Ann Med Res 2021;28(11):2065-70

Annals of Medical Research

DOI: 10.5455/annalsmedres.2021.03.206

Original Article

Efficacy and safety of ruxolitinib plus extracorporeal photopheresis in acute and chronic graft versus host disease: A single center experience

Ahmet Sarici[1], Mehmet Ali Erkurt[1], Omer Faruk Bahcecioglu[2], Lokman Hekim Tanriverdi[3], Ilhami Berber[1], Emin Kaya[1], Soykan Bicim[1], Selim Gok[2], Mustafa Ozgul[1], Irfan Kuku[1]

[1]Department of Adult Hematology, Faculty of Medicine, Inonu University, Malatya, Turkey
[2]Department of Clinical Pharmacy, Faculty of Medicine, Inonu University, Malatya, Turkey
[3]Department of Medical Pharmacology, Faculty of Medicine, Inonu University, Malatya, Turkey

Abstract

Aim: There is no standard treatment for corticosteroid refractory acute and chronic graft versus host disease (GVHD). Ruxolitinib and extracorporeal phopheresis (ECP) are promising treatment options in GVHD. In this study, we aimed to share our clinical experience in steroid refractory GVHD patients treated with ruxolitinib plus ECP.

Materials and Methods: The data of patients receiving ruxolitinib plus ECP for corticosteroid refractory acute and chronic GVHD patients were analyzed retrospectively.

Results: A total of 11 cases, 6 of which were acute, were included in this retrospective, observational and single-center study. Acute GVHD developed in the 6 patients after allogeneic HSCT (median onset of GVHD=27, between 20 and 60 days). Chronic GVHD developed in the 5 patients after allogeneic HSCT (median onset of GVHD= 159 between 60 and 380 days. The overall response rate of acute GVHD patients to ruxolitinib ECP combination therapy was 16.7% (complete response: 16.7%, partial response: 0%). The overall response rate of chronic GVHD patients to combination therapy was 60% (complete response: 20%, partial response: 40%). As a result of combination therapy, thrombocytopenia occurred in 36% (4/11) of patients, neutropenia in 27% (3/11) of patients, and CMV reactivation in 9% (1/11) of patients.

Conclusion: We observed a low rate of overall response to ruxolitinib plus ECP treatment in acute GVHD patients but a high rate in chronic GVHD patients. According to our trial, ruxolitinib ECP combination may be beneficial in GVHD, especially in chronic GVHD, but prospective trials comparing its efficacy with other agents are needed.

Keywords: Allogeneic transplantation; corticosteroids; extracorporeal photopheresis; graft-versus host disease; ruxolitinib

INTRODUCTION

Graft-versus-host disease (GVHD) is a significant multisystem disorder that occurs after allogeneic hematopoietic stem cell transplantation (HSCT). GVHD is thought to occur as a result of the activation and expression of non-identical donor T-cells and an increased immune reaction to the host (1). While the main organs affected in patients with acute GVHD are the skin, the gastrointestinal tract and the liver, the main organs affected in chronic GVHD patients are the skin, liver, gastrointestinal tract, lungs and eyes (2).

Acute GVHD generally occurs within the early post transplantation period and affects approximately one-third to one-half of HSCT recipients (3). Chronic GVHD affects approximately one third of the HSCT recipients and its incidence is gradually increasing (4). Although chronic GVHD was formerly thought to occur after the 100th day of allogeneic HSCT, it can occur any time after allogeneic HSCT. The National Institute of Health (NIH) stated in 2005 that GVHD subtypes (acute or chronic) should be discriminated by clinical manifestations in place of the time from HSCT (100 days) (5).

In both acute and chronic GVHD, the first-line treatment is corticosteroids (1-2 mg/kg methylprednisolone, depending on the severity of GVHD and the site of involvement). According to GVHD treatment guidelines, there is no standard treatment for corticosteroid refractory acute and chronic GVHD (6,7). Agents such as calcineurin inhibitors, ruxolitinib, alemtuzumab, anti-thymocyte globulin (ATG), mycophenolate mofetil, mTOR inhibitors, pentostatin or extracorporeal photopheresis (ECP) can

Received: 04.03.2021 **Accepted:** 31.03.2021 **Available online:** 22.11.2021
Corresponding Author: Mehmet Ali Erkurt, Department of Adult Hematology, Faculty of Medicine, Inonu University, Malatya, Turkey
E-mail: erkurtali@hotmail.com

be used in second-line therapy. Among these agents, ruxolitinib (5 to 10 mg twice daily), an inhibitor of JAK1 and JAK2, has been approved by the FDA for the treatment of steroid refractory acute GVHD (8). In addition, there are retrospective observational studies reporting high responses (57-85%) to ruxolitinib in the treatment of chronic GVHD (9,10).

ECP is also an acceptable option in acute and chronic GVHD patients. High rates of responses have also been reported to ECP treatment used in both acute and chronic GVHD (11). There are studies examining the efficacy and safety of ECP in GVHD prophylaxis and first-line treatment, based on the high responses obtained in steroid refractory GVHD patients (12).

Recently, there are studies examining the efficacy and safety of using ruxolitinib combined with ECP in a small number of steroid refractory patients with acute and chronic GVHD (13,14). In this study, we aimed to share our clinical experience in steroid refractory GVHD patients treated with ruxolitinib plus ECP and to contribute to the literature due to the limited number of studies on this subject in the literature.

MATERIALS and METHODS

Patient Profile and Study Design

Patients who underwent allogeneic HSCT and developed steroid-resistant acute or chronic GVHD at the Turgut Özal Medical Center Adult Bone Marrow Transplant Service between January 2010 and July 2020 and who treated with ruxolitinib plus ECP were included in the study. Within the scope of the study, data on demographics, clinical features, survival rates, and transplant-related morbidity and mortality were retrospectively collected.

The study was conducted by the principles of the Declaration of Helsinki and was approved by the Non-Invasive Clinical Research Ethics Committee of Inonu University (Approval number: 2020/1022).

GVHD Definition, Grading and Treatment

The distinction between acute and chronic GVHD was made with the clinical characteristics of the patients in line with the criteria recommended by the NIH. The diagnosis was made by cutaneous, endoscopic, or surgical digestive biopsy whenever possible. In the presence of hepatic GVHD, the diagnosis was hypothetical considering the risk of percutaneous liver biopsy. The disease was graded according to standard classifications: Gluksberg for acute and NIH for chronic GVHD (15,16). The local GVHD treatment protocol in mild acute or chronic cases includes symptomatic relief therapy, topical clobetasol propionate ointments, budesonide PO/ enemas for gastrointestinal symptoms, and corticosteroid mouthwashes for oropharyngeal symptoms. In severe cases of acute or chronic GVHD, the first-line treatment was prednisone 1-2 mg/kg per day for 2 weeks. If there was a failure in corticosteroid treatment, the second-line is cyclosporine or mycophenolate mofetil. Then, the third line is extracorporeal photopheresis and/or ruxolitinib. Ruxolitinib was started at a dose of 5 mg twice a day for the first 3 days, and then continued at 10 mg twice a day. ECP treatment was started as 2 courses/week in the first two weeks, then continued as a weekly or monthly course according to the patient's condition.

GVHD Response Criteria

For acute GVHD

• Complete response: Elimination of symptoms associated with GVHD

• Partial response: Provided that improvement is achieved in at least one of the affected organs, but there is no deterioration in other affected organs.

• No response: No improvement or worsening of GVHD-related clinical or involvement were defined as used by Gomez et al (9).

Evaluation of clinical responses for chronic GVHD was made according to the NIH criteria as summarized below (16):

• Complete response: Elimination of all symptoms related to chronic GVHD in one of the affected organs

• Partial response: Detection of clinical improvement after treatment.

• No response: Failure to improve clinically or in the affected organs.

Statistical Analysis

Considering the absence of multiple groups in the study and the main purpose being only descriptive, advanced statistical methods were not needed in the study.

RESULTS

Patients' characteristics

A total of 11 cases, 6 of which were acute, were included in this retrospective, observational and single-center study. The median age was 26 years (range, 19-57). The most common underlying diseases were acute myeloid leukemia (27.2%, n=3), acute lymphoblastic leukemia (18.2%, n=2), and non-Hodgkin lymphoma (18.2%, n=2). Baseline characteristics of the patients included in the study are presented in Table 1. Eight (72.7%) of the 11 patients had skin involvement, 63.6% (7/11) had GIS involvement, 63.6% (7/11) had liver involvement, and one chronic GVHD patient had lung involvement.

The vast majority of patients (90.9%, n=10) received myeloablative conditioning regimens before HSCT. Acute GVHD developed in the 6 patients after allogeneic HSCT (median onset of GVHD=27, between 20 and 60 days).. Chronic GVHD developed in the 5 patients after allogeneic HSCT (median onset of GVHD= 159 between 60 and 380 days.

Table 1. Detailed characteristics of steroid refractory acute and chronic GVHD patients

Patients with steroid refractory acute GVHD

Patient No	Age	Gender	Disease	Donor	Involved Organ(s)	Grade	GVHD prophylaxis	Drugs used for GVHD after steroid application
1	26	Male	NHL	MRD	GIS, skin	IV	CsA-MTX-Post-Tx CsA	CsA, 2 months + MMF, 1 months
2	49	Male	HL	MRD	GIS, skin, liver	IV	CsA-MTX-Post-Tx CsA	CsA, 1,5 months + MMF, 1 months
3	57	Male	NHL	MRD	Skin	III	CsA-MTX-Post-Tx CsA	CsA, 3 months + MMF, 4 months
4	23	Female	AA	UMD	GIS, skin, liver	IV	CsA-MTX-Post-Tx CsA	CsA, 2 months
5	19	Male	ALL	UMD	Liver	III	CsA-MTX-Post-Tx CsA	MMF, 1 months
6	23	Female	BTM	UMD	GIS, liver	IV	CsA-MTX-Post-Tx CsA	CsA, 1 months + MMF, 1 months

Patients with steroid refractory chronic GVHD

Patient No	Age	Gender	Disease	Donor	Involved Organ(s)	Grade	GVHD prophylaxis	Drugs used for GVHD after steroid application
7	23	Male	ALL	UMD	GIS, liver	severe	CsA-MTX-Post-Tx CsA	MMF,8 months + RTX, 1 months
8	26	Female	CML	MRD	Lung, skin	moderate	CsA-MTX-Post-Tx CsA	CsA, 3 months
9	47	Female	AML	MRD	Skin	moderate	CsA-MTX-Post-Tx CsA	CsA, 12 months + MMF, 1 months
10	57	Female	AML	UMD	GIS, skin, liver	severe	CsA-MTX-Post-Tx CsA	CsA, 1 months + MMF, 2 months
11	41	Male	AML	MRD	Skin, GIS, liver	moderate	CsA-MTX-Post-Tx CsA	CsA, 6 months + MMF, 15 months

NHL: Non-Hodgkin lymphoma, AML: Acute myeloid leukemia; HL: Hodgkin lymphoma, AA: Aplastic anemia, ALL: Acute lymphoblastic leukemia, BTM: Beta Thalassemia Major, CML: Chronic myeloid leukemia MRD: Matched-related donor, UMD: Unrelated-matched donor, GIS: Gastrointestinal System, CsA: Cyclosporin, MTX: Methotrexate, Post-Tx: Post-transplant, MMF: Mycophenolate Mofetil, RTX: Rituximab,

Table 2. Survival, treatment response and mortality data of ruxolitinib plus ECP treated-patients with steroid refractory acute and chronic GVHD

Patient no	7-day survival	28-day survival	90-day survival	180-day survival	PR (%)	CR (%)	NR (%)	GVHD mortality	Non-GVHD mortality
Patients with steroid refractory acute GVHD									
1	+	-					YES	NO	YES
2	+	-					YES	NO	YES
3	+	+	+	+		YES		NO	NO
4	+	-					YES	NO	YES
5	+	+	-				YES	NO	YES
6	+	-					YES	NO	YES
Patients with chronic GVHD									
7	+						YES	YES	
8	+	+	+	+		YES		NO	NO
9	+	+	+	+	YES			NO	NO
10	+	-					YES	NO	YES
11	+	+	+	+	YES			NO	NO

PR: Partial response, CR: Complete response, NR: No response

Treatment response and adverse effects in acute GVHD patients

Patients started receiving ruxolitinib or ECP after a median of 39 (16-210) days after the occurrence of acute GVHD. ECP was started before ruxolitinib in 4 (66.7%) patients and ruxolitinib was administered before ECP in 2 (33.3%) patients. The patients received ruxolitinib ECP combination for a median of 18 (9-35) days. Median 4 (3-5) course ECP was applied in combination with ruxolitinib. In total, ruxolitinib was applied median 19 (9-420) days, ECP treatment was median 32 (15-64) days. A total of median 5.5 (4-10) course ECP was applied to the patients.

The overall response rate of acute GVHD patients to ruxolitinib ECP combination was 16.7% (complete response: 16.7%, partial response: 0%). Five (83.4%) patients have no response to combination therapy, and these patients died due to infections (Table 2). Three of the five patients had cytomegalovirus (CMV) reactivation

before combination therapy, but we administered ruxolitinib-ECP in combination with ganciclovir, since the patients had grade IV GVHD.

As a result of ruxolitinib ECP combination therapy, neutropenia occurred in 33.3% (2/6) of patients, thrombocytopenia in 33.3% (2/6), and CMV reactivation in 16.7% (1/6).

Treatment response and adverse effects in chronic GVHD patients

The patients started to receive ruxolitinib or ECP after a median of 41 (30-580) days after the diagnosis of chronic GVHD. While only 1 (20%) patient was started with ECP first, 80% of the patients first started ruxolitinib. Median duration of administration of ruxolitinib ECP combination to patients is 35 (20-210) days with median 6 (4-10) ECP courses. The patients received a median of 7 (4-10) courses of ECP in total, and the patients received ruxolitinib for a median of 264 (24-330) days.

One (20%) of the 5 patients had a complete response to the ruxolitinib ECP combination, and 40% had a partial response (Table 2). Two (40%) patients had no response to combination therapy, one patient died due to acute pancreatitis and the other died of multiorgan failure due to GVHD.

As a result of combination therapy, thrombocytopenia occurred in 40% of the patients, and neutropenia occurred in 20%. CMV reactivation was not observed in any of the patients.

DISCUSSION

GVHD is a significant complication seen in allogeneic HSCT recipients, which increases the length of hospital stay and patient care costs by approximately 2 times and increases mortality by approximately 3 times (17). However, with the introduction of new therapies into clinical use in recent years, mortality rates in GVHD patients have decreased (18).

Approximately half of both acute and chronic GVHD patients develop resistance to corticosteroids, which is the first-line treatment of acute and chronic GVHD (19,20). In these patients, it is recommended to use a second immunosuppressive agent in addition to steroids, but there is no consensus on which agent should be used (6,7). Among the most commonly used agents in the treatment of steroid refractory GVHD are calcineurin inhibitors (tacrolimus and cyclosporine), sirolimus, mycophenolate mofetil, ATG, alemtuzumab, pentostatin, ECP and ruxolitinib. In the literature, the overall response rate of these therapies in steroid refractory GVHD treatment varies between 33-83% (12,21-24).

In the present study, data on the efficacy and safety of ruxolitinib ECP combination in acute and chronic GVHD patients, for which there is little data on its efficacy and safety, are shared with the literature.

In a phase 2 trial (REACH1 trial) of 71 patients with refractory acute GVHD, an overall response rate to ruxolitinib was 54.9% at the end of 28 days and 73.2% at any time, and response to ruxolitinib occurred in a median of 7 days (25).

In the randomized controlled phase 3 trial (REACH2 trial) in patients with grade 2-4 refractory acute GVHD, patients were randomized 1:1 as the ruxolitinib group and the control group. Patients in the control group were given ATG, ECP, mesenchymal stromal cells, methotrexate, mycophenolate, everolimus, sirolimus, etanercept or infliximab, depending on the researcher's choice, while the other group received ruxolitinib 10 mg twice a day. It was found that the overall response rate in the ruxolitinib group was significantly higher than in the control group at the end of 28 days (62.3% vs 39.4%, $p<0.001$) and 56 days (39.6% vs 21.9%, $p<0.001$). In the group receiving ruxolitinib, the most frequent toxic effect was seen with a higher incidence of thrombocytopenia than was observed in the control group (26). In our population, the most common side effect associated with ruxolitinib ECP combination therapy is thrombocytopenia (all patients: 36.4%, acute GVHD: 33.3%, chronic GVHD: 40%).

In a retrospective observational study that examined the efficacy and safety of ruxolitinib ECP combination therapy in 18 steroid refractory acute GVHD patients published in May 2020, 44% of the patients had a complete response and 11% had a partial response to the combination therapy. The most common side effects observed in patients were CMV reactivation, leukopenia and thrombocytopenia (14). In our study, response rate to ruxolitinib and ECP combination was 16.7% in acute GVHD patients, and 5 (83.3%) patients died due to infectious complications. The presence of CMV reactivation before combination therapy in 3 of 5 patients who died due to infection suggests that the use of ruxolitinib ECP combination is not safe in acute GVHD patients with CMV reactivation.

A retrospective study has recently been published evaluating the response rates of patients to the ruxolitinib ECP combination in 23 patients with chronic GVHD. According to this study, 8.7% of the patients had a complete response to the combination therapy, and 65.2% had a partial response. CMV reactivation was observed in six patients (26.1%), and cytopenias were observed in five patients (21.7%) (13). Similar to this study, our chronic GVHD patients had a high response rate to ruxolitinib ECP combination (complete response: 20%, partial response: 40%), and we observed cytopenias in 40% of our patients, but we did not observe CMV reactivation.

Our study is an important study that will contribute to the literature since there are only two studies in the literature that examine the efficacy and safety of ruxolitinib ECP combination in GVHD patients. However, the limitations of the study are that it is a retrospective observational study and that a small number of patients were included in the study.

CONCLUSION

In this retrospective observational study, we observed a low rate of overall response to ruxolitinib plus ECP treatment in acute GVHD patients but a high rate in chronic GVHD patients. The presence of CMV reactivation before ruxolitinib ECP combination therapy in 3 of 5 acute GVHD patients who died due to infection suggests that the use of ruxolitinib ECP combination is not safe in acute GVHD patients with CMV reactivation. According to our trial, ruxolitinib ECP combination may be beneficial in GVHD, especially in chronic GVHD, but prospective trials comparing its efficacy with other agents are needed.

Competing Interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical Approval: The study was conducted by the principles of the Declaration of Helsinki and was approved by the Non-Invasive Clinical Research Ethics Committee of Inonu University (Approval number: 2020/1022).

REFERENCES

1. Aladag E, Kelkitli E, Goker H. Acute Graft-Versus-Host Disease: A Brief Review. Turk J Haematol 2020;37:1.
2. Jacobsohn DA, Kurland BF, Pidala J, et al. Correlation between NIH composite skin score, patient-reported skin score, and outcome: results from the Chronic GVHD Consortium. Blood 2012;120:2545-52.
3. Jacobsohn DA, Vogelsang GB. Acute graft versus host disease. Orphanet J Rare Dis 2007;2:35.
4. Arai S, Arora M, Wang T, et al. Increasing incidence of chronic graft-versus-host disease in allogeneic transplantation: a report from the Center for International Blood and Marrow Transplant Research. Biol Blood Marrow Transplant 2015;21:266-74.
5. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant 2005;11:945-56.
6. Saad A, de Lima M, Anand S, et al. Hematopoietic Cell Transplantation, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Cancer Netw 2020;18:599-634.
7. Penack O, Marchetti M, Ruutu T, et al. Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation. Lancet Haematol 2020;7:e157-e67.
8. Przepiorka D, Luo L, Subramaniam S, et al. FDA Approval Summary: Ruxolitinib for Treatment of Steroid-Refractory Acute Graft-Versus-Host Disease. Oncologist 2020;25:e328.
9. Gómez VE, García-Gutiérrez V, Corral LL, et al. Ruxolitinib in refractory acute and chronic graft-versus-host disease: a multicenter survey study. Bone Marrow Transplant 2020;55:641-8.
10. Zeiser R, Burchert A, Lengerke C, et al. Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. Leukemia 2015;29:2062-8.
11. Greinix HT, Worel N, Just U, Knobler R. Extracorporeal photopheresis in acute and chronic graft-versus-host disease. Transfus Apher Sci 2014;50:349-57.
12. Kaloyannidis P, Mallouri D. The role of the extracorporeal photopheresis in the management of the graft-versus-host disease. Transfus Apher Sci 2012;46:211-9.
13. Maas-Bauer K, Kiote-Schmidt C, Bertz H, et al. Ruxolitinib–ECP combination treatment for refractory severe chronic graft-versus-host disease. Bone Marrow Transplant 2020:1-8.
14. Modemann F, Ayuk F, Wolschke C, et al. Ruxolitinib plus extracorporeal photopheresis (ECP) for steroid refractory acute graft-versus-host disease of lower GI-tract after allogeneic stem cell transplantation leads to increased regulatory T cell level. Bone Marrow Transplant 2020:1-8.
15. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus conference on acute GVHD grading. Bone Marrow Transplant 1995;15:825.
16. Lee SJ, Wolff D, Kitko C, et al. Measuring therapeutic response in chronic graft-versus-host disease. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 Response Criteria Working Group report. Biol Blood Marrow Transplant 2015;21:984-99.
17. Yu J, Parasuraman S, Shah A, et al. Mortality, length of stay and costs associated with acute graft-versus-host disease during hospitalization for allogeneic hematopoietic stem cell transplantation. Curr Med Res Opin 2019;35:983-8.
18. Bashey A, Zhang X, Morris LE, et al. Improved Survival of Patients Diagnosed with Severe (Grade 3-4) Acute GVHD or Severe NIH Grade Chronic GVHD in the Current Era Compared to Historic Controls. Blood 2019;134:2006.
19. Yalniz FF, Murad MH, Lee SJ, et al. Steroid refractory chronic graft-versus-host disease: cost-effectiveness analysis. Biol Blood Marrow Transplant 2018;24:1920-7.
20. Khoury H, Kashyap A, Adkins D, et al. Treatment of steroid-resistant acute graft-versus-host disease with anti-thymocyte globulin. Bone Marrow Transplant 2001;27:1059-64.
21. Ragon BK, Mehta RS, Gulbis AM, S et al. Pentostatin therapy for steroid-refractory acute graft versus host disease: identifying those who may benefit. Bone Marrow Transplant 2018;53:315-25.
22. Gomez-Almaguer D, Ruiz-Argüelles GJ, del Carmen Tarín-Arzaga L, et al. Alemtuzumab for the treatment of steroid-refractory acute graft-versus-host disease. Biol Blood Marrow Transplant 2008;14:10-5.

23. Hoda D, Pidala J, Salgado-Vila N, et al. Sirolimus for treatment of steroid-refractory acute graft-versus-host disease. Bone Marrow Transplant 2010;45:1347-51.
24. Krejci M, Doubek M, Buchler T, et al. Mycophenolate mofetil for the treatment of acute and chronic steroid-refractory graft-versus-host disease. Ann Hematol 2005;84:681-5.
25. Jagasia M, Ali H, Schroeder MA, et al. Ruxolitinib in combination with corticosteroids for the treatment of steroid-refractory acute graft-vs-host disease: results from the phase 2 REACH1 trial. Biol Blood Marrow Transplant 2019;25:52.
26. Zeiser R, von Bubnoff N, Butler J, et al. Ruxolitinib for glucocorticoid-refractory acute graft-versus-host disease. N Engl J Med 2020;382:1800-10.