haematologica
Journal of the Ferrata Storti Foundation

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Received: January 15, 2026.
Accepted: April 16, 2026.

Citation: Dana Yehudai-Ofir, Hazim Khatib, Ofrat Beyar-Katz, Avraham Frisch, Baher Krayem, Tsila Zuckerman and Israel Henig. Favorable safety and efficacy profiles of α-1-antitrypsin in steroid- and ruxolitinib-refractory acute graft-versus-host disease of the gastrointestinal tract: a retrospective, single center study.
Haematologica. 2026 Apr 23. doi: 10.3324/haematol.2026.300541 [Epub ahead of print]

Favorable safety and efficacy profiles of α-1-antitrypsin in steroid- and ruxolitinib-refractory acute graft-*versus*-host disease of the gastrointestinal tract: a retrospective, single center study

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Running title: Alpha-1-antitrypsin in refractory acute GVHD

Declaration of Interests

Authors declare no competing interests.

Author Contribution Statement

DY-O: designed the study, interpreted the data, wrote the paper.

HK: Collected and analyzed the data

OB-K: Collected and analyzed the data

TZ: Collected and analyzed the data

IH: conceived, designed and supervised the study, interpreted the data, wrote the paper.

All the authors contributed to writing and/or editing of the manuscript and approved the final version of the paper.

Funding

This research was supported in part by a grant from Kamada Ltd. (associated with the study IRB number RMB-D-0043-25)

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgments

The authors wish to acknowledge with thanks the assistance of Sonia Kamenetsky in the preparation of the manuscript.

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Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for multiple malignant and non-malignant hematologic diseases. Acute graft-versus-host disease (aGVHD) remains a major complication, occurring at grades 2-4 in 30-40% of patients, with only about 50% of patients responding to standard treatment with high-dose corticosteroids. In steroid-refractory aGVHD (SR-aGVHD), the JAK1/2 inhibitor ruxolitinib has demonstrated superiority over other second-line therapies in the REACH2 trial, with initial responses exceeding 60%, although only ~40% maintain response at two months[1]. To date, no standard therapy exists for patients refractory to ruxolitinib.

Alpha-1 antitrypsin (AAT) is a liver-derived serine protease inhibitor that primarily inhibits neutrophil elastase released during inflammation. Beyond this, AAT exerts anti-inflammatory and immunomodulatory effects, including suppression of pro-inflammatory cytokines, inhibition of apoptosis, and modulation of immune cell function, contributing to tissue protection[2].

Both preclinical and clinical studies demonstrated the efficacy of AAT in aGVHD. In murine models, AAT reduced pro-inflammatory cytokines, enhanced regulatory T-cell recovery, and decreased mortality[3]. In a phase I/II study of 12 patients with severe SR-aGVHD, AAT was well tolerated without relevant toxicities and induced responses in 8 patients [4 complete responses (CR)], with 50% long-term survival[4]. A multicenter prospective phase II trial, evaluating AAT in 40 patients with SR-aGVHD, reported the day-28 overall response rate (ORR) of 65% (35% CR), with 47% maintaining response at day 60 without additional immunosuppression. No drug-related adverse events were observed, and 6-month infection-related mortality was 10%[5]. These findings led to the inclusion of AAT in SR-aGVHD treatment guidelines[6].

Since 2018, AAT has been used at the bone marrow transplant unit of the Rambam Health Care Campus (Haifa, Israel). The regimen comprised AAT (Glassia provided by Kamada Ltd on a compassionate basis) 90 mg/kg on day 1, followed by maintenance doses of 30 mg/kg on days 2, 4, 6, 8, 10, 12 and 14[4]. All patients had aGVHD of the gastrointestinal (GI) tract refractory to both steroids and second-line therapies such as ruxolitinib or extracorporeal photopheresis (ECP) + ruxolitinib. Refractoriness was defined as previously described[7]. AAT was initiated in addition to ongoing lines of therapy, primarily ruxolitinib and ECP.

The present single-center retrospective study evaluated the safety and efficacy of AAT applied as a third-line therapy or beyond for the treatment of ruxolitinib-refractory aGVHD of the lower GI tract (IRB approval RMB-D-0043-25).

Eighteen consecutive patients were treated with AAT between 2018 and 2025. Seventeen patients [7 females; median age 45 years (range, 19-74)] were included in this analysis, as one patient received only a single AAT dose and died the following day due to an infectious complication, precluding

evaluation of GVHD response. All patients received peripheral blood stem cell grafts. Eleven underwent transplantation from a matched related donor, and 10 received a myeloablative conditioning regimen. The maximal lower GI aGVHD was stage 4 in 11 patients and stage 3 in 6 patients (Table 1).

Patients received a median of 3 prior lines of therapy (range, 2-5) for their GI aGVHD before initiation of AAT, which was administered as third-, fourth-, fifth-, and sixth-line therapy in 3, 8, 4, and 2 patients, respectively. Twelve patients were refractory to previous lines of treatment, and five achieved only a partial response (PR), defined as decrease of at least one stage in the GI aGVHD score (Figure S1). Fourteen patients were treated with steroids, ruxolitinib, and ECP prior to AAT, with 6 of them also receiving fecal microbiota transplantation (FMT) before AAT initiation. In the remaining 3 patients, AAT was administered as the third-line therapy after steroids and ruxolitinib (Table 1, Table 2).

The best overall response to AAT included CR and PR at any time point following AAT initiation. The best overall response rate (ORR) was 64.7% (11/17), including 41.2% (7/17) achieving CR and 23.5% (4/17) achieving PR (Table 2, Figure S1).

In responding patients, the median time to best response was 25 days (range, 10-71). One patient progressed after the initial response to AAT and was treated with FMT, resulting in PR. Notably, the best ORR was 83.3% (5/6 patients) versus 54.5% (6/11 patients) among those who did or did not receive FMT prior to AAT, respectively. Among thirteen patients who met criteria for ruxolitinib-refractory disease[7], the best ORR was 61.5% (8/13).

At day 28 from the AAT start, 10 patients achieved at least one-stage reduction in GI GVHD severity and maintained response, one more patient improved but lost response, one patient experienced worsening, and five showed no change. Overall, the AAT treatment failure rate at day 28 was 41.2% (7/17; Table 2).

During the GVHD course, 11 patients (65%) experienced infectious events prior to AAT initiation, whereas 12 patients (70%) had infectious events during this treatment. Totally, 27 infectious episodes occurred before and 17 during the AAT treatment (Table S1).

These findings underscore the substantial infectious burden observed in this profoundly immunocompromised population and are consistent with prior reports of median bloodstream infections (BSI) rates reaching up to 75% among patients with grade 4 aGVHD[8]. Notably, no higher rate of infections, including BSI, was observed among patients treated with FMT prior to AAT (Table S1).

Six patients (6/17, 35.3%) died from infections, three (17.6%) from GVHD progression, and one (5.9%) from relapse of the underlying hematologic disease while remaining in complete GVHD

response (Table 2). Infections and other events (Table S2) were attributed to patients' severe underlying clinical condition rather than to AAT. No specific AAT-related toxicities were observed, consistent with its well-established favorable safety profile.

At a median follow-up of 250 days from the transplant day (range, 68-1,718), 7 patients (41%) remained alive. Among the 11 patients who responded to AAT, the overall survival reached 63.6% (7/11). Notably, none of the 6 AAT-refractory patients survived (Table 2, Figure S1).

To the best of our knowledge, this is the first report using AAT for ruxolitinib-refractory aGVHD. Efficient treatment of ruxolitinib-refractory aGVHD of the lower GI tract represents an unmet clinical need. Recently, a retrospective study by Brehm et al. reported that teduglutide, administered as third-line therapy and beyond, induced an ORR of 64.7% with 41% CR[9]. Furthermore, in the randomized prospective STARGAZE trial, a combination of apraglutide with ruxolitinib, given as second-line therapy for GI SR-aGVHD, yielded an ORR of 58% (29% CR), with durable responses observed in 45% of patients[10]. Likewise, a multicenter analysis from Germany assessing the use of an allogeneic mesenchymal stromal cell preparation for ruxolitinib-refractory aGVHD demonstrated an ORR of 46% in adults, with a 6-month survival rate of 47%[11]. Another study evaluating a subgroup of 20 patients refractory to both steroids and ruxolitinib who were treated with combined cytokine-blockade therapy (basiliximab plus infliximab) showed an ORR of 25%, including 15% CR and 10% PR[12]. The outcomes observed in our cohort, i.e., an ORR of 64.7% with a CR rate of 41.2% following AAT treatment, are broadly comparable with reports, where other therapeutic agents were applied.

This study has several limitations, primarily related to its retrospective, single-center design and the small cohort size. Nevertheless, the study population consisted exclusively of consecutive patients with severe (stage 3-4) lower GI tract aGVHD who had failed corticosteroids, second-line therapy, or successive treatments. While the prevalence of such patients has markedly decreased over the years owing both to PTCy prophylaxis[13] and current therapeutic strategies[1], the resulting paucity limits the evaluation of interventions within single-center cohorts. Furthermore, the cohort size and heterogeneity in the timing and use of AAT precluded analysis of predictive factors for response. Additionally, since AAT treatment initiation criteria were not standardized, a selection bias may have influenced the results. As not uncommon for real-world practice in this setting, AAT was introduced on top of ongoing lines of therapy and in some cases, PR to previous interventions had already been attained. Therefore, it cannot be determined with certainty whether the responses observed during AAT treatment were directly attributable to this therapy alone, a delayed effect of previous therapies, or to a potential synergistic interaction between the two, as might be reflected in the high response rate among patients receiving FMT prior to AAT.

Evaluating the effect of new interventions for refractory aGVHD is challenging. Phase II and observational data on refractory GVHD are difficult to interpret due to some unpredictability in the disease course, and quite a number of substances have not found confirmation in controlled trials[14]. Therefore, while this study findings might be encouraging, they should not be over-interpreted unless validated with controlled data.

Within these constraints, the findings of the present study suggest that in patients with severe, ruxolitinib-refractory aGVHD of the lower GI tract, AAT administered as third-line or later therapy is safe and potentially effective. In light of encouraging preliminary results from the BMT CTN 1705 study demonstrating significant efficacy of corticosteroids combined with AAT compared with corticosteroids plus placebo as first-line treatment for high-risk aGVHD[15], our observations warrant further investigation in a prospective setting evaluating AAT either as third-line monotherapy or in combination with ruxolitinib as second-line therapy for steroid-refractory aGVHD.

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Table 1. Patient characteristics

Number of patients, N	17
Age in years, median (range), years	45 (19-74)
Female, N (%)	7 (41.2)
Diagnosis, N (%)	
Acute myeloid leukemia	5 (29.4)
Myelodysplastic syndrome	5 (29.4)
Myeloproliferative neoplasm	3 (17.6)
Acute lymphoblastic leukemia	2 (11.8)
Non-Hodgkin lymphoma	1 (5.9)
Multiple myeloma	1 (5.9)
Conditioning intensity, N (%)	
Myeloablative	10 (58)
Reduced-toxicity	1 (5.9)
Reduced-intensity	5 (29.4)
Non-myeloablative	1 (5.9)
Donor, N (%)	
Matched related	11 (64.7)
Matched unrelated	3 (17.6)
Mismatched unrelated (9/10)	1 (5.9)
Haploidentical	2 (11.8)
GVHD prophylaxis, N (%)	
Cyclosporine + methotrexate	12 (70.6)
Cyclosporine + MMF	5 (29.4)
ATG use, N (%)	
Yes	5 (29.4)
No	12 (70.6)
PTCy use, N (%)	
Yes	3 (17.6)
No	14 (82.4)
Overall aGVHD grade at onset, median (range)	3 (1-4)
GI aGVHD stage at onset, N (%)	
Stage 1	2 (11.8)
Stage 2	6 (35.3)
Stage 3	8 (47)
Stage 4	1 (5.9)
Maximal overall aGVHD grade, N (%)	
Grade 3	12 (70.6)
Grade 4	5 (29.4)
Maximal GI aGVHD stage, N (%)	
Stage 3	6 (35.3)
Stage 4	11 (64.7)
Previous lines of therapy for aGVHD, median (range)	3 (2-5)
Treatment received, N (%)	
Methylprednisolone 2 mg/kg	17 (100)
Ruxolitinib	17 (100)
ECP	14 (82.3)
FMT	6 (35.3)

MMF	2 (11.8)
GI aGVHD stage before AAT, N (%)	
Stage 2	3 (17.6)
Stage 3	5 (29.4)
Stage 4	9 (53)
Met criteria for ruxolitinib-refractory aGVHD, N	13
Progression (GVHD grade increasing), N (%)	2 (15.4)
Lack of improvement (GVHD grade unchanged), N (%)	9 (69.2)
Loss of response (GVHD grade increase after initial decrease), N (%)	1 (7.7)
Not achieving CR after >28 days	1 (7.7)

ATG: Antithymocyte globulin; PTCy: post-transplant cyclophosphamide; aGVHD: acute graft-versus-host disease; GI: gastrointestinal; ECP: extracorporeal photopheresis; FMT: fecal microbiota transplantation; MMF: mofetil mycophenolate; AAT: alpha-1-antitrypsine. All percentages presented in parentheses are derived from the total cohort of 17 patients, except for those reported under the "met criteria for ruxolitinib-refractory aGVHD" category. In that category, percentages are calculated for the cohort of 13 patients who fulfilled the definition of ruxolitinib-refractory disease.

Table 2. GVHD characteristics

N	Age	Gender	Dx	DRI	Donor	Conditioning	Max GI GVHD stage	Pre-AAT lines	Ruxolitinib refractory per definition	GI GVHD stage before AAT start	GI GVHD stage at day 28 to AAT	AAT treatment failure by day 28****	Best response to AAT by GI GVHD stage	Time to best response to AAT (days)	Relapse of hematologic disease	Time from AAT to death (days)/Alive	Cause of death
1	36	Male	TCL	IR	MUD	MAC	4	Steroid, Ruxo, ECP, FMT	Yes	3	2	No	0	35	No	Alive	
2	30	Male	MDS	IR	MUD	MAC	4	Steroid, Ruxo, ECP	Yes	4	*1	Yes	0	10	No	Alive	
3	23	Female	PH+BALL	IR	MRD	MAC	4	Steroid, Ruxo, ECP	No	3	0	No	0	17	Yes	Alive	
4	27	Male	MDS GATA2	High	MRD	MAC	4	Steroid, Ruxo, ECP	No	2	1	No	1***	13	No	Alive	
5	59	Male	MDS	High	MRD	MAC	4	Steroid, Ruxo, ECP	Yes	4	1	No	0	71	No	Alive	
6	69	Female	AML	High	MRD	RIC	4	Steroid, Ruxo, ECP, FMT	Yes	4	0	No	0	12	No	Alive	
7	72	Male	AML	High	MRD	RIC	3	Steroid, Ruxo, ECP, FMT	Yes	3	2	No	1	48	Yes	Alive	
8	44	Female	AML	High	MUD	RTC	4	Steroid, Ruxo, ECP	Yes	4	0	No	0	26	Yes	140	Relapse
9	62	Male	AML	Low	MRD	MAC	3	Steroid, ECP, MMF, Ruxo, FMT	No	2	0	No	0	10	No	80	Infection
10	45	Male	MM	IR	MRD	RIC	4	Steroid, ECP, MMF, Ruxo, FMT	Yes	4	3	No	1	37	No	41	GVHD

11	20	Male	TALL	Low	MRD	MAC	3	Steroid, Ruxo	Yes	3	4	Yes	4	NA	No	42	GVHD
12	44	Female	CMML	IR	MRD	MAC	4**	Steroid, Ruxo, ECP	Yes	4	3	No	3	25	No	33	Infection
13	19	Male	FA MDS	High	HAPLO	NMA	4	Steroid, Ruxo, ECP	Yes	4	4	Yes	4	NA	No	26	Infection
14	68	Female	MF	IR	HAPLO	RIC	3	Steroid, Ruxo, ECP, FMT	Yes	3	NA	Yes	3	NA	No	3	Infection
15	74	Female	AML	IR	MMUD	RIC	3	Steroid, Ruxo	No	2	NA	Yes	2	NA	No	15	Infection
16	55	Male	MDS	High	MRD	MAC	3	Steroid, Ruxo, ECP	Yes	4	NA	Yes	4	NA	No	6	Infection
17	56	Female	MF	IR	MRD	MAC	4	Steroid, Ruxo	Yes	4	NA	Yes	4	NA	No	11	GVHD

N: Patient number (correlates to patient number in supplementary Figure S1); Dx: diagnosis; TCL: T cell lymphoma; MDS: Myelodysplastic syndrome; PH+BALL: Philadelphia chromosome positive acute lymphoblastic leukemia; AML: Acute myeloid leukemia; CMML: Chronic myelomonocytic leukemia; MM: Multiple myeloma; TALL: T acute lymphoblastic leukemia; FA: Fanconi anemia; MF: myelofibrosis; DRI: Disease risk index; IR: Intermediate risk; MUD: matched unrelated donor; MRD: matched related donor; Haplo: haploidentical; MMUD: mismatched unrelated donor; MAC: myeloablative conditioning; RIC: reduced intensity conditioning; RTC: reduced toxicity conditioning; NMA: non myeloablative conditioning; AAT: alpha-1-antitrypsin; Roxu: ruxolitinib; PR: partial response; NR: no response; CR: complete response; GVHD: graft-versus-host disease; NA: not applicable.

*Patient 2 received AAT and initially responded with GI GVHD stage decreasing to 0, but the response was lost on day 26 from AAT treatment start, with the stage increasing to 1. At that point, FMT was administered without further improvement.

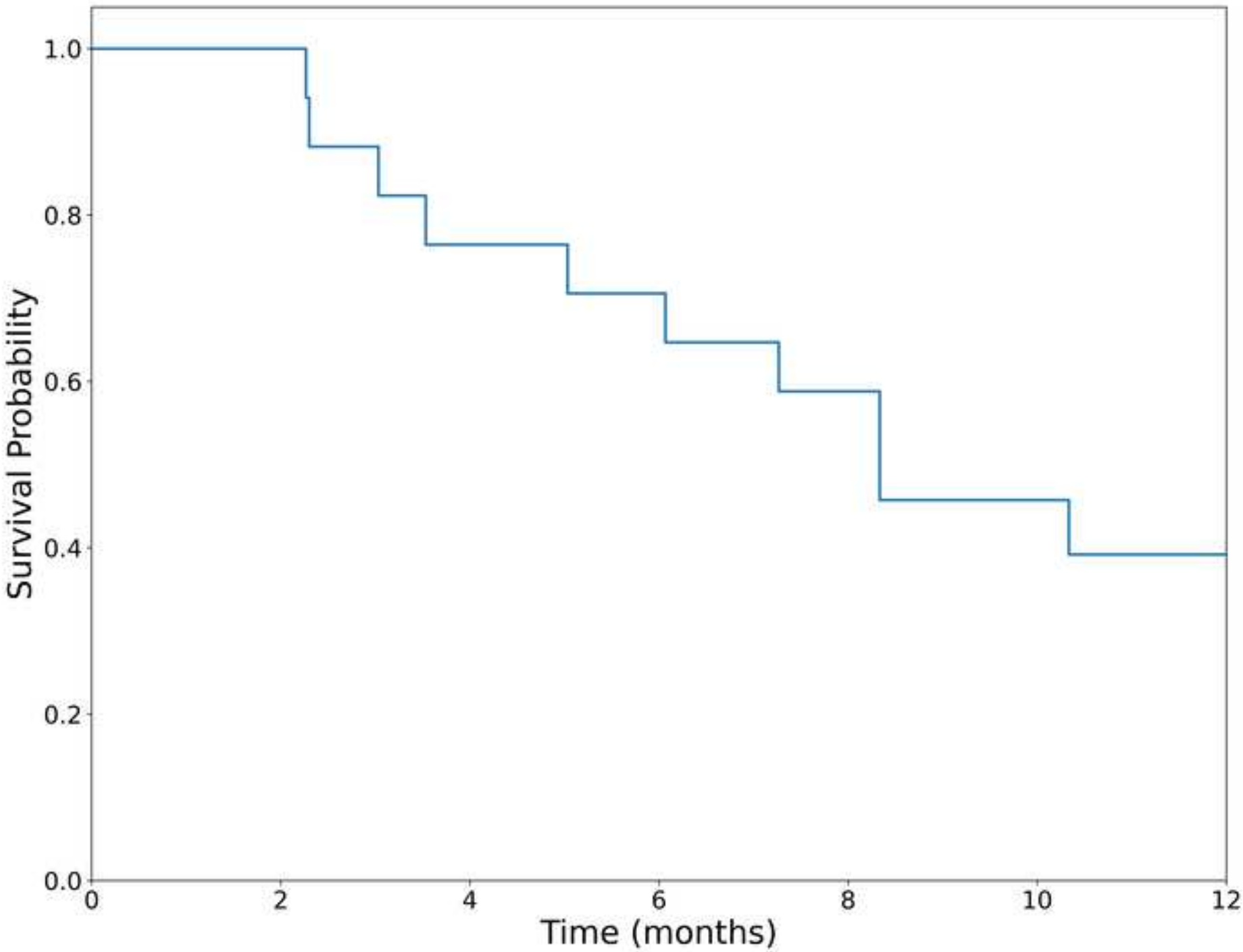
** Patient 12 experienced late onset aGVHD staring on day 126 post-transplant.

*** Patient 4 improved to stage 0 GI aGVHD at 142 days from AAT start. Since this further improvement could not be attributed to the AAT, his stage 1 GI aGVHD was regarded as the best response to AAT.

**** The addition of another intervening therapy, increase in stage and patient death were considered treatment failure

Figure legends

Figure 1. Kaplan-Meier overall survival curve for the entire cohort.


1.0
0.8
0.6
0.4
0.2
0.0
Survival Probability
0
2
4
6
8
10
12
Time (months)

Supplementary material

Table S1. Infection events during the GVHD course

Infection	**Total number of events, N**	**Events before AAT initiation, N**	**Events during AAT treatment course**		
			Total number, N	Prior FMT treatment, N	No prior FMT treatment, N
All events, N	44	27	17	4	13
Bacterial	22	11	11	3	8
BSI	12	5	7	2	5
Skin infection	4	4			
Sepsis/septic shock unknown	2		2	1	1
UTI	2	1	1		1
Pneumonia	2	1	1		1
Viral	16	11	5	1	4
CMV	8	5	3	1	2
BK virus HC	5	4	1		1
Other	3	2*	1**		1
Fungal	6	5	1		1
Candidemia	3	2***	1		1
IPA	2	2			
Mucormycosis	1	1			

AAT- alpha-1-antitrypsin, FMT - fecal microbiota transplantation, BSI - bloodstream infection,–UTI – urinary tract infection,

CMV – Cytomegalovirus, BK – BK virus, HC - hemorrhagic cystitis, IPA - invasive pulmonary aspergillosis

*Rhinovirus in bronchoalveolar lavage, adenovirus in nasal aspirate.

**EBV viremia resolved without therapy.

*** One candidemia event was diagnosed on the day AAT was started, therefore considered as an event occurring before AAT initiation.

Table S2. Non-infectious events during alpha-1-antitrypsin therapy course

Parameters	**Number of patients, N (%)**
All patients	17 (100)
Hematologic	
Pancytopenia	1 (5.8)
Neutropenia	1 (5.8)
Other	
Myopathy/Myalgia	1 (5.8)
Stroke	1 (5.8)
Cardiac	2 (11.7)
PAF	1 (5.8)
SVT	1 (5.8)
DAH	1 (5.8)
Volume overload	2 (11.7)
Elevated LFT	2 (11.7)

PAF – Paroxysmal atrial fibrillation, SVT – Supraventricular tachycardia, DAH – Diffuse alveolar hemorrhage, LFT – Liver function tests

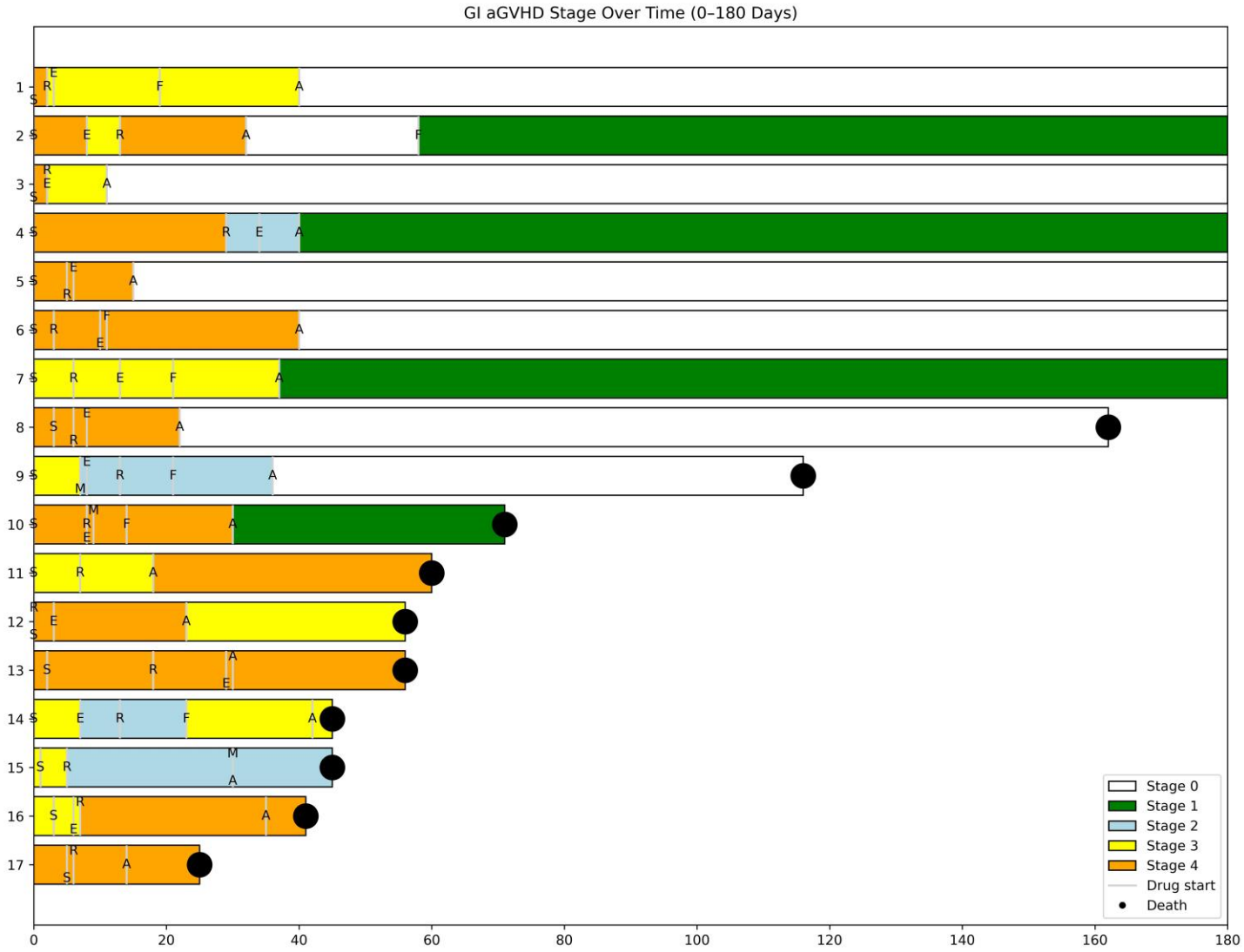


Figure S1. Swimmer plot of response to GVHD treatments.

Day 0 is the starting day of acute graft-versus-host disease. Letters on bars represent the following treatments – S: steroids; E: extracorporeal photopheresis; R: ruxolitinib; F: fecal microbiota transplantation; M: mofetil mycophenolate; A: alpha-1-antitrypsin. Different bar colors represent GI-aGVHD stages and duration of the response.