Therapy in RCDII: Rationale for Combination Strategies?

Petula Nijeboer a Georgia Malamut c Gerd Bouma a Nadine Cerf-Bensussan d Frits Koning b Jeroen van Bergen b Christophe Cellier c Chris J.J. Mulder a

a Department of Gastroenterology, VU University Medical Centre, Amsterdam, and b Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, The Netherlands; c Department of Gastroenterology, and d Inserm U989, Université Paris Descartes, Hôpital Européen Georges Pompidou, Paris, France

Key Words
Refractory coeliac disease type II · Coeliac disease · Enteropathy-associated T-cell lymphoma · Tofacitinib

Abstract
Refractory coeliac disease type II (RCDII) is characterized by a continuous gluten-independent duodenal immune activation with an extremely high risk of malignant transformation. It is therefore considered as an indolent lymphoma. RCDII is characterized by the presence of villous atrophy (Marsh III A-C) in combination with an aberrant intraepithelial lymphocyte (IEL) population consisting of >20% sCD3–CD7+ICD3+ IELs. The sCD3–CD7+ICD3+ IELs are a heterogeneous lineage-negative cell population, consisting of cells that do or do not express CD127/IL7Ra. Experiments using IEL from non-RCDII patients have indicated that while the CD127– cells are IL-15 responsive, the CD127+ cells are not. Together with the observation that some patients express an aberrant (monoclonal) TCRγδ phenotype, this confirms the heterogeneity of the aberrant IEL population in RCDII and suggests that the aberrant cells are heterogeneous with respect to their response to common γ-chain cytokines. Although cladribine with or without autologous stem cell transplantation is effective in the treatment of signs and symptoms of RCDII and improves survival as compared to symptomatic topical steroid therapy, cladribine failures still bear a high risk of malignant transformation, and the rate of enteropathy-associated T-cell lymphoma (EATL) development in this subgroup is extremely high. It might be hypothesized that the heterogenous nature of aberrant IEL and the high risk of malignant transformation require a treatment strategy which is effective despite this heterogeneity. RCDII should be seen more in the light of a low-grade/no mass lymphoma or pre-EATL. We would suggest an upfront combination therapy approach integrating inhibition of downstream Jak-STAT signalling pathways with conventional therapy (2-CDA) to hopefully effectively treat signs and symptoms of RCDII and accomplish a more effective EATL prevention.

Introduction
A small subset of coeliac disease (CD) patients experiences persisting or recurring symptoms despite strict adherence to a gluten-free diet. When other causes of villous atrophy have been excluded, these patients are referred to as refractory coeliac disease (RCD). RCD can be divided
Cytokine Responsiveness in RCDII

It has been described that the presence of IL-15 in RCDII is likely to contribute to the expansion and survival of aberrant IEL [11]. Massive overproduction by enterocytes of IL-15 leads to continuous activation of IELs. Indeed there is evidence that this cytokine is upregulated in patients with RCD II [12]. RCDII IELs activated by enterocyte-derived IL-15 might exert cytotoxicity against epithelial cells through NKG2D and DNAM-1 ligands [8, 11], and be responsible for the severe enteropathy observed in RCDII patients. Finally, the strong anti-apoptotic effect of IL-15 might explain the accumulation and expansion of these cells despite their low in situ proliferative capacity [13]. Besides IL-15, other common γ-cytokines might play a role in the pathogenesis of RCDII as well. It can be hypothesized that the presence of different cytokine subsets in the local intestinal milieu lead to continuous IEL activation and defective apoptotic control through binding to the heterogeneous receptor subsets expressed on aberrant IELs as described above [8]. In a next step towards lymphomagenesis, a subset of IEL undergo clonal expansion and finally when chromosomal aberrations have occurred these cells transform towards a lymphoma.

Current Treatment Strategies

Unfortunately, to date there is no standardized globally accepted treatment approach for RCDII. RCDII has been resistant, at least in part, to most evaluated therapies so far. As RCDII patients often have a chronic form of malnutrition, presenting with a low BMI (<18.5) [6], the primary treatment step should be correction of nutritional deficiencies and metabolic disorders. There is no place for classic immunosuppressive drugs, such as thiopurines, in the treatment of RCDII. Although they might exert clinical effects, corticosteroids have no influence on the onset of EATL and especially do not exclude underlying EATL [14]. In a recent study, of 16 RCDII patients...
who developed EATL, 10 had received immunosuppressants [5]. Moreover, azathiopurine might enhance the risk or accelerate the onset of EATL [5, 15, 16]. Furthermore, combination therapy of azathioprine and prednisone in RCDII patients showed development of EATL in 7 of the 8 treated patients [16]. Based on these discouraging results, cladribine (2-CDA), a synthetic purine nucleoside homologue, has been initiated and shown to be feasible and safe for RCDII [17, 18]. 2-CDA is supposed to be especially active against low-grade CD103+ malignancies, which is one of the characteristics of the aberrant lineage-negative sCD3–CD7+iCD3+ cells. Nevertheless, 2-CDA does not prevent EATL development in all treated patients [18], and some patients died within months of RCDII diagnosis due to progressive refractory disease.

In patients with RCDII refractory to conventional 2-CDA treatment, autologous hematopoietic stem cell transplantation (auSCT) is an increasingly accepted effective treatment option. auSCT appears to be feasible and safe, and might result in clinical remission in 2-CDA failures [19, 20]. Whether the benefits from the addition of auSCT outweigh the costs and the risks of this aggressive treatment strategy needs to be substantiated in a larger cohort with longer follow-up. Furthermore, only a selected RCDII population is able to receive this aggressive treatment strategy. Recent evaluation of factors associated with EATL development in RCDII patients treated with 2-CDA revealed that histological response determines EATL development; when histological remission is achieved after 2-CDA, the frequency of EATL development is low and survival is comparable with the patients treated with 2-CDA-auSCT combination therapy. Although 2-CDA with or without autologous stem cell transplantation are both effective in the treatment of signs and symptoms of RCDII and improve survival as compared to symptomatic topical steroid therapy, 2-CDA failures who are non-eligible for auSCT still bear a high risk of malignant transformation and the rate of EATL development in this subgroup is extremely high (data from P.N.).

In conclusion, RCDII should be seen more in the light of an indolent lymphoma (pre-EATL) and therefore upfront treatment strategies consisting of combination therapy with conventional 2-CDA and a downstream signalling blocker might be required for the initial treatment of RCDII.

Future Perspectives

This underlines the need for new, advanced treatment strategies. It might be hypothesized that a small percentage, of phenotypical ‘atypical’ aberrant IELs might be 2-CDA resistant in some patients and that those IELs undergo continuous IEL activation resulting in persistent enteropathy and evolve into EATL over time. Therefore, we state that the heterogeneous nature of aberrant IELs as described above, and the high risk of malignant transformation, requires a treatment strategy which is effective despite this heterogeneity. As described, both lineage-negative CD127– and lineage-negative CD127+ IELs are frequently expanded in RCDII. As the IL-15 receptor B chain is expressed by the former, and the IL-7 receptor, IL-21 receptor and IL-15 receptor α-chain is expressed by the latter, treatment with anti-IL-15 is unlikely to be sufficient. Therefore, an inhibitor of common downstream signalling molecules of the different receptors expressed by aberrant IELs might be required. Considering the fact that increased Jak3 and STAT5 phosphorylation has been demonstrated in aberrant IELs [11], and these are downstream molecules of the common γ-chain receptors identified in RCDII, Jak3 or STAT5 inhibitors could serve as a potential target therapy. Tofacitinib is a Jak3 inhibitor which blocks signalling through these γ-chain receptors for several cytokines, including IL-2, -4, -7, -9, -15 and -21, and is now safely applied in rheumatoid arthritis [21, 22]. Inhibition of their signalling may thus result in modulation of the continued immune activation and the anti-apoptotic effects seen in RCDII. We expect combination therapy approaches integrating inhibition of Jak-STAT pathways with conventional therapy (2-CDA) might effectively treat signs and symptoms of RCDII and could result in a more effective EATL prevention.

References


Wierdama N. Refractory coeliac disease and EATL patients are characterised by malnutrition and malabsorption at presentation; a comparative study with newly diagnosed coeliac disease patients (abstract). Digestive Disease Week, Chicago, 2014.


