Diagnosis and management of refractory celiac disease: a systematic review

Asma Labidi, Meriem Serghini, Sami Karoui, Jalel Boubaker, Azza Filali

Tunis El Manar University, Faculty of Medicine of Tunis, La Rabta Hospital, Department of Gastroenterology A. Tunis, Tunisia

A. Labidi, M. Serghini, S. Karoui, J. Boubaker, A. Filali

Diagnostic et traitement de la maladie coeliaque refractaire: une revue systematique de la litterature

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R É S U M É

Prérequis : La maladie cœliaque réfractaire est définie par la persistance des symptômes de malabsorption en dépit d'une adhérence stricte au régime sans gluten pendant au moins 6 à 12 mois.
But : Décrire les aspects cliniques et épidémiologiques de la maladie cœliaque réfractaire, et d'identifier les options thérapeutiques au cours de cette pathologie.
Méthodes : Une revue systématique et une analyse critique des études observationnelles, essais cliniques et cas cliniques à propos du diagnostic et du traitement de la maladie cœliaque réfractaire.
Résultats : La maladie cœliaque réfractaire peut être classée en type 1 ou type 2 selon le phénotype des lymphocytes intraépithéliaux. De graves complications comme le lymphome T associé à l'entéropathie, peuvent émailler l'évolution de cette pathologie chez un sous-groupe de ces patients, notamment porteurs du type 2.
Conclusion : La maladie cœliaque réfractaire est un diagnostic d'élimination. Le pronostic reste encore sombre en l'absence de thérapies curatives. Toutefois, certains traitements semblent prometteurs au cours de quelques études de cohorte.

M o t s - c l é s
Maladie cœliaque ; maladie cœliaque réfractaire

S U M M A R Y

Background: Refractory celiac disease is defined by persisting malabsorptive symptoms in spite of a strict gluten free diet for at least 6 to 12 months. Alternatives to gluten free diet seem to be still controversial.
Aim: To describe the clinical and epidemiologic aspects of refractory celiac disease, and to identify therapeutic options in this condition.
Methods: Systematic review and critical analysis of observational studies, clinical trials and case reports that focused on diagnosis and management of refractory celiac disease.
Results: Refractory celiac disease can be classified as type 1 or type 2 according to the phenotype of intraepithelial lymphocytes. Great complications such as enteropathy-associated T-cell lymphoma may occur in a subgroup of these patients mainly in refractory celiac disease type 2. Curative therapies are still lacking.
Conclusion: Refractory celiac disease remains a diagnosis of exclusion. Its prognosis remains still dismal by the absence yet of curative therapies. However, some new treatments seem to hold promise during few cohort-studies.

K e y - w o r d s
Celiac disease; refractory celiac disease

Celiac disease, first described by Samuel Gee in 1887(1), is a chronic systemic disease affecting primarily gastro-intestinal tract. It is caused by an immune response to ingested wheat gluten and similar proteins of rye and barley. It is characterized by chronic inflammation of the small intestinal mucosa that may lead to atrophy of intestinal villi, malabsorption, and a variety of clinical manifestations, which may begin in either childhood or adult life (2), with increased risk of intestinal malignancies.

The true prevalence of this condition is much greater than previously recognized, with increasing numbers of silent cases being diagnosed. Population-based studies, using serologic screening for CD followed by histological confirmation have revealed high prevalence of this condition, between 1:100 and 1:220, in many geographic regions, such as Europe, the USA, India, North Africa, the near and the middle East. In Tunisia, seroprevalence of CD ranges between 1/157 and 1/170 (3).

A strict gluten-free diet (GFD) for life is the cornerstone of treatment for celiac disease (CD); it leads, in most cases, to a dramatic clinical and histological improvement and even eliminates heightened risk of intestinal cancers. However, a tiny minority of patients with CD fails to respond to GFD in spite of strict adherence, and so called refractory celiac disease (RC).

The aim of this review is to describe the clinical and epidemiologic aspects of RC, and to identify therapeutic options in this condition.

METHODS

Database inquiry was initiated into PubMed using the Mesh headings “Celiac disease”, “refractory celiac disease”, “gluten-free diet”, “non-responsive celiac disease” and “refractory sprue”. This search was expanded and modified into the following additional database: Cochrane Library, Embase and Web of Science. Additional relevant studies were identified by manually examining bibliographies of included articles. All studies required approval by Institutional Review Boards (IRBs). Cross-sectional studies, cohort studies, case-control analyses, case series, case reports and expert consensus were acceptable for inclusion (table1).

Studies had to include patients with celiac disease who had persisting symptoms despite strict adherence to gluten-free diet. They had to explicit procedure leading to diagnosis of refractoriness of the celiac disease. All criteria for evaluating treatment were acceptable. Study inclusion was not limited by the study design.

Exclusion criteria were as follows: studies about patients with persisting malabsorptive symptoms whose adherence to gluten free diet was doubtful and that did not explicit diagnostic approach.

The evidence about the effectiveness of treatments in this review has been graded according U.S. Preventive Services Task Force system (USPSTF) (table 2)

Table 1: Eligibility criteria for studies included in the review

Population	Patients with celiac disease who had persistant symptoms despite adherence to gluten-free diet.	Patients with celiac disease whose adherence to gluten-free diet was doubtful.
Diagnosic approach	Studies that explicited diagnostic steps and differential diagnoses of refractory celiac disease.	Studies that did not detailed diagnostic approach.
Response to therapy	Assessement was based on clinical and/or histological findings as well as occurrence of side effects.	None.
Study design	Case-report, case-series, expert consensus, case-control, cohort study, cross-scetional study .	None.

Table 2 : Levels of evidence and grades of recommendations

I	Evidence obtained from at least one properly designed randomized controlled trial.
II-1	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

A	The USPSTF strongly recommends that clinicians provide [the service] to eligible patients. The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.
B	The USPSTF recommends that clinicians provide [this service] to eligible patients. The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.
C	The USPSTF makes no recommendation for or against routine provision of [the service]. The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.
D	The USPSTF recommends against routinely providing [the service] to asymptomatic patients. The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.
E	The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. Evidence that the [service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.

RESULTS

REFRACTORY CELIAC DISEASE: DEFINITION AND PROGNOSIS

Specific definition of refractory celiac disease (RC) is missing in the literature. True RC could be defined as persisting or recurring villous atrophy with crypt hyperplasia and increased intraepithelial lymphocytes in spite of a strict GFD for more than 12 months or when severe persisting symptoms necessitate intervention independent of the duration of the GFD (4). It may not respond primarily or secondarily to GFD. Two types of RC had been recognized: type1 in which there is a normal expression of T-cell antigens and polyclonal TCR gene rearrangement, while type 2 is characterized by an abnormal IEL phenotype with the expression of intra cytoplasmic CD3e, surface CD103, and the lack of classic surface T-cell markers detected by immunophenotyping by flowcytometric analysis or immunohistology of the intestinal mucosa, such as CD8, CD4, and TCR-alpha/beta.

The prognosis of RC may be poor; patients could suffer from severe malabsorption, ulcerative jejunitis or synchronous or metachronous development of an enteropathy-associated T-cell lymphoma (EATL) or gastrointestinal carcinoma (5). It has been reported that in the context of CD, small bowel adenocarcinoma is associated with better survival than the sporadic counterpart (6).

The classification of RC is certainly based on the immunophenotype of intraepithelial lymphocytes, but also supported by the outcome of the disease. In fact, it has been reported in RC type 2 a more frequent progression to overt EATL in comparison to RC type 1(7) due to the presence of abnormal intraepithelial lymphocytes.

A recent paper states that the 5-year survival for types I and II refractory celiac disease is respectively 93% and 44%. According to Rubio Tapia and al. the most common cause of death in the former type was T-cell lymphoma.

EPIDEMIOLOGY

The real prevalence of RC is unknown; however it seems to be rare since low number of cases is reported in the literature. RC may be the cause of underlying persistent or recurrent symptoms in treated CD in just 10 to 18% of the patients evaluated in referral centers(8).

Estimates of the occurrence of RC in non-referral, population-based cohorts are very scarce.

From 204 biopsy-confirmed CD residents of Olmsted County (Minnesota, United States) identified from 1950 to 2006, only 3 (1.47%, 95% CI: 0.3%–4.2%) had a subsequent diagnosis of RC type 1 (n=2) or type 2 (n=1). The incidence per 100,000 person-years was 0.06 (95% CI: 0.0–0.12) adjusted for age and gender to the 2000 US white population (9).

RC affects two to three times as many women than men (10).

RC diagnosis is exceptional before the age of 30 and most cases are diagnosed above the age of 50 years old (9).

DIAGNOSTIC APPROACH AND DIFFERENTIAL DIAGNOSES:

RC remains a diagnosis of exclusion, made on the basis of authentic CD with exclusion of other causes of non-responsive CD and malignancy.

It requires a specific diagnostic approach:

Confirming the diagnosis of celiac disease:

Patients in whom RC is suspected, diagnosis of CD should firstly be reassessed. This requirement is easy to achieve when a combination of CD-specific serologic tests, compatible histological features, family history of CD with an HLA DQ-2 or DQ-8 status, and possibly a past medical history of clinical or histological improvement after GFD is met. Nevertheless, confirming or excluding diagnosis of CD may be debating in some patients. Eventually, all patients with CD carry DQ-2 or DQ-8; the role of HLA status in assessing CD lies in their high negative predictive value. Positive tissue transglutaminase (tTGA) or endomysial antibodies (EMA) at any time in clinical course of the disease helps confirm the diagnosis of CD because of their excellent specificities >99% when villous atrophy is present (11).

Assessing the gluten-free diet:

The second step requires reassessing the observance of gluten-free diet since it is the first cause of missing response. Non-observance of GFD has been reported in up to 50% of cases. In fact, complete avoidance of gluten is almost an impossible task since gluten is present in many food products as an additive or contaminant. Persisting circulating specific CD-antibodies is strongly suggestive of poor compliance to GFD. However, in rare patients with RC, remaining antibody titers may be found despite strict adherence to GFD (12). In all cases, seeking for voluntary or inadvertent gluten contamination by a skilled dietician is required for this purpose.

Search for other causes of "non-responsive CD":

RC is a diagnosis of exclusion: ruling out other causes of diarrhea and/or villous atrophy is required before taking diagnosis of RC as certain. Microscopic colitis, pancreatic insufficiency, small intestine bacterial overgrowth, irritable bowel disease, fructose/lactose intolerance should be thought of in case of non-responsive CD. Crohn's disease with involvement of the duodenum may exceptionally mimic CD and both diseases may meet in one patient (13).

Cases of villous atrophy have been reported to be associated with some autoimmune disorders like: thymoma, protein intolerance with common variable immunodeficiency syndromes and eosinophylic enteritis (14).

Exclusion of malignancy:

Impairment of general condition such as increasing weight loss, fever, night diaphoresis, anorexia should be alarming as it is usually suggestive of underlying complications mainly malignancies such as EATL and small bowel adenocarcinoma or ulcerative jejunitis especially when gastrointestinal bleeding occurs. Suspicion of these complications should lead to further investigations:

Digestive endoscopy, CT-scan of abdomen with enteroclysis,

video-capsule enteroscopy or double balloon enteroscopy so as to obtain histological evidence of malignancy. In some cases, laparotomy with intra-operative biopsy is necessary.

The diagnosis of overt T-cell lymphoma is made on the basis of histological and immuno-histochemical findings with mainly evidence of T-cell proliferation expressing a CD3+ CD8+/- and CD103+ phenotype. The majority presents as CD3+, CD8-, CD30+ large cell lymphoma, however small cell lymphomas often are CD3C, CD8C, CD30K (15).

4-MANAGEMENT OF REFRACTORY COELIAC DISEASE:

Evidence for treatment of RCD is based on case reports, open-label observational or prospective experiences, and expert opinion. There are no randomized controlled trials probably because of the rarity of this entity.

Nutritional support:

This supportive therapy should be the first one to institute; it has to include trace element supplement like copper, zinc, Mg2+ as it has been reported that in rare patients oligopeptide diet reduces cytokine synthesis of the mucosal immune system and improve clinical and morphological anomalies (16). Oral zinc sulphate supplementation in three patients with non-reponsive celiac disease, has been shown to increase the activity of certain of brush border disaccharidases. This was explained by a probable direct stabilization of the brush border membrane. ***(Grade A. level of evidence II-3)***

Addressing metabolic bone disease, one of the main target of nutritional therapy, passes through vitamin D and calcium supplement and in single patients, intravenous therapy with bisphosphonate supplement had good impact (17). ***(Grade A. level of evidence II-3)***

Parenteral nutrition has to be considered particularly in celiacs who do not respond to maximal medical treatment. Despite the fact that in RC, benefit of GFD is still doubtful, the latter remains widely recommended as it is thought to reduce overall morbidity and mortality in CD (18). ***(Grade A. level of evidence II-3)***

4-2 Corticosteroid therapy:

Although small bowel morphology does not improve significantly in some cases, corticosteroids had been reported to induce clinical remission (19). Data about its long-term tolerability and safety in RC are lacking; however, overall, no significant side effects have been reported.

Alfred J et al.(20) had reported histological, ultrastructural and enzymic recovery in 5 patients with RC who had been put on prednisolone for four to five weeks before gradual withdrawal. Incomplete metabolic response had been shown in three out of four patients tested. Relapse had occurred in one patient after steroid withdrawal.

Another steroid, Fluticasone Propionate administered orally, had been tested for six weeks in twelve patients suffering from RC (21). According to HC Mitchison and al. Ten of eleven patients (one was lost to follow-up) had achieved clinical improvement with a mean weight gain of two kilograms as well as histological recovery. Overall no appreciable steroid side-effects have been reported in both studies.

It has been thought steroids do not reduce the risk of EATL and could even disguise the symptoms and delay the diagnosis of enteric lymphoma (22) so as to response to corticosteroid treatment does not exclude underlying EATL, which has already been shown in single case (23)·

Following the pattern of chronic inflammatory bowel disease, the starting dose is usually 1mg/kg/day. It may be administrated parenterally in severe cases then relayed by oral route. Steroid-dependence remains one of the most limiting factors towards the long-term use of corticosteroids (24). Topically acting corticosteroids like budesonide could be a good alternative thanks to its systemic side events- sparing effect. The latter treatment had been administered in twenty-nine patients with RC for a mean period of six months and a half. Brar P et al. (25) had reported clinical response in 76% of the patients. Among them, 55% had complete response. There was no improvement in the duodenal biopsy over the study period and there were no side effects of budesonide. ***(grade B. level of evidence III)***

4-3 Immunosuppressive therapy:

Other immunosuppressive drugs or biological modifiers have been used with some clinical benefit in steroid-dependent or steroid-refractory patients including azathioprine, cyclosporin, infliximab (5 mg/kg/day), and alemtuzumab (30 mg twice a week per 12 weeks).

Azathioprine (2mg/kg/day) in combination with prednisone (1mg/kg/day) is thought to be effective in inducing clinical remission and mucosal improvement in most cases of RC type 1 (7). According to the data of Goerres et al (26), azathioprine should be first line therapy after induction of clinical remission with corticosteroids. This has been asserted after one year of combined therapy based on prednisone and azathioprine administered to nineteen patients in all of whom clinical improvement has been achieved, however histological recovery has been noticed in only 8/10 RC type 1 patients. EATL was developed in 6/8 patients with RC type 2 .In another study, Maurino et al. had tried azathioprine monotherapy in seven patients with refractory coeliac disease. Five of whom had achieved clinical improvement and three died from leukopenic fever. However there is yet no standardization with regard to the dose and duration of treatment with azathioprine.

As mentioned above, special concern should be given to existing risk of lymphomagenesis when using immunosuppressive therapy especially in RC type2, because of the higher risk of EATL development in this subgroup; it has been recommended to reserve it in patients without aberrant T-cells.

Cyclosporin is a cyclic polypeptide with a strong immunosuppressive potential aimed at T lymphocyte proliferation and production as well as release lymphokines. Extensive experience with cyclosporin has been reported in transplantation medicine, graft versus host disease, since the immune reactions and morphological changes in the mucosa during RC have been described to show parallels to graft versus host disease, cyclosporin have been undertaken in RC as immune-modulating agent despite its long-list side effects.

P.J Wahab et al. (27) had reported clinical and histological

response in eight patients from thirteen bearing RC who had benefit from cyclosporin monotherapy for a mean period of seven months(2-12months). No serious side-effects had been noticed during the study period.

On the basis of case-reports, Infliximab (IFX) has also been reported to be effective in RC, as it may induce prompt clinical and histological response (28). IFX is a chimeric antibody that neutralizes circulating and membrane bound TNF. Moreover, a dose-dependent

apoptosis-inducing effect on peripheral blood monocytes from healthy volunteers and patients with Crohn's disease by activation of caspase independently from Fas has been shown .Gillett et *al*. presented the case of a 47-year-old woman with RC resistant to steroids, who responded well to treatment with anti-TNF (28) and so did G. Costantino et *al*. with a case of patient classified as having type1 refractory celiac disease treated initially with a single infusion of infliximab and after 6 months with continuous administrations over 2 years, reversing progressively the small intestinal mucosa to near normal (29). However, further data are required in such indications especially under the light of severe side effect (opportunistic infections, EATL development) mainly in patients with severe malnutrition and previous immunosuppressive therapies. ***(Grade D. level of evidence III)***

4-4 Others :

Cladribine (2-chlorodeoxyadenosine) is a synthetic purine nucleoside homologue being equally toxic to proliferating as to non-dividing lymphoid cells. Because of this unique feature it is supposed to be especially active against low-grade malignancies. Greetje J Tack et *al*. evaluated cladribine therapy in a large prospectively studied open-label cohort of 32 RC type 2 patients, during a mean follow-up time of 3 years. The overall 3- and 5-year survival was 83% in the responder and 63% and 22% in the non-responder group, respectively. The overall 2-year clinical, histological and immunological response rates were 81%, 47% and 41%, respectively. Progression into EATL was reported in 16% (30).

It has also been reported cladribine (0.1 mg/kg/day for 5 days) administrated intravenously, was safe in an open-label study in patients with RC type 2 previously treated with prednisone and/or azathioprine and can induce significant decrease in the number of clonal intraepithelial lymphocytes (35%) (31). ***(Grade D. level of evidence III).***

The overexpression of IL-15, observed in RC type 2, seems to have a major role in the proliferation and the cytoxicity of the aberrant IEL population. That is why for future studies, interleukin-15 may represent a hopeful option for RCD type 2 thanks to its key role to disrupt lymphomagenesis (32).

Eventually, Autologous hematopoietic stem cell transplantation (ASCT) is an

increasingly accepted effective treatment option for patients with severe autoimmune diseases refractory to conventional treatment. The rationale for this strategy is based on the concept of immunoablation by intense immunosuppression using high-dose chemotherapy, with subsequent regeneration of naıve T lymphocytes derived from reinfused hematopoietic progenitor cells. In one pilot study, Al Toma et *al*. reported high-dose chemotherapy followed by ASCT seems feasible and safe and might result in long-term improvement of patients with RC type 2 whose condition did not respond promptly to available drugs. The role of surgery in RC is restricted to the management of complications such as perforation, massive hemorrhage or obstruction and cancer. Its long-term benefit in ulcerative jejunitis after complete resection has been reported in some cases. ***(Grade D. level of evidence III).***

Intra-operative biopsies are less and less considered thanks to the introduction of new endoscopic modalities.

Overall, yet no therapy seems to be curative in RC type 2. Multicentre, randomised clinical trials with other new treatment options are mandatory to standardise the treatment strategy for RC type 2, in order to further decrease morbidity and mortality in this patient group.

CONCLUSION

Refractory celiac disease remains a diagnosis of exclusion: before making the latter diagnosis, a long list of concomitant or differential diagnoses has to be excluded. Immunohistochemical tests are of a great concern for determining abnormal phenotype found in intraepithelial lymphocytes in the majority of refractory celiac patients, that is associated with a heightened risk of EATL. Prognosis remains still dismal by the absence yet of curative therapies, despite the fact some new treatments seem to hold promise during few cohort-studies. Only multicenter randomized controlled trials could provide relevant data with regard to management of this disease.

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