

# Review of the Diagnosis, Treatment, and Outcomes of Immunotherapy-Associated Autoimmune Hemolytic Anemia

MICHAELA HAYES, CAROL A. CARMAN

## ABSTRACT

Immunotherapy has become an integral tool in the treatment of many diseases. Immune checkpoint inhibitors (ICIs) treat certain cancers, enabling the patient's immune system to recognize and destroy abnormal and cancerous cells. Although effective, these treatments do not come without risk of altering the patient's immune system and causing immune-related adverse events (irAE). This narrative review focuses on a rarely reported irAE, ICI-associated autoimmune hemolytic anemia. It provides an overview of reported cases and existing recommendations for diagnosing and treating immunotherapy-associated autoimmune hemolytic anemia.

**ABBREVIATIONS:** ADR - adverse drug reaction, AIHA - autoimmune hemolytic anemia, ASCO - American Society of Clinical Oncology, CLL - chronic lymphocytic leukemia, CTCAE - Common Terminology Criteria for Adverse Events, DAT - direct antiglobulin test, FDA - Food and Drug Administration, irAE - immune-related adverse event, IV - intravenous, IVIG - IV immune globulin, LDH - lactate dehydrogenase.

**INDEX TERMS:** immunotherapy, anemia, hemolytic, autoimmune, immune checkpoint inhibitors, neoplasms, immune system, immune system diseases.

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## INTRODUCTION

Immunotherapy has become standard treatment for many cancers.<sup>1</sup> Immunotherapy facilitates the body's immune system to mobilize its response to otherwise unrecognized abnormal and cancerous cells.<sup>1</sup> There are multiple types of

immunotherapies; however, immune checkpoint inhibitors (ICIs) have been shown to induce long-lasting remission and cures in some patients.<sup>1</sup> ICIs can combat cancer cells' ability to evade immune detection by inhibiting certain immune checkpoint molecules.<sup>2,3</sup> ICIs are the standard of care for malignant melanoma, renal cell carcinoma, lung cancer, Merkel cell carcinoma, and microsatellite instable malignancies.<sup>4</sup>

ICI treatments have improved the prognosis of many diseases.<sup>1</sup> Although ICIs are a valuable treatment, they do not come without possibility of adverse events, and these adverse events are not fully understood.<sup>2,3</sup> ICIs significantly modify the patient's immune system by affecting immune checkpoint molecules involved in self-tolerance.<sup>5</sup> There are several recognized ICI-associated immune-related adverse events (irAEs).<sup>2</sup> Because of nonspecific activation of the immune system, irAEs can involve almost any organ system.<sup>4</sup> Autoimmune hemolytic anemia (AIHA) is a rare and possibly underreported ICI-associated irAE.<sup>2,3</sup> Early diagnosis and treatment of ICI-associated AIHA are necessary to facilitate a positive outcome, although this is made difficult by multiple factors.<sup>5</sup>

This narrative review discusses current recommendations for diagnosis, treatment, and prognosis of ICI-associated AIHA. It also discusses challenges affecting accurate diagnosis, outlines possible diagnostic criteria, and describes specialized treatment protocols for this patient population. Patient diagnosis, treatment, and prognosis are evaluated by reviewing and summarizing published case studies.

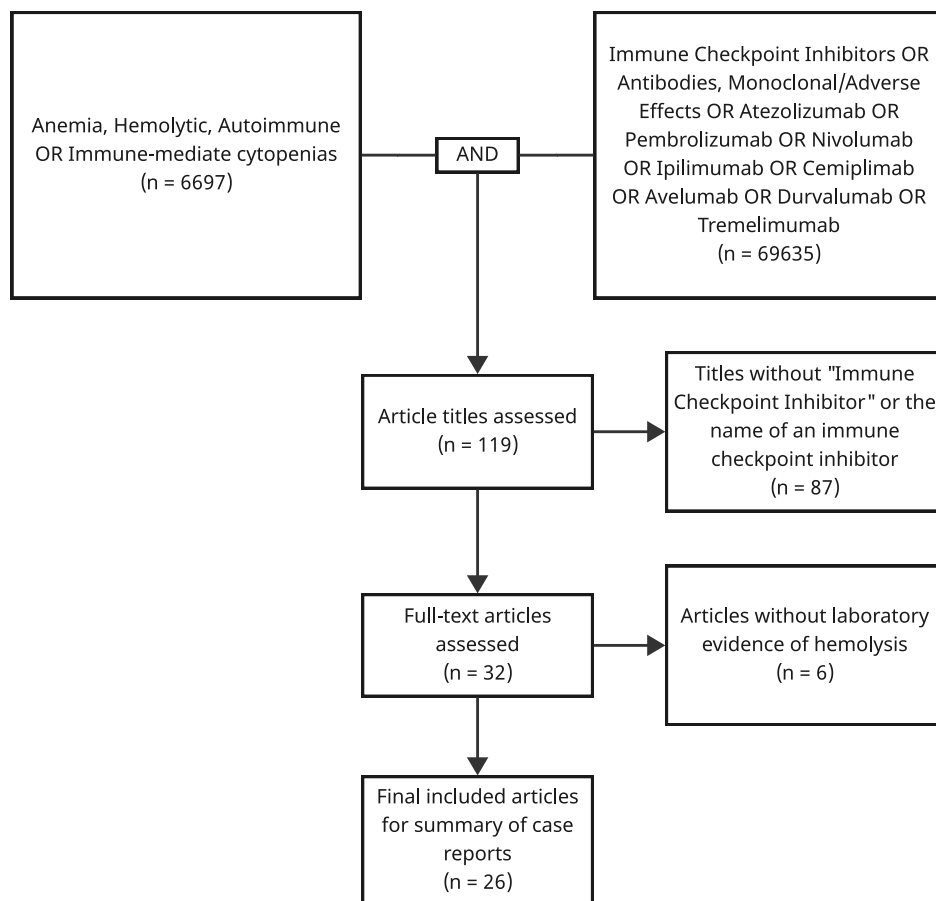
## METHODS

For this narrative review, an Ovid search was conducted to identify articles to be included in the case report summary (Figure 1). This search obtained articles published from July 1, 2009, to July 1, 2024. Articles were retrieved using the following search terms: "Autoimmune Hemolytic Anemia" OR "Immune-mediated Cytopenias," AND, "Immune Checkpoint Inhibitor" OR "Atezolizumab" OR "Pembrolizumab" OR "Nivolumab" OR "Ipilimumab" OR "Cemiplimab" OR "Avelumab" OR "Durvalumab" OR "Tremelimumab" OR "Antibodies, Monoclonal/adverse effects." Articles were limited to those involving humans, written in English, and published within the last 15 years. Included were original scientific research articles, such as

**Michaela Hayes**, *The University of Texas Medical Branch at Galveston*

**Carol A. Carman**, *The University of Texas Medical Branch at Galveston*

**Address for Correspondence:** **Carol A. Carman**, *The University of Texas Medical Branch at Galveston*, [cabartsc@utmb.edu](mailto:cabartsc@utmb.edu)



**Figure 1.** Summary of case reports database search flowchart.

randomized clinical trials, observational studies, and case studies. Review articles were included if they reported a previously unreported patient case study. This search returned 119 results. Titles of these articles were reviewed, and those that did not have “Immune Checkpoint Inhibitor” or the name of an ICI were removed, resulting in 32 articles. Full texts of the remaining articles were reviewed and evaluated to ensure the articles contained documented laboratory evidence of hemolysis (decrease in hemoglobin with abnormal levels of either lactate dehydrogenase (LDH), bilirubin, or haptoglobin or hematuria unexplained by other comorbidities). Twenty-six articles met these criteria and were included in the review. As some of the 26 articles included multiple cases, a total of 30 cases were presented and were evaluated in the summary of case reports as part of this narrative review.

## FINDINGS

### Diagnosis

#### Diagnostic criteria and laboratory evaluation

Currently, there are no standard diagnostic criteria for ICI-associated AIHA; the framework proposed by Leaf et al offers a practical approach for evaluating suspected cases.<sup>6</sup> While this study is not one of the clinical cases

analyzed, its criteria provided a foundation to evaluate the cases included in this narrative review. Leaf et al<sup>6</sup> used several criteria to assess patients based on evidence of hemolysis and strength of the link between use of ICI and hemolysis.<sup>6</sup> These criteria included an abrupt decrease in hemoglobin of at least 2 g/dL; presence of at least 2 laboratory tests supporting active hemolysis, which may include elevated LDH (without other explanation), elevated reticulocyte percentage or absolute count, low serum haptoglobin, and spherocytes present on peripheral blood smear; symptoms of hemolysis occurring after initiation of ICI treatment; exclusion of other causes of anemia; and ICI being designated the cause of AIHA.<sup>6</sup> In addition to laboratory testing, physical examination and evaluation of symptoms were used in many cases reviewed for this study. Symptoms that alert physicians to anemia include fatigue, malaise, pallor, shortness of breath, jaundice, decreased oral intake, and confusion. Although Leaf et al<sup>6</sup> provided criteria that must be included in defining a hemolytic event, the authors did not suggest the definition be used as a diagnostic tool to determine whether ICI treatment is the cause of AIHA.

The first step to diagnose ICI-associated AIHA is detecting evidence of hemolysis. The laboratory testing used by Leaf et al<sup>6</sup> to evaluate for hemolysis included

LDH (without other explanation), elevated reticulocyte percentage or absolute count, low serum haptoglobin, and spherocytes present on peripheral blood smear. This criterion did not include the direct antiglobulin test (DAT); this test is used to detect *in vivo* sensitization of red cells with either IgG or complement proteins. Physicians frequently use DAT and other laboratory tests listed in Leaf's criteria to detect AIHA. Relying on DAT alone may not be prudent because it is well known that negative DATs do not guarantee hemolysis is not occurring.<sup>7</sup> A study involving 14 patients with ICI-associated AIHA reported 5 patients exhibiting negative DATs when assessed using standard diagnostic methods.<sup>6</sup> This is higher than what has been seen in non-drug-related DAT-negative AIHA, which is seen in 5% to 10% of patients with AIHA.<sup>7</sup> This study did not use advanced DAT testing methods, which are known to have higher sensitivity than standard methods.<sup>6</sup> A case report of a man with urothelial carcinoma developed DAT-negative AIHA after 4 cycles of pembrolizumab treatment.<sup>8</sup> This patient was tested using enhanced DAT methods and was found to be negative even though this patient met the first 2 diagnostic criteria defined by Leaf et al.<sup>6</sup> Other cases of DAT-negative ICI-associated AIHA were reported in literature; however, these cases did not use enhanced DAT methods.<sup>5,9,10</sup> DAT-negative AIHA is a diagnosis of exclusion, therefore all other possible causes of anemia were ruled out in these patients.<sup>8</sup> Increased access to enhanced DAT methods may improve the diagnosis of DAT-negative AIHA. Because of the high incidence of DAT-negative ICI-associated AIHA, DATs should not be used as the sole screening test to detect hemolysis.

### Clinical grading of ICI-associated AIHA symptoms

Another method to evaluate ICI-associated AIHA is by using the US Department of Health and Human Services Common Terminology Criteria for Adverse Events (CTCAE), which classifies adverse events on a 5-grade scale.<sup>11</sup> Grade 1 indicates mild or asymptomatic findings with no intervention needed, grade 2 involves moderate symptoms with only minimal or noninvasive treatment, grade 3 reflects severe symptoms requiring hospitalization or prolongation of hospitalization, grade 4 indicates life-threatening symptoms and that urgent intervention is needed, and grade 5 indicates a fatal adverse event. For anemia, CTCAE defines grade 1 as hemoglobin less than the lower limit of normal of 10 g/dL, grade 2 as hemoglobin less than 10 to 8.0 g/dL, and grade 3 as hemoglobin less than 8.0 g/dL. Hemolysis is graded as follows: Grade 1 involves only laboratory evidence of hemolysis, grade 2 includes evidence of hemolysis and at least a 2-g decrease in hemoglobin, and grade 3 requires transfusion or other medical intervention.<sup>11</sup> Cases reviewed for this study all qualified as grade 3 or 4. Similarly, a review of hematological ICI-irAE reported to 3 French pharmacovigilance databases revealed all 9 reported patients with AIHA were either grade 3 or 4.<sup>12</sup> This trend may reflect a

reporting bias, with providers more likely to recognize and attribute severe symptoms to ICI treatment.

### Risk factors

When evaluating patients, it is important to consider risk factors related to autoimmune diseases. Some possible risk factors in presented case studies include a history of autoimmune disease and comorbidity of chronic lymphocytic leukemia (CLL). Four of 30 cases (from the 26 articles included in the review) were previously diagnosed with autoimmune diseases; these included AIHA, autoimmune hypothyroidism, and chronic inflammatory syndrome.<sup>13-16</sup> In all of these cases, the patient was diagnosed with ICI-associated AIHA. The frequency of patients with histories of autoimmune disease suggests this may be a risk factor physicians should consider when prescribing ICI treatment. In addition to a history of autoimmune disease, physicians should also consider comorbidities that have been reported to create a predisposition to developing autoimmune disease. A study of patients with CLL showed 9.4% were observed to have autoimmune complications, 44.4% of which were AIHA.<sup>17</sup> Five patients in the reviewed cases had a history of CLL.<sup>8,18-20</sup> In Delanoy et al,<sup>12</sup> 2 of 9 ICI-associated AIHA patients had preexisting B-cell CLL; however, these patients showed no signs of disease progression, and, therefore, it was determined CLL was not the triggering event.<sup>12</sup> High incidence of patients with CLL may not be a coincidence, as CLL has also been shown to increase risk of developing solid tumors.<sup>21</sup> ICIs are used to treat solid tumors, and because of the relationship between CLL and solid tumors, this may be the cause of disproportionate frequency of CLL as a comorbidity in the review cases. Future studies are needed to determine whether there is a relationship between a CLL comorbidity and a higher risk of developing ICI-associated AIHA.

### Causality and monitoring

Physicians must accurately determine whether ICI is the cause of hemolysis to prevent unnecessary discontinuation of potentially life-saving treatment. An important step is exclusion of all other causes of anemia. ICIs are used to treat cancer, and this patient population frequently develops anemia. To rule out other possible causes of anemia, physicians should perform iron studies, vitamin B12 testing, folate testing, and viral infection testing as well as bone marrow aspirates to rule out aplastic anemia.<sup>4,6,9,10,16,22-24</sup> Few case studies in the literature reported this testing. The tests may have been performed and not reported; however, lack of information makes objectively evaluating these cases more difficult, as patients may have had underlying issues causing AIHA.

There are assessment methods to evaluate the relationship between adverse drug reactions (ADRs) more objectively. The Naranjo algorithm is a tool that has been used widely to assess ADRs. The algorithm uses a questionnaire to evaluate the probability that a drug is the cause of an adverse event. The questionnaire is used to assign a

score, and based on that score, the event can be categorized as a definite, probable, possible, or doubtful ADR.<sup>25</sup> New applications have been developed to make the Naranjo algorithm more accessible to physicians for ADR evaluation.<sup>26</sup> Only 4 cases in the literature used this algorithm to evaluate the relationship between AIHA and treatment with ICIs. Tao et al,<sup>27</sup> Younce et al,<sup>28</sup> and Khosla et al<sup>9</sup> used the Naranjo algorithm to evaluate their patients; all received scores categorizing them as probable ADR. This algorithm provides an objective and reproducible score that can support the identification of an ADR and should be applied in the further diagnosis of patients.

Diagnostic guidelines proposed by Leaf et al<sup>6</sup> are similar to CTCAE grading guidelines. Leaf et al's<sup>6</sup> guidelines discuss areas to include in the screening process as well as increased clinician attention to patient symptom development related to ICI use. Even though ICI-associated AIHA has a higher rate of DAT-negative AIHA, including DAT in the screening process could be valuable. Physicians should maintain a high level of vigilance when prescribing ICIs to patients, especially those that have been shown to cause ICI-associated AIHA.<sup>2,4,6</sup> Certain ICIs should be more highly monitored than others. According to a review of 68 Food and Drug Administration (FDA)-reported cases of ICI-associated AIHA by Tanios et al,<sup>4</sup> there have been no reports to the FDA of ICI-associated AIHA in patients using cemiplimab, avelumab, durvalumab, or tremelimumab, and as of July 13, 2024, no cases have been reported in the literature. Patients on ICI treatments such as atezolizumab, pembrolizumab, nivolumab, or ipilimumab should be monitored for signs of hemolysis using physical examination and laboratory test values regularly throughout treatment, as ICI-associated AIHA has been reported to develop at any time during treatment.<sup>4</sup> Their review showed a median of 10 weeks after start of treatment before symptoms occurred; however, this varied between 2 and 78 weeks.<sup>4</sup> Similarly, the number of ICI doses administered before symptom onset ranged from 1 to 39, with a median of just 3 doses (Table 1). This variability underscores the unpredictable nature of ICI-associated AIHA and highlights the need for frequent monitoring throughout the entire course of immunotherapy. Hemoglobin should be monitored frequently for anemia, and a drop of 2 g/dL should be investigated for hemolysis.<sup>2,19,27</sup> Patients with comorbidities such as a history of autoimmune diseases or CLL should be vigilantly monitored when using ICI treatment. If a patient is determined to have developed AIHA, the Naranjo algorithm should be used to provide an objective score establishing a causal relationship between ICI treatment and development of AIHA.<sup>25,26</sup> If a patient receiving ICI treatment develops symptoms of AIHA, ICI should be held until further investigation and treatment can occur.

## Treatment

### Standard treatment recommendations

The American Society of Clinical Oncology (ASCO) published guidelines for irAEs for patients undergoing ICI treatment.<sup>38</sup> These guidelines recommend physicians educate patients and caregivers about possible irAEs caused by ICI treatment to promote patient and caregiver reporting of new symptoms. The guidelines also advise physicians to consider any newly observed symptoms as potentially treatment related. If hematologic toxicity is detected, ASCO recommends withholding ICI until symptoms are a grade less than 1. For grade 2 toxicities, corticosteroids are the recommended treatment at an initial dose of 0.5 to 1 mg/kg/d of prednisone.<sup>38</sup> For grade 3 toxicities, it is recommended to prescribe high-dose corticosteroids such as prednisone at 1 to 2 mg/kg/d or intravenous (IV) methylprednisolone at 1 to 2 mg/kg/d.<sup>38</sup> Symptoms should improve within 48 to 72 hours, and corticosteroids should be tapered for 4 to 6 weeks.<sup>38</sup> If symptoms improve to a grade of at most 1, the patient may be rechallenged with ICI. However, caution should be taken, and the patient should be vigilantly monitored. ASCO does not recommend rechallenging patients who experience grade 4 toxicity.

### Management of steroid-refractory cases

ASCO's recommendations closely reflect treatments used in the studies discussed in the literature. A range of treatments have been used for ICI-associated AIHA, with corticosteroids as the standard first-line therapy and additional agents used in steroid-refractory cases. Leaf et al<sup>6</sup> reported that all 14 patients in their study were initially treated with either dexamethasone, methylprednisolone, or prednisone. Eleven of these patients required no other treatment, and 3 required further treatment: 1 required rituximab; 1 required rituximab and IV immune globulin (IVIG); and the third required rituximab, IVIG, and azathioprine.<sup>6</sup> Similarly, an observational study of 9 patients with ICI-associated AIHA had 4 patients who required treatment with corticosteroids alone and 5 who required treatment with rituximab.<sup>12</sup>

All patients identified in the case reports were initially treated with corticosteroids (Table 1), and 21 out of 30 responded to this treatment. However, 9 were refractory to steroid treatment alone. Second-line treatment included rituximab, IVIG, and splenectomy, options commonly used in managing steroid-refractory AIHA.<sup>8,10,14,20,23,35</sup> Other treatments included plasmapheresis, ibrutinib, and cyclosporine A.<sup>8,20,27,33</sup> Plasmapheresis was used in a case of penpulimab-associated AIHA, in which the patient received 3 sessions, resulting in symptom resolution.<sup>27</sup> This was the only reported case involving penpulimab, and it remains unclear whether plasmapheresis would be effective in other ICI-related cases. The Association for the Advancement of Blood and Biotherapies issued a grade 2C recommendation for plasmapheresis in AIHA, indicating

**Table 1.** Summary diagnosis, treatment, and outcomes of case reports

Reference	Case #	ICI	# of Doses Before Symptoms	Autoimmune/Predisposition <sup>a</sup>	Treatment	Hgb Recovery <sup>b</sup>	Other irAE	ICI Restarted	Diagnosis <sup>c</sup>
Algaze et al <sup>19</sup>	1	Nivolumab	21	CLL	Methylprednisolone, prednisone, and folic acid	Complete	None Reported	Yes/no recurrence	No <sup>d</sup>
Chambers et al <sup>29</sup>	1	Atezolizumab	29	None reported	Prednisone	Unknown	No	No	Yes
Dirven et al <sup>18</sup>	1	Nivolumab	1	CLL	Methylprednisolone	Complete	None reported	No	Yes
Dutertre et al <sup>16</sup>	2	Nivolumab	3	CLL	Dexamethasone	Complete	Yes	No	Yes
Dutertre et al <sup>16</sup>	1	Atezolizumab	1	Yes	Methylprednisolone, prednisone, and rituximab	Unknown	None reported	Unknown	Yes
Fetter et al <sup>5</sup>	1	Nivolumab and ipilimumab	4	None reported	Prednisone	Complete	Yes	Yes <sup>e/</sup> recurrence	Yes
Fukushima et al <sup>30</sup>	2	Pembrolizumab	2	None reported	Prednisone	Partial	Yes	No	Yes
Fukushima et al <sup>30</sup>	1	Atezolizumab	3	No	Prednisone	Partial	Yes	No	Yes
Hasanov et al <sup>23</sup>	1	Nivolumab	7	None reported	Prednisone and rituximab	Unknown	None reported	No	Yes
Jobson et al <sup>20</sup>	1	Ipilimumab	2	CLL	Methylprednisolone, intravenous immune globulin, cyclophosphamide, and splenectomy	Complete	None reported	Yes/no recurrence	Yes <sup>f</sup>
Johnstone and Khan <sup>31</sup>	1	Pembrolizumab	13	None reported	Prednisone and folic acid	Complete	Yes	No	Yes
Khan et al <sup>14</sup>	1	Nivolumab and ipilimumab	2	Yes	Methylprednisolone & rituximab	Complete	None reported	Yes/ recurrence	Yes
Khosla et al <sup>9</sup>	1	Atezolizumab	NR	None reported	Prednisone	Complete	None reported	No	Yes
Kong et al <sup>13</sup>	1	Nivolumab	5	Yes	Prednisone	Complete	None reported	No	Yes <sup>g</sup>
Ogawa et al <sup>24</sup>	1	Pembrolizumab	1	None reported	Prednisone	No <sup>h</sup>	None reported	No	Yes <sup>g</sup>
Okawa et al <sup>32</sup>	1	Pembrolizumab	1	None reported	Prednisone	Partial	Yes	Unknown	Yes
Olson et al <sup>33</sup>	1	Nivolumab and ipilimumab	4	None reported	Prednisone and cyclosporine A	Complete	Yes	No	Yes
Ramos and Rovere <sup>22</sup>	1	Ipilimumab	20	None reported	Prednisone	Unknown	No	Unknown	Yes

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Table 1. (Continued).

Reference	Case #	ICI	# of Doses Before Symptoms	Autoimmune/Predisposition <sup>a</sup>	Treatment	Hgb Recovery <sup>b</sup>	Other irAE	ICI Restarted	Diagnosis <sup>c</sup>
Robilliard et al <sup>34</sup>	1	Pembrolizumab	4	No	Prednisone	Unknown	Yes	No	Yes
Shaikh et al <sup>35</sup>	1	Nivolumab	39	None reported	Prednisone, vitamin B12, erythropoietin, and rituximab	Complete	None reported	No	Yes
Sun et al <sup>10</sup>	1	Pembrolizumab	1	None reported	Methylprednisolone and prednisone	Complete	None reported	Yes/no recurrence	Yes
Tanios et al <sup>4</sup>	1	Nivolumab	24	None reported	Methylprednisolone	No <sup>j</sup>	None reported	No	Yes
Tao et al <sup>27</sup>	1	Penpulimab	2	None reported	Prednisone, intravenous immune globulin, and plasmapheresis	Partial	None reported	No	No
Tardy et al <sup>36</sup>	1	Nivolumab	2	None reported	Prednisone	Partial	None reported	Yes/no recurrence	Yes
Williams and Aitchison <sup>37</sup>	1	Pembrolizumab	34	None reported	Methylprednisolone	Complete	Yes	No	Yes
Younce et al <sup>28</sup>	1	Atezolizumab	1	None reported	Prednisone, folic acid, darbepoetin, and iron sucrose	Partial	None reported	Yes/no recurrence	Yes
Yun et al <sup>8</sup>	1	Pembrolizumab	3	CLL	Prednisone, rituximab, and ibrutinib	Complete	None reported	No	Yes <sup>f</sup>
Zhang et al <sup>15</sup>	1	Pembrolizumab	1	Yes	Methylprednisolone and prednisone	Unknown	Yes	No	Yes

Note. AIHA, autoimmune hemolytic anemia; CLL, chronic lymphocytic leukemia; Hgb, hemoglobin; HLH, hemophagocytic lymphohistiocytosis; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; ITP, immune thrombocytopenic purpura.

<sup>a</sup>History of autoimmune/predisposition to developing.

<sup>b</sup>Complete hemoglobin recovery is defined as 0.0–1.0 g/dL relative to pretreatment hemoglobin, while partial hemoglobin recovery is characterized as 1.1–2.0 g/dL relative to pretreatment hemoglobin. Unknown recovery is recorded when data are missing, making interpretation impossible.

<sup>c</sup>The treating physician considers ICI the most likely etiology of AIHA.

<sup>d</sup>Physician was unable to exclude other possible causes of AIHA.

<sup>e</sup>This patient was rechallenged with 3 doses of pembrolizumab after developing nivolumab and ipilimumab-associated AIHA.

<sup>f</sup>Patient was diagnosed with exacerbated T-cell dysfunction in CLL causing AIHA.

<sup>g</sup>Patient died of other causes before recovery.

<sup>h</sup>Patient died because of bradycardia and cardiac arrest caused by anemia with a hemoglobin of 3 g/dL.

a weak recommendation supported by low- to very-low-quality evidence.<sup>39</sup> Ibrutinib was used to treat a patient reported by Yun et al,<sup>8</sup> which involved pembrolizumab-associated AIHA unresponsive to corticosteroids. Initially, rituximab was prescribed, but treatment was discontinued because of an anaphylactic reaction. Although the patient's CLL was inactive, ibrutinib was chosen for its known efficacy in both CLL and autoimmune cytopenias and led to the resolution of AIHA.<sup>8</sup> Cyclosporine A was used successfully in a patient receiving both nivolumab and ipilimumab who developed AIHA and pure red cell aplasia.<sup>33</sup>

In addition to immunosuppressive treatment, most patients in the reviewed cases required red blood cell transfusions to maintain hemoglobin levels; only 1 patient did not require transfusion. That patient, reported by Younce et al,<sup>28</sup> was treated with atezolizumab and developed AIHA after 1 dose. The patient had a history of anemia and vitamin B12 deficiency, but her hemoglobin was 12 g/dL.<sup>28</sup> Her hemoglobin was monitored once a week, and a downward trend in her hemoglobin caused an investigation for hemolysis.<sup>28</sup> Because of these findings, a hemolytic event was suspected, and the patient was placed on prednisone, folic acid, darbepoetin alfa, and iron sucrose for supportive care.<sup>28</sup> She was rechallenged with atezolizumab once symptoms resolved without additional medications and did not have a recurrence of AIHA.<sup>28</sup> This suggests frequent hemoglobin monitoring to facilitate early detection and supportive anemia care can positively impact a patient's severity of AIHA and the ability to restart ICI treatment.

### Rechallenge considerations and supportive care

The decision to rechallenge a patient with ICI treatment after an irAE is difficult, as these treatments are very effective; however, there is a risk of recurrence of irAE.<sup>3</sup> According to ASCO guidelines, ICI treatment may be resumed once symptoms have improved to a grade of at most 1, provided they did not exceed grade 3 severity.<sup>38</sup> Of 7 patients rechallenged, 5 did not have a recurrence of hemolysis.<sup>10,19,20,28,36</sup> One of the relapsed ipilimumab and nivolumab-associated AIHAs was reported by Khan et al<sup>14</sup>; this patient was in complete remission for 2 months before being rechallenged with ipilimumab and nivolumab. After 1 dose of treatment, the patient's AIHA reoccurred. Another case of relapsed ipilimumab and nivolumab-associated AIHA was reported by Fetter et al<sup>5</sup>; this patient was in remission for 3 months before being treated with pembrolizumab. After 3 doses, the patient's AIHA reoccurred. Leaf et al<sup>6</sup> reported 6 of 7 patients reexposed to ICI treatment did not develop recurrent AIHA. In a French pharmacovigilance database study of a total of 9 patients diagnosed with ICI-associated AIHA, only 1 was rechallenged and did not have a recurrence of AIHA.<sup>12</sup> Although there are reports of relapsed AIHA after reexposure to ICI treatment, if a physician determines ICI treatment is the best option for their patient, literature supports attempting to rechallenge the patient. If

rechallenging a patient, increased monitoring for recurrence is recommended to ensure early recognition of symptoms.

ASCO recommends initial use of corticosteroids. Additionally, supportive therapy is recommended, such as red blood cell transfusion, iron replacement, folic acid, erythropoietin, and vitamin B12 supplementation. Indications for supportive therapy should be corroborated by patient laboratory test values, such as hemoglobin, iron studies, folate, and vitamin B12. IVIG was also given in 3 cases; however, there is insufficient evidence to determine whether this treatment is necessary.<sup>10,27</sup> If AIHA is refractory to steroid treatment, the second line of treatment should be rituximab. Rituximab successfully treated 4 of 8 patients with refractory ICI-associated AIHA found in the literature.<sup>14,16,23,35</sup> If rituximab is unsuccessful, additional treatments can be considered, including splenectomy, plasmapheresis, and malignancy-specific treatment. If pure red cell aplasia is detected, cyclosporin A should be given. When developing a treatment plan, physicians should consider patient history, comorbidities, and other coexisting irAE if refractoriness continues. If the treating physician decides ICI treatment is the best treatment option, then the patient may be rechallenged with increased monitoring for recurrence of hemolysis.

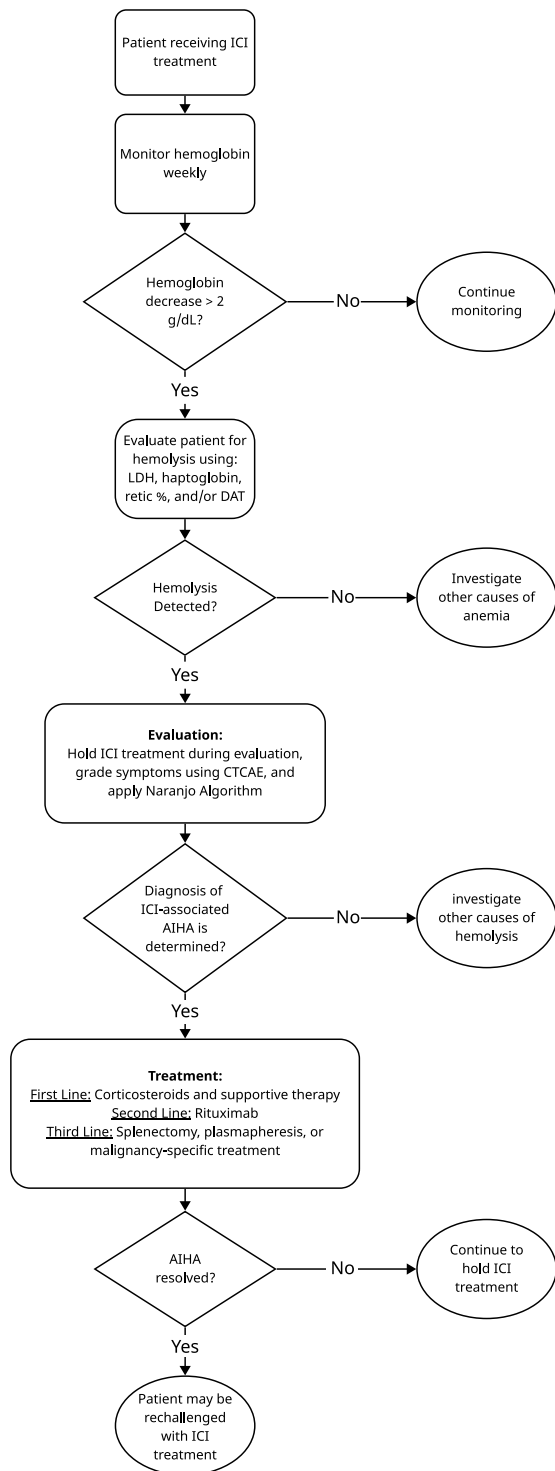
### Prognosis

Prognosis for patients who develop ICI-associated AIHA appears to be favorable, with only 1 reported death attributed to ICI-associated AIHA among 30 case studies in our review. No fatalities were reported in the study of French pharmacovigilance databases.<sup>12</sup> Post-AIHA hemoglobin levels were reported in 24 of the 30 cases in our review: 16 patients showed complete hemoglobin recovery, 6 had partial recovery, and 2 did not recover. Hemoglobin recovery was assessed using criteria proposed by Leaf et al, in which complete recovery is defined as a posttreatment hemoglobin level within 0.0 to 1.0 g/dL of the pretreatment level, and partial recovery as within 1.1 to 2.0 g/dL. In the case series by Leaf et al, 12 of 14 patients met the criteria for complete hemoglobin recovery, and 2 had partial recovery. The 2 patients in our review who did not recover included the fatal case reported by Tanios et al<sup>4</sup> and a case described by Ogawa et al,<sup>24</sup> in which the patient died of bacterial pneumonia before recovery could occur.

### CONCLUSION

ICI treatments improve the prognosis of many malignancies; however, these treatments are not without adverse events. Because of the ICI mechanism of action, patients' immune systems are upregulated, facilitating tumor cell destruction.<sup>2</sup> Unfortunately, this upregulation can also result in a loss of self-tolerance.<sup>2</sup> Immune-related adverse

events result from that loss.<sup>2</sup> AIHA is a rare and possibly underreported ICI-associated irAE. This study synthesized the diagnostic recommendations found in the literature and the assessment of reported cases to develop diagnostic and treatment recommendations. These diagnostic recommendations are to closely monitor patients on ICIs for hemolysis using weekly hemoglobin levels. If a change in



**Figure 2.** Recommended diagnostic and treatment flowchart.

hemoglobin value greater than 2 g/dL is detected, the patient should be evaluated for hemolysis. Hemolysis should be evaluated using laboratory tests such as LDH, haptoglobin, reticulocyte percentage or absolute count, and DAT. If hemolysis is detected, symptoms should be graded using CTCAE guidelines, and the Naranjo algorithm should be used to determine whether ICI is the likely cause of hemolysis. During the investigation, ICI treatment should be held. These recommendations are summarized in Figure 2.

After a diagnosis of ICI-associated AIHA is made, then ASCO guidelines should be followed, which recommend initially treating with corticosteroids. Our study recommends supportive therapy, including red blood cell transfusion, iron replacement, folic acid, erythropoietin, and vitamin B12 supplementation as needed based on patient laboratory values. If AIHA is refractory to steroid treatment, the available literature to date recommends rituximab as a second line of treatment.<sup>14,16,23,35</sup> If rituximab treatment is also unsuccessful, third-line treatment may include splenectomy, plasmapheresis, and malignancy-specific treatment. If pure red cell aplasia is detected, cyclosporin A should be given. Upon resolution of ICI-associated AIHA, the patient may be rechallenged with ICI treatment if it is the best treatment option. These treatment recommendations are summarized in Figure 2. When rechallenged, the patient should be monitored closely for recurrence of AIHA. If these recommendations are followed, early detection and treatment of ICI-associated AIHA are possible and may improve patient prognosis.

Literature on ICI-associated AIHA remains limited; future studies are needed to fully understand the causal mechanisms, the relationship between CLL and ICI-associated AIHA, other risk factors affecting patient outcomes such as a history of autoimmune diseases, and the effect of steroid treatment on ICI antitumor affect.

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