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Efficacy and safety of cyclosporine A treatment in autoimmune cytopenias: the experience of two Italian reference centers

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Abstract

Background: Immune thrombocytopenia (ITP) and autoimmune hemolytic anemia (AIHA) show good responses to frontline steroids. About two-third of cases relapse and require second-line treatment, including rituximab, mainly effective in AIHA, and thrombopoietin-receptor agonists (TPO-RAs) in ITP, while the use of splenectomy progressively decreased due to concerns for infectious/thrombotic complications. For those failing second line, immunosuppressants may be considered.

Objectives: The aim of this study was to evaluate the efficacy of cyclosporine treatment in patients with ITP and AIHA.

Design: In this retrospective study, we evaluated the efficacy and safety of cyclosporine A (CyA) in ITP ($N = 29$) and AIHA ($N = 10$) patients followed at two reference centers in Milan, Italy.

Methods: Responses were classified as partial [Hb $>$ 10 or at least 2 g/dl increase from baseline, platelets (PLT) $> 30 \times 10^9$/l with at least doubling from baseline] and complete (Hb $>$ 12 g/dl or PLT $> 100 \times 10^9$/l) and evaluated at 3, 6, and 12 months. Treatment emergent adverse events were also registered.

Results: The median time from diagnosis to CyA was 35 months (3–293), and patients had required a median of 4 (1–8) previous therapy lines. Median duration of CyA was 28 (2–140) months and responses were achieved in 86% of ITP and 50% of AIHA subjects. Responders could reduce or discontinue concomitant treatment and resolved PLT fluctuations on TPO-RA. CyA was generally well tolerated, and only two serious infectious complications in elderly patients on concomitant steroids suggesting caution in this patient population.

Conclusion: CyA may be advisable in ITP, which is not well controlled under TPO-RA, and in AIHA failing rituximab, particularly if ineligible in clinical trial.

Keywords: autoimmune hemolytic anemia, cyclosporine A, Evans syndrome, immune thrombocytopenia

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Key points

- Cyclosporine A is effective in about 80% of heavily pretreated patients with immune thrombocytopenia and autoimmune hemolytic anemia.
- Cyclosporine A allows tapering/discontinuation of concomitant treatments, particularly thrombopoietin-receptor agonists, and reduces platelets fluctuations.

Introduction

Autoimmune cytopenias (AICs), namely immune thrombocytopenia (ITP) and autoimmune hemolytic anemia (AIHA), are a heterogeneous group of diseases characterized by the presence of autoantibodies directed against platelets (PLT) and erythrocytes.[1,2] Although frontline steroids are the mainstay of treatment, most patients relapse and require further lines of therapy which

slightly differ according to the type of cytopenia.[3–5] Rituximab is mainly effective in AIHA, although only a fraction of cases would experience long-term relapse-free survival. Splenectomy is still a valid option although progressively abandoned given the availability of alternative therapeutic options, and increasing awareness of thrombotic and infectious risks. Regarding ITP, thrombopoietin-receptor agonists (TPO-RA) are effective in more than 70% of patients but may result in great PLT fluctuations, increased bone marrow reticulin fibrosis, and increased thrombotic risk.[2] Therefore, both efficacy and safety issues of standard second-line treatment options still leave a fraction of patients without effective treatment.[1,2,6] For refractory ITP and AIHA cases, novel therapeutic options are being explored in clinical trials, although not all patients are eligible. Classic immunosuppressants have definitively moved to third-line options, although they are still largely used in clinical practice as steroid-sparing agents.[1,2,6] Some of them received recent attention, such as mycophenolate mofetil, that was used frontline in adult ITP patients with interesting results.[7] Cyclosporine A (CyA), which has been widely used in post-transplant settings and in aplastic anemia (AA) since about for more than 30 years, is an oral drug with known but easily manageable toxicities.[8] However, few data exist on CyA efficacy in refractory AIC used either alone or in combination with other treatments. In this study, we aimed at evaluating the efficacy and safety of CyA in a cohort of patients with ITP and AIHA, followed at two reference hematologic centers in Milan, Italy. In addition, a review of the literature on CyA use in AIC is provided.

Patients and methods

We retrospectively investigated consecutive adult patients diagnosed with ITP or AIHA and followed at two Italian reference centers for AIC who received CyA treatment between June 2010 and February 2021. Diagnosis of AIHA and ITP was established according to current guidelines.[1,2,6]

AIHA was classified according to direct anti-globulin test (DAT) results as warm (either IgG-positive or IgG-positive plus complement, C, at low titer), cold (C-positive), mixed (IgG plus complement positive autoagglutination at room temperature, and high titer cold agglutinins), or atypical (DAT-negative, IgA-positive). Anemia severity was categorized according to previous scores for AIHA[6] in moderate (Hb $<$ 10 g/dl), severe (Hb $<$ 8 g/dl), and very severe (Hb $<$ 6 g/dl). ITP was categorized as severe (PLT $<$ 30×10^9/l), or moderate (PLT 30–100×10^9/l).[2] The positivity of anti-PLT autoantibodies was registered when available. The study was conducted according to the Declaration of Helsinki and approved by the local Ethical Committee (Comitato Etico Milano Area 2, code CYTOPAN, date of approval 9 March 2021). All patients' information has been de-identified. At the time of treatment, patients had given informed consent to therapy.

Clinical and hematological parameters at enrollment

Hematological data at the time of CyA start, and previous AIC history was retrospectively collected. Where available, bone marrow features were registered, including evaluation of cellularity, presence of fibrosis and its degree, lymphoid infiltrate and its phenotype, and cytogenetic study. The treatments administered were collected, including steroids, intravenous immunoglobulins (IVIG), rituximab, splenectomy, cytotoxic immunosuppression, thrombopoietin-receptor analogues (TPO-RA) eltrombopag and romiplostim, and recombinant erythropoietin (rEPO).

CyA treatment: efficacy and safety

All patients received a CyA starting dose of 3–5 mg/kg/day in two divided doses, and cyclosporine blood levels were initially monitored to avoid overdosing. The drug was subsequently tapered to a maintenance dose of 1.5–3 mg/kg/day according to hematological response. Responses were assessed at 3, 6, and 12 months and divided into partial (PR, for Hb $>$ 10 or at least 2 g/dl increase from baseline, PLT $>$ 30×10^9/l with at least doubling from baseline) and complete (CR, for Hb $>$ 12 g/dl and normalization of hemolytic markers; PLT $>$ 100×10^9/l). All relapses were registered, and adverse events, including infectious, thrombotic, and bleeding complications, graded according to the common terminology criteria CTCAE version 5. The occurrence of death and the relative causes were registered for all patients.

Statistical analysis

For statistical analysis, Student's *t*-test was used for continuous variables. Chi-square or Fisher's

exact tests were used for the comparison of categorical variables, where appropriate. Analysis of variance was performed using mean, median, ranges, and standard errors.

Review of the literature

A review of literature on CyA use in ITP and AIHA was performed by searching for indexed articles and published abstracts up to September 2021 in MEDLINE through PubMed and the National Library of Medicine.

Results

Baseline features

A total of 39 patients, 29 ITP (74%) and 10 AIHA (26%), 17 men (44%) and 22 women (66%), with a median age of 51 (range 21–81) years were included in the analysis (Table 1). Anti-PLT autoantibodies tested positive in 52% of ITP cases. AIHA were all warm forms, with DAT positivity for IgG in three patients, IgG + C in six, and IgA in one subject only. Bone marrow evaluation was performed in 33 cases (85%) and showed reduced cellularity in 11 (28%). ITP patients predominantly showed normal/increased megakaryocytes (75%), a low prevalence of dysplastic features, and had a polyclonal lymphoid infiltrate in 28% of cases, mainly of T cell phenotype (62%). Bone marrow fibrosis was detected in 53% of patients, of whom one grade 2 and one grade 3, both in patients treated with TPO-RA. Among AIHA patients, 40% of subjects displayed dyserythropoiesis, and two patients had a mixed (B/T cell phenotype) polyclonal lymphoid infiltrate. Overall, three patients (two ITP and one AIHA) showed a non-myelodysplastic syndrome defining cytogenetic abnormality.

Median time from diagnosis to CyA start was 35 months (range 3–293), and patients had required a median of 4 (1–8) previous therapy lines, including steroids (100%), IVIG (49%), splenectomy (41%), rituximab (13%), TPO-RA (65% of ITP cases, seven subjects had received both eltrombopag and romiplostim in sequence prior to CyA), danazol (13%), and cytotoxic immunosuppressors (10%; two azathioprine, one mycophenolate mofetil, one vincristine). Only two patients received CyA as second-line treatment: an ITP elderly patient who was not eligible to either splenectomy or TPO-RA therapy due to age and recent ischemic cardiopathy, and a young steroid-refractory wAIHA patient who refused splenectomy in the pre-rituximab era (2001).

Table 1. Baseline features of ITP and AIHA patients.

N	ITP	AIHA
	***N* = 29**	***N* = 10**
Sex, M/F	M = 15/F = 14	M = 2/F = 8
Age at AIC onset (years)	48 (24–68)	54 (21–81)
Autoimmunity tests	*N* = 23	*N* = 10
Anti-PLT positivity, *N* (%)	12/23 (52)	–
DAT positivity, *N* (%)	–	10 (100)[a]
Bone marrow evaluation	*N* = 28	*N* = 5
Cellularity (%)	40 (10–80)	25 (10–25)
Hypocellularity, *N* (%)	9 (32)	2 (40)
Megakaryocytes		
Reduced, *N* (%)	7 (25)	0 (0)
Normal/increased, *N* (%)	21 (75)	5 (100)
Dysplasia, *N* (%)	3 (11)	2 (40)
Bone marrow fibrosis, *N* (%)[b]	15 (53)	2 (40)
Lymphoid inflitrate, *N* (%)	8 (28)	2 (40)
T, *N* (%)	5 (62)	0 (0)
Mixed, *N* (%)	3 (38)	2/2 (100)
Altered cytogenetics, *N* (%)	2 (7), DELY	1 (20), tX;20
Previous lines of therapy	4 (1–8)	4.5 (3–5)
Steroids, *N* (%)	29 (100)	10 (100)
IVIG *N* (%)	15 (52)	4 (40)
Splenectomy, *N* (%)	13 (45)	3 (30)
Rituximab, *N* (%)	3 (10)	2 (20)
Romiplostim, *N* (%)	12 (41)	–
Eltrombopag, *N* (%)	14 (48)	–
Immunosuppressors *N* (%)	1 (3)	3 (30)
Danazol, *N* (%)	2 (7)	3 (30)

AIC, autoimmune cytopenia; AIHA, autoimmune hemolytic anemia; DAT, antiglobulin test; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulins; PLT, platelets.
[a]DAT positivities were as follows: 3 IgG + ; 6 IgG + C; 1 IgA.
[b]Bone marrow reticulin fibrosis WHO grade 1, before treatment with eltrombopag or romiplostim.

As shown in Table 2, at the time of CyA start, 93% of ITP and 40% of AIHA patients were receiving a concomitant medication including steroids ($N = 19$), IVIG (3), or TPO-RA (16). The main reason to start CyA in ITP was no response to previous treatments (72%), followed by the development of bone marrow fibrosis on TPO-RA (20%), contraindication for splenectomy (14%; two due to age and two due to recent ischemic cardiopathy on double anti-PLT agents), platelets fluctuations (10%), and wish to become pregnant (7%). In AIHA, CyA was mainly started due to non-response to previous therapy (100%), followed by contraindication for splenectomy in six patients (60%; four due to age and two due to recurrent infections). Finally, in three ITP and two AIHA patients, the choice of CyA was also supported by the presence of a polyclonal T cell infiltrate at bone marrow evaluation.

Efficacy evaluation

Median duration of CyA therapy was 28 (2–140) months, and response to treatment was achieved in 25 ITP (86%) and 5 AIHA (50%) patients. Median time from CyA start to response was 68 (31–131) days. Considering the various time points, in ITP overall response raised from 72% at month 3 to 91% of evaluable subjects at month 12, and in AIHA from 40% at month 3 to 83% at month 12 (Table 2). Specifically, in ITP responders median PLT increase from baseline was 32×10^9/l at month 3, 121×10^9/l at month 6, and 43×10^9/l at month 12. In AIHA, median Hb improved by 0.5 g/dl at month 3, by 1 g/dl at month 6, and by 2.6 g/dl at month 12. As regards additional endpoints, concomitant medications were reduced or discontinued in 81% of ITP and 50% of AIHA patients, including 10 subjects who stopped or tapered TPO-RA (five each). Moreover, 3/3 ITP patients resolved PLT fluctuations on CyA treatment. By statistical analysis, we did not identify any baseline clinical or laboratory factors significantly associated with response to CyA, including age, gender, disease duration, bone marrow features, or DAT positivity.

Overall, 16 patients (9 ITP and 7 AIHA) stopped therapy, mainly due to non-response (33% ITP and 72% AIHA) or relapse of the autoimmune cytopenia (33% of ITP and 28% of AIHA). Interestingly, three ITP patients who had achieved a complete response (CR) on treatment were able to taper and discontinue CyA, maintaining a long-term remission off-treatment. These subjects were one male and two females, with a median age of 66 (52–77) years, who had received a median of 4 lines (4–5) of therapies before CyA, including splenectomy.

Safety evaluation

Adverse events were mainly grade 1–2, occurring in 28% of patients, and included asthenia, dyspnea, myalgia, nausea, vomiting, diarrhea and abdominal pain, hypertrichosis, epistaxis, petechiae, and an Escherichia coli cystitis. Three patients had a slight increase in creatinine values (median 1.5 g/dl) that was resolved by increasing water intake and by reducing CyA dose. Two patients on concomitant long-term steroids developed a $G \geqslant 3$ event, including one aspergillus lung infection (in a previously splenectomized AIHA patient) and one fatal pneumocystis jirovecii pneumonia. Notably, none of the patients was receiving anti-pneumocystis prophylaxis. Finally, lymphocyte counts did not show any significant changes during CyA treatment, and some subjects previously treated with rituximab showed persistent lymphopenia.

Review of the literature

A total of 23 reports have been published involving the use of CyA in AIC for a total of 441 patients (Table 3). They were mainly pediatric studies (60%) and included 10 case reports/series,[9–18] 8 clinical trials,[19–26] and 5 retrospective studies[27–31] of CyA used as single agent or in combination.

ITP reports included patients with relapsed or refractory disease, and the overall response to CyA was about 65% (180/278 patients, case reports excluded), without differences among pediatric and adult settings.[20–25,27–29] Regarding combined regimens, the association of CyA and recombinant thrombopoietin (rTPO) *versus* rTPO single agent yields similar response rates (over 80%), but fewer relapses (29% *versus* 88% at 3 months).[21] In a clinical trial of 20 adult ITP patients, the association of CyA plus steroids and rituximab achieved a relapse-free survival of 92% and 76% at 12 and 24 months, respectively.[22] These results, although in a small series, seem better than those observed in larger studies with

Table 2. CyA treatment in ITP and AIHA patients.

N	**ITP**	**AIHA**
	N **= 29**	***N*** **= 10**
Time from first line to CyA (months)		
Reason to start CyA	43.6 (3–293)	7 (6–69)
Refractory disease, *N* (%)	21 (72)	10 (100)
PLT fluctuations, *N* (%)	3 (10)	–
BM fibrosis on TPO-RA, *N* (%)	6 (20)[a]	–
Splenectomy contraindicated, *N*(%)	4 (14)	6 (60)
Wish of pregnancy, *N* (%)	2 (7)	–
T cell infiltrate, *N* (%)	3 (10)	2 (20)
Concomitant medications		
Steroids, *N* (%)	15 (52)	4 (40)
IVIG, *N* (%)	3 (10)	0 (0)
Romiplostim, *N* (%)	6 (20)	–
Eltrombopag, *N* (%)	10 (34)	–
Time on CyA (months)	28.2 (2.3–140)	27.85 (9.3–39)
Hematalogic response[b], *N* (%) CR–PR		
3	12/29(41)–9/29(31)	3/10(30)–1/10(10)
6	13/26(50)–9/26(35)	2/10(20)–2/10(20)
12	8/23(35)–13/23(56)	3/6(50)–2/6(33)
Other outcomes		
Weaning concomitant Med, *N* (%)	22/27 (81)	2/4 (50)
Reduced PLT fluctuations, *N* (%)	3/3 (100)	–
Successful pregnancy, *N* (%)	1/2 (50)	–
Relapses, *N* (%)	3/21 (14)	2/5 (40)
Sop therapy, *N* (%)	9 (31)	7 (70)
Non-response, *N* (%)	3/9 (33)	5/7 (72)
Relapse, *N* (%)	3/9 (33)	2/7 (28)
Persistent remission, (%)	3/9 (33)	0 (0)
Adverse events, *N* (%)	7 (24)	4 (40)
Grade 1–2, *N* (%)	5 (17)	4 (40)

(Continued)

Table 2. (Continued)

N	ITP	AIHA
	N = 29	*N* = 10
Grade 3–4, *N* (%)	2 (7)	0 (0)
Infections, *N* (%)	3 (10)	0 (0)
Death, *N* (%)[c]	5 (17)	4 (40)
Possibly related to CyA, *N* (%)	1/5 (20)	0/4 (0)

AIHA, autoimmune hemolytic anemia; BM, bone marrow; CR, complete response; CyA, cyclosporine A; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulins; PLT, platelets; PR, partial response; TPO-RA, thrombopoietin-receptor agonists.
[a]These patients had increased bone marrow fibrosis (WHO grade 1 *N* = 3, grade 2 *N* = 1, and grade 3 *N* = 1) after therapy with TPO-RA.
[b]The two AIHA patients achieving a PR only had persistently altered LDH and unconjugated bilirubin levels, while those achieving CR, by definition, reached full normalization of hemolytic markers.
[c]Causes of death in ITP included fatal pneumocystis jirovecii pneumonia, COVID pneumonia, end-stage liver disease, and elderly marasmus in two; in AIHA, sepsis, heart failure, thromboembolic event, and elderly marasmus. All events, but the first, occurred in patients of CyA treatment.

rituximab monotherapy, where long-term remission was 20–30%.[32–34] In the setting of secondary ITP, a recent study including 83 adult patients with ITP associated with connective tissue disease showed that CyA was inferior to rituximab in terms of response rates (82% *versus* 54% at 6 months).[28]

AIHA studies mainly consisted of case reports[12–18] with only one retrospective cohort study including relapsed or refractory subjects.[30] Overall response rate was about 70% (51/73, case reports excluded). In a clinical trial enrolling adult patient with AIHA and Evans syndrome (the association of ITP and AIHA), the combination of CyA plus danazol and steroids was more effective than steroids alone with a 89% *versus* 58% of patients achieving a response and a relapse rate of 3% *versus* 70%.[26] Finally, in a recent French retrospective study involving 34 pediatric AIC patients, response rates were higher in AIHA and Evans syndrome (about 50%) compared to ITP subjects who did not respond.[31]

Discussion

In this study, we show that CyA is effective in a large proportion of pretreated and refractory AIC patients with an effect lasting more than 2 years. Responses required at least 3 months to be observed, and some patients showed benefit as late as at 12 months. This may be due to the immunomodulatory effect of CyA, including promotion of regulatory T cells differentiation with restoration of a tolerogenic *milieu*, which takes time to establish.[31] The rationale of using a T cell targeting agent in autoantibody-mediated conditions, such as ITP and AIHA, resides in the dysregulation of cellular immunity in the pathogenesis of these diseases. This includes direct cellular damage, presentation of self-antigens, and cytokine production leading to amplification of the dysregulated immune response and disease chronicization. Consistently, a T cell polyclonal infiltrate may be observed in the bone marrow of a proportion of ITP and AIHA patients,[35,36] and T cell enrichment has been recently reported by RNA single-cell sequencing in ITP and AIHA.[37,38] These observations are also in keeping with the efficacy of other anti-T cell agents, that is, mycophenolate mofetil in the treatment of ITP.[7] In our case series, best responses were observed in ITP (up to 86%), fairly greater than those reported in the literature, although the great heterogeneity of published studies (clinical trials, retrospective studies, and combination regimens) impedes a direct comparison.

Considering current guidelines,[2] it is difficult to establish the position of CyA in ITP. Rituximab, TPO-RA, and splenectomy are considered as equivalent second-line options to be adopted in accordance with patient' age, comorbidities, and quality of life.[2] Splenectomy has been

Table 3. Available literature regarding the use of CyA in patients with ITP, AIHA, and their association (Evans syndrome).

Cytopenia type	No. of patients	Setting	Comments	Ref.	Study type
ITP	3	Pediatric	Low doses of CyA induced a CR in all patients after 1 month of treatment.	Moskowitz *et al.*[9]	Case report
ITP	2	Pediatric	A relapsed or refractory patient who experienced persistent remission in association with steroid.	Gesundheit *et al.*[10]	Case report
ITP	12	Adult	Overall response was observed in 10 patients (83%), 9 complete.	Emilia *et al.*[19]	Clinical trial
ITP	14	Pediatric	CyA at 10 mg/kg/day induced an overall response rate in 49.5% of heavily pretreated ITP patients.	Perrotta *et al.*[20]	Clinical trial
ITP	36	Adult	Patients were randomized to receive recombinant thrombopoietin (rTPO) plus or minus CyA. No differences were observed in the two arms: response rates (89.5% for rTPO + CyA *versus* 94.1% for rTPO alone at week 2). Patients in the CyA arm showed lower rate of relapse (29.4% *versus* 87.5% at month 3).	Cui *et al.*[21]	Clinical trial
ITP	2	Adult	CR was obtained in both patients and persisted after CyA discontinuation. Both subjects had been previously splenectomized.	Hlusi *et al.*[11]	Case report
ITP	20	Adult	Treatment with CyA, steroids, and rituximab induced a response in 60% of patients at 6 months. Responders enjoyed relapse-free survivals of 92% and 76%, respectively, at 12 and 24 months.	Choi *et al.*[22]	Clinical trial
ITP	30	Pediatric	A CR observed in 57% of patients and in seven subjects (23%) was long-lasting on continuing low doses of CyA.	Liu *et al.*[27]	Retrospective study
ITP	40	Adult	Combination of CyA, rituximab, and dexamethasone in relapsed or refractory ITP induced an overall response of 75% at 6 months.	Thabet and Moeen[23]	Clinical trial
ITP	67	Pediatric	Relapsed or refractory ITP children treated with CyA showed more rapid response as compared to sirolimus, although with the same rate (50%).	Mousavi-Hasanzadeh *et al.*[24]	Clinical trial
ITP secondary to connective tissue disease	83	Adult	The comparison of patients treated with CyA *versus* rituximab showed higher response rate with the latter (81.8% *versus* 53.5% at 6 months).	Sun *et al.*[28]	Retrospective study
ITP	46	Adult	Overall response rate to CyA was 78% (54% complete), ITP recurrence rate was 4% at 3 months, 16% at 6 months. However, 6.5% of patients experienced infections during treatment. Response rates were higher in patients with increased megakaryocytes at bone marrow evaluation and in those with higher CD3+ T-cells in peripheral blood.	Wang *et al.*[29]	Retrospective study

(Continued)

Table 3. (Continued)

Cytopenia type	No. of patients	Setting	Comments	Ref.	Study type
AIHA	1	Pediatric	CyA induced 2-year relapse-free survival in a relapsed or refractory AIHA patient.	Baratta *et al.*[12]	Case report
AIHA	1	Pediatric	Anemia recovery in an AIHA patient refractory to steroids and IVIG.	Janic *et al.*[13]	Case report
AIHA	1	Pediatric	CR to CyA in a relapsed or refractory patient.	Sarper *et al.*[14]	Case report
AIHA	1	Adult	The patient developed relapsed or refractory AIHA after small bowel transplant and achieved CR after CyA in combination with alemtuzumab and steroids.	Lauro *et al.*[15]	Case report
AIHA	12	Mixed	CR in 42% of patients, PR in 17%.	Barcellini *et al.*[30]	Retrospective study
AIHA	8	Pediatric	Relapsed or refractory AIHA treated with CyA experienced a response rate 98% at 3 years.	Ito *et al.*[16]	Case series
ITP and AIHA	8	Adult	Long-term therapy with CyA induced a CR in six patients (75%), PR in two subjects (25%).	Emilia *et al.*[25]	Clinical trial
ITP, AIHA, and ES	34	Pediatric	Response rates were higher in AIHA and ES (6/15 and 7/12 patients). ITP subjects did not respond. However, 18 patients with AIHA and ES were able to discontinue steroids.	Penel Page *et al.*[31]	Retrospective study
AIHA and ES	18	Adult	CyA plus steroids and danazol induced higher response rates as compared to steroids alone (88.9% *versus* 57.7%), with a significantly lower relapse rate (3.3% *versus* 70%).	Liu *et al.*[26]	Clinical trial
ES	1	Pediatric	Hematologic response on ITP and Hb in a multitreated ES patient after CyA.	Rackoff and Manno[17]	Case report
ES	1	Pediatric	Hematologic response on ITP and Hb in a multitreated ES patient after CyA in combination with steroids.	Yarali *et al.*[18]	Case report

AIHA, autoimmune hemolytic anemia; CyA, cyclosporine A; ES, Evans syndrome; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulins; rTPO, recombinant thrombopoietin.

progressively abandoned or refused due to thrombotic and infectious complications, and rituximab induces up to 70–80% responses that are however durable in about 20–30% of cases only.[32–34,39] Nowadays, rituximab is discouraged, given the B cell depleting effect impacting on response to vaccination, particularly anti-SARS-CoV-2.[40] Thus TPO-RA are becoming the preferred second-line choice, and the spleen tyrosine kinase inhibitor fostamatinib has been recently licensed, although not worldwide available.[2] Our results and the review of the literature suggest that CyA can be an option for ITP patients whose disease is not well controlled by TPO-RA, who develop side effects (mostly bone marrow reticulin increase) and those who are not eligible for clinical trials. In addition, our data show that the addition of CyA to TPO-RA not only increased PLT counts in refractory patients but also stabilized fluctuations and allowed TPO-RA tapering or discontinuation in a fraction of subjects. This may be pointed at as a 'TPO-RA sparing' effect, which may be particularly relevant in the case of bone marrow fibrosis and in the settings of increased thrombotic risk.

Finally, only about one-third of patients relapsed after CyA, confirming relapse-free survival data from the literature. Of note, three ITP patients obtained a treatment-free remission after CyA therapy, an increasingly recognized outcome for this patient population.

Approximately 50% of AIHA patients achieved a response on CyA, although with the caveat of an old series mainly including patients who did not receive rituximab. The efficacy of the latter in warm AIHA is about 70–80%, clearly better than that reported for ITP and represents the recommended second-line treatment, although not indicated or available worldwide.[1,3,5,6] However, all CyA responders were able to reduce or discontinue steroids, in keeping with well-known steroid-sparing effect of CyA.[30] Translated nowadays, CyA may be an option in AIHA patients who fail rituximab, are not candidate or refused splenectomy, and result ineligible in clinical trials.

Regarding safety, CyA was generally well tolerated with mainly grade 1–2 adverse events. Although infections under CyA are less frequently reported than under other immunosuppressants (i.e. cyclophosphamide, mycophenolate mofetil),[41] we observed two serious infectious complications (5%, one fatality in an elderly) both in patients concomitantly receiving steroids. Thus, particular attention is warranted for elderly, heavily pretreated patients, including anti-pneumocystis prophylaxis in patients receiving >25 mg/day prednisone or equivalent for >4 weeks. Finally, CyA plasma concentrations may be monitored to optimize treatment and reduce renal or liver toxicity.

In conclusion, CyA was effective in a high proportion of heavily pretreated ITP and AIHA patients and allowed tapering or discontinuation of concomitant treatments in about two-third of cases. Responses were higher in subjects with ITP with an interesting *TPO-RA sparing* effect and reduction of PLT fluctuations.

Author contribution(s)

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Juri Alessandro Giannotta: Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

Laura Bandiera: Data curation; Formal analysis; Investigation.

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