

# Deciphering the Different Types of Refractory Celiac Disease

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Fifteen years ago has emerged the concept of refractory celiac disease (RCD). [1,2] RCD is defined by persisting malabsorption and villous atrophy after one year of strict GFD ascertained by a dietician. RCD has been subdivided into two subgroups according to the normal (type I RCD (RCDI)) or abnormal phenotype of intraepithelial lymphocytes (IEL) (type II RCD (RCDII)). RCDI is indistinguishable from active CD and is characterized by a polyclonal repertoire. Survival of patients with RCDI is slightly inferior to that of those with celiac disease. [3,4] In contrast, RCDII is a severe enteropathy with frequent intractable ulcerative duodeno-jejunitis. RCDII is characterized by a clonal repertoire and is considered as a low-grade intraepithelial lymphoma. [1,2] The five year survival rate of patients with RCDII is around 50%. This poor prognosis is due to severe malnutrition and increased risk of overt lymphoma.

One of the current challenges in RCD is to ascertain the type of RCD. Indeed, diagnosis of RCD has become highly specialized. It requires small bowel endoscopic specialized investigations such as capsule endoscopy and double balloon endoscopy. [5,6] Intestinal biopsy needs to be studied by different complementary techniques such as immunohistochemistry, flow cytometry, and Multiplex PCR, all necessary to ascertain the precise diagnosis. Recent studies have reported case series of chronic intestinal diseases mimicking the both types of RCD. RCDI needs to be distinguished from other causes of non clonal villous atrophy such as enteropathy associated with common variable immunodeficiency (CVID). [7] Demonstration of HLA haplotypes encoding HLA-DQ2 or DQ8 can be useful as their absence excludes CD or RCD as a cause of villous atrophy. [8] Nevertheless, genotypes HLA-DQ2/DQ8 are also found in 77% of CVID patients with enteropathy mimicking CD defined by intestinal intra-epithelial lymphocytosis. [7] So evidence of serum hypogammaglobulinemia and histopathological features such as intestinal plasmocytic rarefaction or nodular lymphoid hyperplasia appear essential to distinct CVID enteropathy from RCDI. [7] RCDII needs to be distinguished from other cases of clonal enteropathy with villous atrophy. Flow cytometry allows to tell the difference between RCDII and other intestinal clonal malignancies with villous atrophy. Indeed, demonstration of excess of CD4+IEL with a specific Vbeta repertoire is essential for diagnosis of intestinal CD4 lymphoproliferations. [9] Diagnosis may be particularly tricky when CD4 lymphoproliferation [9] or large granular lymphocytic leukemia (LGL) [10] complicate an authentic

CD. Consequently, spectrum of RCD has been recently substantially extended. Advances in accuracy of diagnostic tools could reduce the number of undiagnosed RCD and increase the frequency of RCD currently estimated to 1 to 2% of CD patients. [11,12] Besides epidemiological interest, improvement of diagnostic tools allowed precise diagnosis of RCD type and appropriate treatment. By example, distinction between RCDII and CD complicated by LGL is crucial as cyclosporin, inefficient in RCDII, is in contrast very useful for treating LGL. Indeed, treatment of RCD remains another challenge particularly in case of RCDII patients who have poor prognosis and for whom referral treatment does not yet exist. Immunosuppressors are poorly efficient and may possibly trigger overt lymphoma. [13] Purine analogues such pentostatine or cladribine (2 CDA) have been largely used in the past with slight therapeutic effect. [4,14,15] Autologous haematopoietic stem cells transplantation represents an interesting alternative but when combined to chemotherapy for hopping sustained reduction of abnormal IEL. [16,17] We are currently evaluating this strategy in a prospective phase II trial. Many advances in the understanding of the pathogenesis of RCDII were made by deciphering the anti-apoptotic signaling pathway of the cytokine IL-15 which prevents the elimination of IEL in CD and RCDII. [18] The IL-15 induced anti-apoptotic signaling pathway includes activation of IL-15R $\beta\gamma$ , Jak3, STAT5 and Bcl-xL [19] which represent so many therapeutic targets. Blocking the effect of IL-15 appears of a particular interest in RCDII but may probably be useful in other types of RCD with possible involvement of IL-15 such as RCDI or LGL-complicated CD. [20] Continuing the characterization of the different forms of RCD will probably guide next pathogenic studies and permit to increase our therapeutic efficacy in the future.

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