

# AGA Clinical Practice Update on Management of Refractory Celiac Disease: Expert Review By Cicily Vachaparambil, MD

#### **Celiac Disease**

- Affects 1% of the US population
- <u>Dx:</u> serologic testing (anti-tissue transglutaminase, anti-deamidated gliadin peptide, and anti-endomysial antibodies) & duodenal biopsies (villous atrophy and intraepithelial lymphocytosis (IELs))
- Txt: strict gluten free diet (GFD)

# Refractory Celiac Disease (RCD)

• RCD: Persistent signs of malabsorption (diarrhea, weight loss, anemia) and villous atrophy despite 12 months of strict GFD (seen in ~1% of those with CD)



#### Type 1 (RCD1):

- villous atrophy
- IELs similar to conventional celiac disease



#### **Type 2 (RCD2):**

- aberrant clonal T-cell expansion in the GI tract and other organs
- poorer prognosis than Type 1
- † ulcerative jejunoileitis and enteropathyassociated T-cell lymphoma (EATL)

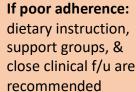
## Diagnosis of RCD

• If there is Celiac disease with persistent or recurrent symptoms or signs, confirm celiac disease diagnosis w/ review of prior endoscopies, histology, & serology

**Not Celiac Disease** 

Consider other causes of villous atrophy (medinduced or autoimmune enteropathy, tropical sprue, giardiasis, CVID, etc.) Celiac Disease

Confirm adherence to GFD w/ serologic testing (↑ celiac Abs), dietitian review, & detection of immunogenic peptides in stool or urine



#### EGD w/ duodenal bx

- Recommend at least **1–2 biopsies** from the duodenal bulb and **4** from the distal duodenum
- Goal is to identify if there is <u>persistent villous atrophy</u> (necessary but not sufficient to dx RCD)
- If strong suspicion for RCD (in pts w/ wt loss, anemia, GI bleeding, persistent nutritional deficiencies), **consider 6 additional biopsies** from the distal duodenum for flow cytometry, IHC, and T cell receptor rearrangement studies to distinguish between RCD1 and RCD2

If persistent villous atrophy → flow cytometry, IHC, & T cell receptor rearrangement studies to distinguish RCD1 & 2, exclude EATL

- IEL phenotype is determined by IHC and flow cytometry
- T cell receptor  $\gamma$  or  $\beta$  gene rearrangement is determined by PCR
- **RCD1** Polyclonal expansion of IELs with normal phenotype
  - Surface (s) CD3b, cytoplasmic(cyt) CD3+, CD8+, and sTCR+, with polyclonal TCR  $\beta$  or  $\gamma$  gene rearrangements
- RCD2 Clonal proliferation of aberrant IELs
  - Most frequently CD7+, sCD3-, cytCD3+, sCD4-, CD103+, CD8-, and sTCR+

#### If no persistent villous atrophy consider:

- Irritable Bowel Syndrome
- Exocrine Pancreatic Insufficiency
- Lactose/fructose intolerance
- Microscopic colitis
- Small Intestinal Bacterial Overgrowth

## **Management of RCD**

RCD1 and RCD2 RCD2

- Assess micro/macro nutrient status
- Test for Vitamin A, D, E, and prothrombin time for vitamin K deficiency, folate, vitamin B12, iron, copper, and zinc
- Assess thiamine, Mg, Se, and vitamin B6, particularly with chronic or severe diarrhea
- Consider parenteral nutrition if severe malnutrition
- Check albumin as an independent prognostic factor

Open capsule budesonide (preferred) or prednisone Second line therapies include azathioprine, 6MP

## **First Line Oral Medication Options**

#### **Open Capsule Budesonide**

- Administer 3 mg 3 times daily with the first capsule opened and placed into applesauce, the second capsule opened and swallowed with water, and the third capsule swallowed intact
  - 92% w/ clinical response and 89% w/ histologic improvement

#### **Oral Prednisone**

- Administer 40–60 mg daily with slow taper over several months

# **Alternative Therapies for RCD 2**

Elemental Diet - 67% see clinical response, 89% w/ histologic remission

Cladribine - 0.1 mg/kg/day IV x 5 d, 1-3 courses every 6 months

Infliximab - 5 mg/kg IV

Small intestine release mesalamine- 2-4 g PO/day

**Autologous Stem Cell Transplant-** 85% clinical response

Anti-IL 15 monoclonal Ab 714- 8 mg/kg IV on d0, d7, and every 2 wk thereafter through wk 10 - Improvement in symptoms but no decrease in aberrant IELs

Small bowel imaging w/ CTE/MRE or VCE to exclude EATL and ulcerative jejunoileitis

**VCE-** can quantify the extent and severity of villous atrophy

**CT/MRE**- can note bowel wall thickening, mesenteric adenopathy, small bowel masses Repeat imaging if clinically worsening as ↑ lymphoma risk

Second line therapies include infliximab and cladribine

# **Second Line Oral Medication Options**

Add an immunosuppressant to steroids

- Azathioprine: 2-2.5 mg/kg/d
- Mercaptopurine: 1 mg/kg/d
- Tioguanine .3 mg/kg/d (not available in the US)

Not advised in those w/ RCD2 given increased risk of lymphoma development

## **Long Term Care**

Patients w/ RCD **require regular follow**-up by a multidisciplinary team, including gastroenterologists and dietitians, to assess clinical and histologic response to therapy

• Clinic visits every 3 months until disease is well controlled, then every 6 months

**Identify local experts** in celiac disease to help w/ management or if no response to steroids, refer to a center with expertise for management and evaluation for inclusion in clinical trials

**Repeat intestinal biopsy 3–6 months after starting therapy** to assess response to treatment, including mucosal recovery and resolution of molecular/ genetic abnormalities in the IEL.

• Mucosal recovery is seen in RCD1 but less likely in RCD2

