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New therapeutic perspectives to manage refractory immune checkpoint-related toxicities: personalized treatment algorithms beyond corticosteroids

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ABBREVIATIONS

AAG	Autoimmune autonomic ganglionopathy
AIDs	Autoimmune disorders
AIDP	Acute inflammatory demyelinating polyradiculoneuropathy
AIH	Autoimmune hepatitis
AIT	Autoimmune toxicity
ATG	Anti-thymocyte antiglobulin
AZA	Azathioprine
CIDP	Chronic inflammatory demyelinating polyradiculoneuritis
CNI	Calcineurin inhibitor
CP	Cyclophosphamide
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
GBS	Guillain-Barré syndrome
ICIs	Immune-checkpoint inhibitors
IBD	Inflammatory bowel disease
irAE(s)	Immune-related adverse event(s)
IS	Immunosuppression
IVIGs	Intravenous immunoglobulins
mAbs	Monoclonal antibodies
MG	Myasthenia gravis
MMF	Mycophenolate mofetil
PD-1	Programmed death 1 receptor
PD-L1	Programmed death-ligand 1
SLE	Systemic lupus erythematosus
SJS	Stevens-Johnson syndrome
TAMs	Tumor-associated macrophages

ABSTRACT

Immune-checkpoint inhibitors (ICIs) are reshaping the prognosis of many cancer types and are progressively becoming a standard of care for many of them. Cancer immunotherapy has started a revolution in the oncology therapeutic landscape, bringing new hope to patients but also a whole new spectrum of toxicities for practitioners to manage. Oncologists and specialists involved in the pluridisciplinary management of immune-related adverse events (irAEs) are increasingly confronted with the therapeutic challenge of severe and/or refractory cases. In this personal view, we summarize the therapeutic strategies reported to manage them. Based on current knowledge of irAE pathogenesis and our immunological expertise, we also transpose the use of new biologic and non-biologic immunosuppressive agents, used to treat primary autoimmune disorders (AIDs), in the context of severe and/or steroid refractory irAE management. Depending on the immune-type predominant infiltrate, we propose a personalized treatment algorithm beyond corticosteroids. A shut-off strategy, intended to treat severe or steroid-refractory irAEs, based on the efficient inhibition of key inflammatory components involved in their pathophysiological processes, and limit potential adverse effects of drug immunosuppression on tumor response is proposed. This approach goes beyond current guidelines, challenging the step-by-step increase in drug immunosuppression proposed so far.

INTRODUCTION

Monoclonal antibodies that block immune checkpoints, such as the cytotoxic T-lymphocyte antigen 4 (CTLA-4)-CD28 and programmed death 1 (PD-1)-programmed death ligand 1 (PD-L1) axes, are the main immunotherapies prescribed in the current oncological practice. Over the last decade, clinicians have been confronted with the management of irAEs resulting from ICI therapies. Because of the increasingly widespread use of ICIs in oncology, new data on toxicities related to these agents are continuously reported, in addition to the ones documented in prospective clinical trials. The advent of double checkpoint inhibition constitutes also a new challenge as the related toxicities often involve multiple organs and occur at higher frequencies compared to monotherapy. For example, the prospective Checkmate 067 trial on ipilimumab/nivolumab combination in advanced melanoma reported a 4% incidence of patients with steroid-refractory irAEs.¹ The spectrum of organ systems affected by irAEs is very broad and their management often requires expertise that goes beyond the specialty of oncology. They vary in frequency and severity, depending on the agent(s) and the affected system(s). Consequently, their optimal management requires experienced multidisciplinary teams. Extensive knowledge in the field of clinical immunology and immunosuppressive therapy, going beyond current 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 should be managed according to grade. Nevertheless, one should not overlook the limitations of current grading systems, and thus should not to substitute them for clinical judgment, especially in frail patients and when confronted with rapidly evolving irAEs. In this personal view, we discuss personalized therapeutic options for severe and/or refractory irAEs, based on current immunopathophysiological knowledge and on extrapolations from primary autoimmune counterparts.

High-quality guidelines regarding the management of irAEs were released by the European Society of Medical Oncology (ESMO)², the National Comprehensive Cancer Network (NCCN) and the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group.^{3,4} They provide treatment algorithms for most frequent irAEs in a comprehensive way and detail their recommendation regarding the use of immunosuppressive drugs according to irAE severity and duration. They also emphasize the

importance of avoiding delays in the work-up to rule-out other differential diagnoses (e.g., infectious complications or tumor progression) before initiating effective immunosuppressive therapy. However, as exhaustive as these guidelines can be, they are still limited regarding the management of severe and/or refractory irAEs, with which clinicians are confronted in the day-to-day practice. Retrospective data on a large ipilimumab-treated cohort reported that more than one-third of patients received corticosteroids to manage an irAE, and one-third of those required additional immunosuppressive drugs.⁵ It is important to be aware that rare yet life-threatening irAEs are constantly reported, representing a diagnostic and therapeutic challenge; for such irAEs, evidence to guide management recommendations is limited due to the scarcity of literature, consisting of only small series or case reports. Some experts are already adopting a first instance cytokine-directed therapy, such as tocilizumab (an IgG1 humanized anti-IL6R mAb), in steroid-refractory cases.⁶

NEW THERAPEUTIC PERSPECTIVES TO MANAGE ICI-INDUCED TOXICITIES

Due to the scarcity of prospective trials regarding drug immunosuppression in the setting of high-grade irAEs, in daily clinical practice one draws from small series, case reports and expert opinion to handle challenging cases. Current guidelines promote a step-by-step approach, starting with high-dose steroids and increasing drug immunosuppression as needed. This consensus will certainly be maintained in the absence of validated clinical or biological biomarkers predictive of steroid-refractoriness. On the other hand, clinicians confronted with severe irAEs should not discard the possibility to add a cytokine-directed mAb from the beginning of a severe irAE with the putative advantage of “shutting-off” early a rapidly evolving immuno-pathophysiological process, thereby avoiding patient exposure to extended courses of immunosuppression. A good example for first instance aggressive drug immunosuppression is myocardial irAEs. In this case, better efficacy of rapid immunosuppression is presumed due to its fulminant clinical presentation, the high associated morbi-mortality rate, as well as the documented increased risk of adverse outcomes with lower steroid doses compared to high-dose therapy.⁷ A recent meta-analysis revealed an incidence of fatalities surrounding 1% in ICI treated patients.⁸ These severe irAEs tended to occur early after treatment initiation with monotherapy (with a median of forty days) and even earlier with ICI combination (with a median of two weeks). Unusual clinical presentations along with diagnosis delays surged as mortality contributing factors.

Biomarker-based approaches are already being explored and will certainly help therapeutic decision. For example, in ICI-related colitis, ulcerative endoscopic findings have recently been suggested as predictive surrogate markers for steroid-refractoriness.⁹ A recent study on 90 colic biopsies from patients with ICI-related colitis showed different profiles of immune infiltrates: 27% of patients had immune infiltrates with predominant intraepithelial lymphocytosis, whereas 73% of patients had predominant monocytic/neutrophilic infiltrates.⁹

Not to mention that transposing therapeutic knowledge from primary autoimmune disorders is also hampered by the different nature of irAEs in terms of disease phenotype, response to treatment and pathophysiological mechanisms. For example, a histologic analysis conducted on liver biopsies showed a more diffuse, cytotoxic T-cell predominant, and lobular infiltrate pattern in comparison to autoimmune hepatitis (AIH), altogether with less CD4 T-cells and plasma cells in the parenchyma.¹⁰ The lack of steroid efficacy in AIH in comparison to most ICI related hepatitis signs also a clear-cut difference highlighting the possible implication of CD4 T-cells in steroid refractoriness.¹¹ Multidrug-refractory cases of severe hepatitis have been treated with anti-thymocyte antiglobulin (ATG), reflecting the relative resistance to selective immunosuppression of this particular irAE.^{12,13} Another contrasting example is the one of ICI-related myasthenia gravis (MG) where a higher risk of crisis compared to their autoimmune counterparts, as well as an increased association with myositis has been reported.^{14,15,16} In the opposite, ICI-related colitis displays some interesting common features with inflammatory bowel disease (IBD). Both of these disorders demonstrate sensitivity to anti-TNF α mAbs and share as well histological and pathophysiological features. The latter is highlighted by the link between IBD and certain CTLA4 polymorphisms in the population.¹⁷ Even though the chronic nature of IBD tends to disrupt the epithelial layer and show granulomatous lesions as characteristic features, a lymphocytic-neutrophilic infiltrate is a shared histologic feature.

In light of the present lack of validated biomarkers, immunopathological patterns could be considered as rational target tools to personalize a shut-off strategy (Figure 2): For a predominant T-cell infiltrate, a T-cell-directed therapy such as anti-IL-6, anti-IL-1R or anti-IL-12/23 blockade strategy could be an optimal approach. A prominent B/plasma cells infiltrate might be optimally targeted by an anti-B-cell strategy (anti-CD20 and/or anti-BAFF blockade). An infiltrate with a predominant neutrophilic/monocytic pattern with or without

granulomas could be optimally targeted by an anti-TNF α strategy. Lastly, the difficulty to obtain a biopsy across clinical contexts and depending on the organs involved, as in the case of neurological, rheumatological and ocular irAEs is recognized. The use of a cytokine-directed mAb, targeting IL-6, TNF α and/or IL-1 pathway is still an upfront option to consider in these cases, as it will be discussed later on.

For the most part, the safety profile of biologic and non-biologic agents used in primary AIDs extrapolated to cancer patients is still incompletely clear. Some of these drugs are considered to have a low likelihood of adverse impact on cancer response, while others may adversely affect T-cell antitumor response and consequently cancer prognosis. Altogether, their use outside of clinical trials should be advised and monitored by specialists in clinical immunology and discussed in light of cancer prognosis, anticipated time of onset of the chosen drugs, and their respective side effect profiles.

Knowledge extrapolated from solid organ transplant patients treated with ICIs supports a significant impact of calcineurin inhibitors (CNI) and mycophenolate mofetil (MMF) on the T-cell response. Even so, the latter is already advised as second line immunosuppressive drugs in current guidelines. However, in our opinion, they should be avoided in immunogenic tumors, especially if a curative intent is at stake, such as in advanced melanoma patients. Knowing the role of IL-6 as a major acute inflammatory phase mediator, in cytotoxic T-cells differentiation, but also its protumor properties, an IL-6 targeting strategy constitutes a robust substitute to older immunosuppressive drugs, without compromising the efficacy of immunotherapy.^{18,19}

Limitations of such strategies regarding their cost and financial impact on health care systems should be acknowledged. Nevertheless, if the strategy is effective, such costs might be amortized thanks to decreased morbidity. In any case, they should be considered in light of the already high costs ensuing from ICI therapies. Prospective clinical trials answering these open questions are urgently advocated, due to the rapid expansion of cancer immunotherapy. Nevertheless, most of these toxicities are so rare that clinical trials are almost inconceivable. This is why it is essential to actively report irAEs to competent national authorities and to publish them in the medical literature, along with empirically treated cases and case series.

The following section provides an overview of standard and off-label agents used to treat severe/refractory irAEs as an adjunct to corticosteroids. In principle, we propose to continue each such therapy until the complete resolution of the respective irAE (Table 1).

Corticosteroids

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

Calcineurin inhibitors (CNI), azathioprine (AZA), mycophenolate mofetil (MMF) and anti-TNF α therapies

Treatments used for IBD and AIH have been used by extrapolation to treat colitis and hepatitis resulting from checkpoint blockade. Severe and refractory irAE colitis can be treated with infliximab (a chimeric monoclonal anti-TNF α antibody) at a single dose of 5 mg/kg, by analogy with Crohn's disease²⁰. This treatment has been shown to be highly effective for corticosteroid-refractory colitis, with rapid responses occurring in 1 to 3 days. In some relapsing cases, 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 with very heterogeneous successes reported in the literature.²¹ Nevertheless, anti-TNF α therapy seems a better alternative than older IS drugs in this indication. As one of the most frequent irAEs during anti-PD-1/PD-L1 therapies, steroid-refractory pneumonitis lacks tremendously of evidence-based therapeutic approaches. This frail population is also frequently subjected to unfortunate long courses of steroids as pneumonitis often demonstrates steroid-dependency. Etanercept, adalimumab, certolizumab and golimumab are also available and could be alternatives to infliximab given their excellent safety profiles and proven effectiveness. A published case of corticosteroid- and methotrexate-refractory ICI-induced polyarthritis treated with adalimumab revealed excellent symptomatic improvement together with clinical regression of joint inflammation.²²

Infliximab is also a rescue option in the treatment of refractory AIH, suggesting that this is another reasonable indication for the other anti-TNF α agents.²³ A special caution in using anti-TNF α mAbs to treat irAEs is also advocated by the rare cases of paradoxical adverse events reported under these treatments. In the literature, these encompass mostly the emergence or aggravation of psoriasis, IBD, lung granulomatous disease and uveitis, but the full spectrum of rarer paradoxical AEs is even wider.^{24,25} Consequently, clinicians should always consider paradoxical AEs in their differential diagnosis in front of refractory irAEs, especially if these tend to change of tissue/organ involvement and phenotype during treatment with biological agents.

Possible protocols could be adalimumab 40 mg every two weeks, golimumab 50 mg once per month, etanercept 50 mg once per week or certolizumab 400 mg once per month.

MMF is considered a second-line treatment for ICI-induced hepatitis and is also advocated by most current guidelines as a second-line therapy based on a relatively low level of evidence; by analogy with AIH, azathioprine could also be a reasonable treatment option.²⁰ CNI have been used as adjunct treatment for corticosteroid-refractory colitis and hepatitis, although evidence supporting their use in this setting is not well documented.²⁶ A case of infliximab-refractory enterocolitis has also demonstrated a rapid improvement after two weeks of cyclosporine. Perhaps a focus on its ability to potentially prevent myocardial fibrosis should also be brought to the attention of clinicians and be addressed in surviving cohorts of ICI-induced myocarditis.²⁷ Plasma dosing and levels-based scheduling of MMF and CNI administration should be performed in order to confirm the therapeutic doses and avoid toxicity.

Beyond the aforementioned tested immunosuppressive/immunomodulatory drugs to treat severe/refractory irAE cases, additional options can be envisaged by extrapolating knowledge from the treatment of primary AIDs (Figure 1).

Anti-IL-1 blockade

IL-1 is one of the main cytokines present during the acute phase of inflammation. Preclinical data have identified the IL-1 β pathway as an important promoter of tumor progression through stimulation of tumor-associated macrophages (TAMs), myeloid suppressive cells and up-regulation of PD-L1 in tumor cells.²⁸ In addition, CNS injury leads to an inflammatory response that is partly mediated by an increase in IL-1 levels through tissue infiltration by

neutrophils.²⁶ As shown in several animal models, IL-1 receptor antagonists possess CNS-protective properties.²⁹ Preclinical studies pointed out the central role of IL-1 in autoimmune encephalitis, through its effect on the differentiation of IL-17 producing T-cells.³⁰ It is also a mediator of T-cell adhesion to brain microvasculature in certain blood-brain barrier preclinical models.³¹ Anakinra, a recombinant IL-1 receptor antagonist, and canakinumab, a monoclonal antibody with anti-IL-1beta activity, are approved for the treatment of rheumatoid arthritis and other auto-inflammatory diseases, respectively. IL-1 blockade is accepted as having no detrimental effect on cancer response.³² An anti-IL-1 strategy employing anakinra or canakinumab may find a place as primary therapy for some irAEs, such as acute phase MG, encephalitis, aseptic meningitis, severe arthritis, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), psoriasis, auto-inflammatory diseases, or severe anti-TNF α -refractory colitis, pneumonitis and myocarditis. A possible protocol could be anakinra 100 mg once/day or canakinumab 300-600 mg every 8 weeks.

Anti-IL-6 blockade

Together with IL-1 and TNF α , one of 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, leading to the deterioration in physical performance and quality of life.³³ Furthermore, anti-IL-6 therapy appears to be very effective for severe IBD that does not respond to traditional therapy targeting TNF α .³⁴

Consequently, the use of anti-IL-6 therapy as an upfront treatment could be an excellent alternative to anti-TNF α or anti-IL-1 agents for many irAE indications, without compromising the efficacy of immunotherapy. Serum IL-6 has proven to be a useful marker of rheumatoid arthritis disease activity.³⁵ However, elevated serum levels of IL-6 are frequent in cancer patients.³⁶ Nevertheless, a 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 sign tumor 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 prospective trial planning to assess the efficacy of first-line tocilizumab treatment in ICI-induced colitis and arthritis is about to initiate (NCT03601611). Amongst other measurements, the levels of IL-6 and CRP will be taken in

an attempt to validate these serum markers as irAE activity biomarkers and evaluate their usefulness in therapeutic decisions. A retrospective trial showed a statistically significant correlation between C-reactive protein levels (an indirect surrogate of IL-1, IL-6 and TNF α serum levels) and irAE emergence as response to tocilizumab therapy in a cohort mainly represented by lung cancer patients and clinical improvement was observed in 79.4% of patients, with 52.9% of the patients requiring only a single dose for symptomatic response.⁶ 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 MG.³⁷⁻⁴² A possible protocol might comprise 8-mg/kg tocilizumab-administered i.v. once per month or 162 mg administered subcutaneously once per week. However, its use should be used carefully in cases of refractory ICI-induced enterocolitis due to a potential increased risk of lower gastrointestinal track perforation, as reported in rheumatoid arthritis patients.^{43,44}

Anti-IL-17 therapy

High IL-17 serum levels have been reported during ipilimumab-induced colitis.⁴⁵ Blockade through monoclonal antibodies such as secukinumab may constitute an interesting strategy to manage this toxicity. However, contradictory evidence regarding IL-17 and its implications in promoting tumor growth and metastasis has raised concern.⁴⁶ For example, a patient with metastatic colon cancer (with a mismatch repair-deficient tumor) who initially responded to PD-1 blockade, showed tumor progression after treatment with secukinumab for a psoriatic rash.⁴⁷ In view of the heterogeneous microenvironment across tumor types and individuals, the identification of profiles that might be able to predict the role of IL-17 in tumor control or, conversely, tumor promotion should be pursued. Possible indications for use of anti-IL-17 therapy are severe psoriasis refractory to anti-TNF α therapy and rheumatoid arthritis. Several mAbs are available and could be used as follows: ixekizumab 80 mg s.c. every two weeks, brodalumab 210 mg s.c. every two weeks and secukinumab 150 mg s.c. every week.

Anti-IL-23/12 therapy

Ustekinumab is a 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 randomized trial comparing

ustekinumab to placebo in the setting of anti-TNF α -refractory Crohn's disease showed that one-third of patients experienced a response at 6 weeks.⁴⁸ Opposing roles of IL-23 and IL-12 in maintaining outgrowth and dormancy of tumors in mice raise concerns regarding the use of ustekinumab in cancer patients. Nevertheless, most clinical trials did not find an unexpected increase in cancer rates across approved indications.^{49,50} In the palliative and refractory irAE setting, ustekinumab treatment may be a conceivable option in selected cases. A possible protocol is: induction dose of 6 mg/kg i.v. followed by 90 mg every 8 to 12 weeks.

Anti-integrin 4

Natalizumab is an anti-integrin 4 antibody that is approved for the treatment of multiple sclerosis. It has also been used in a relapsing case of limbic encephalitis in a patient with stage IV SCLC, leading to cognitive improvement without impairing a durable tumor response with a combined checkpoint inhibition.⁵¹ Vedolizumab is an anti-integrin $\alpha4\beta7$ antibody showing in gut-selective anti-inflammatory activity, with indication for the treatment of refractory IBD.⁵² Its efficacy has been reported in a case-series of seven steroid-refractory cases of ICI-induced colitis, obtaining a 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.⁵³

Janus kinase inhibition

Tofacitinib, a Jak 1/3 inhibitor, is currently used across several rheumatological indications, such as refractory rheumatoid arthritis and ulcerative colitis.⁵⁴ On the other hand, some reports suggest that the risk of lower GI tract perforation associated with tofacitinib treatment among rheumatoid arthritis patients may be more common than with other anti-TNF α agents, suggesting the need for close clinical follow-up during the treatment of ICI-induced colitis.⁴³ A possible dosing scheme could be 5 mg or 10 mg twice per day.

Anti-B-cell strategy

As 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 bullous phenotype) and endocrine irAEs (e.g. in hypophysitis and thyroiditis).⁵⁵⁻⁵⁷ Recently, a first report described peripheral blood changes in B-cell number and qualitative sub-populations in melanoma patients treated with ICIs.⁵⁸ Using flow cytometry, Das et al. revealed a correlation between irAEs occurrence 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 lacking, their potential as predictive biomarkers of irAE occurrence is already raising interest. The absence of measurable auto-antibodies is not an argument discarding 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-fiber polyneuropathy.⁵⁹ Such seronegative cases require more specific diagnostic approaches including neuromuscular or salivary glands biopsy. Rituximab treatment has also demonstrated to be effective in seronegative AIDs, as for example cutaneous vasculitis and ANCA-negative vasculitis.^{60,61,62}

Autoimmune encephalitis is a rare but dreadful irAE that is often associated with double checkpoint blockade, as reported in different tumor types. Cases have been reported in which anti-neural autoantibodies were detected, such as anti-NMDAR⁶³ or anti-Hu⁶⁴; in other cases, such antibodies were undetectable. In several reports, both type of cases (i.e. independently of serologic status), showed an impressive neurologic improvement after treatment with rituximab (anti-CD20 monoclonal antibody); in these cases, patients were mostly unresponsive to corticosteroids and IVIGs.^{63,65} Thus, whether autoantibodies are directly pathogenic (i.e., anti-NMDAR), directed against intra-cytoplasmic antigens (i.e., anti-Hu), or undetectable, rituximab can be considered as a therapeutic alternative, with probably low impact on tumor control. Additionally, rituximab could be an excellent option for ICI-induced AIDs with an autoantibody profile, such as SLE, severe SJS, ANCA-associated vasculitis, cutaneous vasculitis, autoimmune autonomic ganglionopathy (AAG), sensory ganglionopathy, nephritis, MG, transverse myelitis, enteric neuropathy and encephalitis. Furthermore, rituximab can also be used to treat autoimmune hepatitis or refractory hemolytic anemia in patients intolerant or refractory to standard regimens.⁶⁶ Interestingly, tumor-associated B-cells in melanoma have been implicated in drug resistance and to detain a pro-tumorigenic property in part through IGF-1 secretion.⁶⁷ 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 (CART).⁶⁸ A pilot study including ten patients with therapy-resistant melanoma showed an activity of B-cell depletion with ofatumumab in eight of them, thus suggesting at least a good safety profile regarding this kind of immunosuppression on tumor control. Encouraging data from case-series have also been published showing median survival exceeding one year in multi-treated metastatic melanoma patients receiving rituximab.⁶⁹ Possible protocols are two courses of rituximab 1 g two 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. Because these new human anti-CD20 antibodies seem to have an excellent safety profile and at least similar effectiveness as rituximab, they may provide a possible alternative to rituximab. Belimumab (anti-BAFF mAb) has proven its efficacy in SLE and may be an option as an adjunct to rituximab in severe/refractory autoantibody-mediated irAEs, as this combination may induce a more profound B-cell depletion by acting on plasma cells activation.⁷⁰ Thereby, it remains important to define the best combination B-cells therapy as well as the appropriate sequence.

A possible deleterious effect on tumor control should lead to a careful assessment of patient's risk and potential benefits.

Intravenous immunoglobulins (IVIg) and plasmapheresis

IVIg are the standard treatment for Guillain-Barré syndrome (GBS) as well as subacute and CIDP. Dramatic improvements in ICI-induced cases of GBS or CIDP have been reported using standard approaches with protocols of 400 mg/kg/day for 5 days.⁷¹ Immune thrombocytopenia is a rare irAE whose occurrence may cause delays in the instauration of further anticancer treatment and place the patient at life-threatening risk for bleeding, especially in populations with a high prevalence of CNS metastasis, such as melanoma patients. Three-quarters of patients will respond to corticosteroids; refractory cases may require CNI treatment or IVIGs.⁷² Thrombopoietin agonists such as romiplostim have also been used in the setting of anti-PD-1-induced thrombocytopenia.⁷³ Use of IVIGs should be limited in view of their intense, albeit short-lasting, effect. Possible indications for IVIGs are GBS, subacute and chronic inflammatory neuropathies, immune thrombocytopenia, facial nerve palsy, MG, transverse myelitis, enteric neuropathy, ocular myositis and encephalitis.⁷⁴ A case of severe corticosteroid-refractory autoimmune neutropenia responding to IVIG

following ipilimumab treatment has also been reported.⁷⁵ A possible protocol might be 400 mg/kg/day for 5 days once per month for a total of 3 to 4 treatments.

A case of MG crisis showed a favorable outcome for at least 6 months after methylprednisolone, IVIGs and 5 courses of plasmapheresis.¹⁵ As the treatment backbone of GBS relies on the latter, corticosteroid-refractory immune-related AIDP and/or encephalitis patients could be considered as potential candidates for plasmapheresis.⁷⁶

Cyclophosphamide (CP)

Despite its carcinogenic risk, a pulse of CP may be very useful as an induction treatment for remission in multiple severe irAEs, such as symptomatic sarcoidosis, steroid-refractory pneumonitis, GBS, severe SJS with central and neurological symptoms, AAG, sensory ganglionopathy, polyneuropathy and central neuritis. An induction protocol is CP (10 to 15 mg/kg) at weeks 0, 2, 4, 7, 10 and 13 (cumulative dose of ~7 g) or 500 mg every two weeks for a total of 6 cures, similar to its use for SLE nephritis.

Cyclophosphamide-rituximab

In order to achieve rapid remission with minimal exposure to the carcinogenic risk of CP, an appropriate alternative protocol to 6 CP cures could comprise 4 administrations of rituximab (375 mg/m²) at weeks 0, 1, 2 and 3 and two administrations of CP (10 to 15 mg/kg) at weeks 0 and 2.⁷⁷

CONCLUSION

The development of cancer immunotherapy is one of the major medical breakthroughs. We are only at the beginning of a new era and we are still learning how to make the best use of these novel potent therapies in the management of cancer patients. We have however been facing the appearance of severe toxicity associated with immunotherapy, often with substantial challenges in the management of severe irAEs. Because their clinical course and response to therapy may differ from the ones observed in primary AIDs, we are still learning how to adapt and optimize classic immunosuppressive interventions for the treatment of

irAEs. This learning process will take time and will require advances in three areas: (i) the development of biomarkers predictive of steroid-refractoriness, early response to immunosuppressive therapy and safety of ICIs administration; (ii) the development of appropriate therapeutic regimens using classic immunosuppression, i.e. corticosteroids, together with efficient mAb/small molecule therapies blocking inflammation; and (iii) the training of a new generation of physicians with specific expertise in immunotherapy.

Because the clinical presentation of irAEs and their severity vary from patient to patient, in part due to intrinsic factors, the identification of genetic, epigenetic or surrogate predictive markers of irAEs development is expected to allow a better safety appraisal of ICI therapies in patients at high risk of irAEs (as well as for those with preexisting AIDs) and to guide the development of preventive interventions. High-throughput RNA sequencing of peripheral mononuclear blood cells or circulating micro-RNAs could be explored to identify predictive signatures 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 stem cell transplant recipients at risk of graft-versus host disease.^{78,79} Biomarkers are also needed to develop personalized treatment algorithms by choosing the most appropriate shut-off strategy to manage severe and refractory irAEs, e.g., according to the immune type of the predominant infiltrate from the affected organ(s), as determined by biopsy. A crucial incentive from the medical community should also be given to include prospective investigations on side effect management in future advanced phase trials.

Such approaches could inform the direct and selective targeting of main inflammatory cytokines, such as IL-6, TNF α and/or IL-1, together with ICIs 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 tumor development promoted by IL-1 and IL-6.

Finally, a new generation of clinicians with specific training and expertise in immunotherapy is needed, due to the evolving complexity of cancer care and the large spectrum of immune-related toxicities. Furthermore, the proper management of severe irAEs requires the efficient response and concerted decision and of multidisciplinary teams, thus, this type of training crosses the traditional boundaries of medical specialties. Such efforts will ensure that cancer patients benefit from the highest quality care during the ongoing immunotherapy revolution.

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SEARCHSTRATEGY AND SELECTION CRITERIA:

We searched PubMed for papers published in English between 2010 and 2018. Keywords used included: “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”, “TNF α ”, “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”, “immunoglobulins”, “plasmapheresis”, and “romiplostim”. A paper published earlier than 2010 was identified and included due to its relevance for pathogenesis and management.

AUTHOR CONTRIBUTIONS:

FM wrote the manuscript and prepared the figures and tables; MO conceived the review, wrote the manuscript and prepared the figures and tables. All authors wrote, commented on and corrected the manuscript.

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Table 1. New therapeutic perspectives for the management of irAEs

Figure 1. Immunosuppressive drug summary according to respective targets. In response to the acute inflammatory phase, many cytokines are continuously secreted, notably IL-1, IL-6 and TNF α . By analogy with IBD treatment, blocking TNF α by infliximab has been proposed to treat irAE colitis. New humanized anti-TNF α 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, NK cells, macrophages, plasma cells and hematopoietic stem cells, as well as their endothelial activation properties. This could be more efficient than classically advocated anti-TNF α strategies. Using a shut-off interruption strategy by applying an anti-IL6 (tocilizumab) or anti-IL1 (anakinra, canakinumab) agent may have additional advantages because of the pro-tumor and pro-metastatic activities of IL-6 and IL-1. Anti-IL-1 therapy could also be a useful adjunctive treatment in cases of ICI-induced encephalitis in which the inflammatory response is mainly driven by IL-1 increase. B-cell depletion (with rituximab, obinutuzumab, ofatumumab or belimumab) could be helpful for neurological or hematological complications of ICIs, as well as in ICI-induced connective tissue diseases, severe SJS and vasculitis-related irAEs. In addition, IL-12/23 targeting could suppress the acute inflammation phase by impairing the positive stimulatory effect of IL-23 on TNF α secretion, which could thus be indicated in irAE cases refractory to anti-TNF α agents. Anti-IL-17 strategy could be used to treat cutaneous irAEs, such as anti-TNF α -refractory psoriasis-like reactions.

Figure 2. Personalized shut-off treatment algorithms for refractory irAEs according to immune-type predominant infiltrate. For a predominant T-cell infiltrate, a T-cell-directed therapy such as anti-IL-6 blockade could be considered, whereas for a prominent B/plasma cell infiltrate component, an anti-B-cell strategy (anti-CD20 and/or anti-BAFF blockade) could be considered. Regarding an infiltrate with predominant neutrophilic and monocytic features with or without granulomatous features, an anti-TNF α strategy would be a plausible option. In case of a clinical and/or biological improvement, another administration could be performed two weeks later if the initial response is not considered sufficient. Also, in case of response, steroid tapering should be initiated and pursued over a 4-6-week period. If a tissue biopsy is not available, an anti-IL-6, anti-IL-1 or anti-TNF α strategy are reasonable options. As second-line treatment, an anti-IL1, anti-IL-12/23 or anti-IL-17 agent may be considered

after a first line with an anti-IL-6 therapy; if not available, then an anti-TNF α strategy may be an option. If no improvement is observed after the second administration repeated after two weeks, a third line should be considered. For that, we propose an anti-integrin 4 agent (Natalizumab) as a first choice; if not available, then a non-selective IS or a Janus Kinase inhibitor could also be considered. If no improvement is observed after the second administration repeated after two weeks, a fourth line could be considered, such as cyclophosphamide 10-15 mg/kg and/or plasmapheresis. The fourth line could be repeated more than twice until irAE resolution. The administration of IVIG could be considered for GBS and CDIP at any moment.

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New therapeutic options	irAE indications	Protocols
Anti-IL-1 blockade	Severe irAE during acute phase Severe or refractory arthritis Chronic inflammatory demyelinating polyradiculoneuritis (CIDP) Psoriasis-like reactions/ Psoriasis exacerbation Severe and/or anti-TNF α refractory colitis Myasthenia gravis Encephalitis Aseptic meningitis Myocarditis Pneumonitis	- Anakinra: 100 mg 1x/d - Canakinumab 300-600 mg 1x/ 8 weeks
Anti-IL-6 blockade	Severe irAE during acute phase Severe or refractory arthritis Large vessel vasculitis Uveitis Myocarditis Pneumonitis Myasthenia gravis	-Tocilizumab at 8 mg/kg, intravenously 1x/month or subcutaneous 162 mg 1x/week
Intravenous immunoglobulins (IVIgGs)	Guillain-Barré syndrome Subacute and chronic inflammatory demyelinating polyradiculoneuritis (CIDP) Subacute and chronic inflammatory neuropathies Immune neutropenia Immune thrombocytopenia Facial nerve palsy Myasthenia gravis Transverse myelitis Enteric neuropathy Encephalitis Aseptic meningitis	400 mg/kg/day for 5 days, 1x/month for a total of 3-4 cures.
Anti-CD20 depletion	Systemic lupus erythematosus SLE Severe Sjögren's syndrome SjS ANCA associated vasculitis Cutaneous vasculitis Autoimmune autonomic ganglionopathy Sensory ganglionopathy Nephritis Myasthenia gravis Transverse myelitis Enteric neuropathy Encephalitis Aseptic meningitis Hepatitis	-Rituximab: 1g every two weeks for 2 cures or 375 mg/m ² 1x/week for 4 cures - Ofatumumab 300 mg day 1 and 1000 mg day 2 - Obinutuzumab 1000 mg at day 1 - Ocrelizumab 300 mg at day 1 and day 4.
Anti-IL-17 blockade	Severe colitis and anti-TNF α refractory colitis Severe or refractory arthritis	-Ixekizumab 80 mg sc 1x/2 weeks -Brodalumab 210 mg sc 1x/2 weeks -Secukinumab 150 mg sc 1x/2 weeks

Anti-TNFα blockade	Severe colitis Hepatitis Severe or refractory arthritis Nephritis Uveitis Pneumonitis Myocarditis	-Infliximab 5 mg/kg 1x/2 weeks -Adalimumab 40 mg 1x/ 2 weeks -Golimumab 50 mg 1x/month -Etanercept 50 mg one time by week -Certolizumab 400 mg one time by month.
Anti-integrin 4 blockade	Limbic encephalitis	-Natalizumab 300 mg 1x/month
Anti-IL-23/12 blockade	Acute phase Severe or anti-TNF α refractory colitis Severe or anti-TNF α refractory psoriasis Severe or refractory arthritis	-Ustekinumab initial dose 40 mg than 45 mg after 4 weeks and then 45 mg every 12 weeks
Janus Kinase inhibitor	Severe or refractory arthritis	-Tofacitinib 5 mg 2x/day

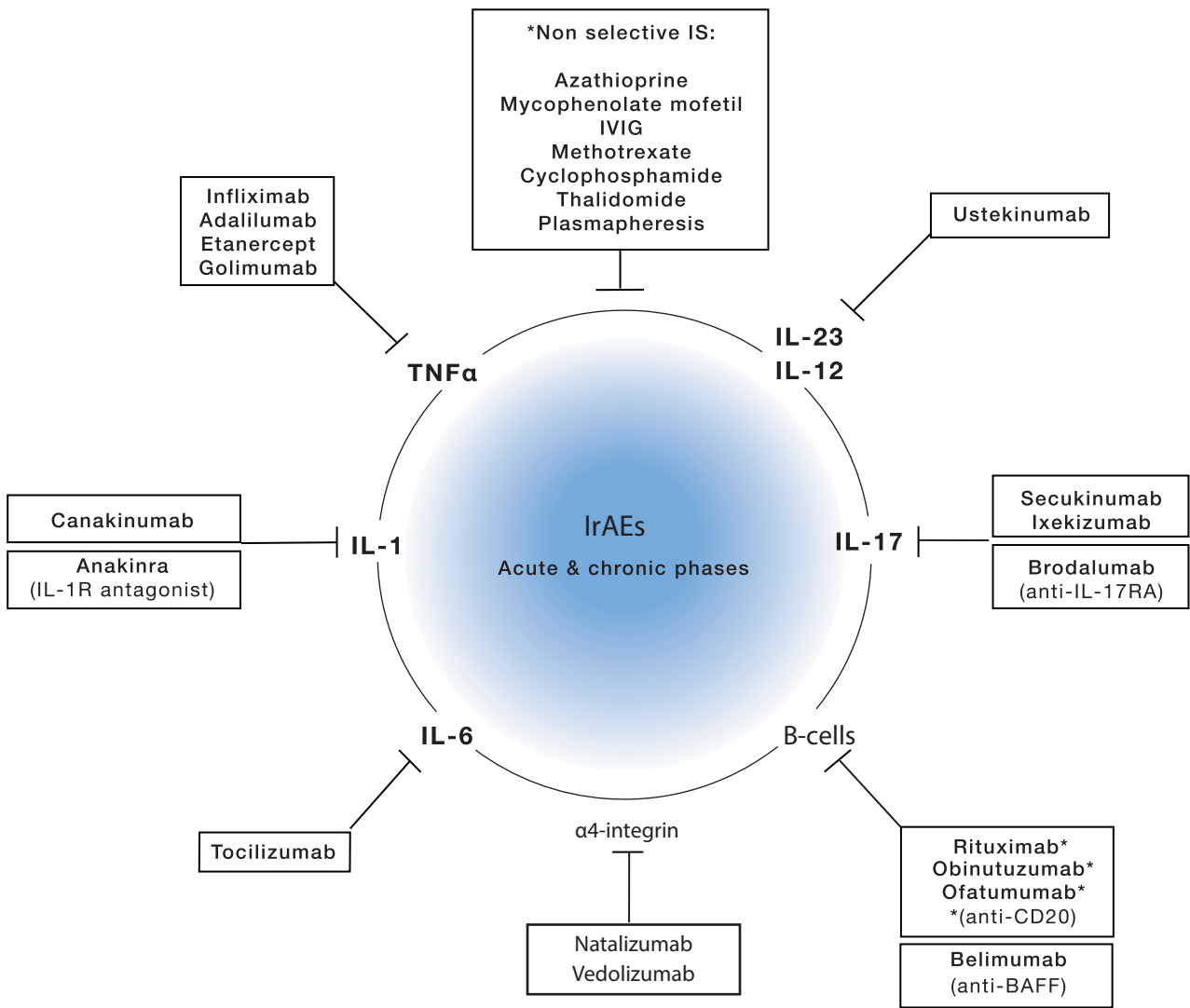


Figure 1

**Steroid-refractory irAE/
Severe/rapidly evolving irAE (in selected cases)**

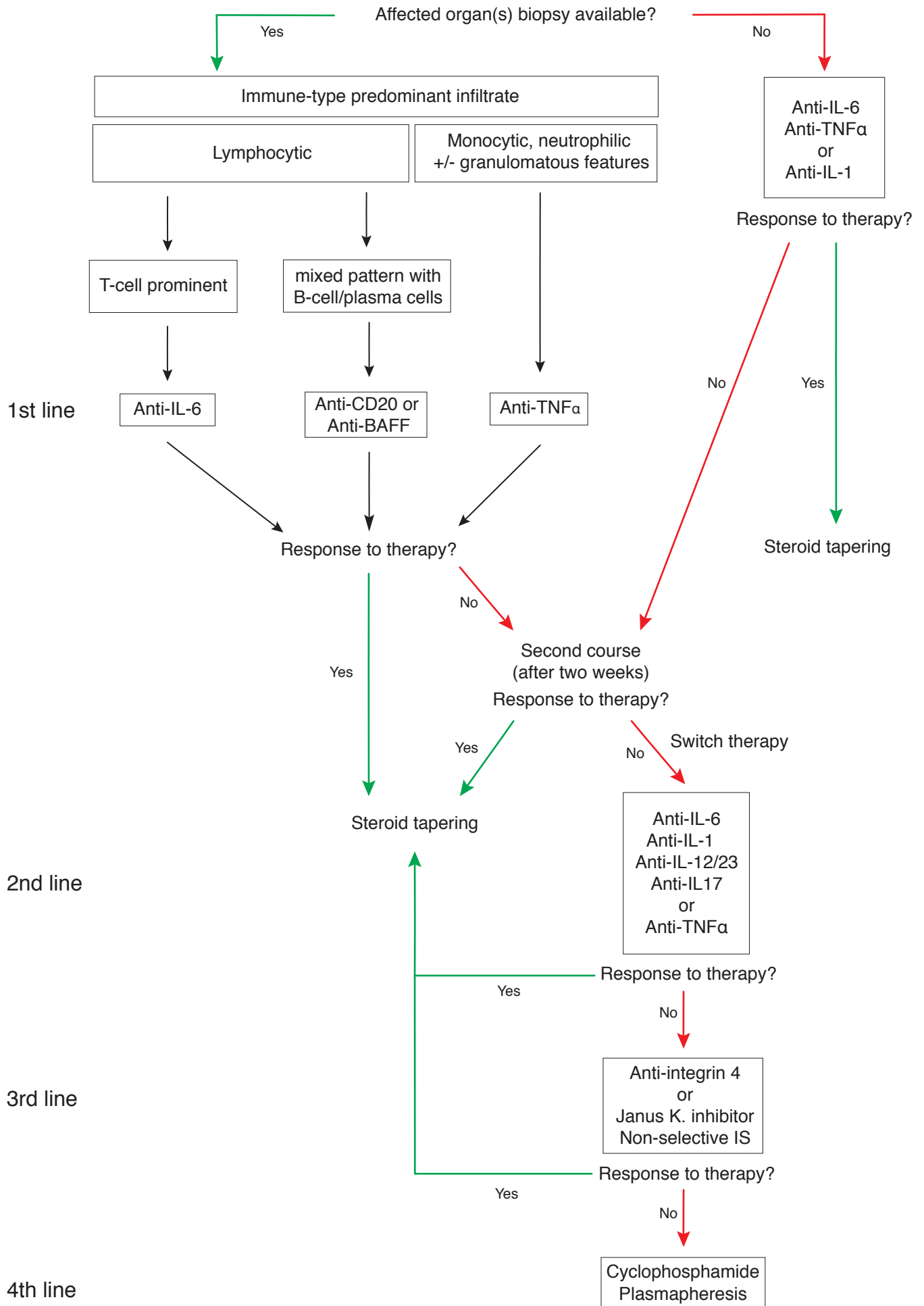


Figure 2