Bibliographic reference (Ref ID)	Al-tp,a et al (2006)
Study characteristics	**Study design:** case series **Prospective/retrospective:** Prospective **Consecutive patients:** unclear **Country:** Netherlands
Patient characteristics	**Recruitment period:** 2000 to 2005 **Inclusion criteria:** patients with RCDII referred to one of 2 tertiary referral centres for treatment and with aberrant T cells of 25% or more

	of intraepithelial lymphocytes **Definition of RCD:** RCDII defined as clinical relapse or persisting malabsorpotion after at least a year of strict adherence to GFD, histopathology showing at least partial villous atrophy (Marsh IIIA, B, C or ulcerative jejunitis) after excluding other causes of villous atrophy, and at least 25% or more of IELs showing aberrant T-cells on T-cell flow-cytometry. **Exclusion criteria:** Presence of enteropathy-associated T-cell lymphoma determined radiologically (small-bowel follow-through, CT scan of the thorax and abdomen; plus whole body PET scan), endoscopically (upper GI endoscopy, VCE, and/or DBE), as well as with bone marrow aspirates; history of malignant disease; serious cardiovascular disease, renal disease or active infection; abnormalities found on imaging, endoscopy, histology, and/or bone marrow examination suggestive of malignant lymphoma; haemoglobin level less than 5.0 mmmol/L, leukocyte count less than 4000 per mm3, platelet count less than 100 000 per mm3; pregnancy or women breastfeeding; serum hepatitus C virus positive, serum hepatitus B surface antigen positive, serum anti-human immunodeficiency virus positive; cyclosporin therapy in last 6 months; experimental drug within 30 days of study entry **Length of time on a gluten-free diet:** at least 1 year **Description of gluten-free diet (and how adherence was monitored):** not described **RCD type:** II **Number of patients included:** 17 **Concomitant conditions:** not reported **Comments:** all had WHO performance status of 0-1; most patients had prednisone for months before inclusion but this was stopped before treatment with 2-CDA
Treatment	**Details:** other immunomodulatory drugs not permitted **Arm No:** 1 **Name:** cladribine (2-CDA) **N:** 17 **Pharmacological agent:** cladribine agent 1: administration: intravenous agent 1: dosage (intravenous): 0.1 Comments: patients were hospitalised before 2-CDA was given intravenously (0.1 mg/kg) - this occurred for 2 hours daily for 5 days; cotrimoxazole 960 mg (gluten-free suspension) was given orally 2 times daily and for 2 days a week at week) until 6 months after 2-CDA therapy (prophylaxis against Pneumocystis carinii pneumonia); some patients had supplemental folic acid, vitamin B12 and/or iron if indicated; those who had clinical, histologic, and/or immunologic response received an additional second course (6 patients) or a third course (7 patients)
Other	**Source of funding:** not reported

	Authors' conflicts of interest: not reported **Additional comments:** EATL diagnosis was established with WHO Classification of Tumour of Haematopoietic and Lymphoid Tissues with large- or medium-size T-cell proliferation expression CD3+, CD8(+/-), CD103+ (all those who developed EATL had CD3+, CD8-, CD30+ large-cell lymphoma)
Notes on outcomes	**Clinical response –** defined as disappearance of diarrhoea, improvement in performance status according to WHO scale or at least 2 of the following: increase of BMI >1 point, increase albumin 10% or more from baseline, or increase in haemoglobin >1 point **serological response:** Proportion of IELs per100 epithelial cells (%) - decrease of 20% or more was considered significant

Baseline characteristics

		All study participants		
		N	**k**	**mean**
Patient characteristics:				
Age	Continuous	17		60.88 [rng 46–76][a]
Sex (n female)	Dichotomous	17	9	(52.9%)
HLA-DQ status - DQ2 homozygous	Dichotomous	17	7	(41.2%)
HLA-DQ status - DQ2 hetergozygous	Dichotomous	17	10	(58.8%)
TCDy-PCR - monoclonal	Dichotomous	17	17	(100.0%)
TCRy-PCR - polyclonal	Dichotomous	17	0	(0.0%)

a age at diagnosis of RCD

Results

		cladribine (2-CDA)		
		N	**k**	**mean**
Clinical response:				
body mass index (kg/m2) – 0d	Continuous	17		20.6 (SD 2.12)
body mass index (kg/m2) – 48d	Continuous	17		21.2 (SD 3.14)[a]
proportion achieved – 88d	Dichotomous	17	6	(35.3%)
serological response:				
mean haemoglobin (mmol/L) – 0d	Continuous	17		7.65 (SD 1.35)

	mean haemoglobin (mmol/L) – 48d	Continuous	17		7.69 (SD 1.29)*a*
	mean corpuscular volume (FL) – 0d	Continuous	17		85 (SD 6.3)
	mean corpuscular volume (FL) – 48d	Continuous	17		92 (SD 6.9)*a*
	leukocytes (x 10 exp 9 per L) – 0d	Continuous	17		7.27 (SD 1.85)
	leukocytes (x 10 exp 9 per L) – 48d	Continuous	17		7.07 (SD 1.48)*a*
	neutrophils (%) – 0d	Continuous	17		56 (SD 12)
	neutrophils (%) – 48d	Continuous	17		60 (SD 13)*a*
	lymphocytes (%) – 0d	Continuous	17		19.5 (SD 10.2)
	lymphocytes (%) – 48d	Continuous	17		21.7 (SD 7.68)*a*
	monocytes (%) – 0d	Continuous	17		7.9 (SD 5.8)
	monocytes (%) – 48d	Continuous	17		8.2 (SD 6)*a*
	platelets (x 10 exp 9 per L) – 0d	Continuous	17		334 (SD 94.9)
	platelets (x 10 exp 9 per L) – 48d	Continuous	17		296 (SD 89.5)*a*
	mean albumin level (g/L) – 0d	Continuous	17		30 (SD 7.2)
	mean albumin level (g/L) – 48d	Continuous	17		33.7 (SD 7.49)*a*
	Proportion of IELs per100 epithelial cells (%) – 0mo	Continuous	17		72.7 (SD 23.3)
	Proportion of IELs per100 epithelial cells (%) – 22mo	Continuous	17		57.7 (SD 26.9)
	histological response:				
	disappearance of ulcerative jejunitis	Dichotomous	5	5	(100.0%)
	proportion achieved improvement – 48d	Dichotomous	17	10	(58.8%)
	no response – 48d	Dichotomous	17	5	(29.4%)
	deterioration – 48d	Dichotomous	17	2	(11.8%)
	Marsh IIIC – 0mo	Dichotomous	17	6	(35.3%)
	Marsh IIIC – 22mo	Dichotomous	17	4	(23.5%)
	Marsh IIIB – 0mo	Dichotomous	17	1	(5.9%)
	Marsh IIIB – 22mo	Dichotomous	17	3	(17.6%)
	Marsh IIIA – 0mo	Dichotomous	17	5	(29.4%)

	Marsh IIIA – 22mo	Dichotomous	17	8	(47.1%)
	Marsh II – 0mo	Dichotomous	17	0	(0.0%)
	Marsh II – 22mo	Dichotomous	17	1	(5.9%)
	Marsh I – 0mo	Dichotomous	17	0	(0.0%)
	Marsh I – 22mo	Dichotomous	17	1	(5.9%)
	presence of ulcerative jejunitis – 0mo	Dichotomous	17	5	(29.4%)
	presence of ulcerative jejunitis – 22mo	Dichotomous	17	0	(0.0%)
	Immunological response:				
	proportion > or = 20% decrease in aberrant IELs – 48d	Dichotomous	17	6	(35.3%)
	deterioration (signficant increase in % aberrant IELs) – 48d	Dichotomous	17	2	(11.8%)
	Overall response:				
	Clinical, histologic and/or immunological response – 48d	Dichotomous	17	1[b]	(5.9%)
	adverse events:				
	nausea and vomiting – 88d	Dichotomous	17	3	(17.6%)
	diarrhoea – 88d	Dichotomous	17	1	(5.9%)
	bronchitis – 88d	Dichotomous	17	1	(5.9%)
	lymphopenia – 88d	Dichotomous	17	0	(0.0%)
	monocytopenia – 88d	Dichotomous	17	0	(0.0%)
	anaemia requiring transfusion – 88d	Dichotomous	17	0	(0.0%)
	survival/overall mortality:				
	overall mortality – 56d	Dichotomous	17	7[c]	(41.2%)
	overall mortality – 88d	Dichotomous	17	2[d]	(11.8%)
	a uncertain of denominator included in this outcome *b patient considered to have complete remission* *c developed EATL at start of treatment and subsequently died (mean 14 months)* *d 1 from bronchiectasis from persistent postnasal discharge in association with EATL localisation in paranasal sinuses and another from progressive refractory emanciation*				
	period is mean follow-up of 22 months (range 7 to 67 months)				

Bibliographic reference (Ref ID)	Al-Toma,A. et al. (2007)
Study characteristics	**Study design:** case series **Prospective/retrospective:** Retrospective **Consecutive patients:** unclear **Country:** Netherlands
Patient characteristics	**Recruitment period:** records from 1992 to 2005 **Inclusion criteria:** patients with complicated forms of coeliac disease at tertiary referral centre for coeliac disease **Definition of RCD:** persisting villous atrophy with crypt hyperplasia and increased IELs in spite of a GFD for more than 12 months or when severe symptoms necessitate intervention independent of the duration of the diet (RCD II - aberrant IEL population) **Exclusion criteria:** patients treated with cyclosporin or interleukin-10 **Length of time on a gluten-free diet:** more than 12 months (or severe symptoms) **Description of gluten-free diet (and how adherence was monitored):** not described; adherence to diet was checked by a dietician (in addition to clinical assessment, all patients with positivity for EMA and/or anti-tTG at time of diagnosis of CD were negative after GFD confirming strict adherence) **RCD type:** I and II (reported separately) **Number of patients included:** 93 **Concomitant conditions:** not reported **Comments:** it is possible that some patients reported in this study were also reported in Goerres 2003 (those treated between 1992 and 1998 may be included in both studies); study also included patients with primary and secondary EATL but results with these patients were not extracted; EATL was excluded in RCD patients using radiological and endoscopic methods (small bowel follow-through, CT scanning, whole-body PET, upper gastrointestinal endoscopy, VCE and/or DBE) as well as trephine bone-marrow biopsies (pre-2003: small bowel follow-through or CT scans but post-2003 also have negative PET, VCE and/or DBE); details about reason for allocation to different treatment groups not reported so unclear if groups were similar
Treatment	**Arm No:** 1 **Name:** Patients with any combination of treatments **N:** 93 **Pharmacological agent:** prednisone alone, prednisone+azathioprine,or clad

	agent 1: administration: oral Comments: includes 6 patients treated with ASCT only and 9 with partial small-intestine resection only **Arm No:** 2 **Name:** Prednisone **N:** 47 **Pharmacological agent:** prednisone agent 1: administration: oral Comments: 40 mg/d for 6 weeks then tapered to 10 mg/d over 6 weeks and, then tapered to 2.5-0 mg/d after 3 months, depending on response **Arm No:** 3 **Name:** Azathioprine + prednisone **N:** 46 **Pharmacological agent:** azathioprine+prednisone agent 1: administration: oral agent 2: administration (if different): oral Comments: prednisone - 40 mg/d for 6 weeks then tapered to 10 mg/d over 6 weeks and, then tapered to 2.5-0 mg/d after 3 months, depending on response; azathioprine at 2 mg/kg/d for 52 or more weeks **Arm No:** 4 **Name:** Azathioprine and prednisone, followed by cladribine **N:** 23 **Pharmacological agent:** azathioprine+prednisone followed by cladribine agent 1: administration: oral agent 2: administration (if different): oral agent 3: administration (if different): intravenous Comments: prednisone - 40 mg/d for 6 weeks then tapered to 10 mg/d over 6 weeks and, then tapered to 2.5-0 mg/d after 3 months, depending on response; azathioprine at 2 mg/kg/d for 52 or more weeks; cladribine - 0.1 mg/kg/d for 5 days, in 1-3 courses every 6 months, depending on response
Other	**Source of funding:** not reported **Authors' conflicts of interest:** none reported
Notes on	**n/a**

outcomes					
Baseline characteristics			**All study participants**		
			N	**k**	**mean**
	Patient characteristics:				
	Sex (n female)	Dichotomous	93	62	(66.7%)
	RCD type 1				
	Patient characteristics:				
	Age	Continuous	43		49 (SD 14)[a]
	Sex (n female)	Dichotomous	43	31	(72.1%)
	HLA-DQ status - DQ2 homozygous	Dichotomous	34	11	(32.4%)
	HLA-DQ status - DQ2 hetergozygous	Dichotomous	34	23	(67.6%)
	Proportion of IELs per100 epithelial cells (%)	Continuous	43		60 (SD 25.9)[b]
	Proportion of IELs per100 epithelial cells (%)	Continuous	50		3 (SD 1.9)*b*
	presence of ulcerative jejunitis	Dichotomous	43	0	(0.0%)
	RCD type 2				
	Patient characteristics:				
	Age	Continuous	50		59 (SD 9.5)[c]
	Sex (n female)	Dichotomous	50	31	(62.0%)
	HLA-DQ status - DQ2 homozygous	Dichotomous	46	23	(50.0%)
	HLA-DQ status - DQ2 hetergozygous	Dichotomous	46	23	(50.0%)
	a *age at diagnosis of RCD (mean 47 at diagnosis of CD)*				
	b *this does not appear to have been measured again after treatment*				
	c *age at diagnosis of RCD (mean 50 at diagnosis of CD)*				
			Azathioprine and prednisone, followed by cladribine		
			N	**k**	**mean**

	RCD type 2				
	Patient characteristics:				
	presence of ulcerative jejunitis	Dichotomous	23	5[a]	(21.7%)
	a all patients treated with cladribine had RCDII				
Results			**Patients with any combination of treatments**		
			N	**k**	**mean**
	RCD type 1				
	survival/overall mortality:				
	5-year survival (Kaplan-Meier)	Time-to-event	43		(SD 58)
	overall mortality	Dichotomous	43	3[a]	(7.0%)
	RCD type 2				
	survival/overall mortality:				
	5-year survival (Kaplan-Meier)	Time-to-event	50		96
	overall mortality	Dichotomous	50	28[b]	(56.0%)
	a due to unrelated causes: COPD, alcoholic cirrhosis, lung carcinoma *b 23 due to EATL, 4 refractory state and emaciation, 1 neurocoeliac (unclear which treatment they had except neurocoeliac was due to ASCT)*				
				Prednisone	
				N **k**	**mean**
	survival/overall mortality:				
	5-year survival (Kaplan-Meier)	Time-to-event		47	25%
				Azathioprine + prednisone	

			N	**k**	**mean**
	survival/overall mortality: 5-year survival (Kaplan-Meier)	Time-to-event	46		36%

			Azathioprine and prednisone, followed by cladribine		
			N	**k**	**mean**
	survival/overall mortality: 5-year survival (Kaplan-Meier)	Time-to-event	23		22%

	baseline characteristics for RCDII include 5 patients who were treated with autologous stem-cell transplantation; patients were followed-up for a mean period of 5 years (range 2 - 14) to determin transition to a more severe state (ie. to RCDII or EATL) Mean follow up was 72 montns range 24-240) for RCDI and 44 months (range 8-146) for RCDII

Definitions of abbreviations are given at the end of this document.

Bibliographic reference (Ref ID)	**Brar,P. et al. (2007)**
Study characteristics	**Study design:** case series **Prospective/retrospective:** Retrospective **Consecutive patients:** No **Country:** USA
Patient characteristics	**Recruitment period:** Jan 2000 to April 2005 **Inclusion criteria:** patients with coeliac disease in the university-based coeliac centre's database who were compliant but responding poorly to a GFD **Definition of RCD:** RCD type I and II definitions based on the PCR analysis for T-cell receptor gene rearrangemnet: type I showed polyclonal product and type II clonal

	Exclusion criteria: patients not compliant to GFD, bacterial overgrowth (ova and parasites detected from stool specimens, and breath tests), autoimmune enteropathy (in the presence of antijejunal antibodies) **Length of time on a gluten-free diet:** variable times (see comments) **Description of gluten-free diet (and how adherence was monitored):** Not stated; compliance was assessed by an experienced dietician. Some patients had positive EMA and/or tTG despite strict adherence for less than 12 months but all tests became negative during the study period. All patients had persistent villous atrophy and intrepithelial lymphocytosis despite the diet. **RCD type:** I and II (reported together) **Number of patients included:** 29 **Concomitant conditions:** 7 had microscopic colitis (4 responded to treatment), 6 had lymphocytic colitis and 1 had collagenous colitis (the last had moderate response to therapy) **Comments:** 1 patient was excluded from the study because they were lost to follow-up; 24 were on a GFD for at least 6 months and 5 for less than 3 months (each of these 5 required hospitalisation because of serious disease manifestations); all patients except 5 had coeliac for at least 6 months (range 1-249); patients treated with budesonide also received azathioprine or prednisone (or both) if they had more severe symptoms so groups are not comparable
Treatment	**Details:** Patients received pancreatic supplements, bismuth, and antibiotics prior to use of steroid or immunosupressants **Arm No:** 1 **Name:** Budesonide only **N:** 15 **Pharmacological agent:** budesonide agent 1: administration: oral agent 1: dosage (oral): 9 agent 1: length of treatment (mean): 6.7 agent 1: SD of treatment length: 8.5 Comments: Using Entocort EC (controlled-release budesonide); treatment length 7 months (range 1-36 months) **Arm No:** 2 **Name:** Budesonide + prednisone **N:** 3 **Pharmacological agent:** budesonide+prednisone agent 1: administration: oral agent 1: dosage (intravenous): 9

	agent 1: length of treatment (mean): 6.7 agent 1: SD of treatment length: 8.5 agent 2: length of treatment (mean): 8.5 Comments: prednisone was given at 20 to 40 mg/day, dependent on the patient (efforts were made to taper the dosage as the patient responded) **Arm No:** 3 **Name:** azathioprine + budesonide + prednisone **N:** 7 **Pharmacological agent:** azathioprine+budesonide+prednisone agent 1: administration: oral agent 1: dosage (oral): 50 agent 1: length of treatment (mean): 9.6 agent 2: dosage (oral): 9 agent 2: length of treatment (mean): 6.7 agent 2: SD of treatment length: 8.5 agent 3: length of treatment (mean): 9.6Comments: 3 patients received 75 mg/day of azathioprine (but it was not clear which other treatments these patients were receiving); prednisone was given at 20 to 40 mg/day, dependent on the patient (efforts were made to taper the dosage as the patient responded) **Arm No:** 4 **Name:** budesonide + azathioprine **N:** 4 **Pharmacological agent:** azathioprine+budesonide agent 1: administration: oral agent 1: dosage (oral): 50 agent 1: length of treatment (mean): 9.6 agent 2: dosage (oral): 9 agent 2: length of treatment (mean): 6.7 Comments: 3 patients received 75 mg/day of azathioprine (but it was not clear which other treatments these patients were receiving) **Arm No:** 5 **Name:** Budesonide on its own or with any other treatment

	N: 29 **Pharmacological agent:** budesonide with or without other therapy
Other	**Source of funding:** study reports that there were no conflicts of interest related to financial support **Authors' conflicts of interest:** study reports that there were no potential competing interests
Notes on outcomes	**Clinical response** complete (symptom resolution and no steroids) moderate (symptom resolution and steroid reduction) poor (persistent symptoms)

Baseline characteristics

		All study participants		
		N	**k**	**mean**
Patient characteristics:				
Age	Continuous	29		56.3 (SD 15.4)
Sex (n female)	Dichotomous	29	21	(72.4%)
Duration of CD (months)	Continuous	29		60.9 (SD 71.3)
positive EMA or tTGA	Dichotomous	29	31[a]	(106.9%)
negative EMA or tTG	Dichotomous	29	69	(237.9%)
primary RCD	Dichotomous	29	55	(189.7%)
secondary RCD	Dichotomous	29	45	(155.2%)
TCDy-PCR - monoclonal	Dichotomous	29	5[b]	(17.2%)
TCRy-PCR - polyclonal	Dichotomous	29	23[c]	(79.3%)
Classical presentation (diarrhoea predominant)	Dichotomous	29	90	(310.3%)
Atypical presentation (diarrhoea absent)	Dichotomous	29	10	(34.5%)
partial villous atrophy	Dichotomous	29	69	(237.9%)
total villous atrophy	Dichotomous	29	31	(106.9%)

a *authors say these patients had strict adherence and had been on the diet for less than 12 months but that all serological tests came back negative during the period of the study*

b *defined as type II refractory disease*

c defined as type I refractory disease

Results

			Budesonide only		
			N	**k**	**mean**
Clinical response:					
complete (symptom resolution and no steroids) – 7mo	Dichotomous		15	12	(80.0%)
moderate (symptom resolution and steroid reduction) – 7mo	Dichotomous		15	0	(0.0%)
poor (persistent symptoms) – 7mo	Dichotomous		15	3	(20.0%)

		Budesonide + prednisone		
		N	**k**	**mean**
Clinical response:				
complete (symptom resolution and no steroids) – 7mo	Dichotomous	3	1	(33.3%)
moderate (symptom resolution and steroid reduction) – 7mo	Dichotomous	3	1	(33.3%)
poor (persistent symptoms) – 7mo	Dichotomous	3	1	(33.3%)

		azathioprine + budesonide + prednisone		
		N	**k**	**mean**
Clinical response:				
complete (symptom resolution and no steroids) – 7mo	Dichotomous	7	0	(0.0%)
moderate (symptom resolution and steroid reduction) – 7mo	Dichotomous	7	5	(71.4%)
poor (persistent symptoms) – 7mo	Dichotomous	7	2	(28.6%)

			budesonide + azathioprine		
			N	k	mean
Clinical response:					
complete (symptom resolution and no steroids) – 7mo		Dichotomous	4	3	(75.0%)
moderate (symptom resolution and steroid reduction) – 7mo		Dichotomous	4	0	(0.0%)
poor (persistent symptoms) – 7mo		Dichotomous	4	1	(25.0%)

		Budesonide on its own or with any other treatment		
		N	k	mean
Clinical response:				
body mass index (kg/m2) – 0mo	Continuous	29		20.8 (SD 3.9)
body mass index (kg/m2) – 7mo	Continuous	29		21.1 (SD 3.6)
complete (symptom resolution and no steroids) – 7mo	Dichotomous	29	16	(55.2%)
moderate (symptom resolution and steroid reduction) – 7mo	Dichotomous	29	6	(20.7%)
poor (persistent symptoms) – 7mo	Dichotomous	29	7	(24.1%)
Survival/overall mortality:				
overall mortality – mo	Dichotomous	29	1[a]	(3.4%)
those with complete response				
Clinical response:				
bowel movements (time period unspecified) – 0mo	Continuous	16		6.3 (SD 6.6)
bowel movements (time period unspecified) – 7mo	Continuous	16		1.2 (SD 0.6)

	those with moderate response			
	Clinical response:			
	bowel movements (time period unspecified) – 0mo	Continuous	6	6.7 (SD 6.5)
	bowel movements (time period unspecified) – 7mo	Continuous	6	1.3 (SD 0.5)
	those with poor response			
	Clinical response:			
	bowel movements (time period unspecified) – 0mo	Continuous	7	5.5 (SD 2.2)
	bowel movements (time period unspecified) – 7mo	Continuous	7	5.5 (SD 2.9)
	a from sepsis and malnutrition; unclear when patient died			
	Follow-up is average 7 months (range 1-249) - all outcomes are recorded over average follow-up (duration of budesonide use is 6.7 months, SD 8.5)			

Definitions of abbreviations are given at the end of this document.

Bibliographic reference (Ref ID)	**Cellier,C. et al. (2000)**
Study characteristics	**Study design:** case series **Prospective/retrospective:** Retrospective **Consecutive patients:** No **Country:** France
Patient characteristics	**Recruitment period:** 1974 to 1998 **Inclusion criteria:** adults patient with severe symptomatic villous atrophy mimicking coeliac disease but refractory to a strict GFD of at least 6 months (termed 'refractory sprue' defined with Trier's criteria) with no initial evidence of overt lymphoma and were diagnosed at gastrointestinal referral centres between 1974 and 1998 **Definition of RCD:** Patients with severe symptomatic villous atrophy mimicking coeliac disease but refractory to a strict gluten-free diety and with no evidence of overt lymphoma (CD diagnosed if patients had severe (total or subtotal) small-intestinal villous atrophy associated with increased number of IEL, circulating antigliandin and/or antiendomysium IgA and/or IgG antibodies before a GFD or during periods of poor adherence (17 of 21 cases), HLADQw2 phenotype in 8 cases) **Exclusion criteria:** other causes of villous atrophy and overt intestinal lymphoma

	Length of time on a gluten-free diet: at least 6 months **Description of gluten-free diet (and how adherence was monitored):** not stated; compliance was assessed with either a dietician or a physician in charge of the patient. **RCD type:** not reported **Number of patients included:** 21 **Concomitant conditions:** lymphocytic colitis in 4 patients, collageous colitis in 2 patients, collagenous sprue in 7 patients (some presenting features of patients included hyposplenism in 5 patients, dermatitus herpetiformis in 1) **Comments:** it is possible that some patients reported in this study were also reported in Malamut 2009 (those treated between 1992 and 1998 may be included in both studies); the study also included 20 'controls' with coeliac disease that were not refractory to GFD but these were not included as they did not have RCD
Treatment	**Arm No:** 1 **Name:** prednisolone (0.5 to 1.0 mg/kg per day) **N:** 15 **Pharmacological agent:** prednisolone agent 1: administration: oral agent 1: length of treatment (mean): 41 Comments: 0.5 to 1.0 mg/kg per day; treatment period ranged from 1 to 114 months
Other	**Source of funding:** not reported **Authors' conflicts of interest:** not reported **Additional comments:** A questionnaire was sent to 56 different French gastroenterology referral centres in January 1997
Notes on outcomes	**Clinical response:** defined as regression of diarrhoea and improvement in nutritional status) extended steroid therapy to maintain improvement **Notes: phenotypical analysis of peripheral-blood lymphocytes was reported in the study but not extracted.**

Baseline characteristics			**All study participants**		
			N	**k**	**mean**
Patient characteristics:					
Age		Continuous	21		51 [rng 29–73]
Sex (n female)		Dichotomous	21	16	(76.2%)

	Duration of CD (months)	Continuous	21		
	Proportion of IELs per100 epithelial cells (%)	Continuous	19		70.947 [rng 9–98][a]
	presence of ulcerative jejunitis	Dichotomous	21	6	(28.6%)
	mesenteric lymph node cavitation	Dichotomous	21	6	(28.6%)
	clonal TCRy configuration present	Dichotomous	17	4	(23.5%)
	clonal TCRy configuration absent	Dichotomous	17	13	(76.5%)
	AGA and/or EMA IgA or IgG present	Dichotomous	21	21[b]	(100.0%)

a biopsies not available for 2 patients; these were considered to be abnormal in all but 3 (which were 30% or less)
b these were present in all but 4 before GFD and reappeared after times of less adherence to GFD

Results

		prednisolone (0.5 to 1.0 mg/kg per day)		
		N	**k**	**mean**
Clinical response:				
proportion achieved – 41mo	Dichotomous	15	11	(73.3%)
extended steroid therapy to maintain improvement – 41mo	Dichotomous	11		3
Histological response:				
complete villous recovery – 41mo	Dichotomous	14	3[a]	(21.4%)

a not all patients re-assessed

Definitions of abbreviations are given at the end of this document.

Bibliographic reference (Ref ID)	**Daum,S. et al. (2006)**
Study characteristics	**Study design:** case series **Prospective/retrospective:** Retrospective **Consecutive patients:** No **Country:** Germany

Patient characteristics	**Recruitment period:** 1997 to 2004 **Inclusion criteria:** patients with RCD identified from patient records at a tertiary referral centre who were treated with budesonide, with or without receiving systemtic corticosteroid treatment **Definition of RCD:** at least partial villous atrophy documented on duodenal histology with no clinical or histological response to a GFD after at least 6 months and persistent villous atrophy and clinical deteriorration requiring earlier therapeutic intervention despite a GFD. **Exclusion criteria:** other causes for villous atrophy including giardiasis and other parasitic infections (determined from negative stool tests and histology), bacterial overgrowth (determined from normal hydrogen breath test), tropical sprue (travel history to endemic countries), hypogammaglobulinemic sprue (normal serum IgA, IgG, and IgM and normal plasma cell numbers in duodenal biopsy), manifest lymphoma (no detectable tumour enlarged lymph nodes suggesting lymphoma in abdominal CT or MRT, normal lactate dehydrogenase), Crohn's disease (normal ileocolonoscopy, no histological hinting at Crohn's disease, no typically cicumscribed strictures), microscopic colitis (normal histology of the colon) and pancreatic insufficienty (normal stool chymotrypsin); inadvertent persisting gluten intake (determined by documented repeated dietary counselling including a visit with an experienced dietician) **Length of time on a gluten-free diet:** at least 6 months **Description of gluten-free diet (and how adherence was monitored):** not stated; compliance with GFD determined/monitored through repeated dietary counselling including a visit with an experienced dietician (who excluded inadvertent persistent gluten intake) **RCD type:** I and II (reported separately) **Number of patients included:** 4 **Concomitant conditions:** not reported **Comments:** study included 9 patients - 1 had autoimmune enteropathy and another had C4 positive sprue-like intestinal T cell lymphoma so data on these patients has notbeen extracted; the study included another 3 patients with different additional treatments on top of budesonide and pre-treatment with prednisolone (one with CD25 antibodies, another with azathioprine, and a third with tacrolimus) – data from these patient was not extracted as they are essentially case reports
Treatment	**Arm No:** 1 **Name:** Budesonide + pre-treatment with prednisolone **N:** 2 **Pharmacological agent:** budesonide+prednisolone agent 1: administration: oral agent 1: average dosage (oral): 10.2 agent 1: length of treatment (mean): 24 agent 2: administration: oral agent 2: average dosage (oral): 35

	agent 2: length of treatment (mean): ? Comments: budesonide dosage ranged from 9 to 12 mg/day over 1 to 60 months; 5 patients had pre-treatment with prednisone ranged at 40 mg/d from mean 4 months (1 to 144 months); of those patients who had pre-treatment with prednisone **Arm No:** 2 **Name:** Budesonide only **N:** 2 **Pharmacological agent:** budesonide agent 1: administration: oral agent 1: average dosage (oral): 10.2 agent 1: length of treatment (mean): 24 Comments: no pre-treatment with prednisolone
Other	**Source of funding:** not reported **Authors' conflicts of interest:** not reported
Notes on outcomes	**Clinical response** – defined as increase of BMI by at least 10% or more OR a clinically significant decrease in bowel movements and an at least stable BMI
Baseline characteristics	

		All study participants		
		N	**k**	**mean**
Patient characteristics:				
Age	Continuous	4		52.5 [rng 31–69]
Sex (n female)	Dichotomous	4	1	(25%)
Duration of CD (months)	Continuous	4		100 [rng 9–252]
HLA-DQ status - DQ2 homozygous	Dichotomous	4	2	(50%)
HLA-DQ status - DQ2 hetergozygous	Dichotomous	4	2	(50%)
primary RCD	Dichotomous	4	3	(75.0%)
secondary RCD	Dichotomous	4	1	(25.0%)
TCDy-PCR - monoclonal	Dichotomous	4	1[a]	(25.0%)
TCRy-PCR - polyclonal	Dichotomous	4	2[b]	(50.0%)

	TCRy-PCR - unclear	Dichotomous	4	1	(25.0%)
	RCD type 1				
	Patient characteristics:				
	Sex (n female)	Dichotomous	2	0	(0.0%)
	HLA-DQ status - DQ2 homozygous	Dichotomous	2	1	(50.0%)
	HLA-DQ status - DQ2 hetergozygous	Dichotomous	2	1	(50.0%)
	primary RCD	Dichotomous	2	1	(50.0%)
	secondary RCD	Dichotomous	2	1	(50.0%)
	RCD type 2				
	Patient characteristics:				
	Sex (n female)	Dichotomous	2	1	(50.0%)
	HLA-DQ status - DQ2 homozygous	Dichotomous	2	2	(100.0%)
	HLA-DQ status - DQ2 hetergozygous	Dichotomous	2	0	(0.0%)
	primary RCD	Dichotomous	2	0	(0.0%)
	secondary RCD	Dichotomous	2	2	(100.0%)

a authors state were positive clonality (for one patient it was not clear if they were positive or negative)
b authors state were negative clonality (for one patient it was not clear if they were positive or negative)

Results			**Budesonide + pre-treatment with prednisolone**		
			N	**k**	**mean**
	Clinical response:				
	bowel movements per day – 0mo	Continuous	2		5 [rng 2–8]
	bowel movements per day – 24mo	Continuous	2		2 [rng 1–3]
	body mass index (kg/m2) – 0mo	Continuous	2		19.7 [rng 19.6–19.8]
	body mass index (kg/m2) – 24mo	Continuous	2		21.5 [rng 21.3–21.8]
	proportion achieved	Dichotomous	2	2[a]	(100%)

serological response:				
Proportion of IELs per100 epithelial cells (%) – 0mo (median)	Continuous	1		90[b]
Proportion of IELs per100 epithelial cells (%) – 24mo (median)	Continuous	2		58.5 [rng 50–67]*b*
Histological response:				
remained at Marsh IIIC at 0mo and 24 mo	Dichotomous	1	1	
Marsh IIIA at 0mo to Marsh IIIB at 24 mo	Dichotomous	1	1	
Adverse events:				
skin fragility – 14mo	Dichotomous	2	1	(50.0%)
postprandial abdominal pain and weight loss with budesonide–	Dichotomous	2	1	(50.0%)

a *at average of 28.5 months (range21 to 36)*
b *this was not measured in one patient*

		Budesonide only		
		N	**k**	**mean**
Clinical response:				
bowel movements per day – 0mo	Continuous	2		5.5 [rng 5–6]
bowel movements per day – 24mo	Continuous	2		3.5 [rng 2–5]
body mass index (kg/m2) – 0mo	Continuous	2		20.6 [rng 18.4–22.8]
body mass index (kg/m2) – 24mo	Continuous	2		20.75 [rng 18.4–23.1]
proportion achieved	Dichotomous	2	1[a]	(50.0%)
Serological response:				
Proportion of IELs per100 epithelial cells (%) – 0mo (median)	Continuous	2		64 [rng 50–78]

	Proportion of IELs per100 epithelial cells (%) – 24mo (median)	Continuous	1		87 [b]
	Histological response:				
	Marsh IIIB at 0mo and 24 mo	Dichotomous	1 [c]	1	
	Adverse events:				
	skin fragility	Dichotomous	2	0	(0.0%)
	postprandial abdominal pain and weight loss with budesonide–	Dichotomous	2	0	(0.0%)
	a *at 28 months* *b* *this was not measured in one patient* *c* *Marsh was IIIC in one patient initially but was not measured after budesonide*				
	budesonide was taken for 24 months (range 1 to 60) across all patients.				

Definitions of abbreviations are given at the end of this document.

Bibliographic reference (Ref ID)	**Goerres,M.S. et al. (2003)**
Study characteristics	**Study design:** case series **Prospective/retrospective:** Prospective **Consecutive patients:** unclear **Country:** Netherlands
Patient characteristics	**Recruitment period:** 1998 - 2000 **Inclusion criteria:** patients initally referred to an out-patient clinic of a tertiary referral centre for coeliac disease with RCD **Definition of RCD:** malabsorption in the presence of persisting or recurring severe inflammatory infiltration of the epithelium and lamina propria with lymphocytes, hyperplasia of crypts and/or partial, subtotal or total villous atrophy in the small intestinal mucosa despite strict adherence to a GFD for at least a year. **Exclusion criteria:** diagnosis of other possible underlying diseases, such as bacterial overgrowth, giardiasis, eosinophilic enteritis, inflammatory bowel disease, hypogammaglobulinemic sprue, primary idiopathic collagenous colitis, tropical sprue, malignancy and EATL; poor compliance to a GFD; presence of anti-endomysium antibodies and high levels of antigliandine antibodies for at least 2 months; presence of other severe pathology such as a history or presence of cancer or any other premalignant disease, severe cardiovascular disease, presence of any concurrent infection, ulcerative colitis or lymphoma; breast-feeding or pregnancy; positive serum anti-hepatitis C

	virus, serum hepatitus B surface antigen, or anti-HIV **Length of time on a gluten-free diet:** at least 1 year **Description of gluten-free diet (and how adherence was monitored):** not reported; compliance to GFD confirmed for inclusion with the aid of a dietician, the referring physician, the consulting GP, and the treatment team **RCD type:** I and II (reported separately) **Number of patients included:** 19 **Concomitant conditions:** a number of concomitant conditions (ie. ulcerative colitis, inflammatory bowel disease, etc) excluded **Comments:** it is possible that some patients reported in this study were also reported in Al-Toma 2007 (those treated between 1992 and 1998 may be included in both studies); all but 1 patient had more than 70% aberrant T-cells (one patient had 25%)
Treatment	**Arm No:** 1 **Name:** Azathioprine after pre-treatment with prednisone **N:** 0 **Pharmacological agent:** azathioprine+prednisone agent 1: administration: oral agent 1: length of treatment (mean): 13 agent 2: administration (if different): oral Comments: at least 52 weeks of treatment; 2 mg/kg/day of azathioprine; prednisone was started at 40 mg/d for 6 weks and tapered to 10 mg/d after 6 weeks and, if possible, 2.5-0 mg/d after 3 months (depending on the clinical condition and biochemical parameters of the patient)
Other	**Source of funding:** not reported **Authors' conflicts of interest:** not reported
Notes on outcomes	**Clinical response**- defined as diappearance of diarrhoea, or loss of fatigue or weakness **Serological response:** decrease in intraepithelial lymphocytosis - not clear how this was defined (ie. what was considered a decrease) **Histological response –** 'improved' defined as improvement of small intestinal histology which may or may not have had a decrease of intra-epithelial lymphocytosis **survival/overall mortality** overall mortality - there is some inconsistency in the study between the patient IDs in the table and the text which appears to report on 19 patients. The information from the table in the study was extracted into this evidence table.
Baseline characteristics	**All study participants**

			N	k	mean
	RCD type 1				
	Patient characteristics:				
	Age	Continuous	10		58.5 (SD 12.7)[a]
	Sex (n female)	Dichotomous	10	8	(80.0%)
	TCDy-PCR - monoclonal	Dichotomous	9	0	(0.0%)
	TCRy-PCR - polyclonal	Dichotomous	9	6	(66.7%)
	TCRy-PCR - unknown	Dichotomous	9	3[b]	(33.3%)
	HLA-DQ - D2	Dichotomous	10	8	(80.0%)
	HLA-DQ - DQ2 negative	Dichotomous	10	1	(10.0%)
	HLA-DQ - D8	Dichotomous	10	1	(10.0%)
	RCD type 2				
	Patient characteristics:				
	Age	Continuous	8		57 (SD 9.9)*a*
	Sex (n female)	Dichotomous	8	7	(87.5%)
	TCDy-PCR - monoclonal	Dichotomous	7	4	(57.1%)
	TCRy-PCR - polyclonal	Dichotomous	7	2	(28.6%)
	TCRy-PCR - unknown	Dichotomous	7	1*b*	(14.3%)
	HLA-DQ - D2	Dichotomous	8	8	(100.0%)
	HLA-DQ - DQ2 negative	Dichotomous	8	0	(0.0%)
	HLA-DQ - D8	Dichotomous	8	0	(0.0%)
	a *age at treatment* *b* *reported to be 'weak clonal'*				

		Azathioprine after pre-treatment with prednisone		
Results		**N**	**k**	**mean**

Clinical response:					
proportion achieved – 52wk	Dichotomous	18	17[a]		(94.4%)
histological response:					
Marsh IIIC – 0wk	Dichotomous	18	4		(22.2%)
Marsh IIIC – 52wk	Dichotomous	15	1		(6.7%)
Marsh IIIB – 0wk	Dichotomous	18	9		(50.0%)
Marsh IIIB – 52wk	Dichotomous	15	4		(26.7%)
Marsh IIIA – 0wk	Dichotomous	18	4		(22.2%)
Marsh IIIA – 52wk	Dichotomous	15	5		(33.3%)
Marsh II – 0wk	Dichotomous	18	1		(5.6%)
Marsh II – 52wk	Dichotomous	15	2		(13.3%)
Marsh I – 0wk	Dichotomous	18	0		(0.0%)
Marsh I – 52wk	Dichotomous	15	1		(6.7%)
survival/overall mortality:					
overall mortality – 52wk	Dichotomous	18	7		(38.9%)
Development of cancer:					
EATL	Dichotomous	18	6		(33.3%)
RCD type 1					
Clinical response:					
body mass index (kg/m2) – 0wk	Continuous	10			20.2 [rng 17–23.4]
body mass index (kg/m2) – 52wk	Continuous	10			21.5 [rng 14.5–27.1]
body weight (kg) – 0wk	Continuous	10			58.5 [rng 46–70]
body weight (kg) – 52wk	Continuous	10			62.4 [rng 43–76]
proportion achieved – 52wk	Dichotomous	10	10*a*		(100.0%)
serological response:					
mean haemoglobin (mmol/L) – 0wk	Continuous	10			12.7 [rng 10.9–13.5]
mean haemoglobin (mmol/L) – 52wk	Continuous	10			13.4 [rng 9.1–14.3]

	mean albumin level (g/L) – 0wk	Continuous	10		38 [rng 33–47]
	mean albumin level (g/L) – 52wk	Continuous	10		39 [rng 37–44]
	decrease in intraepithelial lymphocytosis – 52wk	Dichotomous	10	8	(80.0%)
	histological response:				
	proportion achieved improvement – 52wk	Dichotomous	10	[b]	8
	Marsh IIIC – 0wk	Dichotomous	10	3	(30.0%)
	Marsh IIIC – 52wk	Dichotomous	10	1	(10.0%)
	Marsh IIIB – 0wk	Dichotomous	10	5	(50.0%)
	Marsh IIIB – 52wk	Dichotomous	10	2	(20.0%)
	Marsh IIIA – 0wk	Dichotomous	10	2	(20.0%)
	Marsh IIIA – 52wk	Dichotomous	10	3	(30.0%)
	Marsh II – 0wk	Dichotomous	10	0	(0.0%)
	Marsh II – 52wk	Dichotomous	10	3	(30.0%)
	Marsh I – 0wk	Dichotomous	10	0	(0.0%)
	Marsh I – 52wk	Dichotomous	10	1	(10.0%)
	survival/overall mortality:				
	overall mortality – 52wk	Dichotomous	10	0	(0.0%)
	Development of cancer:				
	EATL	Dichotomous	10	0	(0.0%)
	RCD type 2				
	Clinical response:				
	body mass index (kg/m2) – 0wk	Continuous	8		19.9 [rng 16.6–25.3]
	body mass index (kg/m2) – 52wk	Continuous	8		22.3 [rng 19.4–25.2]
	body weight (kg) – 0wk	Continuous	7		53.428 [rng 44–67]
	body weight (kg) – 52wk	Continuous	8		60.25 [rng 49–67]
	proportion achieved – 52wk	Dichotomous	8	7*a*	(87.5%)
	serological response:				
	mean haemoglobin (mmol/L) – 0wk	Continuous	8		11.6 [rng 10.1–13.2]

	mean haemoglobin (mmol/L) – 52wk	Continuous	8		12.2 [rng 10.5–13.8]
	mean albumin level (g/L) – 0wk	Continuous	8		30 [rng 17–43][c]
	mean albumin level (g/L) – 52wk	Continuous	8		33 [rng 31–37]
	histological response:				
	proportion achieved improvement – 52wk	Dichotomous	5	2[d]	(40.0%)
	Marsh IIIC – 0wk	Dichotomous	8	1	(12.5%)
	Marsh IIIC – 52wk	Dichotomous	5	0	(0.0%)
	Marsh IIIB – 0wk	Dichotomous	8	4	(50.0%)
	Marsh IIIB – 52wk	Dichotomous	5	2	(40.0%)
	Marsh IIIA – 0wk	Dichotomous	8	2	(25.0%)
	Marsh IIIA – 52wk	Dichotomous	5	2	(40.0%)
	Marsh II – 0wk	Dichotomous	8	1	(12.5%)
	Marsh II – 52wk	Dichotomous	5	1	(20.0%)
	Marsh I – 0wk	Dichotomous	8	0	(0.0%)
	Marsh I – 52wk	Dichotomous	5	0	(0.0%)
	survival/overall mortality:				
	overall mortality – 52wk	Dichotomous	8	7[e]	(87.5%)
	Development of cancer:				
	EATL	Dichotomous	8	6[f]	(75.0%)

a *associated with weight gain and albumin and haemoglobin increase*
b *decrease of intra-epithelial lymphocytosis in 8*
c *2 patients had very low levels and this increased dramatically in one after treatment*
d *but these patients did not have a reduction in IEL infiltration*
e *3 died before finishing 52 week treatment, others died later, most from EATL but one due to sepsis*
f *3 of these died during the treatment period*

Definitions of abbreviations are given at the end of this document.

Bibliographic	**Jamma,S. et al. (2011)**

reference (Ref ID)	
Study characteristics	**Study design:** case series **Prospective/retrospective:** Retrospective **Consecutive patients:** unclear **Country:** USA
Patient characteristics	**Recruitment period:** Nov 2007 to Dec 2008 **Inclusion criteria:** patients seen in clinic with RCD (with biopsy proven coeliac disease who did not respond to a GFD for at least 6 months) in whom a therapeutic trial of small intestinal release mesalamine was prescribed **Definition of RCD:** RCD type based on IEL immunohistochemistry (where CD3=CD8) - confirmed by evaluation of duodenal biopsies **Exclusion criteria:** It appears that patients underwent some testing and this may have been done to rule out other conditions (ie. all patients underwent colonoscopy for microscopic colitis so it appears this may have been an exclusion criteria, patients had breath testing for small intenstinal bacterial overgrowth, small bowel series, enterosocpy, capsule endscopy, antienterocyte antibody, cross-sectional imaging in clinical indicated); it also appears patients with other food intolerances like lactose may have been excluded **Length of time on a gluten-free diet:** at least 6 months **Description of gluten-free diet (and how adherence was monitored):** Not described; all patients were assessed by an expert coeliac dietician to assess for inadvertent gluten exposure and for other food intolerances such as lactose. Patients were on a GFD for a median of 24 months (range 10 to 300 months) **RCD type:** I **Number of patients included:** 10 **Concomitant conditions:** colonoscopy showed that 3 patients had lymphocytic colitis (2 treated with mesalamine and budesonide and one with mesalamine alone) and 1 had collagenous colitis (treated with both mesalamine and budesonide); 1 patien treated with mesalamine only had IgA deficiency **Comments:** those who had responded to budesonide were tapered off this drug before being treated with mesalamine but 1 patient was not able to discontinue (they were on a stable dose of 3 to 9 mg daily); those who did not respond from mesalamine were discontinued after a mean of 4.5 weeks; 3 had poly-clonal T-cell receptor, 9 had diarrhoea present (classical presentation), 7 had secondary RCD (and 3 primary)
Treatment	**Arm No:** 1 **Name:** Small intestinal release mesalamine alone **N:** 4 **Pharmacological agent:** mesalamine agent 1: administration: oral

	agent 1: average dosage (oral): 3.3 agent 1: length of treatment (mean): 22.7 Comments: one patient treated with mesalamine was previously on budesonide but did not respond to this drug; mesalamine was given in a dosage from 2 to 4 gm per day for from 3 to 53 months **Arm No:** 2 **Name:** Mesalamine + budesonide **N:** 6 **Pharmacological agent:** mesalamine+budesonide agent 1: administration: oral Comments: these patients were kept on budesonide if they had responded to the drug and were unable to taper and discontinue this medication (all were on a stable dose from 3 to 9 mg/day for at least 1 month); mesalamine was given in a dosage for 2 to 4 gm per day and budesonide from 3 to 9 mg/day **Arm No:** 3 **Name:** mesalamine with or without budesonide **N:** 10 **Pharmacological agent:** budesonide with or without other therapy agent 1: administration: oral Comments: mesalamine was given in a dosage for 2 to 4 gm per day
Other	**Source of funding:** all funding provided by the Celiac Centre at Beth Israel Deaconess Medical Centre **Authors' conflicts of interest:** no conflicts
Notes on outcomes	**Clinical response** Complete - total symptom reduction partial - at least 50% symptom reduction non-responsive - <50% symptom reduction
Baseline characteristics	

		All study participants		
		N	**k**	**mean**
Patient characteristics:				
Age	Continuous	10		53.4

	Sex (n female)	Dichotomous	10	9	(90.0%)
	primary RCD	Dichotomous	10	3	(30.0%)
	secondary RCD	Dichotomous	10	7	(70.0%)
	Classical presentation (diarrhoea predominant)	Dichotomous	10	9	(90.0%)
	Atypical presentation (diarrhoea absent)	Dichotomous	10	1	(10.0%)
	Marsh IIIA	Dichotomous	10	5[a]	(50.0%)
	Marsh IIIB	Dichotomous	10	1*a*	(10.0%)
	Marsh IIIC	Dichotomous	10	4*a*	(40.0%)

a *this does not appear to have been re-assessed after treatment*

Results

		Small intestinal release mesalamine alone		
		N	**k**	**mean**
Clinical response:				
Complete (total symptom reduction) – 65wk	Dichotomous	4	3	(75.0%)
partial (at least 50% symptom reduction) – 65wk	Dichotomous	4	0	(0.0%)
non-responsive (<50% symptom reduction) – 65wk	Dichotomous	4	1	(25.0%)

		Mesalamine + budesonide		
		N	**k**	**mean**
Clinical response:				
Complete (total symptom reduction) – 65wk	Dichotomous	6	2[a]	(33.3%)
partial (at least 50% symptom reduction) – 65wk	Dichotomous	6	1[b]	(16.7%)
non-responsive (<50% symptom reduction) – 65wk	Dichotomous	6	3	(50.0%)

a *or if symptoms remained in remission after stopping budesonide*

b *or if reduction in budesonide dose of at least 3 mg/d without symptom worsening*

		mesalamine with or without budesonide		
		N	**k**	**mean**
Clinical response:				
Complete (total symptom reduction) – 65wk	Dichotomous	10	5[a]	(50.0%)
partial (at least 50% symptom reduction) – 65wk	Dichotomous	10	1*a*	(10.0%)
non-responsive (<50% symptom reduction) – 65wk	Dichotomous	10	4*a*	(40.0%)
adverse events:				
overall adverse events – 65wk	Dichotomous	10	1[b]	(10.0%)
primary lack of response to GFD				
Clinical response:				
Complete (total symptom reduction) – 65wk	Dichotomous	3	1*a*	(33.3%)
partial (at least 50% symptom reduction) – 65wk	Dichotomous	3	1*a*	(33.3%)
non-responsive (<50% symptom reduction) – 65wk	Dichotomous	3	1*a*	(33.3%)
secondary lack of response to GFD				
Clinical response:				
Complete (total symptom reduction) – 65wk	Dichotomous	7	4*a*	(57.1%)
partial (at least 50% symptom reduction) – 65wk	Dichotomous	7	0*a*	(0.0%)
non-responsive (<50% symptom reduction) – 65wk	Dichotomous	7	3*a*	(42.9%)
classic presentation (diarrhoea)				
Clinical response:				
Complete (total symptom reduction) – 65wk	Dichotomous	9	4*a*	(44.4%)
partial (at least 50% symptom reduction) – 65wk	Dichotomous	9	1*a*	(11.1%)
non-responsive (<50% symptom reduction) – 65wk	Dichotomous	9	4*a*	(44.4%)
atypical presentation (no diarrhoea)				
Clinical response:				
Complete (total symptom reduction) – 65wk	Dichotomous	1	1*a*	(100.0%)

	partial (at least 50% symptom reduction) – 65wk	Dichotomous	1	0*a*	(0.0%)
	non-responsive (<50% symptom reduction) – 65wk	Dichotomous	1	0*a*	(0.0%)
	Marsh IIIA				
	Clinical response:				
	Complete (total symptom reduction) – 65wk	Dichotomous	5	3[c]	(60.0%)
	partial (at least 50% symptom reduction) – 65wk	Dichotomous	5	0*a*	(0.0%)
	non-responsive (<50% symptom reduction) – 65wk	Dichotomous	5	2*d*	(40.0%)
	Marsh IIIB				
	Clinical response:				
	Complete (total symptom reduction) – 65wk	Dichotomous	1	0*a*	(0.0%)
	partial (at least 50% symptom reduction) – 65wk	Dichotomous	1	1*a*	(100.0%)
	non-responsive (<50% symptom reduction) – 65wk	Dichotomous	1	0*a*	(0.0%)
	Marsh IIIC				
	Clinical response:				
	Complete (total symptom reduction) – 65wk	Dichotomous	4	2*a*	(50.0%)
	partial (at least 50% symptom reduction) – 65wk	Dichotomous	4	0*a*	(0.0%)
	non-responsive (<50% symptom reduction) – 65wk	Dichotomous	4	2*a*	(50.0%)
	a *calculated from percentage* *b* *one had headache leading to withdrawal* *c* *approximated to nearest integer (percentages only presented in text)* *d* *calculated from percentage; approximated to nearest integer (percentages only presented in text)*				
	Average follow-up was 65.3 weeks ranging from 39 to 95 weeks (responders were followed for an average of 67.2 weeks from 39 to 95 weeks and non-responderrs discontinued after 3 to 6 weeks but were followed for an average of 62.5 weeks from 44 to 80 weeks); one patient discontinued due to headache (despite complete response) - she started mesalamine after the headache subsided but it returned so she discontinued again (not clear if this patient was also being treated with budesonide) - no other patients had side effects				

Definitions of abbreviations are given at the end of this document.

Bibliographic	**Malamut,G. et al. (2009)**

reference (Ref ID)	
Study characteristics	**Study design:** case series **Prospective/retrospective:** Retrospective **Consecutive patients:** unclear **Country:** France
Patient characteristics	**Recruitment period:** 1992 to 2007 **Inclusion criteria:** patients treated at 1 of 6 large hospitals in France for RCD **Definition of RCD:** Clinical relapse (chronic diarrhoea and/or severe abdominal pain) with persisten malabsorption syndrome (decreased serum leves of iron, folate, vitamin B12, and/or calcium) and on histology showing persistent villous atrophy with increased numbers of IELs after 1 year of strict adherence to a GFD. (RCDI - normal IEL phenotype with < 25% CD103+ or CD45+ IELs lacking surface CD3 on flow cytometry or < 50% CD3+CD8-IELs AND the absence of detectable clonality in duodenal biopsy speciments; RCDII - abnomal phenotypes of IELs such as > 25% CD103+ or CD45+ IELS lacking surfac CD3/TCR complexes on flow cytometry or > 50% IELs expressing intracellular CD3 but no CD8 AND/OR presence of a detectable clonal TCR rearrangement in duodenal biopsy specimens) **Exclusion criteria:** primary hypogammaglobulinemia, collageous sprue, autoimmune enteropathy and lamina propria CD4+ T-cell or CD9+ small T-cell lymphomas, indeterminate RCD because of unknown IEL phenotype, coeliac disease revealed by overt lymphoma **Length of time on a gluten-free diet:** at least 1 year **Description of gluten-free diet (and how adherence was monitored):** not reported **RCD type:** I and II (reported separately) **Number of patients included:** 57 **Concomitant conditions:** a number of concomitant conditions were excluded; 1 patient with RCD1 andf 19 with RCDII had lymphocytic gastritis, 4 with RCDI and 14 with RCDII had lymphocytic colitis **Comments:** it is possible that some patients reported in this study were also reported in Cellier 2000 (those treated between 1992 and 1998 may be included in both studies)
Treatment	**Arm No:** 1 **Name:** Corticosteroids **N:** 42 **Pharmacological agent:** corticosteroids agent 1: administration: not reported Comments: dosage not reported

	Arm No: 2 **Name:** Azathioprine **N:** 6 **Pharmacological agent:** azathioprine agent 1: administration: not reported Comments: dosage not reported **Arm No:** 3 **Name:** Methotrexate **N:** 8 **Pharmacological agent:** methotrexate agent 1: administration: not reported Comments: dosage not reported **Arm No:** 4 **Name:** Anti-tumor necrosis factor alpha **N:** 4 **Pharmacological agent:** Anti-tumor necrosis factor alpha agent 1: administration: not reported Comments: dosage not reported **Arm No:** 5 **Name:** Cyclosporin **N:** 2 **Pharmacological agent:** cyclosporin agent 1: administration: not reported Comments: dosage not reported **Arm No:** 6 **Name:** Cladribine **N:** 2 **Pharmacological agent:** cladribine agent 1: administration: not reported

	Comments: dosage not reported **Arm No:** 7 **Name:** All treated patients **N:** 57 **Pharmacological agent:** any treatment agent 1: administration: not reported Comments: dosages not reported **Comments:** authors also state that fludarabine, imatinib, cyclophosphamide-doxorubicin-etopside-steroids, mechlorethamine and bexarotene were all attempted but had no therapeutic effect; authors also report results from alemtuzumab but these results were not extracted as this drug is not licensed in the UK
Other	**Source of funding:** supported by Lymphocoeliaque, Institut National du Cancer **Authors' conflicts of interest:** not reported
Notes on outcomes	**Clinical response** – defined as reduction in diarrhoea with a decrease of 50% of the number of stools or of weight stools per day and/or the recovering of 50% of weight loss **Histological response** complete villous recovery - if villous architecture was restored to normal partial histological response - if villous architecture improvement by at least one grade

Baseline characteristics

		All study participants		
		N	**k**	**mean**
RCD type 1				
Patient characteristics:				
Age (median)	Continuous	14		41.6[a]
Sex (n female)	Dichotomous	14	11	(78.6%)
one or more positive serology test	Dichotomous	14	4	(28.6%)
Proportion of IELs per100 epithelial cells (%)	Continuous	14		66.9
body mass index (kg/m2)	Continuous	14		18.8 (SD 2.7)
partial villous atrophy	Dichotomous	14	4[b]	(28.6%)

	total villous atrophy	Dichotomous	14	5*b*	(35.7%)
	presence of ulcerative jejunitis	Dichotomous	14	4[c]	(28.6%)
	HLA-DQ2	Dichotomous	11	10	(90.9%)
	HLA-DQ8	Dichotomous	10	1	(10.0%)
	HLA-DQ2/DQ2	Dichotomous	10	4	(40.0%)
	HLA-DQ status - DQ2/8	Dichotomous	10	0	(0.0%)
	anaemia	Dichotomous	12	6	(50.0%)
	dermatis herpetiformis	Dichotomous	14	0	(0.0%)
	autoimmune diseases	Dichotomous	14	2	(14.3%)
	liver dysfunction (chronic cytolysis)	Dichotomous	14	8	(57.1%)
	diarrhoea	Dichotomous	14	12	(85.7%)
	abdominal pain	Dichotomous	14	9	(64.3%)
	proportion with low albuminemia (< 35 g/L)	Dichotomous	11	6	(54.5%)
	unexplained liver dysfunction	Dichotomous	8	4	(50.0%)
	viral hepatitis	Dichotomous	8	3	(37.5%)
	other identified cause of liver dysfunction	Dichotomous	8	1	(12.5%)
	subtotal villous atrophy	Dichotomous	14	5*b*	(35.7%)
	RCD type 2				
	Patient characteristics:				
	Age (median)	Continuous	43		49.1*a*
	Sex (n female)	Dichotomous	43	25	(58.1%)
	one or more positive serology test	Dichotomous	36	10	(27.8%)
	Proportion of IELs per100 epithelial cells (%)	Continuous	43		91.5
	body mass index (kg/m2)	Continuous	43		17.8 (SD 1.6)
	partial villous atrophy	Dichotomous	41	9*b*	(22.0%)
	total villous atrophy	Dichotomous	41	14*b*	(34.1%)
	presence of ulcerative jejunitis	Dichotomous	43	29[d]	(67.4%)
	HLA-DQ2	Dichotomous	26	26	(100.0%)

	HLA-DQ8	Dichotomous	24	3	(12.5%)
	HLA-DQ2/DQ2	Dichotomous	24	16	(66.7%)
	HLA-DQ status - DQ2/8	Dichotomous	24	3	(12.5%)
	anaemia	Dichotomous	41	32	(78.0%)
	dermatis herpetiformis	Dichotomous	43	4	(9.3%)
	autoimmune diseases	Dichotomous	43	13	(30.2%)
	liver dysfunction (chronic cytolysis)	Dichotomous	43	21	(48.8%)
	diarrhoea	Dichotomous	43	38	(88.4%)
	abdominal pain	Dichotomous	43	23	(53.5%)
	proportion with low albuminemia (< 35 g/L)	Dichotomous	41	38	(92.7%)
	unexplained liver dysfunction	Dichotomous	21	13	(61.9%)
	viral hepatitis	Dichotomous	21	4	(19.0%)
	other identified cause of liver dysfunction	Dichotomous	21	4	(19.0%)
	subtotal villous atrophy	Dichotomous	41	18*b*	(43.9%)

a *age at diagnosis of RCD*
b *detected by upper endoscopy*
c *detected by upper endoscopy; none were greater than 1cm*
d *detected by upper endoscopy; all were greater than 1cm*

Results			**Corticosteroids**		
			N	**k**	**mean**
	RCD type 1				
	Clinical response:				
	proportion achieved	Dichotomous	10	9	(90.0%)
	histological response:				
	complete villous recovery – mo	Dichotomous	10	4	(40.0%)
	partial histological response	Dichotomous	10	0	(0.0%)

adverse events:				
drug dependency	Dichotomous	10	8	(80.0%)
RCD type 2				
Clinical response:				
proportion achieved	Dichotomous	30	23	(76.7%)
histological response:				
complete villous recovery – mo	Dichotomous	30	3	(10.0%)
partial histological response	Dichotomous	30	7	(23.3%)
adverse events:				
drug dependency	Dichotomous	31	23	(74.2%)

		Azathioprine		
		N	**k**	**mean**
RCD type 1				
Clinical response:				
proportion achieved	Dichotomous	1	1	(100.0%)
histological response:				
complete villous recovery – mo	Dichotomous	1	0	(0.0%)
partial histological response	Dichotomous	1	0	(0.0%)
RCD type 2				
Clinical response:				
proportion achieved	Dichotomous	4	2	(50.0%)
histological response:				
complete villous recovery – mo	Dichotomous	4	0	(0.0%)
partial histological response	Dichotomous	4	0	(0.0%)

			Methotrexate		
			N	k	mean
RCD type 2					
Clinical response:					
proportion achieved		Dichotomous	7	5	(71.4%)
histological response:					
complete villous recovery – mo		Dichotomous	7	0	(0.0%)
partial histological response		Dichotomous	7	2	(28.6%)

		Anti-tumor necrosis factor alpha		
		N	k	mean
RCD type 1				
Clinical response:				
proportion achieved	Dichotomous	1	1	(100.0%)
histological response:				
complete villous recovery – mo	Dichotomous	1	0	(0.0%)
partial histological response	Dichotomous	1	0	(0.0%)
RCD type 2				
Clinical response:				
proportion achieved	Dichotomous	3	2	(66.7%)
histological response:				
complete villous recovery – mo	Dichotomous	3	0	(0.0%)
partial histological response	Dichotomous	3	1	(33.3%)

		Cyclosporin		
		N	**k**	**mean**
RCD type 2				
Clinical response:				
proportion achieved	Dichotomous	2	1	(50.0%)
histological response:				
complete villous recovery – mo	Dichotomous	2	0	(0.0%)
partial histological response	Dichotomous	2	0	(0.0%)

		Cladribine		
		N	**k**	**mean**
RCD type 2				
Clinical response:				
proportion achieved	Dichotomous	2	1	(50.0%)
histological response:				
complete villous recovery – mo	Dichotomous	2	0	(0.0%)
partial histological response	Dichotomous	2	1	(50.0%)
Development of cancer:				
Overt lymphoma	Dichotomous	2	2[a]	(100.0%)

a occurred just after the 3rd cycle and at 2 months

		All treated patients		
		N	**k**	**mean**

	survival/overall mortality:				
	overall mortality	Dichotomous	57	29	(50.9%)
	overall mortality in those with overt lymphoma	Dichotomous	18	16[a]	(88.9%)
	RCD type 1				
	survival/overall mortality:				
	5-year survival (Kaplan-Meier)	Time-to-event	14		92.9
	overall mortality	Dichotomous	14	3[b]	(21.4%)
	overall mortality in those with overt lymphoma	Dichotomous	2	1[c]	(50.0%)
	Development of cancer:				
	Overt lymphoma	Dichotomous	14	2[d]	(14.3%)
	5-year development of overt lymphoma (Kaplan-Meier)	Time-to-event	14		14.3
	RCD type 2				
	survival/overall mortality:				
	5-year survival (Kaplan-Meier)	Time-to-event	43		43.9
	overall mortality	Dichotomous	43	26[e]	(60.5%)
	overall mortality in those with overt lymphoma	Dichotomous	16	15*c*	(93.8%)
	Development of cancer:				
	Overt lymphoma	Dichotomous	43	16[f]	(37.2%)
	5-year development of overt lymphoma (Kaplan-Meier)	Time-to-event	43		32.6
	a after median of 11.5 months *b over lymphoma progression with sepsis and malnutrition (n=1), and malnutrition (n=2)* *c after median of 11.5 months (overall for RCDI and II)* *d treatment of these 2 patients not reported; none had received immunosuppressants* *e tumoural progression and malnutrition (n=9), infections (n=4), intestinal haemorrhage (n=3), lethal thrombosis (n=2), and 1 each of oesophageal bleeding from portal hypertension & hep C and pulmonary embolism* *f 2 of these patients had cladribine and 1 had alemtuzumab; 6 had not received immunosuppressants*				
	reported follow-up periods are mean duration of treatment except for cladribine and anti-tnf alpha which were administered in cycles; none of the treatments attempted in patients with RCDII had any significant or durable effect on the number of abnomral IELS; authors also state				

	that fludarabine, imatinib, cyclophosphamide-doxorubicin-etopside-steroids, mechlorethamine and bexarotene were all attempted but had no therapeutic effect; a univariate analysis showed that abnormal IEL phenotype and increase in age at diagnosis of RCD were predictive risk factors for overt lymphoma and that abnormal IEL phenotype, clonality, and onset of overt lymphoma were predictive factors for short survival (multi-variate analysis showed that only abnormal IEL phenotype and onset of overt lymphoma were predictive of short survival)

Definitions of abbreviations are given at the end of this document.

Bibliographic reference (Ref ID)	**Maurino,E. et al. (2002)**
Study characteristics	**Study design:** case series **Prospective/retrospective:** Prospective **Consecutive patients:** Yes **Country:** Argentina
Patient characteristics	**Recruitment period:** Oct 1998 to July 2000 **Inclusion criteria:** patients with a previous diagnosis of refractory sprue or if they were diagnosed with coeliac-like enteropathy and had proven lack of clinical and/or histological response to a GFD and steroids, and/or if they required high doses of steroids to maintain their clinical status. **Definition of RCD:** Refractory sprue was defined based on presence of severe enteropathy refractory to conventional therapeutic measures. All patients had severe malabsorption and requiring intensive treatment. **Exclusion criteria:** recent or current infections, high suspicion or diagnosis of lymphoma, pregnancy or low white blood cell count (< 3000 cells/mm3); other causes of villous atrophy and other malignancies also appear to have been excluded (from small bowel double-contrast radiological exam - n=7, push enteroscopy and multiple biopsies - n=4, CT - n=7, and laparotomy n=6), **Length of time on a gluten-free diet:** not reported **Description of gluten-free diet (and how adherence was monitored):** not reported **RCD type:** not reported **Number of patients included:** 7 **Concomitant conditions:** unclear (some excluded) **Comments:** these patients were among those included in Maurino 2006 at a longer follow-up but this study has been included because Maurino did not report outcomes by different treatments received; 5 patients were treated inpatient and 2 outpatient; duration of symptoms is median with range 3-54 months; 4 of the 5 patients that finished the trial had monoclonal T-cell receptor alpha gene rearrangement
Treatment	**Details:** Treatment period 1 year only (patients stopped receiving treatment after this time but were observed)

	Arm No: 1 **Name:** azathioprine **N:** 5 **Pharmacological agent:** azathioprine agent 1: administration: oral Comments: 1 patient started steroids in addition to azathioprine after developing sepsis from a small intesntinal perforation after laparatomy
Other	**Source of funding:** not reported **Authors' conflicts of interest:** not reported
Notes on outcomes	**Notes: Change in fecal alpha 1-antitrypsin clearance and phenotypical analysis of the epithelium and lamina propria were reported in the study but not extracted.**

Baseline characteristics

		All study participants		
		N	k	mean
Patient characteristics:				
Age (median)	Continuous	7		41 [rng 28–56]
Sex (n female)	Dichotomous	7	5	(71.4%)
Duration of CD (months)	Continuous	7		48
positive IgA EMA	Dichotomous	7	2	(28.6%)
negative IgA EMA	Dichotomous	7	5	(71.4%)
iTG (U A/ml)	Continuous	7		23.42857 [rng 2–98]
IgA antiglaidin antibodies (IU/ml)	Continuous	7		31.2 [rng 2–147]
IgG antiglaidin antibodies (IU/ml)	Continuous	7		47.14 [rng 17–105]
TCDy-PCR - monoclonal	Dichotomous	7	5	(71.4%)
TCRy-PCR - polyclonal	Dichotomous	7	2	(28.6%)
presence of ulcerative jejunitis	Dichotomous	7	5	(71.4%)
jejunal stenosis	Dichotomous	7	1[a]	(14.3%)
jejunal ulcers	Dichotomous	5	3	(60.0%)

	mesenteric lymph node cavitation	Dichotomous	7	1	(14.3%)
	a patient also had ulcers on surgical macroscopic examination				

Results			azathioprine		
			N	k	mean
	Clinical response:				
	body mass index (kg/m2) – 0mo (median)	Continuous	5		17 [rng 12–21]
	body mass index (kg/m2) – 12mo (median)	Continuous	5		26 [rng 19–30]
	proportion with diarrhoea – 0mo	Dichotomous	5	4	(80.0%)
	proportion with diarrhoea – 12mo	Dichotomous	5	0	(0.0%)
	proportion with abdominal pain – 0mo	Dichotomous	5	5	(100.0%)
	proportion with abdominal pain – 12mo	Dichotomous	5	0	(0.0%)
	proportion with fever – 0mo	Dichotomous	5	2	(40.0%)
	proportion with fever – 12mo	Dichotomous	5	0	(0.0%)
	body weight (kg) – 0mo (median)	Continuous	5		46 [rng 42–54]
	body weight (kg) – 12mo (median)	Continuous	5		60 [rng 49–77]
	serological response:				
	mean haemoglobin (mmol/L) – 0mo (median)	Continuous	5		10 [rng 8–12]
	mean haemoglobin (mmol/L) – 12mo (median)	Continuous	5		13 [rng 12–14]
	mean albumin level (g/L) – 0mo (median)	Continuous	5		2 [rng 1–3]
	mean albumin level (g/L) – 12mo (median)	Continuous	5		4 [rng 3–4]
	Proportion of IELs per100 epithelial cells (%) – 0mo (median)	Continuous	5		48 [rng 12–55][a]
	Proportion of IELs per100 epithelial cells (%) – 12mo (median)	Continuous	5		12 [rng 7–16]
	EMA positive – 0mo	Dichotomous	5	2	(40.0%)
	EMA positive – 12mo	Dichotomous	5	0	(0.0%)
	Anti-tTG antibodies negative – 0mo	Dichotomous	5	2	(40.0%)
	Anti-tTG antibodies negative – 12mo	Dichotomous	5	0	(0.0%)

	histological response:				
	Marsh III (not otherwise specified) – 0mo	Dichotomous	7	1	(14.3%)
	Marsh III (not otherwise specified) – 12mo	Dichotomous	5	0	(0.0%)
	Marsh IIIC – 0mo	Dichotomous	7	4	(57.1%)
	Marsh IIIC – 12mo	Dichotomous	5	0	(0.0%)
	Marsh IIIB – 0mo	Dichotomous	7	2	(28.6%)
	Marsh IIIB – 12mo	Dichotomous	5	0	(0.0%)
	Marsh II – 0mo	Dichotomous	7	0	(0.0%)
	Marsh II – 12mo	Dichotomous	5	2	(40.0%)
	Marsh 0 – 0mo	Dichotomous	7	0	(0.0%)
	Marsh 0 – 12mo	Dichotomous	5	3	(60.0%)
	adverse events:				
	leukopenia and maxillary and ethmoidal sinus infection – 7mo	Dichotomous	5	1[b]	(20.0%)
	pneumonia – 4mo	Dichotomous	5	1[c]	(20.0%)
	sepsis after small intestinal perforation from laparotomy – mo	Dichotomous	5	1[d]	(20.0%)
	super mesenteric artery infarction – 14mo	Dichotomous	5	1[e]	(20.0%)
	survival/overall mortality:				
	overall mortality – 12mo	Dichotomous	5	3[f]	(60.0%)
	Development of cancer:				
	EATL – 23mo	Dichotomous	5	0[g]	(0.0%)

a unclear of actual value since text says 38% and table says 48% (authors say most had intraepithelial lymphocytosis)
b patient withdrew and then died of sepsis 2 months later
c successfully treated but died due to opportunistic infection (ventricular fibrillation)
d unclear of timing; patient started on steroids and azathioprine according to protocol
e occurred 2 months after trial completed; resulted in death
f 3 patients with adverse events: one with pneumonia after 10 months, one with leukopenia after 9 month, and the other from super mesenteric artery infarction after 14 months
g after end of trial with mean 11 month follow-up after trial (range 4 to 16 m)

	All 4 patients who completed the 1 year trial experienced improvement of their condition; once these patients were no longer being treated with azathioprine (after the 1 year), all but the one patient who died of superior mesenteric artery continued to be in good health on a GFD only after the end of the trial (mean 11 months after the trial, range 4 to 16 months) with no evidence of lymphoma

Definitions of abbreviations are given at the end of this document.

Bibliographic reference (Ref ID)	**Peters,T.J. et al. (1978)**
Study characteristics	**Study design:** case series **Prospective/retrospective:** unclear **Consecutive patients:** unclear **Country:** UK
Patient characteristics	**Recruitment period:** not reported **Inclusion criteria:** patients with non-responsive coeliac disease who had received a GFD **Definition of RCD:** authors just report non-responsive coeliac disease and this is those who have not responded to a GFD **Exclusion criteria:** not reported **Length of time on a gluten-free diet:** at least 3 years **Description of gluten-free diet (and how adherence was monitored):** not reported **RCD type:** not reported **Number of patients included:** 5 **Concomitant conditions:** - **Comments:** the purpose of the study was to perform analytical subcellular fractionation and enzymic microassay to examine the pathology of patients non-responsive and compare this with those who do respond to a GFD
Treatment	**Details:** - **Arm No:** 1 **Name:** Prednisolone **N:** 5 **Pharmacological agent:** prednisolone agent 1: administration: oral agent 1: dosage (oral): 20

	agent 1: length of treatment (mean): 1.6 Comments: Patient received treatment for 5, 5, 6, 9, and 7 weeks, respectively
Other	**Source of funding:** Medical Research Council and The Wellcome Trust **Authors' conflicts of interest:** not reported
Outcomes	**Notes: only outcomes relevant to this review question were extracted (results from analytical subcellular fractionation and enzymic microassay were not extracted)**

Baseline characteristics

		All study participants		
		N	**k**	**mean**
Patient characteristics:				
Age	Continuous	5		54.8 [rng 31–72]
Sex (n female)	Dichotomous	5	3	(60.0%)
primary RCD	Dichotomous	5	1	(20.0%)
secondary RCD	Dichotomous	5	4	(80.0%)

Results

		Prednisolone		
		N	**k**	**mean**
histological response:				
subtotal villous atrophy – 0wk	Dichotomous	5	5	(100.0%)
subtotal villous atrophy – 6wk	Dichotomous	5	0	(0.0%)
partial villous atrophy – 0wk	Dichotomous	5	0	(0.0%)
partial villous atrophy – 6wk	Dichotomous	5	4	(80.0%)
normal histology – 0wk	Dichotomous	5	0	(0.0%)
normal histology – 6wk	Dichotomous	5	1	(20.0%)

	follow-up recorded is average (patients were treated for 5, 5, 6, 9, and 7 weeks, respectively)

Definitions of abbreviations are given at the end of this document.

Bibliographic reference (Ref ID)	Rubio-Tapia,Alberto et al. (2009)
Study characteristics	**Study design:** case series **Prospective/retrospective:** Retrospective **Consecutive patients:** unclear **Country:** USA
Patient characteristics	**Recruitment period:** June 1998 to October 2007 **Inclusion criteria:** patients with RCD treated at the Mayo Clinic Rochester in the specified recruitment period **Definition of RCD:** recurrence or persistence of symptoms (diarrhoea, involuntary loss of weight and/or abdominal pain) and intestinal damage (at least partial villous atrophy) who needed alternative therapy because of a lack of response to a GFD for at least 6 to 12 months, and EMA or tTGA autoantibodies (positive to indicate CD diagnosis and negative to support GFD compliance and that patients were refractory) (RCDI/RCDII determined by absence or presence of aberrant monoclonal phenotype of IEL determined by immunohistochemical and/or T-cell clonality analyses) (previous diagnosis of CD was biopsy-proven with history of clinical response to GFD, positive serologic coeliac tests, presence of HLA alleles at risk of CD DQ2 or DQ8, family history of CD were all considered supportive for diagnosis of CD, especially patients with primary non-response to GFD) **Exclusion criteria:** other causes of nonresponsive CD inccluding dietary inquiry to exclude intentional or inadvertent gluten contamination, overt intestinal or systemic lymphoma, presence of anti-enterocyte antibodies, diagnosis of EATL prior to CD, other refractory sprue-like conditions such as adult autoimmune enteropathy, hypogammaglobulinemia sprue, collageous sprue, tropical sprue **Length of time on a gluten-free diet:** at least 6 months **Description of gluten-free diet (and how adherence was monitored):** not reported; there was a dietary inquiry to exclude intentional or inadvertent gluten contamination **RCD type:** I and II (reported separately) **Number of patients included:** 57 **Concomitant conditions:** a large number of common concomitant conditions excluded but, of all 57 patients (all but 2 treated with pharmacological treatments), 19 had microscopic colitis (17 were RCDI), and 4 had ulcerative jejunoileitis (all RCDII), and 3 had cavitating mesenteric lymphdenopathy (all RCD II);5 had small-intestine bacterial overgrowth (3 with RCDI) but diagnosis of RCD was considered only after lack of clinical response to oral antibiotics **Comments:** Purpose of study was to describe the clinical characteristics and outcome of a cohort of patients with RCD but some results

	were available about response to specific treatments - results that were reported by treatment that patients received were extracted; 2 of 57 patients did not receive any drug therapy so had parenteral nutrition alone and 1 was treated with ASCT; all patients had villous atrophy and intraepithelial lymphocytosis
Treatment	**Details:** total parenteral nutrition was given to 16 patients (12 with RCDI) and 4 required long-term home parenteral nutrition; pancreatic enzyme supplementation was used as ancillary therapy in 6 patients. **Arm No:** 1 **Name:** Prednisone **N:** 30 **Pharmacological agent:** prednisone agent 1: administration: oral Comments: 0.5 to 1 mg/kg of body weight **Arm No:** 2 **Name:** Azathioprine+prednisone **N:** 7 **Pharmacological agent:** azathioprine+prednisone agent 1: administration: oral agent 2: administration (if different): oral Comments: 0.5 to 1 mg/kg prednisone and 1-2 mg/kg per tday for azathioprine (50-150 mg/day) **Arm No:** 3 **Name:** Budesonide **N:** 15 **Pharmacological agent:** budesonide agent 1: administration: oral agent 1: dosage (oral): 9 **Arm No:** 4 **Name:** Cladribine (2-CDA) **N:** 2 **Pharmacological agent:** cladribine Comments: cladribine was 5 mg/m2day for days 1 to 5 (the paper then says 'q28 days per 2 cycles') **Arm No:** 5

	Name: All treatment groups **N:** 54 **Pharmacological agent:** any treatment
Other	**Source of funding:** National Institutes of Health grants **Authors' conflicts of interest:** none
Outcomes	**Clinical response –** defined as disappearance of diarrhoea and at least 2 of the following: increase of BMI > 1 point, increase in albumin > 10% of baseline, increase of haemoglobin > 1 point, and/or reversion > or = to 1 stage of modified Marsh classification after treatment **Clinical and histological response**: clinical response defined above and histological response defined as normal intestinal biopsy during follow-up)

Baseline characteristics

		All study participants		
		N	**k**	**mean**
Patient characteristics:				
Age (median)	Continuous	57		59 [rng 30–76]
Sex (n female)	Dichotomous	57	38[a]	(66.7%)
length of time on GFD (months) (median)	Continuous	57		18 [rng 12–276]
HLA-DQ status - DQ2/8	Dichotomous	57	32	(56.1%)
positive EMA or tTGA	Dichotomous	48	29[b]	(60.4%)
Marsh IIIA	Dichotomous	57	32	(56.1%)

	Marsh IIIB	Dichotomous	57	7	(12.3%)
	Marsh IIIC	Dichotomous	58	18	(31.0%)
	diarrhoea	Dichotomous	57	57	(100.0%)
	RCD type 1				
	Patient characteristics:				
	Marsh IIIA	Dichotomous	15	26	(173.3%)
	Marsh IIIB	Dichotomous	15	4	(26.7%)
	Marsh IIIC	Dichotomous	15	12	(80.0%)
	abdominal pain	Dichotomous	42	19	(45.2%)
	RCD type 2				
	Patient characteristics:				
	Marsh IIIA	Dichotomous	42	6	(14.3%)
	Marsh IIIB	Dichotomous	42	3	(7.1%)
	Marsh IIIC	Dichotomous	42	6	(14.3%)
	abdominal pain	Dichotomous	15	14	(93.3%)

a approximated to nearest integer (percentages only presented in text)
b before onset of GFD or during follow-up

			Prednisone		
			N	**k**	**mean**
Results	Overall response:				
	Clinical and histological response	Dichotomous	11	2	(18.2%)
	RCD type 2				
	serological response:				
	presence of aberrant clone	Dichotomous	6	5[a]	(83.3%)
	Development of cancer:				
	EATL	Dichotomous	6	3[b]	(50.0%)

a *uncertain of denominator as not all patients had follow-up biopsy*
b *of the 5 who had persistent clone despite treatment and 1 without aberrant clone; 18 and 24 months after clone detection*

		Azathioprine+prednisone		
		N	**k**	**mean**
Overall response: Clinical and histological response	Dichotomous	2	1	(50.0%)

		Budesonide		
		N	**k**	**mean**
Overall response: Clinical and histological response	Dichotomous	9	4	(44.4%)

		Cladribine (2-CDA)		
		N	**k**	**mean**
RCD type 2 serological response: presence of aberrant clone	Dichotomous	2	1[a]	(50.0%)

a *uncertain of denominator as not all patients had follow-up biopsy*

	All treatment groups

		N	k	mean
Clinical response:				
proportion achieved	Dichotomous	57	44[a]	(77.2%)
Overall response:				
Clinical and histological response	Dichotomous	26	9[b]	(34.6%)
survival/overall mortality:				
overall mortality	Dichotomous	57	15	(26.3%)
RCD type 1				
Overall response:				
Clinical and histological response	Dichotomous	18	6	(33.3%)
survival/overall mortality:				
5-year survival (Kaplan-Meier)	Time-to-event	15		80
overall mortality	Dichotomous	18	8[c]	(44.4%)
RCD type 2				
serological response:				
presence of aberrant clone	Dichotomous	8	5[d]	(62.5%)
Overall response:				
Clinical and histological response	Dichotomous	8	3	(37.5%)
survival/overall mortality:				
5-year survival (Kaplan-Meier)	Time-to-event	42		45
overall mortality	Dichotomous	42	7[e]	(16.7%)
Development of cancer:				
EATL	Dichotomous	42	10[f]	(23.8%)

a the numerator includes 1 patient treated with ASCT and 2 that had parenteral nutrition alone
b biopsy data only available for 26 patients; numerator may include 3 patients not treated with pharmacological treatments
c due to refractory state and emaciation in most
d in 8 of those with follow-up biopsy after median 15 months (range 7-41)

	e due to EATL in most *f after median 18 months (range 9-34)*
	Follow-up biopsies were available 23.5 months (range 6 to 54) in 26 patients; no association between subgroup (ie. RCDI or RCDII) was found after adjusting for age; 5 factors present at RCD diagnosis were found to be associated with mortality albumin (3.2 or greater g/decileter), haemoglobin 11 or more g per deciliter), age 65 or greater years, presence of aberrant IEL, and total villous atrophy (stage IIIc)

Definitions of abbreviations are given at the end of this document.

Bibliographic reference (Ref ID)	**Tack,G.J. et al. (2011)**
Study characteristics	**Study design:** case series **Prospective/retrospective:** unclear **Consecutive patients:** unclear **Country:** Netherlands
Patient characteristics	**Recruitment period:** 2000 to 2010 **Inclusion criteria:** patients diagnosed with RCD II and treated with one or two courses of cladribine at the VU University Medical Centre **Definition of RCD:** based on persisting or recurring clinical symptoms and small intestinal villous atrophy after a former good response to a strict GFD (secondary RCD), despite strict adherence to the diet for more than 12 months; 20% aberrant IELs detected by flow cytometric analysis was cut-off value used to distinguish between RCD I and RCD II **Exclusion criteria:** EATL (diagnosis confirmed with WHO Classification of Tumours of Haematopoetic and Lymphoid tissues); pre-treatment with immunomodulatory drugs within 6 months or any experimental drug within 30 days not permitted (though the study appears to compare 10 who failed on pre-treatment with immunosuppressive drugs with 22 who had not previously been treated with immunosupressive drugs) **Length of time on a gluten-free diet:** at least 1 year **Description of gluten-free diet (and how adherence was monitored):** not reported; nutritional screening performed by a dietician who specialised in CD. **RCD type:** II **Number of patients included:** 32 **Concomitant conditions:** not reported **Comments:** includes 14 of 17 patients in Al-Toma 2006 with longer follow-up (the other 3 patients were followed up at another hospital);

	includes 10 patients who had pre-treatment with other immunosupressive drugs (azathioprine or prednisone) and reports some outcomes separately for those who did or did not receive pre-treatment
Treatment	**Arm No:** 1 **Name:** Cladribine +/- pre-treatment with azathioprine or prednisone **N:** 32 **Pharmacological agent:** cladribine with or without immunosuppression agent 1: administration: intravenous agent 1: dosage (intravenous): 0.1 Comments: Given for 5 days
Other	**Source of funding:** not reported **Authors' conflicts of interest:** not reported
Notes on outcomes	**Clinical response -** defined as improvement in diarrhoea, abdominal discomfort and/or signs of malapsorption, combined with at least 2 out of the following parameters of intestinal integrity within the normal range or an improvement of 1 or more points in haemoglobin, BMI and albumin **Histological response** - complete histological remission defined as normalisation of architecture of duodenum, classified as Marsh 0 or 1 lesion according to Modified Marsh classification

Baseline characteristics

		All study participants		
		N	**k**	**mean**
Patient characteristics:				
Age (median)	Continuous	32		64 [rng 45–78][a]
Sex (n female)	Dichotomous	32	14	(43.8%)
Duration of CD (months)	Continuous	32		
HLA-DQ status - DQ2 homozygous	Dichotomous	32	12	(37.5%)
HLA-DQ status - DQ2 hetergozygous	Dichotomous	32	17	(53.1%)
HLA-DQ status - DQ2/8	Dichotomous	32	2	(6.3%)
HLA-DQ status - not measured/unknown	Dichotomous	32	1	(3.1%)
Proportion of IELs per100 epithelial cells (%) (median)	Continuous	32		61 [rng 21–96]

	serum albumin (g/DL) (median)	Continuous	32		36 [rng 23–47][b]
	body mass index (kg/m2) (median)	Continuous	32		21 [rng 16–27]
	haemoglobin (g/dL) (median)	Continuous	32		7.8 [rng 6–9.8]
	TCDy-PCR - monoclonal	Dichotomous	32	18	(56.3%)
	TCRy-PCR - polyclonal	Dichotomous	32	9	(28.1%)
	TCRy-PCR - unknown	Dichotomous	32	5	(15.6%)
	Marsh IIIA	Dichotomous	32	13	(40.6%)
	Marsh IIIB	Dichotomous	32	11	(34.4%)
	Marsh IIIC	Dichotomous	32	8	(25.0%)

a *at start of treatment (start of diagnosis median 64, range 42 to 78)*
b *reference value 35-52 g/L*

Results

		Cladribine +/- pre-treatment with azathioprine or prednisone		
		N	**k**	**mean**
Clinical response:				
body mass index (kg/m2) – 0mo (median)	Continuous	32		20.9 [rng 16–27]
body mass index (kg/m2) – 31mo (median)	Continuous	32		23[a]
proportion achieved – 12mo	Dichotomous	32	26	(81.3%)
proportion achieved – 24mo	Dichotomous	32	26	(81.3%)
Serological response:				
mean haemoglobin (mmol/L) – 0mo (median)	Continuous	32		7.8 [rng 6–9.8]
mean haemoglobin (mmol/L) – 31mo (median)	Continuous	32		7.9*a*
mean albumin level (g/L) – 0mo (median)	Continuous	32		36 [rng 23–47]
mean albumin level (g/L) – 31mo (median)	Continuous	32		39*a*
Proportion of IELs per100 epithelial cells (%) – 0mo (median)	Continuous	32		61 [rng 21–96]

	Proportion of IELs per100 epithelial cells (%) – 31mo (median)	Continuous	32		56*a*
	Histological response:				
	proportion achieved improvement – 12mo	Dichotomous	32	3[b]	(9.4%)
	proportion achieved improvement – 12mo	Dichotomous	32	3*b*	(9.4%)
	proportion achieved improvement – 24mo	Dichotomous	32	15	(46.9%)
	proportion achieved improvement – 24mo	Dichotomous	32	15	(46.9%)
	partial remission – 24mo	Dichotomous	32	2[c]	(6.3%)
	Immunological response:				
	proportion > or = 20% decrease in aberrant IELs – 12mo	Dichotomous	32	12*b*	(37.5%)
	proportion > or = 20% decrease in aberrant IELs – 24mo	Dichotomous	32	13	(40.6%)
	Overall response:				
	Histological, immunological and clinical response – 12mo	Dichotomous	32	8[d]	(25.0%)
	Histological, immunological and clinical response – 24mo	Dichotomous	32	13[e]	(40.6%)
	Survival/overall mortality:				
	overall mortality – 31mo	Dichotomous	32	12	(37.5%)
	death due to EATL – 31mo	Dichotomous	32	5[f]	(15.6%)
	Development of cancer:				
	EATL – 31mo	Dichotomous	32	5[g]	(15.6%)
	pre-treatment with immunosuppressive drugs				
	Clinical response:				
	proportion achieved – 12mo	Dichotomous	10	7*b*	(70.0%)
	proportion achieved – 24mo	Dichotomous	10	7*b*	(70.0%)
	Histological response:				
	proportion achieved improvement – 12mo	Dichotomous	10	1*b*	(10.0%)
	proportion achieved improvement – 12mo	Dichotomous	10	1*b*	(10.0%)
	proportion achieved improvement – 24mo	Dichotomous	10	2*b*	(20.0%)
	proportion achieved improvement – 24mo	Dichotomous	10	2*b*	(20.0%)

	Immunological response:				
	proportion > or = 20% decrease in aberrant IELs – 12mo	Dichotomous	10	1*b*	(10.0%)
	proportion > or = 20% decrease in aberrant IELs – 24mo	Dichotomous	10	1*b*	(10.0%)
	Overall response:				
	Histological, immunological and clinical response – 12mo	Dichotomous	10	2*b*	(20.0%)
	Histological, immunological and clinical response – 24mo	Dichotomous	10	4*b*	(40.0%)
	no immunosupressive pre-treatment				
	Clinical response:				
	proportion achieved – 12mo	Dichotomous	22	21*b*	(95.5%)
	proportion achieved – 24mo	Dichotomous	22	21*b*	(95.5%)
	Histological response:				
	proportion achieved improvement – 12mo	Dichotomous	22	4*b*	(18.2%)
	proportion achieved improvement – 12mo	Dichotomous	22	4*b*	(18.2%)
	proportion achieved improvement – 24mo	Dichotomous	22	13*b*	(59.1%)
	proportion achieved improvement – 24mo	Dichotomous	22	13*b*	(59.1%)
	Immunological response:				
	proportion > or = 20% decrease in aberrant IELs – 12mo	Dichotomous	22	11*b*	(50.0%)
	proportion > or = 20% decrease in aberrant IELs – 24mo	Dichotomous	22	13*b*	(59.1%)
	Overall response:				
	Histological, immunological and clinical response – 12mo	Dichotomous	22	6*b*	(27.3%)
	Histological, immunological and clinical response – 24mo	Dichotomous	22	9*b*	(40.9%)
	responders				
	Survival/overall mortality:				
	3-year survival (Kaplan-Meier) – 36mo	Time-to-event	18		83[h]
	5-year survival (Kaplan-Meier) – 60mo	Time-to-event	18		83*h*
	overall mortality – 31mo	Dichotomous	18	3[i]	(16.7%)

	non-responders				
	Survival/overall mortality:				
	3-year survival (Kaplan-Meier) – 36mo	Time-to-event	14		63*h*
	5-year survival (Kaplan-Meier) – 60mo	Time-to-event	14		22*h*
	overall mortality – 31mo	Dichotomous	14	9[j]	(64.3%)

a *unclear of denominator*
b *approximated to nearest integer (percentages only presented in text)*
c *From marsh 3B to 2 and 3C to 3A*
d *estimated from percentage*
e *approximated to nearest integer (percentages only presented in text); however this appears different from the text which says 18 (56%) achieved this*
f *all patients who developed EATL died with a median survival of 4.4 months after diagnosis*
g *all died with a median survival of 4.4 months after diagnosis*
h *the overall median survival was 4.5 years*
i *refractory disease status (n=1), EATL (n=2)*
j *EATL (n=3), refractory disease (n=6)*

	median follow-up was 31 months (range 4 - 120 months); time to a 50% response rate was 3 years; authors report a Cox regression analysis which they state that the following values have no predictive value for response to cladribine: age at infusion, sex, TCR-gamma-clonality, percentage of averrant IELs, degree of small intestinal villous atrophy, BMI, albumin and haemoglobin (however, age was borderline not significant)

Definitions of abbreviations are given at the end of this document.

Bibliographic reference (Ref ID)	**Tack,G.J. et al. (2012)**
Study characteristics	**Study design:** case series **Prospective/retrospective:** Retrospective **Consecutive patients:** No **Country:** Netherlands
Patient characteristics	**Recruitment period:** June 2001 and Nov 2010 **Inclusion criteria:** all patients diagnosed with RCDI and who received tioguanine as first or second-line therapy at the Gastroenterology department of a tertiary referral centre

	Definition of RCD: diagnosis of RCD I based on persisting or recurring symptoms and small intestinal villous atrophy despite strict adherence to a GFD for at least 1 year, determined from negative serology and a specialised dietician; proportion of aberrant IELs detected with flow cytometric analysis of small intestinal biopsy had to be less than 20% **Exclusion criteria:** EATL **Length of time on a gluten-free diet:** at least 1 year **Description of gluten-free diet (and how adherence was monitored):** Not reported; adherence monitoring from negative serology and assessment by a specialist dietician **RCD type:** I **Number of patients included:** 12 **Concomitant conditions:** not reported **Comments:** one patient was excluded from the study due to loss of follow-up; at baseline, duodenal biopsy showed intraepithelial lymphocytosis, crypt hyperplasia, and villous atrophy in all patients; patients had weight loss and gastrointestinal symptoms including diarrhoea prior to treatment
Treatment	**Details:** study reports that four of the 10 patients who tolerated treatment for at least 6 months had been using corticosteroids at baseline (prednisone > or = 10 mg or budesonide > or = 9 mg) (all showed clinical response but only 2 showed histological response); patients were withdrawn from treatment after both clinical and complete histological response (this occurred at median 17 months) - 4 of the 6 patients withdrawn for this reaason had further endoscopic evaluation: 3 had clinical response but only 2 of these had histological response (the other evolved from Marsh I to IIIA) and one needed treatment afain after 5 months because of symptoms returning (this corresonded with developemnt of Marsh II). **Arm No:** 1 **Name:** Tioguanine **N:** 0 **Pharmacological agent:** tioguanine agent 1: administration: oral agent 1: dosage (oral): 0.36 Comments: median dosage with range 0.26 to 0.69 mg/kg corresponding to median 19 mg/day (range 18-40); administered as 18, 21 or 24 mg capsules or 20 mg tablets
Other	**Source of funding:** not reported (but paper states no funding interests) **Authors' conflicts of interest:** paper states no personal interests
Notes on outcomes	**Clinical response** – defined as amelioration of GI symptoms, combined with at least 2 of the following witih their reference range or with an improvement of 1 or more point: BMI, albumin, haemoglobin

	histological response – complete response characterised by normalisation of the small mucosal architecture as Marsh 0 or 1 (partial was improvement in Marsh by 2 or more steps) **Notes: 6-tioguanine nucleotide concentrations were reported in the study but not extracted.**

Baseline characteristics

		Tioguanine		
		N	**k**	**mean**
Patient characteristics:				
Age	Continuous	12		46.6
Sex (n female)	Dichotomous	12	8	(66.7%)
length of time on GFD (months) – 0mo	Continuous	12		107.1
HLA-DQ status - DQ2 homozygous	Dichotomous	12	5	(41.7%)
HLA-DQ status - DQ2 hetergozygous	Dichotomous	12	5	(41.7%)
HLA-DQ status - DQ2/8	Dichotomous	12	1	(8.3%)
HLA-DQ status - not measured/unknown	Dichotomous	12	1	(8.3%)
Negative EMA at diagnosis	Dichotomous	12	10	(83.3%)
Dubious EMA at diagnosis	Dichotomous	12	2	(16.7%)
Negative tTGA at diagnosis	Dichotomous	12	11	(91.7%)
Dubious tTGA at diagnosis	Dichotomous	12	1	(8.3%)
primary RCD	Dichotomous	12	6	(50.0%)
secondary RCD	Dichotomous	12	6	(50.0%)
first-line treatment	Dichotomous	12	8	(66.7%)
second-line treatment	Dichotomous	12	4[a]	(33.3%)

a due to intolerance or resistance to azathioprine or corticosteroid dependency

Results

	Tioguanine		
	N	**k**	**mean**

Clinical response:					
body mass index (kg/m2) – 0mo (median)	Continuous	12		19.5 [rng 16.7–27.8]
body mass index (kg/m2) – 12mo (median)	Continuous	12		22.4 [rng 19.7–27.1]
body weight (kg) – 0mo (median)	Continuous	12		56.5 [rng 46–86]
body weight (kg) – 12mo (median)	Continuous	12		65 [rng 53–84]
proportion achieved – mo	Dichotomous	12	10	(83.3%)
Serological response:				
mean haemoglobin (mmol/L) – 0mo (median)	Continuous	12		7.7 [rng 6.5–9.7]
mean haemoglobin (mmol/L) – 12mo (median)	Continuous	12		8 [rng 7.3–9.9]
mean albumin level (g/L) – 0mo (median)	Continuous	12		38 [rng 27–44]
mean albumin level (g/L) – 12mo (median)	Continuous	12		40 [rng 32–45]
Histological response:				
proportion achieved improvement – 18mo	Dichotomous	9	7[a]	(77.8%)
no response – mo	Dichotomous	9	2[b]	(22.2%)
Marsh IIIC – 0mo	Dichotomous	12	1	(8.3%)
Marsh IIIC – 12mo	Dichotomous	9	0[c]	(0.0%)
Marsh IIIC – 24mo	Dichotomous	8	0[d]	(0.0%)
Marsh IIIB – 0mo	Dichotomous	12	2	(16.7%)
Marsh IIIB – 12mo	Dichotomous	9	1*c*	(11.1%)
Marsh IIIB – 24mo	Dichotomous	8	0*d*	(0.0%)
Marsh IIIA – 0mo	Dichotomous	12	9	(75.0%)
Marsh IIIA – 12mo	Dichotomous	9	2*c*	(22.2%)
Marsh IIIA – 24mo	Dichotomous	8	1*d*	(12.5%)
Marsh II – 0mo	Dichotomous	12	0	(0.0%)
Marsh II – 12mo	Dichotomous	9	1*c*	(11.1%)
Marsh II – 24mo	Dichotomous	8	0*d*	(0.0%)
Marsh 0 – 0mo	Dichotomous	12	0	(0.0%)

	Marsh 0 – 12mo	Dichotomous	9	5*c*	(55.6%)
	Marsh 0 – 24mo	Dichotomous	6	1[e]	(16.7%)
	Adverse events:				
	leukopenia	Dichotomous	12	0	(0.0%)
	liver test abnormalities – 3wk	Dichotomous	12	1[f]	(8.3%)
	muscle spasm – 9mo	Dichotomous	12	1[g]	(8.3%)
	anaemia	Dichotomous	12	0	(0.0%)
	thrombopaenia	Dichotomous	12	0	(0.0%)
	Survival/overall mortality:				
	overall mortality – 4mo	Dichotomous	12	1[h]	(8.3%)
	a achieved at average 18 months (one beyond 48m); not determined in 3 *b* after 12 to 14 months (these patients had clinical response) *c* not determined in 3 *d* not determined in 4 *e* not determined in 4; 4 of those who had achieved Marsh 0 at 12 months were not measured again at 24 months *f* gama glutamyltransferase, alanine aminotransferase, and aspartate aminotransferase all 2x limit (alkaline phosphatase normal) not responding to dose reduction; withdrawn after 17 months due to achievement of clinical &histological response (values returned to normal during follow-up after cessation of tioguanine) *g* causing withdrawal from treatment (resolved after treatment stopped & corticosteroids started); no lab abnormalities; patient refractory to previous azathioprine treatment *h* progression of RCDI with severe diarrhoea not responding to prednisone, severe metabolic dysregulation including metabolic acidosis, hypokalaemia & hypoalbumaenia complicated with septic shock & multi-organ failure				
	Follow-up at average of 14 months ranging from 8 weeks to 8 years; study reports that four of the 10 patients who tolerated treatment for at least 6 months had been using corticosteroids at baseline (prednisone > or = 10 mg or budesonide > or = 9 mg) and 2 were dependent on corticosteroids during follow-up - all showed clinical response but only 2 showed histological response				

Definitions of abbreviations are given at the end of this document.

Bibliographic reference (Ref ID)	**Wahab,P.J. et al. (2000)**
Study characteristics	**Study design:** case series **Prospective/retrospective:** Prospective

	Consecutive patients: unclear **Country:** Netherlands
Patient characteristics	**Recruitment period:** between 1993 and 1997 **Inclusion criteria:** adults with refractory CD treated as out-patients **Definition of RCD:** malabsorption in the prescencce of gluten-related partial, subtotal or total villous atrophy on small intestinal biopsy supported by additional arguments for gluten-free sensitivity before starting a GFD (such as serum antigliandin and/or antiendomysial antibodies) **Exclusion criteria:** other possible pathology which could be responsible for malabsorpotion in the presence of villous atrophy such as: bacterial overgrowth, giardiasis, eosinophilic enteritis, hypgammaglobulinaemic sprue, lymphoma, carcinoma and collagenous colitis (determined from histological, serological and radiological investigations) **Length of time on a gluten-free diet:** at least 1 year **Description of gluten-free diet (and how adherence was monitored):** not reported; compliance determined from repeated interviews and dietary advice by the treatment team, including a dietician **RCD type:** not reported **Number of patients included:** 13 **Concomitant conditions:** a number excluded (see exclusion criteria); authors noted that no other concomitant conditions were noticed in these patients
Treatment	**Details:** treatment given for 2 months in all but then continued for up to a year in those who had histological improvement and/or symptom resolution **Arm No:** 1 **Name:** Cyclosporin **N:** 0 **Pharmacological agent:** cyclosporin agent 1: administration: oral agent 1: dosage (oral): 5 Comments: divided in 2 doses per day
Other	**Source of funding:** not reported **Authors' conflicts of interest:** not reported
Notes on outcomes	**Clinical response** – defined as patient symptoms after treatment improved (ie. improvement of fatigue, abdominal complaints and diarrhoea); those without response had no change in symptoms

	histological response – improvement considered a nomalisation of villi (to Marsh I or II)) **Notes: Cyclosporin serum concentration, range of antigliandin antibodies (IU/mL), and change in sugar absorption were reported in the study but not extracted.**

Baseline characteristics

		All study participants		
		N	**k**	**mean**
Patient characteristics:				
Age	Continuous	13		55[a]
Sex (n female)	Dichotomous	13	12	(92.3%)
length of time on GFD (months)	Continuous	13		86.8
HLA-DQ status - DQ2 homozygous	Dichotomous	13	5	(38.5%)
HLA-DQ status - DQ2 hetergozygous	Dichotomous	13	5	(38.5%)
HLA-DQ status - not measured/unknown	Dichotomous	13	3	(23.1%)
Negative EMA at diagnosis	Dichotomous	5	3[b]	(60.0%)
Dubious EMA at diagnosis	Dichotomous	5	2*b*	(40.0%)

a range 32-75
b 8 did not have the test done

Results

		Cyclosporin		
		N	**k**	**mean**
Clinical response:				
proportion achieved – 2mo	Dichotomous	13	8[a]	(61.5%)
proportion not achieved – 2mo	Dichotomous	13	5	(38.5%)
Histological response:				
proportion achieved improvement	Dichotomous	13	6	(46.2%)
Marsh IIIC – 0mo	Dichotomous	13	4	(30.8%)
Marsh IIIC – 2mo	Dichotomous	13	2	(15.4%)

	Marsh IIIC – 12mo	Dichotomous	7	0	(0.0%)
	Marsh IIIB – mo	Dichotomous	13	2	(15.4%)
	Marsh IIIB – 2mo	Dichotomous	13	0	(0.0%)
	Marsh IIIB – 12mo	Dichotomous	7	0	(0.0%)
	Marsh IIIA – mo	Dichotomous	13	8	(61.5%)
	Marsh IIIA – 2mo	Dichotomous	13	9	(69.2%)
	Marsh IIIA – 12mo	Dichotomous	7	3	(42.9%)
	Marsh II – mo	Dichotomous	13	0	(0.0%)
	Marsh II – 2mo	Dichotomous	13	3	(23.1%)
	Marsh II – 12mo	Dichotomous	7	4	(57.1%)
	Marsh I – mo	Dichotomous	13	0	(0.0%)
	Marsh I – 2mo	Dichotomous	13	1	(7.7%)
	Marsh I – 12mo	Dichotomous	7	0	(0.0%)
	Overall response:				
	Clinical and/or histological response	Dichotomous	13	7[b]	(53.8%)
	Adverse events:				
	nausea and abdominal cramps	Dichotomous	13	2	(15.4%)
	gingivitis	Dichotomous	13	1	(7.7%)
	a *6 also had improvement in histology* *b* *all patients continued treatment beyond 2 months*				
	All patients were treated for at least 2 months and 7 received treatment beyond this for up to a year (mean of 7.3 months, range 6 to 12)				