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Syed Ather Hussain
Department of Internal Medicine, Rochester General Hospital, Rochester, New York, drsahussain121@gmail.com

Aneeqa Zafar
Division of Hospital Medicine, University of California San Francisco, 500 Parnassus avenue, San Francisco, California

Hafsa Faisal
Department of Internal Medicine, Rochester General Hospital, Rochester, New York

Mohammad Ammad Ud Din
Department of Internal Medicine, Rochester General Hospital, Rochester, New York

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REVIEW ARTICLE

Acquired Amegakaryocytic Thrombocytopenic Purpura: A Review of Therapeutic Options

Syed A. Hussain [a,*], Aneeqa Zafar [b], Hafsa Faisal [a], Mohammad A. Ud Din [a]

[a] Department of Internal Medicine, Rochester General Hospital, Rochester, NY, USA
[b] Division of Hospital Medicine, University of California San Francisco, 500 Parnassus Avenue, San Francisco, CA, USA

Abstract

Acquired amegakaryocytic thrombocytopenic purpura (AATP) is a rare bone marrow disorder characterized by either a marked decrease or a complete absence of megakaryocytes with the preservation of all other cell lines. To date, more than 60 cases of AATP have been reported in the literature. Due to the rarity of this disease, no standard treatment guidelines have been established, and therapy is based on a handful of case studies and expert opinions. Herein, we provide a comprehensive review of currently utilized therapeutic options for AATP.

Keywords: Acquired amegakaryocytic thrombocytopenic purpura, Megakaryocytic hypoplasia, Platelet disorders, Bone marrow transplantation

1. Introduction

Acquired amegakaryocytic thrombocytopenic purpura is an uncommon hematological disorder triggered by alcohol abuse, certain infections such as HIV and Hepatitis C, chemotherapy, radiation, autoimmune diseases, such as systemic lupus erythematosus (SLE), systemic sclerosis, paroxysmal nocturnal hemoglobinuria (PNH), or other hematopoietic disorders such as Fanconi's anemia, myelofibrosis, and pre-leukemia [1–4]. AATP usually presents with bleeding, bruising and severe thrombocytopenia in the absence of splenomegaly and is often initially misdiagnosed as immune thrombocytopenic purpura (ITP). Due to the rarity of this disease, no standard treatment guidelines have been established. Treatment is based on a handful of case studies and expert opinions. Steroids, intravenous immunoglobulin (IVIG), danazol, cyclosporine, cyclophosphamide, azathioprine, alemtuzumab, rituximab, anti-thymocyte globulin (ATG), and bone marrow transplantation (BMT) have been attempted with varying degrees of success (see .

1.1. Incidence

More than 60 cases of AATP have been reported in the literature [5]. AATP can be congenital or acquired. The congenital form of AATP is rare and characterized by reduced or absent megakaryocytes in the bone marrow. In contrast, the acquired form of AATP, the focus of this review, is diagnosed in later stages [5]. The exact incidence of AATP remains unknown; however, it may be higher than that reported as many cases are misdiagnosed as ITP. Females are commonly diagnosed between 40 and 60 years of age, whereas males show a bimodal incidence pattern at both ends of age distribution with the highest incidence in their 60s [5].

1.2. Clinical presentation

The clinical presentation is very similar to that observed with other causes of thrombocytopenia. Patients may present with petechiae, purpura, ecchymosis, easy bruising, epistaxis, or fatigue. A physical exam shows an absence of splenomegaly. Marked thrombocytopenia is noted in laboratory

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* Corresponding author at: 1425 Portland Avenue, Rochester, NY, 14621, USA.
E-mail address: drsahussain121@gmail.com (S.A. Hussain).

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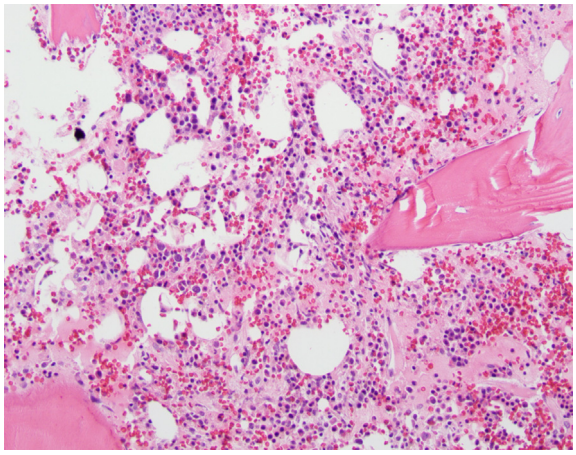

Fig. 1. Bone marrow core biopsy showing hypercellular marrow with normally maturing myeloid and erythroid series but markedly reduced megakaryocytes.

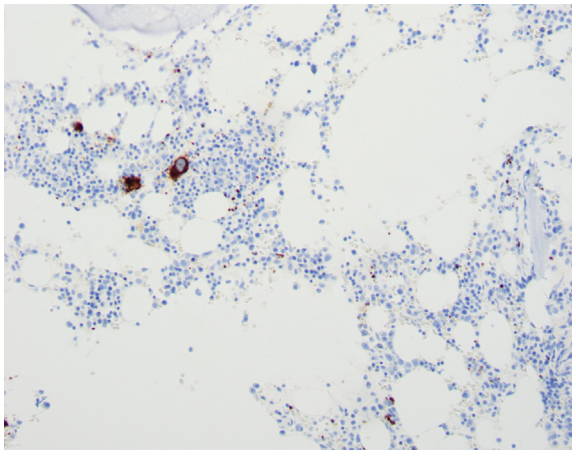

Fig. 2. Bone marrow core biopsy with CD61 staining showing significantly reduced megakaryocytes (Image borrowed with permission from publisher. Tirthani E, Said MS, De Jesus O. Amegakaryocytic Thrombocytopenia. Stat Pearls 2021. https://www.ncbi.nlm.nih.gov/books/NBK568795/).

assessment in the absence of neutropenia or anemia.

1.3. Differences with ITP & overlap with aplastic anemia

AATP and ITP have many similarities. Hence, most patients with AATP are initially misdiagnosed with ITP and administered systemic steroids, which may mildly improve platelet counts. However, in contrast to ITP, the platelet counts continue to worsen gradually over the years, and patients respond poorly to subsequent doses of systemic steroids. Additionally, in AATP, bone marrow biopsy reveals an absence of megakaryocytes, whereas ITP demonstrates a compensatory increase in megakaryocytes (Figs. 1 and 2). Table 1 summarizes the differences between AATP and ITP.

Certain overlap exists between AATP and aplastic anemia (AA); however, it is important to highlight the key differences. Patients with AATP demonstrate an isolated reduction in platelet production, whereas patients with AA show a reduction in all three cell lines [6]. Some patients initially diagnosed with AATP can develop AA in the later stages.

2. Methods

We conducted a comprehensive search on PubMed for all reported cases of AATP using the keywords "acquired amegakaryocytic thrombocytopenia" and "acquired amegakaryocytic thrombocytopenic purpura". All articles and abstracts retrieved from the literature were screened by S.A.H to identify studies that met the eligibility criteria. All potentially eligible studies were then independently reviewed in depth by S.A.H and A.Z. We included case reports and series published between 2000 and 2022 for an updated review of currently utilized therapies. We excluded non-English articles and review articles and case reports published before the year 2000. In total, 44 articles met our eligibility criteria, and data on 49 patients were extracted. Our findings are summarized in Table 2.

3. Pathogenesis

The exact pathogenesis of AATP has not been well elucidated; however, two theories are widely accepted. The first hypothesis indicates the presence of an intrinsic defect at the megakaryocytic (MK) progenitor cell level. This can either be attributed to an inhibitor that targets megakaryocyte-colony forming units (MK-CFU) or to cytotoxic T lymphocytes acting against the MK progenitor cells [7].

The second theory states that patients with autoimmune diseases, such as SLE, produce anti-c-Mpl antibodies that bind to the thrombopoietin (TPO) receptor on the platelets, thereby tagging them for destruction in the spleen [7–9]. Once

Table 1. Differences between AATP and ITP.

	AATP	ITP
Pathology	Congenital or acquired	Autoimmune
Splenomegaly	Absent	Absent
Bone marrow biopsy	Absent megakaryocytes	Increased megakaryocytes
Response to steroids	Poor	Good

AATP; Acquired amegakaryocytic thrombocytic purpura, ITP; idiopathic thrombocytopenic purpura.

Table 2. All patients with acquired amegakaryocytic thrombocytopenic purpura (AATP) published in Pubmed database between years 2000–2022.

Study	Age (yrs)/Gender	Initial presentation	Initial platelet count (x $10^3/\mu L$)	Initial therapy	Definitive therapy	Definitive therapy regimen	Platelet count at Follow-up ($10^3/\mu L$)	Follow-up duration (mo)
Ueda et al. 2001 [30]	17/F	Dyspnea, palpitations	24	Steroids	Steroids, ATG, CsA	Methylprednisolone 1 g/d x 3 d → PO prednisone 30 mg/d x ~180 d, ATG 15 mg/kg/d x 5 d & CsA 100 mg/d	244	3
Azuno et al. 2002 [27]	72/F	Easy bruising	6	Steroids	CsA	CsA 6 mg/kg/d (300 mg/d)	90	4
Quintas-Cardama 2002 [23]	20/F	Easy bruising	22	Steroids, IVIG	CsA	CsA 5 mg/kg/d x 365 d	50–70	14
Katsumata et al. 2003 [8]	61/F	Gingival bleeding	2	IVIG	Steroids	IV methylprednisolone 1 g/d x 3d→ Prednisolone 50 mg/d→ tapered to Prednisolone 10 mg/d maintenance dose	100	12
Chaudhary et al. 2004 [26]	52/M	Easy bruising, epistaxis, petechiae	4	IVIG, MTX	CsA, steroids, ATG	CsA 350 mg BID → 300 mg/d initially, ATG 40 mg/kg/d & methylprednisolone after relapse	300	96
Colovic et al. 2004 [52]	44/M	Gingival bleeding, purpura	10	CsA, danazol, fludarabine, litalir	–	–	–	–
Tristano et al. 2005 [53]	23/F	Easy bruising, gingival bleeding	3	–	Steroids	Methylprednisolone 1 g/d x 3 d → prednisone 1 g/kg/d	–	–
Agarwal et al. 2006 [24]	48/F	Easy bruising	25	Steroids, IVIG, recombinant IL-11	CsA	CsA 250 mg BID	225	4
Doubek et al. 2006 [51]	63/F	–	10	Steroids, CsA	Alemtuzumab	Alemtuzumab 10 mg three times weekly x 9 wks	67	9
Her et al. 2007 [54]	29/M	Easy bruising, epistaxis, gingival bleeding, menorrhagia	14	IVIG	Steroids, CsA	Methylprednisolone 1 g/d x 2 d → prednisolone 60 mg/d & CsA 300 mg/d	263	15

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Table 2. (continued)

Study	Age (yrs)/Gender	Initial presentation	Initial platelet count (x 10^3/μL)	Initial therapy	Definitive therapy	Definitive therapy regimen	Platelet count at Follow-up (10^3/μL)	Follow-up duration (mo)
Fukushima et al. 2008 [39]	42/F	Thrombocytopenia	14	Steroids, CsA	Steroids, CsA, rituximab	Prednisolone 50 mg/d tapered to 15 mg/d x 11 mo, CsA 200 mg/d x 11 mo & rituximab 375 mg/m^2 weekly x 2 doses	90	11
Lai et al. 2008 [55]	34/F	Petechiae	5	–	IVIG, steroids, CsA	IVIG 500 mg/kg/d x 3 d, prednisone 60 mg/d & CsA 5 mg/kg/d	280	4
Niparuk et al. 2008 [34]	77/M	Thrombocytopenia	28	Steroids	ATG, CsA	ATG 3.5 mg/kg/d x 4 d & CsA	>150	1
	60/F	Thrombocytopenia	11	Steroids	ATG, CsA	ATG 3.5 mg/kg/d x 4 d & CsA	>150	5.5
	38/F	Menorrhagia	21	Steroids, IVIG	ATG, CsA	ATG 3.5 mg/kg/d x 4 d & CsA	>150	6
	68/M	GI bleeding	18	Steroids, CP	ATG, CsA	ATG 3.5 mg/kg/d x 4 d & CsA	50–150	2.5
Cela et al. 2010 [12]	55/M	Chest pain, thrombocytopenia	28	Steroids, rituximab, CsA	Eltrombopag	Eltrombopag 50 mg/d	179	1.5
Deeren et al. 2010 [41]	89/M	GI bleeding	3	Steroids, IVIG	Rituximab	Rituximab 375 mg/m2 weekly x 4 doses	95	1
Chang et al. 2011 [49]	69/F	Gingival bleeding	4	Steroids	AZA	AZA 3 mg/kg/d	146	1.5
Jain et al. 2012 [3]	8/M	Petechiae, hematuria	20	Steroids	CsA	CsA 12 mg/kg/d	160	9
Brown et al. 2014 [56]	40/F	Easy bruising, epistaxis, fatigue	12	Steroids	ATG, CsA	ATG 40 mg/kg/d x 4 d & CsA 350 mg BID x 6 mo	115	4
Gay et al. 2014 [36]	31/M	Thrombocytopenia	12	ATG	Steroids, CsA	Prednisone 60 mg/d & CsA 200 mg BID → 200 mg daily	213	38
Mirzania et al. 2014 [40]	50/M	Petechiae, ecchymosis, hematuria, shoulder & periumbilical pain	12	Steroids, IVIG, CsA	Rituximab	Rituximab 375 mg/m^2 every 3 wks x 3 doses	>150	25
Patel et al. 2014 [57]	61/M	Dyspnea, fatigue, weight loss	13	Steroids, IVIG	–	–	–	–
Khan et al. 2015 [58]	34/M	Gingival bleeding, neurologic symptoms, purpura	5	Steroids	IVIG, CsA	IVIG x 5 d & CsA	60	1.5

Mulroy et al. 2015 [48]	65/M	Easy bruising, petechiae	8	Steroids, IVIG	Danazol	Danazol 400 mg daily initially→ 100 mg daily every other day maintenance dose x 18 mo	90	5
Shigekiyo et al. 2015 [37]	55/M	Ecchymosis, petechiae, thrombocytopenia	4	Steroids, CsA, ATG, danazol, CP, rituximab, eltrombopag	Romiplostim	Romiplostim 1-5 μg/kg weekly	1002	13
Ai et al. 2016 [59]	49/F	Petechiae	2	–	Recombinant IL-11	Recombinant IL-11 × 2 doses	34	3
Hashimoto et al. 2016 [60]	61/F	Intra-oral hematomas, ecchymosis, petechiae, thrombocytopenia	4	–	CsA	CsA 150 mg BID x 10 mo	100	12
Onuki et al. 2016 [61]	67/F	Fatigue, bipedal edema	6	–	CsA	CsA 300 mg/d	20.4	7.5
Novotny et al. 2017 [5]	61/M	Easy bruising, epistaxis, petechiae	0	Steroids, IVIG, eltrombopag, romiplostim, CsA	HSCT evaluation	–	–	–
Dahal et al. 2018 [29]	60/M	Cough, dyspnea, dizziness, hemoptysis	16	Steroids, CsA	Patient left AMA	–	43	0.3
Levy et al. 2018 [62]	40/M	Left groin pain, hematuria, petechiae, purpura	0.78	Steroids, IVIG, romiplostim	ATG, CsA, eltrombopag	–	>150	2
Nishino et al. 2018 [18]	43/M	Petechiae, thrombocytopenia	4	–	Steroids	Prednisolone 60 mg/d → taper	220	11
Ichikawa et al. 2019 [63]	67/F	Diffuse rash, fatigue, thrombocytopenia, appetite loss	63	Steroids, IVIG	CsA, Tocilizumab	CsA & Tocilizumab 8 mg/kg (560 mg) q 4 wks	130	3
Rajpurkar et al. 2019 [64]	16/M	Thrombocytopenia	–	Steroids, sirolimus, abatacept	–	–	–	–
Simkins et al. 2019 [42]	61/F	Dyspnea, fatigue, petechiae	2	Steroids, CsA, eltrombopag, ATG	Allogeneic HSCT	–	36–45	10.5
Son et al. 2019 [65]	60/F	Gingival bleeding, petechiae, GI bleeding	6	–	Steroids, IVIG, CsA	Methylprednisolone 1 mg/kg → oral prednisone x 12 wks, CsA 200 mg/d x 6 wks & IVIG 1 g/kg/d x 2 d	>100	12
Zimmerman et al. 2019 [66]	35/F	Easy bruising, gingival bleeding	12	Steroids, IVIG	Romiplostim	Romiplostim 10 μg/kg weekly x 12 mo	80–90	12
Dragani et al. 2020 [67]	62/M	Mucocutaneous bleeding	14	Steroids, CsA, eltrombopeg	–	–	–	–

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Table 2. (continued)

Study	Age (yrs)/Gender	Initial presentation	Initial platelet count (x 10^3/μL)	Initial therapy	Definitive therapy	Definitive therapy regimen	Platelet count at Follow-up (10^3/μL)	Follow-up duration (mo)
Gupta et al. 2020 [50]	48/F	Fever, thrombocytopenia	10	Steroids, IVIG	AZA	AZA 25 mg/d initially ↑to 125 mg/d	>100	2
Iyama et al. 2020 [68]	54/F	Thrombocytopenia	12	Steroids, IVIG	CsA	CsA 3 mg/kg	125	1
Obi et al. 2020 [69]	20/F	Abdominal pain, epistaxis, gingival bleeding, hematuria, petechiae, purpura, hemoperitoneum	3.9	Steroids	MMF	MMF 1 g daily	50	3
Roy et al. 2020 [70]	50/M	Easy bruising, thrombocytopenia, prolonged bleeding after trauma	19	Steroids	CsA	CsA 150 mg BID (2.5 mg/kg/d) ↑ to 200 mg BID	63	10
Suyama et al. 2021 [43]	78/M	Thrombocytopenia	7	Steroids	Eltrombopag	Eltrombopag 25 mg ↑ to 50 mg × 3 mo	223–480	9
Tian et al. 2021 [71]	15/M	Thrombocytopenia	1	Rh-TPO, steroids, IVIG	Eltrombopag, CsA	Eltrombopag 50 mg/d x 8 mo & CsA 3 mg/kg/d x 11 mo	>150	18
	16/M	Epistaxis, hematuria	5	Rh-TPO, steroids, rituximab	Eltrombopag, CsA→ tacrolimus	Eltrombopag 75 mg/d ↑ to 150 mg/d x 24 mo & CsA 3 mg/kg/d → to tacrolimus due to gingival hyperplasia	>150	36
Tu et al. 2022 [72]	67/M	Thrombocytopenia and petechiae after tislelizumab administration	48	Rh-TPO, steroids, IVIG, CsA, eltrombopag	Avatrombopag	Avatrombopag 40 mg daily x 4 mo	100	2
	71/F	Thrombocytopenia and petechiae after tislelizumab administration	26	Rh-TPO, steroids, IVIG, eltrombopag, G-CSF	Avatrombopag	Avatrombopag 40 mg daily x 1 mo	94	2

AMA-Against medical advice; ATG-Anti-thymocyte globulin; AZA-Azathioprine; CP-Cyclophosphamide; CsA-Cyclosporine; d-Days; G–CSF–Granulocyte colony stimulating Factor; HSCT-Hematopoietic stem cell transplantation; IL-11-Interleukin 11; IVIG-Intravenous immune globulin; mo-Months; MMF-Mycophenolate Mofetil; MTX-methotrexate; Rh-TPO-Recombinant human thrombopoietin; wks- Weeks.

enough platelets have been destroyed, the antibodies then bind to the TPO receptor on the megakaryocytes. These antibodies prevent TPO from stimulating its receptor, thereby arresting the development of the megakaryocytic cell lineage, resulting in AATP [9].

4. Therapeutic options

Hoffman et al. described an approach for the empirical treatment of AATP based on the mechanism underlying thrombocytopenia [10]. In patients with presumed or measured antibodies against MK-CFU, the use of immunosuppressive therapies (ISTs), such as steroids, IVIG, cyclophosphamide, and cyclosporine shows favorable results [11]. For patients with T-cell-mediated inhibition of megakaryopoiesis being the primary mechanism, ATG demonstrates a good response. For cases associated with other primary disorders, such as infections or autoimmune diseases, therapy targeted towards the primary disorder has shown benefits [12].

Over the past few decades, many novel therapies have been proposed for the management of AATP. However, no standard guidelines have been established on management, and randomized control trials are unlikely to be conducted, given the rarity of this disease. At least initially, most patients are treated with steroids; however, a sustained response is not observed. Cyclosporine has been used since 1985 and is one of the most used therapeutic agents for AATP. Other commonly used agents include ATG and cyclophosphamide. Most studies describing the use of cyclosporine or ATG have demonstrated sustained and durable responses. We present a review of all treatment options for AATP, describing them in order of preference, where applicable.

4.1. Most commonly used agents

4.1.1. Steroids

Unlike ITP, steroids do not demonstrate a durable response in patients with AATP; however, isolated reports and case series demonstrate such treatments as transiently effective [1,13–15]. In 31 cases of AATP treated with steroids (either oral or intravenous (IV) steroids), 24 cases were refractory with no improvement in their platelet counts, and seven cases showed a positive response, albeit transient [16]. Typically, 40–60 mg of prednisone was orally administered [17]. In cases that showed improved platelet counts after steroid therapy, the underlying cause was possibly secondary to SLE [14,15].

Recently, Tristano et al. reported a sustained response to IV and oral steroids in a patient with AATP. Nishino et al. reported rebound thrombocytosis diagnosed after steroid therapy [16,18]. Hence, long-term follow-up is needed to determine the durability of the response and overall effectiveness.

4.1.2. Cyclosporine

Prior to its use in AATP, the effectiveness of cyclosporine in ITP and thrombotic thrombocytopenic purpura (TTP) has been demonstrated [19,20]. Cyclosporine is a calcineurin inhibitor that decreases the expression of genes encoding for interleukin 2 (IL-2), interleukin 4 (IL-4), and CD40 ligand, subsequently mediating an increase in megakaryopoiesis due to the suppression of both cell-mediated and humoral immunity [21]. The first reported case of AATP that was successfully treated with cyclosporine dates back to 1985 [22]. Since then, approximately a dozen more cases have shown a favorable response, rendering it one of the most used and effective treatment approaches for AATP [3,23–26]. The usual dosage is 6 mg/kg/day. The dosage is adjusted to maintain trough levels between 150 and 300 ng/mL [27,28]. Cyclosporine shows a remarkable increase in platelet counts, with an average of 2–7 x $10^3/\mu L$ at the baseline to 50–150 $\times$ $10^3/\mu L$ after 2–8 weeks of therapy. In a few cases, the response was diminished after the cyclosporine dose was tapered; however, platelet counts increased again when the cyclosporine dose was repeated [3,23–26]. AATP associated with pure red cell aplasia (PRCA) in the setting of thymoma has also been effectively treated with cyclosporine [29]. One study reported achieving a second successful remission for relapsed AATP with repeated cyclosporine therapy administered four years after the patient achieved the first remission with cyclosporine [28].

4.1.3. Anti-thymocyte globulin

ATG has been well examined for use in patients with AA and graft-versus-host disease (GVHD) [30,31]. It eliminates antigen-reactive T-lymphocytes in peripheral blood or alters the function of T-lymphocytes involved in humoral immunity [30]. Its role in mediating remission in patients with AATP can be extrapolated from its favorable response in patients with AA and the fact that a small percentage of AATP patients show eventual progress to AA. ATG may restore marrow function by correcting immune-mediated marrow suppression as well as stimulating hematopoiesis directly.

In 1989, Manoharan et al. reported the case of a 15-year-old female who showed a favorable

response to ATG after the failure of steroid treatment [32]. A positive and sustained response has been observed with most patients receiving ATG therapy. Khelif et al. followed four patients who had previously failed to respond to steroids, IVIG, and cyclophosphamide therapies and were subsequently treated with ATG along with cyclosporine [33]. Three patients achieved complete remission within 28–178 days, and the response duration was 16–60 months from the beginning of treatment. Another study documented the clinical course of four patients with AATP who were treated with ATG at a dose of 40 mg/kg/day for four days and then with an extended course of cyclosporine [34]. Three of the four patients showed a response within six weeks and remained in complete remission after 60 months following treatment [26,35]. Patients with AATP who show progression to AA also had a positive response to ATG [36].

Despite overwhelmingly positive responses, the potential for relapse has also been documented for ATG. King et al. reported a patient that rapidly progressed to AA and failed to respond to two cycles of ATG [6]. More recently, a Japanese group reported a patient showing a positive response to ATG initially but relapsing one year after treatment [37].

4.1.4. Cyclophosphamide

Saghir et al. reported a case of an 83-year-old male who was diagnosed with AATP and gastrointestinal bleeding and had an excellent response to treatment with cyclophosphamide [38]. The patient initially received 100 mg of cyclophosphamide daily, which was later adjusted to 50 mg daily. After four weeks of treatment, his platelet count improved beyond $100 \times 10^3/\mu L$. He continued to remain in complete remission during follow-up conducted after five months, and bone marrow biopsy showed a normal number of megakaryocytes. However, cyclophosphamide can increase the risk of progression to AA; hence, the treatment should be preceded by bone marrow culture studies [38].

4.1.5. Rituximab

Rituximab is a chimeric monoclonal antibody directed against CD20, a B cell surface protein. CD20 is present on most B cells, including naïve B cells, immature B cells, germinal center B cells, and memory B cells [39]. However, it is not present on pro-B cells or plasma cells [39]. Rituximab is used in AATP to target pathogenic B cell clones that produce anti-c-Mpl antibodies and are resistant to conventional IST [39]. Mirzania et al. reported using rituximab to treat AATP, which was refractory to IVIG, steroids, and cyclosporine [40]. Three doses of 375 mg/m^2 of rituximab were administered at three-week intervals. Prior to rituximab administration, the platelet count of the patient was $10 \times 10^3/\mu L$, which remarkably increased to $20 \times 10^3/\mu L$ on day six and $30 \times 10^3/\mu L$ on day 29, finally reaching $200 \times 10^3/\mu L$ on day 42. During follow-up after twenty-five months, the patient maintained normal platelet counts without any medications [40]. Rituximab is a relatively safe and efficacious option for paraneoplastic AATP for which medications like cyclosporine and mycophenolate mofetil should be avoided due to the theoretical risk of tumor growth [41]. Rituximab has also been used to treat SLE-associated AATP and reduces the titers of c-MpL antibodies [39]. Rituximab increases the risk of progressive multifocal leukoencephalopathy (PML) due to the reactivation of the John Cunningham virus; hence, patients should be monitored closely for any new neurological deficits [39].

4.2. Definitive treatment

4.2.1. Bone marrow transplant

BMT can be considered for patients who are relatively young and able to tolerate a transplant and have a suitable bone marrow donor available. Lonial et al. reported a case of a 43-year-old female with AATP who had failed to respond to therapy comprising IVIG, prednisone, cyclophosphamide, and vincristine [11]. The patient subsequently underwent allogeneic BMT from a 6/6 human leukocyte antigen (HLA)-matched sibling. Prior to the transplant, she was subjected to a preparative regimen comprising busulfan (4 mg/kg) administered in divided doses each day for four days followed by cyclophosphamide (60 mg/m^2) administered for two days. She also received the standard GVHD prophylaxis regimen comprising tacrolimus and methotrexate. However, the post-transplant period was complicated by positive polymerase chain reaction (PCR) results for cytomegalovirus (CMV) and pancytopenia, requiring treatment with ganciclovir, granulocyte-colony stimulating factor (GCSF), and erythropoietin. After day 175, the bone marrow appeared hypercellular with adequate megakaryocytes. During follow-up after one year, she showed complete donor chimerism and restoration of normal thrombopoiesis [11]. Similarly, Simkins et al. reported a case of a 61-year-old female with AATP who had failed to respond to initial therapy comprising cyclosporine, eltrombopag, and steroids [42]. She showed progression to AA for which she was administered ATG in combination with the initial therapy. The patient showed a transient response three months after

starting ATG; the marrow showed 30% cellularity with the re-emergence of megakaryocytes. However, she still remained severely pancytopenic several months later and underwent matched unrelated stem cell transplantation. She also received a preparative regimen comprising fludarabine (30 mg/m^2), cyclophosphamide (300 mg/m^2), and intravenous alemtuzumab (20 mg). She was treated with tacrolimus for GVHD prophylaxis. In the post-transplant period, she did not require any platelet transfusions after day 14, and the bone marrow biopsy at six months showed 60% cellularity with trilineage hematopoiesis. Chimerism studies after day 323 showed 100% myeloid and 46% donor T cells [42].

4.3. Infrequently used treatments

4.3.1. Thrombopoietin mimetics

Although initially approved for the treatment of ITP refractory to immunosuppressants, thrombopoietin mimetics, such as eltrombopag, are now regarded as the standard of care for patients with thrombocytopenia attributed to AA. Given their potent stimulatory effects on the marrow, they have also been used to treat AATP with varying success.

Cela et al. reported the first such case of AATP that responded to eltrombopag after failing to achieve remission with steroids, cyclosporine, and rituximab [12]. Eltrombopag is a non-peptide TPO mimetic that binds to and activates the TPO receptor at a site different than the endogenous TPO [12]. The patient showed normal platelet counts after 50 mg of eltrombopag administered daily for six weeks [12]. Suyama et al. initially administered 25 mg of eltrombopag daily to the patient, and the dose was later increased to 50 mg administered daily after three weeks. The patient received the same dose before it was tapered down over a period of five weeks [43].

Another study from Japan reported a 55-year-old male with refractory AATP who responded to romiplostim, a TPO peptide mimetic [37,44,45]. The patient was treated with 1 μg/kg/week of romiplostim for the first four months followed by a fixed dose of 3–5 μg/kg/week for the next several months. After treatment, the patient became less susceptible to bleeding and required fewer platelet transfusions. Interestingly, this patient had failed to respond to one-month treatment with eltrombopag prior to starting romiplostim. Romiplostim and eltrombopag not only have different molecular structures but also possess different modes of activation of the TPO receptor [44,45]. In vitro, both medications stimulate the cytoplasmic tyrosine phosphorylation of JAK2, STAT5, and MAPK signaling proteins; however, romiplostim also activates the PI3K/AKT signaling pathway, which may be crucial for platelet production. Hence, some patients might respond to romiplostim after the failure of eltrombopag [44,45]. Patients receiving TPO mimetics need to be closely monitored due to the risk of progression to acute myeloid leukemia [37].

4.3.2. Danazol

Danazol is a C-19 steroid derivative of 17-A ethinyl testosterone. It has been infrequently used to treat cyclic AATP, which is characterized by periodic fluctuations in platelet counts ranging from severe thrombocytopenia to normal or high platelet counts [46]. The first successful use of danazol for the treatment of AATP was reported in 1985 [47]. It works by mediating a negative feedback loop in the hypothalamus, leading to a hypoestrogenic and hyperprolactinemic state that promotes megakaryocyte maturation [47]. Danazol also decreases the expression of Fc receptors on the surface of macrophages that are involved in the pathogenesis of AATP via an unelucidated mechanism [46]. Kashyap et al. reported a case of a 42-year-old premenopausal woman with cyclic AATP who was successfully treated with danazol after she failed to achieve sustained remission with IVIG and splenectomy. The patient was treated with 10 mg/kg/day of oral danazol for six months. Subsequently, variations in her platelet counts decreased, and her platelet counts remained over 200 $\times$ 10^3/μL during treatment. After therapy, the patient remained in clinical remission, and the platelet counts did not fall below 160 $\times$ 10^3/μL during follow-up after ten months [46]. Mulroy et al. successfully treated their patient who had previously failed to respond to steroids and IVIG with 100 mg of danazol administered daily before escalating to 400 mg daily for 18 months, followed by tapering the dose [48].

4.3.3. Azathioprine

Very limited data are available on azathioprine; most data are obtained from isolated case reports or extrapolated from its use in other etiologies of autoimmune thrombocytopenia. In a patient with AATP who had failed to respond to steroids, Chang et al. reported successful remission after six weeks of daily azathioprine therapy [49]. The dose used was 3 mg/kg/day, and platelet counts increased from 13 to 146 $\times$ 10^3/μL after six weeks of therapy [49]. Another study showed a favorable response to azathioprine against steroid refractory AATP in a patient with SLE [50]. After two months of treatment, the platelet count remained stable at

approximately 100 × 10^3/μL for three years [50]. Generally, azathioprine has a better safety profile than cyclosporine or ATG. It is also cost-effective when used for a long duration [49].

4.3.4. Alemtuzumab

Alemtuzumab is a monoclonal antibody that targets CD52 antigen-bearing leukocytes and mediates their destruction. Megakaryopoiesis is regulated by T-cells, and alemtuzumab causes severe T-cell depletion with both CD4+ and CD8+ cells being equally affected. This, in turn, increases the number of megakaryocytes. Doubek et al. showed that incubation of lymphocytes with alemtuzumab increased MK-CFU by a median of five times than that observed in control groups ($P < 0.001$) [51]. Doubek et al. also reported a case of a 63-year-old female with severe refractory AATP who failed to respond to treatment with steroids and cyclosporine and was treated with aletuzumab 10mg three times weekly for nine weeks. Even though the patient's course was complicated by cytomegalovirus reactivation resulting in the interruption of treatment for a few weeks, her platelet counts increased from 10 × 10^3/μL to 67 × 10^3/μL upon completion of therapy. The patient remained in remission during follow-up at nine months and did not require any further treatment [51].

4.4. Miscellaneous

Other attempted treatment modalities include IVIG, vincristine, splenectomy, and plasma exchange; however, they demonstrate minimal benefit [16,24].

5. Conclusion

AATP is a rare and complex disease that can be difficult to manage and shows relapse potential. Given the lack of clinical trials, no standard of treatment exists; however, ATG and cyclosporine have shown the most favorable results and durable responses. We recommend larger, multi-center studies to improve our understanding of this disease and develop evidence-based standardized treatment regimens.

Author contributions

SAH conceived the idea for the manuscript. SAH, AZ, and HF were involved in drafting the initial manuscript. MAUD was involved in critically reviewing and revising the manuscript.

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Conflict of interest

The authors have no competing interests to declare.

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