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Review

Hematopoietic Stem Cell Transplantation in Refractory Celiac Disease: An Overview with Focus on Infectious Complications

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Abstract

Refractory celiac disease (RCD) is a rare condition in which a known celiac patient, usually an adult, suffers from persistence or recurrence of gluten-related symptomatology, laboratory abnormalities, and inflammatory enteropathy despite following an optimal dietary therapy with gluten-free diet (GFD). Arbitrarily, a duration of at least 12 months of GFD has been recommended prior to establishing such a diagnosis. Furthermore, exclusion of the other possible causes of non-celiac villous atrophy, particularly enteropathy associated T-cell lymphoma (EATL), is a prerequisite for establishing a diagnosis of RCD. RCD is subdivided into two types, depending on the percentage of immunophenotypically aberrant intraepithelial lymphocytes (IEL). The refractory patients having a high percentage of abnormal 'aberrant' IEL (RCD-II) are regarded as having *pre*-lymphoma due to the high probability of developing EATL. In addition, they are at high risk for infection owing to the impaired immunity resulting from malnutrition, bacterial overgrowth and translocation in the small intestine, and the presence of hyposplenism (*functional asplenia*). The RCD-II patients are generally non-responsive to the currently available pharmacological treatments. However, both clinical and histopathological remissions have been achieved using the purine analog cladribine (2-CDA). Autologous hematopoietic stem cell transplantation (auto-HSCT) appears to be an effective

therapy for these patients as it is well tolerated and has a low risk of post-transplant infections or other complications. The present review provides an overview of the application of auto-HSCT for the treatment of patients with RCD-II, which is a classic example of an autoimmune disorder. The focus is particularly on the infectious complications developing after the application of auto-HSCT.

Keywords
Celiac disease; refractory celiac disease; hematopoietic stem cell transplantation; enteropathy associated T-cell lymphoma; cladribine; gluten

1. Introduction

Celiac disease (CeD) is a gluten-related enteropathy that develops in those individuals who are genetically predisposed. The presence of the associated genetic constitution is an essential element responsible for the development of inflammatory enteropathy. Gluten peptides are relatively indigestible by human endoluminal proteases. The 33-mer and 17-mer oligopeptides of gliadin contain toxic epitopes that are deamidated by the enzyme tissue transglutaminase. The deamidated gluten peptides bind HLA DQ2/DQ8 heterodimers present on the antigen-presenting cells, which then stimulate the gluten-specific CD4 T-cells to generate a pro-inflammatory phenotype in the small intestine. This step is crucial for the development of CeD [1-3]. Histopathologically, this inflammatory reaction results in the infiltration of T-lymphocytes in the small intestinal epithelium and a progressive loss of the villi [4, 5]. The severity of the histopathological changes in CeD is classified according to the modified Marsh classification [4, 5], with Marsh 0 representing a normal duodenal mucosa, Marsh 1 representing an increased percentage of intraepithelial lymphocytes (>25% lymphocytes/100 epithelial cells), Marsh 2 representing crypt hyperplasia, and Marsh 3 representing a condition characterized by villous atrophy. Marsh stage 3 is further divided into: partial (3A), subtotal (3B), and total (3C) villous atrophy.

In the vast majority of CeD patients, elimination of gluten from the diet leads to the healing of small intestinal mucosa [6]. In rare cases (0.5%–1%), a state of refractoriness to the gluten-free diet (GFD) develops, and such patients are classified as having the refractory celiac disease (RCD) [7-9]. RCD is a rare condition in which a known celiac patient, usually an adult, suffers from the persistence or recurrence of gluten-related symptomatology, laboratory abnormalities, and inflammatory enteropathy despite having followed an optimal dietary therapy with GFD. An arbitrary duration at least 12 months with GFD has been recommended prior to establishing the diagnosis of RCD, although a diagnosis at an earlier stage may be made in those patients with severe clinical course. In addition, exclusion of the other possible causes of non-celiac villous atrophy, particularly enteropathy associated T-cell lymphoma (EATL), is a prerequisite for establishing the diagnosis of RCD [10, 11].

Currently, immunophenotyping of the intra-epithelial lymphocytes (IELs) of the small intestine is the standard method used for classifying RCD [12, 13]. This technique may be performed using the flow cytometric analysis. A category of IEL is regarded as ‘aberrant’ because contrary to their

normal counterparts, these IELs retain the intracellular CD3 expression while losing the CD3 and CD8 receptors from their surface membrane. Although this population of aberrant IELs is also present in the individuals with "uncomplicated CD", there is an abnormal expansion of this subset in RCD. When the proportion of these abnormal cells is less than 20%, the patients are classified as RCD-I, while the patients are classified as RCD-II when they have 20% or greater percentage of these aberrant cells [13, 14].

RCD-II usually follows an aggressive clinical course and diarrhea, weight loss, and hypoalbuminemia are its prominent features. Endoscopically, larger areas of the small intestine are affected and jejunal ulceration may be observed [15]. RCD-II is regarded as *pre*-lymphoma due to the high probability of EATL development. In addition, the RCD-II patients carry a high risk of infection owing to the decreased immunity caused by malnutrition, bacterial overgrowth and translocation in the small intestine, and the presence of hyposplenism (functional asplenia) [16-18].

Retrospective studies or case series conducted on RCD-II have evaluated several agents, including steroids, immunosuppressants (such as azathioprine), biologicals, mesalazines, and cyclosporine. However, the results have generally been disappointing [14, 19-21].

Nutritional support (enteral or even parenteral) and a high dose of steroids for a short duration are indispensable, especially in the acute setting. Immunosuppressive drugs have a limited or no role in RCD-II therapy [19]. The associated risk of developing EATL necessitates the development of treatments that involve targeting the abnormal 'aberrant' IELs, which are regarded as the precursors of malignant cells [22]. In the patients treated with the purine analog cladribine (2-chlor-2'-deoxyadenosine, 2-CDA), both clinical and histopathological remissions have been reported to be achieved [20, 21, 23]. The percentage of the aberrant T-cells was also reported to be reduced, although total elimination could not be achieved [21, 23]. Among the patients who responded positively, survival was observed to have improved significantly compared to the non-responders (5-year survival: 83% versus 22%). However, it appeared that the risk of EATL development was not eliminated entirely. Therefore, further aggressive treatment options based on the pathogenesis are being explored currently.

2. Principals for the Application of Auto-HSCT in Autoimmune Disorders

Long-term remission has been achieved in several refractory autoimmune diseases through the application of auto-HSCT [24-27]. Examples of such applications that achieved encouraging results include refractory Crohn's disease (with or without fistula), systemic sclerosis, rheumatoid arthritis, and chronic liver diseases (viral and autoimmune) [28]. This strategy has been increasingly applied since 1994.

Following the immune depletion achieved through the application of high-dose chemotherapy (HDC), auto-HSCT serves to reset the immune system by renewing the $CD4^+$ T-cell compartment, particularly the regulatory T-cells [29]. This results in the resetting of the immune system, and consequently in losing the autoimmunity.

Several factors render the application of auto-HSCT in non-malignant inflammatory disorders feasible, such as the availability of important supportive measures (antibiotics used both prophylactically or targeted at treating infections during the period of bone marrow aplasia, transfusion support, etc.) and hematopoietic growth factors which are used to "mobilize" the

hematopoietic stem cells (HSCs) from the bone marrow to the peripheral circulation. HSCs may be harvested from the peripheral blood and subsequently utilized to hasten the hematological recovery after marrow ablation [29, 30].

In the patients undergoing auto-HSCT, HSCs derived from peripheral blood are preferred over those obtained from the marrow because the former provides a larger $CD34^+$ cells harvest and more efficient engraftment compared to the marrow-derived HSCs, resulting in a more rapid reconstitution of the hematopoiesis.

Special chemotherapy combination regimens, growth factors (e.g., granulocyte colony-stimulating factor), and plerixafor are able to increase the HSCs in the peripheral blood, thereby providing adequate HSCs harvest [31, 32].

In order to be applied to treat severe systemic autoimmune diseases, the HDC followed by the auto-HSCT approach requires producing lower mortality and morbidity in comparison to the regimens used for treating oncology patients. Auto-HSCT has been reported to be associated with low morbidity and mortality rates, both in oncology and immune disorders, and is, therefore, preferred over allogenic-HSCT [26].

The autoimmune disease working party database of the European Group for Blood and Marrow Transplantation (EBMT) provides important details regarding the outcomes, transplant-related mortality (TRM), and treatment response for a large number of patients treated since 1994, as reported by 247 centers spread across 40 countries [26, 33]. In general, the patients receiving cyclophosphamide during mobilization exhibit a better response. Advanced age constitutes a bad prognostic indicator. Disease progression depends on the type of disease being treated and the intensity of the conditioning regimen (being higher in those receiving low-intensity regimens compared to those receiving high-intensity regimens). These extensive data underscore the positive role played by auto-HSCT to positively alter the course of severe autoimmune disease.

Toxicity and TRM after the application of auto-HSCT are dependent on multiple factors, such as which autoimmune disease is being treated, stage of the disease, patient's age, duration between the diagnosis of the disease and the application of auto-HSCT, and the intensity of the conditioning regimens. Auto-HSCT for autoimmune disorders is associated with TRM of approximately 7% ±3%. There is a stepwise increase in TRM from 3% in the patients receiving low-intensity conditioning to up to 15% in the patients receiving high-intensity conditioning has been reported [26]. The main causes of TRM are infections (50%) and hemorrhage (12%), while the less common causes are cardiac toxicity, interstitial pneumonitis, veno-occlusive disease, and liver failure.

3. Approach to RCD-II

3.1 Required Workup in Slow-Responders

In adult CeD, a slow-response to GFD is often observed, with persistent or recurrent symptoms, signs, or laboratory abnormalities [34, 35]. An extensive evaluation is required in such slow-responders in order to identify the treatable causes. A review of the small-intestine biopsies and serology data obtained at the time of diagnosis is the first step of this evaluation. In the patients with correctly established CeD, gluten intake, either purposeful or inadvertent, has been identified as the most common cause (35%–50%) for the slow-response. A review of the diet identifies most

of these cases, and in addition, detects the other intolerances, such as lactose intolerance and the use of gluten-containing medications. Celiac serology is essential, as a positive celiac serology may suggest gluten exposure, although it cannot be relied upon as a marker for persisting villous atrophy [36].

Small-Intestinal biopsy needs to be repeated. Villous atrophy and active inflammation are consistent with gluten intake, RCD, or the other causes of non-celiac villous atrophy [37-40]. The further details are given in Section 3.3 regarding the workup required for establishing the diagnosis of RCD. EATL should be excluded when necessary.

3.2 Clinical Aspect

RCD is usually diagnosed in older patients with late diagnosis. However, sporadic cases involving younger patients have been reported as well [41]. *Primary refractoriness* is considered to occur when a patient experiences persisting symptoms after CeD diagnosis, while *secondary refractoriness* occurs in the patients experiencing the recurrence of symptoms despite an initial response to GFD [11]. RCD-II includes features such as malnutrition, weight loss, protein-losing enteropathy, and mucosal ulcerations in the small intestine (ulcerative jejunitis) [35, 42].

3.3 Establishing Diagnosis of RCD-II

i. *Dietary Assessment:* Revision of diet by a dietitian and Serology testing using anti-transglutaminase titer are necessary.

ii. *Exclude misdiagnosis of CeD:* Misdiagnosis is possible when the HLA-DQ2/8 genotypes and certain specific serology markers are absent at the time of initial CeD diagnosis.

iii*. Histopathological examination:* The presence of Marsh IIIA-C in duodenal biopsies is required to establish the diagnosis of CeD.

iv. *Small intestinal immunophenotyping:* Flow cytometry technique is used to perform immunophenotyping of small intestinal IELs. This is the most crucial investigation required to exclude or establish the diagnosis of RCD and to differentiate RCD-I from RCD-II. Although immunohistochemistry (IHC) is less superior to flow cytometry, it may nevertheless be used to aid in the diagnosis of RCD-II [7, 43]. IELs have a normal T-cell phenotype in RCD-I patients. Up to 14% of small intestinal IELs carry the $\gamma\delta$ T-cell receptor, and a higher percentage suggests active CeD [12, 44]. Aberrant T-cells are abundant (20% or more) in RCD-II.

v. *Other Investigations:* Video Capsule Endoscopy may provide an estimate of the extent of the lesions [45, 46]. Device-assisted endoscopy (such as balloon-enteroscopy) may detect lesions at a considerable distance from the duodenum, providing an opportunity to obtain tissue diagnosis [15, 47].

Computed tomography (CT-scan) or other radiological modalities may detect mesenteric lymphadenopathy, bowel-wall thickening, and spleen atrophy in RCD-II and EATL [17, 47-49]. Positron emission tomography (PET-scan) assists in excluding lymphoma from the diagnosis [50, 51].

3.4 Pathogenesis of RCD-II

RCD-II patients exhibit HLA-DQ2 allele homozygous condition more often (44%–60%) than diet-responsive CeD [52], implying a possible gene dose effect, which strengthens the gluten-specific T-cell response and may influence the progression to RCD-II and/or EATL [53].

The expansion of aberrant IEL is central to the pathogenesis of RCD-II. Only the patients having the most mature aberrant cells (those expressing the IL-15 receptor) may develop EATL [54]. An overproduction of IL-15 by the enterocytes leads to persistent activation of IELs. IL-15 overproduction leads to severe enteropathy due to its effect on the expression of cytotoxic proteins and the stimulation of natural killer cell-dependent cytotoxicity. Furthermore, IL-15 exerts a powerful anti-apoptotic effect, which might explain the accumulation and the subsequent expansion of the aberrant T-cells [55].

3.5 Therapeutic Options

The data regarding the application of budesonide (open capsule or non-slow release budesonide) are encouraging yet limited [56].

Eradication of the aberrant T-cells is considered the real target in the management of RCD-II. In the patients treated with intravenous administration of cladribine (2-CDA) or oral administration of fludarabine, both clinical and histopathological remissions have been reported to be achieved [20, 21, 23]. Cladribine was reported to induce clinical response in 81% of the treated patients. The percentage of aberrant T-cells was also reduced, although the total elimination of these cells could not be achieved [21, 23]. However, it appeared that the risk of EATL development was not eliminated entirely. Therefore, further aggressive treatment options based on the pathogenesis are being explored currently.

High-dose chemotherapy followed by auto-HSCT serves as a feasible alternative strategy [24, 57, 58]. Treatment with auto-SCT resulted in an impressive improvement, both clinically and biochemically, along with improvement in the overall quality-of-life (QoL). The clinical response rate in the treated patients was 85%. Despite the observation that the reduction in the percentage of aberrant T-cells was not maintained, the long-term outcomes were favorable (unpublished data). As a rule, therapy involving auto-HSCT should be used only in symptomatic patients. In other words, such a therapy is not indicated just to eradicate the aberrant IELs in the asymptomatic patients.

Another investigational option being tested currently is Tofacitinib (a pan-JAK inhibitor), which may influence the pathogenesis of CeD by blocking IL-15 signaling and CD8+ T-cell activity. No results are available so far [59, 60]. In addition, a clinical trial testing the anti-IL-15 monoclonal antibody AMG 714 is currently in progress. Patients received either AMG 714 or a placebo for a duration of ten weeks. The published results revealed that AMG 714 was well tolerated, although the reduction observed in the percentage of aberrant IELs from the baseline was not significantly different between the groups [61].

Table 1 summarizes the currently available therapeutic options for RCD-II.

Table 1 Summary of the available therapeutic options for refractory CeD.

Therapeutic option	Summary of results and references
Budesonide (Open capsule or non-slow release)	Results seem encouraging, but the data are still limited [56]
Prednisone (Oral or Parenteral)	Only in severe clinical conditions [11]
Immunosuppressive drugs	Limited role. There is some risk in precipitating overt lymphoma; Not indicated in RCD-II [7, 19]
Cladribine (2-CDA)	Remission (clinical and histopathological) may be achieved. There is a histological improvement and a reduction of aberrant T-cells. Responders have 5-yr survival of 83% vs. 22% in no-responders [7, 21, 23]
Auto-HSCT	Auto-HSCT is to be used only in symptomatic patients. There is an impressive clinical and laboratory improvement with a substantial gain in QoL. The significant histological improvement achieved but no significant/persistent decrease in the percentage of aberrant T-cells [57, 58]
Anti-IL-15 monoclonal antibody (AMG 714)	Ongoing clinical trial. Patients received either AMG 714 or a placebo for ten weeks. Published results showed that AMG 714 is well tolerated; however, the reduction in the percentage of aberrant IELs from baseline is not different between the groups [61]
Tofacitinib	May influence the pathogenesis of CeD by blocking IL-15 signaling and CD8+ T-cell activity. No results are yet available [59, 60].

3.6 Prognosis of RCD-II and Risk of EATL

RCD-II has a poor prognosis, with 5-year survival ranging between 44% and 58%. This alarmingly high mortality is related mainly to the consequent development of EATL. The incidence of EATL in RCD patients is 33%–52% within five years [62, 63]. This type of EATL is labeled as type-I or secondary EATL in order to differentiate it from type-II or de novo EATL which develops without the pre-existence of CeD. EATL secondary to CeD is the most common one (80%–90% of EATL) [64, 65].

The aberrant T-cells in RCD-II may localize at extra-intestinal sites, such as mesenteric lymph nodes, bone marrow, skin, and paranasal sinuses [63], which is why the localization of EATL is not limited to just the small intestine. In order to establish the diagnosis of EATL, PET-scan-guided biopsy or explorative laparoscopy is usually required. In certain cases, the diagnosis is made with laparotomy in the patients presenting with an acute abdomen because of Intestinal perforation or obstruction [66].

EATL is usually treated with combination therapy, which begins with surgical debulking, followed by an intensified chemotherapy regimen (CHOP in combination with etoposide or methotrexate) and then by auto-HSCT [67]. The resection of the tumor mass, usually a partial

small intestinal resection, performed as early as possible after the establishment of diagnosis, improves the chance to receive chemotherapy, and thereby improving survival. The reported 5-year overall survival in the patients treated with intensified chemotherapy followed by auto-HSCT is approximately 50%–60% [64, 66, 68].

Intestinal perforation is the most common cause of mortality in these patients. The factors known to be associated with poor prognosis include poor general and nutritional status, pre-existent RCD-II, the extent of disease, involvement of multiple intestinal segments, and intestinal perforation that renders chemotherapy almost impossible [69]. Second-line chemotherapy might benefit certain patients [70].

Brentuximab (anti-CD30 antibody) has been used successfully in patients with Hodgkin's lymphoma. The antibody results in cell-cycle arrest and apoptosis [71]. Only a single case report describing the use of this agent in EATL has been published so far [71]. Brentuximab was administered in cycles, every three weeks. After the third cycle, a remarkable response was observed in the CT-scan results. After 8 cycles, complete remission was documented. Therefore, Brentuximab is a promising agent for the treatment of patients who are unable to tolerate chemotherapy.

4. Auto-HSCT in RCD-II

Patients should be selected carefully and subjected to detailed screening prior to treatment with auto-HSCT. The potential benefit of transplantation should outweigh the risks associated with it. Also, it must be ensured that the patient is in an acceptable clinical condition for receiving the transplantation. Furthermore, it is required that the treatment is conducted in centers with adequate gastroenterological and hematological expertise, especially with auto-HSCT, and providing optimal supportive care.

4.1 Mobilization and Collection of Stem Cells

Different mobilization regimens, with or without cyclophosphamide, are currently available. In the RCD-II patients, only granulocyte colony-stimulating factor (G-CSF) has been used to mobilize the marrow hematopoietic progenitor cells into the peripheral blood. G-CSF is administered subcutaneously, daily for a minimum of four days. One possible consequence of G-CSF administration is that the disease may be exacerbated; therefore, close monitoring is required.

Subsequent to mobilization, HSCs are collected through leukapheresis and stored in a frozen condition until after auto-HSCT. The number of $CD34^+$ cells to be harvested and stored is at least $3–5 \times 10^6$/kg. A minimum of 2×10^6/Kg $CD34^+$ cells are required to be reinfused.

4.2 Conditioning Regimen and Performing Auto-HSCT

The conditioning regimens used in auto-HSCT for autoimmune disorders vary considerably. However, the regimens generally used are immuno-ablative rather than myeloablative, and they aim at eliminating the autoreactive T-cells from the host and to deplete the T-cells (which are present at the time of stem cell infusion as well) from the graft. In addition, the intensity of the regimen varies from a low to a high level.

A low-intensity regimen used for the patients with RCD-II comprises orally administered fludarabine for five days (40 mg/m^2/day) and intravenous melphalan for two days (70 mg/m^2/day). Fludarabine, a purine analog, works to deplete the T-cells from the graft, while myeloablation is achieved using a modified dose of melphalan [57, 58].

Subsequently, the infusion of stem cells is performed. The patient is discharged from the hospital when the neutrophil counts have recovered, which generally occurs within 1–3 weeks after the HSC infusion. In the following period, which may vary from weeks to months, a gradual recovery of the immune system occurs.

Figure 1 presents a summary of the regimen for auto-HSCT in Refractory CeD-II.

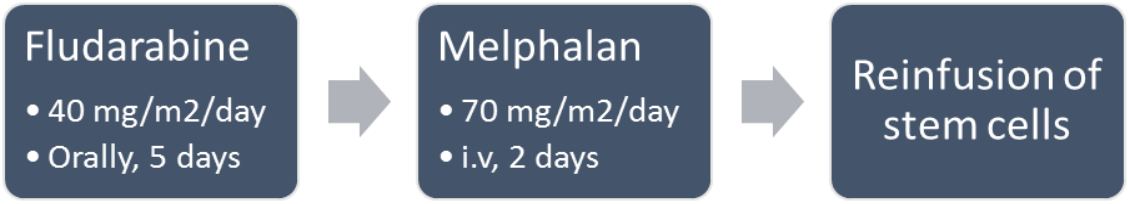

Figure 1 Scheme for auto-HSCT regimen used in Refractory CeD-II.

4.3 Contraindications

The most important contraindications for performing auto-HSCT in RCD-II patients are as follows:

- Presence of neoplasms (EATL in particular).
- Severe comorbidity (respiratory, cardiovascular, renal or liver failure, and therapy-resistant hypertension).
- Evidence for myelodysplasia or bone marrow dysfunction (anemia, leukopenia, and thrombocytopenia).
- Poor performance status.
- Pregnancy.
- Drugs or alcohol abuse.
- Therapy-resistant acute or chronic infection, including HIV.
- Prior radiotherapy, total body irradiation, or treatment with alkylating agents.
- Predicted poor compliance of the patient.

4.4 Supportive Care

Patients are frequently required to be nutritionally optimized using parenteral feeding if the enteral feeding is difficult or insufficient. Post-transplant mucositis of the oro-pharyngeal mucosa may impede enteral feeding, while mucositis of the small intestine may temporarily exacerbate malabsorption. Certain patients require continued support with a feeding tube, with/without parenteral nutrition, for weeks or even for a few months.

Recovery of the bone marrow function is expected at around 11–13 days after the stem cell reinfusion. When indicated, blood and platelet transfusions are provided. At the time of admission,

all the patients are provided with antibacterial and antifungal prophylaxis. Prophylaxis against *Pneumocystis jiroveci* is also provided.

If the presence is confirmed, the patients with evidence of hyposplenism are offered pneumococcal vaccination.

5. Infectious Complications in Auto-HSCT for RCD-II

Safety in the auto-HSCT application remains a major concern that must be addressed prior to be widely applied for RCD-II. The data on the risk of infection after the application of auto-HSCT in the RCD-II patients are limited. In an almost similar indication, although using a different conditioning regimen, the patients with Crohn's disease receiving auto-HSCT presented viral infections as the most commonly observed complications of auto-HSCT during the first 12-month period post-transplant [72, 73]. The most important infections were observed to be associated with the pancytopenia induced by the conditioning regimen. A meta-analysis demonstrated that the application of auto-HSCT in Crohn's disease patients could lead to minor adverse reactions such as peri-anal sepsis; however, serious adverse reactions leading to hospitalization are less common, and perhaps related to the underlying Crohn's disease activity [74].

Hawkey et al. reported that infections were common in Crohn's patients in the auto-HSCT group, and were more common in the initial 100 days following the conditioning and transplantation [72]. In 23 patients who were treated with auto-HSCT, 17 serious adverse events (SAEs) were observed, in 13 patients in the auto-HSCT group vs. 0 patients in the control group. Among the infections classified as SAE, 9 were viral infections in five patients, comprising Epstein-Barr virus reactivation (n = 3), cytomegalovirus reactivation (n = 2), herpes zoster (n = 1), BK virus (n = 1), intestinal adenovirus (n = 1), and varicella zoster virus (n = 1). The rest included 8 cases with presumed neutropenic sepsis with an organism isolated on 1 occasion, 2 were pneumonia (Klebsiella [n = 1] and pneumocystis [n = 1]), and 3 were anal or perianal abscesses (the latter 3 were observed in a single patient).

In another study conducted by Jauregui-Amezaga et al., it was reported that the most frequent and severe adverse events during the first 12-month period after auto-HSCT in Crohn's disease patients were related to viral infections [73]. In the 26 patients that were treated, CMV disease was documented in two cases, leading to death in one case eight weeks after the transplant. Despite receiving intensive therapy and supportive measures, the patient developed multi-organ failure and succumbed to death. The post-mortem examination of this patient revealed systemic CMV infection. A second patient presented with severe CMV and EBV-positive colitis that did not respond to ganciclovir, foscarnet, or rituximab. This patient ultimately underwent colectomy. The other infections reported were primary CMV infection and EBV infection (mononucleosis).

The following sub-sections outline the specific risk factors for the infections arising in the post-auto-HSCT therapy period in RCD-II patients:

5.1 The Immune System

The immune system of the RCD-II patients is often significantly impaired due to the disease process itself (particularly, malabsorption with wasting) as well as because of the use of steroids or immunosuppressants [16, 17]. Stem cells mobilization, the conditioning regimen, and T‑cell

depletion in the graft are associated with an increased risk of infections, both acquired and the reactivation of the dormant infections [75].

In the early phase of neutropenia after auto-HSCT, bacterial or fungal infections may develop, while the reactivation of latent viruses and other opportunistic infections might occur if lymphopenia is prolonged. This may threaten the patients until the reconstitution of the immune system occurs. Therefore, during aplasia, all the patients should receive antibacterial (broad-spectrum), anti-fungal, and anti-herpes prophylaxis, for a period of 3–6 months post-transplantation. Furthermore, as stated earlier, prophylaxis against *Pneumocystis jiroveci* should be provided to all the patients. In CeD patients, every effort should be put to provide gluten-free medications.

5.2 Effect of the Source of Stem Cells on Infection Risk

In auto-HSCT for RCD-II patients, stem cells from the peripheral blood are used. These cells achieve faster hematopoietic and immune reconstitution compared to the cells obtained from bone marrow. Grafts of peripheral blood HSCs contain a greater number of T-lymphocytes and B-lymphocytes (>10 times) compared to the marrow grafts. Therefore, the recipients of peripheral blood HSCs may be less immunocompromised compared to those who receive marrow grafts, and are consequently less prone to acquire infections or develop reactivation of dormant pathogens [76].

5.3 Effect of Other Patient Characteristics

Infection with bacteria has been reported in CeD [16, 77]. Functional asplenia (hyposplenism) is diagnosed when the spleen size is clearly smaller than the normal size range or when there are Howell-Jolly bodies detected in blood examination [17]. Pneumococcal vaccine should be offered to such patients [11]. The patients, who have not been previously vaccinated against *Hemophilus*, *Meningococcus*, and influenza, may also be provided vaccination [77].

Small Intestinal Bacterial Overgrowth (SIBO) has been hypothesized to be associated with CeD [78]. Factors such as dysmotility, inflammation, and gut microbiota have been reported as the possible risk factors for SIBO in CeD [79, 80]. A systematic review concluded that SIBO could be more common in CeD when the symptoms do not improve after GFD [78]. In comparison to the asymptomatic controls, CeD was observed to be associated with a higher risk of SIBO, with an OR of 10.5 (95% CI: 2.6–41; P = 0.0007). Therefore, the presence of SIBO might predispose the patients to systemic infections after treatment with chemotherapy and auto-HSCT.

6. Reported Results on Auto-HSCT in RCD-II

Randomized clinical trials evaluating the auto-HSCT treatment in patients with RCD-II are lacking. The age limit for performing auto-HSCT in RCD-II patients is seventy years [57, 58]. However, this limit may be changed when further data are available. The use of auto-HSCT is targeted to achieve a good QoL and to reintegrate the patients in their work and social activities as soon as possible [81].

Auto-HSCT was evaluated in a cohort of 18 patients having RCD-II who had already exhibited a response (complete or partial) or had failed to respond to cladribine therapy [57, 58]. Conditioning

and subsequent reinfusion of HSCs were conducted in 13 among the 18 patients. All 13 patients continued to be on a regular follow-up after the completion of their treatment. Complete histological remission is defined as the normalization of the architecture of small intestinal mucosa, i.e., achieving Marsh 0 or Marsh I lesion based on the modified Marsh criteria [4, 82]. A decline of >20% in the percentage of aberrant IELs was considered a significant immunological remission. In the transplanted group, one transplant-related death occurred due to septicemia with subsequent meningitis, eight months after the auto-HSCT treatment. Autopsy results confirmed the presence of chronic encephalitis of the right temporal lobe with oligoclonal T-lymphocyte infiltration. Immunohistochemistry results revealed that the lymphocyte infiltrate was $CD3^+$ and that the majority of the cells expressed CD8 positivity. Two other patients succumbed to death because of EATL, four years after the auto-HSCT. The overall 3- and 4-year survival after undergoing the auto-HSCT therapy was 80% and 66%, respectively.

Within one year of receiving auto-HSCT, majority of the patients (11 among a total of 13 patients) demonstrated impressive clinical improvement, with normalization of stool frequency, the disappearance of the gastrointestinal symptoms, and normal or improved body mass index (BMI), albumin levels, and/or hemoglobin. These patients had a WHO performance status of 0, and reported a significant improvement in their QoL at the end of the one-year follow-up.

The median serum albumin levels were observed to increase from 36 to 42 g/L. Endoscopically, a disappearance of erosions and ulcerations in the jejunum was observed in all the patients who had ulcerative jejunitis prior to the auto-HSCT therapy, and the histology of small intestine demonstrated significant healing as evidenced by the down-staging of the Marsh class. A complete histological remission, defined as achieving Marsh 0 or Marsh I, was achieved in five patients, while the other 6 demonstrated an improvement in the histological stage.

After auto-HSCT, the percentage of immunophenotypically aberrant T-lymphocytes was not observed to change significantly compared to the baseline. This is interesting, particularly in the view of the improved Marsh stage. Although this percentage is crucial in the diagnostic work-up for distinguishing between the RCD types I and II, the data suggest that the percentage of aberrant IELs was not suitable for monitoring therapy and predicting prognosis. In fact, the percentage of aberrant T-cells was not the same as the overall depletion of T-cells after auto-SCT. It remains to be proven, however, if an absolute load of aberrant T-cells quantified using flow cytometry or other quantitative methods is more suitable than the percentage of aberrant T-cells for the prediction of prognosis in the RCD-II patients.

Furthermore, clonal expansion of these aberrant IELs is considered responsible for progression into EATL, although in our series, the persisting high percentage of aberrant IELs after auto-HSCT did not reflect in an increased EATL development. Moreover, the T-cell receptor-gamma (TCR-g) rearrangement performed after auto-HSCT could not detect a clonal peak.

However, it is generally accepted that the aberrant T-cells are the precursors for EATL development. Therefore, further reduction in the T-cell mass through the intensification of the conditioning regimen pre-auto-HSCT might improve the outcome. One such possibility is combining a higher dose of fludarabine/cladribine with anti-CD52 (alemtuzumab), antithymocyte globulin, or other specific anti-T-cell agents. Unpublished follow-up data (10–15 years) demonstrate excellent long-term survival and good QoL, with no new cases of EATL in the remainders.

Furthermore, the beneficial effects of auto-HSCT have also been reported in RCD-II [41, 83]. One such report described the successful use of auto-HSCT in a 10-year-old girl with CeD.

In RCD-II patients, auto-HSCT has been proven to be well-tolerated, and long-term remission with a good QoL and a delay or even prevention of EATL development may be achieved.

A remarkable case report on the treatment of an RCD-II patient with serial mesenchymal stem cells (MSCs) infusions is available in the literature. The patient underwent four systemic infusions of MSCs at four-month intervals. No adverse side-effects were reported. The general condition of the patient improved. Diarrhea disappeared, laboratory tests normalized, and the patient regained weight. Most importantly, the expression of IL-15 and its receptor disappeared [84]. It has been hypothesized that since MSCs lack immunogenicity, they might gain preference over the HSCs, as the MSC transplantation may be performed without requiring a myeloablative conditioning regimen. In addition, MSCs have strong regenerative capabilities and strong modulatory effects on the cells involved in the immune response [85].

7. Conclusions

Refractory CeD with aberrant T-cells is a rare disease. It represents a state of pre-lymphoma and is usually refractory to the currently available therapies, particularly to the immunosuppressants. There is a requirement for a further effective treatment option for the condition, which would also be able to prevent its progression to EATL. Currently, an add-on or a combination treatment strategy, which begins with steroids and 2-CDA, may serve as the most feasible treatment option, while auto-HSCT or anti-IL-15 are to be added later.

According to the current evidence, auto-HSCT serves as an attractive treatment option for these patients. However, careful patient selection is necessary. The potential benefit of transplantation should outweigh the risks associated with it. The patient should be in an acceptable clinical condition to receive the transplantation. Furthermore, it is important that the treatment is conducted in centers with adequate gastroenterological and hematological expertise, especially with auto-HSCT, and with optimal supportive care.

The risk of infections in the post-transplant period appears low. The use of prophylactic antimicrobials and vaccination against certain pathogens further decreases the infection risk.

Author Contributions

A. Al-Toma revised the published literatures, provided detailed revision of refractory celiac disease and prepared the manuscript.

H.R. Koene revised the manuscript and provided the hematological data on auto-HSCT.

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Competing Interests

The authors have declared that no competing interests exist.

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