Correspondence
James N. George, MD, College of Public Health, University of Oklahoma Health Sciences Center, 801 NE 13th Street, Oklahoma City, OK 73104.
Email: james-george@ouhsc.edu

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SUPPORTING INFORMATION

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Predictors of refractoriness to therapy and healthcare resource utilization in 378 patients with primary autoimmune hemolytic anemia from eight Italian reference centers

To the Editor:

Autoimmune hemolytic anemia (AIHA) is a rare and heterogeneous disease with a presentation/phenotype ranging from mild/compensated to life-threatening.[1,2] Moreover, some cases show refractoriness to/relapse after first and further therapy lines, leading to significant and underestimated healthcare burden. Here, we retrospectively analyzed 378 primary AIHA cases (135 M and 243 F, median age 61 years, range 5-94) from eight Italian hematological centers and followed for a median of 4.3 years (range 1-27) focusing on predictors of multiple refractoriness to second and further therapy lines and healthcare resource utilization.

Figure 1A shows clinical and laboratory characteristics of AIHA patients at onset, divided according to the serological type in warm (direct antiglobulin test-[DAT]-positive for IgG or IgG + C), cold (CAD, usually IgM driven, DAT-positive for C), mixed (both IgG and high titer cold agglutinins), and atypical forms (DAT negative, IgA only or warm IgM). Hemoglobin values were significantly lower and LDH higher in IgG + C wAIHA, mixed and atypical cases ($P < .001$ and $P = .0034$, respectively), and hemoglobin and LDH values were negatively correlated ($P < .001$). Absolute reticulocytes were reduced in CAD and mixed forms ($P = .0013$), and the reticulocyte index was lower in CAD ($P = .023$) and in cases with Hb ≤ 6 g/dL (53 vs 86 $P < .001$) (Figure 1B). Overall, inadequate reticulocytosis was observed in more than half of patients. Second therapy line was mostly administered in mixed, IgG + C wAIHA, and in CAD ($P = .011$), and the ultrarefractory cases requiring four or more lines of therapy were mainly CAD, mixed, and atypical AIHA. Infections were observed in 14% of cases, mostly wAIHA and mixed forms ($P = .02$). Thrombosis occurred in 15% mostly IgG + C wAIHA and atypical AIHA ($P = .04$). Evans' syndrome was more frequent in mixed AIHA and, to a lesser extent, in atypical ($P = .033$) and in severe forms (74% with Hb < 8 g/dL vs 26%, $P = .005$). Acute renal failure was reported in 3% of patients, with no relationship with AIHA type/Hb values.

Predictors of relapse/refractoriness were analyzed in a total of 304 relapses, of whom 211 (69%) after first-line, 69 (23%) after second-line, 19 (6%) after third-line, and 5 (2%) after further therapy lines. Multivariate Cox regression analysis demonstrated that anemia severity at onset was associated with an increased risk of relapse, with the following hazard ratios: 1.98 (95%CI 1.22-3.21) for patients with Hb ≤ 6 g/dL, 1.74 (95%CI 1.09-2.77) for cases with Hb 6.1-8 g/dL, and 1.61 (95%CI 0.99-2.62) for those with Hb 8.1-10 g/dL. Even considering hemoglobin as a continuous variable, each gram of reduction yielded a 7% greater risk of relapse (95%CI 2-13, $P < .013$). In addition, analysis showed increased hazard risks for forms other than wAIHA (1.21, 95%CI 0.95-1.54), and for Evans association (1.84, 95% CI 1.24-2.74). Notably, the presentation of an AIHA other than wAIHA together with Evans syndrome or with Hb < 8 g/dL resulted in a 2-fold higher risk of relapse; the presence of both Hb < 8 g/dL and Evans syndrome gave a 3-fold increased risk, and the association of the three conditions led to a ~4-fold increased risk of multiple relapses.

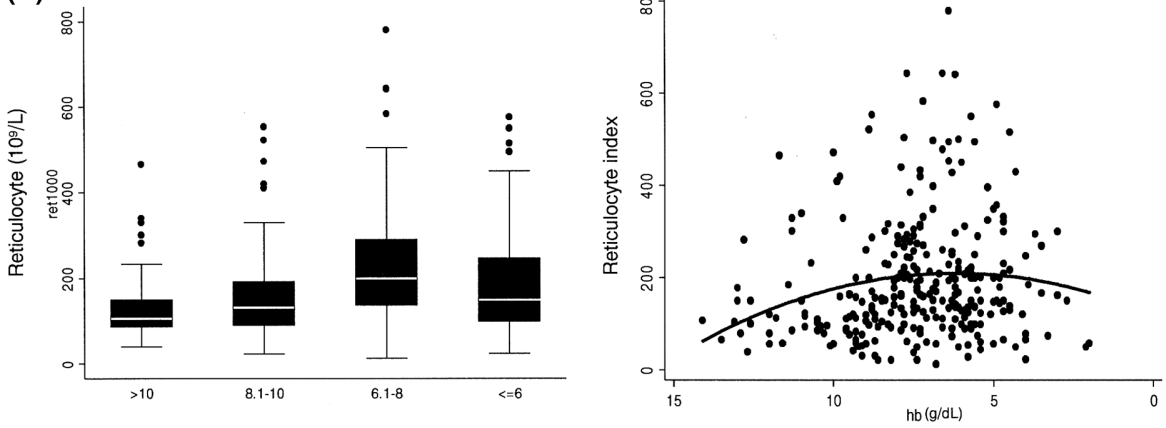
Seventy-five patients died during the follow-up, of whom 13 because of AIHA. Overall mortality was higher in more severe cases (24% for cases with Hb <6 g/dL vs 18% for those with Hb >6 g/dL, $P = .04$), with the following hazard risks: Evans syndrome (8, 95% CI 2.5-26, $P = .001$), acute renal failure (6.3, 95% CI 1.4-29, $P = .016$), and infections (4.8, 95% CI 1.5-15, $P = .007$). Thrombotic events did not result in increased risk of death.

Response to treatment is shown in supplementary material. In summary, ~80% of cases displayed an overall response (OR) after first line treatment with glucocorticoids, however only 25% had a sustained response. Rituximab and immunosuppressants were comparably used in second line (31% and 26%), with better responses for the former

(A)

	wAIHA (n=225)		CAD	Mixed AIHA	Atypical AIHA
	IgG (n=158)	IgG+C (n=67)	(n=107)	(n=24)	(n=22)
Median Age at diagnosis (yrs, range)	67 (5-94)	65 (21-92)	70 (28-94)	61 (20-86)	45 (25-78)
Hb (g/dL), median (range)	7.3 (2.1-14.1)	6.5 (2.0-11.5)	8.2 (4.0-13.5)	6.4 (4.3-10.7)	6.6 (3.0-10.9)
LDH (ULN), median (range)	1.7 (0.6-26.7)	1.8 (0.8-7.2)	1.4 (0.3-12.2)	1.7 (0.6-9.8)	2 (0.7-18.1)
Ret (x10⁹/L), median (range)	180 (22-644)	143 (53-641)	123 (13-644)	181 (45-576)	195 (29-780)
inadequate reticulocytosis, n of pts (%)	86 (54)	35 (52)	69 (64)	15 (62)	14 (64)
Therapy					
No therapy (%)	8 (5)	1 (1)	23 (22)	0 (0)	1 (5)
1 line of therapy, n of pts (%)	150 (95)	66 (98)	84 (79)	24 (100)	21 (95)
2 lines of therapy, n of pts (%)	60 (38)	39 (58)	51 (53)	16 (67)	8 (36)
3 lines of therapy, n of pts (%)	23 (15)	13 (19)	26 (24)	8 (33)	5 (22)
4 or more lines of therapy, n of pts (%)	6 (4)	2 (3)	10 (9)	2 (8)	2 (9)
Complications					
Infections, n of pts (%)	21 (13)	17 (25)	9 (8)	4 (17)	1 (5)
Thrombosis, n of pts (%)	21 (13)	18 (27)	14 (13)	1 (4)	4 (18)
Acute renal failure, n of pts (%)	5 (3)	3 (4)	1 (1)	1 (4)	1 (4)
Evans syndrome, n of pts (%)	11 (7)	5 (7)	1 (1)	4 (17)	2 (9)
Death, n of pts (%)	31 (19)	10 (15)	25 (23)	7 (29)	2 (9)
Death for AIHA, n of pts (%)	5 (3)	2 (3)	3 (3)	3 (13)	0 (0)

(B)



(C)

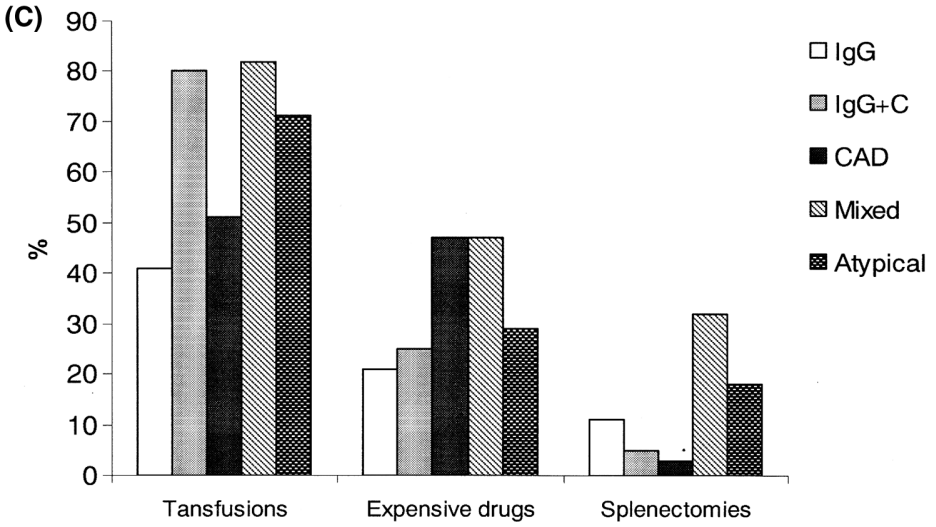


FIGURE 1 (A) Clinical and laboratory characteristics of patients at onset, therapy lines, complications and death, divided according to AIHA serological type. (B) Reticulocyte counts as a function of Hb at onset: AIHA cases are grouped in mild (Hb > 10 g/dL), moderate (Hb 8.1-10 g/dL), severe (Hb 6.1-8 g/dL), and very severe (Hb ≤ 6 g/dL) (left). Individual values of Hb are shown in relation to reticulocyte index (absolute reticulocyte count × patient' Hb/normal Hb), with the corresponding equation line (ret(× 1000) = 119 + 29.2 × Hb - 2.4 × Hb^2) (right). Both panels A and B indicate that compensatory reticulocytosis increases until Hb values of about 8 g/dL, but more severe cases are characterized by reticulocytopenia/inadequate reticulocytosis. (C) Healthcare resource utilization: Percentage of patients receiving transfusions, highly expensive drugs (rituximab, bortezomib, eculizumab), and splenectomized, grouped according to AIHA serological type

(88% OR, 53% complete responses, CR); immunosuppressants gave mainly partial responses (PR, 46%) and were generally administered together with glucocorticoids. Rituximab had a longer relapse free survival compared with immunosuppressants (22 months, range 2-71 vs 12 months, range 2-43), and a greater proportion of sustained responses (23/35, 51% vs 13/31, 42%). Splenectomy (n = 38, ~10% of the whole series) had been performed mostly in second line (63%), particularly before 2000 (8/9), with very good responses (85%). Regarding third line therapy, rituximab was preferred compared to immunosuppressants (46% vs 15%). Importantly, OR and CR to rituximab were comparable to those observed in second line (92% and 41%). Splenectomy had become a third line option in most recent years (11/24, 46%) and confirmed its excellent performance. Further lines were required in 29 multirefractory patients (8% of cases), and included glucocorticoids/rituximab, glucocorticoids/immunosuppressants, regular transfusions, bortezomib (1.3 mg/m^2 iv single agent on days 1, 4, 8, 11, n = 8), plasma-exchange (N = 5), eculizumab (N = 2), erythropoietin (N = 12), high dose cyclophosphamyde/vincristine (N = 1), and autologous peripheral stem cell transplant (N = 1). Response to treatments is difficult to assess, due to their combinations/overlap. Notably, six cases underwent splenectomy as forth or further line, all obtaining a response. Considering all the 32 cases that respond to splenectomy (either performed in second, third, or further lines), 13 (41%) relapsed after a median of 16 months (range 2-147), while 19 (59%) cases are still on remission at the time of the study. Regarding response to treatment according to AIHA type, a CR to glucocorticoids was mostly observed in wAIHA, mixed and atypical cases (~50%), whereas CR rate was lower in CAD (24%) (P = .0015), and generally observed at high dosages. A complete response to rituximab was mainly observed in IgG wAIHA (62%), whereas the drug was less effective in IgG + C wAIHA, CAD, and mixed forms (44%-54%).

Figure 1C and Supporting Information show healthcare utilization in a subgroup of 190 cases comparable to the remaining 188 in terms of demographics, hematological parameters, number, and type of therapy lines. One hundred twenty-one patients (64%) required at least one hospital admission, with 9% needing three or more. The median admission duration was 15 days, with 13% of cases needing more than 30 days, and admissions length was negatively correlated to Hb levels (r = −0.26, P < .001). The higher frequency was observed in IgG + C wAIHA, mixed and atypical cases (P = .006). Concerning outpatients, median number of visits per year was five, but 42 cases (22%) required more than a monthly visit. As regards therapeutic procedures, 103 patients (54%) required at least one transfusion, with 11/103 patients (11%) needing more than 20 transfusions (the established threshold for chelation), and six cases more than 50. Transfusion need was higher in IgG + C wAIHA, mixed and atypical cases (P = .004), and correlated with a more severe disease, that is, anemia, hemolysis and inadequate bone marrow compensation (Hb r = −.26, P < .001; LDH r = .21, P < .01; BMRI r = .15, P < .05). Considering transfusions as a function of follow-up length, the median was 2 per year, with 27 cases necessitating 4 or more (one subject about a weekly support). Highly expensive drugs were administered in 65 cases (34%, 56 rituximab, 8 bortezomib, and 2 eculizumab), and splenectomy performed in 20 patients (11%). The administration of highly expensive drugs was higher in CAD and mixed cases (P = .01).

In conclusion, this is the largest study aimed at identifying predictors of refractoriness to multiple therapy lines and healthcare resource utilization in primary AIHA in the real-life and outside clinical trials. We found that hemoglobin level at onset is the only laboratory parameter associated with an increased risk of refractoriness, from 2-fold for moderate to 3-fold for severe cases. Anemia severity was associated with reticulocytopenia/inadequate reticulocytosis, present in more than a half of patients, typically CAD and mixed forms. Thrombocytopenia (Evans syndrome) resulted in a 2-fold increased relapse risk, highlighting the detrimental effect of a more complex immune dysregulation involving multiple hematological lineages. Moreover, refractory/relapsing AIHAs were those with complement involvement (warm IgG + C, mixed, and CAD), suggesting the primary role of this powerful amplification system in the degree of AIHA immune dysregulation. Regarding therapy, known to be mainly based on experts opinion,[3–5] rituximab had a longer relapse free survival (~2 years), and was effective in ~50% of cases in first and further lines. The drug was used as first or early-second line in very severe cases, particularly in CAD cases that are known to respond to unacceptable high glucocorticoid doses only. At variance, immunosuppressants induced partial responses with decreasing efficacy after first line. Splenectomy had high response rates (~85%) and was curative in ~60% of warm AIHA cases, even when performed as third or further lines. This option, although marked by infectious and thrombotic complications, and contraindicated in CAD, should not be forgotten, given its potential curative ability, as recently suggested for immune thrombocytopenia.[6] Healthcare resource utilization was important in AIHA, with ~2/3 of patients requiring hospital admissions, 1/2 transfusions, and ~1/3 highly expensive drugs. In a small group of severe/ultrarefractory cases (10%-15%, mainly CAD, IgG + C wAIHA, mixed and atypical forms) admissions lasted more than 30 days, transfusion need exceeded 20 units per year, the established threshold for chelation, and several highly expensive drugs were administered, representing a significant burden on the patient and the medical system.

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CONFLICT OF INTERESTS

All the Authors disclose no commercial affiliation as well as consultancies, stock or equity interests, and patent licensing that could be considered to pose a conflict of interest regarding the submitted article.

AUTHOR CONTRIBUTIONS

Study design: WB
Patients follow-up: JAG, ML, AF, APL, NM, LS, SC, FC, PDF
Data collection: WB, AZ, BF, JAG, ML, AF, APL, NM, LS, SC, FC, PDF
Data analysis: WB, AZ, BF, DC
Data interpretation: WB, DC
Manuscript writing: WB, AZ, BF

Revised manuscript: JAG, ML, AF, APL, NM, LS, SC, FC, PDF, GR, DC, JAG, AZ, AC

ORCID

Wilma Barcellini http://orcid.org/0000-0003-1428-9944
Anna Zaninoni http://orcid.org/0000-0002-8614-3904
Bruno Fattizzo http://orcid.org/0000-0003-0857-8379

Wilma Barcellini MD[1]
Anna Zaninoni BS[1]
Bruno Fattizzo MD[1]
Juri Alessandro Giannotta MD[1]
Monia Lunghi MD[2]
Antonella Ferrari MD[3]
Anna Paola Leporace MD[3]
Nilla Maschio MD[4]
Laura Scaramucci MD[5]
Silvia Cantoni MD[6]
Federico Chiurazzi MD[7]
Dario Consonni MD[8]
Giuseppe Rossi MD[9]
Paolo De Fabritiis MD[5]
Gianluca Gaidano MD[2]
Alberto Zanella MD[1]
Agostino Cortelezzi MD[1,10]

[1]*UO Ematologia, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*
[2]*SCDU Ematologia, Dipartimento di Medicina Traslazionale, Università del Piemonte Orientale Amedeo Avogadro, Novara, Italy*
[3]*UO Ematologia, Ospedale Sant'Andrea, Facoltà di Medicina e Psicologia, Università "Sapienza", Rome, Italy*
[4]*UO Trasfusionale e immunologia, Centro Regionale Malattie del Sangue, Castelfranco Veneto, Italy*
[5]*UO Ematologia, Ospedale S. Eugenio, Rome, Italy*
[6]*SC Ematologia, Niguarda Cancer Center, ASST Niguarda, Milan, Italy*
[7]*Ematologia, Università degli Studi di Napoli Federico II, Napoli, Italy*
[8]*UO Epidemiologia, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*
[9]*SC Ematologia, Spedali Civili di Brescia, Brescia, Italy*
[10]*Università degli Studi di Milano, Milan, Italy*

Correspondence
Wilma Barcellini, UOC Ematologia, UOS Fisiopatologia delle Anemie - Padiglione Granelli, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via F. Sforza 35 - 20122 Milano, Italy.
Email: wbarcel@policlinico.mi.it

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Rapid intravenous infusion of velaglucerase-alfa in adults with type 1 Gaucher disease

To the Editor:

Gaucher disease (GD) is a lysosomal storage disorder for which safe and effective intravenous enzyme replacement therapy (ERT) has been available for more than 25 years.[1] The safety of the several ERTs for GD has also afforded the possibility of home infusions, reported by patients to be less stressful than those received in the hospital setting.[2] ERT is usually a life-long commitment to infusions, and many patients find the every-other-week (EOW) hourly infusions onerous, impacting aspects of their quality of life, including time taken off school/work. Over the past 2 decades, we became aware of several anecdotal reports from patients who while responsible for their infusions at home, decreased the infusion duration from the standard 60 min to as little as 2-5 min without apparent untoward effect.

Previous experience with a rapid intravenous infusion of biological materials, in particular, monoclonal antibodies, have defined a variable potential for reactions ranging from mild local irritations at the access site, various inflammatory and immunological responses to life-threatening hypersensitivities and anaphylactoid reactions. These reactions could conceivably occur too quickly for an effective response by a medical team, particularly in the home environment. Even in patients previously exposed to a particular drug without a reaction when infused at a standard rate, such concern is never trivial. Thus, in designing a study protocol to assess the safety of reduction of infusion duration of an ERT, the decision was taken to employ velaglucerase alfa (Shire, Zug Switzerland); an agent with good safety and tolerability profiles established during clinical trials and in postmarketing surveillance.[3,4] This investigator-initiated study aimed to ascertain the safety of decreased infusion time of velaglucerase alfa from 60 to 10 min using a step-wise reduction in time and allowing for home infusions in the final phase.