Transfusion and Apheresis Science 61 (2022) 103371

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Rational use of chronic graft-versus-host treatment alternatives: A systematic review

Mahmut Yeral [1,*], Can Boğa [1]

Department of Hematology, Adana Adult Bone Marrow Transplantation Center, Baskent University, Ankara, Turkey

ARTICLE INFO

Keywords:
cGVHD
Allogeneic PSCT
Stem cell
Treatment

ABSTRACT

Chronic graft versus host disease (cGVHD) is an important transplant complication that affects the quality of life of the recipient by causing organ damage after hematopoietic stem cell transplantation. Prospective controlled studies conducted to date for the treatment of the disease are limited. The results obtained in current studies are not sufficient to establish a standard treatment algorithm. Therefore, clinical experience and adequate clinical observations of the transplant team come to the fore for the treatment strategy to be established. Rational use of available instruments is possible, provided that we understand the mechanisms of the disease and use validated diagnostic and response criteria. In this study, we tried to create a practical workflow by evaluating current literature data.

1. Introduction

Chronic graft versus host disease (cGVHD) can be defined as a chronic multisystemic immune deviation disease, which is accompanied by the absence of an adequate immune tolerance of donor-derived immune effector cells against the recipient's tissues and cells after the engraftment of the allogeneic hematopoietic stem cells. As an important complication, cGVHD can develop classically beyond the 100th day after allogeneic hematopoietic stem cell transplantation (Allo HSCT) and can lead to 20–30 % mortality. The cumulative incidence of cGVHD is approximately 50 % [1]. Inflammation may result in increased fibrosis and deformities. Skin, muscle tissue and joints are the most affected tissues. The slowly and progressively increasing serum bilirubin level affects the intra and extra hepatic bile clearance, as in Sjögren's syndrome. In the digestive tract, deterioration of the mucosal structure (mucositis, ulcer, lichenoid plaques, atrophy and fibrosis) causes structural and functional (absorption) problems. Eyes, genitals, lungs are among the most frequently involved organs. In overlap GVHD, acute GVHD (aGVHD) and cGVHD findings may coexist. In 2013, the National Institude of Health (NIH) helped standardize clinical definitions and criteria of cGVHD, as it has prognostic implication [2].

Although the pathogenetic mechanism is not fully known, it involves thymus atrophy, humoral immunity defect, transformation of naive T cells into deviated effector T cells with the aid of T helper 17, interleukin 4 (IL-4) and IL-7. Development of autoantibodies as a result of continuous stimulation of B cell receptors are held responsible for the emergence of cGVHD [3,4]. Due to this chronic inflammatory process that results in organ damage to the recipient, it is often not possible to discontinue immunosuppressive drugs in the recipient. The result is organ damage, immune deficiency, and secondary malignancies due to long-term immunosuppressive drugs [5].

The emergence of cGVHD is facilitated by the widespread use of peripheral blood stem cells, HLA and non-HLA tissue group antigens, female donor and donors lymphocyte infusions. The management of the disease is very difficult. The use of systemic immunosuppressive drugs, particularly corticosteroids and calcineurin inhibitors may be insufficient to keep the chronic inflammatory process under control for a long time. It is reported that clinical efficacy can be achieved with a large number of molecules in the treatment [6]. However, due to complex immunological factors, multiple patient and disease-related factors, it is not easy to establish immune tolerance. For this reason, treatment options are always discussed, but these efforts are often insufficient to reach a standard treatment approach. In this study, it is aimed to establish a logical workflow in the management of cGVHD by systematically evaluating scientific studies on treatment options.

* Corresponding author at: Baskent University, Adana Adult Bone Marrow Transplantation Center, Yuregir, 01250, Adana, Turkey.
E-mail addresses: myeral@baskent.edu.tr (M. Yeral), cboga@baskent.edu.tr (C. Boğa).
[1] Baskent University Adana Adult Bone Marrow Transplantation Center, Adana, Turkey.

https://doi.org/10.1016/j.transci.2022.103371

Available online 24 January 2022

2. Methods

This systematic review adheres to the Preferred Reporting Items for Systematic Research guidelines.

2.1. Data sources and searches

The Pubmed/ MEDLINE and COCHRANE database were searched in September 2021, in order to identify all published work on the topics of interest. The searches were performed using keywords and Medical Subject Headings terms.

Search terms: ((((("stem cell transplant*"[Text Word] OR "hematopoietic stem cell transplant*"[Text Word] OR "bone marrow transplant*"[Text Word])) AND (chronic graft-versus-host disease [Text Word] AND "methyl prednisolone "[Text Word] OR, "mycophenolate mofetyl" [Text Word] OR, "fluticasone" [Text Word] OR "rapamycine"[Text Word] OR ruxolutinib [Text Word] OR ibrutinib [Text Word] OR imatinib [Text Word] OR dasatinib [Text Word] OR cyclosporine [Text Word] OR tacrolimus [Text Word] OR rituximab [Text Word] hydroxyl chloroquine [Text Word] OR pentostatin [Text Word] OR, alemtuzumab [Text Word] OR abaltecept [Text Word] OR etanercept [Text Word] OR bortezomib [Text Word] OR methotrexate [Text Word] OR photopheresis

2.2. Data extraction and Bias assessment

The total number of cases in the articles and the total follow-up period were determined. The articles were reviewed by two researchers (MY and CB) in terms of suitability or exclusion. From the articles found, the cumulative incidence of cGVHD, life expectancy without cGVHD, response rate, non-relapse mortality rate (NRM), relapse rate (RR), and significant authors' messages were extracted according to the study design and treatment options used for cGVHD management, organ damage risk factors and side effects and toxicities were noted.

The risk of bias in individual studies was evaluated using the Cochrane Risk of Bias assessment tool for randomised clinical trails (RCTs) [7].

2.3. Eligibility criteria

Randomized clinical trials, prospective observational studies, multicenter retrospective studies, meta-analyses, and single center retrospective studies investigating cGVHD management in adults undergoing allogeneic HSCT were considered eligible for inclusion in this review. We only included studies published after 2000.

We did not include case reports, narrative reviews, surveys, animal studies and unpublished records. In addition, we decided to focus on adult patients receiving allogeneic transplantation, thereby excluding trials in pediatric patients or autologous transplanted subjects.

2.4. Definitions

Classical cGVHD was defined as GVHD without characteristics of aGVHD, while overlap GVHD was defined as the presence of features of chronic and acute GVHD appearing together. Extensive GVHD, persistent, recurrent, or late onset acute GVHD: features of classic acute GVHD occurring beyond 100 days post-transplantation or donor lymphocyte infusion (DLI) in a patient not meeting criteria for the diagnosis of chronic GVHD (often seen during the taper or after withdrawal of immune suppression) [8]. Patients with localized skin involvement, with or without hepatic dysfunction are considered to have limited disease. Extensive chronic GvHD is defined as either generalized skin involvement or localized skin involvement in association with eye and/or oral involvement, abnormal liver histology (chronic progressive hepatitis, bridging necrosis, or cirrhosis), or other target organ involvement [9].

Diarrhea was deemed present if stated as such by the authors or if an increased frequency or volume or watery consistency of stools was described. Elevated liver enzymes was any increase (above the upper limit of normal as specified in the publication) in aminotransferases, alkaline phosphatase, and/or bilirubin. Pancytopenia was deemed present if explicitly stated by authors or if a decline in 3 cell lines (leukocytes, red bloodcells, and platelets) below the lower limit of normal was reported.

3. Results

A total of 798 references was identified through a systematic search of the Cochrane Library and PubMed/MEDLINE after exclusion of duplications. Abstracts from relevant conference case reports, pediatric studies, and animal studies were 562 (Fig. 1). Two hundred thirty six references were potentially relevant and retrieved for full details. Of the 236 studies, 186 were excluded due to the lack of an study design. Fifty studies conducted between 2001 and 2021 met the inclusion criteria.

Seven RCTs were included in the current analysis [10,15,23,35,39,52,57](Table 1). The following domains were assessed individually: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data reporting, selective outcome reporting, and other bias. We assessed each domain separately and graded them as low risk of bias, unclear risk (lack of information or uncertainty regarding the potential for bias), or high risk of bias according to the criteria specified in the Cochrane handbook for RCTs (version 5.1.0) [9]. The quality assessment is described in Table 2.

Due to consistency in the risk of bias across included studies, we could not perform a sensitivity analysis according to methodological quality domains.

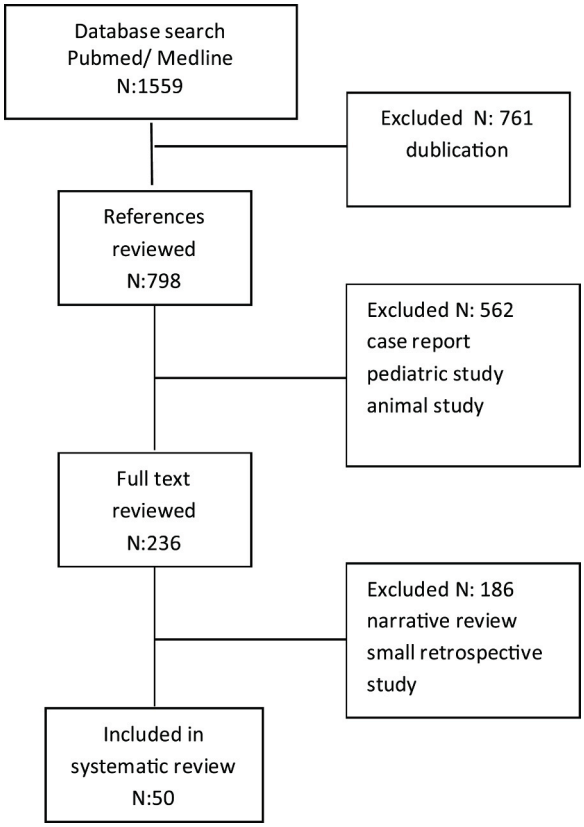

Fig. 1. Study selection.

Table 1
Baseline characteristics of randomised trials.

Characteristics	Zeiser 2021 [15]	Arai 2016 [35]	Koc 2002 [10]	Chen 2019 [57]	Curtis 2021 [39]	Carpenter 2018 [52]	Flowers 2008 [23]
Prior IS drug for cGVHD	Glucocorticoids or, glucocorticoids plus 1 IS drug or ruxolutinib	Glucocorticoids	None	Unclear	Any IS drug and/or ECP	Glucocorticoids or, glucocorticoids plus non-sirolimus IS	Corticosteroid, MMF, FK-506, cyclosporine A
Center	Multicenter, International (Germany)	Multicenter, national (United States)	Single center (Fred Hutchinson)	Multicenter, national (China)	Multicenter, national (United States)	Multicenter, national (United States)	Multicenter, International
Study duration	2017–2019	2011–2014	1985–1992	2014–2017	2013–2016		2002–2005
No. of patients	319	30 vs 31	287	81 (49 vs 32)	34	72 vs 66	48 vs 47
Primary outcome	OR, FFS	SCR	TRM	RR, DP	OR	OR, CR, PR	TSS
Secondary outcome	BOR, DR, OS, QOL, change in glucocorticoid dose	TF, change in glucocorticoid dose, PRO, Skin biopsy, B cell profiles	Time-to- event, DIS, RM	TEFEV1 decline, LFS, OS, infections, AE	TD, median daily dose of pomalidomide, QOL, AE, changes in biomarkers	FFS, OS, QOL, AE	change in glucocorticoid dose
Median follow-up, mo	14.3	6	60	19.8 vs NA	24	6	
Treatment arms	Ruxolutinib vs BAC	Imatinib vs rituximab	Cylosporine plus prednisone vs prednisone	MSC plus prednisone plus azithro vs. prednisone plus azithro	Pomalidomid 0.5 vs pomalidomid 2 mg	Prednisone/ sirolimus vs prednisone/ sirolimus/ CNI	ECP /CTA vs CTA
Disease type	NA	NA	NA	AML, ALL	Myeloid, lymphoid malignency	AL, CL, MDS, lymphoma	AML, ALL, KML, NHL
Transplant type	Related, unrelated	Related, unrelated	MRD, MUD, MMRD, MMUD	MRD, MUD, MMRD, MMUD	Related, unrelated	Related, unrelated	Related, unrelated
Cell source	NA	PBSC, BM	NA	PBSC, PBSC/BM	PBSC, BM, UCB	PBSC, BM, UCB	PBSC, BM
Median age (range), y	49 (13–73) vs 50 (12–76)	56 (19–72) vs 56 (21–78)	30 (2–56) vs 31 (0.9–571)	32 (18–59) vs 25 (18–52)	47 (20–73) vs 52 (21–68)	50 (5–67) vs 55 (2–64)	41(16–67) vs 43 (13–67)
Male sex, no (%)	66 vs 56	56 vs 51	65 vs 53	55 vs 59	65	67 vs 50	63 vs 55

CR. Complate response, PR: Partial response, IS: Immunosuppressive, OR: Overall response, TF: Treatment failure, FFS: failure free survival, BOR: Best overall response, TSS:Total skin score SCR: Significant clinical response, DR: Duration of response, QOL: Quality of life, BAC: Best available care, CTA: conventional treatment arm, DP: Disease progression, AE : Adverse event, TEFEV1: Treatment effect of FEV1, Azithro: Azithromycine, NA: None available, TRM: Transplantation-related mortality, DIS: Discontuniation of immunosppressive drugs, RM: Recurrent malignancy, MRD: Matched related donor, MUD: Matched unrelated donor, MMRD: Mismatched related donodr, MMUD: Mismatched unrelated donor, PBSC: Peripheral blood stem cell, BM: Bone marrow, ECP: Extracorporeai photopheresis, TD: Therapy duration, UCB: Umblical cord blood, MSC: Mesenchymal stem cell.

Table 2
Risk of bias in the included studies by Zeisser et al. [15], Arai et al. [35], Koc et al. [10], Chen et al. [57], Curtis et al. [39], Carpenter et al. [52] and Flowers et al. [23].

Randomized trials	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment	Incomplete outcome data	Selective reporting (reporting bias)	Other bias
Zeisser 2021	+	–	–	+	+	?	+
Arai 2016	+	+	–	+	+	+	+
Koc 2002	?	?	–	?	?	+	?
Chen 2019	–	?	–	?	+	+	+
Curtis 2021	+	?	–	?	?	?	+
Carpenter 2018	?	–	–	?	?	+	?
Flowers 2008	+	+	?	+	?	?	+

+indicates low risk of bias.
?indicates unclear risk of bias.
-indicates high risk of bias.

3.1. Cyclosporine

Second-line treatment options in steroid-refractory cGVHD are controversial in terms of their efficacy and superiority. Studies comparing these options are scarce. Koc et al. (2002), in a randomized prospective study comparing prednisone with prednisone and cyclosporine, showed that overall survival (OS) was 67 % and 72 %, respectively, at 5 years. They found no difference in the rate of discontinuation of immunosuppressives (54 % vs 53 %), and there was no difference in the frequency of development of avascular necrosis (13 % vs. 22 %). Transplant-related mortality (TRM) was found to be 17 % and 13 %, respectively. While the addition of cyclosporine reduced steroid-related complications, it did not alter the clinical course [10].

Axt et al. (2019) compared second-line treatments in 72 patients in a single-center and retrospective manner. The overall response rate (ORR) was 45.5 % for calcineurine inhibitors (CNI), 50 % for mycophenolate mofetil (MMF), 60 % for mTOR inhibitors, 56.3 % for extracorporeal photopheresis (ECP), and 16.7 % for rituximab in all patients, respectively. While ORR was found to be 44.4 % for the all group [11].

In a retrospective study of Villanueva (2009), oral beclamethasone and cyclosporine were used in 33 patients with severe gastrointestinal involvement. At the end of 16 weeks, they achieved a CR of 84.6 % and a

PR of 7.7 %. However, 7% of the patients were able to maintain their response [55].

3.2. Mycophenolate mofetil

A total of 3 studies were found in the search that met the study criteria. These studies were multicenter retrospective studies and included 141 patients. In a study conducted by the Japanese group including 84 patients, a subjective response was observed in 69.1 % of patients. When MMF was administered at a dose of 250−3000 mg/day, resulting in discontinuation or reduction of the combined immunosuppressive agents in 75.9 % of patients. Bacterial infections are the most common cause of death in 22 % of patients [12]. In another study of 50 patients, the ORR was found to be 52 % (complete remision [CR] 10 %) [13]. Kim et al. (2004) reported an ORR of 76.9 (CR 7.7 %) at a median follow-up of 107 months of 13 patients. In this study, OS was found to be 53.9 % at 2 years [14]. The response rate is higher than in other studies, but the number of patients is quite small. In all studies, the most common side effects were found to be infection and diarrhea.

3.3. Ruxolutinib

It is known that ruxolutinib has an immunomodulatory effect by inhibiting the JAK/STAT pathway and an anti-inflammatory effect through cytokines.

After screening and exclusion according to our study design, 1 prospective randomized double-arm, 1 prospective single-arm, and 7 retrospective studies on ruxolutinib were evaluated. Zeiser et al. (2021), in a recent prospective phase III study, compared ruxolutinib with a control group in 329 steroid-resistant or steroid dependent cGVHD patients. The investigators' choice of therapy (10 commonly used options) constituted the control group. At 24 weeks, the response rate was found to be statistically significantly higher in the ruxolutinib arm compared to the control arm (49.7 % vs. 25.6 %). Failure free survival (FFS) was >18.6 months in the ruxolutinib group and 5.7 months in the control group. Anemia and thrombocytopenia as the most common side effects of Grade III and above toxicity were 12.7 % and 15.2 % in the first arm, 7.6 % and 10.1 % in the second arm [15]. Moiseev et al. (2020) evaluated 43 steroid-refractory cGVHD patients in as a single center. Median drug use was 2, CR 21 %, ORR 81 %, OS 85 %, and Grade III-IV neutropenia 44 % [16].

Similar to prospective studies, the response rate was found to be high in retrospective studies. A total of 7 retrospective studies, 3 of which were multicentric and 4 of which were single-center, which met our screening criteria were evaluated. Zeiser et al. (2015) reported that ORR was 85.4 %, OS 97.4 % at 6 months in 41 patients, and relapse rate (RR) was 5.7 % in responding cases [17]. Modi et al. (2019) reported that ORR was 47.8 % at 6 months in 46 patients, FFS 45.7 at 12 months and the rate of reducing dose of steroids was 59 % [18]. Escamilla Gomez (2020) reported ORR as 81 %, CR 3.5 % at 12 months, OS 81 % at 12 months, Grade III toxicity 32.9 % in 56 patients [61]. Zhao et al. (2021) showed that ORR was 89.5, CR 26.3 %, relapse rate 16 % in 19 patients who underwent haploidentical hematopoietic stem cell transplantation [19]. Wu et al. (2021) reported that ORR was 70.7 %, CR 36.6 % at 6 months, OS 77.3 % at 12 months, and NRM 8.6 % in 41 patients [20]. Ferreira et al. (2021) reported that ORR was 89 %, CR 26 %, OS 67 % at 4 weeks, FFS 71.1 at 6 months, FFS 54 % at 2 years in 35 patients [21]. Bondeelle et al. (2020) investigated the effect of ruxolutinib in patients with impaired lung function due to sclerotic cGvHD or bronchiolitis obliterans. He stated that no statistically significant improvement was achieved with ruxolutinib compared to those who did not use it [22].

3.4. Extracorporeal photopheresis

Extracorporeal photopheresis (ECP) is one of the treatment approaches used in cases of steroid-refractory or dependent cGVHD. We found 1 prospective randomized, 1 prospective non-randomized and 7 retrospective studies under this topic. Flowers et al. (2008) compared ECP and standard therapy (n = 48) with standard therapy alone (n = 47). The median percentage improvement in total skin score at week 12 was 14.5 % for the ECP arm and 8.5 % for the control arm (P = .48) [23]. Sakellari et al. (2018) followed 82 patients for a median of 68.1 months in their prospective study. They achieved CR in 35 patients and partial remission (PR) in 25 patients. ORR was 73 %. 5-year TRM and OS, were 27.1 % and 64.5 %, respectively. The best response was seen in those with the cutaneous form. An RR of 83 % in sclerotic patients, 53 % in patients with visceral involvement, and 27 % in pulmonary involvement has been reported [24].

Regarding retrospective studies, ECP studies on steroid-refractory or steroid-dependent cGVHD complied with our study protocol. Apisarntthanarax et al. (2003) reported a median photopheresis session of 36, ORR was 56 %, CR 22 %, steroid dose reduction rate 64 %, and cGVHD or infection-related mortality 34 % in 32 patients [25]. Oarbeascoa at al. (2020) with median photopheresis session of 19 in 48 patients, ORR was 67 % and CR was 23 % [26], Okamoto (2018) reported that ORR was 66.7 % at 6 months in 15 patients [27]. Bisaccia et al. (2006) reported that ORR was 50 % and CR was 21 % for skin in 14 patients [28]. Couriel et al. (2006) reported that ORR was 61 %, CR 20 %, and OS at 1 year in 71 patients. Steroid discontinuation rate was 73 % in severe and heavily pre-treated patients [29]. Gunduz et al. (2019) evaluated the importance of early initiation of photopheresis. In their study, ORR was 70 % and CR was 29 % in 34 patients. Starting ECP treatment after 3 months reduced the ORR from 92 % to 59 % [30]. Ussowich (2013) investigated steroid sparing effect of ECP in 13 patients. After median 28 sessions, OS was 67.7 % at 4 years. Steroid discontinuated in 46 % of patients and reduced in 38 % [31].

3.5. Ibrutinib

There are few well-designed, prospective studies of ibrutinib, an inhibitor of Bruton tyrosine kinase. A phase Ib/II study initiated as a multicentric prospective and updated 1 year later included 42 patients [32,33]. In this steroid-dependent or refractory group, the CR was 31 % and the ORR was 69 %, at a median follow-up of 26 months. During the study, a reduction of <15 mg/kg/day corticosteroids was achieved in 64 % of 42 patients. Grade III drug toxicity, which was observed at a rate of 75 % in the first year, decreased to 25 % in the second year [33]. Doki et al. (2021) evaluated the efficacy, safety and side effects of ibrutinib in 19 patients in a new multicentric prospective single-arm study. The best overall response was found to be 73.7 % in this patient group with 2 or more organ involvements [34]. Toxicity was the most common aetiology for drug withdrawal 15.8 % [34].

3.6. Imatinib

A total of 140 patients were evaluated in 2 prospective and 1 retrospective studies. All who met the study criteria for imatinib, which is a tyrosine kinase inhibitor and is especially preferred in sclerotic skin involvement. In a prospective, multicentric randomized phase II study designed by Arai (2016), imatinib was compared with rituximab. After 6 months, a significant clinical response was achieved in 9 of 35 (26 %) patients in the imatinib arm and in 10 (27 %) of 37 patients in the rituximab arm. However, 6 patients (17 %) in the imatinib arm and 5 patients (14 %) in the rituximab arm were able to achieve CR without crossover and recurrence [35]. Baird et al. (2015) achieved a clinical improvement between 3% and 94 % in 11 of 14 (78.6 %) patients after 6 months with imatinib in steroid resistant cGvHD [36]. Moles-Poveda (2018) reported a single center retrospective study, and CR and PR rates were found to be 22 % and 50 %, respectively [37]. The most common side effects were hypophosphatemia, nausea, vomiting, and fluid retention. Drug tolerance increased with dose reduction [36,37].

No data suitable for the study criteria were found for dasatinib. One

prospective study was found on nilotinib, and it was given sequentially with rituximab [38].

3.7. Pomalidomide

Pomalidomide has a positive effect by showing an antifibrotic effect and increasing Treg cells. Curtis et al. (2021) reported in this prospective trial that 34 patients receiving median 5 drug therapy for sclerotic cGVHD were randomized to compare low dose (0.5 mg/d) with high dose (2 mg/d). Eight of the high-dose patients required dose reduction due to toxicity. There was no difference in the 6-month ORR in the low-dose and high-dose arm [39].

3.8. Rituximab

Within the scope of our study, a total of 127 patients were evaluated in 5 prospective and 1 retrospective studies on rituximab [40–45]. The prospective studies were phase II and non-randomized trial. Teshima (2009) investigated 7 patients with early phase II study in terms of efficacy and safety. In the study, ORR was 43 % and OS was 71.5 % [40]. Although there was no toxicity in the early period, infections were noted in the late period. In the study of Solomon SR (2015) 25 patients received first-line therapy with MMF, tacrolimus, or sirolimus without corticosteroids, and demonstrated ORR, CR, and OS at 2 years as 88 %, 84 %, and 82 %, respectively. Immunosuppressive agents were discontinued in 77 % of patients at a median of 300 days. However, cGVHD recurred in 37 % after immunosuppressive drugs were discontinued [41]. Malard (2017) aimed to achieve a faster response and to discontinue the drugs earlier by administering cyclosporine and rituximab in addition to steroids in newly developed cGVHD patients. They reported 1-year CR, ORR, and OS non-relapse mortality (NRM) as 29 %, 83 %, 83 %, and 14 %, respectively [42]. It is understood that when rituximab is added to single immunosuppressive regimens, its side effects are low and manageable, but when it is added to dual immunosuppressive treatment protocols containing steroids, Grade III and above infectious and non-infectious complications will occur [40–42]. Van Drop (2011) observed that the ORR was 61 % in steroid-refractory patients, and the best response was in skin involvement [43]. Van der Wagen (2018) evaluated sequential treatment with nilotinib after rituximab in a prospective non-randomized study in 24 sclerotic cGVHD patients with 89.7 %-75.9 % of cases involving fascia, mouth, and eyes. The objective response rate was 71 %, steroid reduction rate was 50 % [44]. In the Klobuch's (2019) single-center retrospective study, 3 months after rituximab administration in 29 patients with 2 or more organ involvement, the ORR was reported as 31 % and CR 7%. It has been stated that the response is better in those who are steroid dependent than in those who are resistant [45].

3.9. Alemtuzumab

Gutiérrez-Aguirre (2012), in a prospective non-randomized study of 15 patients, reported that the ORR and CR at day 30 were 100 % and 33 %, and at day 90, 78 % and 28 %, respectively, with low-dose alemtuzumab and rituximab combination therapy in steroid-resistant cGVHD. The most common side effects were infections with a rate of 67 %. Cytomegalo virus (CMV) infection was seen in 3 patients and 1 patient died due to lung infection [46]

3.10. Tocilizumab

No prospective studies on IL6 inhibitor were found. One retrospective study belongs to Kattner (2020). In 11 patients with advanced cGVHD, they reported an ORR of 70 %, CR 0, FFS 55 % at 12 months with tocilizumab [47].

3.11. Abaltecept

Wertheimer (2021) retrospectively analyzed the effect of abatecept in 15 patients. Previous exposure to 4 or more immunosuppressive drugs was present in 67 % of the cases. They reported the six-month and 12-month ORR as 33 % and 25 %, and the FFS as 64 % and 25 %. However, 3 patients died due to infection [48].

3.12. Bortezomib

We found one prospective phase II multicentric study. Herrera (2014) reported that in 120 patients who received bortezomib in combination with steroids as first-line therapy, the ORR was 80 %, CR10 %, and FFS 82 % after 15 weeks. In 70 % of the patients, the prednisone dose could be reduced by more than 50 %. However, at the end of 1 year, 50 % of patients required additional drug treatment [49].

3.13. Thalidomide

In the study conducted by Kulkarni (2003), combination therapy with steroid and cyclosporine in 59 steroid refractory patients resulted in ORR 39 % in patients with limited cGVHD and 33 % in extensive cGVHD [50].

3.14. Methotrexate

Two studies were found on the use of methotrexate in chronic GVHD. One could not be evaluated because its fulltex could not be reached. Wang et al. (2009), in his studies, reported that the ORR was 83 % and the CR 62 % in cases used in combination with other immunosuppressive drugs (n 86). The best response was seen in skin involvement and single organ involvement [51].

3.15. M-tor inhibitors

One prospective randomized and two retrospective multicentric studies were evaluated. The Carpenter (2018) phase II/III randomized multicentric study compared prednisone/sirolimus versus prednisone/sirolimus/CNI. The 6-month ORR was 48.6 % and 50 % in the two-drug and three-drug arms, and the CR at 12 months was 14.7 % and 15.5 %. The OS at two years was reported as 81.5 % and 74 %. Grade III toxicity was similar in the two-drug arm, but kidney toxicity was statistically significantly higher in the 3-drug arm [52]. In multicentric retrospective studies of Mialke (2014), everolimus was used in 42 steroid-refractory patients and found an ORR of 43 %, and above Grade III toxicity 37 %. The drug withdrawal rate was 27 % [53]. Jurado (2007) reported the ORR 81 % and CR 38 % with the combination of sirolimus with other immunosuppressive agents in cGVHD. The main toxicity was seen especially in combination with CNI (30 % renal toxicity, 8% microangiopathy) [54].

3.16. Bronchiolitis obliterans (BOP)

Williams et al. (2016) found that when they treated new-onset BOP patients with FAM (inhaler fluticasone/azithromycin/inhaler montelukast) in a prospective phase II single-arm study, the ORR on lung function was 36 % and the FFS at 6 months was 36 %. In addition, the steroid dose could be reduced below 50 % in 48 % of the patients [56]. The efficacy of mesenchymal stem cells (MSCs) for BOP was evaluated in a randomized double-arm study by Chen (2019). The choice of prednisone and azithromycin in combination with or without MSCs was based on patient preferences. The response rate was 35/49 patients (71 %) and 14/32 (44 %) in MSCs and non-MSCs group, respectively ($p = 0.013$). MSCs offer an effective and safe therapeutic option for BOS after allo-HSCT [57].

We could not find any study that met the criteria for etanercept,

hydroxychloroquine and pentostain.

4. Discussion

A standard approach to the treatment of cGVHD, which leads to a complex pathogenetic mechanism and a heterogeneous clinical situation, has still not been established in the third decade of the 21 st century. It has been determined that studies have been carried out on various agents for the treatment of the disease, but randomized controlled studies are quite limited [10,15,23,35,39,52,57]. Most of the studies are observational studies or retrospective studies with a small number of cases [62–64]. In the content of these studies and/or medical congress presentations, the agents used in the treatment of cGVHD are discussed, but according to the available information, a clear interpretation cannot be made about which agent should be used at which stage of the treatment. The European Society for Blood and Marrow Transplantation guideline on the management of cGVHD lists treatment options that can be used in steroid-refractory disease [58]. However, the guideline does not contain a clear treatment algorithm to overcome the difficulties encountered in the management of cGVHD, and the guideline needs to be updated. An ideal treatment option cannot be presented from real-world data.

When examining the limited number of available RCTs, it is demonstrated that most of the studies are open-label, and the investigator and the patients know which arm they fall in [10,15,23,35,39,52]. It is noteworthy that in some of the studies, adequate power analysis was not performed and a clear view did not emerge in the calculation of the number of cases. It seems that a standard approach cannot be established with validated methods for the identification and response assessment of cGVHD. It appears that only a few studies use standardized NIH diagnostic and response criteria [15,52]. One of the most important problems is that studies have been conducted for a single organ or tissue for cGVHD, which is a multisystem disease [35,39,57]. Finding the results insignificant in most of the available RCTs is another handicap. It is understood that patient characteristics that may affect disease management, such as the patient groups in which a significant part of the studies were conducted, and previous treatments, were not given. The causes of mortality are also not clearly presented.

Since clinical studies are limited for the treatment of cGVHD, it is a rational treatment approach to make an individual treatment plan, taking into account the pathogenetic characteristics of the disease and the clinical condition of the patients. In order to develop an adequate immune tolerance, treatment alternatives targeting B lymphocytes as well as effector T cells of donor origin should be considered. Proinflammatory cytokines should also be suppressed. Increasing the mass of Treg cells in the blood should be the top priority for the control of cGVHD. In fact, the basic rationale of cGVHD prophylaxis is to develop immune tolerance by increasing Treg cells.

A prospective study of extracorporeal photopheresis indicates that photopheresis may reduce steroid exposure when used in combination with prednisolone [23]. In the event of moderate/severe cGVHD development during acute GVHD treatment, it is recommended to add prednisone to the treatment and to change it if patients are taking a calcineurin inhibitor (CNI) [58].

On the other hand, it should be taken into account which tissue or organ is involved. For example, photopheresis, rituximab and tyrosine kinase inhibitors are known to be more effective in skin involvement [15,35,39]. In the involvement of the gastrointestinal tract, agents such

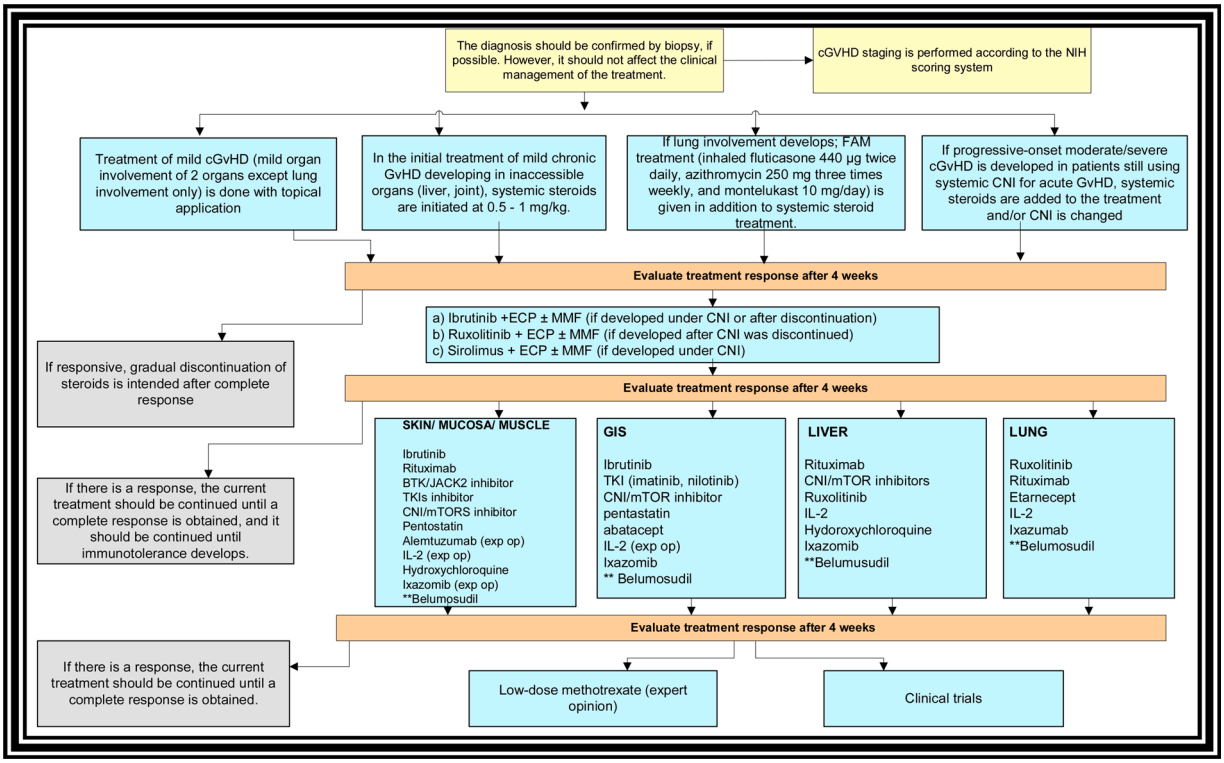

Fig. 2. Proposition of treatment algorithm of cGVHD.
Initial treatment of mild cGvHD (mild organ involvement of 2 organs except lung involvement only) in accessible organs is topical.
Second-line therapy (photopheresis and/or ruxolutinib) should be initiated before disease progression and different organ involvements develop in steroid-resistant cases.
Microangiopathy should be considered when switching from calcineurin inhibitors (CNI) to sirolimus.
Steroids are discontinued after initiation of second-line therapy in steroid-resistant cGvHD.
The efficacy of second-line therapy for steroid-resistant cGvHD is evaluated one month later.
ECP: Extracorporal photopheresis, CNI: Calcineurin inhibitors, IL-: Interleukin-2, MMF: mucophenolate mofetil, GIS: Gastrointestinal system.

as JAK-2 inhibitors, and ibrutinib may be preferred [15,16,18,20,32–34] (Fig. 2). The patient's comorbid status, humoral immunity defect (such as acquired hypogammaglobulinemia), previous immunochemotherapy regimens, previous infections, avascular bone lesion and renal functions should be considered.

Supportive treatment is one of the issues that should not be neglected. When necessary, agents such as immunoglobulin support, adequate vaccination, nutritional support, prevention of fluid loss for intestinal cGVHD, agents such as loperamid, octreotide, budesonide, and cholestyramine can be used because bile acid reabsorption is impaired. Ursodeoxycholic acid should be considered for liver GVHD [65].

In the light of prospective and retrospective study methods, it is understood that prednisone is used in the first-line treatment [10,52]. In cases with moderate and severe cGVHD, the initial dose of prednisone should be maintained at 0.5−1 mg/kg for two weeks, if a complete response is obtained, it should be reduced to 0.5−1 mg/kg every other day with an alternative dose strategy, after continuing for 4–6 weeks, then reduce the dose and continue the treatment for up to 8 months [58]. It is not clear when glucocorticoid therapy should be discontinued. The duration of treatment may be affected by the patient's clinical condition, haematological diseases or previous treatments, and comorbid conditions. However, it is important that the clinical signs of cGVHD is observed for reasonable time in terms of exacerbations.

In the event of moderate/severe cGVHD development during acute GVHD treatment, it is recommended to add prednisone to the treatment and to change it if patients are taking a calcineurin inhibitor (CNI) [58]. It is not clear what the treatment strategy will be in cases with avascular bone necrosis or who develop necrosis during treatment. A prospective study of extracorporeal photopheresis indicates that photopheresis may reduce steroid exposure when used in combination with prednisolone [23]. It has been reported that as a result of continuous stimulation of antigen-specific B cell receptors (BCR) in cGVHD, B lymphocytes turn into mature and antigen presenting cells to CD4 + T cells. The formation of apoptosis-resistant B lymphocytes through cytokines leads to the production of donor-derived alloantibodies from donor cells that are continuously stimulated with the help of B-cell activating factor. Increasing understanding of the role played by B cells in the pathogenesis of cGVHD has given rise to the idea of applying therapies targeting B cells. Clinical studies show that rituximab has a 75 % protective effect from steroids [59,60].

In order to benefit from the steroid-sparing effect of the drugs, it may be considered that ECP or rituximab is started early in cases with skin involvement, In the second-line treatment, ECP and/or MMF are considered, and a third drug can be added depending on the organ involved [8,19,23,25] (Fig. 2).

An effective treatment plan is not sufficient to control cGVHD. Regular follow-up of patients, facilitating patient access to hospital, and using a validated definition or response criteria are essential for disease management. The importance of implementing a standardized and improved clinical patient care program within the framework of the quality management plan is evident. Another point that needs attention is the evaluation of the patient's quality of life during follow-up.

In this study, it is seen that studies with evidence value are limited. In this case, rational evaluation of available drugs becomes important. Further work is needed to develop a new and more efficient algorithm.

References

[1] Mohty M, Kuentz M, Michallet M, Bourhis JH, Milpied N, Sutton L, et al. Blaise D; Société Française de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC). Chronic graft-versus-host disease after allogeneic blood stem cell transplantation: long-term results of a randomized study. Blood 2002;100(November (9)):3128–34. https://doi.org/10.1182/blood.V100.9.3128. PMID: 12384409.

[2] Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. the 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant 2015;21(March (3)): 389–401.e1. https://doi.org/10.1016/j.bbmt.2014.12.001. Epub 2014 Dec 18. PMID: 25529383; PMCID: PMC4329079.

[3] Cutler CS, Koreth J, Ritz J. Mechanistic approaches for the prevention and treatment of chronic GVHD. Blood 2017;129(January (1)):22–9. https://doi.org/10.1182/blood-2016-08-686659. Epub 2016 Nov 7. PMID: 27821505; PMCID: PMC5216263.

[4] Magenau J, Runaas L, Reddy P. Advances in understanding the pathogenesis of graft-versus-host disease. Br J Haematol 2016;173(April (2)):190–205. https://doi.org/10.1111/bjh.13959. Epub 2016 Mar 27. PMID: 27019012.

[5] Sanders JE. Chronic graft-versus-host disease and late effects after hematopoietic stem cell transplantation. Int J Hematol 2002;76(August Suppl 2):15–28. https://doi.org/10.1007/BF03165081. PMID: 12430895.

[6] Holtzman NG, Pavletic SZ. The clinical landscape of chronic graft-versus-host disease management in 2021. Br J Haematol 2021;(October 2). https://doi.org/10.1111/bjh.17835. . Epub ahead of print. PMID: 34599519.

[7] Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928. https://doi.org/10.1136/bmj.d5928.

[8] Baird K, Steinberg SM, Grkovic L, Pulanic D, Cowen EW, Mitchell SA, et al. National Institutes of Health chronic graft-versus-host disease staging in severely affected patients: organ and global scoring correlate with established indicators of disease severity and prognosis. Biol Blood Marrow Transplant 2013;19(April (4)): 632–9. https://doi.org/10.1016/j.bbmt.2013.01.013. Epub 2013 Jan 20. PMID: 23340040; PMCID: PMC3619213.

[9] Atkinson K, Horowitz MM, Gale RP, Lee MB, Rimm AA, Bortin MM. Consensus among bone marrow transplanters for diagnosis, grading and treatment of chronic graft-versus-host disease. Committee of the International Bone Marrow Transplant Registry. Bone Marrow Transplant 1989;4(May (3)):247–54. PMID: 2659110.

[10] Koc S, Leisenring W, Flowers ME, Anasetti C, Deeg HJ, Nash RA, et al. Therapy for chronic graft-versus-host disease: a randomized trial comparing cyclosporine plus prednisone versus prednisone alone. Blood 2002;100(July (1)):48–51. https://doi.org/10.1182/blood.v100.1.48. PMID: 12070007.

[11] Axt L, Naumann A, Toennies J, Haen SP, Vogel W, Schneidawind D, et al. Retrospective single center analysis of outcome, risk factors and therapy in steroid refractory graft-versus-host disease after allogeneic hematopoietic cell transplantation. Bone Marrow Transplant 2019;54(November (11)):1805–14. https://doi.org/10.1038/s41409-019-0544-y. Epub 2019 May 14. PMID: 31089279.

[12] Iida M, Fukuda T, Uchida N, Murata M, Aotsuka N, Minagawa K, et al. Mycophenolate mofetil use after unrelated hematopoietic stem cell transplantation for prophylaxis and treatment of graft-vs.-Host disease in adult patients in Japan. Clin Transplant 2014;28(September (9)):980–9. https://doi.org/10.1111/ctr.12405. Epub 2014 Jul 17. PMID: 24943923.

[13] Iida M, Fukuda T, Ikegame K, Yoshihara S, Ogawa H, Taniguchi S, et al. Use of mycophenolate mofetil in patients received allogeneic hematopoietic stem cell transplantation in Japan. Int J Hematol 2011;93(April (4)):523–31. https://doi.org/10.1007/s12185-011-0817-8. Epub 2011 Apr 5. PMID: 21465117.

[14] Kim JG, Sohn SK, Kim DH, Lee NY, Suh JS, Lee KS, et al. Different efficacy of mycophenolate mofetil as salvage treatment for acute and chronic GVHD after allogeneic stem cell transplant. Eur J Haematol 2004;73(July (1)):56–61. https://doi.org/10.1111/j.1600-0609.2004.00247.x. PMID: 15182339.

[15] Zeiser R, Polverelli N, Ram R, Hashmi SK, Chakraverty R, Middeke JM, et al. Ruxolitinib for glucocorticoid-refractory chronic graft-versus-Host disease. N Engl J Med 2021;385(July (3)):228–38. https://doi.org/10.1056/NEJMoa2033122. PMID: 34260836.

[16] Moiseev IS, Morozova EV, Bykova TA, Paina OV, Smirnova AG, Dotsenko AA, et al. Long-term outcomes of ruxolitinib therapy in steroid-refractory graft-versus-host disease in children and adults. Bone Marrow Transplant 2020;55(July (7)): 1379–87. https://doi.org/10.1038/s41409-020-0834-4. Epub 2020 Feb 18. PMID: 32071418.

[17] Zeiser R, Burchert A, Lengerke C, Verbeek M, Maas-Bauer K, Metzelder SK, et al. Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. Leukemia 2015;29(October (10)): 2062–8. https://doi.org/10.1038/leu.2015.212. Epub 2015 Jul 31. PMID: 26228813; PMCID: PMC4854652.

[18] Modi B, Hernandez-Henderson M, Yang D, Klein J, Dadwal S, Kopp E, et al. Ruxolitinib as salvage therapy for chronic graft-versus-Host disease. Biol Blood Marrow Transplant 2019;25(February (2)):265–9. https://doi.org/10.1016/j.bbmt.2018.09.003. Epub 2018 Sep 8. PMID: 30201397.

[19] Zhao JY, Liu SN, Xu LP, Zhang XH, Wang Y, Chen YH, et al. Ruxolitinib is an effective salvage treatment for multidrug-resistant graft-versus-host disease after haploidentical allogeneic hematopoietic stem cell transplantation without posttransplant cyclophosphamide. Ann Hematol 2021;100(January (1)):169–80. https://doi.org/10.1007/s00277-020-04273-2. Epub 2020 Nov 7. PMID: 33159239.

[20] Wu H, Shi J, Luo Y, Tan Y, Zhang M, Lai X, et al. Evaluation of ruxolitinib for steroid-refractory chronic graft-vs-Host disease after allogeneic hematopoietic stem cell transplantation. JAMA Netw Open. 2021;4(January (1)):e2034750. https://doi.org/10.1001/jamanetworkopen.2020.34750. PMID: 33502484; PMCID: PMC7841467.

[21] Ferreira AM, Szor RS, Molla VC, Seiwald MC, de Moraes PA, da Fonseca ARBM, et al. Long-term follow-up of ruxolitinib in the treatment of steroid-refractory chronic graft-versus-Host disease. Transplant Cell Ther 2021;27(September (9)): 777.e1–6. https://doi.org/10.1016/j.jtct.2021.06.002. Epub 2021 Jun 9. PMID: 34118469.

[22] Bondeelle L, Chevret S, Hurabielle C, Samy L, Goletto T, Costantini A, et al. Effect of ruxolitinib on lung function after allogeneic stem cell transplantation. Biol Blood Marrow Transplant 2020;26(November (11)):2115–20. https://doi.org/10.1016/j.bbmt.2020.07.033. Epub 2020 Jul 29. PMID: 32738501.
[23] Flowers ME, Apperley JF, van Besien K, Elmaagacli A, Grigg A, Reddy V, et al. A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. Blood 2008;112 (October (7)):2667–74. https://doi.org/10.1182/blood-2008-03-141481. Epub 2008 Jul 11. Erratum in: Blood. 2009 Apr 30;113(18):4478. PMID: 18621929.
[24] Sakellari I, Gavriilaki E, Batsis I, Mallouri D, Panteliadou AK, Lazaridou A, et al. Favorable impact of extracorporeal photopheresis in acute and chronic graft versus host disease: prospective single-center study. J Clin Apher 2018;33(December (6)): 654–60. https://doi.org/10.1002/jca.21660. Epub 2018 Nov 5. PMID: 30394564.
[25] Apisarnthanarax N, Donato M, Körbling M, Couriel D, Gajewski J, Giralt S, et al. Extracorporeal photopheresis therapy in the management of steroid-refractory or steroid-dependent cutaneous chronic graft-versus-host disease after allogeneic stem cell transplantation: feasibility and results. Bone Marrow Transplant 2003;31 (March (6)):459–65. https://doi.org/10.1038/sj.bmt.1703871. PMID: 12665841.
[26] Oarbeascoa G, Lozano ML, Guerra LM, Amunarriz C, Saavedra CA, Garcia-Gala JM, et al. Retrospective multicenter study of extracorporeal photopheresis in steroid-refractory acute and chronic graft-versus-Host disease. Biol Blood Marrow Transplant 2020;26(April (4)):651–8. https://doi.org/10.1016/j.bbmt.2019.12.769. Epub 2020 Jan 7. PMID: 31917270.
[27] Okamoto S, Teshima T, Kosugi-Kanaya M, Kahata K, Kawashima N, Kato J, et al. Extracorporeal photopheresis with TC-V in Japanese patients with steroid-resistant chronic graft-versus-host disease. Int J Hematol 2018;108(September (3)): 298–305. https://doi.org/10.1007/s12185-018-2483-6. Epub 2018 Jun 29. PMID: 29959747.
[28] Bisaccia E, Palangio M, Gonzalez J, Adler KR, Scarborough R, Goldberg SL, et al. Treatment of extensive chronic graft-versus-host disease with extracorporeal photochemotherapy. J Clin Apher 2006;21(October (3)):181–7. https://doi.org/10.1002/jca.20084. PMID: 16607632.
[29] Couriel DR, Hosing C, Saliba R, Shpall EJ, Anderlini P, Rhodes B, et al. Extracorporeal photochemotherapy for the treatment of steroid-resistant chronic GVHD. Blood 2006;107(April (8)):3074–80. https://doi.org/10.1182/blood-2005-09-3907. Epub 2005 Dec 20. PMID: 16368882.
[30] Gunduz M, Atilla E, Atilla PA, Topcuoglu P, Ilhan O. Early initiation of extracorporeal photochemotherapy increases response for chronic graft versus host disease following steroid failure. Transfus Clin Biol 2019;26(February (1)):32–7. https://doi.org/10.1016/j.tracli.2018.03.005. Epub 2018 Apr 12. PMID: 29655590.
[31] Ussowicz M, Musiał J, Mielcarek M, Tomaszewska A, Nasiłowska-Adamska B, Kałwak K, et al. Steroid-sparing effect of extracorporeal photopheresis in the therapy of graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. Transplant Proc 2013;45(9):3375–80. https://doi.org/10.1016/j.transproceed.2013.07.053. PMID: 24182819.
[32] Miklos D, Cutler CS, Arora M, Waller EK, Jagasia M, Pusic I, et al. Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. Blood 2017;130 (November (21)):2243–50. https://doi.org/10.1182/blood-2017-07-793786. Epub 2017 Sep 18. PMID: 28924018; PMCID: PMC6033048.
[33] Waller EK, Miklos D, Cutler C, Arora M, Jagasia MH, Pusic I, et al. Ibrutinib for chronic graft-versus-Host disease after failure of prior therapy: 1-Year update of a phase 1b/2 study. Biol Blood Marrow Transplant 2019;25(October (10)):2002–7. https://doi.org/10.1016/j.bbmt.2019.06.023. Epub 2019 Jun 28. PMID: 31260802.
[34] Doki N, Toyosaki M, Shiratori S, Osumi T, Okada M, Kawakita T, et al. An Open-Label, Single-Arm, Multicenter Study of Ibrutinib in Japanese Patients With Steroid-dependent/Refractory Chronic Graft-Versus-Host Disease. Transplant Cell Ther 2021;27(October (10)):867.e1–9. https://doi.org/10.1016/j.jtct.2021.05.019. Epub 2021 Jun 6. PMID: 34102349.
[35] Arai S, Pidala J, Pusic I, Chai X, Jaglowski S, Khera N, et al. A randomized phase II crossover study of imatinib or rituximab for cutaneous sclerosis after hematopoietic cell transplantation. Clin Cancer Res 2016;22(January (2)):319–27. https://doi.org/10.1158/1078-0432.CCR-15-1443. Epub 2015 Sep 16. PMID: 26378033; PMCID: PMC4715914.
[36] Baird K, Comis LE, Joe GO, Steinberg SM, Hakim FT, Rose JJ, et al. Imatinib mesylate for the treatment of steroid-refractory sclerotic-type cutaneous chronic graft-versus-host disease. Biol Blood Marrow Transplant 2015;21(June (6)): 1083–90. https://doi.org/10.1016/j.bbmt.2015.03.006. Epub 2015 Mar 12. PMID: 25771402; PMCID: PMC4425991.
[37] Molés-Poveda P, Montesinos P, Sanz-Caballer J, de Unamuno B, Piñana JL, Sahuquillo A. Botella-estrada R. Sclerodermatous chronic graft-versus-Host disease treated with imatinib: a dermatological perspective. Actas Dermosifiliogr (Engl Ed) 2018;109(April (3)):241–7. https://doi.org/10.1016/j.ad.2017.11.003. . Epub 2017 Dec 15. PMID: 29254596 English, Spanish.
[38] van der Wagen L, Te Boome L, Schiffler M, Nijhof I, Schoordijk M, van Dorp S, et al. Prospective evaluation of sequential treatment of sclerotic chronic graft versus host disease with rituximab and nilotinib. Bone Marrow Transplant 2018;53(October (10)):1255–62. https://doi.org/10.1038/s41409-018-0158-9. Epub 2018 Mar 16. PMID: 29549292.
[39] Curtis LM, Ostojic A, Venzon DJ, Holtzman NG, Pirsl F, Kuzmina ZJ, et al. A randomized phase 2 trial of pomalidomide in subjects failing prior therapy for chronic graft-versus-host disease. Blood 2021;137(February (7)):896–907. https://doi.org/10.1182/blood.2020006892. . PMID: 32976576; PMCID: PMC7918188.
[40] Teshima T, Nagafuji K, Henzan H, Miyamura K, Takase K, Hidaka M, et al. Rituximab for the treatment of corticosteroid-refractory chronic graft-versus-host disease. Int J Hematol 2009;90(September (2)):253–60. https://doi.org/10.1007/s12185-009-0370-x. Epub 2009 Jun 20. PMID: 19543951.
[41] Solomon SR, Sizemore CA, Ridgeway M, Zhang X, Smith J, Brown S, et al. Corticosteroid-free primary treatment of chronic extensive graft-versus-Host disease incorporating rituximab. Biol Blood Marrow Transplant 2015;21 (September (9)):1576–82. https://doi.org/10.1016/j.bbmt.2015.04.023. Epub 2015 May 16. PMID: 25985915.
[42] Malard F, Labopin M, Yakoub-Agha I, Chantepie S, Guillaume T, Blaise D, et al. Rituximab-based first-line treatment of cGVHD after allogeneic SCT: results of a phase 2 study. Blood 2017;130(November (20)):2186–95. https://doi.org/10.1182/blood-2017-05-786137. Epub 2017 Sep 1. PMID: 28864814.
[43] van Dorp S, Resemann H, te Boome L, Pietersma F, van Baarle D, Gmelig-Meyling F, et al. The immunological phenotype of rituximab-sensitive chronic graft-versus-host disease: a phase II study. Haematologica 2011;96(September (9)): 1380–4. https://doi.org/10.3324/haematol.2011.041814. Epub 2011 May 5. PMID: 21546493; PMCID: PMC3166111.
[44] van der Wagen L, Te Boome L, Schiffler M, Nijhof I, Schoordijk M, van Dorp S, et al. Prospective evaluation of sequential treatment of sclerotic chronic graft versus host disease with rituximab and nilotinib. Bone Marrow Transplant 2018;53(October (10)):1255–62. https://doi.org/10.1038/s41409-018-0158-9. Epub 2018 Mar 16. PMID: 29549292.
[45] Klobuch S, Weber D, Holler B, Edinger M, Herr W, Holler E, et al. Long-term follow-up of rituximab in treatment of chronic graft-versus-host disease-single center experience. Ann Hematol 2019;98(October (10)):2399–405. https://doi.org/10.1007/s00277-019-03768-x. Epub 2019 Aug 3. PMID: 31375860.
[46] Gutiérrez-Aguirre CH, Cantú-Rodríguez OG, Borjas-Almaguer OD, González-Llano O, Jaime-Pérez JC, Solano-Genesta M, et al. Effectiveness of subcutaneous low-dose alemtuzumab and rituximab combination therapy for steroid-resistant chronic graft-versus-host disease. Haematologica 2012;97(May (5)):717–22. https://doi.org/10.3324/haematol.2011.054577. Epub 2011 Dec 1. PMID: 22133770; PMCID: PMC3342974.
[47] Kattner AS, Holler E, Holler B, Klobuch S, Weber D, Martinovic D, et al. IL6-receptor antibody tocilizumab as salvage therapy in severe chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation: a retrospective analysis. Ann Hematol 2020;99(April (4)):847–53. https://doi.org/10.1007/s00277-020-03968-w. Epub 2020 Feb 21. PMID: 32086584; PMCID: PMC7069928.
[48] Wertheimer T, Dohse M, Afram G, Weber D, Heidenreich M, Holler B, et al. Abatacept as salvage therapy in chronic graft-versus-host disease-a retrospective analysis. Ann Hematol 2021;100(March (3)):779–87. https://doi.org/10.1007/s00277-021-04434-x. Epub 2021 Jan 30. PMID: 33515310; PMCID: PMC7914235.
[49] Herrera AF, Kim HT, Bindra B, Jones KT, Alyea 3rd EP, Armand P, et al. A phase II study of bortezomib plus prednisone for initial therapy of chronic graft-versus-host disease. Biol Blood Marrow Transplant 2014;20(November (11)):1737–43. https://doi.org/10.1016/j.bbmt.2014.06.040. Epub 2014 Jul 10. PMID: 25017765; PMCID: PMC4465759.
[50] Kulkarni S, Powles R, Sirohi B, Treleaven J, Saso R, Horton C, et al. Thalidomide after allogeneic haematopoietic stem cell transplantation: activity in chronic but not in acute graft-versus-host disease. Bone Marrow Transplant 2003;32(July (2)): 165–70. https://doi.org/10.1038/sj.bmt.1704033. PMID: 12838281.
[51] Wang Y, Xu LP, Liu DH, Chen H, Chen YH, Han W, et al. First-line therapy for chronic graft-versus-host disease that includes low-dose methotrexate is associated with a high response rate. Biol Blood Marrow Transplant 2009;15(April (4)): 505–11. https://doi.org/10.1016/j.bbmt.2008.12.493. Epub 2009 Feb 12. PMID: 19285639.
[52] Carpenter PA, Logan BR, Lee SJ, Weisdorf DJ, Johnston L, Costa LJ, et al. BMT CTN.. A phase II/III randomized, multicenter trial of prednisone/sirolimus *versus* prednisone/ sirolimus/calcineurin inhibitor for the treatment of chronic graft-*versus*-host disease: BMT CTN 0801. Haematologica 2018;103(November (11)): 1915–24. https://doi.org/10.3324/haematol.2018.195123. Epub 2018 Jun 28. PMID: 29954931; PMCID: PMC6278959.
[53] Mielke S, Lutz M, Schmidhuber J, Kapp M, Ditz D, Ammer J, et al. Salvage therapy with everolimus reduces the severity of treatment-refractory chronic GVHD without impairing disease control: a dual center retrospective analysis. Bone Marrow Transplant 2014;49(November (11)):1412–8. https://doi.org/10.1038/bmt.2014.170. Epub 2014 Aug 4. PMID: 25089598.
[54] Jurado M, Vallejo C, Pérez-Simón JA, Brunet S, Ferra C, Balsalobre P, et al. Sirolimus as part of immunosuppressive therapy for refractory chronic graft-versus-host disease. Biol Blood Marrow Transplant 2007;13(June (6)):701–6. https://doi.org/10.1016/j.bbmt.2007.02.003. PMID: 17531780.
[55] Villanueva FN, Pérez-Simón JA, Silva FF, Caballero-Velázquez TT, Sánchez-Guijo FF, Cañizo CC, et al. Oral beclomethasone dipropionate for the treatment of gastrointestinal chronic graft-versus-host disease. Biol Blood Marrow Transplant 2009;15(October (10)):1331–6. https://doi.org/10.1016/j.bbmt.2009.05.018. Epub 2009 Jul 22. PMID: 19747642.
[56] Williams KM, Cheng GS, Pusic I, Jagasia M, Burns L, Ho VT, et al. Fluticasone, azithromycin, and montelukast treatment for new-onset bronchiolitis obliterans syndrome after hematopoietic cell transplantation. Biol Blood Marrow Transplant 2016;22(April (4)):710–6. https://doi.org/10.1016/j.bbmt.2015.10.009. Epub 2015 Oct 22. PMID: 26475726; PMCID: PMC4801753.
[57] Chen S, Zhao K, Lin R, Wang S, Fan Z, Huang F, et al. The efficacy of mesenchymal stem cells in bronchiolitis obliterans syndrome after allogeneic HSCT: a multicenter prospective cohort study. EBioMedicine 2019;49(November):213–22. https://doi.org/10.1016/j.ebiom.2019.09.039. Epub 2019 Oct 23. PMID: 31668569; PMCID: PMC6945279.

[58] Penack O, Marchetti M, Ruutu T, Aljurf M, Bacigalupo A, 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(2):e157–67.

[59] Cutler C, Kim HT, Bindra B, et al. Rituximab prophylaxis prevents corticosteroid-requiring chronic GVHD after allogeneic peripheral blood stem cell transplantation: results of a phase 2 trial. Blood 2013;122(8):1510–7.

[60] Jaglowski SM, Blazar BR. How ibrutinib, a B-cell malignancy drug, became an FDA-approved second-line therapy for steroid-resistant chronic GVHD. Blood Adv 2018;2(August (15)):2012–9. https://doi.org/10.1182/bloodadvances.2018013060. PMID: 30108109; PMCID: PMC6093735.

[61] Escamilla Gómez V, García-Gutiérrez V, López Corral L, García Cadenas I, Pérez Martínez A, Márquez Malaver FJ, et al. Grupo Español de Trasplante Hematopoyético (GETH). Ruxolitinib in refractory acute and chronic graft-versus-host disease: a multicenter survey study. Bone Marrow Transplant 2020;55(March (3)):641–8. https://doi.org/10.1038/s41409-019-0731-x. Epub 2019 Nov 7. PMID: 31700138; PMCID: PMC7051903.

[62] Giaccone L, Mancini G, Mordini N, Gargiulo G, De Cecco V, Angelini S, et al. 'Real-life' report on the management of chronic GvHD in the Gruppo Italiano Trapianto Midollo Osseo (GITMO). Bone Marrow Transplant 2018;53(January (1)):58–63. https://doi.org/10.1038/bmt.2017.223. Epub 2017 Oct 30. PMID: 29084200.

[63] Neumann T, Schneidewind L, Weigel M, Plis A, Vaizian R, Schmidt CA, et al. Ruxolitinib for therapy of graft-versus-Host disease. Biomed Res Int 2019;2019 (March 6):8163780. https://doi.org/10.1155/2019/8163780. PMID: 30956985; PMCID: PMC6431395.

[64] Drobyski WR, Pasquini M, Kovatovic K, Palmer J, Douglas Rizzo J, Saad A, et al. Tocilizumab for the treatment of steroid refractory graft-versus-host disease. Biol Blood Marrow Transplant 2011;17(December (12)):1862–8. https://doi.org/10.1016/j.bbmt.2011.07.001. Epub 2011 Jul 13. PMID: 21745454; PMCID: PMC3716013.

[65] Naymagon S, Naymagon L, Wong SY, Ko HM, Renteria A, Levine J, et al. Acute graft-versus-host disease of the gut: considerations for the gastroenterologist. Nat Rev Gastroenterol Hepatol 2017;14(December (12)):711–26. https://doi.org/10.1038/nrgastro.2017.126. Epub 2017 Sep 27. PMID: 28951581; PMCID: PMC6240460.