Immunotherapy Advances, 2022, **2**, 1–11
https://doi.org/10.1093/immadv/ltac012
Advance access publication 27 May 2022
Review

Plasma exchange for severe immune-related adverse events from checkpoint inhibitors: an early window of opportunity?

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Summary

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of several advanced malignancies leading to durable remission in a subset of patients. Their rapidly expanding use has led to an increased frequency of immune-related adverse events (irAEs). The pathogenesis of irAEs is poorly understood but may involve aberrant activation of T cells leading to inflammatory cytokine release or production of pathogenic antibodies leading to organ damage. Severe irAEs can be extremely debilitating and, in some cases, life threatening. IrAEs may not always be corticosteroid responsive or may require excessively high, often toxic, corticosteroid doses. Therapeutic plasma exchange (PLEX) is a treatment modality that has shown promising results for the management of certain severe irAEs, including irAEs that are not mentioned in current treatment guidelines. PLEX may attenuate ongoing irAEs and prevent delayed irAEs by accelerating clearance of the ICI, or by acutely removing pathogenic antibodies, cytokines, and chemokines. Here, we summarize examples from the literature in which PLEX was successfully used for the treatment of irAEs. We posit that timing may be a critical factor and that earlier utilization of PLEX for life-threatening irAEs may result in more favorable outcomes. In individuals at high risk for irAEs, the availability of PLEX as a potential therapeutic mitigation strategy may encourage life-saving ICI use or rechallenge. Future research will be critical to better define which indications are most amenable to PLEX, particularly to establish the optimal place in the sequence of irAE therapies and to assess the ramifications of ICI removal on cancer outcomes.

Keywords: therapeutic plasma exchange, plasmapheresis, immunotherapy, immune checkpoint inhibitors, immune-related adverse event

Abbreviations: ANCA, Antineutrophil cytoplasmic antibody; ASCO, American Society for Clinical Oncology; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, Cytotoxic T-lymphocyte-associated protein 4; DIRE, Delayed immune-related event; ESMO, European Society for Medical Oncology; FFP, Fresh frozen plasma; GBS, Guillain-Barre syndrome; ICI, Immune checkpoint inhibitor; IFNγ, Interferon gamma; irAE, Immune-related adverse event; IVIG, Intravenous immunoglobulin; MG, Myasthenia gravis; NCCN, National Comprehensive Cancer Network; MOG, Myelin oligodendrocyte glycoprotein; MPO, Myeloperoxidase; NMO, Neuromyelitis optica; PD-1, Programmed cell death protein 1; PD-L1, Programmed cell death ligand 1; PLEX, Plasma exchange; RRT, Renal replacement therapy; SITC, Society for Immunotherapy of Cancer; TNFα, Tumor necrosis factor-alpha; TRALI, Transfusion acute lung injury; TTP, Thrombotic thrombocytopenic purpura.

Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized oncology, producing durable responses in a subset of patients [1]. Immune checkpoint molecules, such as CTLA-4 and PD-1/PD-L1, mediate negative regulatory signaling pathways that play a critical role in dampening autoreactive T-cell signals and help to maintain self-tolerance. Blockade of CTLA-4, a molecule primarily involved in regulating T-cell priming, leads to expansion of T-cell clonal diversity and enhanced anti-tumor responses. The PD-1/PD-L1 checkpoint mediates peripheral tolerance, and upregulation of the PD-L1 checkpoint pathway may enable tumors to evade immune attack by T cells. Thus, ICIs targeting CTLA-4, PD-1, and PD-L1 can effectively unleash the host immune system to generate a productive anti-tumor response by stimulating T-cell-mediated killing of tumor cells [2].

ICIs were initially approved for metastatic cancers, notably melanoma, non-small cell lung cancer, and genitourinary cancers. Indications for ICIs have rapidly expanded to multiple additional cancer types. Their use has moved to earlier lines of therapy, as well as in earlier cancer stages including the adjuvant and neoadjuvant settings. As of 2018, 43.63% of cancer patients were considered eligible for ICI therapy [3]. ICIs are being used as monotherapy (i.e. PD-1

Received: March 22, 2022; Accepted: May 24, 2022

inhibitors nivolumab, pembrolizumab, cemiplimab, and PD-L1 inhibitors atezolizumab, avelumab, durvalumab), in combination with other ICIs (i.e. CTLA-4 inhibitor ipilimumab), in combination with chemotherapy (i.e. pemetrexed), with targeted agents such as kinase inhibitors (i.e. cabozantinib, axitinib), or in combination with radiation therapy [4,5]. Beyond the currently targeted immune checkpoint molecules CTLA-4, PD-1, and PD-L1, strategies are being developed to target additional checkpoint molecules such as LAG-3, TIM-3, TIGIT, CD73, B7-H3, and VISTA [6].

Targeting negative regulators that disrupt immune tolerance mechanisms can lead to the anticipated consequence of generating autoimmune and autoinflammatory toxicities that are referred to as immune-related adverse events (irAEs), which can affect virtually any organ system. The increased use of ICIs in growing numbers of indications and in combinations with other therapies has led to an increasing frequency of irAEs. Severe irAEs may lead to ICI discontinuation and sometimes death or long-term disability [7]. Hence, there exists an important need for biomarkers predicting severe irAEs to guide therapeutic decisions regarding risk/benefit considerations around ICI use, as well as to assess the safety of ICI rechallenge following irAE development. There is an urgent need to identify more effective treatments for severe irAEs; earlier and more effective interventions may be key in reversing damage, which in some cases can develop rapidly.

As the field of immuno-oncology gains more experience with irAEs, there are growing numbers of case reports citing the successful use of plasma exchange (PLEX) in the management of severe irAEs. Although the mechanisms by which PLEX may exert its effects are not completely understood, PLEX can remove ICIs because of their large molecular weight. In addition, the removal of pathogenic antibodies and cytokines may modulate the immune milieu favorably. As many ICIs have prolonged half-lives and sustained pharmacodynamic effects, increasing clearance of ICIs may reduce both the severity and the duration of irAEs. Here, we review the current guidance on indications for PLEX in irAE management. In addition, we discuss the scientific rationale for why PLEX may be a useful adjunctive treatment for certain severe irAEs and review clinical considerations, particularly patient selection, regarding its application. Finally, we pose questions to the community on the specific indications and thresholds for PLEX, the timing of PLEX in the severe and life-threatening irAE treatment algorithm, and optimal clinical trial designs.

Immune-related adverse events

IrAEs can affect any organ system, and classic irAE manifestations include rash, colitis, endocrine dysfunction, pneumonitis, hepatitis, arthritis, as well as the more rare neurologic, hematologic, cardiac, and even ophthalmologic adverse events [8]. Adverse events in clinical trials are graded using the Common Terminology Criteria for Adverse Events (CTCAE) scale from the US National Cancer Institute. Although the majority of irAEs are mild to moderate (CTCAE grade 1 or 2), a substantial proportion are severe to life threatening (CTCAE Grade 3 or 4), with death (CTCAE Grade 5) in up to 2% [9]. In the systematic review by Arnaud-Coffin *et al.*, the rate of irAE development with anti-PD-(L)1 inhibitors was 74% (with 14% Grade 3 or greater), 89% with anti-CTLA-4 inhibitors (with 34% Grade 3 or greater), and 90% in those treated with combination therapy (with 55% Grade 3 or greater) [9]. Toxicities and deaths vary by regimen: 70% of CTLA-4 inhibitor-related deaths were attributed to colitis, whereas PD-1 and PD-L1 inhibitor-related deaths were more often from pneumonitis (35%), hepatitis (22%), and neurotoxicity (15%) [10].

Based on two large meta-analyses of clinical trials, the rates of organ-specific irAEs of any grade were the following: colitis (11.9–14.5%), hypothyroidism (8.3–13.8%), hepatitis (1.2–10.4%), hypophysitis (0.5–10%), hyperthyroidism (0.4–9.3%), and pneumonitis (3.0–4.6%) [11, 12]. Rates of organ-specific irAEs vary widely, based on the population being studied: for example, in the clinical trial setting (in which patients with pre-existing autoimmunity are often excluded) vs. real world; malignancy type (i.e. pneumonitis is more common in lung cancer patients, and vitiligo in melanoma patients); and checkpoint inhibitor type (i.e. higher rates of colitis and hypophysitis with anti-CTLA-4 treatment).

As prescription of ICIs has increased, two high-risk populations have emerged: (i) cancer in patients with pre-existing autoimmune disease and (ii) patients needing retreatment of relapsed cancer with ICIs despite prior irAEs. Although excluded from early pivotal trials, patients with pre-existing autoimmune or inflammatory conditions are more frequently receiving ICIs in the real-world setting. Their risk for flare of their underlying disease may be up to 50% [13], and they may be at higher risk for other irAEs given their autoimmune predisposition [14]. As enthusiasm for ICI use in this population is dampened, there is a need for prospective studies that aim to better characterize this risk [15]. In oncology patients with limited therapeutic options, rechallenge with ICIs in spite of a prior irAE may be considered. Retrospective studies show irAE recurrence rates ranging from 18% to 30%, suggesting that ICI rechallenge may be a reasonable option in some circumstances [16]. Assuming PLEX were an effective means of managing severe irAEs, the availability of a mitigation strategy might provide reassurance and could lower the activation barrier for the use of ICIs in these higher-risk populations.

Guidelines for the diagnosis and management of irAEs have been published by several oncology organizations (NCCN, ASCO, SITC, ESMO); however, these recommendations are largely based on expert opinion without supportive high-quality evidence [17–20]. In general, for irAEs that are Grade 2 or higher, recommendations are to hold the ICI and consider corticosteroids at doses typically ranging from 0.5 to 1 mg/kg/d of prednisone or equivalent. For Grade 3 or 4 irAEs, pulse dosing of corticosteroids ranging from 500 to 1000 mg of methylprednisolone (or equivalent) may be recommended. The well-known negative side effects of corticosteroids highlight the need for more mechanistically informed corticosteroid-sparing treatment options. The impact of high intensity and/or prolonged treatment with corticosteroids on anti-tumor immunity is not fully understood. The use of corticosteroids at doses of greater than 10 mg before ICI initiation has shown a negative impact on anti-tumor immunity [21]. Furthermore, a more recent study suggests that early use of corticosteroids within the first 2 months of starting ICI may hinder ICI efficacy [22]. In a retrospective study of melanoma patients with ICI-induced hypophysitis, overall survival was significantly lower in the group receiving high-dose vs. low-dose corticosteroids [23]. Thus, therapies designed to

reduce corticosteroid dose intensity and duration might improve tumor outcomes and significantly reduce irAE treatment toxicity.

Diverse pathogenic mechanisms of irAEs

Given the clinical heterogeneity of irAE phenotypes, the pathogenesis of irAEs, not surprisingly, appears to be multifaceted. A recent review by Esfahani *et al*. emphasizes the need to define these driving pathogenic mechanisms precisely to optimize and personalize irAE treatments. In addition, to avoid the potential risk of nonspecific therapies such as corticosteroids, the authors particularly highlight the need for targeted therapies that are less likely to impair the anti-tumor response [24].

Treatment algorithms beyond corticosteroids for specific irAEs have typically been based on their cognate conditions, such as the use of infliximab or vedolizumab for ICI colitis, the use of mycophenolate mofetil for ICI hepatitis, and the use of rituximab and/or intravenous immunoglobulin (IVIG) for hematologic complications such as ICI autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura. However, it is also recognized that irAEs may not fully phenocopy their cognate conditions. Many irAEs are 'seronegative', without the presence of the classically associated autoantibodies: for example, rheumatoid factor and cyclic citrullinated peptide antibodies that are frequently seen in rheumatoid arthritis are typically absent in ICI-associated arthritis [25]. Pathogenic antibodies may be different from the classically defined autoantibodies [26] or have yet to be identified. Furthermore, the kinetics of irAE onset may be more rapid and disease severity may be greater. For a limited subset of severe or refractory irAEs, recent oncology guidelines recommend the use of therapeutic plasma exchange (PLEX) and/or IVIG for certain neurological conditions; however, there may be mechanistic rationale to explore the use of PLEX in a wider range of severe non-neurological irAEs.

Understanding irAE pathogenesis remains an active area of investigation. Proposed mechanisms include the following: (i) T-cell cross-reactivity between shared tumor antigens and normal human tissue, (ii) development of autoantibodies due to generation and/or expansion of autoreactive T and B cells with ICI therapy, (iii) release of inflammatory cytokines that results in immune-mediated damage in tissues with an anatomic predisposition, (iv) complement-mediated inflammation that may result from direct binding of ICI antibody to its ligand expressed on normal tissue, and (v) influence of the microbiome that may impact irAE development [24, 27]. More recent studies have identified that levels of circulating activated CD4 memory T cells and T-cell receptor diversity are two pretreatment T-cell characteristics associated with severe irAEs [28]. Elegant mechanistic work in ICI colitis has recently highlighted that not only are CD8+ tissue-resident memory T cells (T_{RM}) the predominant activated cell type; their activation status correlates with disease severity [29, 30]. In addition, several cytokines, in particular interferon-gamma (IFNγ) and tumor necrosis factor-alpha (TNFα), chemokines, and other cell surface receptors have emerged as potential therapeutic targets in refractory colitis cases. PLEX may not be expected to have efficacy in predominantly T-cell-driven processes, especially if the damage is mediated by local cytokine release. Hence, a more detailed mechanistic understanding of the different irAEs is critical to best define appropriate indications for the use of PLEX.

Background on therapeutic plasma exchange

Therapeutic plasma exchange (PLEX, also referred to as therapeutic plasma exchange or plasmapheresis) is a procedure by which blood is removed from a patient and is then separated by either centrifugation or filtration into its components. Centrifugation is much more efficient and rapid than filtration. As antibodies are more effectively removed with centrifugation, centrifugation is the more commonly used technique for PLEX. Plasma is removed, while the remaining blood components and replacement fluids (albumin, fresh frozen plasma [FFP], or a combination) are returned to the patient. PLEX can be used as a standalone or adjunctive therapy, with the most recent American Society for Apheresis guidelines citing 157 indications and 84 diseases for which apheresis modalities should be considered, with varying levels of strength and quality of evidence [31]. PLEX extracts substances dependent on size, the volume of distribution, the amount that is bound to albumin, intravascular and extravascular distribution, speed of equilibration, and rate of synthesis [32]. PLEX can remove pathologic substances from plasma, such as autoantibodies, immune complexes, cryoglobulins, toxins, or lipids, as well as therapeutic monoclonal antibodies [33]. This potentially beneficial impact of PLEX can confound laboratory-based monitoring of biomarkers, such as serum creatinine kinase in myositis, by both removing biomarker and diluting any remaining biomarker during and immediately after PLEX. Alternate indicators of irAE activity may be required during and immediately after PLEX.

Randomized controlled trials have demonstrated the efficacy of PLEX for indications such as thrombotic thrombocytopenic purpura (TTP), acute inflammatory demyelinating polyneuropathy (AIDP), and central nervous system demyelination, and acute myasthenia gravis crises [32, 34].

PLEX and irAEs

For certain severe and potentially life-threatening irAEs, PLEX could be considered early, as a complement to other immunosuppression, as there is likely a small window of opportunity in which to quickly reverse the disease process and prevent its progression. In all four oncology society guidelines for irAE management (NCCN, ASCO, SITC, and ESMO), PLEX is recommended for ICI-related myasthenia gravis and Guillain Barre Syndrome (Table 1). A recent study described better outcomes for all patients who received front-line IVIG or PLEX in addition to corticosteroids for ICI-related myasthenia gravis, underscoring the importance of early intervention [35]. However, there is not a consensus across the four guidelines on the use of PLEX for other neurologic indications including myositis, encephalitis, and transverse myelitis. Beyond neurologic conditions, there are other indications for which PLEX has been used but which are not articulated in current guidelines.

Rationale for PLEX

Removal of pathogenic antibodies

PLEX, in conjunction with immunosuppression, can provide rapid relief of symptoms in cases where pathogenic auto- and allo- antibodies mediate disease pathology. The natural half-life of IgG is approximately 21 days. Theoretically, if one were to assume that the use of an immunosuppressive agent was capable of stopping pathogenic antibody production completely

Table 1. Summary of current oncology treatment guidelines regarding use of PLEX

	NCCN [20]	ASCO [17]	SITC [18]	ESMO [19]
Myasthenia Gravis	**Grade 3-4:** "Initiate plasmapheresis or IVIG if no improvement/ worsening on steroids or severe symptoms"	**Grade 3-4:**"Initiate IVIG 2 g/kg IV over 5 d or plasmapheresis x 5 d"	**Grade 3-4:**"IVIG 2 g/kg over 5 d or plasmapheresis over 5 days may be considered"	"In the case of GBS or myasthenia-like symptoms, consider adding plasmapheresis or IVIG"
Guillain-Barre Syndrome	**Grade 2 or 3-4: "**Start IVIG or plasmapheresis in addition to pulse methylprednisolone 1 g daily x 5 d"	**Grade 2 or 3-4: "**Start IVIG or plasmapheresis."	"Patients with any grade of encephalitis or GBS should receive pulse-dose methylprednisolone at 1000 mg IV daily for 3-5 d and should additionally receive IVIG or PLEX"	"In the case of GBS or myasthenia-like symptoms, consider adding plasmapheresis or IVIG"
Demyelinating diseases including transverse myelitis	"Methylprednisolone pulse dosing 1 g/d for 3-5 days, Strongly consider IVIG or plasmapheresis"	**Grade 3-4:**"Methylprednisolone pulse dosing 1 g/d and consider IVIG or plasmapheresis if no improvement or symptoms worsen after 3 days"		
Myositis		**Grade 3-4:**"Consider plasmapheresis in patients with acute or severe disease as guided by rheumatology or neurology"	**Grade 3:**"For muscle weakness severely limiting mobility, cardiac or respiratory involvement, or dysphagia, 1-2 mg/kg methylprednisolone IV or higher dose bolus may be considered as well as plasmapheresis or IVIG"	
Encephalitis		**Grade 3-4:**"If severe or progressing symptoms or oligoclonal bands present, consider pulse dose CS plus IVIG 2 g/kg x 5 d or plasmapheresis"	"If ICI-related encephalitis does not respond to pulse-dose corticosteroids, patients may receive IVIG (2 g/kg in divided doses over the course of 5 d), PLEX (one session every other day for 5-7 cycles), or rituximab"	

ASCO: American Society of Clinical Oncology; CS: corticosteroid; ESMO: European Society for Medical Oncology; GBS: Guillain-Barre Syndrome; IVIG; intravenous immunoglobulin; NCCN: National Comprehensive Cancer Network; PLEX: plasma exchange; SITC: Society for Immunotherapy of Cancer.

and immediately (which is not the case), serum levels of this pathogenic antibody would still be at 50% of their initial values for at least 21 days after initiating immunosuppressive therapy. In cases where an aggressive autoantibody mediates disease pathology, this delay in antibody clearance could lead to severe and potentially even fatal consequences [33].

PLEX has been shown to rapidly reduce pathogenic antibodies and simultaneously improve clinical strength in myasthenia gravis, one of the best understood antibody-mediated diseases with a close relationship between antibody levels and symptom burden [36]. Similar efficacy of PLEX has been demonstrated in other well-known IgG-mediated antibody diseases such as neuromyelitis optica spectrum disorders [37]. PLEX is considered as the first-line therapy for anti-glomerular basement membrane disease (anti-GBM, also known as Goodpasture disease), a rare small vessel vasculitis that can affect glomerular and pulmonary capillaries leading to rapid organ dysfunction (crescentic glomerulonephritis and diffuse alveolar hemorrhage) [38]. In essence, if disease burden is directly related to antibody titer, PLEX should be able to improve clinical state by rapidly reducing pathogenic antibody levels.

Autoantibodies have been associated with the development of some irAEs, although their direct pathogenicity has yet to be formally proven. One study found that patients with anti-thyroid antibodies after ipilimumab treatment developed significantly more thyroid dysfunction compared with those without antibodies, and interestingly, these antibody-positive patients showed a trend toward improved survival [39]. Das *et al.* showed that ICI-treated patients who developed changes in B cells (including the increased proliferation of CD21 low B cells and plasmablasts, and clonal proliferation of circulating B cells) experienced higher rates of severe irAEs following combined checkpoint blockade, supporting a potential pathogenic role for B cells and autoantibodies [40]. Antibody discovery efforts using cDNA expression libraries revealed the association of novel antibodies that correlated with the development of ICI-related hypophysitis (anti-GNAL and anti-ITM2B autoantibodies) and pneumonitis (anti-CD74 autoantibody) [26]. This raises the possibility that many irAEs considered to be 'seronegative' by standard testing may in fact be driven by novel antibodies that have yet to be identified.

Removal of therapeutic monoclonal antibodies

PLEX has been used to remove therapeutic monoclonal antibodies, typically IgG1 and IgG4 constructs, to mitigate toxicities that can occur as a result of their prolonged half-lives and pharmacodynamic effects. PLEX is a standard procedure

Table 2. Pharmacologic characteristics of immune checkpoint inhibitors.

ICI	T 1/2	Vd	IgG subclass	MoA
Nivolumab	25 days	6.8 l	IgG4	anti-PD-1
Pembrolizumab	22 days	6 l	IgG4	anti-PD-1
Cemiplimab	20 days	5.3 l	IgG4	anti-PD-1
Dostarlimab	23.5 days	5.3 l	IgG4	anti-PD-1
Camrelizumab	14 days	5.4 l	IgG4	anti-PD-1
Atezolizumab	27 days	6.9 l	IgG1	anti-PD-L1
Avelumab	6.1 days	4 l	IgG1	anti-PD-L1
Durvalumab	17 days	6.9 l	IgG1	anti-PD-L1
Ipilimumab	15 days	7.2 l	IgG1	anti-CTLA-4

ICI: immune checkpoint inhibitor; T1/2: Half-life; Vd: Volume of distribution; MoA: Mechanism of action; L: Liter; IgG: Immunoglobulin G; anti-PD(L)1: anti-Programmed Cell Death (Ligand)1; anti-CTLA-4: anti-cytotoxic T-lymphocyte-associated protein 4. From reference [43].

for drug removal in the mitigation of monoclonal antibody-induced progressive multifocal leukoencephalopathy (PML). As an example, natalizumab, an anti-alpha 4 beta 1 integrin IgG4 monoclonal antibody, inhibits leukocyte trafficking in multiple sclerosis and can, rarely, lead to PML. One study demonstrated that 12 patients with multiple sclerosis who underwent three 1.5-volume PLEX sessions over 5 or 8 days had a reduction in natalizumab levels by a mean of 92% from baseline [41]. The rate of clearance of ICIs by PLEX has not been studied extensively, but one case report demonstrated that two sessions with two plasma volume procedures led to a 90% reduction in pembrolizumab levels, which decreased from 10 200 ng/ml to 1200 ng/ml and was associated with a favorable clinical outcome for myocarditis [42].

ICIs are fully humanized IgG1 molecules (ipilimumab targeting CTLA-4, and atezolizumab, avelumab, and durvalumab targeting PD-L1) and IgG4 molecules (nivolumab, pembrolizumab, and cemiplimab targeting PD-1) (Table 2) [43]. Their half-lives range from 6 to 27 days, with receptor-mediated clearance with a combined linear and non-linear phase [44, 45]. They have limited diffusion out of the vascular space, with the volume of distributions (Vd) ranging from 4.5 to 7.2 liters. Five PLEX procedures with 1-volume plasma exchange will reduce IgGs by approximately 70–90% for actively produced substances; considering that ICIs are not actively produced, the rate of decline with PLEX is considered to be higher. Thus, it is likely that less than 5 PLEX procedures would reduce the ICI level considerably [33]. The kinetics of ICI removal by PLEX needs to be studied further to better define the PLEX schedule needed to remove ICI during a severe irAE.

Although the majority of irAEs occur within the first 4 months of starting ICI therapy [46], notably many may occur later throughout the course of ICI treatment or even months after ICI therapy has been discontinued, referred to as delayed immune-related events (DIREs) [47–49]. The potential for ICIs to cause persistent irAEs or DIREs may be due to their long half lives and lasting pharmacodynamic effects [47]. After a single dose of nivolumab, which has a serum half-life of 12–20 days, PD-1 receptor occupancy on T cells plateaus at approximately 80% as late as 90 days later. Following three doses of nivolumab, receptor occupancy remains at 40% for greater than 8 months after the last dose [50]. Since ICI binding to its respective targets is reversible, a reduction in serum levels of ICI might lead to reduced binding and prevent further ICI-related toxicity. An important consideration is that irAEs may, in some cases, be mediated by epigenetic reprogramming, leading to sustained immune activation independent of ongoing ICI receptor occupancy [2]. However, several Grade 1 irAEs are monophasic and resolve after discontinuation of the ICI, suggesting reversibility of the underlying immune activation that may in part be related to ICI washout.

Removal of cytokines and chemokines

The efficacy of PLEX for removing cytokines and chemokines have shown variable impacts in different contexts [32]. However, there have been a plethora of recent studies in severe COVID-19 patients who develop hyperinflammation and cytokine storm, with a systematic review of 18 papers describing 220 patients who received PLEX, including one randomized controlled trial. In general, biochemical improvement was observed in the majority of studies, showing decreases in C-reactive protein, IL-6, ferritin, lactate dehydrogenase, and D-dimer concentrations, with the enhancement of respiratory function [51]. As cytokines play a prominent role in mediating several irAEs, the use of PLEX may be beneficial, especially in cases of severe irAEs. In addition to the above, removal of chemokines by PLEX seen in animal studies has demonstrated decreased leukocyte infiltration into end organs, suggesting yet another potential therapeutic mechanism [52].

Potential risks and costs of PLEX

Potential complications of PLEX are related to the need for central venous access, anticoagulation, and the use of replacement with 5% albumin and/or plasma. Although in our center we routinely rely on large-bore peripheral IVs, other centers do require central venous catheters. Central venous catheters may introduce risks for infection and septicemia, thrombosis, and pneumothorax. Citrate is typically used as an anticoagulant which may lead to hypocalcemia that can cause paresthesias, muscle cramps, or in severe cases, cardiac arrhythmias. Repeated PLEX sessions with albumin replacement fluid may lead to depletion of coagulation factors and immunoglobulins. The risk for bleeding and infections may increase and necessitate the substitution of FFP for 5% albumin. FFP carries the risks of adverse reactions to donor plasma such as anaphylaxis, transfusion-related acute lung injury (TRALI) and the very rare risk of exposure to infectious pathogens [53]. One commonly used strategy for minimizing FFP exposure is to conduct PLEX every other day, rather than daily. Overall, adverse events related to PLEX were reported to occur in about 2–3% of cases. The majority of adverse events were mild (improved with no intervention) or moderate (resolved after medication) and only 0.1% were considered severe (leading to interruption of the procedure). There was only one reported death in over 100 000 procedures, which occurred in a patient with multiple comorbidities [54].

From a practical standpoint, the efficiency of PLEX is greatest when the drug to be removed is either a large protein or is highly protein bound, and the drug has a small volume of distribution. This includes intravenous immune globulin, therapeutic monoclonal antibodies, such as rituximab, as well as protein-bound drugs such as cyclophosphamide

and azathioprine. Corticosteroids such as prednisone and methylprednisolone are not substantially impacted by PLEX [55]. PLEX is associated with considerable logistical considerations and resource utilization, as PLEX requires coordination of a multidisciplinary team including subspecialty clinicians, transfusion medicine, nursing support, and a service for central line placement. Access can be a significant barrier, as not every institution may be readily able to deploy these services urgently, either on an inpatient or outpatient basis. Although cost is another limiting factor for PLEX, one study reported five sessions of PLEX to be more cost-effective than five doses of IVIG (approximately 10,000 dollars vs. 5000 dollars [56]). The costs of PLEX need to be factored into the risk–benefit equation; however, this must also be balanced with the potential for clinical benefit, including metrics such as shorter hospital stays, and improved quality of life (e.g. decreased need for skilled nursing support).

Potential indications for PLEX

Here, we highlight severe and life-threatening irAEs where utilization of PLEX as an adjunct to immunosuppression may be helpful, citing examples of compelling case reports (Table 3). We recognize the lack of rigorous evidence in this domain. We emphasize the importance of clinical acumen in driving the decision if and when to initiate PLEX. The optimal timing and use of PLEX remains to be more rigorously tested, but a reasonable recommendation might be to consider its use in rapidly progressive severe or life-threatening irAEs after the failure of an initial course of high-dose corticosteroids (including pulse doses). There are several case reports in which PLEX was used unsuccessfully: possible explanations include clinical deterioration driven by other mechanisms, and/or the possibility that implementation of PLEX occurred too late, after inflammatory processes had become irreversible.

Neurologic

Neurologic irAEs are rare with an overall incidence of <1% [72] but can have high morbidity and mortality such that expedited diagnosis and treatment is paramount. Autoantibodies play a prominent role in the pathogenesis of ICI-related myasthenia gravis (MG) and Guillain Barre syndrome (GBS). PLEX is routinely used in severe forms of MG and GBS and so PLEX has been fairly well adapted in ICI-related MG or GBS. There are many other neurological syndromes that may be mediated by autoantibodies, including paraneoplastic disorders such as limbic encephalitis or subacute cerebellar ataxia. Commercially available antibody testing only detects a known antibody in approximately half of the patients, raising the possibility of unidentified antibodies driving pathogenesis [73]. There are several cases of severe irAE encephalitis that have been successfully managed with PLEX, and in some cases, IVIG [58, 59]. Transverse myelitis is another complication that can be especially debilitating and there are well-known antibody-mediated causes of transverse myelitis (NMO, MOG), although some cases of transverse myelitis do not have any described antibody. A recent study highlighted classical antibody-mediated neurological syndromes that were seronegative after ICI use. All patients had excellent neurological outcomes when treated with steroids, PLEX and IVIG along with ICI discontinuation [74]. Wilson *et al.* argue that rapid recovery and positive antibody staining on brain or nerve tissues by sera from these patients suggests a likely novel, yet unidentified antibody-mediated process.

Another common neurological irAE is myositis, and overall incidence of myositis from clinical trials of ICI is about 0.38% (odds ratio 1.96) for patients receiving ICIs compared with controls [75]. Sometimes myositis is associated with myasthenia gravis and occasionally myocarditis, the greatly feared 'triple M syndrome'. Patients with associated myocarditis are likely to have worse outcomes and require aggressive therapy including corticosteroids, IVIG and sometimes PLEX. In most published reports, when patients develop MG or myocarditis with myositis, PLEX seems to be considered an option and has been used. However, at least one large case series which reviewed all the patients with ICI-myositis (with or without MG or myocarditis) documents PLEX use in about 30% of cases with ICI myositis alone and near 100% PLEX use in patients with myositis and MG [76].

Cardiac

Although rare with incidences ranging from 0.04% to 1.14%, cardiotoxicity from ICIs has an extremely high mortality rate which ranges from 35% to 50% [77–79]. In ICI-mediated myocarditis, T-cell infiltration of the myocardium is observed in the absence of B cells or antibody deposits [80]. The findings of similar T-cell clones in both myocardium and tumor may suggest either T-cell reactivity to a heart-specific antigen or cross-reactivity between T cells recognizing an antigen shared by tumor and normal cardiac tissue [81]. Additionally, cross-talk between key T-cell and antigen-presenting cell subsets may play an important role in potentiating autoimmunity in the heart [82, 83]. Although randomized trial data does not yet exist for the usage of PLEX in ICI myocarditis, several compelling clinical cases exist in which PLEX was used successfully to mitigate severe myocardial inflammation in cases in which corticosteroids and even abatacept appeared to have had limited efficacy [42, 63, 64]. Although the mechanism of efficacy of PLEX in these cases is not known, potential mechanisms include the removal of cytokines/chemokines critical to cell–cell communication between key pathogenic cell subsets (e.g. between T-cell subsets, between T-cells and antigen-presenting cells, etc.) as well as direct removal of the immune checkpoint inhibitor and subsequent reduction of activation of myocardial-directed cytotoxic T-cells.

Renal vasculitis

Another uncommon but dangerous complication of checkpoint inhibitor therapy is ICI-associated renal vasculitis. Although the most common kidney condition related to ICI irAE is acute interstitial nephritis, the glomerular disease can occur. Among the reported glomerular diseases, vasculitis is the most common [84]. Unlike other medication-associated vasculitides which are typically anti-neutrophil cytoplasmic antibody (ANCA) positive, ICI-associated vasculitis is often ANCA negative [69]. We identified two reported cases of ANCA-positive and two cases of ANCA-negative renal vasculitis, all successfully treated with PLEX in combination with other treatment modalities.

Laamech *et al.* report the case of an 81-year-old with non-small cell lung cancer treated with nivolumab who developed pulmonary hemorrhage and crescentic glomerulonephritis 3 weeks after his last dose of nivolumab [70]. He was myeloperoxidase (MPO) antibody positive and initially treated with pulse methylprednisolone and rituximab without

Table 3. Case reports of successful use of PLEX in the treatment of irAEs

irAE	Reference	Patient Demo	Malignancy	Checkpoint Inhibitor	Days until PLEX	# of PLEX	Concurrent Treatments	AutoAb Identified?	Outcome of irAE
Encephalitis	Burke M [57]	64, F	Ovarian, Clear Cell	Nivolumab	~2	10	Steroids	GAD65	Resolution
	Ozdirik B [58]	70, F	HCC	Atezolizumab	5	3	Steroids	No	Partial Response
	Chung M [59]	36, F	Thymic NET	Ipilimumab, Nivolumab	~10	5	Steroids, IVIG	GAD65	Resolution
Myositis	Kamo H [60]	78, M	Renal & Pelvic, NOS	Pembrolizumab	–	–	Steroids	PM-Scl 75	Partial Response
Transverse Myelitis	Wang L [61]	70, F	SCLC	Durvalumab	–	–	Steroids, IVIG	CV2, SOX1, ZIC4	Resolution
NMO	Nasralla S [62]	30, F	Hodgkin Lymphoma	Nivolumab	–	3	Steroids	No	Relapse
Myocarditis	Schiopu SR [63]	75, M	Mesothelioma	Pembrolizumab	10-15	10	Steroids	Anti-Titin	Resolution
	Yogasundaram H [42]	69, M	Prostate	Pembrolizumab	~10	2	Steroids, MMF	No	Resolution
	Compton F [64]	67, F	Renal Cell	Nivolumab	10-15	5	Steroids, MMF, Abatacept	No	Partial Response
TTP	De Filippis S [65]	61, M	NSCLC	Pembrolizumab	8	5	Steroids	ADAM-TS13	Partial Response
	Youssef A [66]	42, F	Renal Cell	Ipilimumab, Nivolumab	5	8	Steroids, Rituximab	ADAM-TS13	Resolution
	Ali Z [67]	46, M	Renal Cell	Ipilimumab, Nivolumab	1	6	Steroids, Rituximab, Caplacizumab	ADAM-TS13	Relapse, resolution
CRS	Ohira J [68]	70, M	Renal Cell	Ipilimumab, Nivolumab	~7	6	Steroids, MMF, IVIG	Mi-2, TIF1-γ	Partial Response
Renal Vasculitis	Mamlouk O [69], Case 2	70s, M	Renal Cell	Tremelimumab	~4	6	Steroids, Rituximab	MPO	Partial Response
	Mamlouk O, Case 4	60s, M	Liposarcoma	Nivolumab	~4	2	Steroids, Rituximab	No	Partial Response
	Mamlouk O, Case 5	50s, F	Uveal Melanoma	Ipilimumab, Nivolumab	~4	7	Steroids, Rituximab	No	Partial Response
	Laamech R [70]	81, M	NSCLC	Nivolumab	~21	7	Steroids, Rituximab	MPO	Partial Response
GVHD	Amerikanou R [71]	18, M	Hodgkin Lymphoma	Nivolumab	4	5	Steroids	No	Resolution

HCC: hepatocellular carcinoma; MMF: mycophenolate mofetil; NET: neuroendocrine tumor; NSCLC: non-small cell lung cancer; QOD: every other day; SCLC: small cell lung cancer.
Resolution: significant improvement in clinical and/or laboratory parameters with return to baseline or near-baseline. Partial response: some improvement with persistent symptoms without documented return to baseline.

renal response and ultimately required renal replacement therapy (RRT). His nivolumab level at this time was 4.1 μg/ml, and PLEX was initiated. He received seven sessions with corresponding improvement in serum creatinine, return of renal function, and post-treatment nivolumab level <3 μg/ml. His estimated glomerular filtration rate recovered to 20 ml/min/1.73 m^2 (baseline 84), and he did not require further RRT.

Mamlouk *et al.* report one case of ANCA-positive and two cases of ANCA-negative renal vasculitis all initially unsuccessfully treated with steroids [69]. All three received IV methylprednisolone for 3 days (one had initially received an outpatient oral prednisone taper for rash), followed by a combination PLEX and rituximab. All patients briefly required RRT, but eventually experienced partial kidney recovery. None of the above four cases experienced relapse of the vasculitis, nor did any patient experience an adverse event related to PLEX.

These successful experiences are in contrast with the mixed enthusiasm for PLEX in *de novo* ANCA vasculitis among nephrologists [85]. Revisions for guidelines of PLEX indications in ANCA vasculitis are under consideration after a large randomized controlled trial failed to show benefit, although there was a signal for potential short-term benefit among those with severe renal disease [86]. Possible explanations for the difference in outcomes between ICI-related cases and the *de novo* ANCA vasculitis literature include publication bias for those with favorable outcomes, a unique benefit derived from ICI removal, earlier initiation of PLEX in ICI-related cases before the onset of irreversible damage, or potential differences in the pathogenicity of the antibodies mediating vasculitis.

Hematologic

Hematologic irAEs, while rare, include diseases for which there is the considerable published experience of application of PLEX as the first line or as salvage therapy in the non-ICI setting: TTP; cold agglutinin syndrome; post-transfusion purpura; cryoglobulinemia; catastrophic antiphospholipid syndrome; and cytokine release syndromes including macrophage activation syndrome and hemophagocytic lymphohistiocytosis. Other described hematologic irAEs, including warm autoimmune hemolytic anemia, immune thrombocytopenic purpura, pure red cell aplasia, and agranulocytosis are not typically treated with PLEX [87, 88].

PLEX is considered first-line therapy for TTP, as it can not only remove anti-ADAMTS13 autoantibodies but also infuse the ADAMTS13 protease by using FFP as the replacement fluid. To date, there have been seven cases of ICI-related TTP reported [65], which in general showed favorable responses if PLEX was initiated early. Although outcomes were not available for all cases, it is notable that two patients showed durable remission and one showed complete response following PLEX, suggesting that removal of the ICI was not detrimental to their cancer outcome.

While Ohira *et al.* report a case of fulminant cytokine release syndrome (CRS) in the setting of ICI-related dermatomyositis that was successfully treated with pulse dose corticosteroids, PLEX, and mycophenolate mofetil [68], there are several other cases of CRS described in the literature that did not utilize PLEX [89, 90]. Therefore, the specific clinical indication and impact of PLEX on CRS outcome remains unclear: in particular, whether PLEX can induce a faster resolution of CRS and/or result in decreased corticosteroid use.

GVHD

Amerikanou *et al.* report a striking case of severe multi-organ graft-versus-host disease after nivolumab therapy for relapsed Hodgkin's lymphoma that permits speculation that the early timing of PLEX may have driven the positive outcome. The patient experienced rapid deterioration, including reduced level of consciousness with decorticate posturing, status epilepticus, and worsening skin features (widespread erythematous lesions, peri-orbital swelling, oral desquamation). PLEX was initiated early on day 8, and after 3 days of PLEX, the patient had no residual neurologic deficits with significant improvement in his mucosal ulceration and rash. Measurement of plasma nivolumab level by enzyme-linked immunosorbent assay (ELISA) confirmed a steep decline in the drug level 6 days after PLEX [71]. The patient experienced remission at 12 months following PLEX, with the absence of chronic GVHD.

First-line and second-line indications for therapeutic PLEX are articulated in the 2019 guidelines from the American Society for Apheresis [31]. Although many of these indications may not commonly be seen in conjunction with ICIs, awareness of indications that have a higher likelihood of therapeutic success with early initiation of PLEX may be clinically useful.

Conclusions and future directions

There remain many research questions for the field that should be prioritized, including:

- In which severe or life-threatening irAEs should PLEX be utilized?
- What is the optimal timing for the use of PLEX?
- What are the mechanisms by which PLEX may be exerting its beneficial effect?
- Do the pharmacokinetics of ICI removal correlate with the patient outcome?
- Should PLEX protocols (including the number of sessions, schedule of sessions, and amount of plasma exchanged per session) be drug specific, e.g. vary by the IgG subtype and antibody–drug constructs?
- How should disease-specific responses be measured, and should we be putting more emphasis on "time to improvement" as an outcome? Does use of PLEX result in more rapid clinical improvement, leading to shorter hospital stays, decreased disability, and/or improved quality of life?
- What are acceptable disease-specific surrogates for a response when PLEX transiently removes a usual clinical biomarker of disease (e.g. CK levels)?
- What are the risk/benefit and cost/benefit considerations for the use of PLEX?
- Does early use of PLEX minimize the amount and duration of corticosteroid use?
- What is the impact of PLEX on tumor-related outcomes?
- Can patients be rechallenged with ICI after PLEX, and what is the likelihood of irAE recurrence?

We discuss the use of PLEX in addition to immunosuppression for the treatment of severe irAEs that may be steroid-refractory and/or rapidly progressive, leading to the risk of death or disability. We posit that early use of PLEX may lead to more favorable outcomes, including faster time to recovery with decreased long-term disability, and decreased

corticosteroid toxicities. PLEX has the ability to remove pathogenic antibodies (many of which have yet to be identified in irAEs), cytokines, chemokines, and importantly, the ICI itself. ICIs may exert a prolonged pharmacodynamic effect that can lead to perpetuation of irAEs. A number of case reports suggest that PLEX may not negatively affect the antitumor response, however larger studies are needed to more definitively address this question. In reviewing the available case reports of PLEX for irAEs, earlier utilization of PLEX may be associated with a more positive outcome, suggesting an early window of opportunity.

Acknowledging that current data are based on case series and are thus hypothesis-generating, we propose that sufficient evidence exists to warrant rigorous studies that engage PLEX earlier in the treatment algorithm of severe and rapidly progressive irAEs. We recognize the operational complexities associated with rapid deployment of PLEX, which requires seamless collaboration amongst several specialties (which at some centers may include transfusion medicine, hematology, nephrology, neurology, oncology, and/or immunology) along with extensive nursing support. The relative cost of PLEX and its attendant resource utilization are significant. However, if PLEX works as a mitigation strategy for severe irAEs, this may enable the safer and more effective use of ICIs, especially in high-risk populations, including those with pre-existing autoimmune disease and/or those with prior irAEs who are rechallenged. Ultimately, there is a need for prospective multi-center randomized controlled studies of PLEX for irAEs in order to robustly demonstrate its potential value.

Acknowledgements

The Editor-in-Chief, Tim Elliott, and handling editor, Stephanie Dougan, would like to thank the following reviewer, Ala Abudayyeh, and an anonymous reviewer, for their contribution to the publication of this article.

Author contributions

Conceptualization: T.R.K., S.M., M.Y., and B.A.M. Writing original draft, review and editing: all authors.

Funding

T.R.K. receives research support from Sanofi and the Koret Foundation. H.Z. receives research support from NIH 1K08HL161405-01. S.A. receives research support from NIH R01DK127138.

Conflict of interest

T.R.K. has served as a medical consultant/advisor for Genentech and Sonoma Biotherapeutics and receives research support from Sanofi. S.M. has served on advisory boards for Alexion, Ra Pharmaceuticals, Argenx, and Horizon Therapeutics. The other authors declare that they have no conflicts of interest to disclose.

Ethical approval

Not applicable.

Data availability

No new data were generated or analyzed in support of this manuscript.

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