Received: 13 February 2024 | Revised: 17 April 2024 | Accepted: 26 April 2024

DOI: 10.1002/ajh.27361

CORRESPONDENCE

Intravenous immunoglobulin as a rescue therapy for severe adult autoimmune hemolytic anemia: Results from a French multicenter observational study

To the Editor:

Adult autoimmune hemolytic anemia (AIHA) is a rare but potentially life-threatening acquired autoimmune disease in which autoantibodies directed toward antigens of autologous red blood cells (RBC) membrane lead to their accelerated destruction. Corticosteroids are the cornerstone first-line therapy for primary warm AIHA (wAIHA) and rituximab is commonly used off-label as a second-line option in most countries,[1] whereas for patients with cold agglutinin disease (CAD) who need to be treated, corticosteroids are of little efficacy and treatment with rituximab alone or in combination with bendamustine may be used depending on patients' age and comorbidities.[1] Adult patients with severe AIHA who are admitted in the intensive care unit (ICU) have a short-term mortality rate of 13% in ICU and of 30% after 1 year of follow-up.[2] In such severe, life-threatening cases of AIHA, the off-label use of IVIg is often considered[1–3] by analogy with immune thrombocytopenia (ITP) and other autoantibody-mediated autoimmune diseases. Based on its pathophysiology AIHA can be seen as a good candidate for the use of IVIg, but there is actually only little evidence supporting the efficacy of IVIg in this setting, as the sole large retrospective series focused on this topic was published in 1993.[4]

We report here the results of an observational multicenter retrospective (2013–2021) study. The aim of the study was to assess the immediate efficacy and safety of IVIg used as a "rescue" therapy for the management of adult AIHA and to identify some predicting factors of response. Most of the patients were identified via the CARMEN-FRANCE AIHA registry (NCT02877706), a prospective, multicenter, nationwide registry set up in 2016 for adult patients with a new diagnosis of AIHA. To be included in the study, patients had to (1) be ≥18 years old; (2) have a diagnosis of AIHA defined as hemoglobin level <12 g/dL, with ≥2 features of hemolysis (i.e., low haptoglobin level and/or elevated lactate dehydrogenase (LDH) level and/or elevated indirect bilirubin level), and a positive direct antiglobulin test (DAT) with no other underlying cause of acquired or hereditary hemolytic anemia; and (3) have received at least one course of IVIg for the management of AIHA. Patients with primary or secondary wAIHA, CAD, mixed AIHA, or Evans syndrome based on consensual criteria[1] could be included. Patients with DAT-negative AIHA were excluded as well as those with Evans syndrome who received IVIg specifically for the management of ITP. Previous treatment lines were defined by every type of treatment (erythropoietin, corticosteroids, immunosuppressors, etc.) received for treating AIHA before the first administration of IVIg except for RBC transfusions which were considered separately. Concomitant therapies were defined either as ongoing treatments at the time of IVIg administration or treatments initiated/administered for AIHA within 14 days after IVIg administration.

The primary endpoint was to assess the overall response rate (ORR) to IVIg on day 7. Response (R) was defined as an increase of the Hb level ≥2 g/dL on day 7 ± 1 post-IVIg compared to the baseline Hb level (i.e., on the day of the first IVIg administration), in the absence of any transfusion within 7 days after IVIg. A good response (GR) was defined as a Hb level ≥10 g/dL on day 7 ± 1 post IVIg, with at least a 2 g increase from baseline and in the absence of any transfusion within 7 days after IVIg. Patients with an Hb increase <2 g/dL and/or those who were transfused within 7 days after IVIg were considered as nonresponders (NR). Based on the same response criteria, the overall response rate (R + GR) was also assessed at day 14 ± 1 when data were available. Patients who received RBC transfusion between day 7 and day 14 were considered as NR on day 14. Continuous variables were presented as median (min-max). Categorical variables were expressed as numbers and percentages (%). The reference date for day 0 (D0) was defined as the date of the first administration of the first course of IVIg.

The primary outcome variable was calculated based on the change in Hb levels between D0 and D7 post-IVIg. For assessing the variables associated with R achievement (vs. NR) at D7, we conducted logistic regression model. The following variables were included in the model for univariate analyses: the time elapsed since between AIHA onset and the first IVIg administration patient age <or ≥60 years, gender, type of autoimmune hemolytic anemia (i.e., cold, warm, or mixed-AIHA), primary or secondary form of AIHA, severe form (Hb < 6 g/dL at D0), normal reticulocyte count (<120 × 10^9/L), positive DAT for the C3 fraction of complement, identification of an infectious trigger for AIHA, newly diagnosed versus relapsed AIHA, concurrent use of corticosteroids or other concomitant treatments, and the number of transfusions received from D0 and D7. A significance threshold of $p < 0.05$ was applied for all statistical tests.

In total, among the 78 patients who were initially screened, 34 patients from 14 centers fulfilling eligibility criteria whose main baseline characteristics are described in Table 1 were eventually included (Figure S1). Patients had received a median of 1 (0–8)

TABLE 1 Baseline characteristics of the patients ($n = 34$).

Median age and (min-max)	59 years (19–91)
Sex ratio, *n* (%)	*N* = 18 females (53%)/16 males (47%)
AIHA subtype, *n* (%)	Warm AIHA: *n* = 23 (68%) including 7 Evans syndrome Cold AIHA: *n* = 6 (18%) Mixed-AIHA: *n* = 5 (14%)
Number (%) of secondary AIHAs and causes	*N* = 12 (35%) including: lymphoma (*n* = 3), primary immunodeficiency (*n* = 3), infection (*n* = 2), myeloid neoplasia (*n* = 2), SLE (*n* = 1), anti-PD1 (*n* = 1)
Baseline median Hb level (g/dL) and (min-max)s	6.1 (2.7–8.9)
Median Hb nadir (g/dL) pre-IVIg	4 .4 (1.7–7.6)
Median reticulocytes count ($\times 10^9$/L) and (min-max)	185 (24–675) *N* = 10 patients (29%) with a count <120
Main reason(s) raised by the clinician for the use of IVIg	AIHA severity (82%) Transfusion dependency (41%) Corticosteroid-refractoriness (38%) Infectious trigger (32%)
IVIg dose, number (%)	2 g/kg: *n* = 31 (91%) 1 g/kg: *n* = 3 (9%)
Median number of previous treatment lines for AIHA and type of treatment, *n* (%)	1 (0–8)
Corticosteroids	*N* = 30 (88%)
EPO	*N* = 13 (38%)
Rituximab	*N* = 8 (24%)
Immunosuppressor	*N* = 4 (12%)
Plasma exchange	*N* = 0 (0%)
Splenectomy	*N* = 1 (3%)
Eculizumab	*N* = 0 (0%)
Number of patients (%) with previous transfusion of RBCs and median number of packed RBcs (min-max)	*N* = 21 (62%) 2 (1–15)
Concomitant therapies[a]	Corticosteroids: *n* = 28 (82%) Recombinant Epo: *n* = 12 (41%) Rituximab: *n* = 10 (29%) Immunosuppressor/immunomodulator: *n* = 8 (24%) Plasma exchange: *n* = 5 (15%) Splenectomy: *n* = 1 (3%) Eculizumab: *n* = 1 (3%)
Number of patients who received RBC transfusion within 14 days after IVIg administration[b]	Transfusion: *n* = 14 (41%)

Abbreviations: AIHA, autoimmune hemolytic anemia; Hb, hemoglobin; IVIg, intravenous immunoglobulin; PD1, programmed cell death protein; RBC, red blood cells; SLE, systemic lupus erythematosus.

[a]Therapies received from within Days 0 and 14 after IVIg.

[b]Ongoing treatments at time of IVIg administration or treatments initiated/administered for AIHA within 14 days after IVIg.

previous treatment lines prior to IVIg and up to a median of 5 (1–12) at the end of follow-up (Table 1). In total, 21 patients (62%) were transfused at least once prior to IVIg administration (median number of packed-RBC: 2 [1–15]). At time of IVIg administration, 82% of the patients were on corticosteroids and 41% were on weekly subcutaneous recombinant Epo.

Overall, 11 patients (32.4%) responded to IVIg on day 7, including two with GR and nine with R. Thirteen patients (38.2%) were transfused between D0 and D7 and were therefore considered NR. On day 14 after IVIg first administration, data on the Hb level were available for 28 patients (82.4%) and the ORR was 57%, including six patients who achieved a GR and 10 who achieved R. Different patterns of response (GR, R, and NR) observed after IVIg administration are illustrated in Figure S2.

On univariate analysis (Table S1) as well as multivariate analysis (data not shown), the only factor that was significantly associated with a higher response rate to IVIg was the early time of IVIg administration after AIHA onset (ORR 14.571 [1.866–338.736], $p = 0.030$).

Regarding safety, no case of AIHA exacerbation due to IVIg-induced hemolysis was observed.

One case of thromboembolic event with a good outcome (partial thrombosis of the splenic artery followed by a thrombosis of the inferior vena cava and pulmonary embolism) occurred 5 days after IVIg administration in a 60-year-old man.

In the present retrospective series on 34 adult patients with severe and/or transfusion-dependent AIHA treated with IVIg, the ORR was 32.4% on Day 7. The safety of IVIg was good as only one potentially related thromboembolic event was observed, in a patient with recent COVID-19 and active hemolysis. To the best of our knowledge, this is the largest study focused on this topic since 1993.[4] Among responders, different patterns of response to IVIg were observed including an immediate and clear increase in the Hb level suggesting an FcR-blockade like mechanism in few of them. The only parameter associated with a better response to IVIg was the early administration of IVIg in newly diagnosed AIHA. In the previous pilot study on 37 patients (including 32 adults and five children) reported in 1993, the ORR (i.e., increase of Hb level of at least 2 g/dL within 10 days) to IVIg was 39.7%.[4] However, the authors did not specify whether some patients had been transfused during this period of time[4] and interestingly higher doses of IVIg (5–7 g/kg) were not associated with a higher efficacy. Furthermore, two other small observational studies with respectively five and 17 patients with AIHA did not find any evidence for IVIg efficacy, with an unchanged survival rate of 51Cr-labeled autologous RBC in 4/5 patients studied.[5,6] Our study has some limitations: first, due to its retrospective and uncontrolled design, some data could have been missed, and memorization bias could not be excluded for the few patients recruited outside the CARMEN registry. Moreover, since most of the patients included had severe AIHAs with a relatively high (14%) rate of mixed AIHAs which are known to be more severe,[1] and were receiving concomitant therapies, efficacy of IVIg was difficult to assess in some patients and the results cannot be extrapolated to every type of AIHA. Lastly, the relative low number of patients included may have reduced the chance to identify some parameters that could be associated with a higher response rate and in particular the DAT pattern and the type of AIHA (i.e., warm, mixed or cold).

In conclusion, based on this retrospective observational study, we confirm that in addition to standard of care, the off-label use of IVIg may be helpful in one third of adults managed for severe AIHA. In the absence of any clear predicting factor of response, and taking into account the cost and the recurrent problems of IVIg shortage, the use of IVIg in this setting should be limited and well weighed.

CONFLICT OF INTEREST STATEMENT

Marc Michel received honoraria (advisory boards and speaker fees) from Sanofi, Novartis, Sobi, Argenx, Alexion, and Amgen. Guillaume Moulis received honoraria (advisory boards and speaker fees) from Argenx, Amgen, Novartis, and Sobi and research funding from Amgen, Novartis, Sanofi, and Grifols. Bertrand Godeau received honoraria (advisory boards and speaker fees) from Amgen, Novartis, Sobi, and Grifols. Matthieu Mahevas received honoraria (speaker fees) from Amgen and Novartis and research funding from Glaxo-Smith-Kline.

DATA AVAILABILITY STATEMENT

Data are available at the Department of Internal Medicine and Clinical Immunology, Aix Marseille Univ, APHM, La Timone Hospital, Marseille, France.

M. Michel[1], M. Saïr[2], E. Rivière[3], G. Moulis[4], T. Comont[5], N. Costedoat-Chalumeau[6], C. Pouchelon[1], D. Boutboul[7], A. Benyamine[8], A. Bert[9], P. -Y. Jeandel[10], S. Hamrouni[11], N. Belfeki[11], H. Lobbes[12], A. Dossier[13], D. Gobert[14], M. Mahevas[1], B. Godeau[1], Y. Gallien[15], M. Ebbo[2]

[1]*Department of Internal Medicine and Clinical Immunology, French National Reference Center for Adult' Immune Cytopenias, Henri-Mondor University Hospital, Assistance Publique Hôpitaux de Paris, Université Paris-Est Créteil, Créteil, France*

[2]*Department of Internal Medicine and Clinical Immunology, Aix Marseille Univ, APHM, La Timone Hospital, Marseille, France*

[3]*Department of Internal Medicine and Clinical Immunology, Bordeaux University Hospital, Bordeaux, France*

[4]*Department of Internal Medicine and Clinical Immunology & Clinical Investigation Center 1436, Purpan Hospital, Toulouse University Hospital, Toulouse, France*

[5]*Department of Internal Medicine and Clinical Immunology, Oncopole Hospital, Toulouse University Hospital, Toulouse, France*

[6]*Department of Internal Medicine and Clinical Immunology, Assistance Publique Hôpitaux de Paris, APHP, Cochin University Hospital, Créteil, France*

[7]*Department of Internal Medicine and Clinical Immunology, Assistance Publique Hôpitaux de Paris, APHP, St Louis Hospital, Paris, France*

[8]*Department of Internal Medicine and Clinical Immunology, Aix Marseille Univ, APHM, Hopital Nord, Marseille, France*

[9]*Department of Internal Medicine and Clinical Immunology, CHU de Lyon, Hospices Civils, Lyon, France*

[10]*Department of Internal Medicine and Clinical Immunology, CHU de Nice, l'Archer Hospital, Nice, France*

[11]*Department of Internal Medicine and Clinical Immunology, Groupe Hospitalier Sud, CH de Melun, Melun, France*

[12]*Department of Internal Medicine and Clinical Immunology, CHU de Clermont Ferrand, Clermont Ferrand, France*

[13]*Department of Internal Medicine and Clinical Immunology, Assistance Publique Hôpitaux de Paris, APHP, Bichat Hospital, Paris, France*

[14]*Department of Internal Medicine and Clinical Immunology, Assistance Publique Hôpitaux de Paris, APHP, St Antoine Hospital, Paris, France*

[15]*Santé Publique, Agence Régionale de Santé, Ile de France, Saint Denis, France*

Correspondence

M. Michel, Service de Médecine Interne, Henri-Mondor University Hospital, Université Paris-Est Créteil, 1 avenue du Gal de Gaulle, 94010 Créteil cedex, France.

Email: marc.michel2@aphp.fr

ORCID

M. Michel https://orcid.org/0000-0002-9822-7400
T. Comont https://orcid.org/0000-0002-6891-9238
D. Boutboul https://orcid.org/0000-0002-5006-8279
H. Lobbes https://orcid.org/0000-0002-8511-8432
M. Mahevas https://orcid.org/0000-0001-9182-1434

REFERENCES

1. Jäger U, Barcellini W, Broome CM, et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: recommendations from the First International Consensus Meeting. *Blood Rev*. 2020;41:100648.
2. Fattizzo B, Zaninoni A, Nesa F, et al. Lessons from very severe, refractory, and fatal primary autoimmune hemolytic anemias: severe, refractory and fatal autoimmune hemolytic anemias. *Am J Hematol*. 2015;90(8):E149-E151.
3. Pouchelon C, Lafont C, Lafarge A, et al. Characteristics and outcome of adults with severe autoimmune hemolytic anemia admitted to the intensive care unit: results from a large French observational study. *Am J Hematol*. 2021;97(10):E371.
4. Flores G, Cunningham-Rundles C, Newland AC, Bussel JB. Efficacy of intravenous immunoglobulin in the treatment of autoimmune hemolytic anemia: results in 73 patients. *Am J Hematol*. 1993;44(4):237-242.
5. Mueller-Eckhardt C, Salama A, Mahn I, Kiefel V, Neuzner J, Graubner M. Lack of efficacy of high dose intravenous immunoglobulin in autoimmune haemolytic anaemia: a clue to its mechanism. *Scand J Haematol*. 2009;34(5):394-400.
6. Gil-Fernández JJ, Flores Ballester E, González Martínez M, et al. Are intravenous immunoglobulins useful in severe episodes of autoimmune hemolytic anemia? Comparative results in 21 episodes from a single center. *Med Clin*. 2013;141(5):201-204.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.