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Infliximab for Immune Checkpoint Inhibitor Therapy-Related Toxicities

Rapid Review

Key Messages

What Is the Issue?

- Immune checkpoint inhibitor (ICI) therapy has become a treatment option for various types of advanced cancer, resulting in significant improvement in disease outcomes.
- However, ICIs can overstimulate the immune system leading to various side effects known as immune-related adverse events (irAEs) that can occur in any organ system.
- Administration of corticosteroids is the initial mainstay treatment of irAEs. However, there is little evidence of how to treat steroid-resistant irAEs. Treatment of steroid-resistant irAEs includes holding ICI and starting immunosuppressive therapy.
- Decision-makers are interested in understanding the use of infliximab, a selective immunosuppressive drug, for the treatment of steroid-resistant irAEs affecting various organs.

What Did We Do?

- We identified and summarized the literature regarding the efficacy and safety of infliximab for the treatment of steroid-resistant irAEs. Due to the limitation of evidence, we included studies of any design, including case reports and case series.
- A research information specialist conducted a literature search of peer-reviewed and grey literature sources published between January 1, 2019 and April 8, 2024. One reviewer screened citations for inclusion based on predefined criteria, critically appraised the included studies, and narratively summarized the findings.

What Did We Find?

- The evidence presented in this report was based on 2 systematic reviews (SRs) of case reports and case series, 1 retrospective cohort study, and 40 additional publications consisting of 29 case reports and 11 case series.
- We identified 4 main irAEs, which were colitis, hepatitis, pneumonitis, and myocarditis.
- Very low-quality evidence, which was mainly derived from case reports and case series, suggests that infliximab may be effective for the treatment of steroid-resistant immune-induced colitis, while there are concerns regarding its use for the treatment of hepatitis due to potential hepatotoxicity and infectious complications. There is mixed evidence

Key Messages

regarding the use of infliximab for the treatment of immune-induced pneumonitis and myocarditis.

- Recent consensus guidelines recommend the use of infliximab as first-line treatment for steroid-resistant immune-induced colitis, while its use for hepatitis is not recommended due to potential hepatotoxicity and infectious complications. The use of infliximab for the treatment of pneumonitis is an option, while its use for myocarditis remains to be determined.
- The usual dose of infliximab was 5 mg/kg, administered by IV. A higher dose of 10 mg/kg was seen in some cases. The number of infusions, the period between infusions and the length of treatment varied depending on the responsiveness of infliximab and the type and severity of irAEs.
- Treatment with infliximab as compared with vedolizumab resulted in comparable immune-induced colitis response rates, higher recurrent rate of colitis, and more hospitalizations despite a shorter time to clinical response.

What Does This Mean?

- The very low-quality evidence identified suggests the potential benefits of infliximab in the management of immune-induced colitis due to its efficacy and fast response.
- When using the clinical evidence and recommendations summarized in this report to inform decisions, decision-makers should consider that the evidence is of very low quality, mainly derived from case reports and case series.
- Large prospective and comparative studies are needed to verify the findings and to determine the role of infliximab in the treatment of other irAEs.

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Abbreviations

ASCO	American Society of Clinical Oncology
CTLA-4	cytotoxic T-lymphocyte antigen 4
ESMO	European Society for Medical Oncology
ICI	immune checkpoint inhibitor
irAE	immune-related adverse event
NCCN	National Comprehensive Cancer Network
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
SITC	Society for Immunotherapy of Cancer
SR	systematic review

Context and Policy Issues

What Are ICIs and Their Related Adverse Events?

ICIs are monoclonal antibodies against the immune checkpoint receptors on T-cells such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed-death ligand 1 (PD-L1).[1] Cancer cells can evade destruction from the immune system by triggering the expression of those proteins, whose role is to inhibit T-cell function.[1] By blocking those receptors, ICIs reactivate T-cell mediated immune response against tumour cells and destroy them.[1] ICI therapy has improved overall survival and delayed progression in some advanced cancers with poor prognosis and limited treatment options.[2]

Seven ICIs have been approved by Health Canada for immune therapy of various cancer types.[1] These are anti-CTLA-4 (ipilimumab), anti-PD-1 (pembrolizumab, nivolumab, cemiplimab), and anti-PD-L1 (atezolizumab, avelumab, durvalumab).[1] The reactivation of the immune response from monotherapy or combination therapy of those ICIs can result in the occurrence of irAEs that can target virtually any organ system.[3,4] Gastrointestinal, endocrine and dermatological toxicities are common side effects, while cardiotoxicity and pulmonary toxicities are relatively rare but can be deadly.[4] The incidence of irAEs of any grade varies according to the immune checkpoint target, ranging from 66% to 75% for PD-L1 inhibitors and 87% for CTLA-4 inhibitors.[5] Toxicities of various organs can vary from mild to severe, and, according to the Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE, v.5), the European Society for Medical Oncology (ESMO) guideline, and the American Society of Clinical Oncology (ASCO) guideline, the symptoms vary from asymptomatic or mild symptoms (grade 1) to life-threatening consequences (grade 4),[3,4] and grade 5 is death.

What Is the Current Practice?

In general, current management algorithms for irAEs of different organs[3] can be summarized as follows:

- For grade 1 irAEs, ICI therapy should be maintained with close monitoring of symptoms and affected organs.
- For grade 2 irAEs, ICI therapy should be held, and oral prednisone should be started.
- For grade 3 irAEs, ICI therapy should be held, and higher doses of systemic corticosteroids should be started.
- When irAEs resolved to grade 1, corticosteroids should be tapered for at least 2 to 4 weeks, depending on the dose.
- If irAEs do not improve with corticosteroids, other immunosuppressant drugs may be considered.
- ICI therapy can be resumed when irAEs have improved to grade 1.
- For most grade 4 irAEs, ICI therapy should be discontinued.

What Is Infliximab?

Infliximab is an anti–tumour necrosis factor-alpha monoclonal antibody that has been shown to be highly effective in the treatment of Crohn disease and ulcerative colitis.[6] It has also been indicated for the treatment of other inflammatory diseases, including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and chronic severe plaque psoriasis.[6] Several consensus guidelines[7-10] recommend infliximab for the treatment of immune-induced colitis in corticosteroid nonresponder patients or patients with recurrent symptoms during the steroid tapering period. The doses and schedules are adapted from the treatment of Crohn disease and ulcerative colitis (i.e., 5 mg/kg; 1 infusion or more separated by 2 to 4 weeks; 10 mg/kg may be considered in patients who do not have complete response with lower dose).[6,11] However, the choice of treatment regimens is usually based on a case-by-case approach.[11] Additional immunosuppressive treatment options for irAEs are vedolizumab, mycophenolate mofetil, calcineurin inhibitors (tacrolimus and cyclosporin), tocilizumab, cyclophosphamide, immunoglobulin, abatacept, alemtuzumab, and antithymocyte globulin.[7-9]

Why Is It Important to Do This Review?

The efficacy and safety of infliximab for patients with various irAEs who do not respond to corticosteroids have not been established. Due to the paucity of evidence, recommendations on the use of infliximab for irAEs are not well-defined.

Objective

To support decision-making about the role of infliximab for immune checkpoint-related toxicities, we prepared this Rapid Review to summarize and critically appraise the available studies on the clinical efficacy and safety of infliximab treatment for irAEs in any organ system.

Research Questions

1. Is there evidence to support the use of infliximab in
    - grades 1 or 2 gastrointestinal toxicity in patients who have failed to respond to steroid therapy (IV or oral) defined as lack of clinical improvement or the need to re-escalate steroid dosing in situations where a tapering schedule had been prescribed?
    - nongastrointestinal immunotherapy-induced toxicity?
2. Infliximab for immunotherapy-induced gastrointestinal or other organ toxicities is an off-label use. What is the usual dosage used (i.e., specific amount, number, and frequency of doses over a specific period of time)?

Methods

Literature Search Methods

An information specialist conducted a literature search on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were infliximab and immune checkpoint inhibitors. No filters were applied to limit the retrieval by study type. Comments, newspaper articles, editorials, and conference abstracts were excluded. Retrieval was limited to the human population. The search was completed on April 8, 2024, and was limited to English-language documents published since January 1, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed, and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Criteria	Description
Population	• Individuals receiving Immune checkpoint inhibitors. • Individuals receiving Immune checkpoint inhibitors who present with gastrointestinal toxicities attributable to immunotherapy and have failed to respond to steroid therapy (IV or oral) defined as a lack of clinical improvement or the need to re-escalate steroid dosing in situations where a tapering schedule had been prescribed. • Individuals receiving Immune checkpoint inhibitors who present with any organ toxicities that are considered attributable to immunotherapy. • Adults • Pediatrics
Intervention	• Infliximab for immunotherapy-induced gastrointestinal toxicities (grades 1 or 2). • Infliximab for immunotherapy-induced gastrointestinal adverse effects (grades 3 or 4). • Infliximab for immunotherapy-induced nongastrointestinal organ toxicity (any grade).
Comparator	Comparative drugs to infliximab for immunotherapy-induced gastrointestinal toxicity as well as non-gastrointestinal organ toxicity, including: • adalimumab, etanercept and golimumab (TNF-alpha mediated) • canakinumab, anakinra, tocilizumab, natalizumab, vedolizumab, ustekinumab, secukinumab, rituximab • nonselective immunosuppressives: azathioprine, mycophenolate mofetil, disease-modifying antirheumatic drug (e.g., methotrexate), cyclophosphamide, cyclosporine, IVIg, abatacept, antithymocyte globulin, alemtuzumab thalidomide, plasmapheresis

Criteria	Description
	• corticosteroids • no comparator.
Outcomes	Efficacy, harms and safety; related patient outcomes and quality of life; reduction of irAEs, reduction of symptoms and harms of irAEs, symptom relief; clinical utility (e.g., time to symptom relief, morbidity, mortality, quality of life); severity of gastrointestinal toxicities, severity of other organ toxicities; time to resolution of toxicity, time to onset of symptom relief, time to objective symptom relief, duration of symptoms/toxicities, time to onset of symptom relief, time to objective symptom relief; reduction in the need for hospital admissions; consequences of delayed therapy; risk factors for treatment delay and related outcomes; harms associated with the use of infliximab, adverse events, harms.
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, nonrandomized studies, evidence-based guidelines

irAEs = immune-related adverse events; TNF = tumour necrosis factor.

Exclusion Criteria

We excluded articles that did not meet the selection criteria outlined in Table 1, or articles published before 2019. We excluded systematic reviews (SRs) in which all relevant studies were captured in other more recent or more comprehensive SRs. We also excluded primary studies retrieved by the search if they were captured in 1 or more included SRs.

Critical Appraisal of Individual Studies

One reviewer critically appraised the included publications using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2) for SRs and the Downs and Black checklist for nonrandomized studies. Summary scores were not calculated for the included studies; rather, each publication's strengths and limitations were described narratively.

Of note, publications in the form of case reports and case series were not critically appraised due to the inherent very low-quality evidence associated with these study designs. Multiple disadvantages associated with case reports and case series include uncontrolled, difficult to cross compare among cases, case may not be generalizable, and selection bias.

Summary of Evidence

Quantity of Research Available

This report includes 2 SRs,[12,13] 1 retrospective cohort study,[14] 29 case reports[15-43] and 11 case series.[44-54] Study selection details are presented in Appendix 1.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Included Studies for Question 1

Is there evidence to support the use of infliximab in:

- grade 1 or 2 gastrointestinal toxicity in patients who have failed to respond to steroid therapy (IV or oral) defined as lack of clinical improvement or the need to re-escalate steroid dosing in situations where a tapering schedule had been prescribed?
- nongastrointestinal immunotherapy-induced toxicity?

We did not identify any studies that focused on the use of infliximab to treat steroid-resistant grade 1 gastrointestinal toxicity. Most of the included studies included patients with grade 2 to 4 irAEs, including colitis and other nongastrointestinal irAEs such as hepatitis, pneumonitis, and myocarditis.

Study Design

The SR by Daetwyler et al. (2024)[12] included 41 publications, all of which were case reports and small case series on the use of various immunosuppressive drugs for treatment of steroid-resistant irAEs. We extracted and presented only studies that involved the efficacy of infliximab therapy in patients with steroid-resistant irAEs, including colitis (n = 24; published between 2006 and 2022), hepatitis (n = 2; published in 2019), pneumonitis (n = 13; published between 2016 and 2022), and myocarditis (n = 2; published in 2019 and 2021). The authors of the SR[12] conducted a systematic literature search in PubMed. The search period was not reported. The authors of the SR[12] narratively summarized the results of the included studies without pooling.

The SR by Nielsen et al. (2022)[13] included 20 publications (all case series), which studied the efficacy of infliximab therapy in patients with steroid-resistant immune-induced colitis. There were 6 overlapped publications between the 2 SRs (Appendix 5).[12,13] The authors of the SR[13] performed a literature search on multiple databases with no restrictions on language or publication date. The authors of the SR[13] performed a meta-analysis on the response rate of infliximab for the treatment of immune-induced colitis.

We identified additional relevant case reports and case series on the treatment efficacy of infliximab in patients with immune-related colitis (n = 30; published between 2019 and 2024), hepatitis (n = 1; published in 2020), pneumonitis (n = 5; published between 2019 and 2023), and myocarditis (n = 4; published between 2019 and 2021).

We also identified a retrospective cohort study by Zou et al. (2021)[14] comparing the efficacy and safety of infliximab and vedolizumab treatment for immune-induced colitis.

Country of Origin

The Daetwyler et al. (2024)[12] SR was conducted by authors from the US, and the Nielsen et al. (2022)[13] SR was conducted by authors from Denmark.

The retrospective cohort study by Zou et al. (2021)[14] was conducted by authors from the US.

The additionally identified case reports and case series were reported by authors in countries worldwide, including Canada, the US, and Europe.

Patient Population

Patients in the relevant studies included in the SRs,[12,13] in the retrospective cohort study,[14] and in all additionally identified case reports and case series were adults with various types of cancer, undergoing ICI treatment. The ICIs were either monotherapy of anti-CTLA-4, anti-PD-1, anti-PD-L1 antibodies, or combination of ICIs or combination of ICIs with other drugs (e.g., chemotherapy or tyrosine kinase inhibitors).

In the retrospective cohort study by Zou et al. (2021),[14] the median age, median length of ICI treatment, and colitis grade were similar in both infliximab and vedolizumab groups. For cancer type, more patients in the infliximab group had melanoma (47% versus 16%; P < 0.001), and fewer patients in the infliximab group used anti-PD-L1 antibody (43% versus 61%; P = 0.041) compared to the vedolizumab group. In contrast, patients in the infliximab group had a longer duration of steroid use (51 days versus 35 days; P < 0.001) and had fewer doses of selective immunosuppressive therapy (2 doses versus 3 doses; P < 0.001).

Interventions and Comparators

Infliximab was the intervention for the treatment of steroid-resistant irAEs in the included SRs and additionally identified case reports and case series. The retrospective cohort study by Zou et al. (2021)[14] compared the efficacy and safety between infliximab and vedolizumab.

Outcomes

The main outcome reported in the included SRs[12,13] was a response to treatment with infliximab in patients with corticosteroid-resistant irAEs. The SR by Daetwyler et al. (2024)[12] investigated 4 main irAEs, such as colitis, hepatitis, pneumonitis, and myocarditis, while the SR by Nielsen et al. (2022)[13] focused only on immune-induced colitis.

The SR by Daetwyler et al. (2024)[12] also reviewed the diagnostic and therapeutic recommendations for corticosteroid-resistant irAEs (i.e., colitis, hepatitis, pneumonitis, and myocarditis) from 4 major guidelines: ESMO, ASCO, Society for Immunotherapy of Cancer (SITC), and the National Comprehensive Cancer Network (NCCN). The recommendations of those guidelines for the use of infliximab in the treatment of corticosteroid-resistant irAEs are summarized and presented in Table 15 of Appendix 4.

The additionally identified case reports[15-43] and case series[44-54] from the literature search in this report reported responses to treatment with infliximab in patients with corticosteroid-resistant irAEs.

The outcomes considered in the retrospective cohort study by Zou et al. (2021)[14] which compared the efficacy and safety of infliximab and vedolizumab for the treatment of immune-induced colitis, were the rate of clinical remission, time to clinical response, recurrence of immune-mediated diarrhea and colitis, duration of hospitalization, number of hospitalizations, and number of patients being hospitalized.

Included Studies for Question 2

Infliximab for immunotherapy-induced gastrointestinal or other organ toxicities is an off-label use. What is the usual dosage used (i.e., specific amount, number, and frequency of doses over a specific period of time)?

To determine the usual dosage of infliximab, dosage information was captured from the included studies, mostly case reports and case series.

Summary of Critical Appraisal

Appendix 3 provides details regarding the strengths and limitations of the included SRs[12,13] (Table 8) and the retrospective cohort study[14] (Table 9).

Systematic Reviews

Both SRs[12,13] were explicit in their objectives, inclusion criteria for the review, and selection of the study designs for inclusion. The literature search strategy was comprehensive and clearly described in the SR by Nielsen et al. (2022),[13] but not in the SR by Daetwyler et al. (2024).[12] Providing details of the literature search strategy increases the reproducibility of the reviews. Unlike the SR by Nielsen et al. (2022),[13] the SR by Daetwyler et al. (2024)[12] did not report whether a study protocol had been established before conducting the review, and whether study selection and data extraction of the included studies were performed in duplicate. Thus, there was an increasing risk of bias in modifying the methods after the review had been conducted and a risk of inconsistencies in these processes in the SR by Daetwyler et al. (2024).[12] Both SRs[12,13] did not adequately describe patient characteristics as most included studies were case reports and case series. Both SRs[12,13] did not provide a list of excluded studies and the reasons for exclusion. No justification for the excluded studies could bias the results of the review. The authors of the SR by Nielsen et al. (2022)[13] conducted a meta-analysis combining the results of the response rate of infliximab treatment but did not provide a discussion of the heterogeneity observed in the results. The authors of both SRs[12,13] reported that they did not receive any funding and declared that they had no conflicts of interest related to their work.

Primary Study

For reporting, the included retrospective cohort study clearly described the study's objective, the main outcomes to be measured, the characteristics of the participants included in the study, the interventions of interest, and the main findings. Actual P values for the main outcomes and the intervention's efficacy and safety outcomes were reported.

For external validity, patient data were obtained from electronic medical charts and pharmacy databases of 2 hospitals, where the staff, places, and facilities were representative of the treatment most of the patients receive. The study population was relatively large (184 patients), which may be representative of the entire population from which they were treated.

For internal validity relating to bias, the risk of selection bias is a main limitation of a retrospective cohort study.

For internal validity relating to confounding, the authors of the study identified some differences in baseline characteristics between treatment groups, but they did not make any adjustments for those confounders in the analyses, thus increasing the risk of confounding bias. Overall, this study had several limitations related to internal validity relating to bias and internal validity relating to confounding that may reduce the certainty of the findings.

Summary of Findings

Appendix 4 presents the findings, which were summarized as:

- Response to infliximab treatment for immune-induced colitis (Table 10).
- Response to infliximab treatment for immune-induced hepatitis (Table 11).
- Response to infliximab treatment for immune-induced pneumonitis (Table 12).
- Response to infliximab treatment for immune-induced myocarditis (Table 13).
- Comparison of clinical efficacy and safety outcomes of infliximab and vedolizumab-treated patients with immune-induced colitis (Table 14).
- Recommendations for the use of infliximab in the treatment of corticosteroid-resistant irAEs (Table 15).

Research Question 1

Most irAEs from the included SRs[12,13] and in the additionally identified publications (i.e., case reports and case series) were corticosteroid-resistant and of grade 2 or higher. It was unclear if any grade 1 irAEs were treated with infliximab.

Response to infliximab treatment for irAEs was classified as complete response, partial response, insufficient response, or no response (including death).

Response to Infliximab Treatment for Immune-Induced Colitis

Table 10 presents the response rates of infliximab treatment for corticosteroid-resistant immune-induced colitis.

We identified 2 SRs[12,13] that included 11 case reports and 27 case series, with 498 patients with colitis. From the literature search of this report, we additionally identified 30 publications comprising 22 case reports and 8 case series, with 192 patients. Thus, the total number of patients in the included SRs and identified primary studies would be 690.

From our analysis, the complete response rates in the SR by Daetwyler et al. (2024),[12] the SR by Nielsen et al. (2022),[13] and among additionally identified studies were 67.5%, 84.4%, and 44.8%, respectively. When the results were pooled together, the complete response rate of infliximab for the treatment of immune-induced colitis was 67.2%. The separate analysis in the SR by Nielsen et al. (2022),[13] showed that infliximab was efficient in 88% of patients.

Response to Infliximab Treatment for Immune-Induced Hepatitis

Table 11 presents the response rates of infliximab treatment for corticosteroid-resistant immune-induced hepatitis.

There was limited evidence on the use of infliximab for the treatment of immune-induced hepatitis. The SR by Daetwyler et al. (2024)[12] identified 2 publications (1 case report and 1 case series) with 22 patients in total. We identified 1 additional case report. Collectively, the complete response rate of infliximab for the treatment of immune-induced hepatitis was 8.7%, with 91.3% partial response.

Response to Infliximab Treatment for Immune-Induced Pneumonitis

Table 12 presents the response rates of infliximab treatment for corticosteroid-resistant immune-induced pneumonitis.

For this condition, the SR by Daetwyler et al. (2024)[12] identified 6 case reports and 7 case series with 56 patients. Additional publications identified in this report included 3 case reports and 2 case series with 18 patients. Combined analysis of the results from the SR and additional studies showed that the complete response rate of infliximab for the treatment of ICI-induced pneumonitis was 28.4%, with 70.2% no response.

Response to Infliximab Treatment for Immune-Induced Myocarditis

Table 13 presents the response rates of infliximab treatment for corticosteroid-resistant immune-induced myocarditis.

There was limited evidence on the use of infliximab for the treatment of immune-induced myocarditis. The SR by Daetwyler et al. (2024)[12] identified 2 publications (1 case report and 1 case series) with 5 patients total. We identified 4 additional studies (3 case reports and 1 case series) with 5 patients total. Overall, the complete response rate of infliximab for the treatment of immune-induced myocarditis was 50%.

Comparison of Clinical Efficacy and Safety Outcomes of Infliximab and Vedolizumab-Treated Patients with Immune-Induced Colitis

Table 14 presents the comparative efficacy and safety outcomes between infliximab and vedolizumab groups.

- **Rate of clinical remission:** The proportion of patients who achieved clinical remission after infliximab or vedolizumab therapy was similar in both groups (88.3% versus 88.7%; P = 0.785).
- **Median time to clinical response:** Patients in the infliximab group had a shorter time to clinical response than those in the vedolizumab group (13 days versus 18 days; P = 0.012).
- **Recurrence of immune-mediated diarrhea and colitis:** Infliximab treatment was associated with higher recurrent rate of immune-mediated diarrhea and colitis as compared with vedolizumab treatment (28.7% versus 12.9%; P = 0.007).
- **Hospitalization:** Treatment with infliximab compared with vedolizumab resulted in a greater number of hospitalizations (26 versus 10; P = 0.005) and longer hospital stays (14 days versus 10 days; P = 0.043), without affecting the proportion of patients hospitalized (71.3% versus 64.5%; P = 0.367).

Recommendations for the Use of Infliximab in the Treatment of Steroid-Resistant Immune-Induced Adverse Events

Table 15 presents the recommendations on the use of infliximab in the treatment of corticosteroid-resistant irAEs from 4 international consensus guidelines (ESMO, ASCO, SITC, NCCN) that were reported in the SR by Daetwyler et al. (2024).[12]

- For colitis: All 4 guidelines recommend the use of infliximab as first-line treatment for immune-induced colitis after being resistant to steroids.

- For hepatitis: All 4 guidelines recommend against the use of infliximab for the treatment of steroid-resistant immune-induced hepatitis due to potential hepatotoxicity and risk of infectious complications.
- For pneumonitis: All 4 guidelines recommend the use of infliximab as a treatment option, among other immunosuppressive drugs.
- For myocarditis: The ASCO and NCCN guidelines recommend the use of infliximab for the treatment of immune-induced myocarditis as a treatment option among other drugs, whereas the ESMO and SITC guidelines do not recommend infliximab due to concern about the increased risk of cardiovascular death caused by infliximab.

Research Question 2

Infliximab for immunotherapy-induced gastrointestinal or other organ toxicities is an off-label use. What is the usual dosage used (i.e., specific amount, number, and frequency of doses over a particular time period)?

- Usual concentration: 5 mg/kg; in some cases, infliximab dose was 10 mg/kg.
- Mode of administration: IV.
- The time interval to step up with immunosuppressive therapy if steroid treatment fails is 48 to 72 hours.[12]
- Number of infusions: Varied from 1 to 17 infusions;[32] mostly 1 to 2 infusions.
- Periods between doses: Varied; usually separated between 2 to 4 weeks apart.
- Length of treatment: Depending on the responsiveness of infliximab. Some patients had complete resolution after only 1 injection, while some required multiple injections.

Limitations

Evidence Gaps

Most of the evidence was for colitis, followed by pneumonitis. Fewer evidence was found for other irAEs, including hepatitis and myocarditis. Most of the adverse event (AEs) were resistant to corticosteroids before being treated with infliximab.

We did not identify any steroid-resistant irAEs of grade 1 that were treated with infliximab. Although some grade 1 AEs might be present in some case series or case reports where the AE grade was not reported, most of the reported corticosteroid-resistant AEs were grade 2 or higher.

Response to treatment with infliximab was the primary outcome in the included SRs, as well as additional case reports and case series identified in this report. We did not identify other outcomes in Table 1, including clinical utility, harms, infliximab-related AEs, and patient-reported outcomes.

We identified 1 study comparing the efficacy and safety of infliximab with vedolizumab for treating immune-induced colitis. We did not identify any studies comparing infliximab with other comparative drugs for treating different irAEs.

Concerning the population, we did not identify any studies that included children or adolescents. Patients in all the included studies were adults with various types of cancer who had undergone treatment with ICIs.

Generalizability

The clinical findings in this report may be generalizable to the health care context in Canada, as the included studies were conducted by authors in many countries worldwide, including Canada, the US, and Europe.

Certainty of the Evidence

The overall quality of the evidence on the management of corticosteroid-resistant irAEs was extremely low, as evidence regarding the infliximab treatment option is available only in the form of case reports and case series.

The included retrospective cohort study[14] had several methodological limitations, including its study design (i.e., retrospective nature) and the differences of the study and patient characteristics, which were regarded as confounders that were not adjusted in the analyses.

Conclusions and Implications for Decision- or Policy-Making

This review included 2 SRs of case reports and series[12,13] and 40 additional publications (29 case reports[15-43] and 11 case series.[44-54]) on the infliximab treatment of corticosteroid-resistant irAEs, such as colitis, hepatitis, pneumonitis, and myocarditis. Evidence from the included SRs[12,13] was mainly derived from case reports and case series. The review also included 1 retrospective cohort study[14] comparing the efficacy and safety of infliximab with vedolizumab treatment for immune-induced colitis.

According to the literature reviewed in this report, the findings showed that infliximab was the most used drug in managing steroid-resistant immune-induced colitis, with its response rate being relatively high. Recent consensus guidelines recommend using infliximab as the first-line treatment for steroid-resistant immune-induced colitis. Treatment with infliximab, as compared with vedolizumab, resulted in comparable immune-induced colitis response rates, a shorter time to clinical response, but a higher recurrent rate of colitis and more hospitalizations. Thus, vedolizumab could be an alternative drug to infliximab to treat immune-induced colitis or to be used in infliximab-refractory cases.[55] Very few publications attempted to use infliximab for the treatment of immune-induced hepatitis as its response rate was very low, and all guidelines advised against its use due to potential hepatotoxicity and infectious complications. The use of infliximab for the treatment of immune-induced pneumonitis and myocarditis remains to be determined as prospective evidence is yet available.

Considerations for Future Research

Future prospective randomized controlled trials or comparative studies with large populations and various outcomes are needed to investigate the efficacy and safety of infliximab for the treatment of irAEs. Children and adolescents should also be included in the study population. Studies are also needed on the early administration of infliximab on irAEs, regardless of steroid responsiveness, for a potentially faster and better improvement of symptoms.[56]

Implications for Clinical Practice

Although the findings in this report were not robust to produce a strong conclusion as evidence regarding treatment option of infliximab was available mainly in the form of case report and case series, the number of publications and the success rate suggest that infliximab may be used as first-line treatment in steroid-resistant immune-induced colitis. However, the safety of infliximab treatment remains to be determined. The use of infliximab for the treatment of other irAEs, including hepatitis, pneumonitis and myocarditis, remains to be determined. However, until evidence from larger prospective and comparative studies is available to confirm those observations, the findings in this study should be interpreted with caution.

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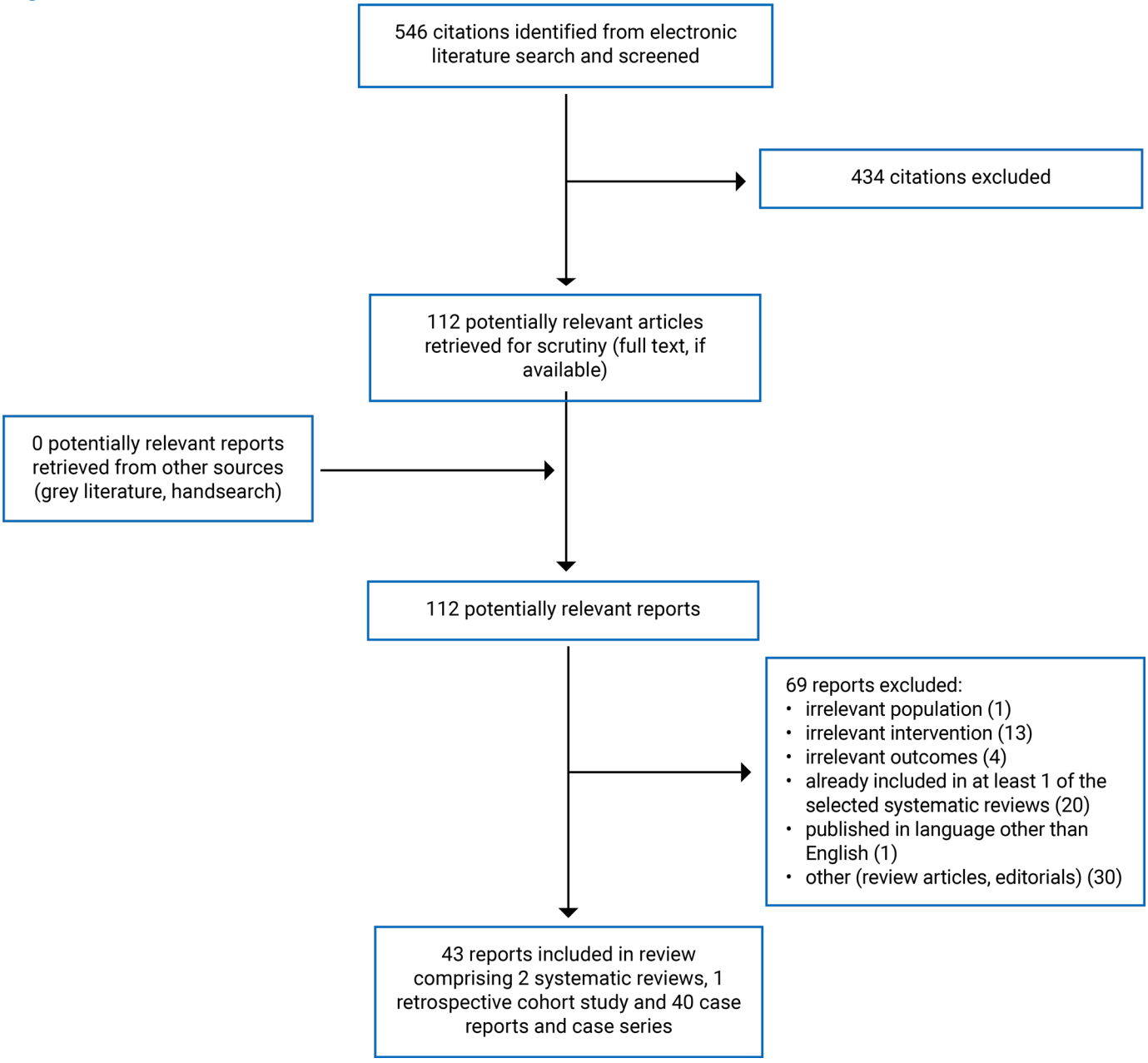
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Note that this appendix has not been copy-edited.

Table 2: Characteristics of Included Systematic Reviews

Study citation, country, funding source	Study design, outcomes	Intervention and comparators	Included studies	Population characteristics
Daetwyler et al. (2024)[12] Switzerland, Germany, US **Funding source:** None	SR Response to immunosuppressive treatment in patients with corticosteroid-resistant irAEs (hepatitis, colitis, pneumonitis, myocarditis)	**Intervention:** Immunosuppressive treatment including infliximab **Comparator**: None	Case reports and case series	Adults with various types of cancer underwent ICI treatment
Nielsen et al. (2022)[13] Country: Denmark **Funding source:** None	SR with MA Response to immunosuppressive treatment in patients with corticosteroid-resistant immune-induced colitis	**Intervention:** Infliximab and vedolizumab **Comparator:** None	Case reports and case series	Adults with various types of cancer underwent ICI treatment

ICI = immune checkpoint inhibitor; irAE = immune-related adverse event; MA = meta-analysis; SR = systematic review.

Table 3: Characteristics of Included Primary Clinical Study

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Zou et al. (2021)[14] US **Funding source:** No funding from any sources	Retrospective cohort study	Patients with various types of cancer (melanoma, genitourinary cancer, lung cancer, and others) Median age (range), years: 64 (49 to 73) Cancer stage: III, IV Colitis: Grade 1 to 4 ICI: Anti-CTLA-4, anti-PD-L1, or combination of antibodies Median length of ICI treatment, days (range): • Infliximab: 70 (28 to 151) • Vedolizumab: 73 (28 to 247); P = 0.846 Melanoma • Infliximab: 47%	**Intervention:** Infliximab (n = 94) **Comparator**: Vedolizumab (n = 62)	Outcomes: • Rate of clinical remission • Time to clinical response • Recurrent of immune-mediated diarrhea and colitis • Duration of hospitalization • Number of hospitalizations • Number of patients being hospitalized Follow-up: Median (range), months: 14 (8 to 27)

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		• Vedolizumab: 16%; P < 0.001 Anti-PD-L1 • Infliximab: 43% • Vedolizumab: 61%; P = 0.041 Median (range) duration of steroid use, days: • Infliximab: 51 (41 to 68) • Vedolizumab: 35 (27 to 43); P < 0.001 Doses of SIT, mean (SD): • Infliximab: 2 (1) • Vedolizumab: 3 (2); P < 0.001		

CTLA-4 = cytokine T-lymphocyte antigen 4; ICI = immune check point inhibitor; PD-L1 = programmed cell death ligand 1; SD = standard deviation; SIT = selective immunosuppressive therapy.

Table 4: Studies on Immune-Induced Colitis

Author (Year)	Study design	Cancer type; ICI	Number of patients	Grade of irAEs or symptoms	Steroid refractory	Infliximab IV (dose; number of infusion)	Response to treatment
Studies included in the systematic review by Daetwyler et al. (2024)[12] (24 studies)							
Dahl (2022)	Case series	Melanoma ICI – Anti-CTLA-4, anti-PD-1, anti-PD-L1, or combination of antibodies	138	Colitis Grade: 2 to 4	Yes	5 mg/kg Median number of infusion (range): 2 (1 to 9)	• Complete response (n = 101; 73%) • Partial response (n = 24; 17%) • Insufficient response (n = 13; 9.4%) • Median time to response after infusion: 3 days (2 to 4 days).
Perez (2022)	Case report	Thyroid cancer ICI – Anti-PD-1 (pembrolizumab) antibody	1	Colitis Grade: NR	Yes	5 mg/kg 5 infusions	No response to infliximab.
Zellweger (2022)	Case report	NSCLC ICI – Anti-PD-1 (pembrolizumab) antibody	1	Colitis Grade: NR	Yes	5 mg/kg 3 infusions	No (persistent) response to infliximab.
Bishu (2021)	Case series	Melanoma (n = 3), NSCLC (n = 1) ICI – Anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) antibodies	4	Colitis Grade: NR	Yes	Dose: NR 4 to 5 infusions	No (persistent) response to infliximab.
Klemm (2021)	Case report	Melanoma ICI – Anti-PD-I (nivolumab) antibody alone or combination therapy	1	Colitis Grade: 3	Yes	Dose: NR 3 infusions	No response to infliximab.

Author (Year)	Study design	Cancer type; ICI	Number of patients	Grade of irAEs or symptoms	Steroid refractory	Infliximab IV (dose; number of infusion)	Response to treatment
Sasson (2021)	Case report	NSCLC ICI – Anti-CTLA-4 and anti-PD-1 antibodies	1	Colitis Grade: NR	Yes	Dose: NR 2 infusions	No (persistent) response to infliximab.
Zhang (2021)	Case series	Melanoma ICI – Anti-CTLA-4 and anti-PD-L1 antibodies (n = 9); anti-PD-L1 antibody (n = 2)	11	Colitis Grade: 2 to 4	Yes	Dose: NR	• No improvement with infliximab • Response to calcineurin inhibitors (n = 8; 72.7%).
Apostalova (2020)	Case report	Melanoma ICI – NR	1	Colitis Grade: NR	Yes	Dose: NR 2 infusions	No (persistent) response to infliximab.
Connolly (2020)	Case report	Melanoma ICI – NR	1	Colitis Grade: NR	Yes	5 mg/kg Number of infusions: NR	Complete response (n = 1; 100%).
Esfahani (2020)	Case report	Gastric cancer ICI – Anti-PD-1 antibody	1	Colitis Grade: NR	Yes	5 mg/kg, 10 mg/kg 2 infusions	No (persistent) response to infliximab.
Abu-Sbeih (2019)	Case series	Melanoma (n = 40); genitourinary cancer (n = 28); thoracic, head or neck cancers (n = 11), others (n = 5) ICI – Anti-CTLA-4, anti-PD-1, anti-PD-L1 alone, or combination	84	Colitis Grade: 2 to 4	Yes	5 mg/kg Infliximab (n = 46) Infliximab and vedolizumab (n = 6) Median 3 infusions	• Recurrence in infliximab mono (n = 12/46; 26%) • Recurrence in infliximab followed by vedolizumab (n = 3/4; 75%) • Recurrence in vedolizumab followed by infliximab1, (n = 0/2; 0%).
Nassri (2019)	Case report	Melanoma ICI – Anti-CTLA-4 (Ipilimumab) and anti-PD-1 antibodies	1	Colitis Grade: NR	Yes	5 mg/kg 1 infusion	Complete resolution (n = 1; 100%).
Abu-Sbeih (2018)	Case series	Melanoma (n = 7); renal cell carcinoma (n = 4), prostate carcinoma (n =	28	Colitis Grade: 2 to 4	Yes	Infliximab (n = 9) Dose: NR	No improvement with infliximab (n = 9; 100%).

Author (Year)	Study design	Cancer type; ICI	Number of patients	Grade of irAEs or symptoms	Steroid refractory	Infliximab IV (dose; number of infusion)	Response to treatment
		4); urothelial cancer (n = 3); other solid tumours (n = 10) ICI – Anti-CTLA-4, anti-PD-1, anti-PD-L1 alone, or combination				Median number of infusions (range): 2 (1 to 3)	
Iyoda (2018)	Case report	NSCLC ICI – Anti-PD-1 (nivolumab) antibody	1	Colitis Grade: 3	Yes	5 mg/kg 2 infusions	• No improvement with infliximab alone • Complete resolution with addition of cyclosporin.
Wang (2018)	Case series	Urothelial cancer (n = 1), prostate cancer (n = 1)	2	Colitis Grade: NR	Yes	Dose: NR 2 infusions	No response to infliximab.
Jain (2017)	Case series	Melanoma ICI – Anti-CTLA-4 (ipilimumab) antibody	9	Colitis Grade: ≥ 2	Yes	5 mg/kg 1 infusion (n = 8) 2 infusions (n = 1)	• Complete resolution (n = 8; 89%) after 1 infusion • Complete resolution (n = 1; 11%) after 2 infusions.
Verschuren (2016)	Case series	Melanoma; prostate cancer ICI – Anti-CTLA-4 (ipilimumab) antibody	12	Colitis Diarrhea; rectal bleeding; abdominal pain	Yes	5 mg/kg 1 infusion (n = 7) 2 infusions (n = 4) 3 infusions (n = 1)	Complete resolution (n = 12; 100%).
Marthey (2016)	Case series	Melanoma; prostate carcinoma; NSCLC ICI – Anti-CTLA-4 (ipilimumab) antibody	5	Colitis Diarrhea; rectal bleeding; abdominal pain; fever, vomiting	Yes	5 mg/kg	• Complete resolution (n = 2; 40%) • Partial resolution (n = 3; 60%), 2 of which relapse.
Cheng (2015)	Case report	Melanoma ICI – Anti-CTLA-4 (ipilimumab) antibody	1	Colitis Grade: NR	Yes	5 mg/kg	Complete resolution (n = 1; 100%).

Author (Year)	Study design	Cancer type; ICI	Number of patients	Grade of irAEs or symptoms	Steroid refractory	Infliximab IV (dose; number of infusion)	Response to treatment
Horwat (2015)	Case series	Melanoma ICI – Anti-CTLA-4 (ipilimumab) antibody	29	Colitis Grade: Any	Yes	5 mg/kg Number of infusion: NR	• Clinical response after 1 to 2 infusions (n = 21; 72%) • No response (n = 8; 27%).
Pagès (2013)	Case report	Melanoma ICI – Anti-CTLA-4 (ipilimumab) antibody	1	Colitis Grade: 3	Yes	5 mg/kg 1 infusion	Complete resolution (n = 1; 100%) after 1 infusion on day 7
Lord (2010)	Case series	Melanoma, prostate cancer ICI – Anti-CTLA-4 (ipilimumab) antibody	4	Colitis Grade: NR	Yes	5 mg/kg infliximab 1 infusion (n = 1) 5 mg/kg infliximab 1 infusion and oral tacrolimus (n = 1) 5 mg/kg infliximab 3 infusions, tacrolimus and rapamycin (n = 1) Tacrolimus (n = 1)	• Clinical resolution with infliximab or tacrolimus (n = 2; 50%) • Relapse off therapy or persistent symptoms (combination therapy; n = 2; 50%).
Johnston (2009)	Case series	Melanoma ICI – Anti-CTLA-4 (ipilimumab) antibody	5	Colitis Grade: NR	Yes	5 mg/kg 1 infusion (n = 4) 2 infusions (n = 1)	• Complete resolution after 1 infusion (n = 4; 80%) • Complete resolution after 2 infusions (n = 1; 20%).
Beck (2006)	Case series	Melanoma, renal carcinoma ICI – Anti-CTLA-4 (ipilimumab) antibody	4	Colitis Grade: 3, 4	Yes	5 mg/kg 1 infusion (n = 4)	Complete resolution after 1 infusion (n = 4; 100%).
Studies included in the systematic review by Neilsen et al. (2022)[13] (14 studies), excluding those included in the systematic review by Daetwyler et al. (2024)[12]							
Kadokawa et al. (2021)[41]	Case series	Melanoma, lung cancer, and renal cancer ICI – Anti-PD-1 (nivolumab), anti-PD-L1 (durvalumab), anti--	7	Colitis Grade: 3	Yes	5 mg/kg 1 infusion (n = 4) 2 infusions (n = 1) 3 infusions (n = 2)	• No response (n = 3; 43%) • Improvement (n = 2; 29%) • Died (n = 2; 29%).

Author (Year)	Study design	Cancer type; ICI	Number of patients	Grade of irAEs or symptoms	Steroid refractory	Infliximab IV (dose; number of infusion)	Response to treatment
		CTLA-4 ipilimumab), or combination of antibodies					
Zhang (2020)	Case series	Melanoma, various types of cancer ICI – Anti-PD-1, anti-PD-L1, or combination of antibodies	13	Colitis Grade: NR	Yes	Dose: NR Number of infusions: NR	Efficacy, clinical remission, no recurrence (n = 13; 100%).
Herlihy (2019)	Case series	Melanoma ICI – Anti-CTLA-4 (ipilimumab) antibody	19	Colitis Grade: NR	Yes (97%)	Dose: NR Number of infusions: NR	Efficacy, clinical remission, no recurrence (n = 17; 89%).
Lesage (2019)	Case series	Melanoma ICI – Anti-CTLA-4, anti-PD-1, or combination of antibodies	27	Colitis Grade: ≥ 3	Yes	Dose: NR Number of infusions: NR	Efficacy, clinical remission, no recurrence (n = 26; 96%) mostly after 1 infusion.
Geukes Foppen (2018)	Case series	Melanoma, NSCLC ICI – Anti-CTLA-4, anti-PD-1, or combination of antibodies	54	Colitis Grade: NR	Yes	Dose: NR 50% received more than 1 infusion	Efficacy, clinical remission, no recurrence (n = 51; 94%).
Spain (2018)	Case series	Melanoma ICI – Anti-CTLA-4 (ipilimumab), anti-PD-1 (pembrolizumab, nivolumab) antibodies	17	Colitis Grade: NR	Yes	Dose: NR 1 infusion (n = 5) ≥ 2 infusions (n = 12)	Efficacy, clinical remission, no recurrence (n = 13; 76%).
Franklin (2017)	Case series	Melanoma ICI – Anti-CTLA-4, anti-PD-1, or combination of antibodies	10	Colitis Grade: NR	?	Dose: NR Number of infusions: NR	Efficacy, clinical remission, no recurrence (n = 6; 60%).

Author (Year)	Study design	Cancer type; ICI	Number of patients	Grade of irAEs or symptoms	Steroid refractory	Infliximab IV (dose; number of infusion)	Response to treatment
Hillock (2017)	Case series	Melanoma, prostate cancer ICI – Anti-CTLA-4 (ipilimumab) antibody	13	Colitis Grade: NR	Yes	Dose: NR 1 infusion (n = 8) ≥ 2 infusions (n = 5)	Efficacy, clinical remission, no recurrence (n = 4; 31%).
Kim (2017)	Case series	Melanoma, NSCLC, renal cell carcinoma ICI – Anti-PD-1 (pembrolizumab, nivolumab) antibodies	6	Colitis Grade: NR	Yes	Dose: NR Number of infusions: NR	Efficacy, clinical remission, no recurrence (n = 6; 100%).
Mir (2017)	Case series	Melanoma ICI – Anti-CTLA-4, anti-PD-1, or combination of antibodies	8	Colitis Grade: ≥ 3	Yes	Dose: NR Number of infusions: NR	Efficacy, clinical remission, no recurrence (n = 8; 100%).
Arriola (2016)	Case series	Melanoma ICI – Anti-CTLA-4 (ipilimumab) antibody	7	Colitis Grade: NR	?	Dose: NR 1 infusion (n = 4) 2 infusions (n = 2) 3 infusions (n = 1)	Efficacy, clinical remission, no recurrence (n = 7; 100%).
Salgado (2016)	Case series	Melanoma ICI – Anti-CTLA-4, anti-PD-1, or combination of antibodies	17	Colitis Grade: ≥ 3	Yes	Dose: NR 1 infusion (n = 9) 2 infusions (n = 6) 3 infusions (n = 2)	Efficacy, clinical remission, no recurrence (n = 17; 100%).
Sidhu (2015)	Case series	Melanoma, lung cancer, renal cancer ICI – Anti-CTLA-4 (ipilimumab), anti-PD-1 antibodies	10	Colitis Grade: NR	Yes	Dose: NR Number of infusions: NR	Efficacy, clinical remission, no recurrence (n = 10; 100%).
Harding (2012)	Case series	Melanoma ICI – Anti-CTLA-4 (ipilimumab) antibody	35	Colitis Grade: NR	?	Dose: NR Number of infusions: NR	Efficacy, clinical remission, no recurrence (n = 26; 74%).

Author (Year)	Study design	Cancer type; ICI	Number of patients	Grade of irAEs or symptoms	Steroid refractory	Infliximab IV (dose; number of infusion)	Response to treatment
Studies identified in this report (30 studies)							
Harvey et al. (2024)[44]	Case series	Melanoma (90%), and other (10%) ICI – Anti-PD-1 and anti-CTLA-4, anti-PD-1, and anti-CTLA-4 antibodies	78	Colitis (n = 74); upper GI (n = 3); upper and lower GI (n = 1) Grade: 2 to 5	Yes	5 mg/kg Number of infusions: NR	• No response (n = 18; n = 23%) • Partial response (improvement, but not to ≤ grade 1(n = 20; 26%) • Initial response (initial improvement to ≤ grade 1, then relapse) (n = 40; 51%).
Ishihara et al. (2024)[15]	Case report	Melanoma ICI – Anti-CTLA-4 (ipilimumab) and anti-PD-1 (Nivolumab) antibodies	1	Colitis Grade: 3	Yes	5 mg/kg 2 infusions	No response.
Baczewska et al. (2023)[16]	Case report	Melanoma ICI – Anti-PD-1 (nivolumab) antibody	1	Colitis Grade: 3	Yes	5 mg/kg 2 infusions	• No response to infliximab • Patient required surgical management for total colectomy.
Cespedes-Martinez et al. (2023)[45]	Case series	Lung, melanoma, and other types of cancer ICI – Anti-PD-1, anti-PD-L1, anti-CTLA-4, or combination of antibodies	5	Colitis Grade: 2 to 4	Yes	10 mg/kg 1 infusion (n = 1) 3 infusions (n = 4)	• Complete resolution after 1 dose of infliximab (n = 1; 20%) • No response after 3 consecutive doses (n = 4; 80%); 2 patients died.
Dai and Huang (2023)[17]	Case report	Lung adenocarcinoma ICI – Anti-PD-1 (nivolumab) antibody	1	Abdominal pain, distension, and vomiting	Yes	Dose: NR Numbers of infusions: NR	Complete resolution (n = 1; 100%).

Author (Year)	Study design	Cancer type; ICI	Number of patients	Grade of irAEs or symptoms	Steroid refractory	Infliximab IV (dose; number of infusion)	Response to treatment
Kou et al. (2023)[46]	Case series	Various types of cancer ICI – Anti-PD-1 antibody alone or in combination with anti-CTLA-4 antibody or other	3	Colitis Grade: 2, 3	Yes	300 mg per infusion 1 infusion (n = 1) 2 infusions (n = 2)	Symptom remission and successful steroid tapering (n = 2; 67%).
Tomsitz et al. (2023)[47]	Case series	Advanced/metastatic skin cancer ICI – NR for specific irAEs	12	Colitis Grade: 2 to 4	Yes	5 mg/kg 1 infusion (n = 6) 2 infusions (n = 6)	• Mean time to first response: 1.3 days (0 days to 7 days) • Complete resolution (n = 9; 75%) • Improvement, but no resolution (n = 1; 8%) • Required 3rd-line therapy (n = 2; 17%).
Townsend et al. (2023)[18]	Case report	Melanoma ICI – Anti-PD-1 (pembrolizumab) antibody	1	Pancreatitis Grade: 3	Yes	5 mg/kg 2 infusions	Complete resolution (n = 1; 100%).
Verhe et al. (2023)[19]	Case report	Enteritis Urothelial cancer stage 4 ICI – Anti-PD-1 (pembrolizumab) antibody	1	Enteritis Grade: 3	Yes	10 mg/kg Multiple infusions	No improvement with infliximab and other immunosuppressive agents (methotrexate, mycophenolate mofetil, and vedolizumab).
Del Nogal et al. (2022)[20]	Case report	Carcinoma ICI – Anti-PD-1 (pembrolizumab) antibody	1	Colitis Severe	Yes	Dose: NR 3 infusions	No response to infliximab.
Fujikawa et al. (2022)[21]	Case report	Lung adenocarcinoma and large-cell neuroendocrine carcinoma stage 4	1	Colitis Grade: 3	Yes	5 mg/kg 1 infusion	No improvement, and later died.

Author (Year)	Study design	Cancer type; ICI	Number of patients	Grade of irAEs or symptoms	Steroid refractory	Infliximab IV (dose; number of infusion)	Response to treatment
		ICI – Anti-PD-1 (Nivolumab) antibody					
Harris et al. (2022)[48]	Case series	Lung, melanoma, genitourinary, endometrial ICI – Anti-CLTA-4 and anti-PD-1 antibodies (n = 7), anti-PD-L1 (n = 3) antibodies	10	Colitis Grade: NR	?	5 mg/kg 1 infusion (n = 2) 2 infusions (n = 6) 3 infusions (n = 1) 4 infusions (n = 1) 10 mg/kg 1 infusion (n = 7) 2 infusions (n = 1) 3 infusions (n = 1) 9 infusions (n = 1)	Efficacy of 5 mg/kg • Nonresponse (n = 8; 80%) • Incomplete response (n = 2; 20%) Efficacy of 10 mg/kg dose escalating • Clinical response (n = 5; 50%) • Refractory (n = 5; 10%)
Kaneoka et al. (2022)[22]	Case report	Melanoma ICI – Anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) antibodies	1	Colitis Grade: 3	Yes	Dose: NR 2 infusions	• No improvement with infliximab • Response to vedolizumab after 3 doses.
Lu et al. (2022)[23]	Case report	Lung cancer with liver metastasis ICI – Anti-PD-L1 (durvalumab) antibody	1	Colitis Severe Grade: NR	Yes	5 mg/kg 2 infusions	Symptoms improved after first dose, but symptoms recurred and later patient died after second dose.
Trystram et al. (2021)[24]	Case report	Melanoma ICI – Anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) antibodies	1	Enteritis Grade: NR (bleeding)	Yes	10 mg/kg 2 infusions	• Complete cessation of bleeding after first infusion • Complete resolution 3 months after second infusion (n = 1; 100%).
Araujo et al. (2021)[49]	Case series	Melanoma (62%), and others (38%) ICI – Anti-PD1, anti--	37	Colitis Grade: NR	?	Dose: NR Median number of infusion (range): 1 (1 to 3)	• Resolved (n = 32; 86.5%) • Not resolved (n = 5; 13.5%).

Author (Year)	Study design	Cancer type; ICI	Number of patients	Grade of irAEs or symptoms	Steroid refractory	Infliximab IV (dose; number of infusion)	Response to treatment
		CTLA4, or combination of antibodies					
Damato et al. (2021)[25]	Case report	Advanced NSCLC ICI – Anti-PD-1 (pembrolizumab) antibody	1	Colitis Grade: 4	No	5 mg/kg 8 infusions	Reduce to grade 1 diarrhea after 10 months follow-up.
Kunogi et al. (2021)[26]	Case report	Adenocarcinoma ICI – Anti-PD-1 (pembrolizumab) antibody	1	Colitis Grade: NR	Yes	400 mg 2 infusions	• No improvement with infliximab 1 • No improvement with vedolizumab • Improvement with tacrolimus
Sisman et al. (2021)[27]	Case report	Ovarian cancer ICI – Anti-PD-1 (pembrolizumab) antibody	1	Colitis Grade: NR	Yes	5 mg/kg 2 infusions	• Symptoms improved after first infusion • Became refractory to infliximab after second infusion; died later from septic shock.
Young et al. (2021)[28]	Case report	Adenocarcinoma stage III ICI – Anti-PD-L1 (atezolizumab) antibody	1	Enteritis Grade: 4	Yes	10 mg/kg 2 infusions	Complete resolution (n = 1; 100%).
Burla et al. (2020)[50]	Case series	Melanoma stage III, IV ICI – Anti-CTLA-4 (ipilimumab), anti-PD-1 (nivolumab, pembrolizumab), or combination of antibodies	20	Colitis Grade: 3 or 4	Yes	5 mg/kg 1 infusion (n = 14) 3 infusions (n = 6)	Complete resolution (n = 20; 100%).

Author (Year)	Study design	Cancer type; ICI	Number of patients	Grade of irAEs or symptoms	Steroid refractory	Infliximab IV (dose; number of infusion)	Response to treatment
Dang et al. (2020)[29]	Case report	Melanoma ICI – Anti-PD-1 (pembrolizumab) antibody	1	Mucositis Grade: NR	Yes	5 mg/kg 2 infusions	Marked improvement.
Karanfilian et al. (2020)[30]	Case report	Colon cancer ICI – Anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) antibodies	1	Colitis Grade: NR	Yes	5 mg/kg 2 infusions	Complete resolution (n = 1; 100%).
Luque Carmona et al. (2020)[31]	Case report	Adenocarcinoma stage 4 ICI – Anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) antibodies	1	Colitis Symptoms: Diarrhea	Yes	5 mg/kg 1 infusion	Complete resolution (n = 1; 100%).
Paparoupa et al. (2020)[32]	Case report	Melanoma ICI – Anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) antibodies	1	Colitis Grade: NR	Yes	5 mg/kg 17 infusions for 12 months	Complete resolution (n = 1; 100%).
Singh et al. (2020)[33]	Case report	Melanoma ICR - Anti-CTLA-4 (ipilimumab) antibody	1	Colitis Grade: 2	Yes	5 mg/kg 2 infusions	Complete resolution (n = 1; 100%).
Vindum et al. (2020)[34]	Case report	Melanoma ICI – Anti-PD-1 antibody	1	Gastritis Weight loss, nausea, and vomiting	Yes	5 mg/kg 2 infusions	Complete resolution (n = 1; 100%).
Badran et al. (2019)[51]	Case series	Meningioma, colon cancer, melanoma, and squamous cell carcinoma ICR – Anti-CTLA-4	5	Colitis 2	Yes	5 mg/kg 1 infusion (n = 5) once or every 4 to 6 weeks	Complete resolution (n = 5; 100%).

Author (Year)	Study design	Cancer type; ICI	Number of patients	Grade of irAEs or symptoms	Steroid refractory	Infliximab IV (dose; number of infusion)	Response to treatment
		(ipilimumab) and anti-PD-1 (Nivolumab), anti-PD-1 (pembrolizumab), anti-CTLA-4, or cemiplimab antibodies					
Tidwell et al. (2019)[35]	Case report	Endometrial carcinoma ICI – Anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) antibodies	1	Colitis Grade: NR	Yes	5 mg/kg 2 infusions 2 weeks apart	Complete resolution (n = 1; 100%).
Zhang et al. (2019)[36]	Case report	Prostate adenocarcinoma ICI – Anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) antibodies	1	Colitis Grade: 3	Yes	5 mg/kg 1 infusion	• Complete resolution after first infusion of infliximab (n = 1; 100%) • But develop acute liver injury (hepatoxicity).

CTLA-4 = cytotoxic T-lymphocyte antigen 4; ICI = immune checkpoint inhibitor; irAE = immune-related adverse event; NSCLC = non–small cell lung cancer; NR = not reported; PD-1 = programmed cell death 1; PD-L1 = programmed cell death ligand 1.

Table 5: Studies on Immune-Induced Hepatitis

Author (Year) Country	Study design	Cancer type; ICI	Number of patients	Grade of irAEs	Steroid refractory	Infliximab (dose; number of infusion)	Response to treatment
Studies included in the systematic review by Daetwyler et al. (2024)[12] (2 studies)							
Cheung et al. (2019)[12]	Case series	Melanoma ICI – Anti-CTLA-4 (ipilimumab) antibodies	21	Hepatitis Grade: 4 (75%)	Yes	Dose: NR 2 infusions	Partial resolution; improvement to grade 1 within 30 days
Corrigan et al. (2019)[12]	Case report	Melanoma ICI – Anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) antibodies	1	Hepatitis Grade: 3	Yes	5 mg/kg 2 infusions 2 weeks apart	Complete resolution at 14 months (n = 1; 100%)
Studies identified in this report (1 study)							
Nakashima et al. (2020)[37]	Case report	Lung squamous cell carcinoma stage III ICI – Anti-PD-L1 (durvalumab) antibody	1	Hepatitis Grade: 3	Yes	5 mg/kg 2 infusions	Complete resolution after 9 months (n = 1; 100%)

CTLA-4 = cytotoxic T-lymphocyte antigen 4; ICI = immune checkpoint inhibitor; irAE = immune-related adverse event; NR = not reported; PD-1 = programmed cell death 1; PD-L1 = programmed cell death ligand 1.

Table 6: Studies on Immune-Induced Pneumonitis

Author (Year) Country	Study design	Cancer type; ICI	Number of patients	Grade of irAEs	Steroid refractory	Infliximab (dose; number of infusion)	Response to treatment
Studies included in the systematic review by Daetwyler et al. (2024)[12] (13 studies)							
Camard (2022)	Case series	NSCLC, Hodgkin lymphoma, breast cancer, urothelial carcinoma ICI – Anti-PD1, anti-PD-L1 antibodies	6	Pneumonitis Grade: 2 to 4	Yes	Infliximab (n = 1) Dose: NR Number of infusions: NR	Died

Author (Year) Country	Study design	Cancer type; ICI	Number of patients	Grade of irAEs	Steroid refractory	Infliximab (dose; number of infusion)	Response to treatment
Chen (2022)	Case report	Small cell lung cancer ICI – Anti-PD-1 (tislelizumab) antibody	1	Pneumonitis Grade: 4	Yes	5 mg/kg 1 infusion	Complete resolution (n = 1; 100%)
Huang (2022)	Case report	NSCLC ICI – anti-PD-L1 antibody	1	Pneumonitis Grade: NR	Yes	5 mg/kg 1 infusion	Complete resolution (n = 1; 100%)
Balaji (2021)	Case series	NSCLC (n = 9) and others (n = 3) ICI – NR	12	Pneumonitis Grade: NR	Yes	Infliximab (n = 2); IVIG and infliximab (n = 3); IVIG (n = 7) Dose: NR Number of infusions: NR	5 died from ICI-pneumonitis or treatment complications, including all who have received infliximab.
Beattie (2021)	Case series	NSCLC, renal cancer, melanoma, others ICI – NR	19	Pneumonitis Grade: 2 to 4	Yes	Dose: NR Number of infusions: NR	• Durable improvement (n = 5) • Other had transient improvement, no improvement, or died.
Luo (2021)	Case series	Lung cancer ICI – Anti-PD-L1, anti-CTLA-4, or combination therapy	10	Pneumonitis Grade: NR	Yes	Dose: NR Number of infusions: NR	Improvement 90 days after infliximab treatment (n = 3; 30%)
Ueno (2021)	Case report	Head and neck cancer ICI – Anti-PD-1 (nivolumab) antibody	1	Pneumonitis Grade: NR	Yes	Dose: NR Number of infusions: NR	No response, died within 2 months
Cooksley (2019)	Case report	Melanoma ICI – NR	1	Pneumonitis Grade: NR	Yes	Dose: NR Number of infusions: NR	Partial resolution
Sawai (2019)	Case report	Lung adenocarcinoma ICI – Anti-PD-1 (pembrolizumab) antibody	1	Pneumonitis Grade: NR	Yes	5 mg/kg 1 infusion	Rapid improvement, but deterioration after 14 days during steroid tapering, and later died.

Author (Year) Country	Study design	Cancer type; ICI	Number of patients	Grade of irAEs	Steroid refractory	Infliximab (dose; number of infusion)	Response to treatment
Andruska (2018)	Case series	NSCLC ICI – Anti-PD-1 (pembrolizumab, Nivolumab) antibody	2	Pneumonitis Grade: NR	Yes	Dose: NR Number of infusions: NR	• Temporary improvement (n = 1), but later died. • 1 died
Ortega (2018)	Case report	Melanoma ICI – Anti-PD-1 antibody	1	Pneumonitis Grade: NR	Yes	Dose: NR Number of infusions: NR	Complete resolution (n = 1; 100%)
Naidoo (2017)	Case series	Melanoma, NSCLC, others ICI – Anti-PD-1, anti-PD-L1, or combination of antibodies	5	Pneumonitis Grade: 1 to 2 (72%)	Yes	Dose: NR Number of infusions: NR	All 5 patients died (1 from pneumonitis, 3 from immunosuppression-associated infection, and 1 from cancer progression
Nishino (2016)	Case series	Melanoma (n = 2), NSCLC (n = 1) ICI – NR	3	Pneumonitis Grade: NR	Yes	Dose: NR Number of infusions: NR	• 1 died • 1 referred for palliative care though improvement • 1 had long-term remission, and no rechallenge
Studies identified in this report (5 studies)							
Al-Saghir et al. (2023)[38]	Case report	Melanoma and lung conditions ICI – Anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) antibodies	1	Pneumonitis Grade: Severe	?	Dose: NR 1 infusion	Patient died due to respiratory compromise
Ogusu et al. (2023)[52]	Case series	Lung Cancer ICI – Anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) antibodies	6	Pneumonitis Grade: ≥ 3	Yes	Dose: NR Numbers of infusion: NR	Complete response (n = 4; 66.7%)
Cheng and Chen (2020)[39]	Case report	Gastric cancer ICI – Anti-PD-1 (nivolumab) antibody	1	Pneumonitis Grade: NR	Yes	5 mg/kg 1 infusion	Complete remission (n = 1; 100%)

Author (Year) Country	Study design	Cancer type; ICI	Number of patients	Grade of irAEs	Steroid refractory	Infliximab (dose; number of infusion)	Response to treatment
Lai et al. (2020)[53]	Case series	Melanoma, pancreatic cancer, lung cancer, acute myeloid leukemia, myelodysplastic syndrome ICI – Anti-CTLA-4 (Ipilimumab), anti-PD-1 (nivolumab) antibodies, or combination	9	Pneumonitis Grade: ≥ 3	Yes	5 mg/kg 1 infusion	• Improvement (n = 4; 44.4%) • Died (n = 5; 55.6%)
Liang et al. (2019)[40]	Case report	Small cell lung cancer ICI – Anti-PD-1 (atezolizumab) antibody	1	Pneumonitis Grade: 2	Yes	5 mg/kg 1 infusion Combination treatment with mycophenolate mofetil and IVIG	Symptoms were relieved; but with progressive liver disease.

CTLA-4 = cytotoxic T-lymphocyte antigen 4; ICI = immune checkpoint inhibitor; irAE = immune-related adverse event; IVIG = IV immunoglobulin; NSCLC = non–small cell lung cancer; NR = not reported; PD-1 = programmed cell death 1; PD-L1 = programmed cell death ligand 1.

Table 7: Studies on Immune-Induced Myocarditis

First Author (Year)	Study design	Cancer type; ICI	Number of patients	Grade of irAEs	Steroid refractory	Infliximab (dose; number of infusion)	Response to treatment
Studies included in the systematic review by Daetwyler et al. (2024)[12] (2 studies)							
Zhang (2021)	Case series	Melanoma (n = 2), renal cell carcinoma (n = 1), ovarian adenocarcinoma (n = 1) ICI – Anti-PD-1 (pembrolizumab, nivolumab), anti-PD-L1 (durvalumab)	4	Myocarditis Grade: NR	Yes	Dose: NR Number of infusions: NR	• Complete of steroid taper (n = 2; 50%) • 2 died due to septic shock

First Author (Year)	Study design	Cancer type; ICI	Number of patients	Grade of irAEs	Steroid refractory	Infliximab (dose; number of infusion)	Response to treatment
Saibil (2019)	Case report	Melanoma ICI – Anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) antibodies	1	Myocarditis and rhabdomyositis Grade: NR	Yes	5 mg/kg 1 infusion	No response, later died
Studies identified in this report (4 studies)							
Kadokawa et al. (2021)[41]	Case report	Kidney cancer stage 4 ICI – Anti-PD-1 (nivolumab) and anti-CTLA-4 (ipilimumab) antibodies	1	Myocarditis Grade: NR	Yes	5 mg/kg 2 infusions	Improvement (n = 1; 100%)
Moriyama et al. (2021)[42]	Case report	Non–small-cell lung cancer ICI – anti-PD-1 (nivolumab) antibody	1	Pericarditis Grade: NR	Yes	5 mg/kg 8 infusions	Improvement (n = 1; 100%)
Weiss et al. (2021)[43]	Case report	Carcinoma ICI – anti-PD-1 (nivolumab) antibody	1	Myocarditis Grade: NR	Yes	Dose: NR 2 infusions	Died from cardiac arrest
Padegimas et al. (2019)[54]	Case series	Ovarian adenocarcinoma, metastatic renal cell carcinoma ICI – Anti-PD-1 (nivolumab or pembrolizumab)	2	Myocarditis Grade: NR	Yes	5 mg/kg 1 infusion	• Complete resolution (n = 1; 50%) • Died (n = 1; 50%)

CTLA-4 = cytotoxic T-lymphocyte antigen 4; ICI = immune checkpoint inhibitor; irAE = immune-related adverse event; IVIG = IV immunoglobulin; NR = not reported; PD-1 = programmed cell death 1; PD-L1 = programmed cell death ligand 1.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 8: Strengths and Limitations of Systematic Reviews Using AMSTAR 2[57]

Strengths	Limitations
Daetwyler et al. (2024)[12]	
The research question or objective and the inclusion criteria for the review clearly include the components of PICO. The review authors explained their selection of eligible study designs, which were case reports and case series due to the limited number of available studies. The authors also included evidence-based guidelines. The review authors declared all competing interests. The review authors declared that they did not receive any commercial or public funding.	No study protocol was established before conducting the review. The literature search strategy was not comprehensive as the search was conducted in PubMed only. However, a search algorithm was provided. The review authors did not report whether study selection and data extraction were performed in duplicate. Quality assessment of the included studies was not performed as the included studies were case reports and case series. The review authors acknowledged that the evidence was very low in quality as it derived from case reports and case series. Patient characteristics were not adequately described. A list of excluded studies and the reasons for exclusion were not provided. Therefore, it was not possible to assess whether any relevant articles were excluded and if so, for what reasons.
Nielsen et al. (2022)[13]	
The research question or objective and the inclusion criteria for the review clearly include the components of PICO. A study protocol was published before conducting the review. The review authors explained their selection of eligible study designs. The review authors performed study selection, data extraction, and quality assessment of the included studies in duplicate. This reduced the risk of inconsistencies in these processes. The review authors used tools to assess risk of bias of the included studies. The McMaster Quality Assessment Scale was used to assess Harms, and the Newcastle-Ottawa Quality Assessment was used for studies on treatment of checkpoint-induced colitis. The review authors used appropriate method for statistical combination of the results. The review authors reported that they did not receive any funding and declared that they had no conflicts of interest related to this work.	The literature strategy was partially comprehensive as it focused on databases search only. The authors did not handsearch the reference lists of the included studies or search trial or study registries. Patient characteristics were not adequately described. A list of excluded studies and the reasons for exclusion were not provided. The review authors did not report the sources of funding for the included studies. The review authors did not provide a discussion of the heterogeneity observed in the results.

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2.

Table 9: Strengths and Limitations of Clinical Studies Using the Downs and Black Checklist[58]

Strengths	Limitations
Zou et al. (2021)[14]	
Reporting: • The objective of the study, the main outcomes to be measured, the characteristics of the participants included in the study, the interventions of interest, and the main findings were clearly described. • Actual P values were reported for the main outcomes. • Efficacy and safety outcomes of the intervention were reported. **External validity:** • The study was conducted in hospital settings. The staff, places, and facilities where the patients were treated, were representative of the treatment most of the patients receive. • The study involved a large patient population (n = 184), which may be representative of the entire population from which they were treated. **Internal validity – bias:** • Statistical tests were appropriately used to compare differences between groups, and the main outcome measures were accurate and reliable.	**Internal validity – bias:** • Risk of selection bias is a main limitation of a retrospective cohort study. **Internal validity – confounding:** • There were some differences in baseline characteristics between treatment groups, thus increasing the risk of confounding bias. • Residual confounding factors may exist, and failure to identify and adjust for those factors in the analyses may have an impact on the findings. • The study applied multivariate analysis for survival outcome only, but not for other outcomes. • The study did not report whether sample size was calculated.

Appendix 4: Main Study Findings

Note that this appendix has not been copy-edited.

Table 10: Response to Infliximab Treatment for Immune-Induced Colitis

Study	Complete	Partial	Insufficient	No
	Number of patients			
Daetwyler et al. (2024)[12] (24 studies)				
Case reports (n = 11; 11 patients)	4	—	—	7
Case series (n = 13; 244 patients)	168	27	13	36
% of total number of patients (255 patients)	67.5	10.6	5.1	16.8
Nielsen et al. (2022)[13] (14 studies)				
Case reports (n = 0)	—	—	—	—
Case series (n = 14; 243 patients)	206	—	—	37
% of total number of patients (243 patients)	84.8	—	—	15.2
Studies identified in this report (30 studies)				
Case reports (n = 22; 22 patients)	12	—	—	10
Case series (n = 8; 170 patients)	74	20	41	35
% of total number of patients (192 patients)	44.8	10.4	21.4	23.4
% of total number of patients in the included SRs and additional studies identified in this report (690 patients)	67.2	6.8	7.8	18.1

ICI = immune checkpoint inhibitor.

Table 11: Response to Infliximab Treatment for Immune-Induced Hepatitis

Study	Complete	Partial	Insufficient	No
	Number of patients			
Daetwyler et al. (2024)[12] (2 studies)				
Case report (n = 1; 1 patient)	1	—	—	—
Case series (n = 1; 21 patients)	—	21	—	—
% of total number of patients (22 patients)	4.5	95.5	—	—
Studies identified in this report (1 study)				
Case reports (n = 1; 1 patients)	1	—	—	—
Case series (n = 0)	—	—	—	—
% of total number of patients (1 patient)	100.0	—	—	—

Study	Complete	Partial	Insufficient	No
	Number of patients			
% of total number of patients in the included SR and additional studies identified in this report (23 patients)	8.7	91.3	—	—

ICI = immune checkpoint inhibitor.

Table 12: Response to Infliximab Treatment for Immune-Induced Pneumonitis

Study	Complete	Partial	Insufficient	No
	Number of patients			
Daetwyler et al. (2024)[12] (13 studies)				
Case reports (n = 6; 6 patients)	3	1	—	2
Case series (n = 7; 50 patients)	9	—	—	41
% of total number of patients (56 patients)	21.4	1.8	—	76.8
Studies identified in this report (5 studies)				
Case reports (n = 3; 3 patients)	1	—	—	2
Case series (n = 2; 15 patients)	8	—	—	7
% of total number of patients (18 patients)	50.0	—	—	50.0
% of total number of patients in the included SRs and additional studies identified in this report (74 patients)	28.4	1.4	—	70.2

ICI = immune checkpoint inhibitor.

Table 13: Response to Infliximab Treatment for Immune-Induced Myocarditis

Study	Complete	Partial	Insufficient	No
	Number of patients			
Daetwyler et al. (2024)[12] (2 studies)				
Case reports (n = 1; 1 patients)	—	—	—	1
Case series (n = 1; 4 patients)	2	—	—	2
% of total number of patients (5 patients)	40.0	—	—	60.0
Studies identified in this report (4 studies)				
Case reports (n = 3; 3 patients)	2	—	—	1
Case series (n = 1; 2 patients)	1	—	—	1
% of total number of patients (5 patients)	60.0	—	—	40.0
% of total number of patients in the included SRs and additional studies identified in this report (10 patients)	50.0	—	—	50.0

ICI = immune checkpoint inhibitor.

Table 14: Comparison of Clinical Efficacy and Safety Outcomes of Infliximab- and Vedolizumab-Treated Patients

Outcomes	Infliximab (N = 94)	Vedolizumab (N = 62)	P value
Rate of clinical remission, n (%)	83 (88.3)	55 (88.7)	0.785
Median time to clinical response (range), days	13 (8 to 29)	18 (10 to 40)	0.012
Recurrence of immune-mediated diarrhea and colitis, n (%)	27 (28.7)	8 (12.9)	0.007
Number of hospitalizations, n (%)	26 (27.7)	10 (16.1)	0.005
Median duration of hospitalization (range), days	14 (8 to 20)	10 (5 to 15)	0.043
Number of patients with multiple hospitalizations, n (%)	67 (71.3)	40 (64.5)	0.367

Table 15: Recommendations for the Use of Infliximab in the Treatment of Corticosteroid-Resistant irAEs[12]

Immune-related AEs	ESMO (2022)	ASCO (2021)	SITC (2021)	NCCN (2023)
Colitis	Yes (1)	Yes (1)	Yes (1)	Yes (1)
Hepatitis	No	No	No	No
Pneumonitis	Yes (1)	Yes (*)	Yes (*)	Yes (*)
Myocarditis	—	Yes (1)	—	Yes (*)

ASCO = American Society of Clinical Oncology; ESMO = European Society for Medical Oncology; irAE = immune-related adverse event; NCCN = National Comprehensive Cancer Network; SITC = Society for Immunotherapy of Cancer.

Note: (1) = First choice; (*) = No treatment sequence mentioned.

Appendix 5: Overlap Between Included Systematic Reviews

Note that this appendix has not been copy-edited.

Table 16: Overlap in Relevant Primary Studies Between Included Systematic Reviews on Immune-Induced Colitis

Primary study citation	Daetwyler et al. (2024)[12]	Nielsen et al. (2022)[13]
Verschuren EC et al. Clin Gastroenterol Hepatol 2016 (14):836 to 42.	Yes	Yes
Johnston RL et al. Dig Dis Sci 2009 (54):2538 to 40.	Yes	—
Marthey L et al. ECCOJC 2016 (10):395 to 401.	Yes	Yes
Beck KE et al. JCO 2006 (24):2283 to 9.	Yes	—
Pagès C et al. Melanoma Res 2013 (23):227 to 30.	Yes	—
Jain A et al. WJG 2017 (23):2023	Yes	Yes
Horvat TZ et al. J Clin Oncol 2015 (33):3193 to 8.	Yes	Yes
Cheng R et al. J Gastroenterol Hepatol 2015 (30):657 to 66.	Yes	—
Nassri AB et al. World J Gastrointest Pharmacol Ther 2019 (10):29 to 34.	Yes	—
Connolly EA et al. Intern Med J 2020 (50):767 to 8.	Yes	—
Klemm N et al. Clin Res Hepatol Gastroenterol 2021 (45):101604.	Yes	—
Dahl EK et al. Aliment Pharmacol Ther 2023 (57):152 to 3.	Yes	—
Abu-Sbeih H et al. J Immunotherapy Cancer 2019 (7).	Yes	Yes
Abu-Sbeih H et al. J Immunother Cancer 2018 (6):142.	Yes	Yes
Lord JD et al. Dig Dis Sci 2010 (55):1396 to 405.	Yes	—
Iyoda T et al. Am J Case Rep 2018 (19):360 to 4.	Yes	—
Zhang E et al. JGH Open 2021 (5):558 to 62.	Yes	—
Perez Del Nogal and Patel N. ACG Case Rep J 2022 (9):e00946.	Yes	—
Esfahani K et al. N Engl J Med 2020 (382):2374 to 5.	Yes	—
Zellweger M et al. Z Gastroenterol 2022 (60):1124 to 30.	Yes	—
Bishu S et al. Gastroenterology 2021 (160):932 to 4.	Yes	—
Sasson SC et al. Gastroenterology 2021 (161):1229 to 44.	Yes	—
Wang Y et al. Nat Med 2018 (24):1804 to 8.	Yes	—
Apostolova P et al. N Engl J Med 2020 (382):294 to 6.	Yes	—
Harding JJC et al. Pigment Cell Melanoma Ress 2012 (25): 862.	—	Yes
Sidhu MS et al. J Gastroenterol Hepatol 2015 (30) (suppl. 3): 139.	—	Yes
Salgado ACC et al. J Immunother Cancer 2016 (4) (suppl. 1): 146 to 147.	—	Yes
Arriola E et al. Clin Cancer Res 2015; 21 (24): 5642 to 5643.	—	Yes

Primary study citation	Daetwyler et al. (2024)[12]	Nielsen et al. (2022)[13]
Hillock NT et al. Asia Pac J Clin Oncol 2017; 13 (5): e284-e290.	—	Yes
Franklin C et al. Eur J Cancer 2017 (86): 248 to 256.	—	Yes
Mir RS et al. J Clin Oncol 2021 (35) (suppl.): e21010.	—	Yes
Kim JS et al. Gastroenterology 2017 (152) (suppl. 1): S-811.	—	Yes
Geukes Foppen MH et al. ESMO Open 2018; 3 (1): e000278.	—	Yes
Spain LC et al. Gut 2018; 67 (suppl. 1): A64-A65.	—	Yes
Herlihy JD et al. South Med J 2019; 112 (3): 154 to 158	—	Yes
Lesage C et al. J Immunother 2019; 42 (5): 175 to 179.	—	Yes
Zhang ML et al. Histopathology 2020; 76 (2): 233 to 243.	—	Yes
Kadokawa Y et al. Mol Clin Oncol 2021; 14 (4): 65.	—	Yes

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