individuals, the identification of profiles that might be able to predict the role of IL-17 in control or promotion of tumours should be pursued. Possible indications for use of anti-IL-17 therapy are severe psoriasis refractory to anti-TNFα therapy and rheumatoid arthritis and anti-IL-6 refractory irAEs. Several mAbs are available and could be used as follows: ixekizumab 80 mg subcutaneously every 2 weeks, brodalumab 210 mg subcutaneously every 2 weeks, and secukinumab 150 mg subcutaneously every week.

Anti-IL-23 and anti-IL-12 therapy

Ustekinumab is an mAb targeting the common p40 subunit of IL-23 and IL-12. It is approved for the treatment of cutaneous psoriasis and related arthritis. A randomised trial[51] comparing ustekinumab to placebo in the setting of anti-TNFα-refractory Crohn's disease showed that a third of patients had a response at 6 weeks. Opposing roles of IL-23 and IL-12 in maintaining outgrowth and dormancy of tumours in mice[52] raise concerns regarding the use of ustekinumab in patients with cancer. Nevertheless, most clinical trials did not find an unexpected increase in cancer across approved indications.[52,53] In the palliative and refractory irAE setting, ustekinumab treatment could be a conceivable option for some patients. A possible protocol is an induction dose of 6 mg/kg intravenous therapy followed by 90 mg every 8–12 weeks.

Anti-integrin 4

Natalizumab is an anti-integrin 4 antibody that is approved for the treatment of multiple sclerosis. It has been used in a patient with stage IV small-cell lung cancer who had a relapse of limbic encephalitis, which led to cognitive improvement without impairing a durable tumour response with combined checkpoint inhibition therapy.[54] Vedolizumab is an anti-integrin α4β7 antibody that is

present in gut-selective anti-inflammatory activity, with indication for the treatment of refractory inflammatory bowel disease.[55] Its activity has been reported in a case series[56] of seven steroid-refractory cases of ICI-induced colitis, obtaining enterocolitis remission in six patients. Two to four vedolizumab administrations seemed enough to obtain steroid-free remission in their cohort, with no adverse side-effect of vedolizumab reported.

Janus kinase inhibition

On one hand, tofacitinib, a Janus kinase (JAK) 1 and JAK3 inhibitor, is used across several rheumatological indications, such as refractory rheumatoid arthritis and ulcerative colitis.[57] On the other hand, one study[46] suggests that the risk of lower gastrointestinal tract perforation associated with tofacitinib treatment in patients with rheumatoid arthritis could be more common than with anti-TNFα drugs, suggesting the need for close clinical follow-up during the treatment of ICI-induced colitis. A possible dosing scheme could be tofacitinib 5 mg or 10 mg twice per day.

Anti-B-cell strategy

The major role of T cells is well established in the pathogenesis of irAEs, yet several studies have also reported a possible contributive role of B cells, especially in skin irAEs (with a bullous phenotype) and endocrine irAEs (eg, hypophysitis and thyroiditis).[58–60] A study[61] showed peripheral blood changes in B-cell number and qualitative sub-populations in patients with melanoma treated with ICIs. Using flow cytometry, the authors showed a correlation between the presence of irAEs and severity to the reduction of B-cell compartment with concomitant increase in $CD21^{low}$ B cells and plasmablasts. Although the pathophysiological mechanisms linking these changes to irAE triggering or promotion are still unclear, their potential as predictive biomarkers of irAE occurrence is already raising interest.[62] The absence of measurable autoantibodies is not a reason to discard the role of B cells in the pathogenesis of irAEs, since they are also absent in 60% of patients with primary Sjögren's syndrome associated to small-fibre polyneuropathy.[63] Such seronegative cases require more specific diagnostic approaches, including neuromuscular or salivary gland biopsy. Rituximab treatment has also been shown to be effective in seronegative autoimmune disorders, such as cutaneous vasculitis and vasculitis negative for anti-neutrophil cytoplasmic antibodies (ANCA).[64–66]

Autoimmune encephalitis is a rare but serious irAE that is often associated with double checkpoint blockade, as reported in different tumour types. Cases have been reported in which anti-neural autoantibodies were detected, such as anti-NMDAR[67] or anti-Hu;[68] however, in other cases such antibodies were undetectable. In several reports, both type of cases (ie, independently of serological status), showed an impressive neurological improvement after treatment with rituximab (anti-CD20 monoclonal antibody); in these cases, patients were mostly unresponsive to corticosteroids and intravenous immunoglobulins.[67,69] Thus, whether autoantibodies are directly pathogenic (ie, anti-NMDAR), directed against intra-cytoplasmic antigens (ie, anti-Hu), or undetectable, rituximab can be considered as a therapeutic alternative, with probably a low effect on tumour control. Additionally, rituximab could be an excellent treatment option for ICI-induced autoimmune disorders with an autoantibody profile, such as systemic lupus erythematosus, severe Stevens-Johnson syndrome, ANCA-associated vasculitis, cutaneous vasculitis, autoimmune autonomic ganglionopathy, sensory ganglionopathy, nephritis, myasthenia gravis, transverse myelitis, enteric neuropathy, and as mentioned encephalitis. Furthermore, rituximab can be used to treat autoimmune hepatitis or refractory haemolytic anaemia in patients intolerant or refractory to standard regimens.[70] Tumour-associated B cells in melanoma have been shown to be involved in drug resistance and to detain a pro-tumorigenic property in part through IGF-1 secretion.[71] CD20 is also aberrantly expressed in subsets of melanoma cells with stem-cell properties and is being studied as a target antigen for chimeric antigen receptor T-cell therapy.[72] A pilot study[71] showed B-cell depletion in eight of ten patients with therapy-resistant melanoma who were administered ofatumumab, which suggests a good safety profile for this type of immunosuppression when used for tumour control. Data from another case series[73] showed median survival exceeding 1 year in patients with multi-treated metastatic melanoma receiving rituximab. Possible protocols are two courses of rituximab 1 g 2 weeks apart, or 375 mg/m² once per week for 4 weeks. Other fully human anti-CD20 antibodies are also available: ofatumumab 300 mg on day 1 and 1000 mg on day 2, obinutuzumab 1000 mg on days 1 and 2, and ocrelizumab 300 mg on days 1 and 4. These antibodies could possibly be used as an alternative to rituximab because they seem to have an excellent safety profile and similar effectiveness as rituximab. Belimumab (anti-B-cell activating factor mAb) has shown efficacy in patients with systemic lupus erythematosus[74] and could be an option as an adjunct to rituximab in severe and refractory autoantibody-mediated irAEs, as this combination might induce a more profound B-cell depletion by targeting plasma cell activation.[75] Therefore, it remains important to define the best combination of B-cell therapy and the appropriate sequence of treatment.

Intravenous immunoglobulins and plasmapheresis

Intravenous immunoglobulins are the standard treatment for Guillain-Barré syndrome and subacute and chronic inflammatory demyelinating polyneuropathy. Dramatic improvements in ICI-induced forms of these conditions have been shown with standard approaches with protocols of 400 mg/kg of intravenous immunoglobulins per day for 5 days.[76] Immune thrombocytopenia is a rare irAE and

Search strategy and selection criteria

We searched PubMed for papers published in English between Jan 1, 2010, and Oct 31, 2018, using the terms "checkpoint inhibitor", "immune-related adverse event", "CTLA4", "PD-1", "PD-L1", "melanoma", "autoimmune hepatitis", "inflammatory bowel disease", "rheumatoid arthritis", "uveitis", "Graves' orbitopathy", "vasculitis", "colitis", "encephalitis", "pneumonitis", "Guillain-Barré syndrome", "inflammatory demyelinating polyradiculoneuritis", "myocarditis", "myasthenia gravis", "TNFα", "IL-1", "IL-6", "IL-23", "IL-12", "corticosteroids", "tocilizumab", "cyclophosphamide", "rituximab", "natalizumab", "vedolizumab", "etanercept", "adalimumab", "certolizumab", "golimumab", "ustekinumab", "ixekizumab", "janus kinase inhibitor", "tofacitinib", "brodalumab", "secukinumab", "belimumab", "ofatumumab", "obinutuzumab", "ocrelizumab", "anakinra", "canakinumab", "immunolgobulins", "plasmapheresis", and "romiplostim". We found a paper published earlier than 2010 and included it because of its relevance for pathogenesis and management.

its occurrence could cause delays in the instauration of further anticancer treatment, and place the patient at life-threatening risk of bleeding, especially in populations with a high prevalence of CNS metastasis (eg, patients with melanoma). Three-quarters of patients will respond to corticosteroids; those with refractory disease might require treatment with calcineurin inhibitors or intravenous immunoglobulins.[77] Thrombopoietin agonists such as romiplostim have also been used in the setting of anti-PD-1-induced thrombocytopenia.[78] Intravenous immunoglobulins should be reserved for cases of profound immune thrombocytopenia and in combination with steroids because of their intense albeit short-lasting effect. Possible indications for intravenous immunoglobulins are Guillain-Barré syndrome, subacute and chronic inflammatory neuropathies, immune thrombocytopenia, facial nerve palsy, myasthenia gravis, transverse myelitis, enteric neuropathy, ocular myositis, and encephalitis.[79] Moreover, a case of severe corticosteroid-refractory autoimmune neutropenia responding to intravenous immunoglobulins after treatment with ipilimumab has also been reported.[80] A possible protocol might be 400 mg/kg of intravenous immunoglobulins per day for 5 days once per month for a total of three to four treatments.

A case of myasthenia gravis crisis showed a favourable outcome for at least 6 months after methylprednisolone, intravenous immunoglobulins, and five courses of plasmapheresis.[17] As the treatment backbone of Guillain-Barré syndrome relies on plasmapheresis, patients with corticosteroid-refractory immune-related acute inflammatory demyelinating polyradiculoneuropathy and encephalitis could be considered as potential candidates for plasmapharesis.[81]

Cyclophosphamide

Despite its carcinogenic risk, a pulse of cyclophosphamide could be very useful as an induction treatment for remission in patients with multiple severe irAEs, such as symptomatic sarcoidosis, steroid-refractory pneumonitis, Guillain-Barré syndrome, severe Stevens-Johnson syndrome with central and neurological symptoms, autoimmune autonomic ganglionopathy, sensory ganglionopathy, polyneuropathy, and central neuritis. An induction protocol is cyclophosphamide 10 to 15 mg/kg at weeks 0, 2, 4, 7, 10, and 13 (cumulative dose of ~7 g) or 500 mg every 2 weeks for a total of six courses, which is similar to the schedule used for systemic lupus erythematosus nephritis.

To achieve rapid remission with minimal exposure to cyclophosphamide, an appropriate alternative protocol to six cyclophosphamide courses could be four administrations of rituximab 375 mg/m² at weeks 0, 1, 2, and 3 and two administrations of cyclophosphamide 10 to 15 mg/kg at weeks 0 and 2.[82]

Conclusion

In this Personal View, we discuss personalised therapeutic options for severe and/or refractory irAEs, based on current immuno-pathophysiological knowledge and on extrapolations of treatment options from primary autoimmune disorders. The development of cancer immunotherapy is one of the major medical breakthroughs in recent years and is still in its early stages. We are still learning how to make the best use of these novel and potent therapies in the management of patients with cancer. However, severe toxicities associated with immunotherapy have started to emerge, and often clinicians are faced with substantial challenges in the management of severe irAEs. Because the clinical course of irAEs and their response to therapy could differ from the ones observed in patients with primary autoimmune disorders, there is still a lot to learn on how to adapt and optimise classic immunosuppressive interventions for their treatment. This learning process will take time and will probably require advances in three areas: the development of biomarkers predictive of steroid-refractory disease, early response to immunosuppressive therapy, and the safety of ICI administration; the development of appropriate therapeutic regimens using classic immunosuppression (eg, corticosteroids with efficient mAb and small molecule therapies that block inflammation); and the training of physicians with specific expertise in immunotherapy.

Because the clinical presentation of irAEs and severity vary in patients (in part due to intrinsic patient factors) the identification of genetic, epigenetic, or surrogate predictive markers of irAE development is expected to allow a better safety appraisal of ICI therapies in patients who are deemed at high risk of irAE development (and in those with pre-existing autoimmune disorders) and to guide the development of preventive interventions. High-throughput RNA sequencing of peripheral-blood mononuclear cells or circulating micro-RNAs could be explored to identify predictive patterns of irAE development and be used as non-invasive biomarkers. As a proof of principle, this area of research has already shown promising results in

patients with stem-cell transplants at risk of graft-versus-host disease.[83,84] Biomarkers are also needed to develop personalised treatment algorithms by choosing the most appropriate shut-off strategy to manage severe and refractory irAEs—according to the immune type of the predominant infiltrate from the affected organs, which could be determined by a biopsy. The medical community should be encouraged to include prospective investigations on side-effect management of ICIs in future advanced-phase trials. These types of approaches could inform the direct and selective targeting of the main inflammatory cytokines, such as IL-6, TNFα, and IL-1, together with ICI discontinuation, without compromising the efficacy of immunotherapy. The expected benefit of this upfront shut-off strategy is two-fold: blockade of the acute phase of the inflammatory reaction, and inhibition of tumour development, which is promoted by IL-1 and IL-6.

Lastly, clinicians with specific training and expertise in immunotherapy are needed, because of the evolving complexity of cancer care and the large spectrum of immune-related toxicities. Furthermore, proper management of severe irAEs requires the efficient response and concerted decision of multidisciplinary teams, which crosses the traditional boundaries of medical specialties. Such efforts will ensure that patients with cancer benefit from the highest quality of care as immunotherapy continues to evolve in the future.

Contributors

FM wrote the manuscript and prepared the figures and table. MO conceived the article, wrote the manuscript, and prepared the figures and table. All authors wrote, commented on, and corrected the manuscript.

Declaration of interests

SP received education grants, provided consultation, attended advisory boards; and provided lectures for Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Clovis, Eli Lilly, F. Hoffmann-La Roche, Janssen, Merck Sharp and Dohme, Novartis, Merck Serono, Pfizer, Regeneron, and Takeda. All other authors declare no competing interests.

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