RIIP

RENCONTRES EN IMMUNOLOGIE & IMMUNOTHERAPIE PRATIQUES

29 et 30 SEPTEMBRE 2022

UIC-P - Espaces Congrès
16, rue Jean Rey - 75015 Paris

IMAGE FREEPIK

Sous l'égide de :

AI2R Filière · aviesan alliance nationale pour les sciences de la vie et de la santé · CeRéMAIA · GRI · European Reference Network for rare or low prevalence complex diseases · Fédération Immunologie · Imidiate · RITA Rare Immunodeficiency AutoInflammatory AutoImmune · Société Française de Dermatologie et de Pathologie Sexuellement Transmissible · Société Française d'Immunologie · SFR société française de rhumatologie · SOFREMIP Rhumatologie & maladies inflammatoires pédiatriques · SNFEM

RIP

RENCONTRES EN IMMUNOLOGIE & IMMUNOTHERAPIE PRATIQUES

Maladie coeliaque ou intolérance au gluten
Comment je diagnostique et comment je traite

Pr Christophe Cellier

HEGP Paris

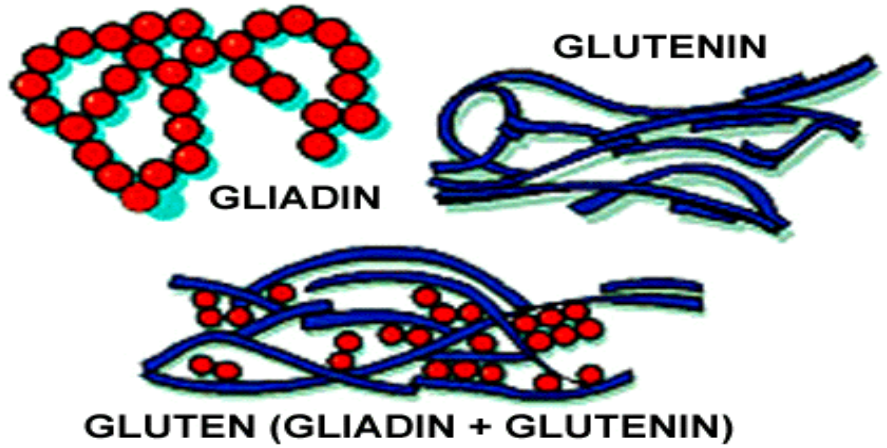
29 et 30 SEPTEMBRE 2022
UIC-P - Espaces Congrès
16, rue Jean Rey - 75015 Paris

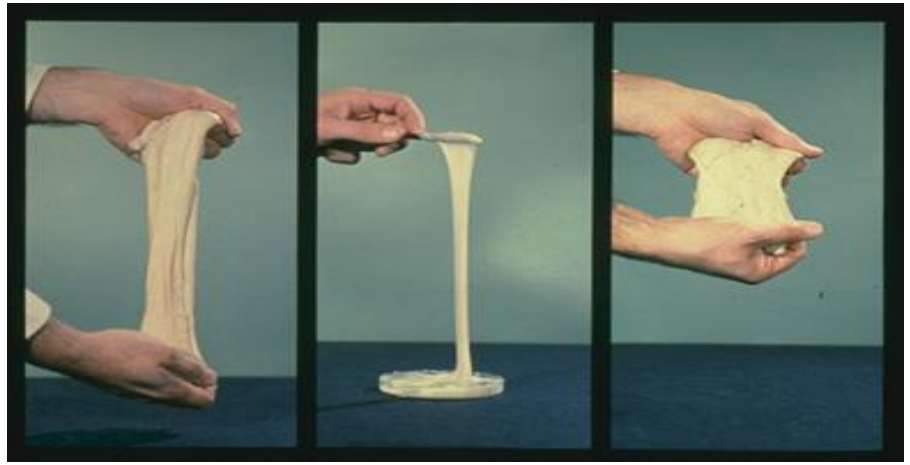
Sous l'égide de :

Liens d'intérêt

- Takeda
- Falk
- Thermofisher
- Dr Shar

Les deux piliers de la fonctionnalité du gluten

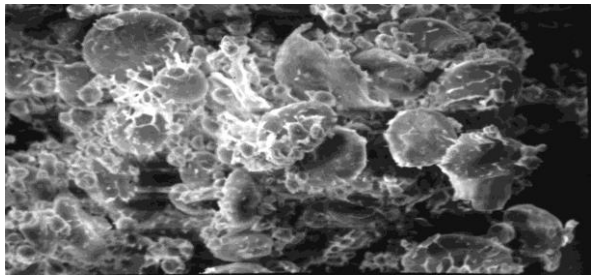




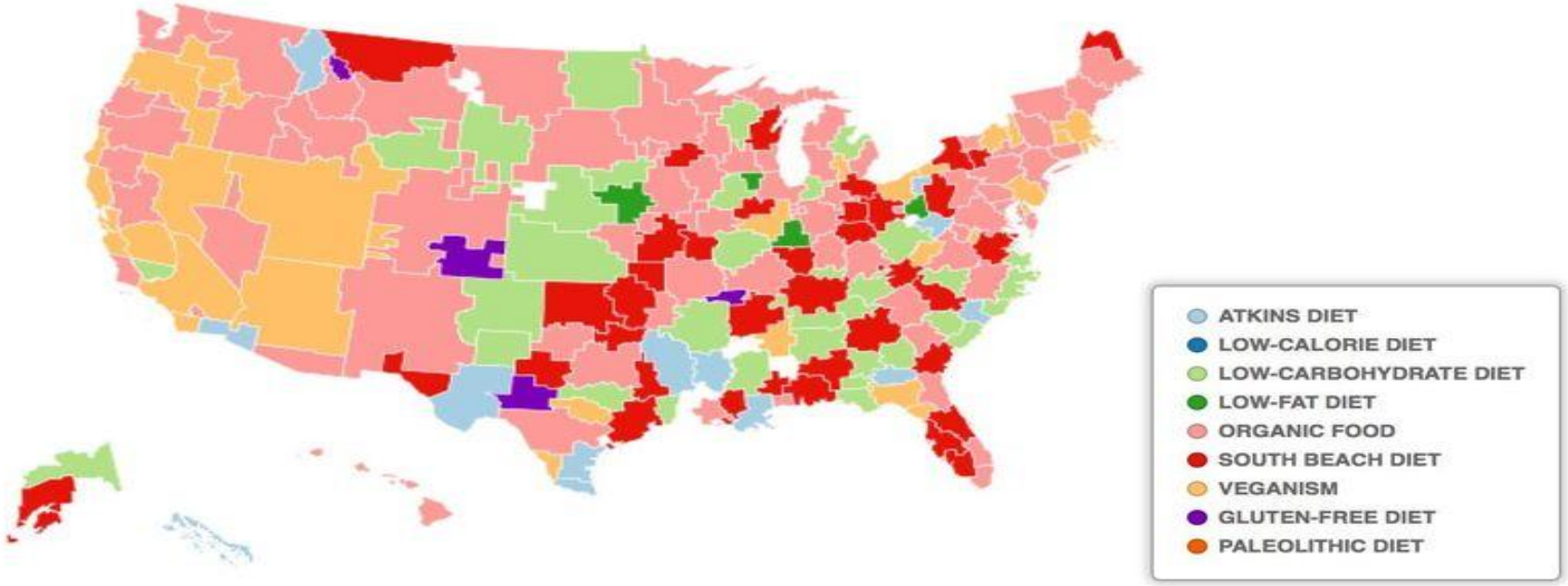
Gluten Gliadine Gluténine

Stabilité fin fermentation

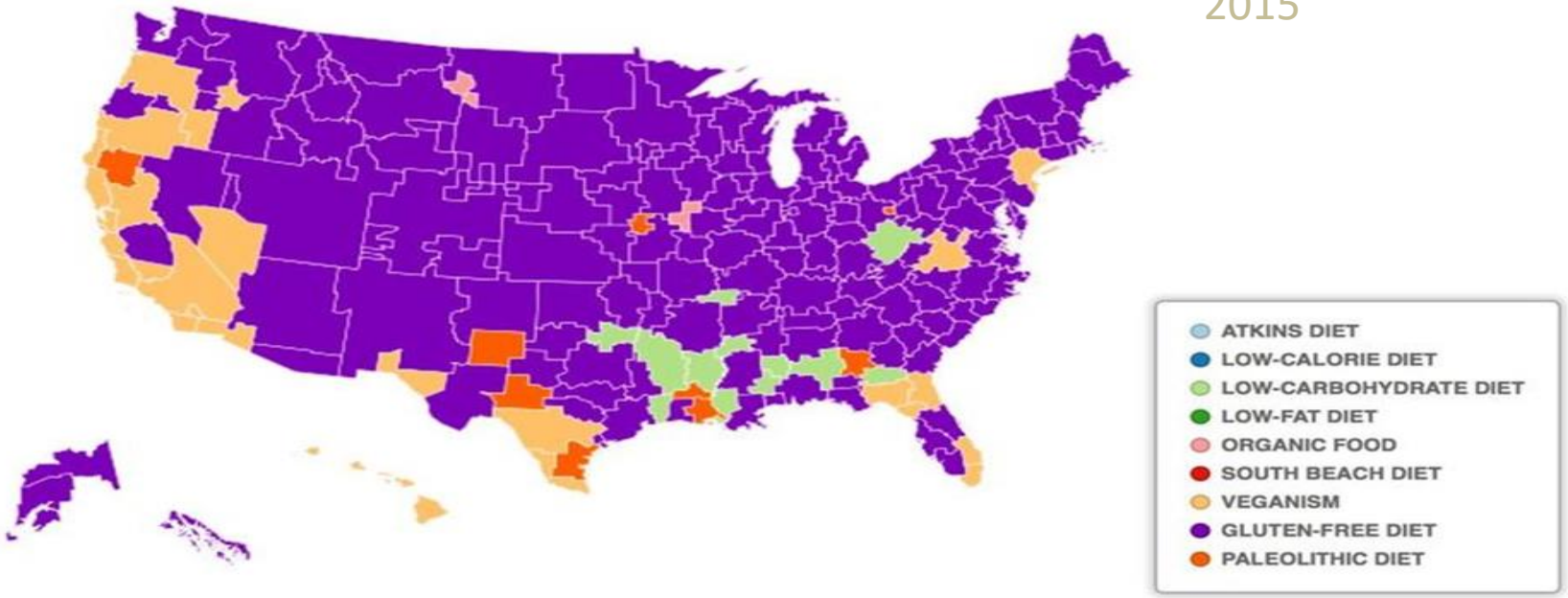
- Les gluténines purifiées (polymères) se caractérisent par leur poids moléculaire élevé et par leur élasticité
- Les gliadines purifiées (monomères) ont un poids moléculaire plus faibles et elles sont visqueuses et très extensibles
- Dans la pâte à pain leurs liaisons et leur interactions avec les autres constituants expliquent ce comportement visco-élastique remarquable.
- Consistance, machinabilité, STABILITE, étanchéité etc



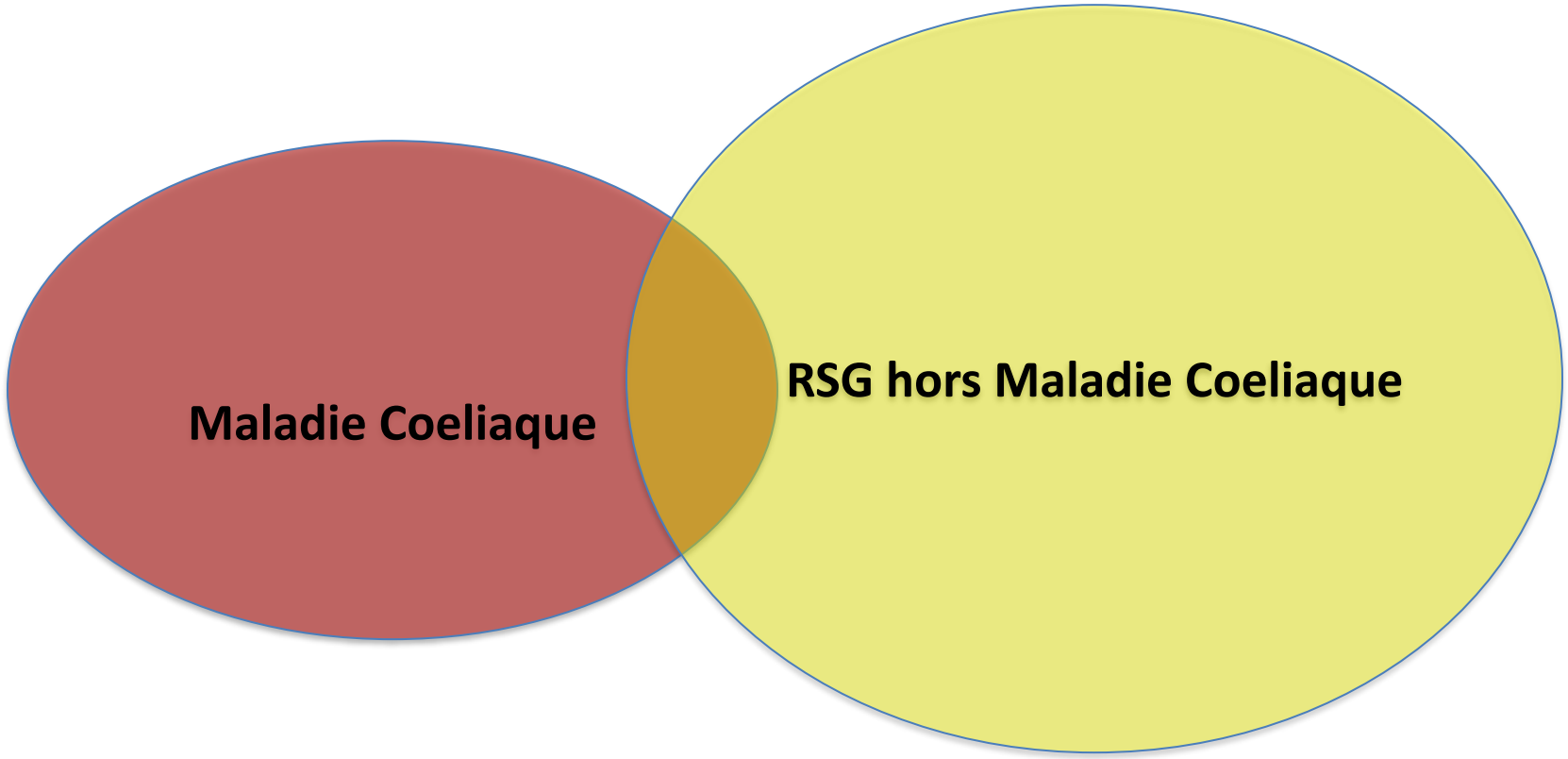
2006


ATKINS DIET
LOW-CALORIE DIET
LOW-CARBOHYDRATE DIET
LOW-FAT DIET
ORGANIC FOOD
SOUTH BEACH DIET
VEGANISM
GLUTEN-FREE DIET
PALEOLITHIC DIET

2015


ATKINS DIET
LOW-CALORIE DIET
LOW-CARBOHYDRATE DIET
LOW-FAT DIET
ORGANIC FOOD
SOUTH BEACH DIET
VEGANISM
GLUTEN-FREE DIET
PALEOLITHIC DIET

Paradoxe du Régime Sans Gluten



Rubio-Tapia, et al. Am J Gastroenterol 2012;107:1538-44.

Gluten et maladies digestives

3 entités distinctes aux mécanismes différents

- Allergie au blé (IgE)

Manifestations immédiates (enfant> adulte)

- nausées, vomissements, urticaire, asthme, Quincke
- Maladie Coeliaque (intolérance au gluten)
- Hypersensibilité non coeliaque au gluten (nouvelle entité?)

Nouvelle communauté

PWAG's (Person Who Avoid Gluten)

Maladie Coeliaque de l'adulte et hypersensibilité au gluten
Recommandations européennes
Pr Christophe Cellier
HEGP Paris

UNITED EUROPEAN GASTROENTEROLOGY ueg journal

Review Article

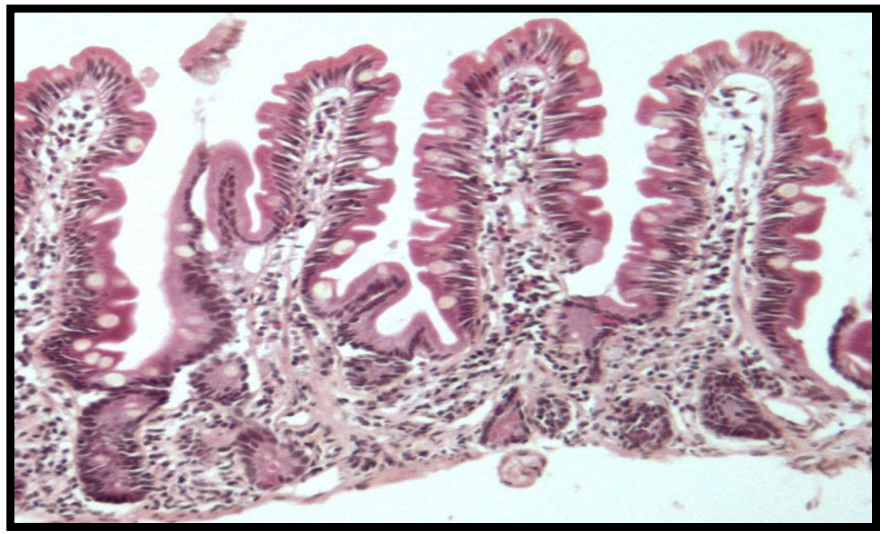
United European Gastroenterology Journal
2019, Vol. 7(5) 583–613

DOI: 10.1177/2050640619844125
journals.sagepub.com/home/ueg
SAGE

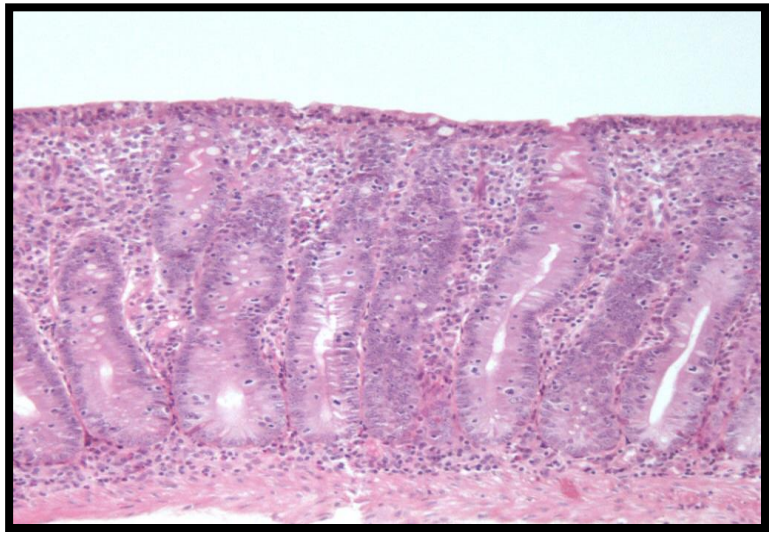
European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders

Abdulbaqi Al-Toma[1], Umberto Volta[2], Renata Auricchio[3,*], Gemma Castillejo[4,*], David S Sanders[5], Christophe Cellier[6], Chris J Mulder[7] and Knut E A Lundin[8,9]

Maladie coeliaque: entéropathie auto-immune



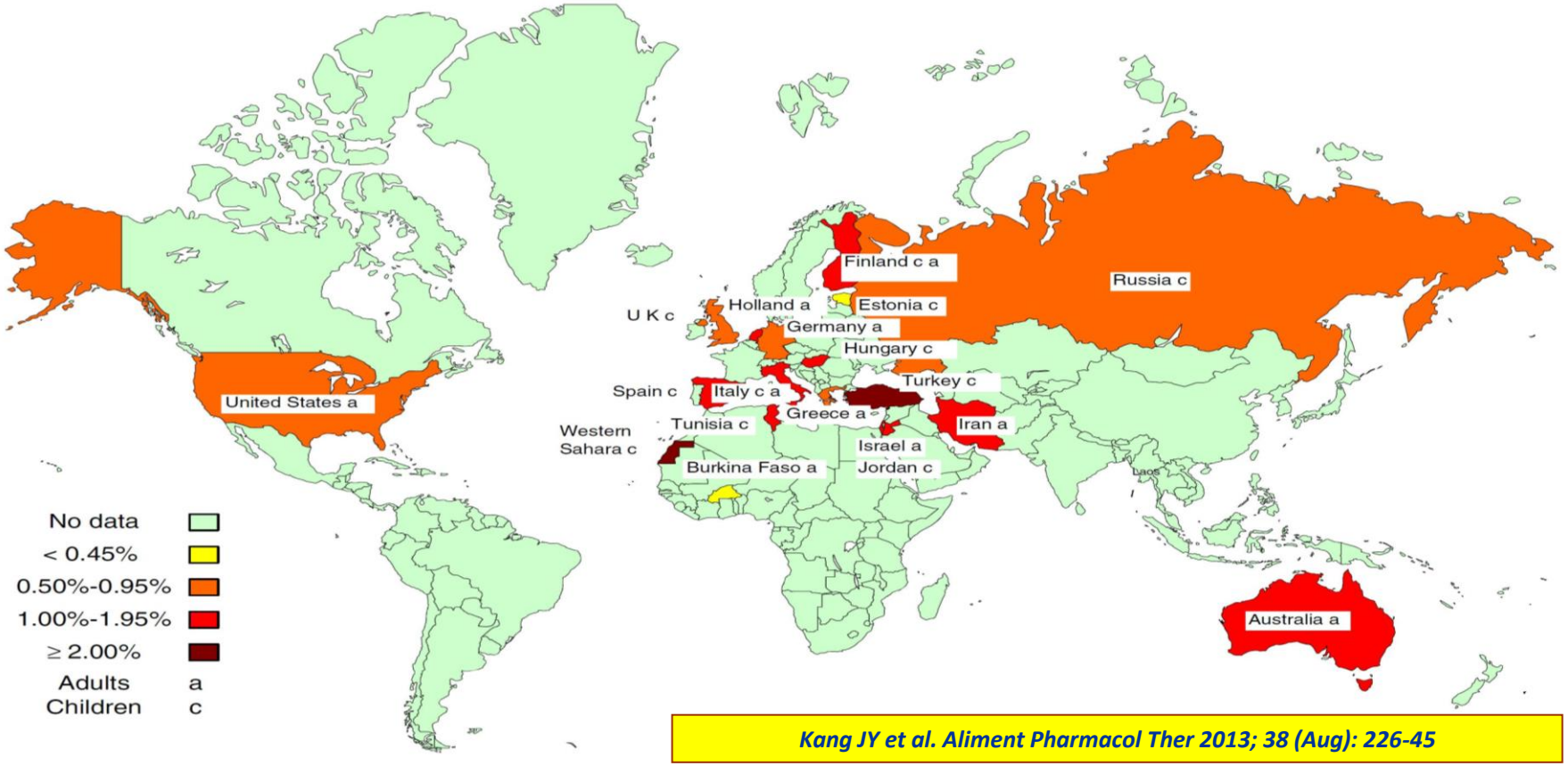
Intestin grêle normal



Maladie cœliaque
- atrophie villositaire
- augmentation des LIE (CD3+/CD8+)
- hyperplasie cryptique

Maladie coeliaque (0.5% à 2%) fréquente et sous diagnostiquée

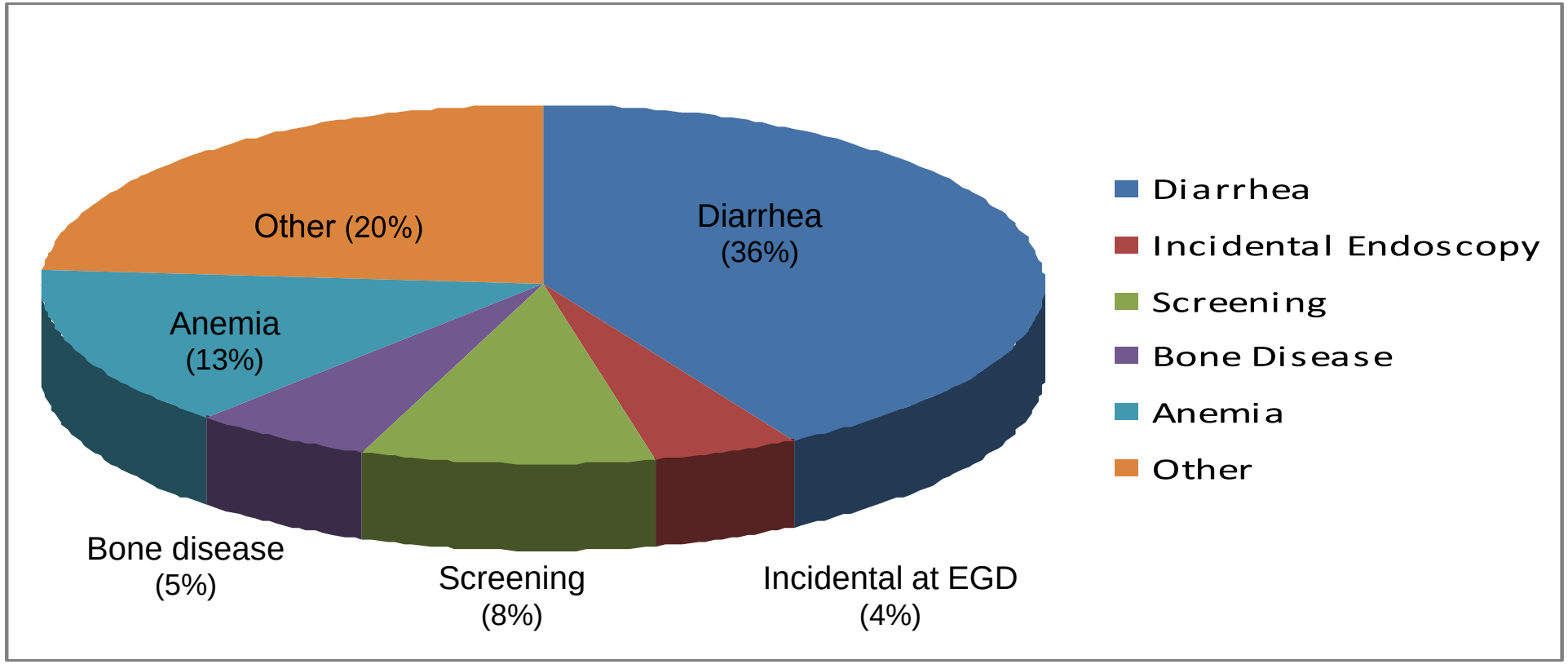
***TTG, transglutaminase**



Kang JY et al. Aliment Pharmacol Ther 2013; 38 (Aug): 226-45

Maladie Coeliaque adulte : Troubles digestifs 1/3 cas

(Green et al Columbia University)



Maladie coeliaque: y penser!

- Formes atypiques ou frustes > 80%
  anémie
    - Fer
    - Folates
    - Vitamine B12 (20-30%)
  hypertransaminasémie - hépatopathie sévère
  aphtes récidivants
  symptômes mimant des troubles fonctionnels intestinaux
  obésité: 30% des MC adultes (USA)
  20% > 60 ans

Green P, Cellier C. NEJM 2007

Présentation “atypique”

- DERMATITE HERPETIFORME
- DOULEURS ABDOMINALES
- ATAXIE
- DEPRESSION
- APHTOSE BUCCALE ET TROUBLE EMAIL DENTAIRE
- ANOMALIES BIOLOGIQUES
  - Transaminases, ferritinémie basse
  - Hypocholesterolemie,
  - Hypoalbuminemie
  - Hyposplenisme
  - TP bas, déficit vitaminique
  - Hypocalcemie, hyperparathyroidie secondaire

Green P, Cellier C. NEJM 2007

Test sérologiques pour le diagnostic de MC

Table 2. Sensitivity and specificity of different serological tests.

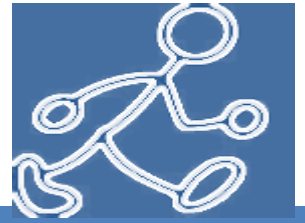
Antigen	Antibody type	Sensitivity, % (range)	Specificity, % (range)
Gliadin	IgA	85 (57–100)	90 (47–94)
	IgG	80 (42–100)	80 (50–94)
Endomysium	IgA	95 (86–100)	99 (97–100)
	IgG	80 (70–90)	97 (95–100)
Tissue transglutaminase	IgA	98 (78–100)	98 (90–100)
	IgG	70 (45–95)	95 (94–100)
Deamidated gliadin peptide	IgA	88 (74–100)	90 (80–95)
	IgG	80 (70–95)	98 (95–100)

France: remboursement SS uniquement anticorps anti-Transglutaminase et AEM pour confirmation

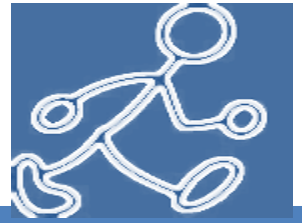
Démarche diagnostique

Suspicion clinique

Sérologie



Biopsie



RSG

Summary of test characteristics of celiac serologies

Test	Sensitivity (reported range) (%)	Specificity (reported range) (%)
IgA AGA	85 (57–100)	90 (47–94)
IgG AGA	85 (42–100)	80 (50–94)
EMA	95 (86–100)	99 (97–100)
IgA anti-tTG[a]	98 (78–100)	98 (90–100)
IgG anti-tTG[b]	70 (45–95)	95 (94–100)
IgA anti-DGP	88 (74–100)	95 (90–99)
IgG anti-DGP	80 (63–95)	98 (90–99)
IgA/IgG anti-DGP	97 (75–99)	95 (87–100)

AGA, anti-gliadin antibody; DGP, deamidated gliadin peptide; EMA, endomysial antibody; tTG, tissue transglutaminase

Leffler, Am J Gastro 2010;105:2520

Maladie coeliaque séro négative: 5-10% cas MC adultes
Biopsies nécessaires

Table 1. Who should be tested for CD?

Endoscopy and duodenal biopsy even if CD serology is negative	**CD serology is indicated: biopsy is needed only when serology is positive**
(1) Chronic (non-bloody) diarrhoea	(1) IBS
(2) Diarrhoea with features of malabsorption, especially weight loss	(2) Elevated otherwise unexplained liver transaminases
(3) Iron deficiency anaemia in absence of other causes	(3) Chronic GI symptoms without a family history of CD or a personal history of autoimmune disease
(4) GI symptoms with a family history of CD	(4) Microscopic colitis
(5) GI symptoms in patient with autoimmune disease or IgA deficiency	(5) Hashimoto's thyroiditis and Graves' disease
(6) Failure to thrive in children	(6) Osteopenia/osteoporosis
(7) Skin biopsy-proven DH	(7) Unexplained ataxia or peripheral neuropathy
(8) Patient with video capsule findings suggestive for villous atrophy	(8) Recurrent aphthous ulcerations/dental enamel defects
(9) Unexplained high output ileo-(colo-)stomy	(9) Infertility, recurrent miscarriage, late menarche, early menopause
	(10) Chronic fatigue syndrome
	(11) Acute or chronic pancreatitis after excluding other known causes
	(12) Epilepsy; headaches including migraines; mood disorders; or attention-deficit disorder/cognitive impairment
	(13) Hyposplenism or functional asplenia
	(14) Psoriasis or other skin lesions than DH
	(15) Down's or Turner's syndrome
	(16) Pulmonary haemosiderosis
	(17) IgA nephropathy

Interêt du typage HLA ?

- HLA DQ2 DQ8 : VPN 99/%
- DQ2 90-95%, DQ8 5-8%
- quelques DQ7
- Intérêt: exclure diagnostic maladie coeliaque

  AV séronégative

  patients déja au RSG

Green P, Cellier C. NEJM 2007

Tests à ne pas prescrire

- tests IG : intolérance alimentaire
- gliadin stool test
- immunopro

valeur scientifique non démontrée

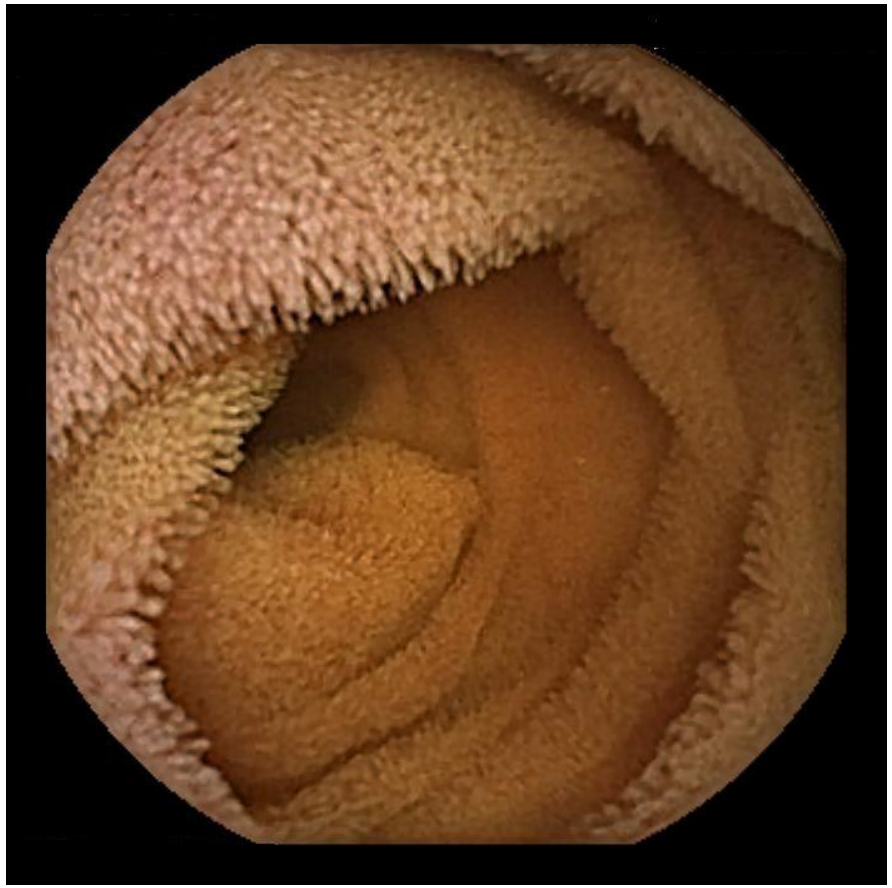
induction de régime restrictifs dangereux

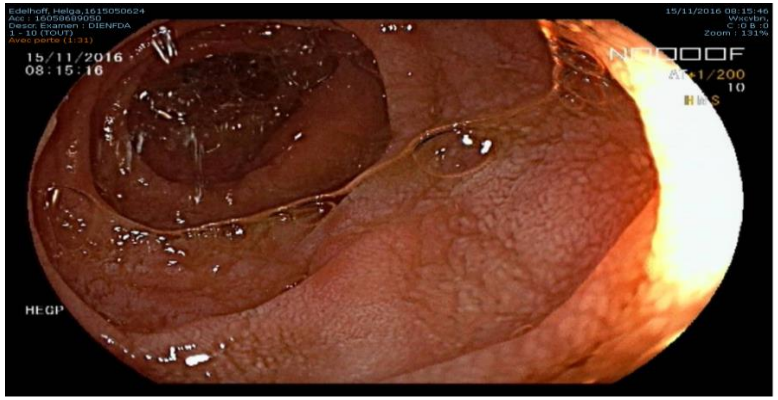
ENDOSCOPIE et BIOPSIES

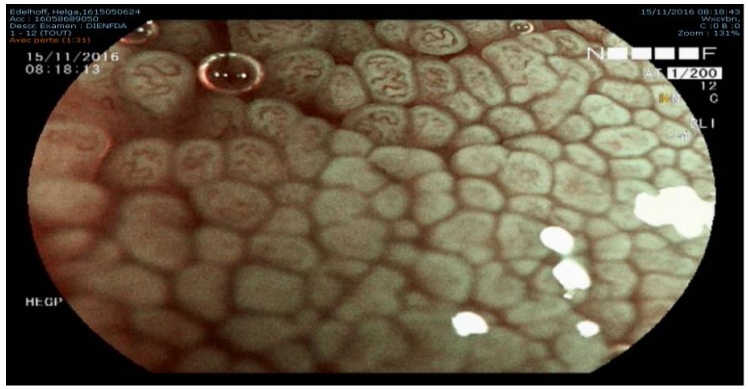
Aspect normal 1/3 cas

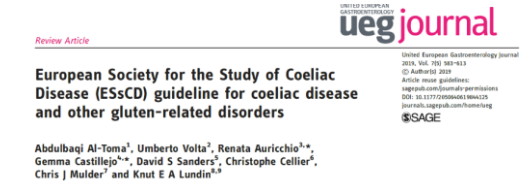
biopsies systématiques

Biopsies duodénum (4) + bulbe (1)(> 10% duodénum seul): « ultra short celiac »









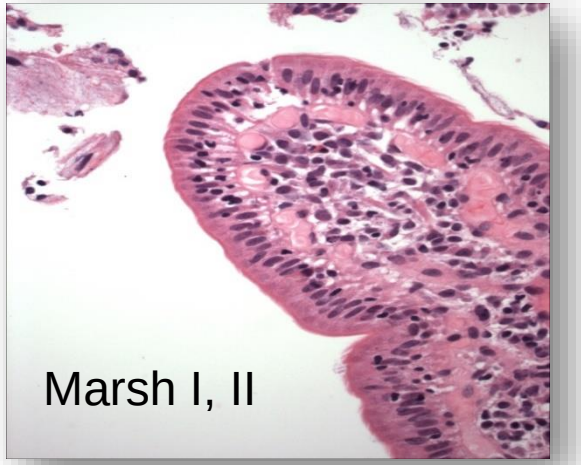
Review Article

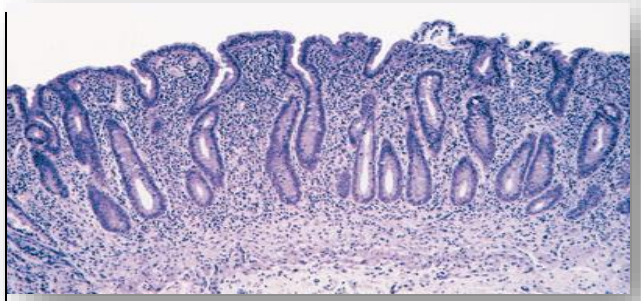
ueg journal

European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders

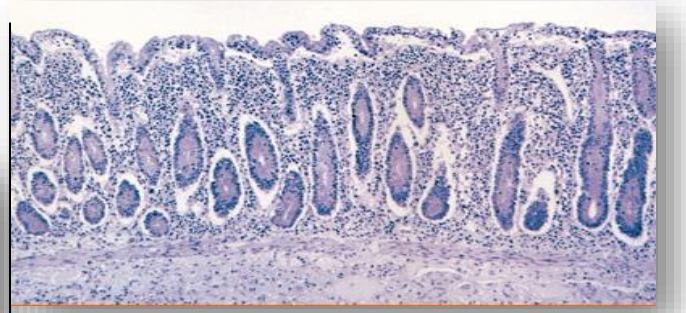
Abdulbaqi Al-Toma[1], Umberto Volta[2], Renata Auricchio[3,*], Gemma Castillejo[4,*], David S Sanders[5], Christophe Cellier[6], Chris J Mulder[7] and Knut E A Lundin[8,9]

Histologie
Gold standard pour le diagnostic chez l’adulte

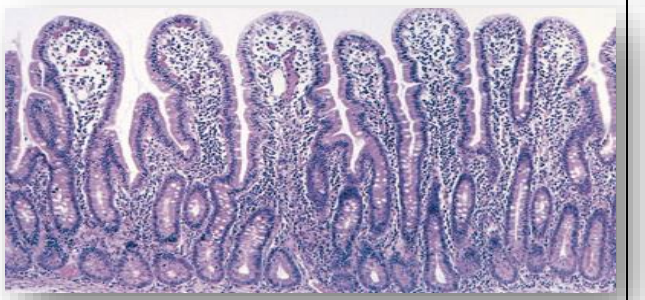




subtotale



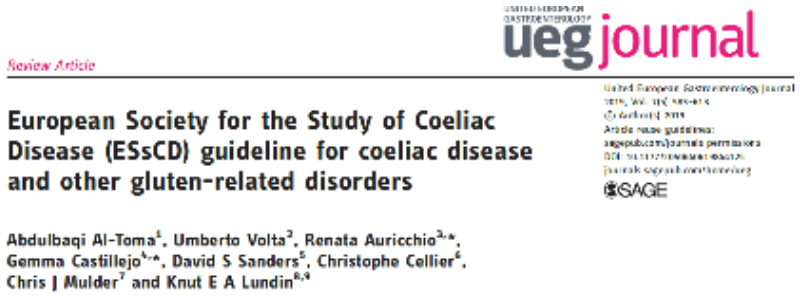
totale



partielle

Atrophie villositaire (Marsh IIIa, b, c)

Avenir: sans biopsies ?


Review Article

ueg journal

European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders

Abdulbaqi Al-Toma[1], Umberto Volta[2], Renata Auricchio[3,*], Gemma Castillejo[4,*], David S Sanders[5], Christophe Cellier[6], Chris J Mulder[7] and Knut E A Lundin[8,9]

SAGE

- Non recommandé chez adulte

- Recommandations ESPGHAN 2019 (enfant)

  Diagnostic sans biopsies si Ac anti-TtG > 10N, AEM + et symptômes typiques (HLA non recommandé)

Atrophie villositaire séronégative

- Maladie coeliaque ++ (1%): terrain (HLA DQ2/8; auto-immunité; gluten)
- Déficits immunitaires (DICV)
- Infections (Giardia lamblia)
- Sprue tropicale
- Sprue collagène
- Entéropathie auto-immune
- Médicaments:
  - Azathioprine, methotrexate, mycophenolate mofetil, ticlopidine
  - Récemment: **olmésartan** (antagoniste des récepteurs de l'angiotensine II)

Sérologie positive sans atrophie villositaire

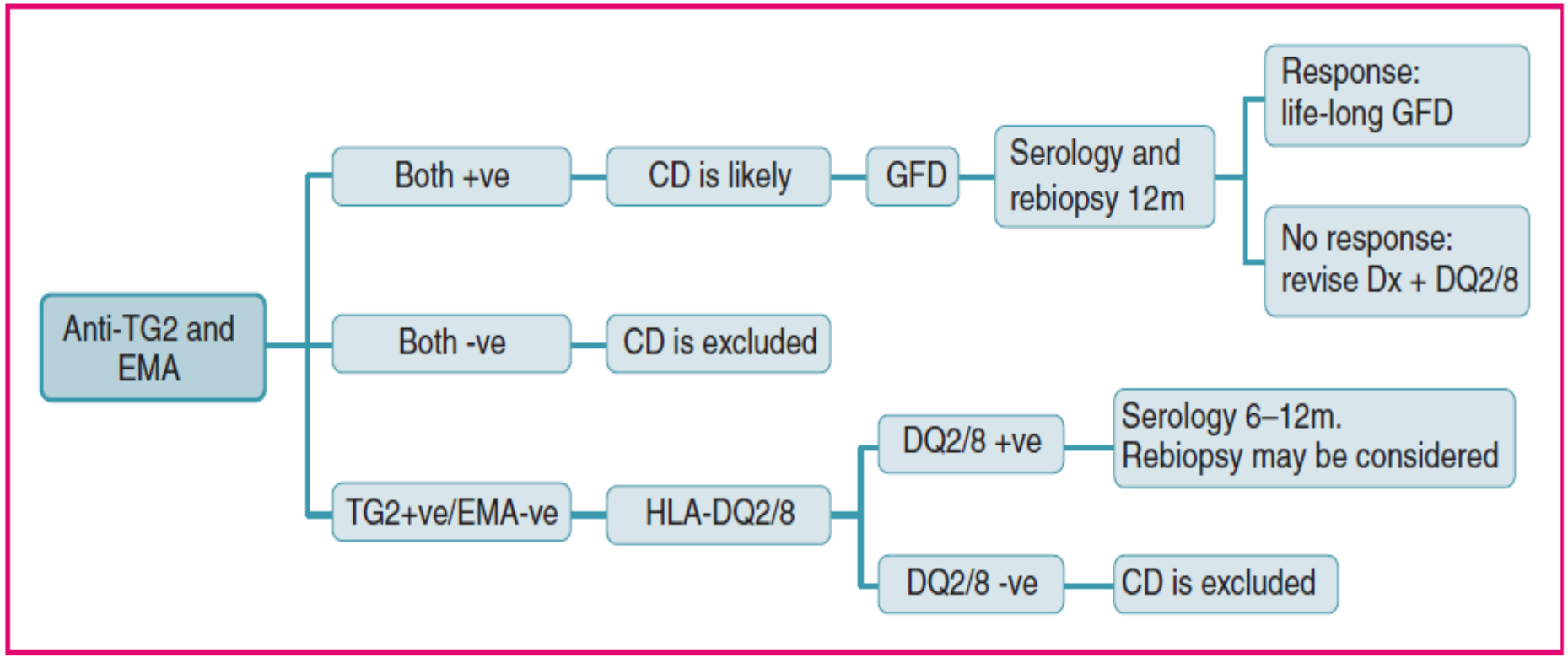
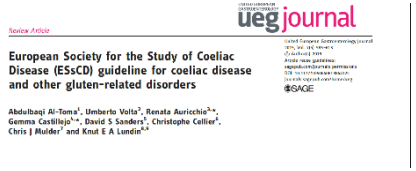


Figure 1. Suggested approach for patients with Marsh I histology with positive serology.



Maladie coeliaque: traitement

Régime sans gluten

- blé, seigle, orge (avoine: OK)
- coût (prise en charge 45 Euros/mois)
- **diététicien ++++**
- AFDIAG (Patient support group)

RSG: suivi imparfait dans 1 cas /2 en France (coût, contrainte sociale et disponibilité des aliments sans gluten)

Recommendations

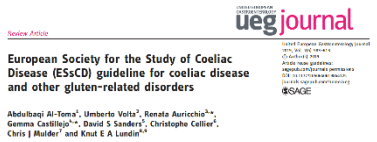
(1) Patients with CD should adhere to a lifelong GFD. *(Strong recommendation, high level of evidence)*

(2) Oats are safely tolerated by the majority of CD patients; its introduction into the diet should be cautious and patients should be monitored for possible adverse reaction. *(Strong recommendation, moderate level of evidence)*

(3) Patients with CD should be referred to a dietitian who is well-trained concerning CD in order to get a detailed nutritional assessment, education on the GFD and subsequent monitoring. *(Strong recommendation, moderate level of evidence)*

(4) A newly diagnosed adult CD patient should undergo testing to uncover deficiencies of essential micronutrient, e.g. iron, folic acid, vitamin D and vitamin B12. *(Strong recommendation, moderate level of evidence)*

(5) Patients should be advised to eat a high-fibre diet supplemented with whole-grain rice, maize, potatoes and ample vegetables. *(Strong recommendation, moderate level of evidence)*


Review Article

uegjournal

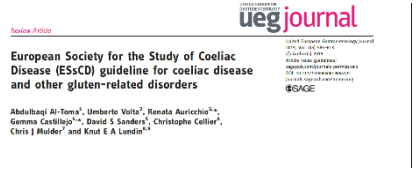
United European Gastroenterology Journal
1(1) 1–19
© Author(s) 2013
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/2050640613491590
journals.sagepub.com/home/uej

SAGE

European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders

Abdulbaqi Al-Toma[1], Umberto Volta[2], Renata Auricchio[3,*], Gemma Castillejo[4,*], David S Sanders[5], Christophe Cellier[6], Chris J Mulder[7] and Knut E A Lundin[8,9]

SUIVI A LONG TERME


Review Article

ueg journal

United European Gastroenterology Journal
Vol. 9, No. 2, 173–204
© The Author(s) 2021
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/2050640620942149
journals.sagepub.com/home/ueg
SAGE

European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders

Abdulbaqi Al-Toma[1], Umberto Volta[2], Renata Auricchio[3,4], Gemma Castillejo[5,6], David S Sanders[7], Christophe Cellier[8], Chris J Mulder[9] and Knut E A Lundin[10]

Diététicien

AC à 1 an et biologie

Biopsies de contrôle à 2 ans

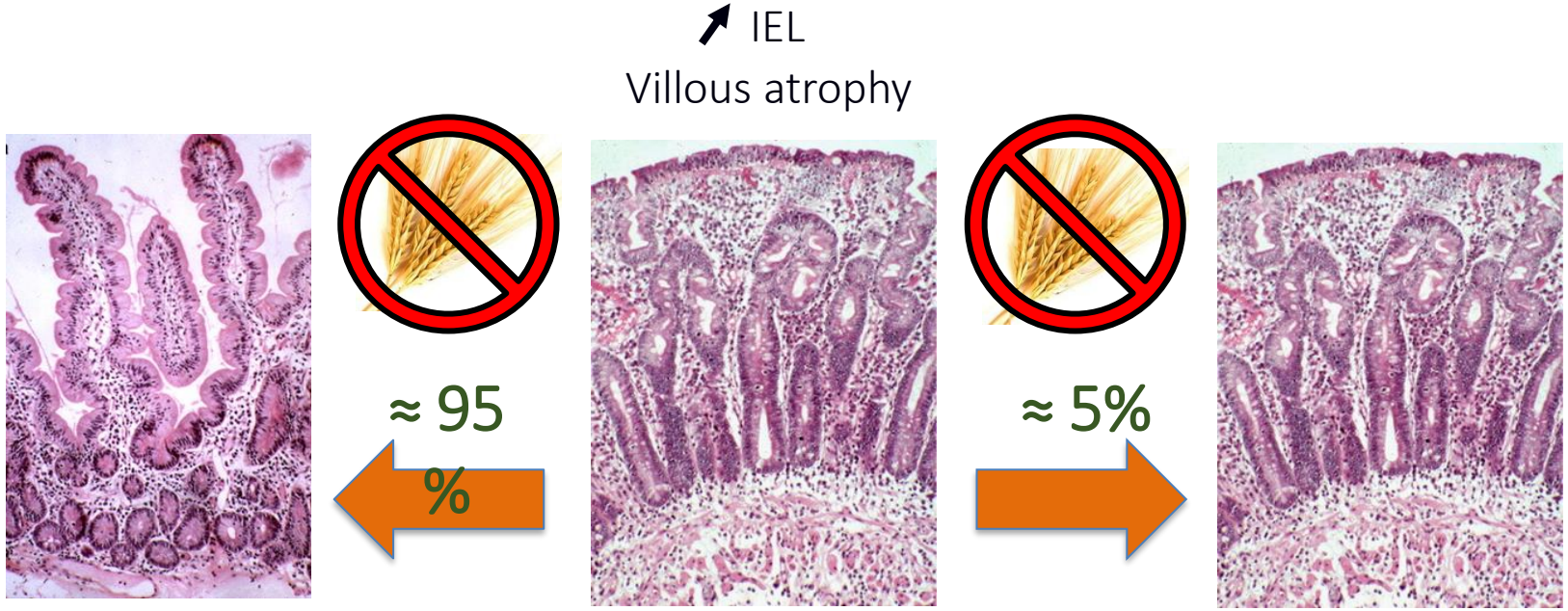
Suivi clinique et biologique à long terme

Table 4. Suggested follow-up scheme for adult CD patients.

At diagnosis (physician and dietitian)	Physical examination including BMI Education on CD Dietary counselling by a skilled dietician Recommend family screening (DQ2/D8 and coeliac serology) Recommend membership of coeliac national society or support group Coeliac serology (if not previously obtained) Routine tests (complete blood count, iron status, folate, vitamin B12, thyroid function tests, liver enzymes, calcium, phosphate, vitamin D)/bone densitometry at diagnosis but not later than 30-35 years of age
At 2nd visit 3–4 months (physician and dietitian)	Assess symptoms and coping skills Dietary review Coeliac serology (IgA-TG2)
At 6 months (physician) (by telephone)	Assess symptoms Dietary review Coeliac serology Repeat routine tests (*if previously abnormal*)
At 12 months (physician and dietitian)	Assess symptoms Physical examination (on indication) Dietary review Coeliac serology Repeat routine tests Small-bowel biopsy (*not routinely recommended, see text*)
At 24 months (physician)	Assess symptoms Consider dietary review Coeliac serology Thyroid function tests Other tests as clinically indicated
At 36 months (physician); thereafter every 1–2 years	Bone densitometry (*if previously abnormal*) Assess symptoms Consider dietary review Coeliac serology Thyroid function tests Other tests as clinically indicated

RSG seul traitement efficace de la MC

Prévention des complications : lymphome, ostéopenie, MAI



Maladie coeliaque avec mauvaise réponse au RSG: Non responsive CD

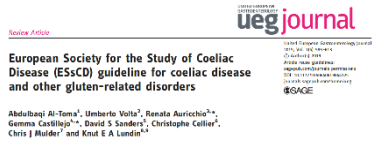
- Clinique (SII):30%
- AV persistante:20/30%
- Maladie coeliaque réfractaire : <1%

CD3+/CD8-; clonalité

Cellier et al, *Lancet*. 2000.
Green P, Cellier C. *NEJM*. 2007.
Cellier et al; Lancet Gastro 2019

RSG difficile à suivre: 30-50% erreurs involontaires ou volontaires

Stratégie en cas de persistance de symptômes malgré un RSG
Non Responsive CD



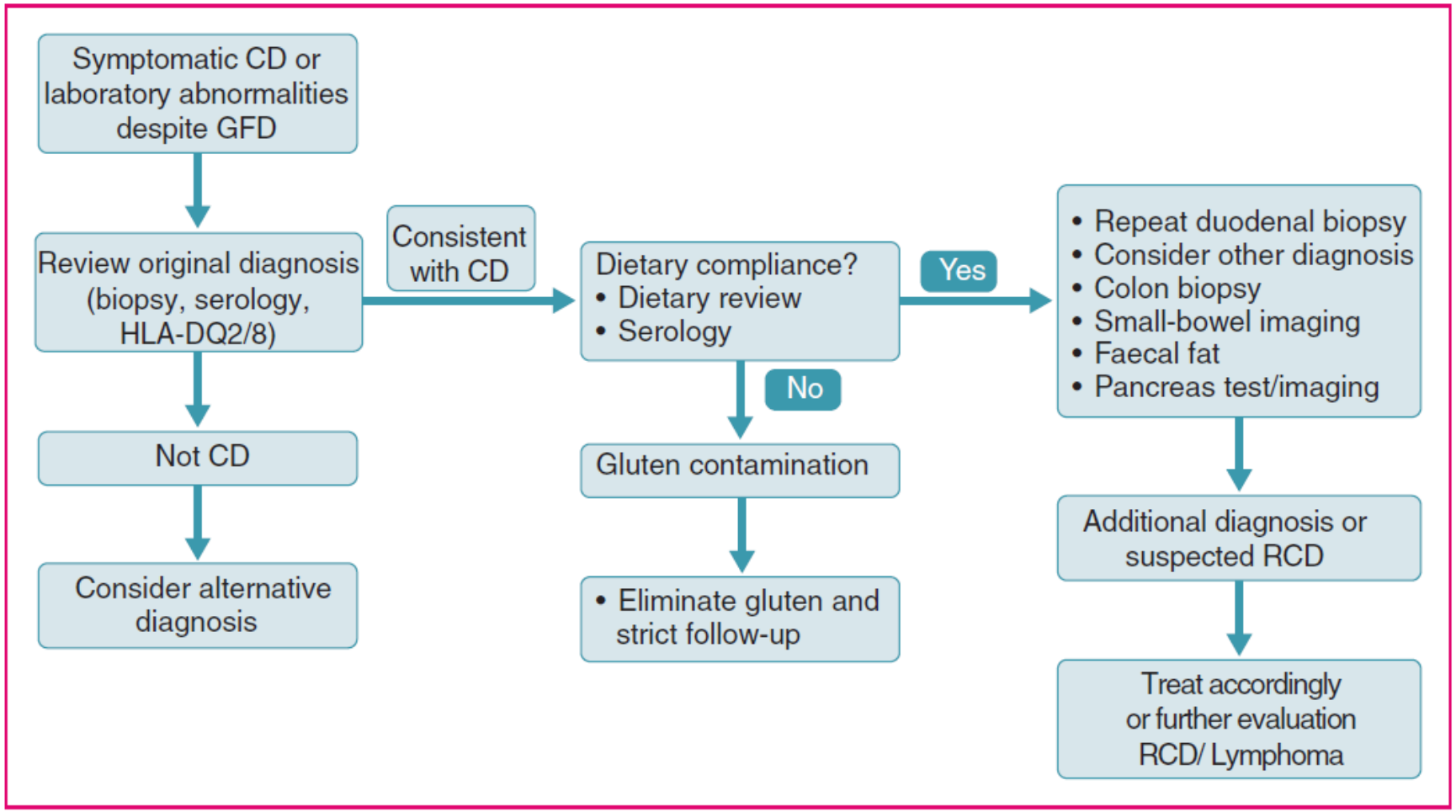
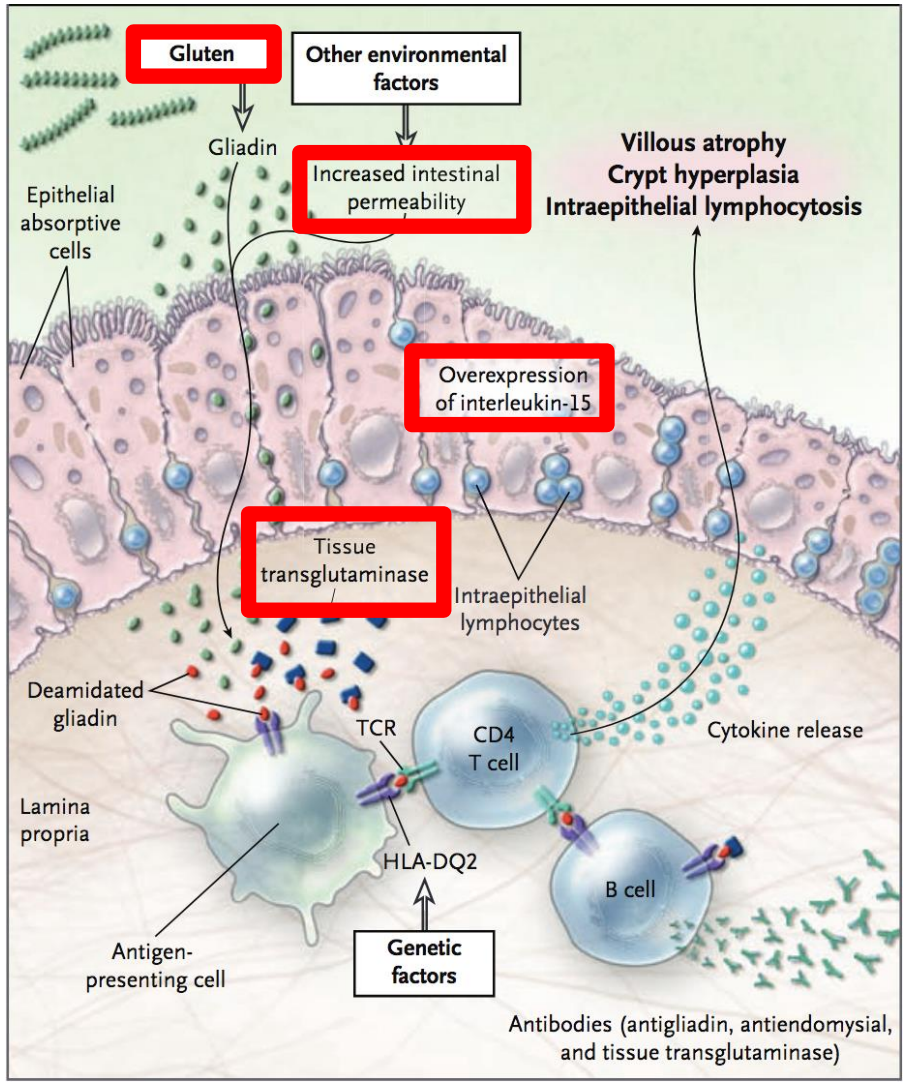


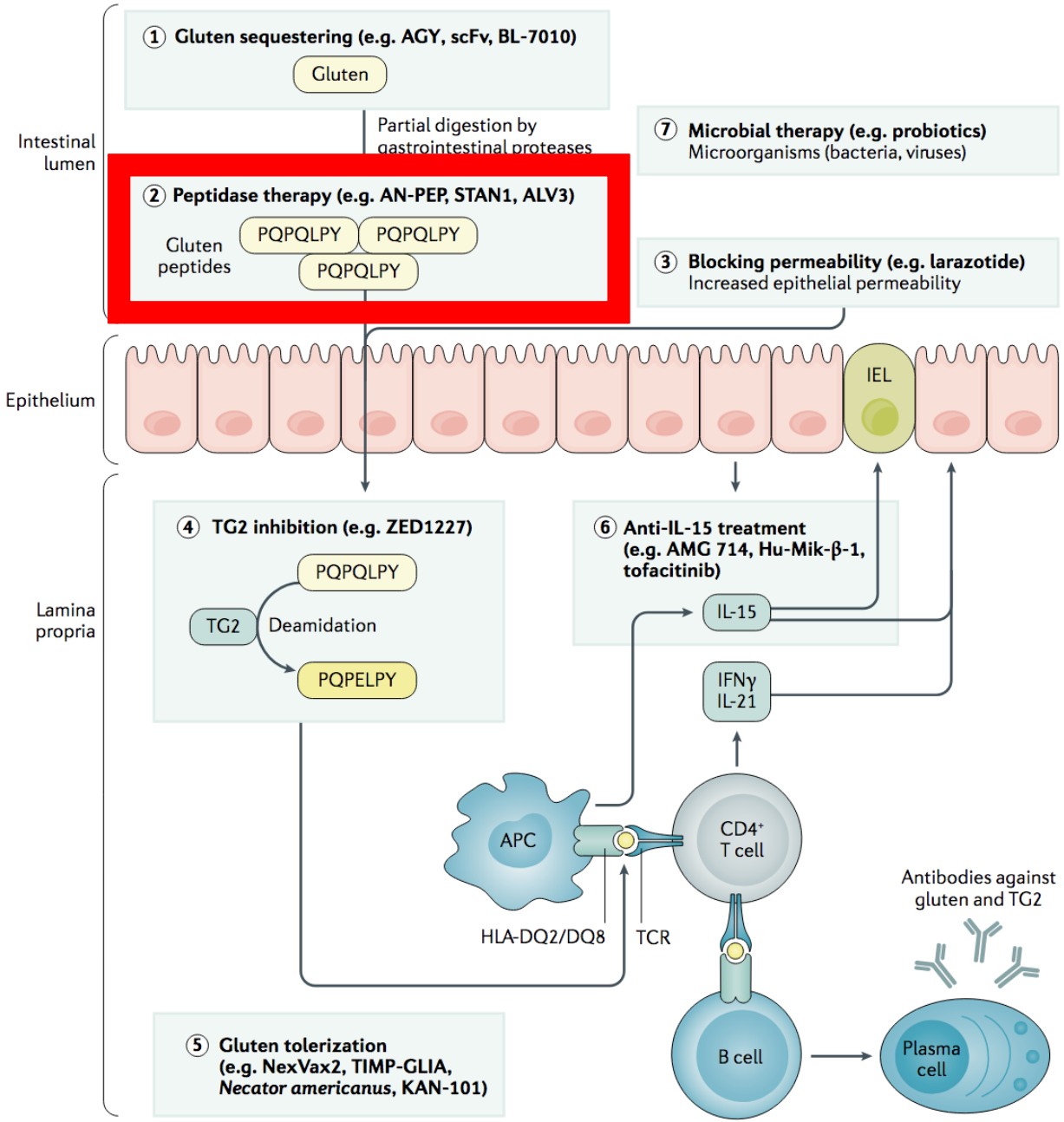
Figure 2. Diagnostic approach to symptomatic CD or laboratory abnormalities despite GFD.

Cibles thérapeutiques

- Immunogénicité du gluten
- Perméabilité épithéliale
- Interleukine 15 et voie Jack/Stat
- Tranglutaminase tissulaire (tTG)
- Induction d'une tolérance



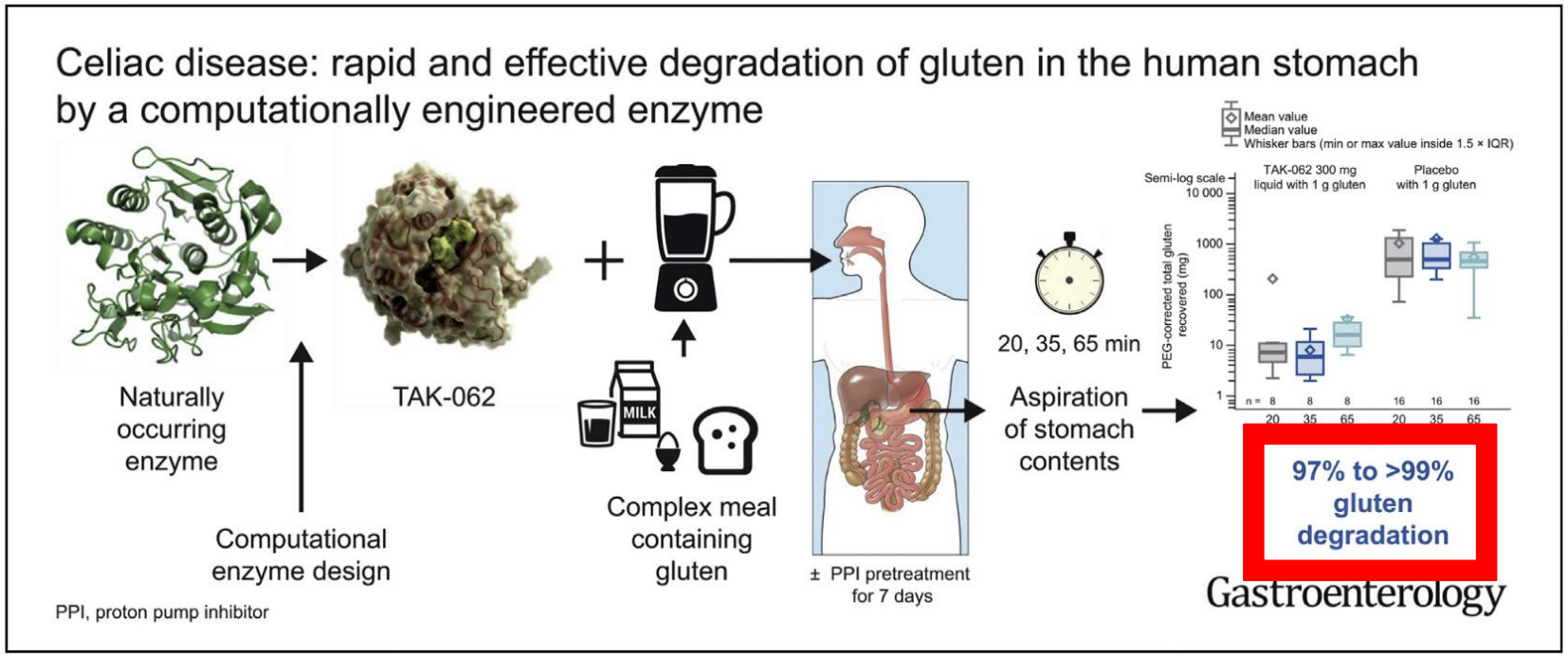
Cerf-Bensussan N, Schuppan D. *Gastroenterology*. 2021;161(1):21-24
Green P, Cellier C, N Engl J Med. 2007;357(17):1731-1743



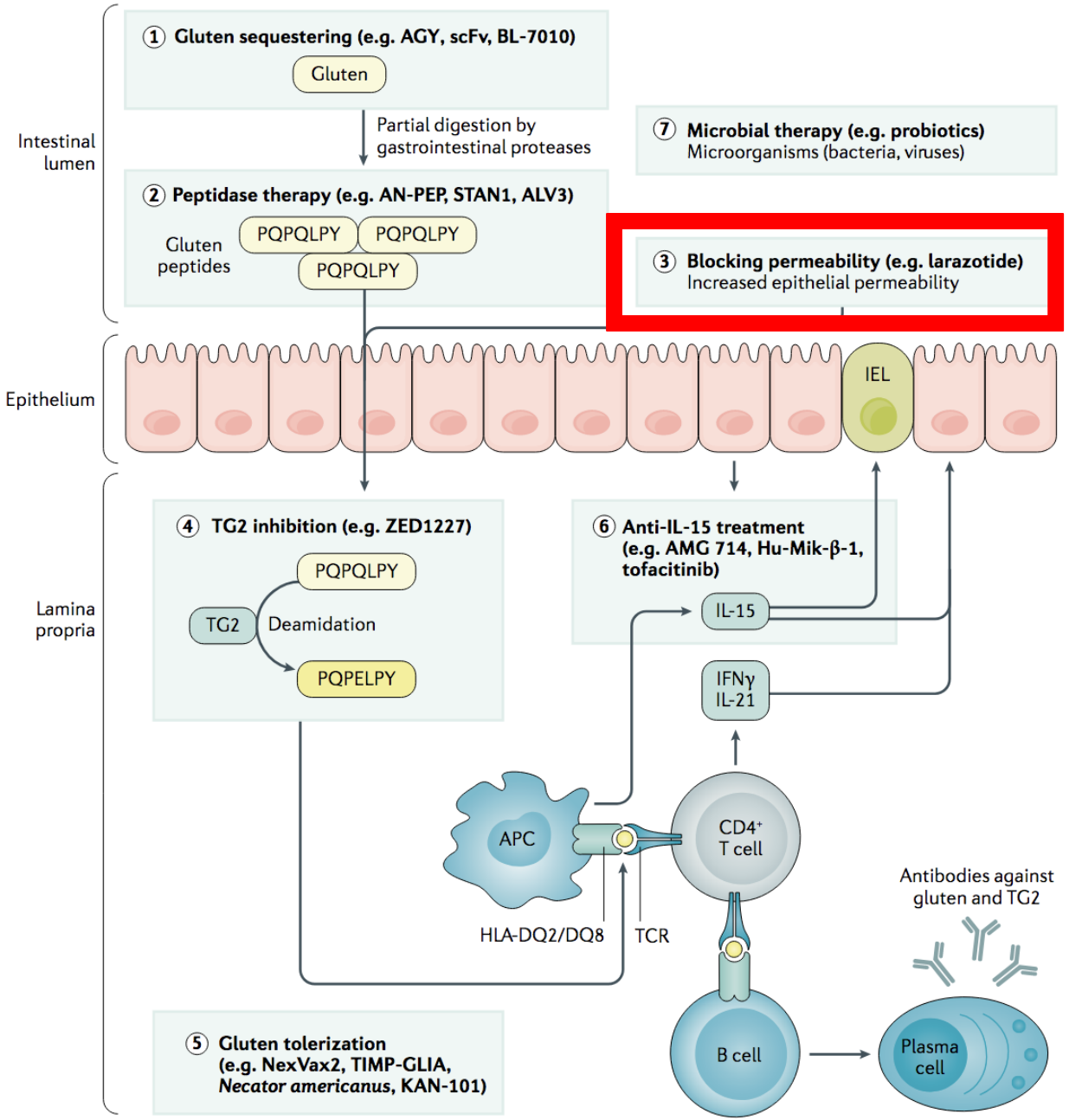
Kivelä L, et al. *Nat Rev Gastroenterol Hepatol*. 2021;18(3):181-195.

Peptidase: TAK-062

- **Endopeptidase ciblant gliadine (proline-glutamine)**
- **Etude phase I**
  - In vitro: Dégradation à 99% en milieu simulant milieu gastrique
  - In vivo



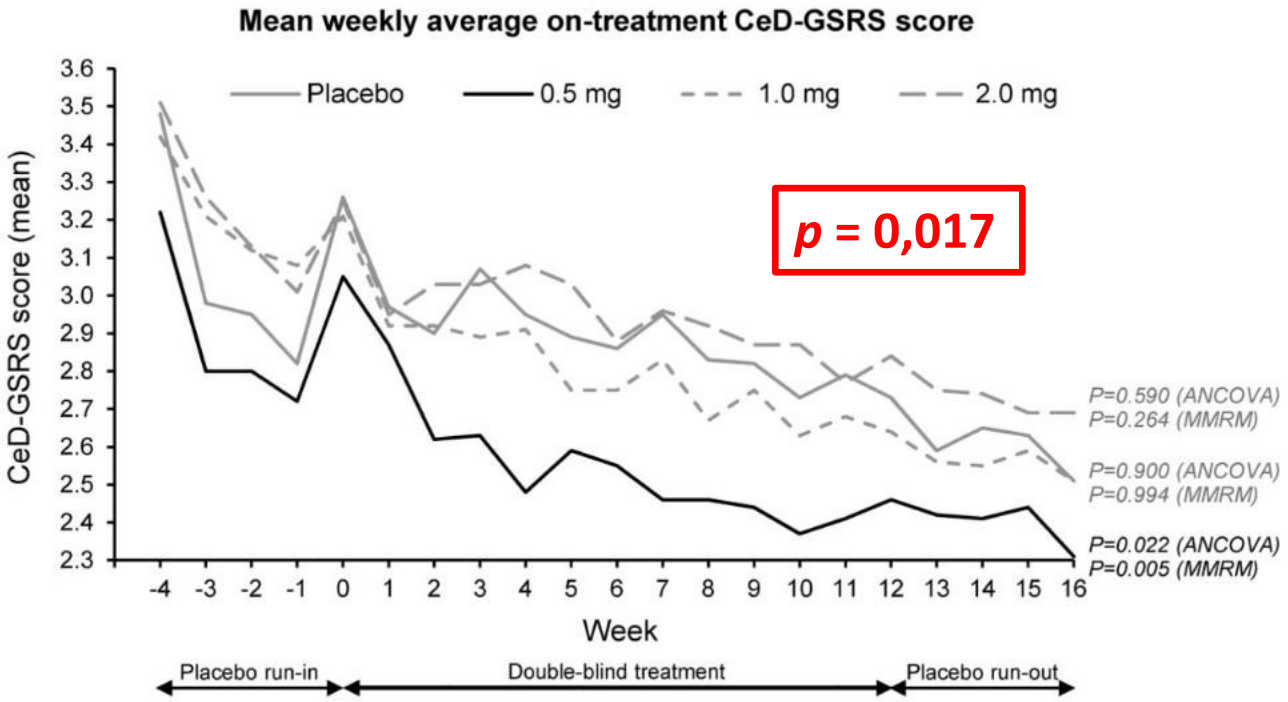
Pultz IS, et al. *Gastroenterology*. 2021;161(1):81-93.e3.



Kivelä L, et al. *Nat Rev Gastroenterol Hepatol*. 2021;18(3):181-195.

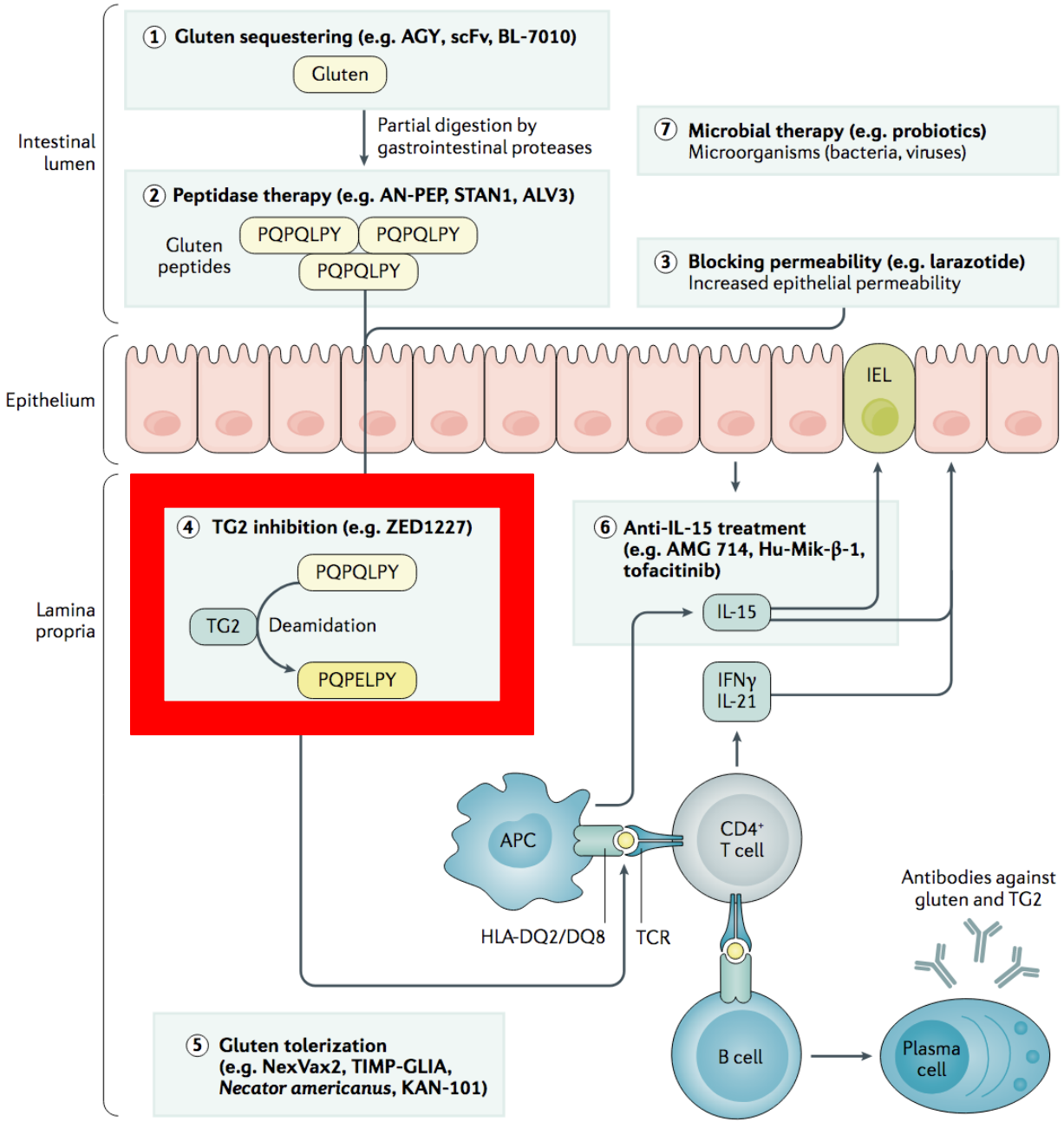
Larazotide – Phase II

- **Multicentrique, double aveugle**
- **Contre placebo**
- **342 patients cœliaques**
- **Inclusion**
  - Symptômes sous RSG
  - Sérologies positives
- **Critère de jugement**
  - Clinique (Score CeD-GSRS)



MITT population, n=328. *P* values are for comparison to Placebo in average on-treatment score adjusted for baseline and covariates. CeD-GSRS = CeD focussed domains (diarrhea, indigestion, abdominal pain) of the Gastrointestinal Symptom Rating Scale; ANCOVA = analysis of covariance; MMRM = mixed model for repeated measurements

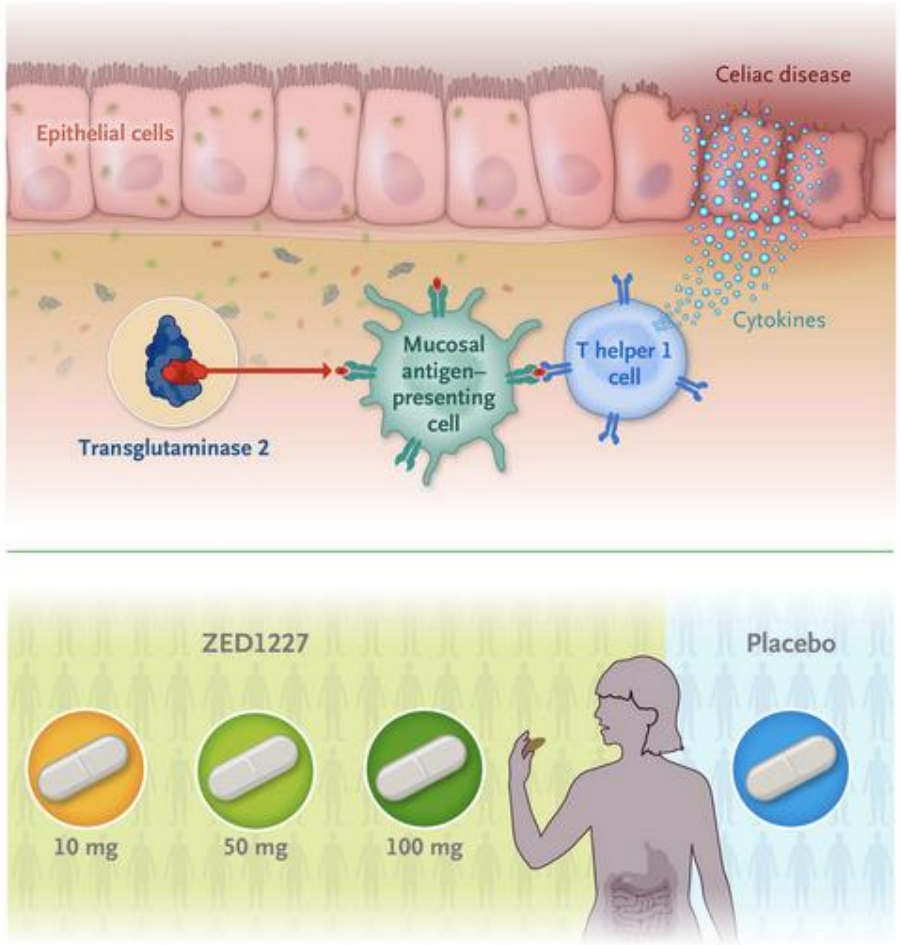
Leffler, D. et al. *Gastroenterology*, 2015, *148*(7), 1311–9.e6.



Kivelä L, et al. *Nat Rev Gastroenterol Hepatol*. 2021;18(3):181-195.

Inhibiteur de tTG

- **Multicentrique, randomisée**
- **Double aveugle - Contre placebo**
- **Exposition à 3g/j de gluten, 6 semaines**
- **159 patients cœliaques**
- **Inclusion**
  - Asymptomatique sous RSG
- **Critère de jugement**
  - Histologique (Vh:Cd)



Schuppan D, et al. *N Engl J Med*. 2021;385(1):35-45.

Inhibiteur de transglutaminase - Vh:Cd

Table 2. Effect of ZED1227 Treatment on the Ratio of Villus Height to Crypt Depth.*

Variable	ZED1227, 10 mg (N=35)	ZED1227, 50 mg (N=39)	ZED1227, 100 mg (N=38)	Placebo (N=30)
Ratio of villus height to crypt depth				
At baseline	2.01±0.30	2.04±0.32	2.09±0.35	1.98±0.33
After gluten challenge at wk 6	1.85±0.53	1.91±0.44	1.94±0.48	1.39±0.61
Change in ratio from baseline (95% CI)†	−0.17 (−0.33 to −0.01)	−0.12 (−0.27 to 0.03)	−0.13 (−0.28 to 0.03)	−0.61 (−0.78 to −0.44)
Estimated difference in ratio vs. placebo (95% CI)†	0.44 (0.15 to 0.73)	0.49 (0.20 to 0.77)	0.48 (0.20 to 0.77)	—
P value	0.001	<0.001	<0.001	—

Schuppan D, et al. *N Engl J Med*. 2021;385(1):35-45.

Inhibiteur de transglutaminase – Vh:Cd

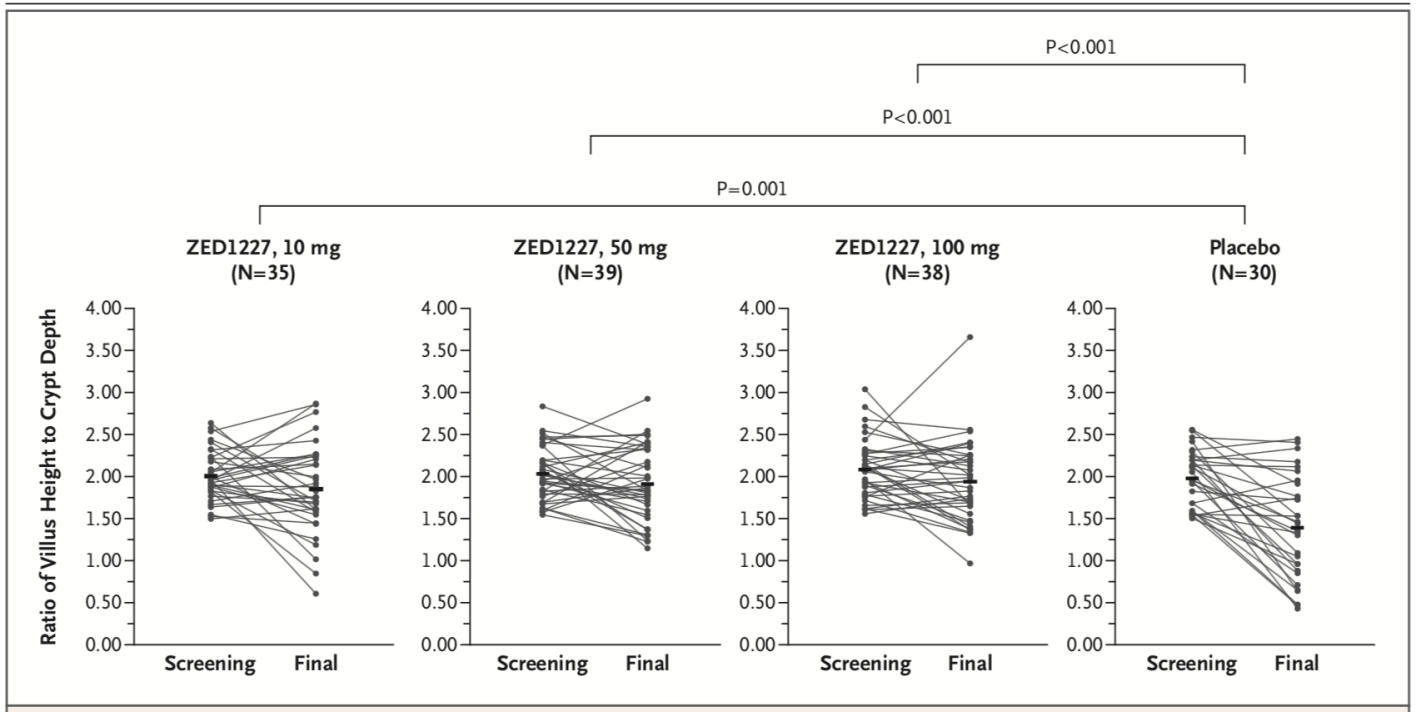
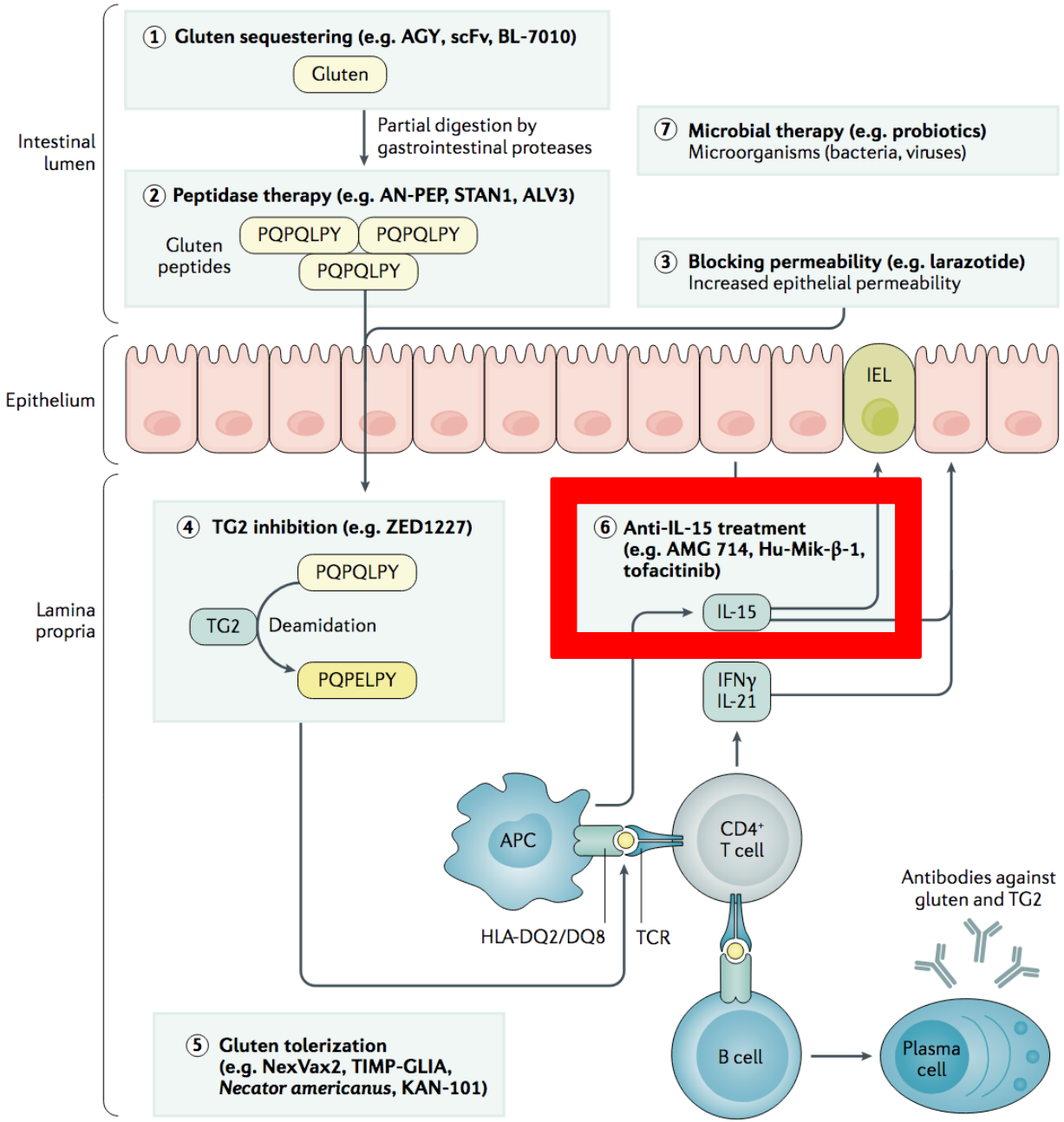


Figure 1. Paired Data Plots of the Mean Ratio of Villus Height to Crypt Depth (Primary End Point).

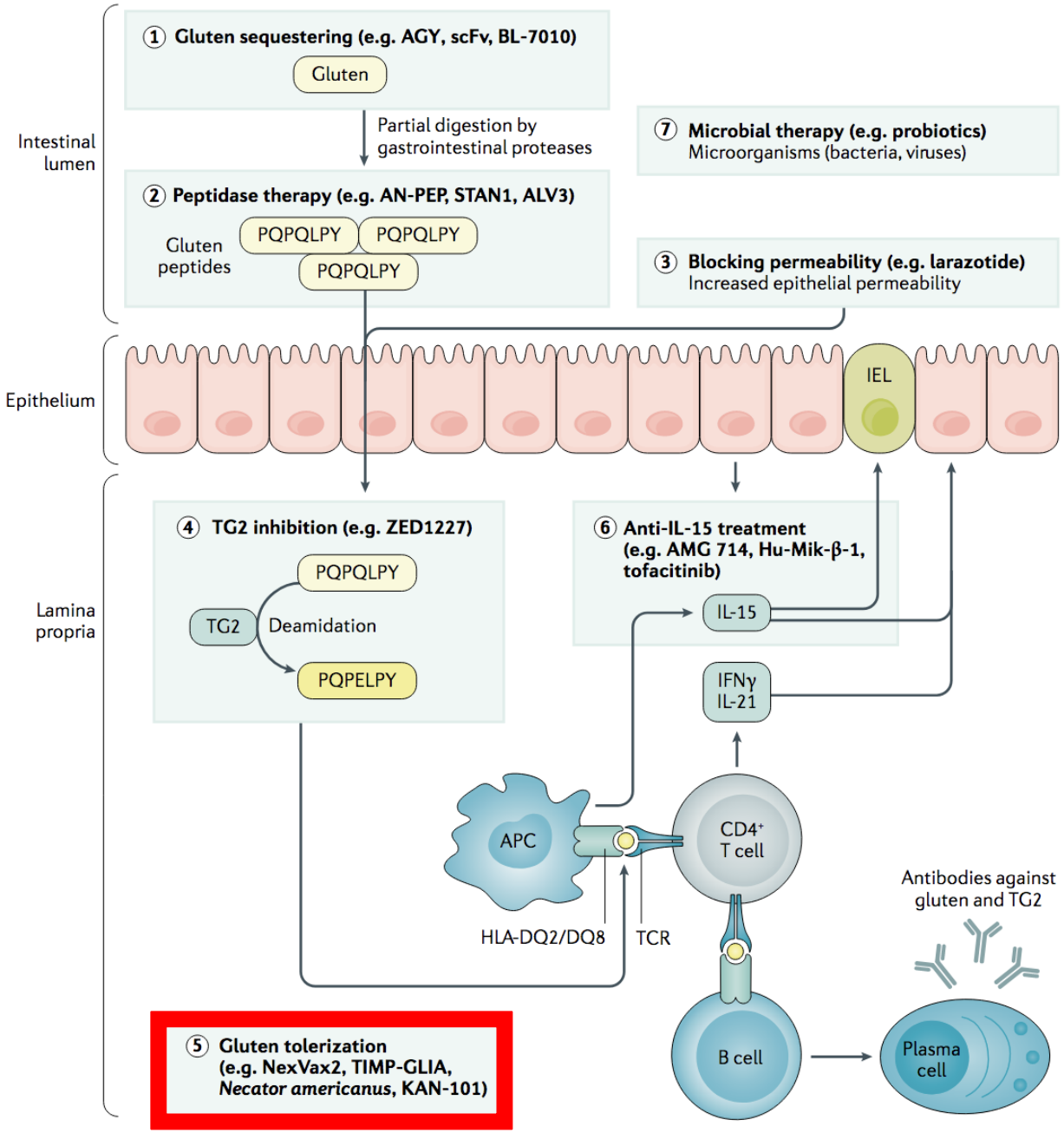
The primary end point was the attenuation of gluten-induced mucosal damage, as measured by the ratio of villus height to crypt depth. The prespecified population for this analysis included the 142 patients who had villus height and crypt depth measurements from at least three villus–crypt units in total from the duodenum biopsies available at both the screening (baseline) visit and the final or withdrawal visit. Horizontal bars indicate mean values in each group at each time point.

***p* < 0,001**

Schuppan D, et al. *N Engl J Med*. 2021;385(1):35-45.



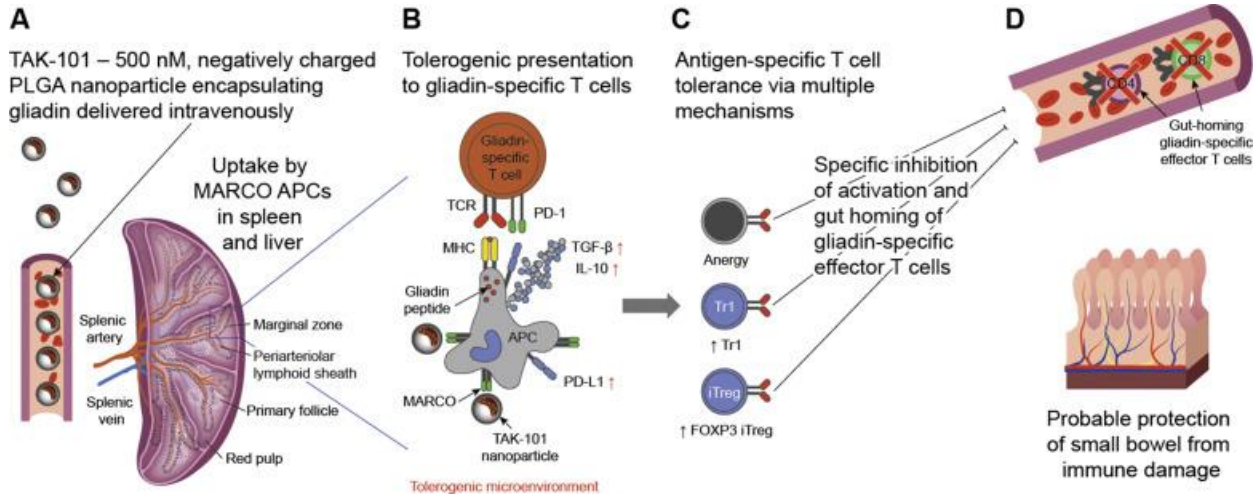
Kivelä L, et al. *Nat Rev Gastroenterol Hepatol*. 2021;18(3):181-195.

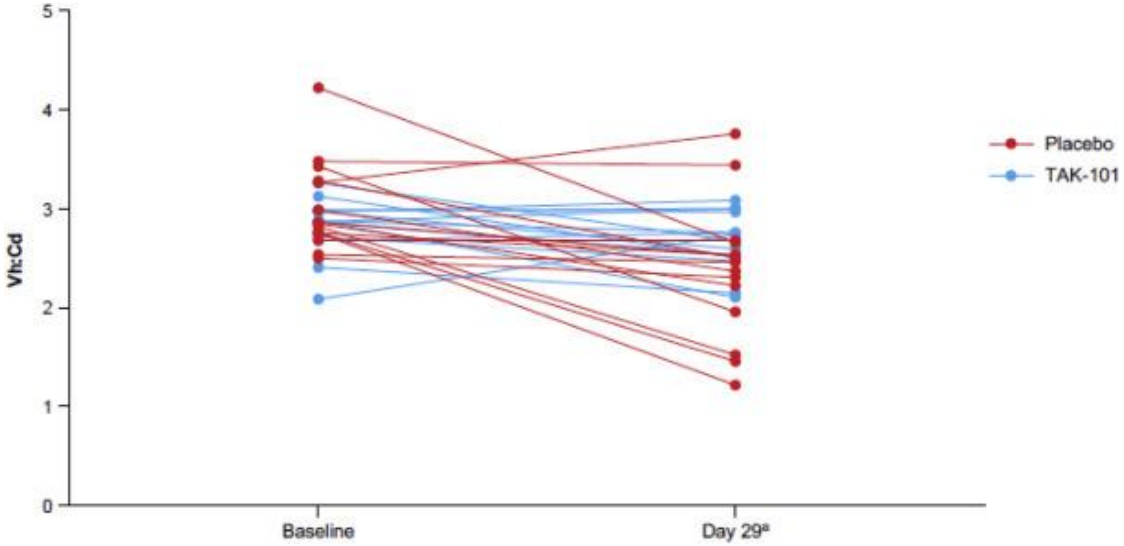


Kivelä L, et al. *Nat Rev Gastroenterol Hepatol*. 2021;18(3):181-195.

TAK-101 Nanoparticles Induce Gluten-Specific Tolerance in Celiac Disease: A Randomized, Double-Blind, Placebo-Controlled Study

Kelly CP, Gastroenterology 2021





Maladie coeliaque: Complications et suivi

Régime sans gluten non suivi

- Ostéopénie (50%): **ostéodensitométrie** recommandée au diagnostic
- Maladies auto-immunes
- Tumeurs (surtout si diagnostic tardif)

  adénocarcinome

  lymphome invasif

  sprue réfractaire

Complications à long terme de la MC

- Monocentric retrospective study of all celiac patients followed in HEGP Paris Hospital from 2000 to 2020
- 898 patients included (prospectively since 2010)
- Median follow-up duration: 9.5 y

Bone disease complications

Metabolic bone disease on Follow up • **Osteopenia** • **Osteoporosis** **Normal Bone mineral density** **Unknown**	**339 (37.7%)** **239 (26.6%)** **100 (11.1%)** **236 (26.3%)** **323 (36%)**
Fracture	48 (5.3%)

Malignant complications on follow-up

Complications	N (%)
Refractory Celiac disease type I	28 (3.1%)
Refractory Celiac disease type II	65 (7.2%)
EATL	47 (5.2 %)
• **With RCD type II**	24 (2.7%)
• **De novo EATL**	23 (2.6%)
Small bowel adenocarcinoma	8 (0.9%)
Duodenal adenoma	1
B-cell lymphoma	5 (0.5%)
• **MALT**	2
• **Mantle cell lymphoma**	1
• **Hodgkin Lymphoma**	2
Other cancers	45 (5%)
• **Large granular lymphocytic leukemia**	4
• **LAL**	1
• **Colorectal cancer**	6
• **Gastric adenocarcinoma**	2
• **ENT neoplasia**	5
• **Skin cancer**	4

NYC Columbia University meeting 2022

Risk factors for progression to EATL

Risk factors	N (%)	Risk of EATL	Univariate analysis		Multivariate analysis	Adjusted analysis for RCD II
			P value	OR (95% CI)		
Age at diagnosis > 50 yo	166 (18,7%)	8.2% vs. 2.4%	<0.001	8.033 (4.263-15.135)	P < 0,05	
Male gender	233 (25,9%)	11.2% vs. 3.2%	<0.001	3.852 (2.122-6.990)		
Abdominal pain*	214/543 (39,4%)	10.3% vs. 4.9%	0.016	2.242 (1.149-4.374)		
Hypoalbuminemia*	43 (22,4%)	34.9% vs. 2%	<0.001	26.071 (7.078-96.035)	P < 0,05	P < 0,05
Weight loss*	198 (36%)	13.6% vs. 2.6%	<0.001	6.018 (2.768-13.080)		
Low level of adherence to GFD	290 (33,4%)	12.1% vs. 1.9%	<0.001	7.075 (3.536-14.153)	P < 0,05	P< 0,05
Persistent villous atrophy despite GFD	96 (13,9%)	7.3% vs. 1.3%	<0.001	5.751 (2.036-16.249)		
Seronegativity	77 (11,5%)	10.4% vs. 4.9%	0.046	2.259 (0.993-5.137)		

* : at diagnosis of CD

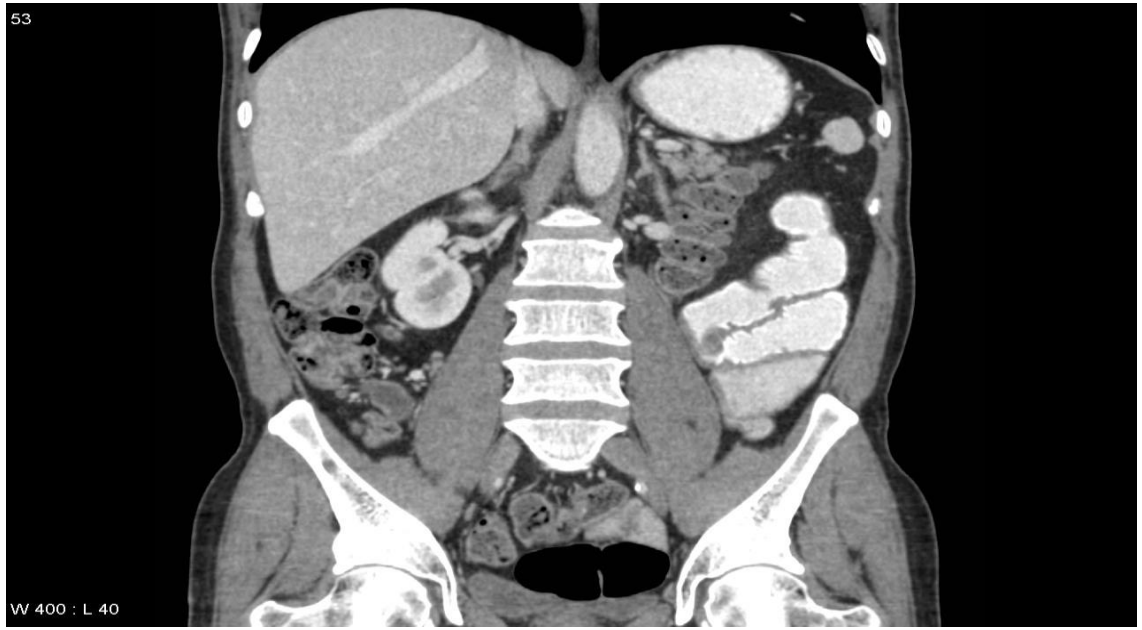
No CD diagnosed < 18 y/old subsequently developped EATL

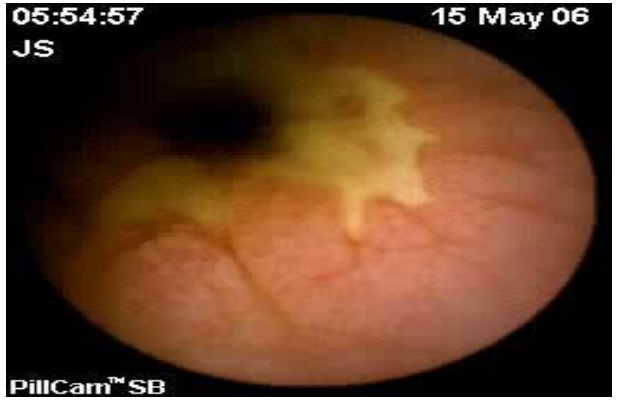
Outils pour les diagnostic des complications de la maladie coeliaque

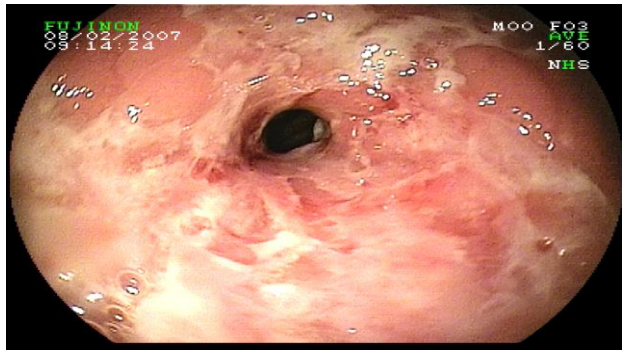
Entéro TDM, IRM (Signes d'alerte)

Pet scan: si suspicion de lymphome (SR2)

Vidéocapsule







Diagnosis of Refractory Celiac Disease type 2 (PRE-EATL, *IN SITU* lymphoma)

CLASSIFICATION OF RCD

Based on characterization of the intraepithelial lymphocytes (IELs)

- **TYPE I**

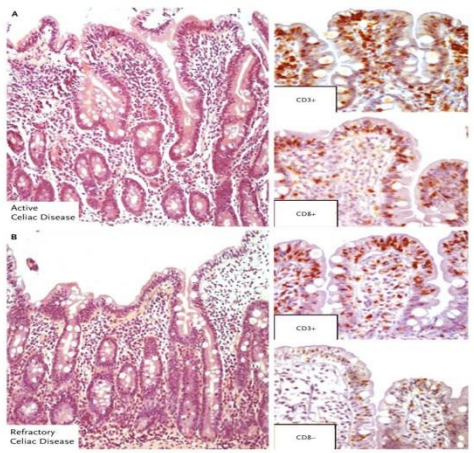
normal IEL surface CD3+, CD8+

- **TYPE II: Key role of IL15**

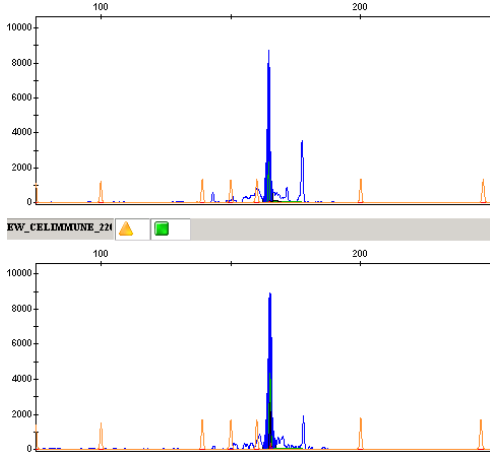
aberrant IEL (IHC, Flow and PCR)

- cytoplasmic CD3+,
- surface markers CD3-, CD8-
- clonal TCRγ gene rearrangement

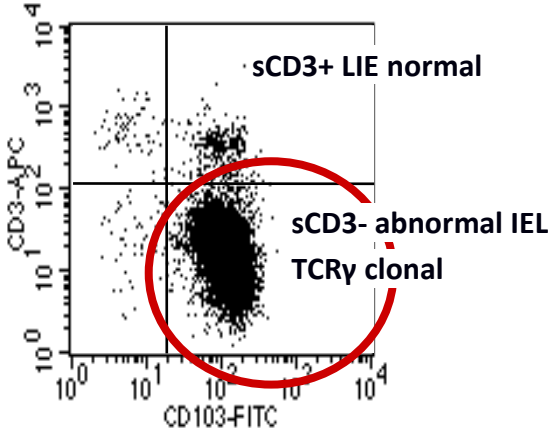
Cryptic T cell lymphoma (Pre-EATL : death 30-50%)



CD3+/CD8- (IHC)



Clonal peak PCR



Flow cytometry (Gold standard Diagnostic test)

Cellier, *Lancet*. 2000.

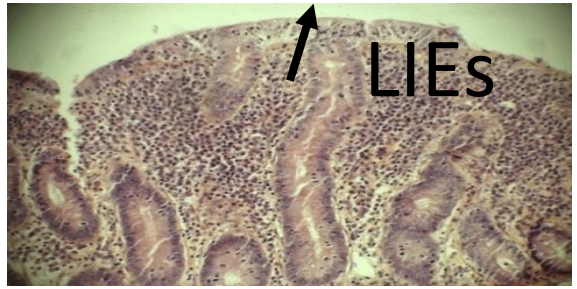
Cerf-Bensussan N, Schuppan D. *Gastroenterology*. 2021;161(1):21-24.

TRAITEMENT SPRUE REFRACTAIRE

SR I
LIE

Phenotype normal
Repertoire polyclonal

Atrophie villositaire

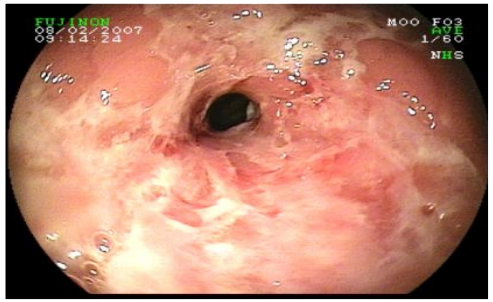


SR II
LIE

Phenotype anormal
sCD3-TCR- iCD3+ :25-98%
CD8 – or CD8 low

Clonal T γ(Tδ)

55%	Malnutrition hypoalbuminemie	plus sévère 93%
10%	Jejunitis ulcéreuse	67%
	Large ulcerations >1 cm	



Budesonide open capsule
IS

Cellier et al Gastroenterology 1998
Cellier et al Lancet 2000
Cellier Lancet Gastro 2019

Budesonide open capsule
Cladribine +Autogreffe
Biothéraphies ac anti IL 15 ?

Safety and efficacy of AMG 714 in patients with type 2 refractory coeliac disease: a phase 2a, randomised, double-blind, placebo-controlled, parallel-group study

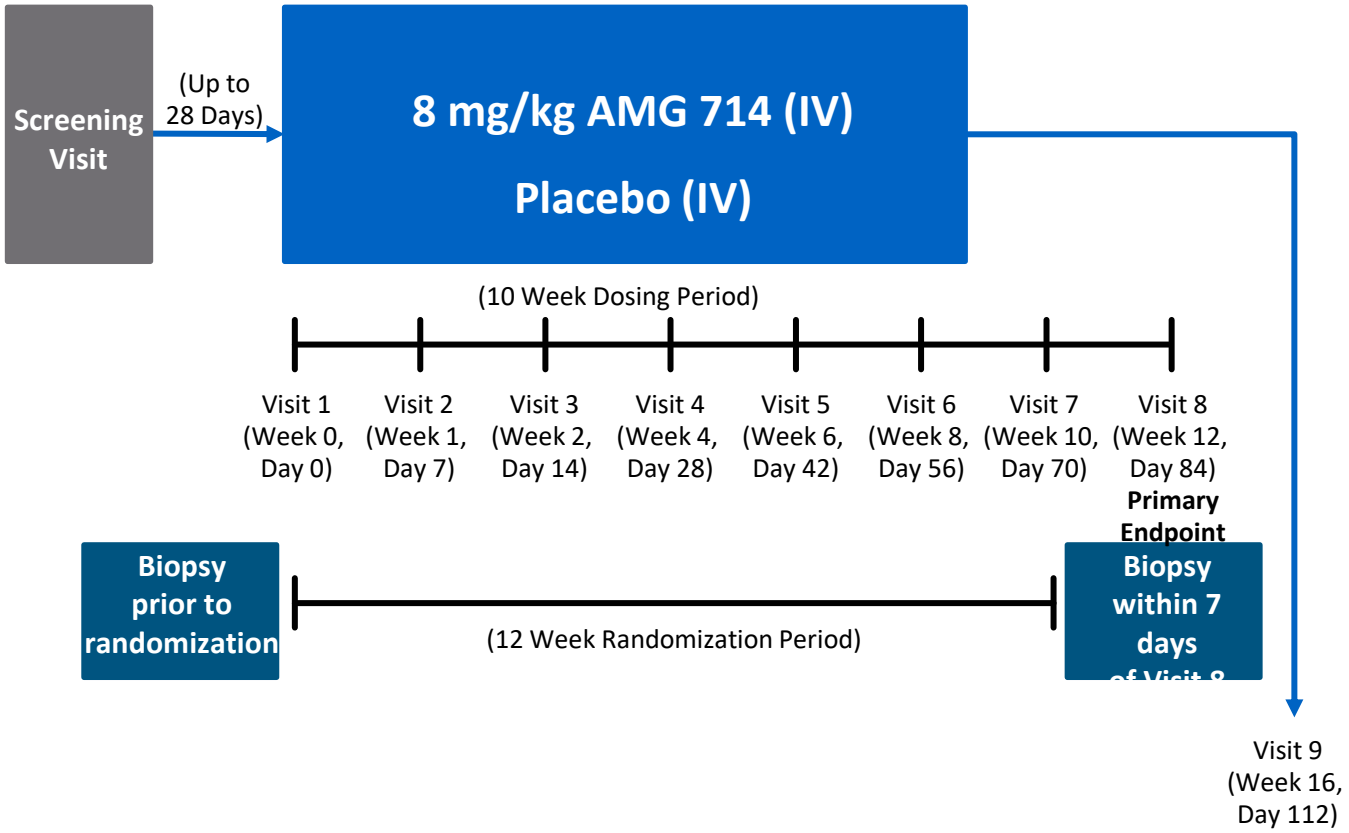
Christophe Cellier, Gerd Bouma, Tom van Gils, Sherine Khater, Georgia Malamut, Laura Crespo, Pekka Collin, Peter H R Green, Sheila E Crowe, Wayne Tsuji, Eric Butz, Nadine Cerf-Bensussan, Elizabeth Macintyre, Jane R Parnes, Francisco Leon, Olivier Hermine, Chris J Mulder, the RCD-II Study Group Investigators*

Summary

Background Refractory coeliac disease type 2 is a rare subtype of coeliac disease with high mortality rates; interleukin 15 (IL-15) is strongly implicated in its pathophysiology. This trial aimed to investigate the effects of AMG 714, an anti-IL-15 monoclonal antibody, on the activity and symptoms of refractory coeliac disease type 2.

Lancet Gastroenterol Hepatol 2019

*Investigators are listed in th

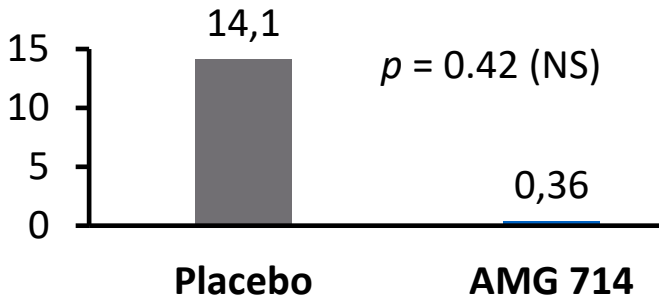


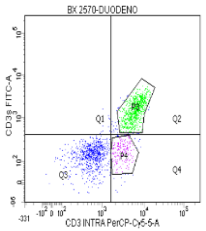
- Patients randomized (N = 28)
- Pure RCD II per-protocol population (N=19)

Lancet Gastro 2019

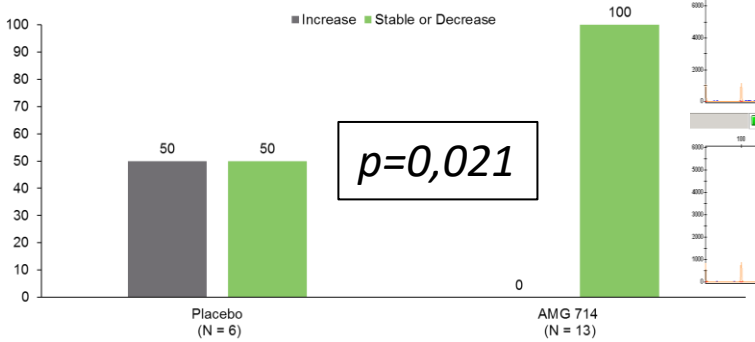
PRIMARY ENDPOINT: IMMUNOLOGICAL RESPONSE (FAILED)
LONG TERM FOLLOW -UP ?

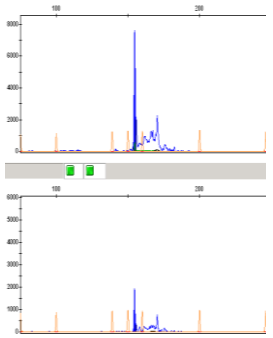
Change in aberrant IELs from baseline to week 12



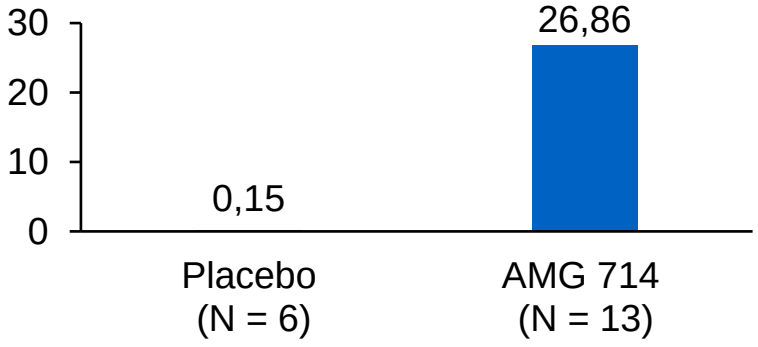


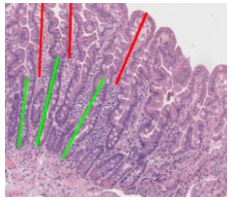
Clonality from baseline to W12



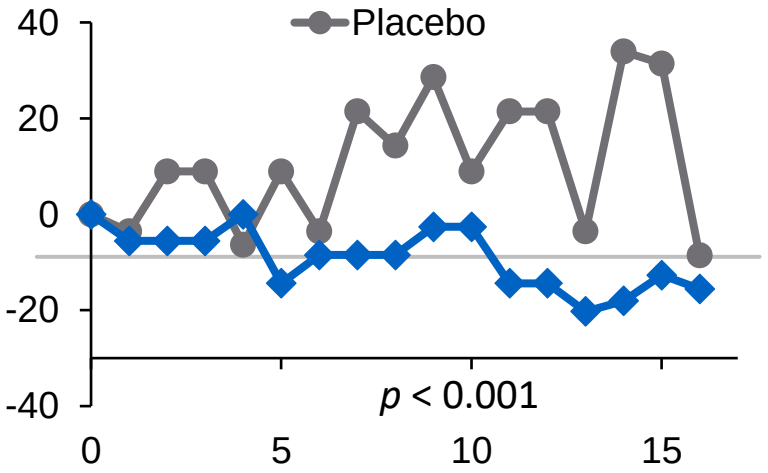


Change in VH:CD ratio between baseline and W12





Improvement in diarrhea



Cellier C, et al. *Lancet Gastroenterol Hepatol*. 2019;4(12):960-970.

Follow-up data after Anti IL 15 treatment (AMG-714)
Long term benefit should be assessed

- 3 patients in placebo group:
  - 1 developed EATL and died
  - 1 developed small bowel adenocarcinoma
- 8 patients in AMG-714 group (1 gamma delta RCD II): 5 villous recovery; 2 polyclonal; all well

	Histology at inclusion	Histology at W12	Histological FU	Clonality
1	Partial VA	Partial VA	No VA	Positive
2	Partial VA	Partial VA	No VA	Weak clone
3	Total VA	VA not evaluable	Total VA	Positive
4	Subtotal VA	Partial to subtotal VA	No VA	Polyclonal
5	Partial VA	Subtotal VA	No VA	Positive
6	Partial VA	No VA	No VA	Weak clone
7	Partial VA	Partial VA	Partial VA	Polyclonal

NYC Columbia University meeting 2022

Sensibilité au gluten non cœliaque

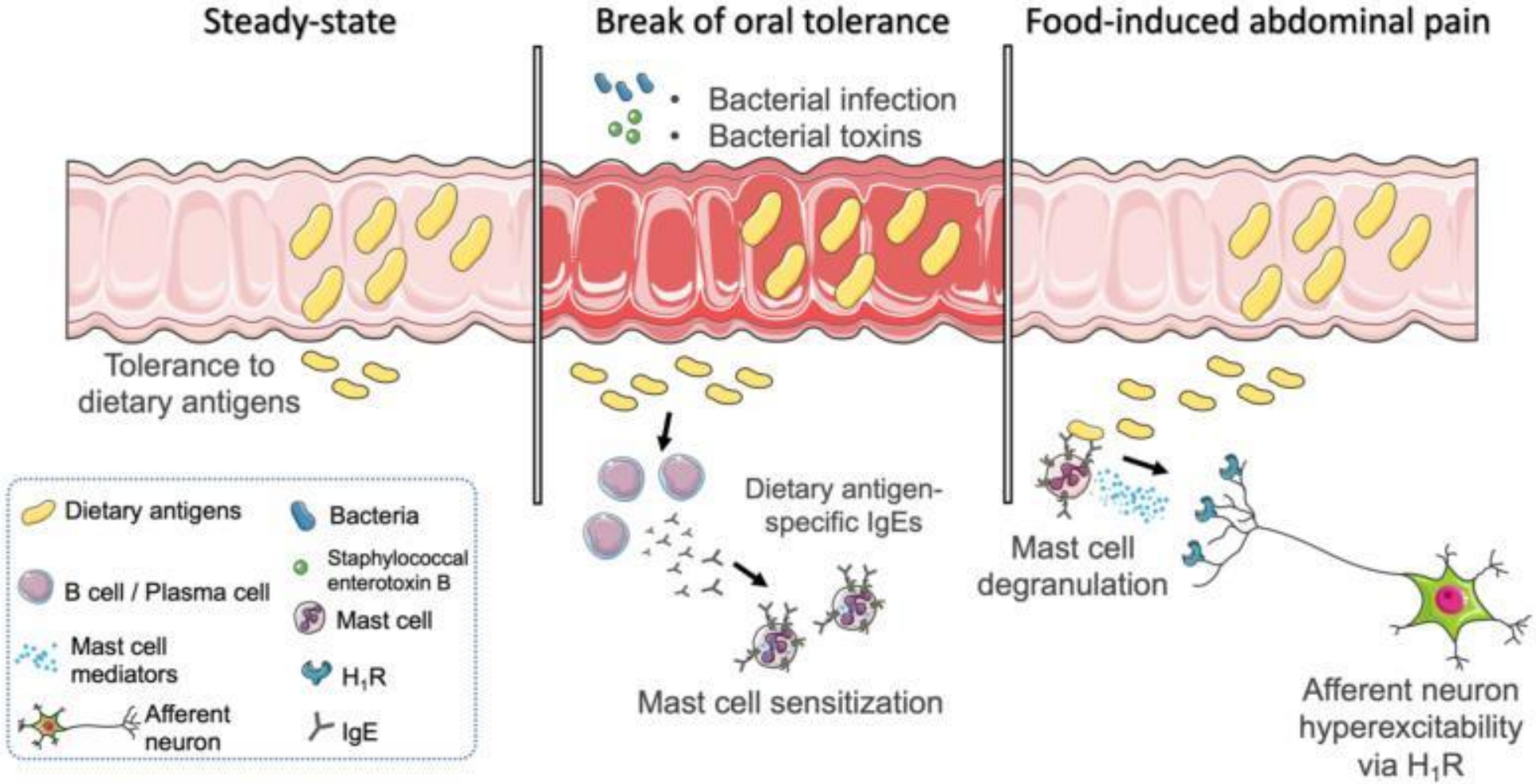
- Symptômes digestifs et extra-digestifs

- déclenchés par l'ingestion de gluten
- disparaissent ou s'améliorent avec l'exclusion du gluten
- Récidivent lors de la réintroduction du gluten

- En l'absence de maladie cœliaque et d'allergie au gluten

- Prévalence non connue, plus fréquente que la maladie cœliaque

The Oslo definitions for celiac disease and related terms, Gut 2013



Article

Local immune response to food antigens drives meal-induced abdominal pain

https://doi.org/10.1038/s41586-020-03118-2

Received: 18 March 2020

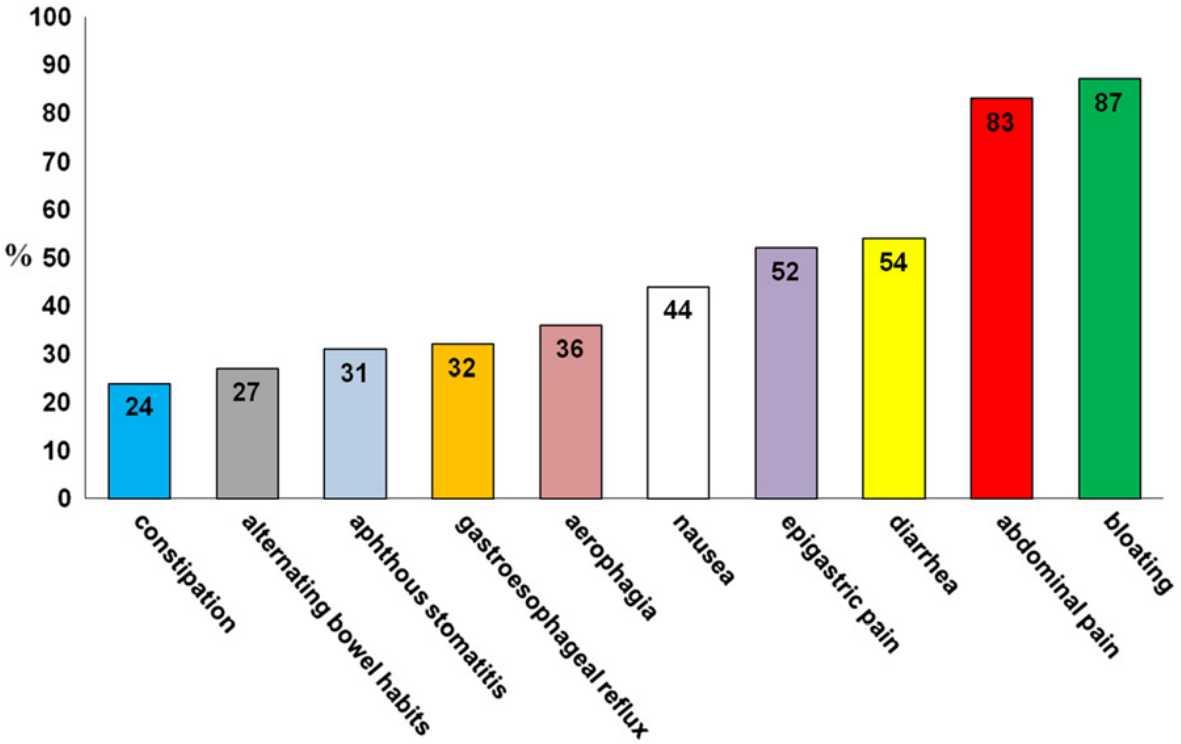
Accepted: 27 November 2020

Published online: 13 January 2021

Check for updates

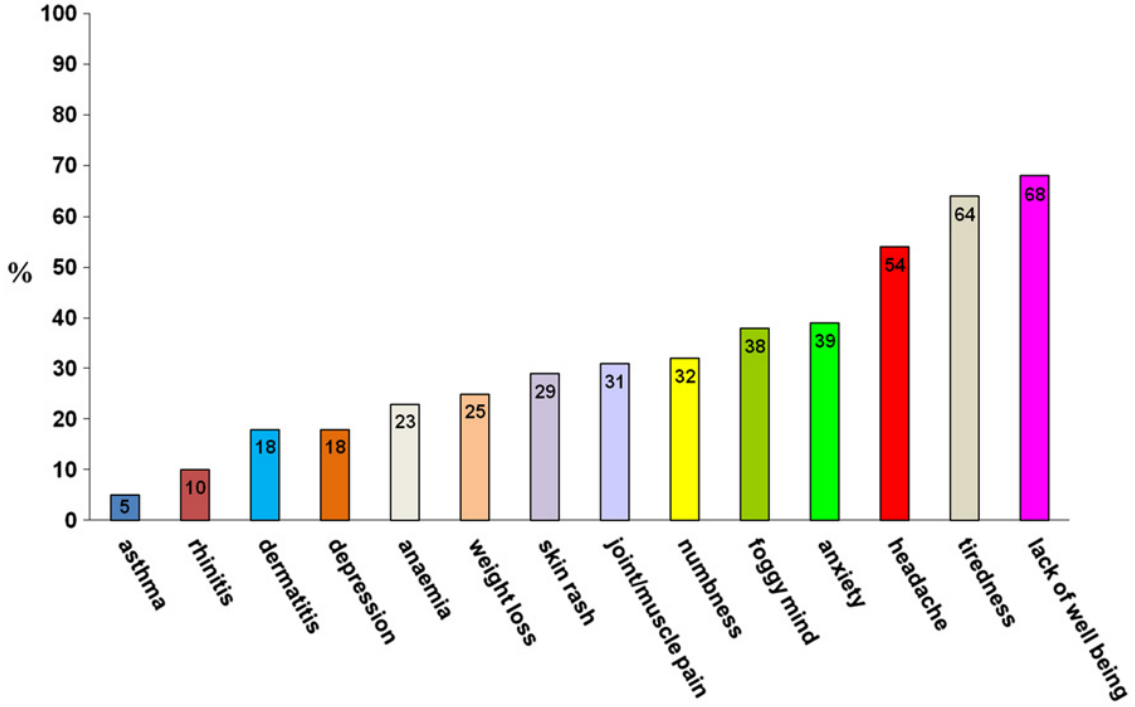
Javier Aguilera-Lizarraga[1,22], Morgane V. Florens[1,22], Maria Francesca Viola[1], Piyush Jain[1], Lisse Decraecker[1], Iris Appeltans[1], Maria Cuende-Estevez[1], Naomi Fabre[1], Kim Van Beek[1], Eluisa Perna[1], Dafne Balemans[1], Nathalie Stakenborg[1], Stavroula Theofanous[1], Goele Bosmans[1], Stéphanie U. Mondelaers[1], Gianluca Matteoli[2], Sales Ibiza Martínez[2,20], Cintya Lopez-Lopez[3], Josue Jaramillo-Polanco[3], Karel Talavera[4], Yeranddy A. Alpizar[5], Thorsten B. Feyerabend[6], Hans-Reimer Rodewald[6], Ricard Farre[7], Frank A. Redegeld[8], Jiyeon Si[9,10], Jeroen Raes[9,10], Christine Breynaert[11], Rik Schrijvers[11], Cédric Bosteels[12,13], Bart N. Lambrecht[12,13,14], Scott D. Boyd[15,16], Ramona A. Hoh[15], Deirdre Cabooter[17], Maxim Nelis[17], Patrick Augustijns[17], Sven Hendrix[18,21], Jessica Strid[19], Raf Bisschops[1], David E. Reed[3], Stephen J. Vanner[3], Alexandre Denadai-Souza[1,23], Mira M. Wouters[1,23] & Guy E. Boeckxstaens[1,23]

Manifestations cliniques digestives



Sapone A, et al, BMC Med. 2012
Volta U, et al, BMC Med. 2014

Manifestations cliniques extra-digestives



Sapone A, et al, BMC Med. 2012
Volta U, et al, BMC Med. 2014

Diagnostic

- Diagnostic d’exclusion
- Pas de marqueur biologique spécifique
- Pas de corrélation HLA

Démarche diagnostique

- Test thérapeutique consistant à supprimer le gluten et à évaluer la réponse clinique au RSG
- Test de provocation consistant à réintroduire du gluten en aveugle contre placebo

Catassi C,, et al. Diagnosis of Non-Celiac Gluten Sensitivity (NCGS): The Salerno Experts' Criteria. Nutrients 2015

Régime sans gluten

- Aucune complication de le la sensibilité au gluten n’a été décrite jusqu'à ce jour
- Le RSG améliore au quotidien les symptômes digestifs ou extra-digestifs des patients
- Aucune prise en charge n’est prévue par la sécurité sociale
- Régime « à la demande »

De nombreuses interrogations…

- Fréquence ?
- Critères objectifs diagnostiques?
- Pathogénie? Rôle exclusif ou non du gluten (FODMAPS, ATI) ? mastocytes (Nature 2021)

Take Home message

Take Home message

- Diagnostic de maladie coeliaque tardif
- Signes cliniques atypiques ou mineurs fréquents
- Test diagnostique: Ac anti TTG ++
- Régime sans gluten : seul traitement validé (à commencer après le diagnostic)
- Complications rares, mais graves

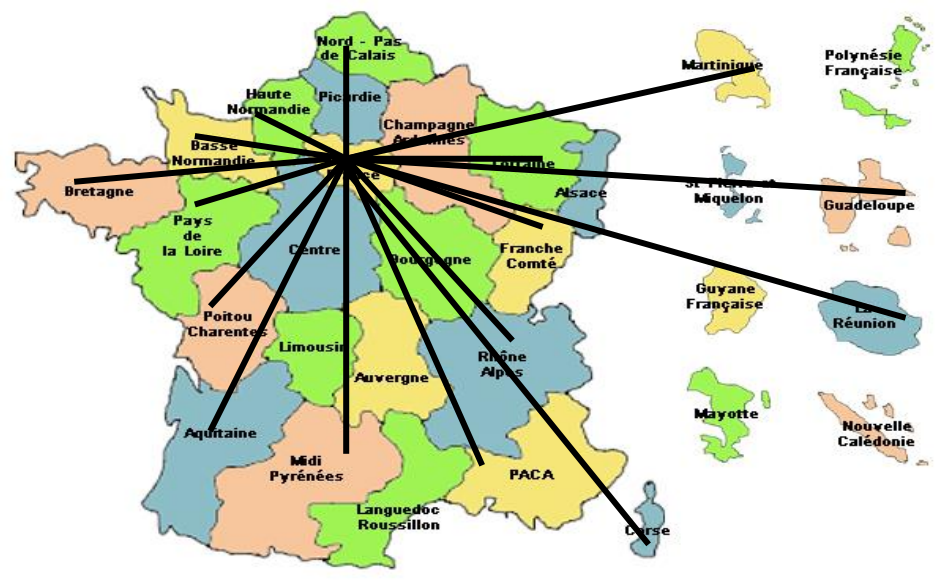
French National Clinical Network of lymphoma associated with celiac disease :CELAC (Centre référence cancer rare INCA)

- *RCP (histological review)*
- *Essais thérapeutiques (anti- CD30, anti-IL15, anti-NKG2D/ anti-IL23, glutenase, antiTtG…)*
- *Coordinateurs:*
- *Pr Cellier (Gastro)*
- *Pr Hermine (Hemato)*
- *Chef de Projet: Dr S Khater*

christophe.cellier@aphp.fr

ou

sherine.khater@aphp.fr



Merci de votre attention

SORRENTO**ICDS2022**

19th INTERNATIONAL CELIAC DISEASE SYMPOSIUM

19th -22nd October 2022 | Hilton Sorrento Palace

www.icds2022sorrento.com