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Corticosteroid-resistant immune-related adverse events: a systematic review

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ABSTRACT

Immune checkpoint inhibitor (ICI) treatment has become an important therapeutic option for various cancer types. Although the treatment is effective, ICI can overstimulate the patient's immune system, leading to potentially severe immune-related adverse events (irAEs), including hepatitis, colitis, pneumonitis and myocarditis. The initial mainstay of treatments includes the administration of corticosteroids. There is little evidence how to treat steroid-resistant (sr) irAEs. It is mainly based on small case series or single case reports. This systematic review summarizes available evidence about sr-irAEs. We conducted a systematic literature search in PubMed. Additionally, we included European Society for Medical Oncology, Society for Immunotherapy of Cancer, National Comprehensive Cancer Network and American Society of Clinical Oncology Guidelines for irAEs in our assessment. The study population of all selected publications had to include patients with cancer who developed hepatitis, colitis, pneumonitis or myocarditis during or after an immunotherapy treatment and for whom corticosteroid therapy was not sufficient. Our literature search was not restricted to any specific cancer diagnosis. Case reports were also included. There is limited data regarding life-threatening sr-irAEs of colon/liver/lung/heart and the majority of publications are single case reports. Most publications investigated sr colitis (n=26), followed by hepatitis (n=21), pneumonitis (n=17) and myocarditis (n=15). There is most data for mycophenolate mofetil (MMF) to treat sr hepatitis and for infliximab, followed by vedolizumab, to treat sr colitis. Regarding sr pneumonitis there is most data for MMF and intravenous immunoglobulins (IVIG) while data regarding infliximab are conflicting. In sr myocarditis, most evidence is available for the use of abatacept or anti-thymocyte globulin (ATG) (both with or without MMF) or ruxolitinib with abatacept. This review highlights the need for prompt recognition and treatment of sr hepatitis, colitis, pneumonitis and myocarditis. Guideline recommendations for sr situations are not defined precisely. Based on our search, we recommend—as first line treatment—(1) MMF for sr hepatitis, (2) infliximab for sr colitis, followed by vedolizumab, (3) MMF and IVIG for sr pneumonitis and (4) abatacept or ATG (both with or without MMF) or ruxolitinib with abatacept for sr myocarditis. These additional immunosuppressive agents should be initiated promptly if there is no sufficient response to corticosteroids within 3 days.

INTRODUCTION

Immune checkpoint inhibitor (ICI) treatment has become important for treating various cancer types. However, ICI can overstimulate the immune system leading to immunological side effects known as immune-related adverse events (irAEs).[1–3] The occurrence of irAEs varies according to the immune checkpoint target (Programmed Death (PD)-1, Programmed Death-Ligand (PD-L)1, and Cytotoxic T-Lymphocyte-Associated Protein (CTLA)-4), the dosage regimen (dose of the CTLA-4 inhibitor), and if combined checkpoint blockage is used.[1–4] Generally, the risk and severity of irAEs are higher with CTLA-4 inhibitors than with PD-1/PD-L1 inhibitors,[5] and even higher with combined immune checkpoint blockage.[6]

Side effects from ICI treatment can be graded from mild to fatal severity.[1–3 7] Most often, irAEs are mild-to-moderate.[1–3 7] An analysis of 36 phase II and phase III trials, including more than 15,000 patients treated with various ICIs, has reported an incidence of any-grade irAEs in the range of 66–75% for PD-(L)1 inhibitors and 87% for the CTLA-4 inhibitor ipilimumab.[8] In this study, the cumulative incidence of grade 3 or 4 adverse events was estimated to be 14–20% for PD-1/PD-L1 inhibitors and 29% for the CTLA-4 inhibitor ipilimumab.[8] Rates of grade 3 or 4 adverse events have been reported as high as 59% for combined ICI treatment with ipilimumab and nivolumab.[6]

The initial treatment of irAEs often includes the administration of corticosteroids, depending on organ involvement and severity.[1–3] If there is no response or only an inadequate response to an initial corticosteroid treatment (within 1–3 days in the case of life-threatening irAEs, such as myocarditis, or within 7–14 days in the case of non-life-threatening irAEs, such as arthritis), the situation is classified as corticosteroid-resistant.[1–3 9] If there is a flaring during steroid-taper, the irAEs is steroid-dependent. A relapse is defined if the irAEs occur again after tapering or on re-exposure of the ICI treatment.[10] However, the definitions are not consistently applied. For the purpose of simplicity and due to the lack of a precise differentiation between the terms 'resistant' and 'refractory', we will use "resistant" in our

review. These circumstances alone justify the great need for consulting experts in these situations.

The incidence of immune-related adverse events resistant to steroids (sr-irAEs) is unknown. It is presumed that the incidence depends on various factors, including the type and severity of adverse events as well as the treatment and disease setting. An exact assessment of the occurrence of sr-irAEs is further complicated by the current lack of a uniform definition.

Rapid and proper treatment escalation is crucial in cases of sr-irAEs, because the consequences of ineffective therapy are fatalities and chronic morbidity. However, the treatment recommendations for sr-irAEs are not defined precisely. They are often based on case reports and case series. This review aims to close this gap and to systematically search for evidence of treatment recommendations for sr-irAEs.

METHODS

We conducted a systematic literature search in PubMed (search algorithms: see online supplemental appendix table A). Case reports were included due to the limited number of available studies. We additionally screened the European Society for Medical Oncology (ESMO), Society for Immunotherapy of Cancer (SITC), American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) Guidelines and added studies, which were not covered by the systematic search. The population of each study had to consist of patients exposed to ICI-treatment who developed irAEs. These irAEs had to be treated initially with corticosteroids and a steroid-resistance had to be documented and/or additional immunosuppressive treatment had to be used. We have decided to limit our search to the corticosteroid-resistant setting of the four most clinically important and life-threatening organ sites affected by irAEs: liver, colon, lung and heart. Our literature search was not restricted to specific types of underlying cancer.

MANAGEMENT OF STEROID-RESISTANT SITUATIONS BY ORGAN SITE (LIVER/COLON/LUNG/HEART)

Hepatitis

Clinical presentation and epidemiology

Immune-related hepatitis is defined as at least a threefold increase of liver enzymes.[1–3 11] It typically manifests during routine blood monitoring with elevated levels of alanine aminotransferase and aspartate aminotransferase with or without elevated bilirubin.[12] Most patients are asymptomatic or present with only mild and non-specific symptoms such as fatigue or fever. The interval between start of ICI-treatment and the onset of liver toxicity varies considerably, depending also on the kind of applied checkpoint inhibitor(s).[12–14]

Immune-related liver injury occurs in approximately 2–6% of patients treated with PD-(L)1-inhibitors, in 2–4% of patients treated with CTLA-4 inhibitors and in 29% of patients (17% grade of toxicity G3–4) with combined CTLA-4/PD-1-inhibitor treatment.[6 13 15–18] The incidence of CTLA-4 inhibitor-related hepatitis is dose-dependent.[19] In a large retrospective real-world cohort of patients treated with ICIs, hepatitis occurred in approximately 5% of patients.[20] The median time to onset of hepatitis ranges between 3 and 9 weeks, with earlier onsets described in patients treated with combined CTLA-4/PD-1 inhibition.[14]

The incidence of steroid-resistant immune-related hepatitis is unknown, however retrospective reports about patients with immune-related (ir)-hepatitis requiring additional immunosuppression are in the range of 23–48%.[20 21] It is defined as either persistently elevated liver enzymes after 3–10 days of steroid treatment or recurrent increase of liver enzymes under steroid treatment.[1–3 11] Most cases of resistant immune-related hepatitis involve the setting of failure to primary corticosteroid treatment. Fewer cases refer to recurrence of elevated liver enzymes after initial resolve under steroid treatment. Reported cases/case series do not indicate a specific initial clinical presentation in these patients.

Management

Consensus guidelines

International Guidelines (ESMO, ASCO, SITC, NCCN) as well as organ specific guidelines (American Gastroenterological Association (AGA)) agree on strict monitoring of liver enzymes and additional diagnostics (exclusion of toxic, viral or autoimmune hepatitis by patient history and serological testing, exclusion of hepatic disease progression by imaging) as basic diagnostic workup of ICI-related hepatitis.[1–3 11] Due to the paucity of evidence regarding steroid-resistant hepatitis, guideline recommendations for additional diagnostic and therapeutic measures are vague. Most guidelines agree in recommending a consultation with an hepatologist and to consider liver biopsy as additional diagnostic steps in case of steroid-resistance. Regarding additional immunosuppressive treatment options, all guidelines recommend mycophenolate mofetil (MMF) for which most retrospective evidence is available. Also, all guidelines advise against infliximab due to its hepatotoxic potential and risk for infectious complications due to immunosuppression (table 1).

Literature review

We have performed a structured literature search and have gathered data about treatment of steroid-resistant immune-related hepatitis (see online supplemental appendix table 5). A total of 22 publications have been identified, most of which are single case reports (n=13) or small case series of three or less patients with steroid-resistant hepatitis.[12 16 20 22–39] The largest available systematic case series by Cheung *et al* counts nine patients with steroid-resistant ICI-related hepatitis and has reported a faster normalization of liver parameters with additional immunosuppressive agents.[20] Another important observation in this series was that a higher dose of prednisone

Table 1 Diagnostic and therapeutic recommendations for steroid-resistant hepatitis

	Guidelines			
	ESMO (2022)[1]	ASCO (2021)[3]	SITC (2021)[2]	NCCN (2023)[40]
Diagnostic procedures				
Repetition of initial workup	✓			✓
Rule out cytomegalovirus infection			✓	✓
Consultation with a hepatologist	✓	✓	✓	✓
Liver biopsy	✓	✓	✓	✓
Referral to tertiary center		✓		
Treatment options (1) First choice of additional immunosuppressive treatment. (2) Other options of immunosuppressive treatment. (*) No treatment sequence mentioned.				
Increase of steroid dose to 1–2 mg/kg/day in grade II	✓(*)			
Change to intravenous administration of steroid treatment	✓(*)			
Mycophenolate mofetil (peroral)	✓(*)	✓(*)	✓(*)	✓(1)
Tocilizumab (intravenous)	✓(*)			
Azathioprine (peroral)	✓(*)	✓(*)		✓(2)
Tacrolimus (peroral)	✓(*)		✓(2)	✓(2)
Anti-thymocyte globulin (intravenous)	✓(*)		✓(2)	✓(2)
Ciclosporin (peroral)	✓(*)			✓(2)
Do not use infliximab	✓(x)	✓	✓	✓

ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; SITC, Society for Immunotherapy of Cancer.

(1 mg/kg daily) was not more efficient compared with a lower dose (50–60 mg daily), yet more likely to cause steroid-associated side effects.[20] Liver biopsy was mentioned in 12 of 22 reports.

Additional immunosuppressive treatment after failure of corticosteroid treatment was most frequently based on MMF in 18 of 22 publications.[16 20–23 25 26 28–33 35–39] Additional treatments with combined MMF plus either ursodeoxycholic acid, tacrolimus or infliximab were reported each in one publication.[20 22 23] Other reported additional treatments were ciclosporin (n=1),[12] azathioprine (n=1),[24] 6-mercaptopurine (n=1).[25] Use of infliximab in steroid-resistant immune-related hepatitis is not recommended by relevant guidelines because it has been associated with potentially severe treatment-related hepatotoxicity in patients with hepatitis.[1–3 40] Severe and fatal cases of hepatic injury from infliximab when used for sr-irAE other than hepatitis have also been reported.[26 41] Nevertheless, the use of infliximab for steroid-resistant hepatitis was reported in three cases, one in combination with MMF.[20 27]

Reported treatment options after failure of MMF were ATG (n=3)[28 30 32] and tacrolimus (n=1).[22] Across all identified case reports/case series, steroid-resistant hepatitis resolved with additional immunosuppression in 94% of all reported patient cases (see online supplemental appendix table 5). Only one case of successful ICI rechallenge was reported after steroid-resistant hepatitis, successfully treated with MMF.[26]

The current treatment rationale for immune-related hepatitis is largely based on historic experiences in treating autoimmune hepatitis (AIH) and other autoimmune diseases with known immunosuppressive agents. More recently it has been shown that immune-related hepatitis is less related to AIH immunologically but rather to hepatic graft versus host disease (GVHD), which is characterized by lobular inflammation with presence of CD8+T cells and impaired activation of regulatory T cells.[42] Novel immune-modulatory treatment options such as extracorporeal photopheresis (ECP) and/or ruxolitinib that are already in use in the context of steroid-refractory acute GVHD could therefore be promising new treatment options.[43–45] ECP is currently investigated in a clinical trial (NCT05414552) (https://clinicaltrials.gov/study/NCT05414552, accessed on September 29, 2023).

Summary and recommendations

The incidence of steroid-resistant immune-related hepatitis is unknown and there is limited evidence regarding diagnostics and treatment. All guidelines agree that an hepatologist experienced in the matter should be consulted and a liver biopsy should be considered. If not

done in the initial workup, viral infections, AIH, hemochromatosis, hepatic disease progression and toxicity from other factors than ICI should be excluded. Evidence regarding treatment options is available only in the form of case reports and small case series. There is much evidence for MMF, which has been reported as a successful treatment of steroid-resistant ICI-related hepatitis in most published case reports. Other treatment options include ATG, azathioprine, ciclosporin and tacrolimus. Infliximab should be avoided due to potential infectious complications and hepatotoxicity. In addition, we recommend that treatment decisions as well as tapering of steroids after successful initiation of additional immunosuppression be discussed with an immune-oncologist as well as an organ expert who is experienced with managing irAEs.

Colitis

Clinical presentation and epidemiology

Immune-related colitis is one of the most common side effects of ICI treatment.[46 47] Its diagnosis requires either clinical, radiologic, or endoscopic evidence of enterocolonic inflammation. Immune-related colitis manifests as diarrhea, which is often accompanied by abdominal pain, hematochezia, weight loss, fever and vomiting.[48 49] Importantly, immune-related colitis increases the risk of complications, such as ileus, perforation or even death.[48 49]

Immune-related colitis occurs most frequently in patients treated by combined immunotherapies with CTLA-4 inhibitor and PD-1 inhibitor (11.8% of all patients), followed by single-agent treatment with CTLA-4 inhibitor (11.6%) and PD-1 inhibitor (1.3%).[50] The incidence of colitis in patients treated with CTLA-4-inhibitors is dose-dependent.[19] The median interval from administration of the first dose of CTLA-4-inhibitor to onset of immune-related colitis has been reported to be approximately 1 month, and 2–3 months after administration of PD-(L)1-inhibitors.[49 51 52]

Patients with persistent colon inflammation revealed in the endoscopic examination and/or lack of clinical response to corticosteroids are considered resistant.[49] It is estimated that about one-third to two-thirds of all patients do not respond to first-line treatment of high-dose intravenous corticosteroids or suffer a relapse during the course of steroid tapering.[11 48] Colonic ulcerations, higher endoscopic scores, such as the often used Mayo Endoscopic Subscore,[53 54] and/or pancolitis are associated with a higher risk of steroid-resistant disease.[53–56]

Management

Consensus guidelines

Guidelines (ESMO, ASCO, SITC, NCCN, AGA) for immune-related colitis focus mainly on the initial management describing three strategies depending on the severity of immune-related colitis and the duration of symptoms: discontinuation of ICI-treatment, start of immunosuppressive corticosteroid-treatment and supportive measures such as hydration.[1–3 40] Unfortunately, failure of these initial management strategies is common due to steroid-resistant situations.

In steroid-resistant colitis, guidelines suggest the following diagnostic management strategy: a complete initial workup with blood analysis and stool analysis to rule out infective disease and to measure calprotectin or lactoferrin and endoscopy with biopsies if not conducted in the initial management. Radiologic diagnosis is not the appropriate diagnostic method to detect immune-related colitis. However, it should be carried out if complications are suspected (eg, perforation, abscess). A gastroenterologist should be involved, also to evaluate re-endoscopy with biopsies (table 2).[1–3 11 40] One of the most frequently used endoscopic measurement scale is the Mayo Endoscopic Subscore, ranging from 0 (no inflammation) to 3 (colonic ulceration).[57 58]

All guidelines recommend the administration of infliximab or vedolizumab as first-line treatment.[1–3 11 40] Since there is currently no available data comparing infliximab to vedolizumab in the first-line treatment, the decision between these two agents should be based on clinical factors, such as expected duration of treatment, degree of severity, concurrent other irAEs, underlying malignancy, comorbidities and risk of infection.[11 16] Additional immunosuppressive agents to treat steroid-resistant colitis are: tofacitinib, ustekinumab, MMF, fecal microbiota transplantation and extracorporeal photopheresis.[1–3 11 40] Surgical options should be evaluated in patients with toxic megacolon, intra-abdominal abscesses or perforation[1] (table 2).

Literature review

We identified in our literature search 27 publications about the management of steroid-resistant colitis, including 12 case reports[59–70] and 15 case series[16 56 71–83] (see online supplemental appendix table 6). Stool examination to rule out infectious disease with/without stool calprotectin or lactoferrin, blood laboratory tests and endoscopic examinations with/without biopsies were carried out according to almost all publications,[56 59–75 77–84] except for one publication in which no diagnostic approach was mentioned.[16] Additional abdominal imaging was recommended in three publications.[64 67 83]

After failure of initial high-dose corticosteroid treatment the following immunosuppressive agents were used: infliximab (n=10),[16 56 59 63–65 71–74] vedolizumab (n=2)[60 75] or a combination of these two agents (n=4).[66 77 82 84] For colitis resistant to infliximab and/or vedolizumab, the use of oral calcineurin inhibitors (tacrolimus, ciclosporin) (n=3),[61 78 79] rapamycin with tacrolimus (n=1),[78] ustekinumab (n=1),[67 80] tofacitinib (n=4),[62 68 70 83] stool transplantation (n=1)[81] and extracorporeal photopheresis (n=1)[69] have been described. Overall, most evidence of evidence exists for infliximab as first-line treatment in steroid-resistant colitis. The administration was successful in most cases, resulting in a complete clinical remission or in relevant clinical improvement of gastrointestinal symptoms after one to three infusions. Additionally, Abu-Sbeih

Table 2 Diagnostic and therapeutic recommendations for steroid-resistant colitis

	Guidelines			
	ESMO (2022)[1]	ASCO (2021)[3]	SITC (2021)[2]	NCCN (2023)[40]
Diagnostic procedures				
Blood analysis (eg, complete blood count, blood chemistry with electrolytes, renal and liver function, thyroid function test)	✓	✓	✓	✓
Stool analysis for enteropathogenes, *Clostridium difficile* toxin, cytomegalovirus (initial or in resistant situation)	✓	✓	✓	✓
Fecal lactoferrin, calprotectin	✓	✓	✓	✓
Abdominal X-ray, CT of the abdomen and/or pelvis (for detecting complications)	✓	✓	✓	✓
Sigmoidoscopy, colonoscopy	✓	✓	✓	✓
Consultation with a gastroenterologist	✓	✓	✓	✓
Repeat endoscopy	✓	✓	✓	✓
Treatment options (1) First choice of additional immunosuppressive treatment. (2) Other options of immunosuppressive treatment.				
Infliximab (intravenous)	✓(1)	✓(1)	✓(1)	✓(1)
Vedolizumab (intravenous)	✓(1)	✓(1)	✓(1)	✓(1)
Tofacitinib (peroral)	✓(2)	✓(2)		
Ustekinumab (intravenous)	✓(2)	✓(2)		
Mycophenolate mofetil (peroral)	✓(2)			
Fecal microbiota transplantation	✓(2)	✓(2)		✓(2)
Extracorporeal photopheresis	✓(2)			
Colectomy	✓(2)			

ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; SITC, Society for Immunotherapy of Cancer.

et al described how the early administration of infliximab and/or vedolizumab within less than 10 days, regardless of corticosteroid responsiveness, was essential for the improvement of the symptoms and that the recurrence rate of immune-related colitis was higher in infliximab monotherapy (26%) than in vedolizumab monotherapy (3%)[84] (see online supplemental appendix table 6). Additionally, there is some evidence available on the use of these agents (infliximab, vedolizumab) to manage immune-related colitis while resuming ICI-treatment.[85 86] However, this approach remains investigational, and we await further studies prior to using it routinely in clinical practise.

The current treatment rationale for immune-related colitis is mainly based on experiences in treating inflammatory bowel diseases (IBD).[87] It is well established that T cells and cytokines/interferons play an important role in immune-related colitis.[74 87 88] In steroid-refractory immune-related colitis, anti-Tumor Necrosis Factor (TNF)-α treatment with infliximab is often initiated, especially when the inflammation is severe (correlation TNF-α and inflammation), according to studies in IBD.[89 90] In contrast to the unspecific action of infliximab, vedolizumab has a specific effect in the intestinal tract by blocking the alpha4-beta7-integrin which is involved in homing of T cells to the intestinal tract.[60 75 91 92] In addition to modulating the immune system pathways, another approach for treating immune-related colitis is targeting the microbiome. Promising outcomes with stool transplantations in the context of recurrent *Clostridium difficile* infections[93–97] and IBD, especially in ulcerative colitis,[98–101] led to considerations of this approach in immune-related colitis.[81]

Summary and recommendations

To conclude, in immune-related colitis prompt diagnostic procedures with mandatory endoscopic examination and the initiation of treatment are crucial. Overall, about half of the patients with moderate-to-severe colitis do not respond to corticosteroids.[1 16] According to the guidelines and based on our literature review infliximab is the most commonly used agent in steroid-resistant colitis, leading to satisfactory improvement for almost all patients, especially if introduced at an early stage. In addition, the

response is fast and shows efficacy in the presence of coexisting irAEs. However, about 11% of these patients are infliximab-refractory and require additional immunosuppressive agents.[1 16] In these situations, vedolizumab should be considered as a gut-specific immunosuppressive treatment. However, the onset of the effect of vedolizumab is slower and is therefore not recommended in severe colitis. However, these recommendations are based on a small number of eligible studies with small population sizes thus limiting the level of evidence. Therefore, a discussion at an immune-oncological board with experts (immune-oncologist and gastroenterologist experienced in managing irAEs) remains important.

Pneumonitis

Clinical presentation and epidemiology

ICI-related pneumonitis has no uniform definition and may refer to different clinical and radiological manifestations. In general, it is defined as inflammation of lung tissue. Patients usually present with one or more of the following symptoms: dyspnea, hypoxia, cough, chest pain, and/or fever.[1–3 40] Characteristic radiographic findings of pneumonitis have been summarized by Naidoo *et al*.[10] Pre-existing non-malignant lung disease, lung cancer, smoking, radiotherapy to the chest and concomitant treatment with pneumotoxic medication have been identified as risk factors of ICI-related pneumonitis[10 102] and these factors also pose a challenge for differentiating ICI-related pneumonitis from other causes of lung damage.

ICI-related pneumonitis is most frequent in patients treated with combined PD-(L)1 and CTLA-4-inhibition (10%).[10] It occurs in approximately 2.5–4% of patients receiving anti-PD-1, in 2% of patients receiving anti-PD-L1 and in 1% of patients receiving anti-CTLA-4 treatment.[10 103 104] A median time to onset of 2.5–2.8 months has been reported.[10 14] While ICI-related pneumonitis is a rare event, it is however frequently serious with up to one-third of patients presenting with events of grade 3 or higher and fatal outcome in up to 12% of patients.[10 105]

Higher grade pneumonitis often does not respond to corticosteroid treatment alone and requires additional immunosuppression. In a review of 64 patients who developed checkpoint-inhibitor induced pneumonitis, 6 patients (9.4%) had fatal pneumonitis and 1 patient (1.6%) had worsening pneumonitis despite prednisone treatment.[105] Another retrospective analysis of 43 patients with pneumonitis by Naidoo *et al* showed that nearly all cases of grade 1 and 2 pneumonitis resolved with corticosteroids, whereas grade 3 and 4 pneumonitis frequently mandated additional immunosuppressive agents.[10] Yet another report has found steroid-resistance in 12 of 65 patients (18.5%) with immune-related pneumonitis.[106] Grade 3 or higher pneumonitis as well as worsening pneumonitis, that is, resistant to steroid treatment and requires additional immunosuppression, have been associated with primary tumor site (especially lung cancer), current smoking, and with underlying lung disease.[10 107]

Recurrent pneumonitis following a first episode of immune-related pneumonitis is frequent (25% of patients), both spontaneously and in patients who had rechallenge to ICIs (recurrent pneumonitis in 25–43% of patients).[10 108] A minority of patients (14% of patients) with pneumonitis may develop chronic low grade pneumonitis, which persists despite ICI-discontinuation and may not resolve after 3 months of corticosteroids.[3 109]

Management

Consensus guidelines

Guidelines (ESMO, ASCO, SITC, NCCN) essentially agree on two recommendations concerning the management of grade 2 or higher immune-related pneumonitis: discontinuation of ICI-treatment and start of immunosuppressive (high-dose) corticosteroid-treatment.[1–3 40] There are no consistent recommendations regarding the diagnostic and therapeutic management of steroid-resistant pneumonitis. Guideline recommendations are summarized in table 3. There is consensus that in the case of higher-grade pneumonitis and/or steroid-resistance, differential diagnoses must be excluded (infection, embolism, effusion, tumor progression/carcinomatosis, or cardiac cause). If not done during the initial workup, diagnostic steps should therefore include high-resolution chest CT, bronchoalveolar lavage and consultation with a specialist.[1–3 40] Transbronchial lesion biopsy can be considered on an individual basis.[3 40]

According to all guidelines, failure of corticosteroid treatment is defined as lack of improvement within 48–72 hours and should prompt immediate treatment escalation.[1–3 40] Steroid-resistant grade 2 pneumonitis should be treated as grade 3 with high-dose intravenous corticosteroids.[1 3 40] Additional immunosuppressive treatment options include MMF, cyclophosphamide, intravenous immunoglobulins (IVIG) and infliximab.[1–3 40]

Literature review

We have performed a structured literature search and have gathered data about treatment of steroid-resistant immune-related pneumonitis (see online supplemental table 7). Seventeen publications have been identified, nine of which are single-case reports.[10 26 39 106 107 110–121] Signs of efficacy to treat steroid-resistant immune-related pneumonitis have been reported for different immunosuppressive agents, including IVIG, MMF, cyclophosphamide, tocilizumab and infliximab.[10 26 106 107 110] However, there is no prospective or comparative data in this situation and there are no treatment recommendations favoring one agent over another. There is a small number of retrospective analyses of patients with pneumonitis that include patients with steroid-resistant pneumonitis.[10 26 106 107 110 111] Common to each of these reports is a high fatality rate of 67–100% for patients with steroid-resistant pneumonitis, regardless which additional suppressive line treatment was chosen.

Most evidence is available for infliximab, however with contradictory results. Several single case reports have

Table 3 Diagnostic and therapeutic recommendations for steroid-resistant pneumonitis

	Guidelines			
	ESMO(2022)[1]	ASCO (2021)[3]	SITC(2021)[2]	NCCN(2023)[40]
Diagnostic procedures				
High resolution chest-CT, if not previously done	✓	✓	✓	✓
Bronchoalveolar lavage, if not previously done	✓	✓		✓
Refer to or consult with specialist	✓	✓		✓
Treatment options (1) First choice of additional immunosuppressive treatment. (2) Other options of immunosuppressive treatment. (*) No treatment sequence mentioned.				
Continue intravenous steroids	✓(x)	✓(x)		✓
Escalate after 48 hours if no improvement		✓(x)		✓
Immunoglobulin (intravenous)	✓(1)	✓(*)	✓(*)	✓(*)
Mycophenolate mofetil (peroral)	✓(2)	✓(*)	✓(*)	✓(*)
Cyclophosphamide (intravenous)	✓(2)	✓(*)	✓(*)	
Infliximab (intravenous)	✓(1)	✓(*)	✓(*)	✓(*)
Tocilizumab (intravenous)	✓(1)		✓(*)	
Consider upfront tocilizumab or infliximab in addition to steroid treatment in case of life-threatening symptoms	✓(x)			

ASCO, American Society of Clinical Oncology ; ESMO, European Society for Medical Oncology ; NCCN, National Comprehensive Cancer Network ; SITC, Society for Immunotherapy of Cancer.

reported significant improvement of steroid-resistant ICI-related pneumonitis on infliximab administration, however such reports harbor selection bias as treatment failures tend to get reported less often. Only low success rates of infliximab in the range of 25–33% have been reported in the retrospective studies of Luo *et al*,[26] Nishino *et al*[107] and Beattie *et al*,[111] whereas all treatment attempts with infliximab were negative in the retrospective studies by Naidoo *et al* and Balaji *et al*.[10 106] Due to these conflicting results, infliximab in the setting of steroid-resistant pneumonitis has more recently been called into question.[106]

IVIG has been suggested as alternative additional immunosuppressive treatment in steroid-resistant pneumonitis, based on one single case report[112] and one retrospective case series by Balaji *et al* which has reported a successful improvement of pneumonitis in four of seven patients treated with IVIG.[106] Currently, a prospective trial is being conducted by Eastern Cooperative Oncology Group (ECOG) and the American College of Radiology Imaging Network (ACRIN) that compares infliximab versus IVIG as additional immunosuppression in steroid-resistant immune-related pneumonitis (NCT04438382) (https://classic.clinicaltrials.gov/ct2/show/NCT04438382, accessed on February 12, 2023).

Signs of efficacy for the use of tocilizumab in the treatment of immune-related pneumonitis comes from a single-center retrospective study including 34 patients (predominantly patients with lung cancer) with sr-irAEs, including 12 patients with pneumonitis.[113] Among all patients, 79.4% demonstrated clinical improvement from tocilizumab treatment, and most patients required only a single or two doses.

Beattie *et al* have reported durable improvement of steroid-resistant ICI-associated pneumonitis in five of six patients treated with MMF as additional immunosuppression.[111] Camard *et al* have reported improvement and survival beyond 5 months in two of four patients treated with cyclophosphamide.[110]

The underlying pathomechanism of ICI-related pneumonitis is likely based on T-cell autotoxicity due to shared epitopes between tumor and lung.[122] Bronchoalveolar lavage (BAL) from patients with ICI-related pneumonitis has shown T-cell dominated lymphocytosis with upregulation of pro-inflammatory CD8/TNF-α/interferons-gamma-positive T cells, upregulation of CD8-positive T cells co-expressing checkpoint-inhibitors such as PD-1 and T-cell immunoglobulin and mucin-domain containing (TIM)-3 and downregulation of anti-inflammatory CD4/PD-1/CTLA4-positive regulatory T cells.[123] Suppression of T-cell mediated auto-immunity is likely the reason why immunosuppressive agents such as MMF and cyclophosphamide might alleviate ICI-related pneumonitis. Pro-inflammatory cytokines were also found to be elevated in BAL of patients with ICI-related pneumonitis, thus providing some rationale for cytokine-directed treatments such as infliximab or tocilizumab, however the main mechanism of inflammation appears to be cellular.[124] Apart from T-cellular mechanisms, also autoimmune antibodies seem to play a role in pneumonitis.[125]

The neutralization of such autoimmune antibodies might be the reason why IVIG have been found to improve ICI-related pneumonitis.

Summary and recommendations

The incidence of immune-related pneumonitis is low, however resistance to steroid treatment may occur in 10–20% of patients and is associated with a high fatality rate. Steroid-resistant pneumonitis is associated with lung cancer, other underlying lung disease and smoking. No prospective data is available with regard to diagnostics and treatment of steroid-resistant pneumonitis. Most retrospective data is available for infliximab, however with conflicting and hardly encouraging results. Other options with less evidence but reports of higher success rates are IVIG, tocilizumab, MMF and cyclophosphamide. Wherever possible, these options should probably be explored before infliximab is applied. However, prospective evidence is necessary to answer this question. We generally recommend that treatment decisions as well as tapering of steroids after successful initiation of additional immunosuppression be discussed with immune-oncologists and pneumologists experienced with managing irAEs.

Myocarditis

Clinical presentation and epidemiology

Immune-related myocarditis is a rare side effect of ICI treatment, but is potentially life-threatening.[126–128] The prevalence of myocarditis is approximately 1.14%.[126] About half of the number of patients with ICI-related myocarditis experience a major adverse cardiac event, defined as occurrence of cardiovascular death, cardiogenic shock, cardiac arrest or hemodynamically significant complete heart block.[126] In a retrospective analysis, 50% of patients diagnosed with immune-related myocarditis died.[127]

Diagnosing ICI-related myocarditis requires either an endomyocardial biopsy or concordant findings from clinical, laboratory, electrocardiographic and imaging examinations.[129 130] The clinical presentation is highly variable, ranging from subclinical disease (ECG or laboratory phenomena with elevated cardiac biomarkers) to chest pain and major cardiac events.[1–3 40 129 130] It is often associated with concurrent myositis and a myasthenia gravis-like syndrome which often require additional immunosuppressive agents beyond corticosteroids.[127 128]

Fortunately, the overall occurrence of immune-related myocarditis remains rare. According to a pharmacological safety database it occurs more often in patients receiving combined anti-PD-1 and anti-CTLA-4 treatment than in patients receiving only an anti-PD-1 monotherapy (0.27% vs 0.06%).[131] The median interval from starting ICI treatment to onset of immune-related myocarditis has been described to be approximately 5 weeks.[1]

Patients with worsening symptoms, persistently elevated or increasing cardiac biomarkers, occurrence of cardiac arrhythmias and/or reduced ventricular ejection fraction despite high-dose corticosteroids are considered resistant.[1] The percentage of patients with steroid resistance is still unknown.

Management

Consensus guidelines

Guidelines (ESMO, ASCO, SITC, NCCN, European Society of Cardiology) for immune-related myocarditis focus mainly on the initial management, recommending discontinuation of ICI-treatment, start of immunosuppressive high-dose corticosteroid-treatment and hospital admittance.[1–3 132] The initial diagnostic assessment should be completed in steroid-resistant myocarditis including a complete initial workup with blood analysis, ECG, echocardiography, cardiac MRI, ruling out vascular heart disease (catheterization or imaging) and evaluation of endomyocardial biopsy as well as the consultation of a cardiologist (table 4).[1–3 129 130 132]

After the diagnostics procedures, the guidelines recommend the following immunosuppressive agents for the treatment of steroid-resistant immune-related myocarditis: infliximab, MMF, ATG, abatacept, alemtuzumab, tocilizumab and immunoglobulins. Hereby, the administration of MMF, ATG, abatacept and alemtuzumab is recommended by all guidelines. But most evidence of efficacy for first line use in steroid-resistance is MMF. Infliximab is recommended by ASCO and NCCN Guidelines, whereas in the SITC and ESMO Guidelines its use is critically evaluated as a result of the study by Cautela *et al* who have shown an increased risk of cardiovascular death after the administration of infliximab (table 4).[1–3 40 133]

Literature review

There is limited available evidence regarding the management of steroid-resistant myocarditis. We have identified 15 publications of which 13 publications[134–146] were case reports, 2 publications were smaller case series with 4 patients[147] and 16 patients[148] and one study included a study population of 30 patients treated with additional immunosuppressive agents[149] (see online supplemental appendix table 8). All the included publications suggested blood analysis, ECG and echocardiography as the first diagnostic approach.[134–149] Four publications recommended in addition conducting a cardiac MRI[134 136 137 139 149] or gallium-68 DOTATOC imaging[146] and eight publications the visualization of the coronary vessels by using imaging or percutaneous catheters.[134 136 138 140–143 145 149] Only in two publications was a cardiac biopsy carried out as a diagnostic procedure in all or at least some study patients.[142 143 149] Cardiac MRI or biopsy is recommended by Zhang *et al*.[147]

The initial management of ICI-related myocarditis included the administration of high-dose corticosteroids in all cases. The following additional immunosuppressive agents were investigated (alone or in combination): abatacept,[134–136 140 149] oral MMF,[135 140 142 144] ruxolitinib,[149] alemtuzumab,[137] infliximab,[138 147 148] IVIG,[138 145 148] plasmapheresis,[139–141] tacrolimus,[139] abatacept,[140] ATG,[142–144] tofacitinib[145 148] and tocilizumab.[146] All the above

Table 4 Diagnostic and therapeutic recommendations for steroid-resistant myocarditis

	Guidelines			
	ESMO (2022)[1]	ASCO (2021)[3]	SITC (2021)[2]	NCCN (2023)[40]
Diagnostic procedures				
Blood analysis (troponin, creatine kinase/-MB, N-terminal pro-B-type natriuretic peptide/brain natriuretic peptide)	✓	✓	✓	✓
ECG	✓	✓	✓	✓
Echocardiography	✓	✓	✓	✓
Cardiac Imaging: Cardiac MRI, cardiac Ga-DOTATOC, FDG-PET-CT	✓	✓	✓	✓
Endomyocardial biopsy (endovascular)	✓	✓	✓	✓
Cardiac stress testing or heart catheterization	✓	✓		
Chest X-ray		✓		
Consultation with a cardiologist	✓	✓	✓	✓
Treatment options (1) First choice of additional immunosuppressive treatment. (2) Other options of immunosuppressive treatment. (*) No treatment sequence mentioned.				
Infliximab (intravenous)		✓(1)		✓(*)
Mycophenolate mofetil (peroral)	✓(1)	✓(1)	✓(*)	✓(*)
Anti-thymocyte globulin (intravenous)	✓(2)	✓(1)	✓(*)	✓(*)
Abatacept (intravenous)	✓(2)	✓(2)	✓(*)	✓(*)
Alemtuzumab (intravenous)	✓(2)	✓(2)	✓(*)	✓(*)
Tocilizumab (intravenous)	✓(1)			
Immunoglobulin (intravenous)				✓(*)

ASCO, American Society of Clinical Oncology ; creatine kinase-MB, heart specific isoenzyme of creatine kinase; ESMO, European Society for Medical Oncology ; FDG-PET, Fluorodeoxyglucose-Positron Emission Tomography; Ga-DOTATOC, Gallium-based ligand binding to somatostatin receptors; NCCN, National Comprehensive Cancer Network ; SITC, Society for Immunotherapy of Cancer.

procedures led to a complete or partial resolution of the clinical symptoms, laboratory findings and echocardiography examinations, except for three studies using infliximab combined with IVIG,[138] infliximab alone[148] or ATG[144] (see online supplemental appendix table 8). In the largest study population, 30 patients were treated with a combination of ruxolitinib and abatacept. Hereby, the fatality rate due to myocarditis could be significantly reduced to 3.4% (control group: fatality rate of 60%) in the first observation interval.[149]

The detailed pathophysiological mechanisms of ICI-related myocarditis are still unclear. An infiltration of T cells into the myocardium seems to be an important condition for ICI-related myocarditis,[131] as observed in a monkey model.[150] To target T-cell activation and thus reducing infiltration, abatacept blocks T-cell interactions with antigen-presenting cells (CD86/CD28). Initially, abatacept was used in rheumatic diseases, and a trial of its effect on myocarditis in rheumatoid arthritis is currently underway (NCT03619876, https://clinicaltrials.gov/study/NCT03619876, accessed on September 29, 2023). ATG also targets the T-cell infiltration by causing a T-cell depletion, similar to patients with heart transplant.[142]

Other important pathways involved in ICI-related myocarditis are the JAK2 signaling pathways.[149] It was shown in mice and human that JAK2 signaling pathways are upregulated in ICI-related myocarditis, thus providing some rationale for JAK1/JAK2 inhibitors such as ruxolitinib[149] in this setting. Additionally, ruxolitinib may decrease the antigen presentation in the myocardium and block the proapoptotic functions of interferons.[151 152]

Summary and recommendations

Although immune-related myocarditis is a rare irAE, it is crucial to identify and treat it promptly due to its potentially fatal outcome. Due to its high fatality rate, even an upfront combination treatment with immunosuppressive agents should be considered. Clear evidence with regard to treatment cannot be provided as all available publications are case reports of one patient or only small case series. Overall, most beneficial evidence is available for the use of abatacept or ATG (both with or without MMF) or ruxolitinib with abatacept in treating steroid-resistant myocarditis. There is no convincing evidence for the use of infliximab in this setting. We generally recommend that treatment decisions should be discussed with

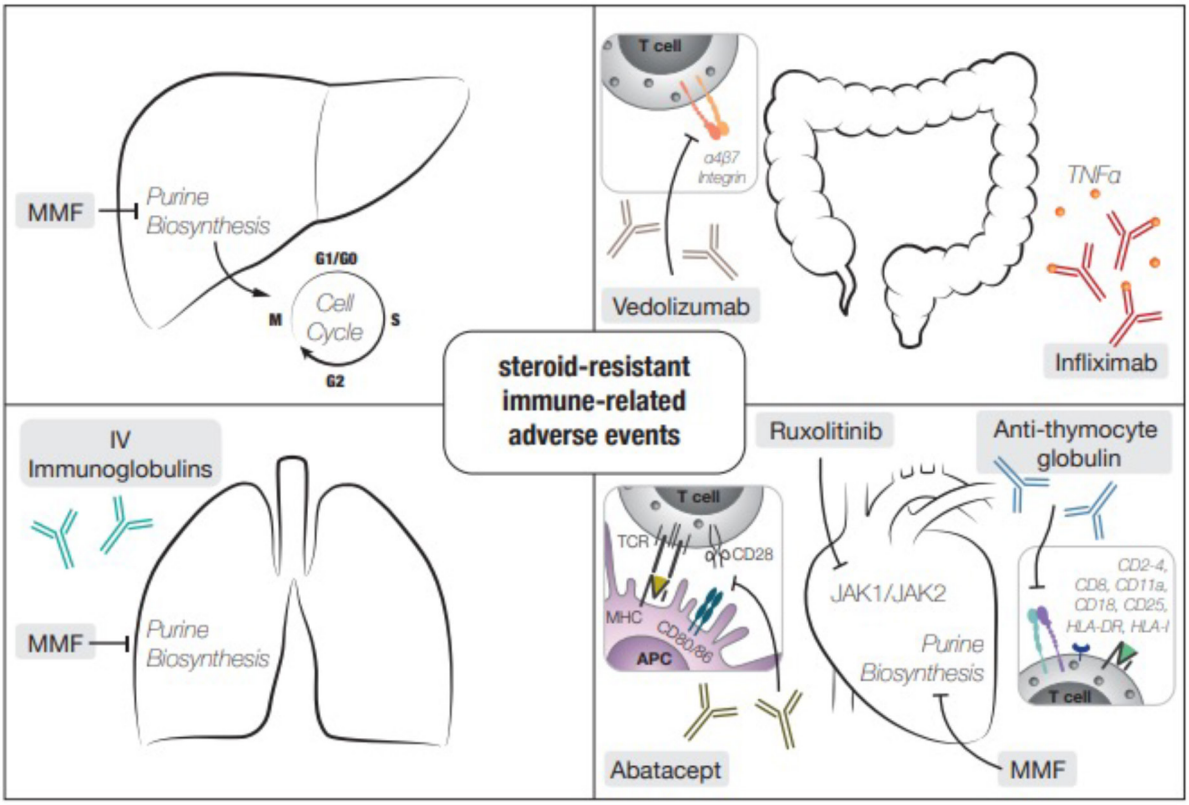

Figure 1 Overview of different activities of immunosuppressants used in the treatment of immune-related organ toxicities. Standard treatment of immune-mediated liver toxicities includes MMF that targets purine synthesis and thereby limits T cell-mediated anti-liver toxicity (upper left quadrant). Secondary immune suppression in patients with colitis consists of biologics targeting TNF-α (eg, infliximab) or integrins (vedolizumab, upper right quadrant). Secondary immune suppression for lung toxicities of ICI includes MMF and IVIG (lower left quadrant). Treatment of steroid-refractory myocarditis can include MMF, abatacept (fusion protein with CTLA-4 inhibiting CD80/86 interactions), ruxolitinib (JAK 1/2 inhibitor) or ATG (lower right).APC, antigen presenting cell; HLA, human leukocyte antigen; IV, intravenous; MHC, major histocompatibility complex; MMF, mycophenolate mofetil; TCR, T cell receptor.

immune-oncologists and cardiologists experienced with managing irAEs.

CONCLUSIONS

In this review we have focused on sr-irAEs of liver, colon, lung and heart, as the four most vital organs that can potentially suffer irreversible and life-threatening damage from uncontrolled checkpoint-inhibitor induced autoimmune inflammation (figure 1). Depending on the immunotherapeutic agents, colitis and hepatitis are frequent events, whereas pneumonitis occurs less often and myocarditis is a rare event. Steroid resistance is rare in each of these organs and exact numbers are unknown. International guidelines recommend a rapid step-up of diagnostic and therapeutic measures for each of these organs if steroid treatment does not produce significant improvement after a short time interval of 48–72 hours.[1–3] If not previously carried out, guidelines recommend liver biopsy for steroid-resistant hepatitis, colonoscopy for steroid-resistant colitis, high resolution chest CT and BAL for steroid-resistant pneumonitis and cardiac imaging for steroid-resistant myocarditis. In each case we recommend consulting with an immune-oncologist and an organ expert experienced with irAE not only to discuss diagnostics and second-line immunosuppression but also to manage steroid taper.

There is no reliable evidence for choosing additional immunosuppression after failure of steroid treatment for any of these organs because no treatment has been prospectively validated. The use of immunosuppressive agents and disease-modifying antirheumatic drugs has been investigated in observational studies in the context of arthritis, providing comparative evidence for the use of interleukin-6 inhibitors, TNF-α-inhibitors and methotrexate.[153 154] However, this kind of comparative evidence is lacking for colitis, hepatitis, pneumonitis and myocarditis. Hence, guideline recommendations remain vague and, in some cases, conflicting. Therefore, we have performed a systematic literature review of available publications about steroid-resistant hepatitis/colitis/pneumonitis/myocarditis, consisting mostly of single-case reports and a few small case series. This review thus has significant limitations, because gathered evidence relies heavily on single case reports or small case series,

thus providing low level evidence. However, currently there is no better evidence and to our knowledge we are providing the first comprehensive compilation of evidence in the case of steroid-resistant hepatitis/colitis/pneumonitis/myocarditis. This shows that there is an urgent need for prospective trials in the setting of steroid-resistant immune-related events, which have become a relevant matter in clinical practise due to the increasing use of checkpoint inhibitors.

Based on the evidence gathered in this review and on our own clinical experience we would recommend using (1) oral MMF for steroid-resistant hepatitis, (2) infliximab for steroid-resistant colitis, followed by vedolizumab if infliximab fails, (3) MMF and IVIG for steroid-resistant pneumonitis, followed by tocilizumab if the first two agents fail, and (4) abatacept or ATG (both with or without MMF) or ruxolitinib with abatacept for steroid-resistant myocarditis. However, treatment decisions should be made on an individual basis, taking into consideration all clinical factors, drug availability, and local experience. In general, we recommend consulting an experienced immune-oncologist and organ expert experienced with irAEs, ideally in the context of a specialized immune-oncology/irAE-board. However, time is of the essence in these often-life-threatening clinical situations and therefore specialist consultations and additional diagnostics should be done immediately in order not to delay necessary treatment decisions (initiation of high-dose steroids and initiation of additional immunosuppression in the case of steroid-resistance).

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Supplementary Appendix

Table 5: Summary of eligible studies on immune checkpoint inhibitors-induced steroid-resistant hepatitis
n = 22 studies

First author Year	Number of patients, diagnosis	Initial treatment	Additional treatment	Response to treatment
Chmiel, 2011 (33)	n=1; melanoma	corticosteroids i.v. methylprednisolone	oral MMF (1g b.i.d. day 6 onward) i.v. anti-thymocyte globulin, day 9-10	Results: Complete resolution ▪ Lasting clinical improvement within days, normalization of liver function tests within 4 weeks without relapse
Horvat, 2015 (20)	n=2 with sr-hepatitis (197 with hepatitis); melanoma	corticosteroids (not further specified)	oral MMF	Results: Not provided
Ahmed, 2015 (34)	n=1; melanoma	corticosteroids i.v. methylprednisolone	oral MMF (day 2) i.v. anti-thymocyte globulin (day 2)	Results: Complete resolution ▪ Improvement of liver values within 24 h, lasting normalization within 1 week, cancer progression after 4 months
Johnscilla, 2015 (30)	n=3 with sr-hepatitis (11 with hepatitis); melanoma	corticosteroids Prednisone	oral MMF (n=2) oral 6-MP (n=1)	Results: Complete resolution ▪ 3/3 normalized liver values ▪ No ICI re-challenges
Spänkuch, 2017 (35)	n=1; melanoma	corticosteroids i.v. methylprednisolone	oral MMF (day 10) i.v. anti-thymocyte globulin (day 17)	Results: Complete resolution ▪ Further increase of liver values after MMF ▪ Normalization of LFT after ATG ▪ Successful ICI re-challenge
Tanaka, 2017 (36)	n=1; melanoma	corticosteroids i.v. methylprednisolone (worsening hepatitis during tapering)	oral MMF	Results: Partial resolution ▪ Liver function tests improving to grade 1, successful taper of steroids and MMF
McGuire, 2017 (37)	n=1; melanoma	corticosteroids i.v. methylprednisone	oral MMF i.v. anti-thymocyte globulin	Results: Partial resolution ▪ Liver function test improving and fluctuating between grade 1-2 up to day 198
Iwamoto, 2017 (29)	n=1: melanoma	corticosteroids i.v. methylprednisone	oral azathioprine	Results: Complete resolution ▪ Normalization of liver values within a month
Huffman, 2017 (16)	n=1 with sr-hepatitis (17 with hepatitis); melanoma	corticosteroids prednisone	oral cyclosporine (day 15)	Results: Complete resolution ▪ Normalization of liver tests day 40, discontinuation of all immunosuppression
Doherty, 2017 (28)	n=3; melanoma (n=2), mesothelioma (n=1)	corticosteroids i.v. methylprednisone	oral MMF+ ursodeoxycholic acid (n=2), ursodeoxycholic acid (n=1)	Results: No response ▪ No swift improvement of liver function tests, monthlong steroid-dependency in all 3 cases (histologically all 3 cases were atypical with bile tract injury and absence of lymphocytic infiltration) ▪ No ICI re-challenge

Corrigan, 2019 (32)	n=1; melanoma	corticosteroids i.v. methylprednisone	i.v. infliximab	Results: Partial resolution ▪ Improvement but no normalization of LFT, re-increase and re-biopsy with new fibrosis, necessitating continued steroid use and initiation of tacrolimus. Normalization and lasting response at 14 months
Cheung, 2019 (24)	n=9 with sr-hepatits (20 with hepatitis); melanoma	corticosteroids i.v. methylprednisone	oral MMF (n=6) i.v. infliximab (n=1) oral MMF and oral tacrolimus (n=1) oral MMF and i.v. infliximab (n=1)	Results: Partial resolution ▪ Improvement of LFT to grade 1 within 30 days.
Nakano, 2020 (38)	n=1; head and neck	corticosteroids i.v. methylprednisone	oral MMF (day 4)	Results: Complete resolution ▪ Normalization to grade 1 by day 31, MMF and steroid tapered by day 91
Ziogas, 2020 (27)	n=1; melanoma	corticosteroids i.v. methylprednisone	oral MMF (day 4) oral tacrolimus (day 60)	Results: Partial resolution ▪ No improvement with MMF alone, normalization after under tacrolimus with successful taper of MMF/tacrolimus/steroid.
Onishi, 2020 (39)	n=1; melanoma	corticosteroids i.v. methylprednisone	oral ursodeoxycholic acid, Bezafibrate	Results: Complete resolution ▪ Normalization of LFT sustained after steroid taper ▪ No ICI re-challenge
Miller, 2020 (40)	n=3 with sr-hepatitis (100 with hepatitis); diagnosis not reported	corticosteroids	oral MMF (2xday29, 1x day15)	Results: Complete resolution ▪ Decline of ALT to grade 1 or lower after 10-20 days
Romanski**,** 2020 (41)	n=2 with sr-hepatitis (43 with hepatitis); melanoma, Not reported	corticosteroids	oral MMF (1x day15, 1x day61)	Results: Complete resolution ▪ Relapse-free normalization
Ruini**,** 2021 (42)	n=1; melanoma	corticosteroids i.v. methylprednisone	oral MMF and ursodeoxycholic acid, tacrolimus, sirolimus	Results: no response ▪ Failure of all immunosuppressants, slow improvement over 2 years under sirolimus to grade 1 ▪ No ICI re-challenge
Au, 2021 (43)	n=1; melanoma	corticosteroids i.v. methylprednisone	oral MMF and budenoside	Results: Complete resolution ▪ LFT return to normal, complete taper of steroids and MMF
Luo, 2021 (31)	n=6 with sr-hepatitis (51 with sr-irAE) lung cancer	corticosteroids	oral MMF	Results: ▪ 5/6 improvement and survival >10 months ▪ 1/6 died ▪ 1/6 successful ICI re-challenge
Ueno, 2022 (44)	n=2; lung cancer	corticosteroids prednisolone	oral MMF	Results: Complete resolution ▪ Normalization of LFT after 3-5 weeks ▪ No ICI re-challenge
Patrinely, 2021 (25)	n=37 with sr-hepatitis (164 with hepatitis), 83% melanoma	corticosteroids	oral MMF (n=31), MMF + tacrolimus (n=3); MMF + tacrolimus + IVIG (n=1), MMF + abatacept (n=1), infliximab (n=1)	Results: Not provided

Table 6: Summary of eligible studies on immune checkpoint inhibitors-induced steroid-resistant colitis
n = 26 studies

First author Year	Number of patients, diagnosis	Initial treatment	Additional treatment	Response to treatment
Verschuren, 2016 (71)	n=12 with sr colitis (27 with colitis); melanoma (n=11), prostate cancer (n=16)	corticosteroids budenoside, hydrocortisone, oral or i.v. prednisone daily	infliximab i.v. (5mg/kg) 1 infusion (n=7), 2 infusions (n=4), 3 infusions (n=1)	Results: Complete resolution ▪ 100% (n=12) of patients with complete clinical resolution after 1-3 infusions
Johnston, 2009 (72)	n=5; melanoma	corticosteroids oral prednisone	infliximab i.v. (5mg/kg) 1 infusion (n=4) 2 infusions (n=1)	Results: Complete resolution ▪ 80% (n=4) of patients with complete clinical resolution within 2-3 days after 1 infusion ▪ 20% (n=1) of patients with recurrence of symptoms within 3 weeks after 1 infusion; complete clinical resolution after a total of 2 infusions
Marthey, 2016 (73)	n=12 with sr colitis (29 with colitis); melanoma (n=35), prostate carcinoma (n=2), NSCLC (n=2)	corticosteroids prednisolone [application N/A]	infliximab i.v.	Results: ▪ 83% (n=10) of patients with clinical resolution ▪ 17% (n=2) of patients with no sufficient response and emergency colectomy in severe relapse
Beck, 2006 (74)	n=4; melanoma	corticosteroids i.v. dexamethasone, followed by tapering	infliximab i.v (5mg/kg) 1 infusion (n=4)	Results: Complete Resolution ▪ 100% (n=4) of patients with complete clinical resolution within median 2 days (1-3 days) after 1 infusion
Pagès, 2013 (59)	n=1; melanoma	corticosteroids i.v. methylprednisolone, followed by oral prednisone and i.v. methylprednisone in relapse	infliximab i.v. (5mg/kg) 1 infusion (n=1)	Results: Complete Resolution ▪ 100% (n=1) of patients with complete clinical within 2 days and complete endoscopic resolution on day 7 after 1 infusion
Jain, 2017 (54)	n=9; melanoma	corticosteroids prednisone (dose equivalent) [application N/A]	infliximab i.v. (5mg/kg) 1 infusion (n=8) 2 infusions (n=1)	Results: Complete Resolution ▪ 89% (n=8) of patients with improvement of gastrointestinal symptoms within 1-2 weeks after 1 infusion ▪ 11% (n=1) of patients with improvement of gastrointestinal symptoms after 2 infusions and within 9 weeks after first dose of infliximab
Horvat, 2015 (20)	n=29; melanoma	corticosteroids prednisone (dose equivalent) [application N/A]	infliximab i.v. (5mg/kg)	Results: ▪ 72% (n=21) of patients with clinical response after 1-2 infusions ▪ 27% (n=8) with no response and use of prolonged courses of corticosteroids

Cheng, 2015 (63)	n=1 melanoma	corticosteroids oral prednisone (1mg/kg), escalation to i.v. methylprednisolone (2mg/kg twice daily)	infliximab i.v. (5mg/kg)	Results: Complete resolution ▪ 100% (n=1) of patients with rapid clinical response
Nassri, 2019 (64)	n=1; renal cell carcinoma	corticosteroids high-dose i.v. corticosteroids	infliximab i.v. (5mg/kg)	Results: Complete response ▪ 100% (n=1) of patients with complete response (clinical)
Connolly, 2020 (65)	n=1; melanoma	corticosteroids i.v. hydrocortisonse	infliximab i.v. (3 infusions)	Results: ▪ 100% (n=1) of patients with response (clinical)
Bergqvist, 2017 (75)	n=7; melanoma (n=6), NSCLC (n=1)	corticosteroids i.v. methylprednisolone (n=1 with infliximab before)	vedolizumab i.v. (300mg i.v. on 0, 2, 6 weeks or until clinical and laboratory regression) 2-4 infusions	Results: ▪ 86% (n=6) of patients with steroid-free remission after median of 56 days (range 52-92 days) ▪ Decrease in plasma CRP and fecal calprotectin after infusion normalisation of neutrophile/lymphocytes
Hsieh, 2016 (60)	n=1; melanoma	corticosteroids oral prednisolone daily, high dose prednisone, oral budesonide	vedolizumab i.v. (300mg i.v. on 0, 2 and 6 weeks) 3 infusions	Results: Complete resolution ▪ 100% (n=1) of patients with complete clinical resolution and decrease in fecal calprotectin after 3 infusions ▪ Decrease in histological findings: moderate mucosal inflammation without ulceration, moderate active colitis after 2 infusions
Klemm, 2021 (66)	n=1; melanoma	corticosteroids oral prednisone	infliximab i.v. (3 infusions) vedolizumab i.v. (2 infusions)	Results: Complete resolution ▪ no response to infliximab ▪ 100% (n=1) of patients with complete response (clinical, endoscopic)
Dahl, 2022 (82)	n=140; melanoma (n=117), NSCLC (n=11), renal cancer (n=6), other (n=6)	corticosteroids	infliximab i.v. (5mg/kg in 77% [n=106] of patients, 10mg/kg in 23% [n=32] of patients) On average: 2 infusions (range 1-9), 14 days apart vedolizumab i.v. (insufficient response to infliximab (n=13) On average: 3 infusions (range 1-5),	Results: ▪ 73% (n=101) of patients with complete response ▪ 17% (n=24) of patients with partial response ▪ 10% (n=14) of patients with no response ▪ Median time to response after infusion 3 days (2-4 days) ▪ 2nd line vedolizumab: 54% (n=7) of patients with complete response; 23% (n=3) with partial response and 23% (n=3) with no response

Abu-Sbeih, 2019 (84)	n=84; melanoma (n=40), genitourinary cancer (n=28), thoracic, head or neck cancers (n=11), others (n=5)	corticosteroids oral or i.v. prednisone daily (depending on grade)	infliximab i.v. (n=46), vedolizumab i.v. (n=32) infliximab i.v and vedolizumab i.v. combined (n=6) median 3 infusions	Results: ▪ SIT effective ▪ Early introduction of SIT (≤ 10 days) (regardless of steroid responsiveness) associated with fewer hospitalizations, fewer steroid taper failure, fewer steroid tapering attempts, shorter course of steroid treatment, shorter duration of symptoms compared to SIT > 10 days ▪ 1-2 infusions of SIT associated with less frequently histological remission, higher fecal calprotectin levels after SI compared to ≥ 3 infusions ▪ recurrence in: -infliximab mono: 26% (n=12/46) -infliximab followed by vedolizumab: 75% (n=3/4) -vedolizumab mono: 3% (n=1/32) -vedolizumab, followed by infliximab: 0% (0/2) ▪ Recurrence rate higher in infliximab than vedolizumab
Abu-Sbeih, 2018 (77)	n=28; melanoma (n=7), renal cell carcinoma (n=4), prostate carcinoma (n=4), urothelial cancer (n=3), other solid tumors (n=10)	corticosteroids i.v. methylprednisolone, followed by oral prednisolon (median duration 96 days)	infliximab i.v. (n=9) median 2 infusions (range 1-3) vedolizumab i.v. (300mg) median 3 infusions (range 1-4)	Results: ▪ no improvement with infliximab (persistent or recurrent diarrhoe after 1 months of infliximab) (n=9) ▪ 86% (n=24) of patients with sustained clinical remission within 5 days after 1-3 infusions (range 1-30 days) ▪ 54% (n=7) of patients with endoscopic remission with initially abnormal endoscopic findings (n=13) ▪ 29% (n=5) of patients with histologic remission ▪ Prior treatment with infliximab is associated with lower clinical success than no prior treatment with infliximab
Lord, 2010 (78)	n=4 with sr colitis (9 with colitis); melanoma (n=6), prostate cancer (n=3)	corticosteroids oral budenoside, prednisone or i.v. methylprednisolone	infliximab i.v. (5mg/kg) 1 infusion (n=1) infliximab (1 infusion) and oral tacrolimus (n=1) infliximab i.v. (3 infusions), tacrolimus p.os and rapamycin p.os (n=1) tacrolimus p.os (n=1)	Results: ▪ 50% (n=2: infliximab or oral tacrolimus) with clinical resolution ▪ 50% (n=2: combination SIT) with improvement but relapse off therapy or persistent symptoms

Iyoda, 2018 (61)	n=1; NSCLC	corticosteroids i.v. dexamethasone, methylprednisolone for 16 days, followed by oral prednisolone	infliximab i.v. (5mg/kg) 2 infusions; first infusion 39th day after onset of diarrhoe cyclosporine p.os (50mg daily) 57th day after onset of diarrhoe infliximab i.v. (5mg/kg) 1 infusion 71th day after onset of diarrhoe	Results: Complete resolution ▪ no improvement with infliximab alone (diarrhoe grade 2-3) ▪ 100% (n=1) of patients with complete resolution with additional cyclosporine
Zhang, 2021 (79)	n=11; melanoma	corticosteroids dosage depending on severity	infliximab i.v. median time 22 days (+/- 55.07) after onset of diarrhoe calcineurin inhibitors p.os (cyclosporine or tacrolimus) median time 70 days (+/- 66.06 days) after onset of diarrhoe cyclosporine p.os: (5mg/kg in split twice-daily dosing, levels in blood: 100-200ng/ml 48h after first dose), i.v. cyclosporine (2mg/kg over 24h, switch to oral after 48h if response)	Results: ▪ no improvement with infliximab alone ▪ 72.7% (n=8) patients with response to calcineurin inhibitors
Thomas, 2021 (80)	n=2; melanoma	corticosteroids	vedolizumab i.v. 6 infusions (n=1) 11 infusions (n=1) ustekinumab initial i.v., followed by s.c. application and maintenance treatment	Results: Complete resolution ▪ no persistent response with vedolizumab alone (n=1 with no re-exposure to ICI, n=1 with re-exposure to ICI) ▪ 100% (n=2) of patients with complete resolution after application of ustekinumab (clinical, endoscopic, histologic) for 4 and 6 months, respectively
Perez, 2022 (67)	n=1; thyroid cancer	corticosteroids i.v. methlyprednisolone (1-2mg/kg daily)	infliximab i.v. (5mg/kg, 3 infusions) vedolizumab i.v. (induction dosing, maintenance every 8 weeks, increased every 4 weeks) fecal microbiota transplantation (FMT) ustekinumab i.v., followed by s.c. applications	Results: Complete resolution ▪ no response to infliximab and vedolizumab ▪ no response to FMT ▪ 100% (n=1) of patients with complete response to ustekinumab (clinical, laboratory, histological)

Esfahani, 2020 (62)	n=1; gastric cancer	corticosteroids high-dose corticosteroids	infliximab i.v. (5mg/kg, 10mg/kg) 2 infusions vedolizumab i.v (300mg, additional doses at 2 and 6 weeks later) tofacitinib p.os (10mg oral twice daily)	Results: Complete resolution ▪ no (persistent) response to infliximab and vedolizumab ▪ 100% (n=1) of patients with complete resolution with tofacitinib within 5 days
Zellweger, 2022 (68)	n=1; NSCLC	corticosteroids	infliximab i.v. (5mg/kg, 3 infusions) vedolizumab i.v. (300mg i.v., induction treatment 0, 2, 6 weeks, followed by 8 weeks administration) infliximab i.v. (5mg/kg, 1 infusion) tofacitinib p.os (2x10mg daily, followed by maintenance with 2x5mg)	Results: Complete resolution ▪ no (persistent) response to infliximab and vedolizumab ▪ 100% (n=1) of patients with complete resolution with tofacitinib
Bishu, 2021 (83)	n=4; melanoma (n=3), NSCLC (n=1)	corticosteroids p.os prednisone	infliximab i.v. (4-5 infusions) (n=3) vedolizumab i.v. (8 infusions) (n=1, after infliximab) ustekinumab i.v. (1 infusion) (n=1, after infliximab and vedolizumab) tofacitinib p.os (n=34) (2x10mg daily)	Results: Complete resolution ▪ no (persistent) response to infliximab ▪ no (persistent) response to infliximab, followed by vedolizumab and ustekinumab ▪ 100% (n=4) of patients with complete resolution with tofacitinib (clinical, endoscopic, laboratory)
Sasson, 2021 (70)	n=1, NSCLC	corticosteroids i.v. corticosteroids	infliximab i.v. (2 infusions) tofacitinib p.os (2x10mg daily)	Results: Complete resolution ▪ no (persistent) response to infliximab ▪ 100% (n=1) of patients with complete resolution with tofacitinib (clinical, endoscopic)
Wang, 2018 (81)	n=2; urothelial cancer (n=1), prostate cancer (n=1)	corticosteroids i.v. corticosteroids	infliximab i.v. (2 infusions), vedolizumab i.v. (1 infusion) (n=1) infliximab i.v. (2 infusions), vedolizumab i.v. (3 infusions) (n=1) fecal microbiota transplantation (n=2)	Results: Complete resolution ▪ no response to infliximab and/or vedolizumab ▪ 100% (n=2) of patients with complete clinical and histological resolution with fecal microbiota transplantation (1 fecal microbiota transplantation in n=1, 2 transplantations in n=1)

Apostolova, 2020 (69)	n=1; melanoma	corticosteroids i.v. corticosteroids	infliximab i.v. (2 infusions) cyclosporine p.os extracorporeal photopheresis	Results: Complete resolution ▪ no persistent response to infliximab and cyclosporine ▪ Complete resolution (clinical, endoscopic) with extracorporeal photopheresis

Table 7: Summary of eligible studies on immune checkpoint inhibitor-induced steroid-resistant pneumonitis
n = 17 studies

First author Year	Number of patients, diagnosis	Initial treatment	Additional treatment	Response to treatment
Naidoo, 2017 (14)	n=5 (43 with pneumonitis), different cancer types (58% melanoma, 23% NSCLC)	corticosteroids	i.v. Infliximab (n=3) i.v. infliximab and cyclophosphamide (n=2)	Results: ▪ all 5 patients died; 1 from pneumonitis, 3 from immunosuppression-associated infection and 1 from cancer progression
Luo, 2021 (31)	n=10; lung cancer	corticosteroids	i.v. infliximab (n=7) oral MMF (n=1) i.v. infliximab and oral MMF (n=2)	Results: ▪ 3/10 (improvement 90 days>infliximab), ▪ 0 ICI re-challenge
Petri, 2019 (97)	n=1; NSCLC	corticosteroids antibiotics	i.v. IVIG (2g/kg day 1-5)	Results: Partial resolution ▪ Near full resolution after 6 weeks, no re-challenge
Cooksley, 2019 (99)	n=1; melanoma	corticosteroids, antibiotics	i.v. infliximab and oral MMF	Results: Partial resolution ▪ Significant radiological and clinical improvement after 1 week
Sawai, 2019 (100)	n=1; NSCLC	corticosteroids, antibiotics mechanical ventilation	i.v. infliximab	Results: no response ▪ Temporary respiratory improvement, deterioration after 14 days during steroid taper, death

Nishino, 2016 (92)	n=3; melanoma (n=2), NSCLC (n=1)	corticosteroids ICU admission (n=2) intubation (n=1)	i.v. infliximab	Results: ▪ 1 death, 1 improvement but referral for palliative care, 1 longterm remission, no re-challenge
Andruska, 2018 (101)	n=2; NSCLC	corticosteroids antibiotics (1) intubation (1)	i.v. infliximab (n=1) Best supportive care (n=1)	Results: no response ▪ 1 death ▪ 1 temporary improvement (death after 1 months from cancer progression)
Balaji, 2021 (91)	n=12; NSCLC (n=9), 1 SCLC (n=1), renal cancer (n=1), oropharyngeal cancer (n=1),	corticosteroids ICU (11) intubation (3)	i.v.IVIG (n=7) i.v. infliximab (n=2) i.v. IVIG and infliximab (n=3)	Results: ▪ 2 improved after IVIG ▪ 2 stabilized after IVIG ▪ 8 died from ICI-pneumonitis or treatment complications, including all who have received infliximab
Beattie, 2021 (96)	n=26; NSCLC (n=8) renal cancer (n=4); melanoma (n=4), other cancer types (n=10)	corticosteroids	i.v. infliximab (n=19) i.v. adalimumab (n=1) oral MMF (n=6) 2nd line: oral MMF (n=3) i.v. cyclophosphamide (n=1) i.v. infliximab (n=1)	Results: ▪ 10 Durable improvement (5>MMF, 5>infliximab) ▪ 13 transient improvements ▪ 3 no improvement ▪ 6 deaths from pneumonitis ▪ 3 deaths from infection
Camard, 2022 (95)	n=6; diagnosis not specified	corticosteroids	i.v. cyclophosphamide (n=4) i.v. infliximab (n=1) i.v. IVIG (n=1)	Results: ▪ 4 died ▪ 2 alive at 5 months (> cyclophosphamide)
Chen, 2022 (102)	n=1; SCLC	corticosteroids IVIG	i.v. infliximab	Results: Complete resolution ▪ Normalized oxygenation, discharge from hospital
Huang, 2022 (103)	n=1; NSCLC	corticosteroids	i.v. infliximab	Results: Complete resolution ▪ Normalized oxygenation, discharge from hospital. ▪ Symptom-free at 8 months. ▪ No re-challenge
Ortega, 2018 (104)	n=1; melanoma	corticosteroids antibiotics MMF	I i.v. infliximab	Results: Complete resolution ▪ Enduring remission

Utsumi, 2020 (105)	n=1; NSCLC	corticosteroids ICU	oral tacrolimus and cyclophosphamide	Results: Complete resolution ▪ Normalization
Ueno, 2021 (44)	n=1; head and neck cancer	corticosteroids antibiotics	i.v. infliximab	Results: no response ▪ transient improvement. death within 4 months
Xie, 2021 (106)	n=1; NSCLC,	corticosteroids	Oral nintedanib	Results: Partial response ▪ Marked improvement. death from cancer progression 2 months later
Stroud, 2019 (98)	n=12 (34 with any steroid-resistant irAE); diagnosis not specified	corticosteroids	i.v. tocilizumab	Results: ▪ Clinical improvement in 79% of all 34 patients

Table 8: Summary of eligible studies on immune checkpoint inhibitors-induced steroid-resistant myocarditis
n = 16 studies

First author Year	Number of patients, diagnosis	Initial treatment	Additional treatment	Response to treatment
Salem, 2019 (115)	n=1; lung cancer	corticosteroids i.v. methylprednisolone for 3 days, followed by i.v. prednisone and oral tapering *combined with* plasmapheresis (day 7-11)	abatacept i.v. (500mg i.v., every 2 weeks) 5 infusions	Results: Complete resolution ▪ 100% (n=1) of patients with clinical resolution and normalisation of ventricular hyperexcitability after 5 infusions
Jespersen, 2021 (116)	n=1; renal cancer	corticosteroids i.v. methylprednisolone	abatacept i.v. (500mg i.v., every 2 weeks), 5 infusions *combined with* MMF p.os (1g twice a day for 3 months) start on day 17 after admission	Results: Partial resolution ▪ 100% (n=1) of patients with clinical improvements but persistent transthoracic echocardiography abnormalities

Kalapurackal, 2021 (117)	n=1; melanoma	corticosteroids i.v. methylprednisolone *combined with* MMF (2x1g peroral)	abatacept (200mg i.v.)	Results: Complete resolution ▪ 100% (n=1) of patients with clinical, laboratory and echocardiographic improvements
Salem 2023 (130)	n=30; lung cancer (n=9), skin (n=9), genitourinary (n=10), others (n=12)	corticosteroids i.v. high-dose corticosteroids	abatacept i.v. ruxolitinib oral	Results: improvement ▪ Decrease in mortality (3.4% versus 60% in first quartile)
Esfahani, 2019 (118)	n=1; melanoma	corticosteroids i.v. methylprednisolone *combined with* plasmapheresis for 5 days *combined with* i.v. rituximab weekly (375 mg/m^2) *combined with* MMF (1g twice daily)	alemtuzumab i.v. (30mg i.v.) 1 infusion	Results: Complete resolution ▪ 100% (n=1) of patients with clinical complete remission (no cardiac adverse event including arrhythmias)
Saibil, 2019 (119)	n=1; melanoma	corticosteroids i.v. methylprednisolone	infliximab i.v. (5mg/kg i.v.) 1 infusion *combined with* IVIG (2 infusions)	Results: No response ▪ No improvements of symptoms (leading to death)
Zhang, 2021 (128)	n=4; melanoma (n=2), renal cell carcinoma (n=1), ovarian adenocarcinoma (n=1)	high-dose corticosteroids	infliximab i.v. (5mg/kg i.v.) 1 infusion	Results: ▪ 50% (n=2) with complete of steroid taper (n=2 death due to septic shock)
Arangalage, 2017 (120)	n=1; melanoma	corticosteroids i.v. methylprednisolone *combined with* IVIG	plasmapheresis for 3 days tacrolimus p.os (target blood level 10-15ng/ml)	Results: Complete resolution ▪ 100% (n=1) of patients with clinical resolution and normalisation of left ventricular ejection fraction
Compton, 2021 (121)	n=1; renal cell carcinoma	corticosteroids i.v. methylprednisolone for 3 days, followed by oral tapering	abatacept i.v. (5 infusions) plasmapheresis 5 cylces MMF p.os (100mg twice daily)	Results: Partial resolution ▪ 100% (n=1) of patients with clinical, laboratory and echocardiographic improvements
Schiopu, 2021 (122)	n=1; mesothelioma	corticosteroids i.v. methylprednisolone (100mg/day)	plasmapheresis 10 cycles	Results: Partial resolution ▪ 100% (n=1) of patients with clinical, laboratory and echocardiographic improvements
Tay, 2017 (123)	n=1; glioblastoma	corticosteroids i.v. methylprednisolone for 3 days, followed by oral tapering *combined with* i.v. 5mg/kg infliximab (on day 2) 1 infusion	ATG therapy ATG 500 mg on day 1, titrating the dose by 250 mg increments to daily CD2/3 levels (aiming for levels of 50–100/ml) for a total of 5 days MMF (1 gm twice daily	Results: Complete resolution ▪ 100% (n=1) of patients with clinical and biochemical improvement within 3 days of ATGAM therapy ▪ Second biopsy (day 10) with pathologic improvement and third biopsy (6 weeks after

			on day 5 of ATG therapy, continued for 4 weeks and weened over 12 week-period)	presentation) with signs of early repair
Jain, 2018 (124)	n=1; melanoma	corticosteroids i.v. methylprednisolone (2x500mg i.v.)	ATG therapy ATG 1.5mg/kg, subsequent daily doses from 0.5-1.5mg/kg (CD3 count adjustment), 6x	Results: Partial resolution ▪ 100% (n=1) of patients with clinical and echocardiographic improvements
Baclig, 2019 (125)	n=1; gastro-esophageal junction adeno-carcinoma	corticosteroids i.v. methylprednisolone	ATG therapy ATG 500 mg on day 1, titrating the dose by 250 mg for a total of 5 days MMF (1 gm twice daily on day 3 of ATG)	Results: No response ▪ 100% (n=1) of patients with development of diastolic heart failure, persistent elevated laboratory findings, death due to heart failure
Xing, 2022 (126)	n=1; nasopharyngeal carcinoma	corticosteroids i.v. methylprednisolone (4mg/kg)	IVIG. (0.4kg/kg for 5 days) tofacitinib (5mg twice daily for 1 weeks)	Results: Complete resolution ▪ 100% (n=1) of patients with clinical and biochemical resolution after administration of tofacitinib
Wang, 2021 (129)	n=16; different carcinoma (most common: hepatic, gastric, colon)	corticosteroids i.v. methylprednisolone	Infliximab i.v. (600mg i.v.) (n=1) tofacitinib p.os (5mg twice daily) (n=2) tofacitinib (5mg twice daily) in combination with IVIG (n=9) IVIG i.v (n=2)	Results: ▪ 64% (n=7) of patients with recovery after administration of tofacitinib (+/- IVIG) ▪ IVIG (n=2) with improvement in symptoms ▪ Infliximab (n=1) no success (death from myocarditis progression)
Doms, 2020 (127)	n=1; lung cancer	corticosteroids i.v. methylprednisolone	tocilizumab i.v. (8mg/KG i.v. weekly for 2 infusions)	Results: Complete resolution ▪ 100% (n=1) of patients with laboratory and clinical improvement

Supplementary Table A: Search terms/Search algorithms for pubmed search regarding steroid-resistant immune-related adverse events	
Search algorithm for steroid-resistant immune-related colitis	((steroid[Title/Abstract]) AND ((immunotherapy[Title/Abstract]) OR (checkpoint[Title/Abstract])) AND ((colon[Title/Abstract]) OR (gastrointestinal[Title/Abstract]) OR (enterocolitis[Title/Abstract]) OR (diarrhoe[Title/Abstract]) (colitis[Title/Abstract])))
Search algorithm for steroid-resistant immune-related hepatitis	((steroid[Title/Abstract]) AND ((immunotherapy[Title/Abstract]) OR (checkpoint[Title/Abstract])) AND ((liver[Title/Abstract]) OR (hepatotoxicity[Title/Abstract]) OR (hepatitis[Title/Abstract])))
Search algorithm for steroid-resistant immune-related pneumonitis	((steroid[Title/Abstract]) AND ((immunotherapy[Title/Abstract]) OR (checkpoint[Title/Abstract])) AND ((lung[Title/Abstract]) OR (pulmonary[Title/Abstract]) OR (pneumonitis[Title/Abstract])))
Search algorithm for steroid-resistant immune-related myocarditis	((steroid[Title/Abstract]) AND ((immunotherapy[Title/Abstract]) OR (checkpoint[Title/Abstract])) AND ((heart[Title/Abstract]) OR (cardiovascular[Title/Abstract]) OR (myocarditis[Title/Abstract])))