Epidemiologic and therapeutic aspects of refractory coeliac disease – a systematic review

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ABSTRACT

INTRODUCTION: Refractory coeliac disease (RCD) is a rare and severe malabsorptive disease. The condition has two subtypes; RCDI and RCDII. Different treatments have been tested; and because RCD has a poor prognosis due to progress to enteropathy-associated T-cell lymphoma, the aim was to review the epidemiologic aspects and the therapeutic options for RCD.

METHODS: A systematic literature search was performed in 18 databases, and 122 records were identified. Incidence, prevalence, treatment methods and their efficacy were evaluated.

RESULTS: Among coeliac disease patients, the cumulative incidence of RCD is 1-4% per ten-year period and the prevalence is 0.31-0.38%. In the general population, the prevalence of RCD is 0.002%. Treatment of RCDI is azathioprine (effect 100%), mesalamine (effect 60%) or tioguanine (effect 83%). Treatment for RCDII is the antimetabolite cladribine (effect 81%) and autologous haematopoetic stem cell transplantation (effect 85%).

CONCLUSION: RCD is a very rare disease. The current evidence for RCDI treatment includes prednisolone in combination with the immunosuppressants azathioprine, mesalamine or tioguanine.

The current evidence for RCDII treatment documents use of the antimetabolite cladribine; and if there is no effect, autologous haematopoetic stem cell transplantation may be attempted. In the future, there is a need for more effective treatments which will also prevent further progression to enteropathy-associated T-cell lymphoma.

Coeliac disease (CD) is a chronic immune-mediated enteropathy of the small intestine that is induced by the ingestion of dietary gluten in genetically predisposed people [1].

The disease occurs worldwide at an estimated prevalence of 0.5-1% [2]. A recent Danish survey has estimated the prevalence of coeliac disease to 0.5% in Denmark [3].

The clinical range of CD is wide; from asymptomatic to severely symptomatic. According to the Oslo definitions [4], classic CD presents with signs of malabsorption, micronutricient deficiency and failure to thrive [4]. The treatment for CD is a lifelong gluten-free diet (GFD), which improves symptoms, nutrition and quality of life [2].

ABBREVIATIONS

Auto-SCT = autologous hematopoietic stem cell transplantation
BMI = body mass index
CD = coeliac disease
EATL = enteropathy-associated T-cell lymphoma
GFD = gluten-free diet
IEL = intraepithelial lymphocytes
RCD = refractory coeliac disease
RCDI = refractory coeliac disease type I
RCDII = refractory coeliac disease type II
RCT = randomised controlled trials

In most cases, a missing response to GFD is due to poor adherence [5]. However, a small group of CD patients are resistant to GFD due to refractory coeliac disease (RCD) [6]. According to the Oslo definitions, RCD is defined as persistent or recurrent malabsorptive symptoms and signs of villous atrophy despite a strict GFD for more than 12 months, or severe persistent symptoms independently of the duration of GFD [4].

RCD is subdivided into two groups. Refractory coeliac disease type I (RCDI) has an increased number of intraepithelial lymphocytes (IEL) with a normal phenotype and the surface markers CD3 and CD8. The symptoms of RCDI resemble those of active CD with the only difference being the resistance towards GFD. In contrast, refractory coeliac disease type II (RCDII) is a severe enteropathy with ulcerative duodenojejunitis, protein deficiency and a clonal expansion of abnormal IEL. These abnormal IEL are characterised by lack of surface markers CD3, CD8 and the T-cell receptor, and a retained expression of intracellular CD3 [6].

Clinical manifestations and prognosis of refractory coeliac disease

The most frequent symptoms are persistent diarrhoea, abdominal pain and involuntary loss of weight. Other common manifestations are vitamin deficiencies, anaemia, fatigue, malaise, thromboembolic events and coexisting autoimmune disorders [7]. The overall prognosis of RCD is poor with the prognosis of RCDI being better than that of RCDII although the rates of complications and mortality are higher in RCDI than in CD. The five-year survival rate for RCDI is 90-93% [8, 9]. In contrast to

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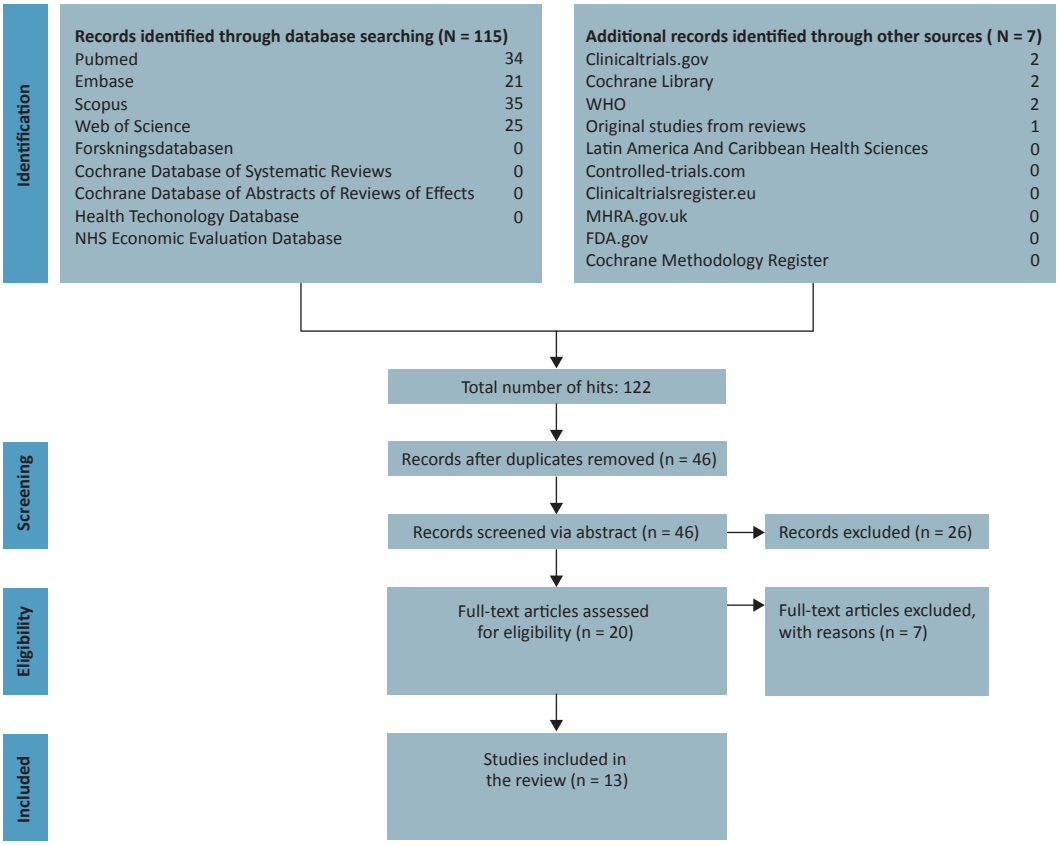
Dan Med J 2016;63(12):A5307

FIGURE 1

A flow chart of the selection process.



RCDI, RCDII has a very poor prognosis with five-year survival rates in the 44-58% range [8, 9]. One of the most important reasons behind this difference is the much higher progression to overt enteropathy-associated T-cell lymphoma (EATL) in patients with RCDII [7].

Over the past two decades, different treatments have been tested, and because RCD is a very rare and severe disease with a poor prognosis, more knowledge about the treatments and the epidemiology of RCD is required. The aim of this study was to review the epidemiologic aspects and the therapeutic options of refractory coeliac disease.

METHODS

A systematic literature search was performed in 18 databases between 18 June 2015 and 29 June 2015 (**Figure 1**). The following search strings were used: refractory coeliac disease AND treatment, or refractory coeliac disease AND incidence, or refractory coeliac disease AND prevalence, or refractory coeliac disease AND management. Other synonyms for RCD were also used, i.e. refractory sprue, refractory coeliac disease. A language restriction was placed; thus, only articles written in English were screened. Furthermore, the search was expanded by using MESH terms for each search string.

After removal of duplicates, the abstracts were screened according to the inclusion and exclusion criteria. The present evidence on incidence, prevalence and treatment for RCD is limited, and no randomised controlled trials were available. Therefore, there was no restriction on sample size or study design except for case reports and case series, which were excluded. The definite inclusion and exclusion criteria for eligible studies are listed in **Table 1**. To see the selection process, please refer to the flow chart, Figure 1. From the 20 full-text articles, seven full-text articles were excluded for various reasons, e.g. not mentioning that the study was based on a case series in the abstract, not explaining diagnostic methods and not adequately diagnosing RCD. Finally, another reason for exclusion was an outcome focused on pathological and immunological mechanism rather than having a clinical response as the main outcome in the cases in which this was not mentioned in the abstract of the articles.

From the final 13 included full-text articles, data were extracted for diagnostics of RCD, epidemiology treatment methods and results.

KEY POINTS

Refractory coeliac disease is a very rare disease.

The disease is divided into two subtypes, refractory coeliac disease type I and refractory coeliac disease type II.

The cumulative incidence of refractory coeliac disease is 1-4% per ten years, and the prevalence is 0.31-0.38% among coeliac disease patients.

Refractory coeliac disease type I may be treated with prednisolone in combination with one of the three immunosuppressants azathioprine, mesalamine or tioguanine.

Refractory coeliac disease type II may be treated with the antimetabolite cladribine and if there is no effect, autologous stem cell transplantation may be attempted.

More effective therapies are needed.

Awareness is needed of this condition in coeliac disease patients who are not responding on gluten-free diet despite a good adherence.

Now there are accurate diagnostic methods that can very precisely determine the type of refractory coeliac disease. The three methods are flow cytometry, immunohistochemistry and molecular analysis.

There seems to be treatments for refractory coeliac disease that may improve the condition, but more controlled studies are needed.

TABLE 1

Inclusion and exclusion criteria for eligible studies in this review.

	Inclusion	Exclusion
Participants	Patients with a verified diagnosis of RCD Subgroups RCD I and RCD I Studies that expound diagnostic steps and differential diagnoses of RCD	Patients with CD who are non-adherent to gluten-free diet Patients with enteropathy-associated lymphoma and other T-cell lymphomas, collagenous sprue and tropical sprue
Purpose of study	Treatment of RCD Estimation of incidence and prevalence	–
Comparators	Any or none	–
Study design	Any	Case reports Conference abstracts Publications without peer review Publications not written in English

CD = coeliac disease; RCD = refractory CD.

TABLE 2

Incidence and prevalence of refractory coeliac disease.

	Reference		
Results	**Roshan et al, 2011 [10]**	**Biagi et al, 2014 [11]**	**Ilus et al, 2014 [12]**
n_{RCD}	34	7	44
Cohort size, n_{CD}	844	1,840	12,243
Prevalence in CD-cohort, %	–	0.38	0.31
Prevalence in general population, %	–	–	0.002
Cumulative incidence in own centre, %/10 yrs	1.5	–	–
Cumulative incidence in own centre including referrals, %/10 yrs	4	–	–

CD = coeliac disease; RCD = refractory CD.

RESULTS

The search identified 122 records. There are no randomised clinical trials evaluating the medical treatment of RCDI or RCDII. After the selection process, a total number of 13 studies were included. Three studies [10-12] deal with the epidemiology of RCD and ten studies [13-22] with the treatment of RCD. The epidemiologic studies all have a retrospective study design including a total of 85 RCD patients.

The ten included treatment studies have a total of 160 patients with population sizes ranging from $n_{RCD} = 7$ to $n_{RCD} = 32$. All patients are adults. The study designs are either prospective or retrospective non-randomised clinical trials.

Overall, there is a trend that the older the studies are, the fewer are the used diagnostic techniques. An example is the application of flow cytometry, molecular analysis and immunohistochemistry, which were not used in the studies from the early 2000s or in the epidemiological, retrospective studies. Diagnosis of RCD is difficult and demanding because the clinical symptoms of RCD resemble those of CD and other gastrointestinal malabsorption diseases. Furthermore, the differentiation between RCDI and RCDII is impossible to perform clinically without the three aforementioned diagnostic techniques.

The epidemiology of refractory coeliac disease

The accurate prevalence and incidence of RCD remain unknown. The literature on the epidemiology of RCD is scarce and limited to a few studies from tertiary referral centres. Most patients with RCD are referred to large tertiary centres and an unavoidable selection bias emerges. Therefore, the results must be interpreted with caution. The selection bias is due to the high number of RCD patients in tertiary centres, which do not reflect the incidence of RCD in the general population. The results are displayed in **Table 2.**

In the study by Roshan et al [10], the cumulative incidence in their own centre was 1.5% per ten years, while the total cumulative incidence in the centre including referrals from other centres was 4% per ten years. There are no results on a calculated or estimated annual incidence of RCD.

In Biagi et al [11] the calculated prevalence is 0.38%, which is comparable to Ilus et al [12], 0.31%. The calculation of the prevalence is carried out by the author of this review. Illus et al [12] is the only study reporting that the prevalence of RCD is 0.002% in the general population. The prevalences calculated by Illus 2014 [12] are probably more reliable because the data material originated from 11 different public hospitals. The reason behind the low prevalence of 0.31-0.38% may be

TABLE 3

Effect of treatment.

Reference	Treatment	n_{RCD}	Effect on patient group, %		
			RCD type not known	RCDI	RCDII
Mulder et al, 2001 [13]	IL-10	10	30	–[a]	–[a]
Maurino et al, 2002 [14]	Azathioprine	7	71	–[a]	–[a]
Goerres et al, 2003 [15]	Azathioprine + prednisolone	18	–[a]	100	63
Al-Toma et al, 2006 [16] + Tack et al, 2011 [20]	Cladribine	32	–[a]	–[a]	81
Al-Toma et al, 2007 [17] + Tack et al, 2011 [19]	Auto-SCT	18	–[a]	–[a]	85
Brar et al, 2007 [18]	Budesonide	29	76	–[a]	–[a]
Jamma et al, 2011 [21]	Mesalamine	10	–[a]	60	–[a]
Tack et al, 2012 [22]	Tioguanine	12	–[a]	83	–[a]

Auto-SCT = autologous haematopoetic stem cell transplantation; IL-10 = interleukin-10; RCD = refractory coeliac disease; RCDI = RCD disease type I; RCDII = RCD disease type II.
a) Treatment was not tested on the type of RCD.

the low incidence and the low five-year survival rate of RCDII, which is 44-58% compared with 90-93% in RCDI according to [8, 9].

Treatment of refractory coeliac disease

In the ten studies regarding treatment, the clinical response is generally well-defined. The clinical response consists of two parts – a subjective part, i.e. relief of the patient's symptoms, and an objective part, i.e. biochemical parameters and BMI and body weight. Seven of ten studies [14, 16-21] have clinical response as their primary outcome. The final three studies differ; Mulder et al [13] and Goerres et al [15] have histological response as their primary outcome and Tack et al [22] use adverse events and tolerability as their primary outcome. All of the tree final studies [13, 15, 22] have clinical response as their secondary outcome.

The efficacy of the treatments against RCD can be summarised for each of the three groups of RCD, RCDI and RCDII. In the first group, RCD, the studies do not distinguish between the two RCD subtypes or the efficacy of the treatment is an evaluation of the two RCD types together.

Table 3 displays the treatments in chronological order and their clinical efficacy of the three patient groups. The clinical response is selected as the efficacy measure for a treatment because the most important response to a treatment is the patient's own evaluation, i.e. the ease of symptoms and quality of life. The blank areas in the table indicate that the treatment was not tested on the type of RCD in question. The calculation of the clinical response is carried out by the author of this review.

1. The refractory coeliac disease, type not known-group

a. IL-10: Treatment with IL-10, an anti-inflammatory cytokine did not induce a desirable effect on RCD, 30%.
b. Azathioprine: In Maurino et al [14], azathioprine did have an effect on RCD, 71%. However, whether the effect was mainly obtained in RCDI or RCDII patients remains unknown, and it is therefore difficult to evaluate the exact effect of azathioprine. It is well documented that azathioprine in combination with prednisolone induces a partial clinical and histological remission in RCDI [6, 7, 15], thus a response to azathioprine in Maurino et al [14] might be due to undiagnosed RCDI patients.
c. Budesonide: Brar et al [18] investigated the effect of budesonide in RCDI and RCDII patients and reported a beneficial clinical response in 76% of cases. A bias in Brar et al [18] is the total evaluation of the effect of budesonide rather than a separate assessment for each RCD subtype. Therefore, the efficacy of budesonide is problematic to examine. Budesonide is a type of steroid and just like prednisolone has a good effect on RCDI [6, 7, 15], although there are no clinical trials in the literature that may support that prednisolone can induce a clinical response in RCDI. The evidence is based on twentieth century literature [7, 23, 24] and expert opinion [7]. The clinical response of budesonide (76%) is most likely to be due to an excess prevalence of RCDI patients.

2. The refractory coeliac disease I-group

Azathioprine, mesalamine and tioguanine are all immunosupressive drugs, which are often used, particularly in the treatment of inflammatory bowel disease.

a. Azathioprine and prednisolone: Goerres et al [15] demonstrated that azathioprine in combination with prednisolone is an effective treatment option against RCDI; hence, Goerres reported a clinical response rate of 100%. This therapy option has long been the first-choice treatment for RCDI [7]. As azathioprine

induces unfortunate side effects [22], alternative immunosuppressants have been tested [21, 22].

b. Mesalamine and tioguanine: Both studies on these drugs [21, 22] induced clinical remission and they reported a response rate of 60% and 83%, respectively, in RCDI. The side effects in the two studies [21, 22] were not documented.

3. The refractory coeliac disease II-group

Treatment of RCDII requires a more aggressive approach due to the low five-year survival rate (44-58%) [6].

a. Azathioprine and prednisolone: Goerres et al [15] attempted azathioprine in combination with prednisolone with a poor response rate of 63% and the study [15] concluded that this treatment is contraindicated in RCDII as azathioprine in combination with prednisolone might possibly further deteriorate RCDII.
b. Cladribine: Al-Toma et al [16] and Tack et al [20] have obtained a good effect with the antimetabolite cladribine. Cladribine can induce a clinical response in 81%. Furthermore, the incidence of EATL is restricted with this treatment; thus, cladribine has been the drug of choice [20]. Unfortunately, not all RCDII-patients respond to cladribine and therefore the alternative autologous haematopoietic stem cell transplantation (auto-SCT) has been tested [19].
c. Autologous hematopoietic stem cell transplantation.

Al-Toma et al [17] and Tack et al [19] demonstrated that high-dose chemotherapy followed by auto-SCT is an effective treatment against RCDII with a clinical response rate of 85%. This therapy also induces histological remission, and Tack et al [19] reported a four-year survival rate of 66% if the transplantation is successful [19]. The immunological response is minor, which means the percentages of aberrant IEL persist after auto-SCT and therefore these patients need to be followed very closely due to a sustained risk of developing EATL.

DISCUSSION

Refractory coeliac disease is a malabsorptive disease with signs of villous atrophy despite strict GFD for 12 months. The condition is not recognised as an independent disease by the International Classification of Diseases, tenth revision (ICD-10). However, RCD could be classified as a variant of coeliac disease in the 11th revision of International Classification of Diseases. It has been suggested that refractory coeliac disease may be the missing link between coeliac disease and T-cell lymphoma [25]. The condition has two subtypes; RCDI with normal IEL and RCDII with aberrant IEL. RCD is difficult to diagnose, and the diagnostic criteria and techniques have changed over time. Therefore, the results reported herein should be interpreted cautiously -especially in regard to the earlier studies.

The incidence and prevalence of RCD remain unknown, but the consensus is that RCD is a very rare disease. The evidence in the literature is scarce and mainly originates from large tertiary referral centres where a selection bias exists. The cumulative incidence of RCD is 1-4% per ten-year period [10] and the prevalence is 0.31-0.38% among CD-patients [11, 12]. In the general population, the prevalence of RCD is 0.002% [12]. All these numbers support the rarity of RCD.

The most reliable epidemiologic data come from Ilus et al [12]. However, it is important to note that the prevalence of RCD is dependent on the methods of registration and diagnostics among CD patients, i.e. the better the healthcare system diagnoses and registers CD, the better it is at capturing RCD patients. Finland has well-developed registration of their CD patients, which gives reliable epidemiologic data, but these data cannot be directly extrapolated to Denmark because of a very high prevalence of CD even though both countries are Scandinavian and represent a similar genetic material. According to [3], the Finish prevalence of CD is approx. three times higher than the Danish prevalence of CD, which could be interpreted as an indication that the RCD prevalence is three times smaller in Denmark than the one found in Finland by [12].

In this review, evidence for treatment of RCD is based mainly on prospective or retrospective open-label clinical trials without any control group. There are no randomised clinical trials. The different RCD treatments can be classified into four different groups: steroids, immunosupressants, chemotherapy and bone marrow transplantation. Steroids have long been used for symptom management in RCDI and RCDII causing side effects and severe steroid-dependency, i.e. the patients cannot withdraw from steroids without RCD relapse [2, 6, 7].

To sum up the current evidence for RCDI treatment, azathioprine in combination with prednisolone induced the highest response rate of 100%, followed by tioguanine 83% and mesalamine 60%. There are no randomised clinical trials to prove which of the three drugs would induce the highest response rate and fewest side effects either compared with the other immunosuppressive drugs or to placebo.

To sum up the current evidence for RCDII treatment, cladribine (chemotherapy) induces a response rate of 81%, and if there is no clinical effect, auto-SCT is the only alternative [17].

Presently, there is no explanation of why RCDII-patients do not respond to cladribine and must proceed to auto-SCT. The main goal of auto-SCT is to achieve a resetting the immune system with subsequent regeneration of naïve T lymphocytes [17].

Today, we have no real efficient treatment for RCDI and RCDII. Optimally, future treatments should be tested as multicentre randomised clinical trials. As a future perspective, there is currently an open-label prospective clinical trial in progress evaluating antibody therapy for RCD with the humanised IL-15 antibody [26]. The expected completion date of the study is in 2017. Another option is the JAK3-inhibitor, currently used for rheumatoid arthritis [27]. This antibody has demonstrated a therapeutic potential against RCD in animal models [28] and the next step will be phase I studies.

CONCLUSION

CD is a very rare disease and there is a need for more effective treatments of the condition, which will also prevent further progression to EATL.

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ACCEPTED: 28 September 2016

CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk

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