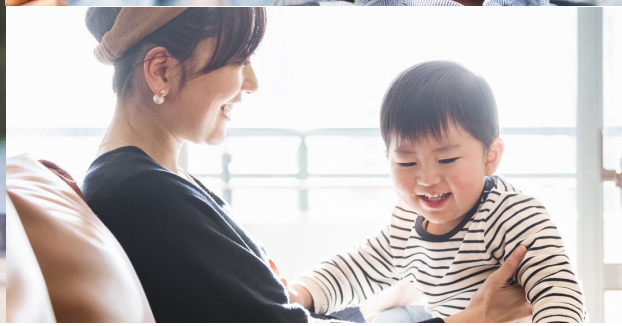

Inflammatory Bowel Disease (IBD)

September 2nd, 2020

Mitsuhiro Shikamura

Senior Clinical Science Director
Therapeutic Strategic Unit (GI)

Takeda Development Center Japan

GASTROENTEROLOGY

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Today’s Topics

1. Takeda's GI Therapeutic Area and Inflammatory Bowel Disease (IBD) Initiatives
2. What is IBD?: Epidemiology, Etiology, and Symptoms
3. Diagnosis and Treatment for IBD
4. Vedolizumab

Today’s Topics

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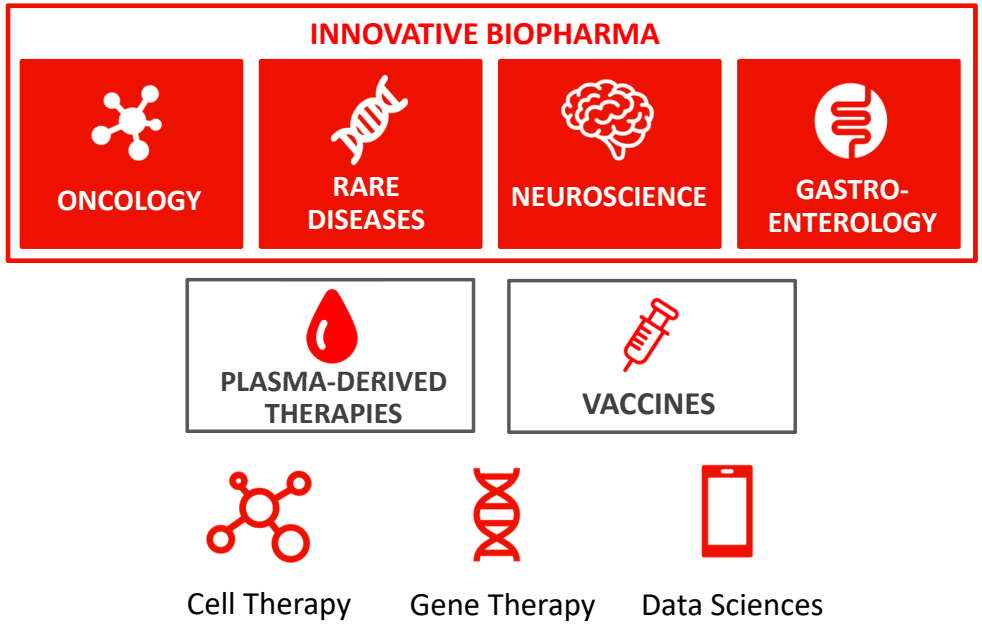
Success built upon deep focus & expertise in core areas

BUSINESS AREA FOCUS

- GASTRO-ENTEROLOGY
- RARE DISEASES
- PLASMA-DERIVED THERAPIES
- ONCOLOGY
- NEUROSCIENCE

R&D FOCUS



We are a leading GI company

GASTROENTEROLOGY THERAPEUTIC AREA

Our vision

Restore Life to Living for patients suffering with GI and liver diseases

Our mission

Deliver **innovative, life-changing therapeutics** for patients with GI and liver diseases

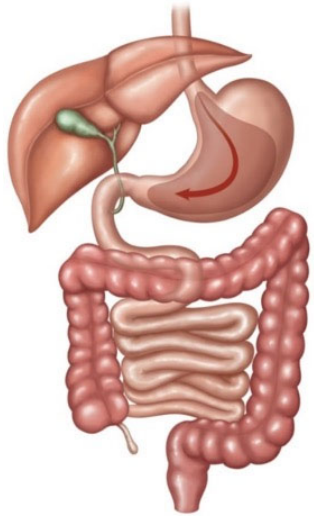
Our strategy expands the portfolio across core disease areas supported by platform technologies

IBD

- Build upon success of Vedolizumab with new formulations
- Expand treatment options with Alofisel

Motility disorders

- Focus on select high unmet medical need areas including gastroparesis and enteral feeding intolerance



Celiac disease

- Advance approaches for the prevention of immune responses to gluten

Liver diseases

- Target early-stage investments in liver fibrosis

Luminal platforms

- Accelerate microbiome investments
- Invest in selective drug delivery technologies

Acid related diseases franchise will continued to be supported, but new pipeline investment will be deprioritized relative to above disease areas.

IBD: Inflammatory Bowel Disease (e.g., Ulcerative Colitis, Crohn's disease)

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Inflammatory bowel disease (IBD) market size and characteristics

The number and market size of patients with inflammatory bowel disease continue to expand

Ulcerative Colitis (UC)

- The prevalence is approximately 1.8 million patients in major markets (2018)
  - US: ~920,000
  - Europe: ~690,000
  - Japan: ~170,000
- Market size is expected to grow from $6.3B (2018) to $9.2B (2028) (3.8% CAGR)
- Major growth drivers
  - Increase in the number of patients diagnosed
  - Successive launches of new products, etc.

Crohn's Disease (CD)

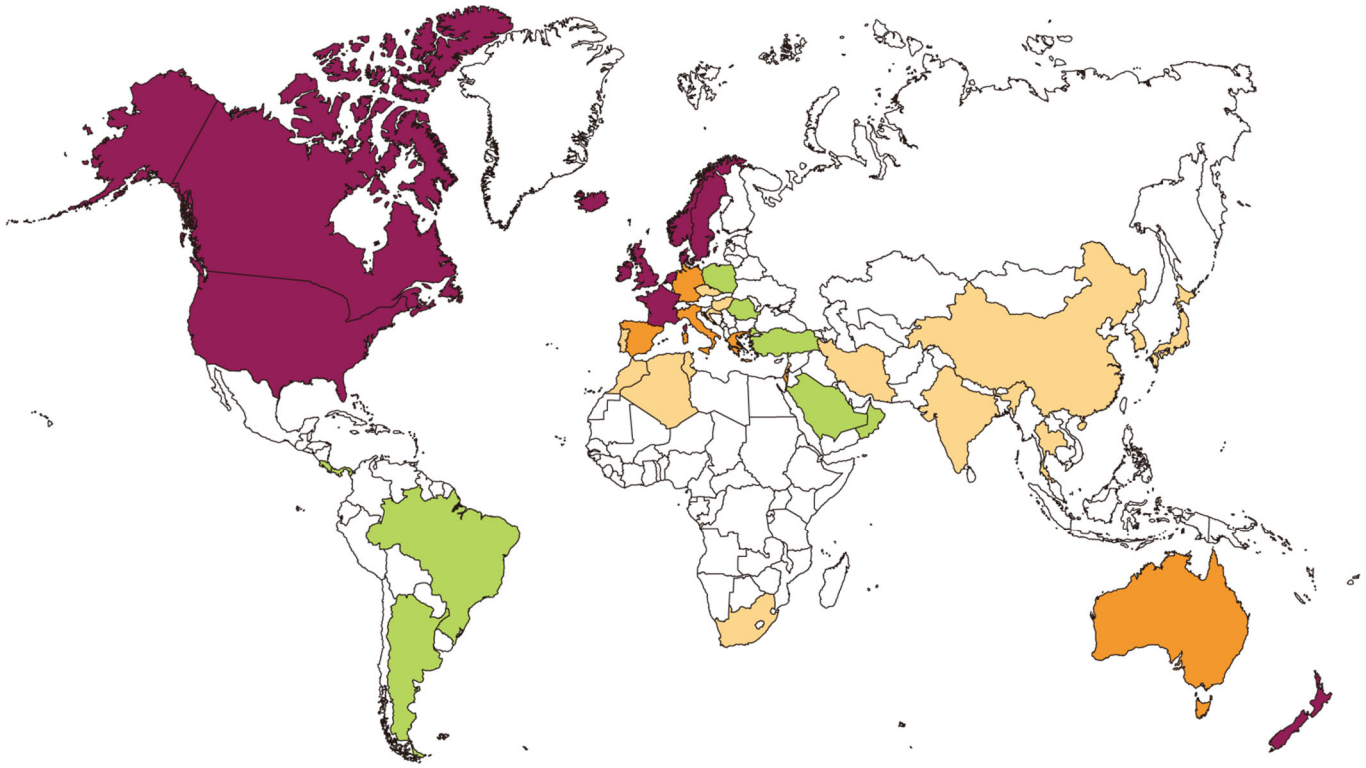
- The prevalence is approximately 1.4 million patients in major markets (2018)
  - US: ~800,000
  - Europe: ~590,000
  - Japan: ~40,000
- Market size is expected to grow from $15.9B (2018) to $17.7B (2028) (1.0% CAGR)
- Major growth drivers
  - Increase in the number of patients diagnosed
  - Penetration of Top-down therapy, etc.

Please refer to slide 38 for explanation of Top-down therapy

Landscape & Forecast, QRG, Feb 2020

Annual Incidence of Inflammatory bowel disease (IBD)

The incidence in Japan is lower than Western countries



Incidence	Low	Low but increased	Moderate	High	No data
Annual incidence (per 100,000):	4 or fewer	4 or fewer	5 to 10	10 or more	

Cosnes J, et al.: Gastroenterology 2011; 140 (6): 1785-1794.

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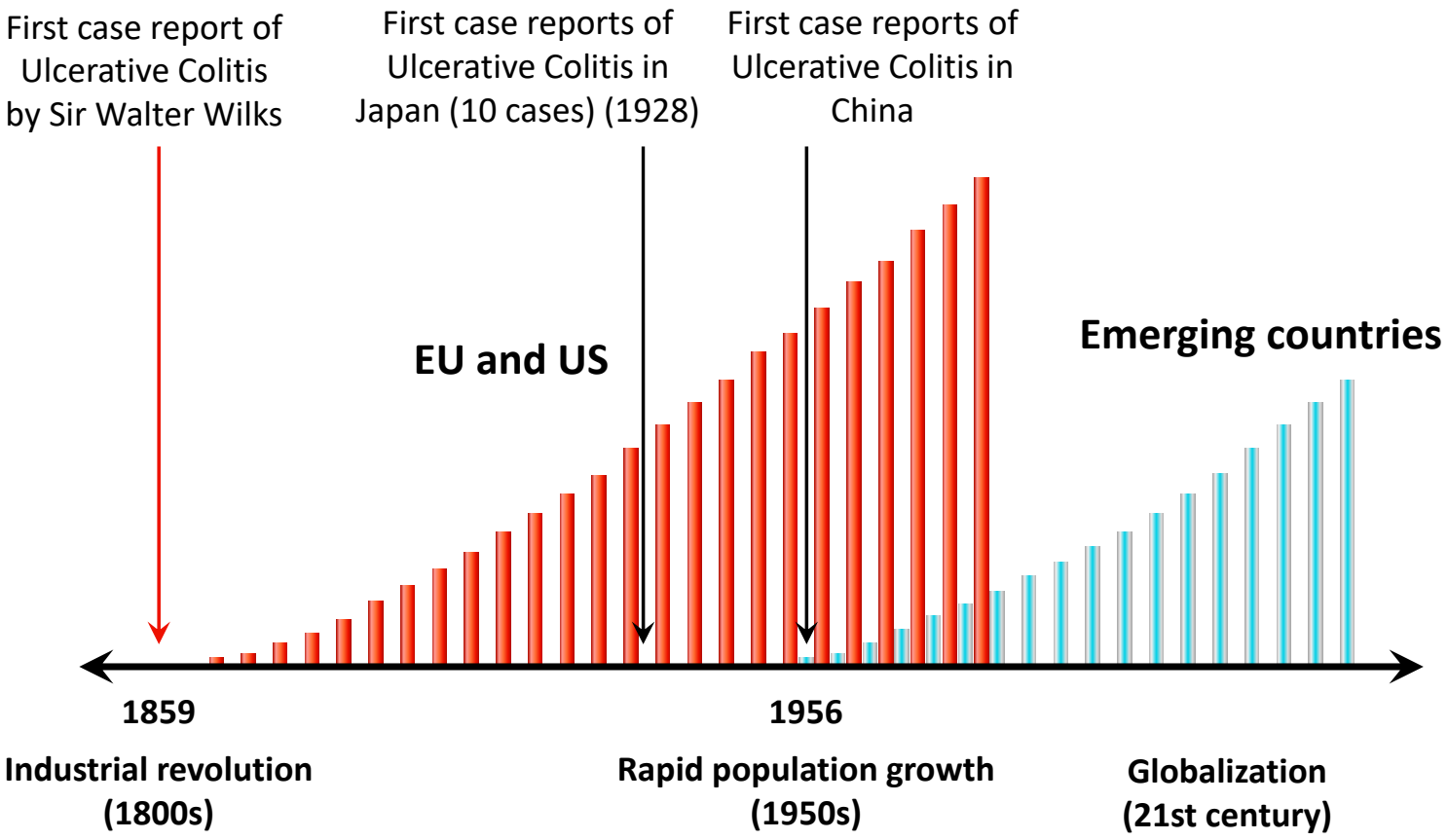
Patient trends with Inflammatory bowel disease (IBD) in Western and Emerging countries (conceptual)

Inflammatory bowel disease is now recognized as a worldwide inflammatory disease



Kaplan GG, et al.: Gastroenterology 2017;152(2):313-321.
Ryukichi Inada: : Journal of Japanese Society of Gastroenterology 1928;27(11):625-638.

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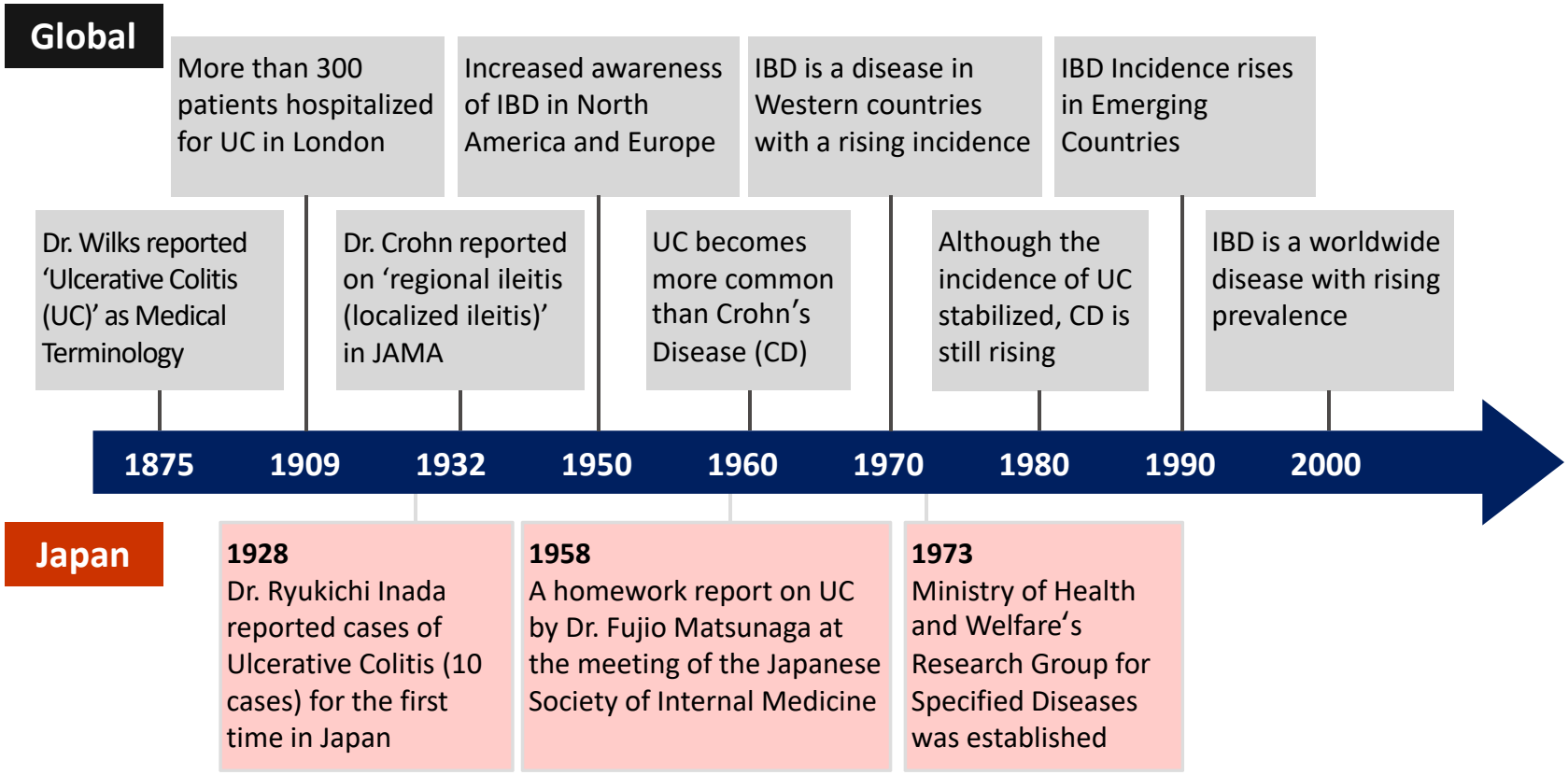
History of IBD in the world and IBD research in Japan

IBD is now recognized as a global inflammatory disease



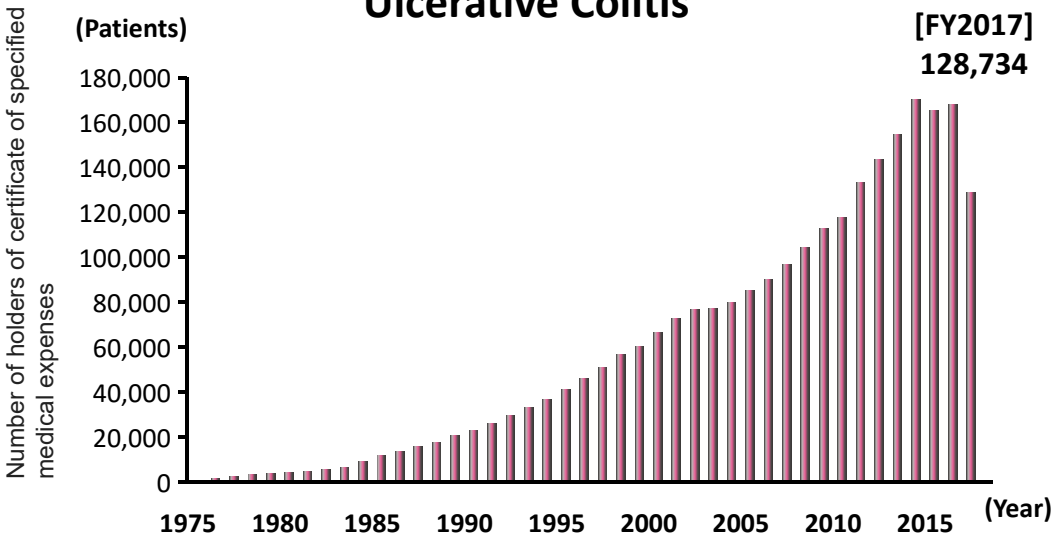
IBD:inflammatory bowel disease
JAMA: Journal of the American Medical Association

Kaplan GG.: Nat Rev Gastroenterol Hepatol 2015;12(12):720-727.
Ryokichi Inada: Journal of Japanese Society of Gastroenterology 1928; 27(11): 625-638.
Fujio Matsunaga et al.: The Journal of the Japanese Society of Internal Medicine. 1958; 47(4): 295-322.
Tetsuichiro Muto: Journal of Japanese Society of Gastroenterology 2008; 105(5): 639-642

Number of patients with specific medical expenditure certificates for IBD in Japan per year

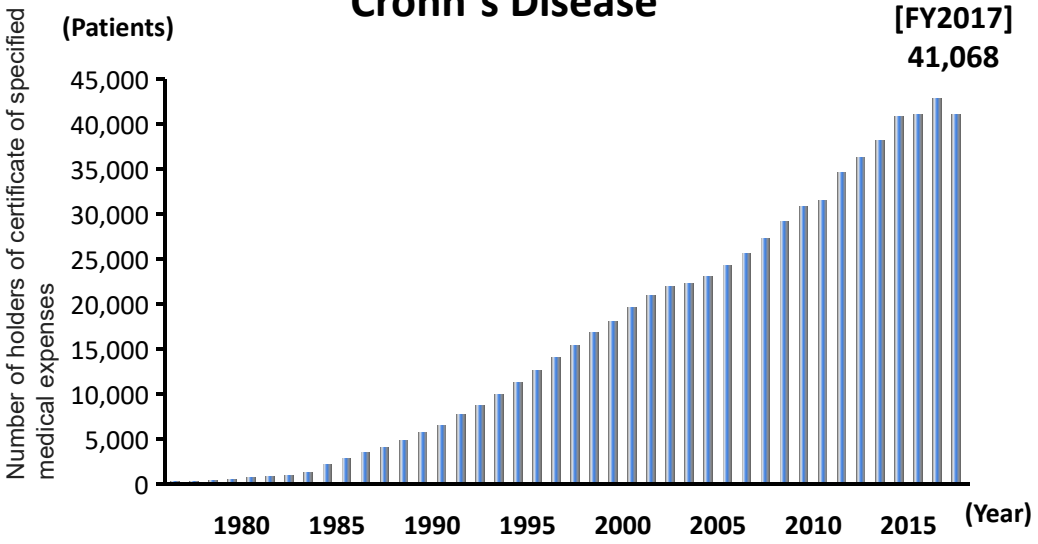
The number of patients with inflammatory bowel disease (IBD) in Japan has been on the rise in the long term

Ulcerative Colitis



Number of patients who have received certifications for specified medical expenses (http://www.nanbyou.or.jp/entry/1356))
Health Administrative Reports by MHLW (https://www.mhlw.go.jp/toukei/list/36-19.html)

Crohn's Disease



Number of patients who have received certifications for specified medical expenses (http://www.nanbyou.or.jp/entry/1356))
Health Administrative Reports by MHLW (https://www.mhlw.go.jp/toukei/list/36-19.html)

	Ulcerative Colitis (UC)	Crohn's Disease (CD)
Peak age at onset	20's to early 40's	10s to 20s
Male to female ratio	About 1:1	About 2:1

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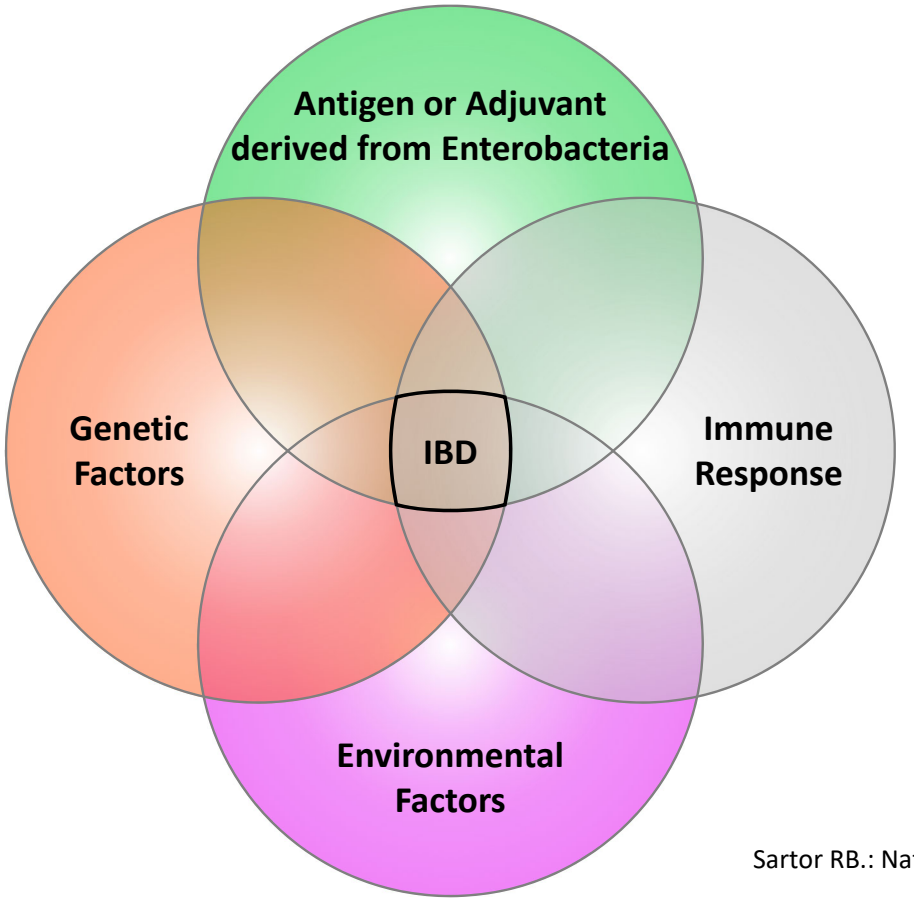
Etiology

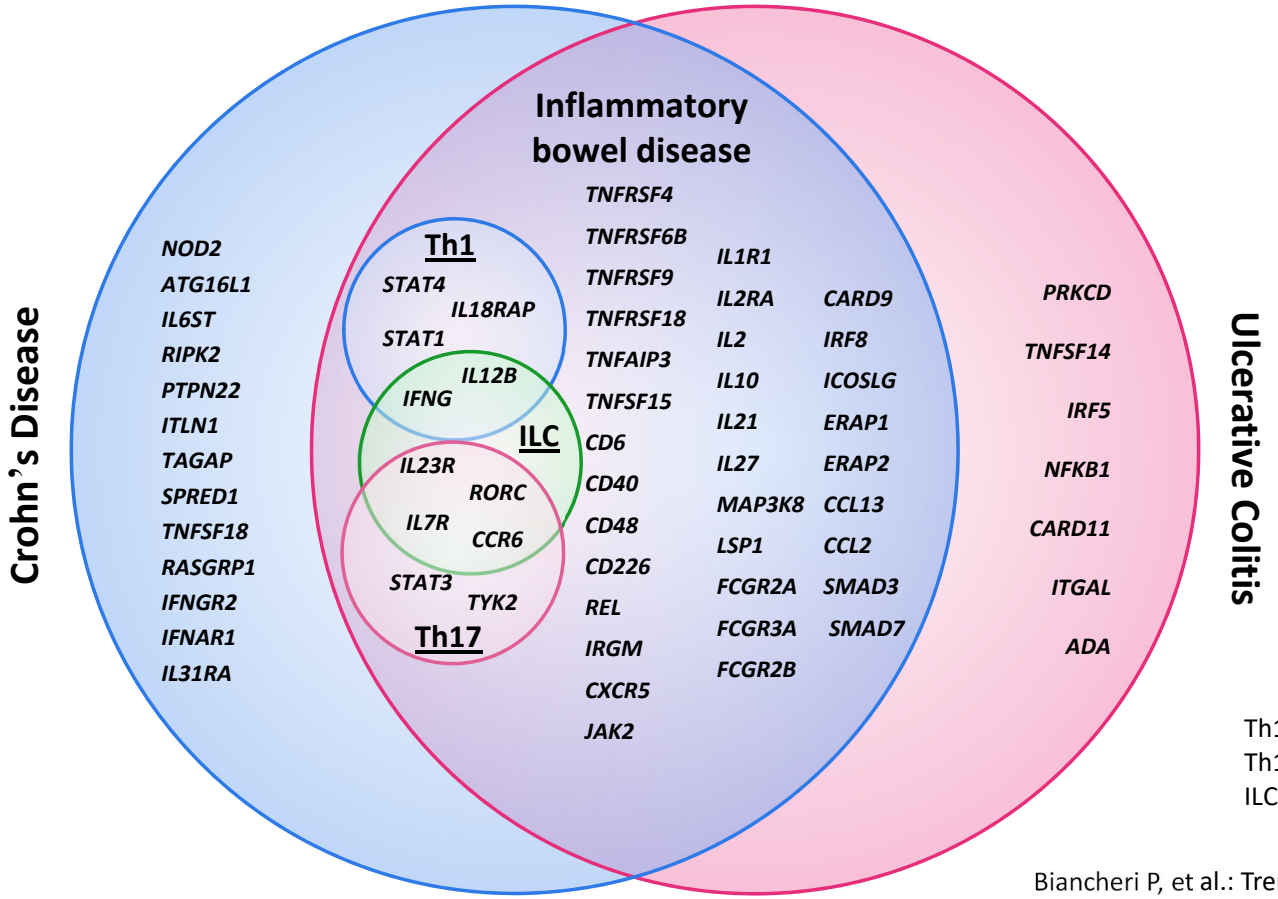
Inflammatory bowel disease (IBD) is a multifactorial disease involving environmental and genetic factors



Sartor RB.: Nat Clin Pract Gastroenterol Hepatol 2006;3(7):390-407.

Inflammatory bowel disease (IBD) related genes

Several genes have been identified that may be associated with inflammatory bowel disease

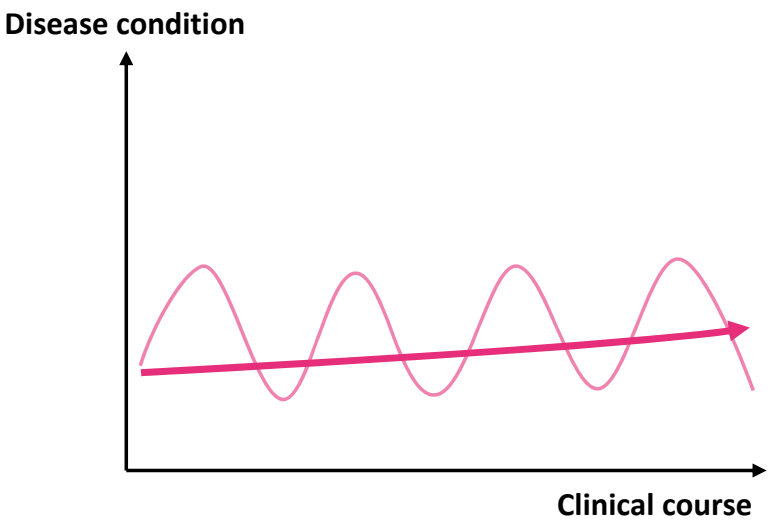


Th1 :T helper type 1
Th17:T helper type 17
ILC :innate lymphoid cell

Biancheri P, et al.: Trends Immunol 2013;34(11):564-571.

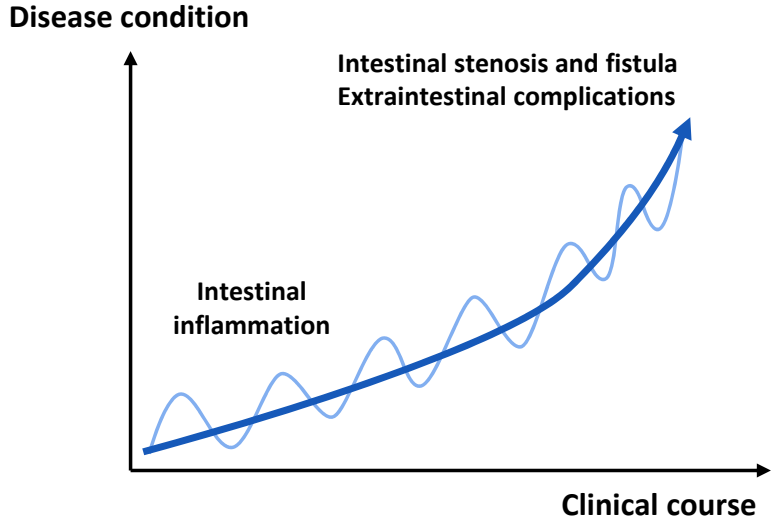
Pattern of disease progression (image)

Inflammatory bowel disease (IBD) follows a course of symptom progression with recurrent flares and remissions. However, the patterns are different in ulcerative colitis and Crohn's disease



Progression of Ulcerative Colitis

Recurring symptoms several times during a prolonged course of relapse and remission



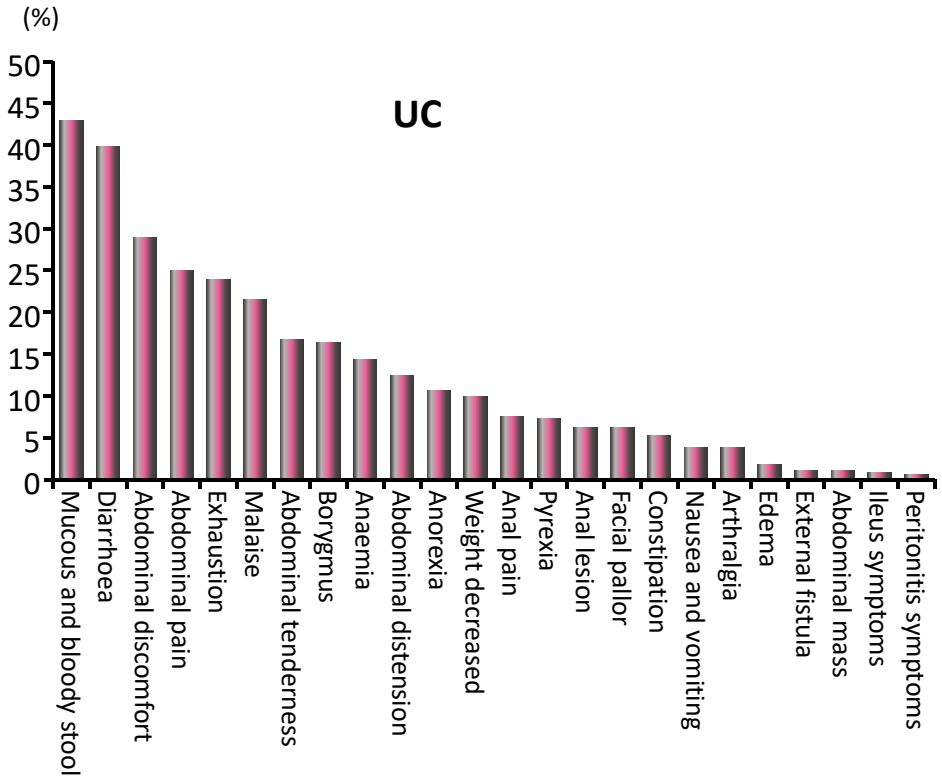
Progression of Crohn's Disease

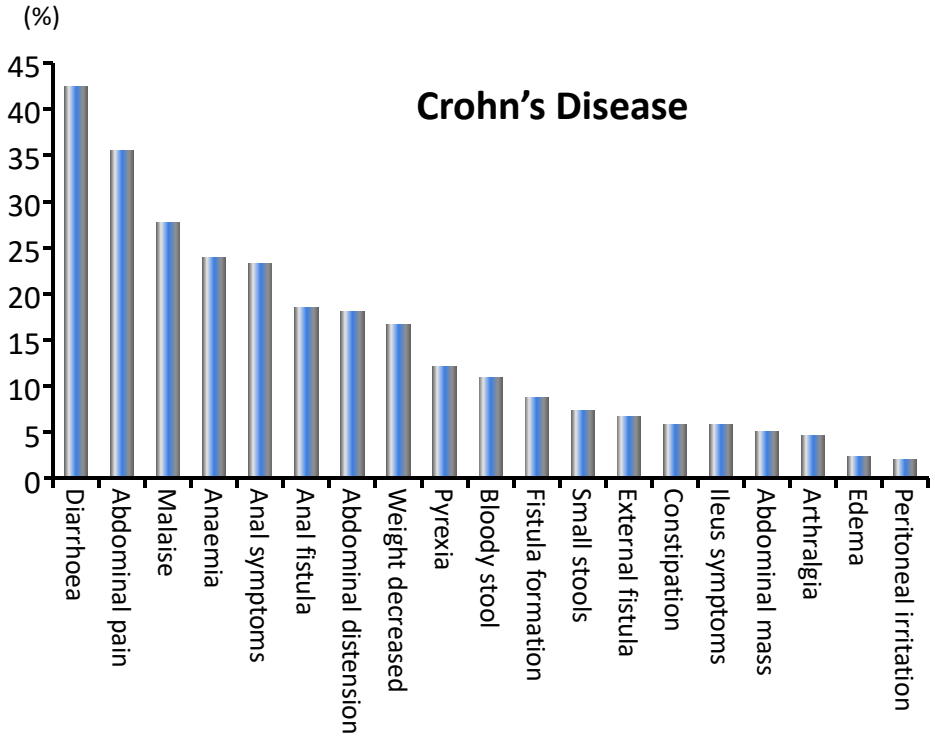
Repeated relapses and remissions progress and worsen the condition

Yasuo Suzuki: Medical Practice in IBD (Toshifumi Hibi, Tadakazu Hisamatsu, et al.), 41-50, Yodosha, 2017

Symptoms

Ulcerative Colitis(UC) is characterized by muco-bloody stools, diarrhea, abdominal discomfort, and abdominal pain.
Crohn's Disease is characterized by diarrhea, abdominal pain, weight loss, fever, and bowel obstruction or fistula





For doctors who are being diagnosed for IBD, to understand IBD at a glance (2nd Edition)
Health, Labour and Welfare Science Research Grant Refractory Disease Policy Research Project "Survey Research on Refractory Inflammatory Bowel Disorders"(Suzuki group), 20, 2015
Hirokazu Nagawa: Research survey on Refractory Inflammatory Bowel Disorders (Team Hibi group) Appendix of the 2006 Research Report, 2007

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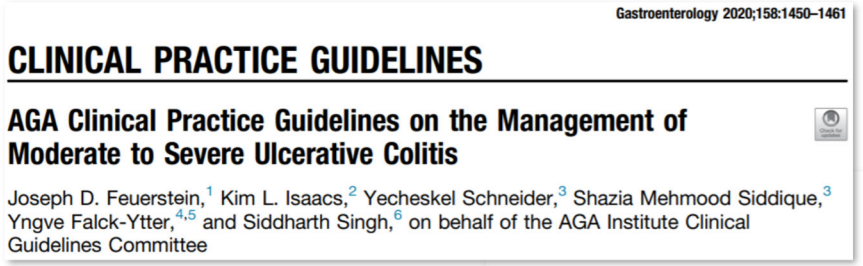
Clinical Practice and treatment Guidelines in Japan and overseas

Clinical Practice Guideline for Inflammatory Bowel Disease 2016; The Japanese Society of Gastroenterology

Diagnostic criteria and treatment guidelines for Ulcerative Colitis and Crohn's Disease; Survey research on refractory inflammatory bowel disorders, 2019 (Suzuki group)

Guidelines outside Japan


Gastroenterology 2020;158:1450–1461

CLINICAL PRACTICE GUIDELINES

AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis

Joseph D. Feuerstein,[1] Kim L. Isaacs,[2] Yecheskel Schneider,[3] Shazia Mehmood Siddique,[3] Yngve Falck-Ytter,[4,5] and Siddharth Singh,[6] on behalf of the AGA Institute Clinical Guidelines Committee


Guidelines

OPEN ACCESS

British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults

Christopher Andrew Lamb, Nicholas A Kennedy, Tim Raine, Philip Anthony Hendy, Philip J Smith, Jimmy K Limdi, Bu'Hussain Hayee, Miranda C E Lomer, Gareth C Parkes, Christian Selinger, Kevin J Barrett, R Justin Davies, Cathy Bennett, Stuart Gittens, Malcolm G Dunlop, Omar Faiz, Aileen Fraser, Vikki Garrick, Paul D Johnston, Miles Parkes, Jeremy Sanderson, Helen Terry, IBD guidelines eDelphi consensus group, Daniel R Gaya, Tariq H Iqbal, Stuart A Taylor, Melissa Smith, Matthew Brookes, Richard Hansen, A Barney Hawthorne


Journal of Crohn's and Colitis, 2017, 3–25
doi:10.1093/ecco-jcc/jjw168
Advance Access publication September 22, 2016
ECCO Guideline/Consensus Paper

ECCO Guideline/Consensus Paper

3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management

Fernando Gomollón,* Axel Dignass,* Vito Annese, Herbert Tilg, Gert Van Assche, James O. Lindsay, Laurent Peyrin-Biroulet, Garret J. Cullen, Marco Daperno, Torsten Kucharzik, Florian Rieder, Sven Almer, Alessandro Armuzzi, Marcus Harbord, Jost Langhorst, Miquel Sans, Yehuda Chowers, Gionata Fiorino, Pascal Juillerat, Gerassimos J. Mantzaris, Fernando Rizzello, Stephan Vavricka, Paolo Gionchetti, on behalf of ECCO


ACG Clinical Guideline: Management of Crohn's Disease in Adults

Gary R. Lichtenstein, MD, FACG[1], Edward V. Loftus Jr, MD, FACG[2], Kim L. Isaacs, MD, PhD, FACG[3], Miguel D. Regueiro, MD, FACG[4], Lauren B. Gerson, MD, MSc, MACG (GRADE Methodologist)[5,†] and Bruce E. Sands, MD, MS, FACG[6]

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Diagnostic criteria for Ulcerative Colitis (2019 Revised edition)

Definite diagnosis: [1] Fulfill A and ① or ② in B, and C

[2] Fulfill ① or ② in B, and C over multiple times

[3] Microscopic and histologic findings, whose characteristic of the disease in sample by surgery or biopsy

A. Clinical symptoms	Patients who currently have, or with a medical history of, persistent or recurrent mucus/bloody stool
B. ① Endoscopy	i) The mucosa is diffusely affected, vascular lucency disappears, and is coarse or finely granular. In addition, it is fragile and easily bleeds (contact bleeding), and muco-purulent secretions are attached. ii) Multiple erosions, ulcers, or pseudopolyposis are noted. iii)As a principle, lesions are recognized continuously from the rectum.
② Barium enema	i) Diffuse changes in coarse or finely granular mucosal surfaces, ii) Multiple erosions, ulcers, iii)Pseudo-polyposis In addition, loss of haustra (lead tract image) and narrowing and shortening of the intestinal tract are observed.
C. Biopsy histology	Diffuse inflammatory cell infiltration, crypt abscesses, and high goblet cell reduction are seen in all layers of the mucosa in the active phase. Since both are non-specific findings, they should be judged comprehensively. In remission phase, abnormal glandular arrangement (tortuosity and bifurcation) and atrophy remain. These changes are usually seen continuously from the rectum to the oral side.

[Note 1] The following diseases could have been ruled out in confirmed cases: Shigellosis, Clostridium difficile enteritis, amebic colitis, Salmonella enteritis, Campylobacter enteritis, colitis, tuberculosis coli, chlamydial enteritis, etc. are predominant infectious enteritis, and Crohn's disease, radiation colitis, drug-induced colitis, lymphoid follicular proliferation, ischemic colitis, intestinal Behcet's disease, etc.

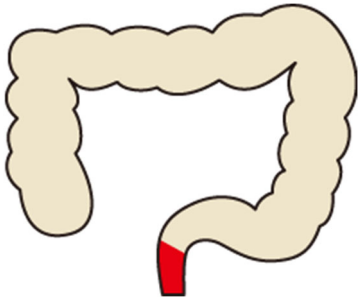
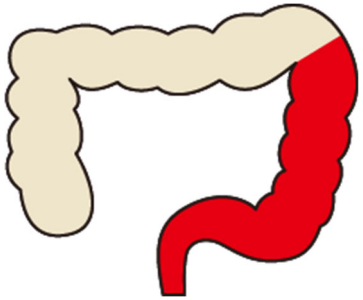
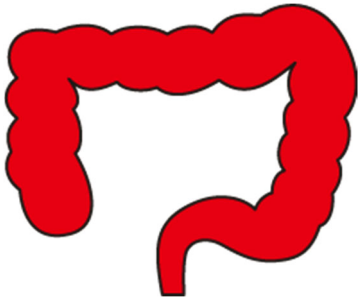
[Note 2] If the findings are mild and the diagnosis is uncertain, it is handled as "suspected diagnosis", and a "definite diagnosis" is made when definite findings are obtained at a later time of relapse, etc.

[Note 3] Difficult case to distinguish: The follow-up is carried out for the case in which the differentiation between Crohn disease and ulcerative colitis is difficult. Cases in which definitive diagnoses cannot be made on the basis of clinical features including endoscopic and biopsied findings are classified as inflammatory bowel disease unclassified (IBDU) If the diagnosis cannot be confirmed by histopathological examination of the post-operative specimen, the disease is classified as indeterminate colitis (IC).Follow-up may reveal more characteristic findings of either disease.

FY2019 Revised (March 31, 2020) Diagnostic Criteria and Treatment Guidance for Ulcerative Colitis and Crohn's Disease
[Government Research Project for Intractable Diseases, etc. "Survey Research on Intractable Inflammatory Bowel Disorders"(Suzuki Group) 2019 Joint Research Report], 1-4, 2020.

Classification of Ulcerative Colitis

The type of Ulcerative Colitis is broadly classified into three groups according to the extent of the inflammatory site

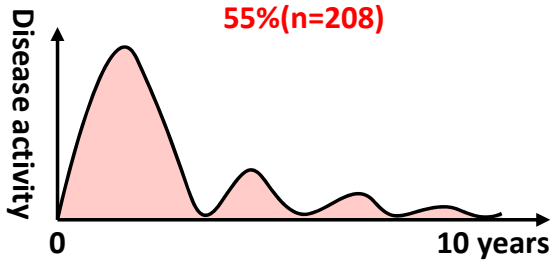
Proctitis type	Left-sided colitis type	Total colitis type
		
25.1%	**25.2%**	**38.3%**
(3,676 pts)	**(3,693 pts)**	**(5,609 pts)**

- Aggregate data calculated only from the electronic data of newly issued medical beneficiaries' certificates
- Types of UC other than the above: 7.8% (1,145 patients); unknown: 3.6% (522 patients)
- The affected areas selected in the individual forms have been converted into the above-mentioned disease type classifications

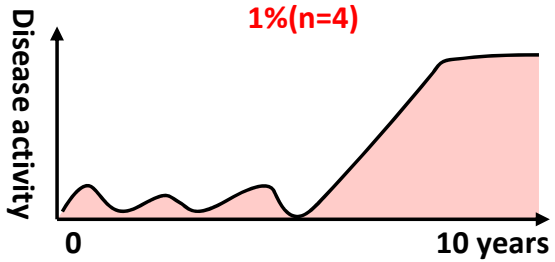
Understanding IBD at a glance (2nd Edition) For doctors who are diagnosing IBD-"Research on Refractory Inflammatory Bowel Disorders"(Suzuki's group), 6, 2015.
Electronic data compilation from the MHLW's 2012 Clinical Survey Individual Questionnaire

Clinical course of patients with Ulcerative Colitis

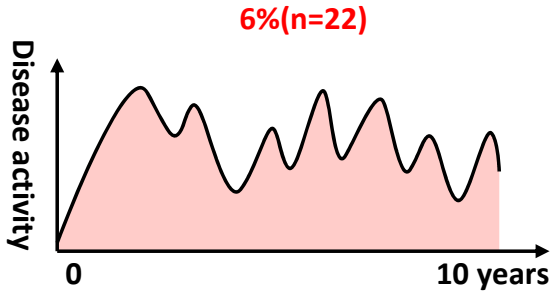
The clinical course of Ulcerative Colitis is often recurrent and remitting



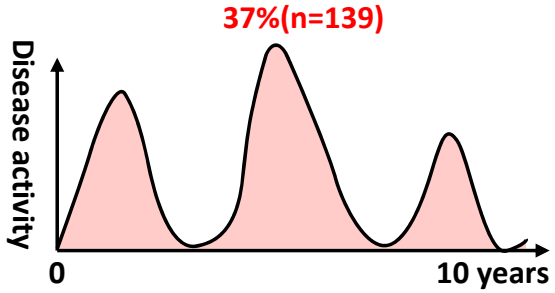
Reduction in the severity of symptoms over time



Symptoms increase over time



Chronic and continuous symptoms



Chronic and intermittent symptoms

Missing: 6 cases

Subjects and Methods : Three hundred seventy-nine patients with unoperated ulcerative colitis who were enrolled in IBSEN between January 1, 1990, and December 31, 1993, were followed up at 1, 5, and 10 years post-diagnosis to determine patterns of symptoms (clinical course)

IBSEN : A Cohort-Study of Inflammatory Bowel Diseases in Inflammatory Bowel disease in South-Eastern Norway

Solberg IC, et al.: Scand J Gastroenterol 2009;44(4):431-440.

GASTROENTEROLOGY

Diagnostic criteria for Crohn's Disease (2019)

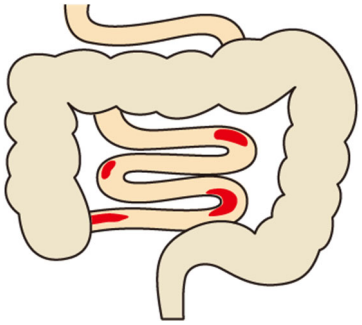
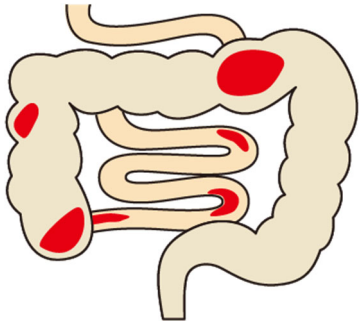
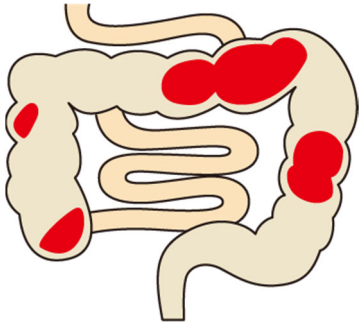
1. Primary finding	A. Longitudinal ulcer [Note 7]
	B. Cobblestone image
	C. Non-caseating epithelioid cell granuloma [Note 8]
2. Secondary Findings	a. Irregular to round ulcers or aphthae in large areas of the gastrointestinal tract [Note 9]
	b. Characteristic anal lesion [Note 10]
	c. Characteristic gastric and duodenal lesions [Note 11]
Confirmed cases	① Those with primary findings A or B. [Note 12]
	② Those with primary finding C, and secondary finding a or b.
	③ Those with all secondary findings a, b, and c.
Suspected cases	① Those with primary finding C and secondary finding c.
	② Those with primary findings A or B but not distinguishable from ulcerative colitis or intestinal Behcet's disease, simple ulcers, or ischemic bowel lesions.
	③ Those with only primary finding C. [Note 13]
	④ Those with any two or only one of the secondary findings.

[Note 7] An ulcer along the long axis of the intestinal tract, it is most commonly found on the side of the mesenteric attachments. Typically length is 4-5 cm; but not essential for the diagnosis.
[Note 8] Serial sectioning improves diagnostic yield. Determination by a pathologist who is familiar with the gastrointestinal tract is desirable.
[Note 9] Extensive involvement of the gastrointestinal tract refers to the distribution over more than one anatomic organ, i.e., the upper gastrointestinal tract (esophagus, stomach, duodenum), the small intestine, and the large intestine. Typically, they are tandem, but sometimes they are not. In addition, it must be present for at least 3 months or more. In capsule endoscopy, multiple lesions may occur in the duodenum and small intestine on Kerckring fold in a ring-like fashion. Intestinal TB, intestinal-type Behcet's disease, uncomplicated ulcers, NSAIDs ulcers, and infectious enteritis must be excluded.
[Note 10] Anal fissure, cavitating ulcer, anal fistula, perianal abscess, edematous cuticle, etc. Referring to Crohn Anal Lesions Gross Finding Atlas, it is preferable to be diagnosed by an anal specialist familiar with Crohn's disease.
[Note 11] Nodal appearance of bamboo, notch-like depression, etc. The diagnosis of a specialist who is familiar with Crohn's disease is desirable.
[Note 12] Longitudinal ulcers alone should exclude ischemic bowel lesions or ulcerative colitis. It is necessary to exclude ischemic bowel lesion and type 4 colorectal cancer only in the case of cobblestone image.
[Note 13] It is necessary to exclude inflammatory diseases with granulomas such as intestinal tuberculosis.

FY2019 Revised (March 31, 2019) Diagnostic Criteria and Treatment Guidance for Ulcerative Colitis and Crohn's Disease
[Government Research Project for Intractable Diseases, etc. "Survey Research on Intractable Inflammatory Bowel Disorders"(Suzuki Group) 2018 Joint Research Report], 26-28, 2020.

Classification of Crohn’s Disease

Many lesions in Crohn's disease are noncontiguous.
Broadly classified into three groups according to the site of the lesion

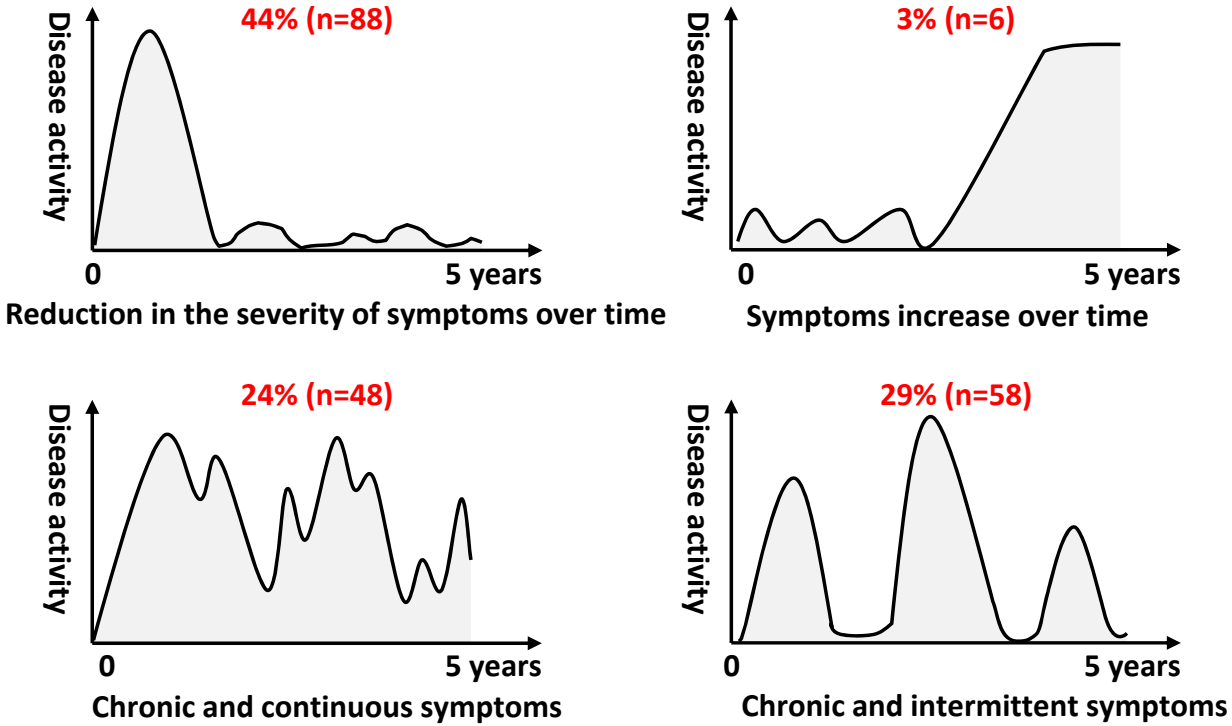
Small intestinal type	Small intestine/ Large intestine type	Large intestine type
		
25.7% (612 pts)	**46.4%** (1,103 pts)	**25.2%** (599 pts)

- Aggregate data calculated only from the electronic data of newly issued medical beneficiaries' certificates
- Types of CD other than the above: 0.8% (19 patients); unknown: 1.9% (45 patients)
- The affected areas selected in the individual forms have been converted into the above-mentioned disease type classifications

Understanding IBD at a glance (2nd Edition) For doctors who are diagnosing IBD-“Research on Refractory Inflammatory Bowel Disorders"(Suzuki's group), 20, 2015.
Electronic data compilation from the MHLW's 2012 Clinical Survey Individual Questionnaire

Clinical course of patients with Crohn's Disease

The clinical course of Crohn's disease is often chronic, intermittent, and persistent, although symptoms recur and remission is repeated



Subjects and Methods : Two hundred patients with Crohn's disease who were enrolled in IBSEN between January 1, 1990, and December 31, 1993, were followed up at 1 and 5 years after diagnosis to determine patterns of symptoms (clinical course)

IBSEN : A Cohort-Study of Inflammatory Bowel Disease in South-Eastern Norway

Henriksen M, et al.: Scand J Gastroenterol 2007;42(5):602-610.

Intestinal complications

Inflammatory bowel disease causes various intestinal complications due to persistent and progressive intestinal inflammation

Ulcerative Colitis

Due to exacerbation of intestinal inflammation
• Massive bleeding
• Toxic megacolon
• Colonic perforation
Long-standing disease
• Colorectal Cancer/ dysplasia
• Colonic stenosis

Crohn's Disease

- Intestinal stenosis and obstruction
- Fistula (internal or external fistula)
- Abscess
- Perforation
- Hemorrhage
- Cancerization
- Anal lesions (hemorrhoids, anal fissures, anal fistulas, anal ulcers, Anal cutaneous appendage, perianal abscess, etc.)

Noritaka Takatsu: Team-based medical care: IBD clinical practice visual text (supervised by Toshifumi Hibi), 58-59, Yodosha, 2016

Extraintestinal manifestation

Inflammatory bowel disease(IBD) also leads to Extraintestinal manifestation.
Collaboration with specialists is also important for treatment and follow-up

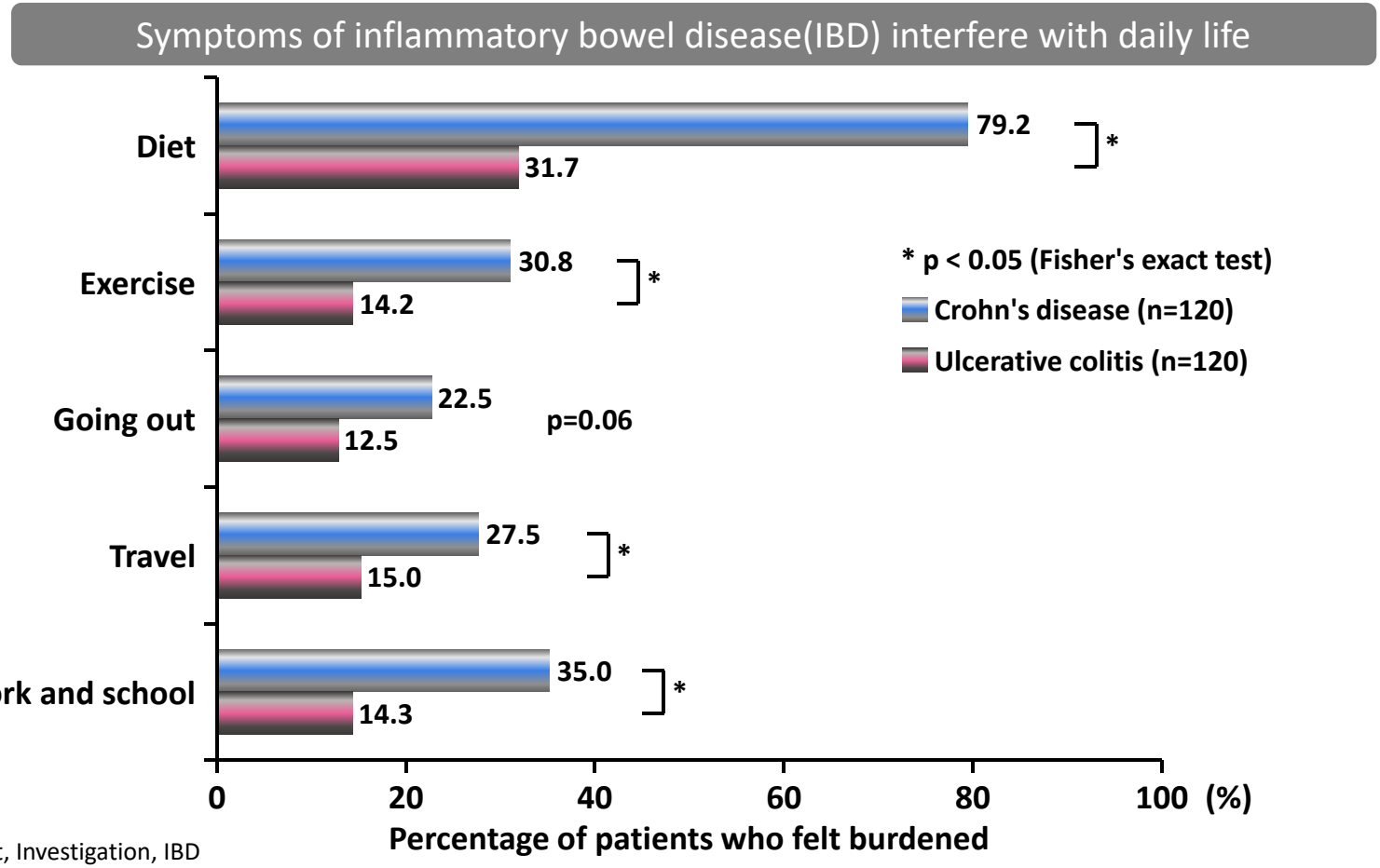
Complications of disease	Crohn's Disease (n=2,227)	Ulcerative Colitis (n=3,499)
Hepatobiliary system (cholelithiasis, primary sclerosing cholangitis, pancreatitis, hyperamylasemia, etc.)	11.9%	6.5%
Urological and genital systems (e.g., urinary calculi)	3.6%	1.6%
Musculoskeletal system (arthritis, arthropathy, ankylosing spondylitis, sacroiliitis, etc.)	6.2%	5.5%
Vascular and blood systems (e.g., anaemic *, thrombophlebitis, arterial thrombosis)	1.4%	2.0%
Skin and mucosal system (oral aphthae, erythema nodosum, pyoderma gangrenosum, etc.)	11.2%	4.6%
Respiratory system (interstitial pneumonia, pulmonary tuberculosis, asthma, bronchial asthma, etc.)	1.4%	1.5%
Collagen diseases (aortitis syndrome, rheumatoid arthritis, etc.)	0.4%	1.3%
Malignant diseases (uterine cancer, gastric cancer, breast cancer, lung cancer, malignant lymphoma, etc.)	1.5%	1.4%
Other (amyloidosis, psychiatric and neurological disorders, etc.)	6.2%	4.3%
Total	43.9%	28.9%

* Iron deficiency anemia not investigated

Subjects and Methods : The number of patients with inflammatory bowel disease under follow-up and the number of patients with complications were interviewed with a questionnaire at 33 facilities in the Kyushu district, and the prevalence of extraintestinal complications by organ system of Crohn's Disease and Ulcerative Colitis was examined.

Toshihiro Sakurai et al. Stomach and Intestine 2013; 48 (5): 591-600. (Modified)

Burden of everyday life for patients with inflammatory bowel disease (IBD)



Internet, Investigation, IBD

Subjects and Methods : 464 patients with Crohn's disease, 360 patients with ulcerative colitis and 4,100 healthy controls were asked to undergo an internet-based survey including quality of life assessment (SF-8), and 120 patients with Crohn's disease, each with ulcerative colitis and 240 healthy controls who responded were examined for burden in daily life, quality of life (SF-8 scores), and satisfaction with biologics.

Matsumoto T, et al.: J Crohns Colitis 2015;9(6):477-482.

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Differences between Ulcerative Colitis and Crohn's Disease

Ulcerative Colitis and Crohn's Disease have many pathognomonic differences

Item	Ulcerative Colitis	Crohn's Disease
Lesion site	Large intestine	Entire gastrointestinal tract
Lesion distribution	Diffuse, circumferential from the rectum Continuity	Discontinuity; segmentality; obligate laterality
X-ray findings	Lead-tube, spiculation, cuff-button-like niche	Fissure ulcer; Stenosis; Fistula; Biased side Sclerotic image
Endoscopic finding	Diffuse redness/edema, granular mucosa, pus mucus adherence	Longitudinal ulcer; Cobblestone image; Relatively Ill-defined irregular ulcer, aphtha, and small ulcer
Pathological findings	Superficial inflammation; homogeneous inflammation; crypt abscess	Full-thickness inflammation; heterogeneous inflammation, Noncaseating granuloma

Yasuo Suzuki: Practice IBD in Medical Practice in IBD (Toshifumi HIbi, Tadakazu Hisamatsu, et al.), 42, Yodosha, 2017

Mayo scores (Ulcerative Colitis)

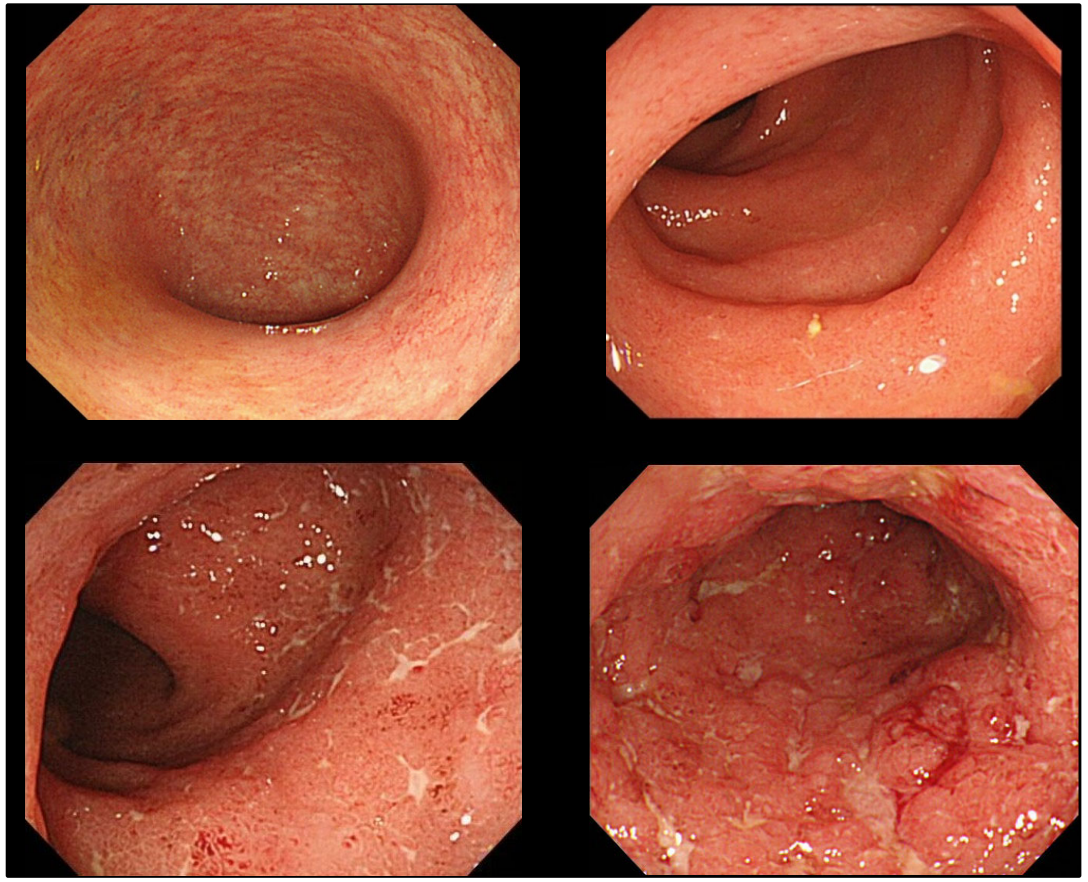
① Frequency of bowel movements	
0	As often as daily bowel movements before ulcerative colitis
1	One to two more bowel movements per day compared to before ulcerative colitis
2	Three to four times more bowel movements per day compared to before ulcerative colitis
3	More than five bowel movements per day compared to before ulcerative colitis
② Rectal bleeding	
0	No blood
1	Fewer than half of the bowel movements produce a small amount of blood
2	Nearly every time well-defined blood is seen
3	Almost exclusively blood
③ Endoscopic finding	
0	Normal or remitting mucosa
1	Mild (redness, decreased vascular visibility, mild fragility)
2	Moderate (marked redness, loss of vascular clarity, fragility, erosion)
3	Severe (spontaneous bleeding, ulcer)
④ Physician's global assessment of disease activity	
0	Normal (in complete remission)
1	Mild
2	Moderate
3	Severe

Reference: The sum score excluding the endoscopic finding may be used as a partial Mayo score

Schroeder KW, et al.: N Engl J Med 1987;317(26):1625-1629.

Mayo endoscopic scores (Ulcerative Colitis)

0
Normal/no activity



1
The mucosa becomes red and the vessels that were visible in the normal mucosa become invisible

2
The mucosa erodes (erosions) and the vessels that were visible in the normal mucosa become invisible

3
Deep mucosal injury (ulcer) and bleeding are visible

Provided: Professor, Katsuyoshi Matsuoka,
Division of Gastroenterology and Hepatology, Department of Internal Medicine, Toho University Sakura Medical Center

CDAI* (Crohn's Disease)

1	Number of loose stools or diarrhea in the past week	×2
2	Abdominal pain in the past week (abdominal pain status assessed daily with the following scores and summed for 7 days) 0 = none, 1 = mild, 2 = moderate, 3 = severe	×5
3	Subjective General Well-being in the Past Week (Clinical Conditions Assessed Daily with Scores below and Total 7 Days) 0 = generally well, 1 = mildly poor, 2 = poor, 3 = very poor, 4 = terrible	×7
4	Number of complications currently experienced by patients 1) Arthritis/arthralgia, 2) iritis/uveitis, 3) erythema nodosum/pyoderma gangrenosum/aphthous stomatitis, 4) Anal fissure, anal fistula or perianal abscess, 5) other fistula, 6) fever ≧37.8°C in the past week	×20
5	Taking loperamide or opiate for diarrhea 0 = No, 1 = Yes	×30
6	Abdominal mass 0 = none, 2-4 = dubious, 5 = present	×10
7	Hematocrit Male (47-hematocrit) Female (42-hematocrit)	×6
8	Body weight 100× (1-body weight/standard body weight)	×1

<150: remission, 150-220: mild, 220-450: moderate, and >450: severe

*CDAI (Crohn's Disease Activity Index)

Best WR, et al.: Gastroenterology 1976; 70 (3): 439-444.

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SES-CD*(Crohn's Disease)

	SES-CD (evaluated for each five-segment ※)			
	0	1	2	3
Size of the ulcer	None	Aphthous ulcer (0.1-0.5cm in diameter)	Ulcer (0.5-2 cm in diameter)	Large ulcer (diameter >2cm)
Ulcer area	None	<10%	10-30%	>30%
Lesion area	None	<50%	50-75%	>75%
Presence or absence of stenosis	None	One site, passing	Multiple, transit possible	No passage

Total SES-CD: Sum of all five-segment scores → 0-56*

※ Ileum, right colon, transverse colon, left colon, and rectum

* A score of 3 for stenosis refers to a condition in which the colonoscope cannot pass, so only one time can observe a score of 3. Therefore, the sum of the stenosis scores is 0-11.

Daperno M, et al.: Gastrointest Endosc 2004; 60 (4):505-512.

* SES-CD (Simple endoscopic score for Crohn's disease)

FY2019 Guidelines for the treatment of Ulcerative Colitis (internal medicine)

Induction therapy

	Mild	Moderate	Severe	Fulminant
Total colitis type Left-sided colitis type	Oral: 5-ASA Enema: 5-ASA enema, steroids enema Foam: budesonide rectal foam ※ Oral prednisolone if moderate inflammation is severe and the inflammatory response is not improved. ※ If not further improved, treat severe or steroid-resistant disease ※ Pentasa suppository is useful for patients with rectal inflammation		• Prednisolone infusion ※ Concomitant use of the following drugs depending on the condition Oral: 5-ASA Enema: 5-ASA enema, steroids enema ※ If not improved, treat patients with fulminant or steroid-resistant disease ※ Investigation of surgical indications according to the condition	• Consider indications for emergency surgery ※ Under cooperation with the surgeon, the following treatments may be tried if the situation permits: • High-dose intravenous steroid therapy • Oral tacrolimus • Continuous intravenous cyclosporine therapy * • Infliximab Infusion ※ Surgery if not improved above
Rectum Inflammatory type	Oral preparations: 5-ASA preparations, suppositories: 5-ASA suppositories, steroid suppositories, enema: 5-ASA enema, steroid enema, foam: budesonide rectal foam * Avoid easily resorting to systemic steroid administration			

Refractory cases	Steroid-dependent cases	Steroid-resistant cases
	Immunomodulators: Azathioprine 6-MP* ※ (if not improved by above): Cytapheresis, oral tacrolimus, intravenous infliximab, subcutaneous adalimumab, subcutaneous golimumab, oral tofacitinib, and intravenous vedolizumab may be considered ※ Tofacitinib is contraindicated in combination with a thiopurine preparation	Moderate : Cytapheresis, tacrolimus oral, infliximab infusion, adalimumab subcutaneous injection, golimumab subcutaneous injection, tofacitinib oral, and vedolizumab intravenous infusion Severe: Cytapheresis, oral tacrolimus, intravenous infusion of infliximab, subcutaneous injection of adalimumab, subcutaneous injection of golimumab, oral tofacitinib, intravenous infusion of vedolizumab, and continuous intravenous infusion of cyclosporine ※ Consider concomitant azathioprine and 6-MP* (other than tofacitinib) ※ Consider surgery if there is no improvement

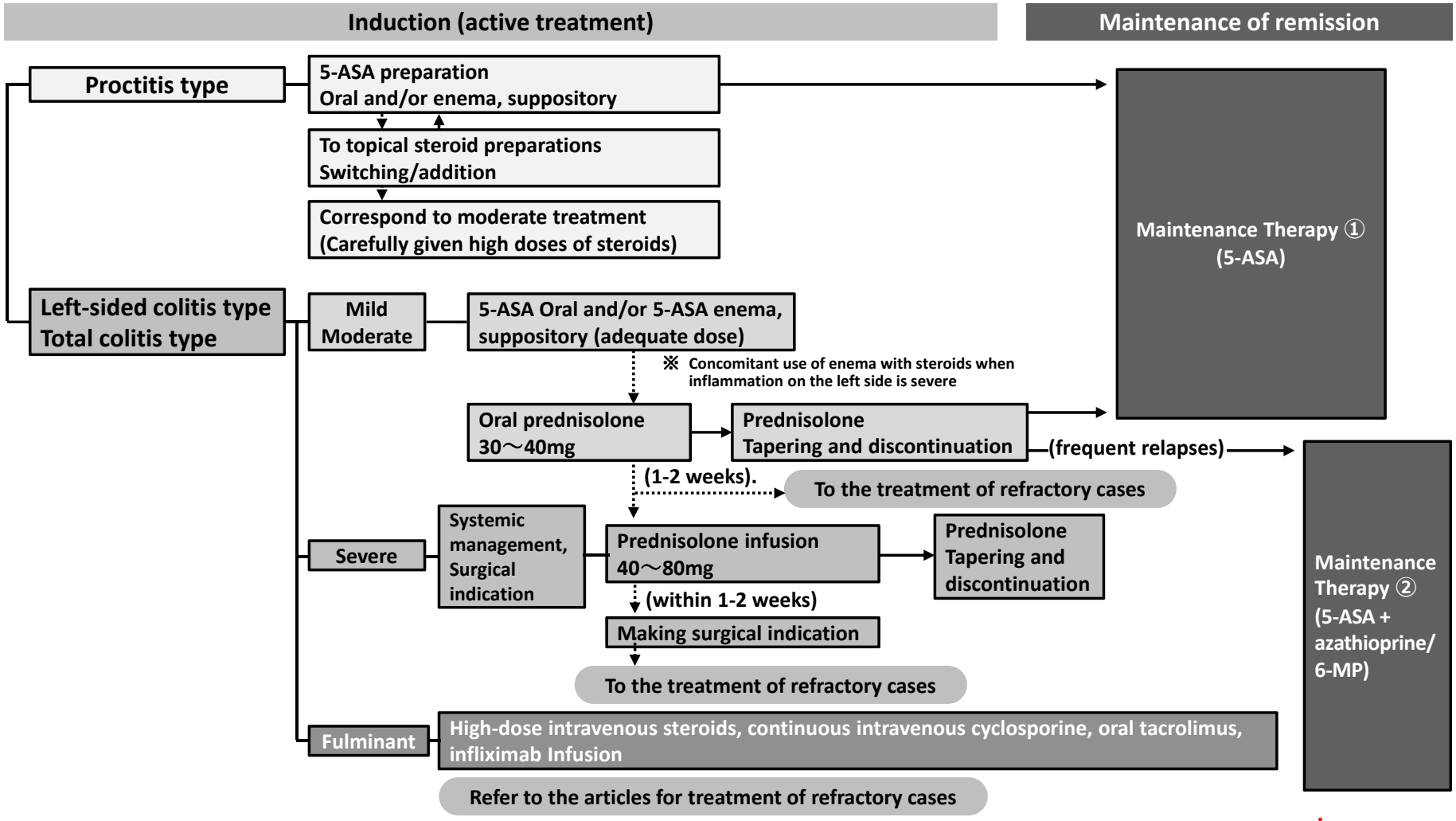
Maintenance of remission

Refractory case	Refractory cases
5-ASA preparations (oral, enema, suppository)	5-ASA preparations (oral, enema, suppository) Immunomodulatory drugs (azathioprine, 6-MP＊), infliximab intravenous infusion **, adalimumab subcutaneous ** and golimmab subcutaneous **, tofacitinib oral **, and bedrizumab intravenous **

*: not currently covered by insurance indication, **: The same treatment is continued as a maintenance therapy as long as remission is induced by a treatment
5-ASA Oral Tablets (Pentasa ® Granules/Tablets, Assacol ® Tablets, Sarazopilin ® Tablets, Rearda ® Tablets), 5-ASA Notes (Pentasa ® Notes), and 5-ASA Suppositories (Pentasa ® Suppositories, Sarazopilin ® Suppositories)
Steroid enema (prednema ® enema, steronema ® enema), budesonide rectal foam (lectable ® rectal foam), and steroid suppository (linderonic ® suppository).
※ (Principles of Treatment) Be aware of the responsiveness to medical treatment and the side effects or complications caused by drugs, hear the opinions of experts if necessary, and avoid mistakes in the timing of surgical treatment, etc. Refer to the text for more information on the dosage and treatment regimens, as well as pediatric and surgical treatments.

Diagnostic Criteria and Treatment Guidelines for Ulcerative Colitis and Crohn's Disease. FY2019 Revised (March 31, 2020)
Policy Research Project for Intractable Diseases, etc. "Survey Research on Intractable Inflammatory Bowel Disorders" (Suzuki Group) 2019 Joint Research Report], 5-16, 2020.

Ulcerative Colitis - flow chart



Diagnostic Criteria and Treatment Guidelines for Ulcerative Colitis and Crohn's Disease. FY2018 Revised (March 31, 2020)
Policy Research Project for Intractable Diseases, etc. "Survey Research on Intractable Inflammatory Bowel Disorders" (Suzuki Group) 2019 Joint Research Report], 5-16, 2020.

Ulcerative Colitis - treatment of refractory cases

Steroid-resistant cases

- Cytapheresis (higher efficacy of twice weekly procedure)
- Oral tacrolimus
- Infliximab Infusion, Adalimumab Subcutaneous Injection, and Golimumab Subcutaneous Injection
- Oral tofacitinib
- Vedolizumab infusion
- Intravenous cyclosporine infusion (uninsured)

※ Multiple use of these options should be carefully considered for infections and complications (hear expert opinion) and also consider surgical treatment

Steroid-dependent cases

Azathioprine /oral 6-MP → (1-2 months) → Steroids tapering and discontinuation → Maintenance Therapy To azathioprine and 6-MP

(active cases)

- ① Cytapheresis
  ② Oral tacrolimus
- ③ Infliximab infusion
  ④ Subcutaneous adalimumab injection
  ⑤ Subcutaneous golimumab injection → Maintenance Therapy: Enables infliximab, adalimumab, golimumab
- ⑥ Oral tofacitinib → Enables tofacitinib
- ⑦ Vedolizumab infusion → Enables vedolizumab

※ In principle, concomitant use of tofacitinib and thiopurines is contraindicated, so thiopurines should be discontinued when tofacitinib is administered

Diagnostic Criteria and Treatment Guidelines for Ulcerative Colitis and Crohn's Disease. FY2019 Revised (March 31, 2020)
Policy Research Project for Intractable Diseases, etc. "Survey Research on Intractable Inflammatory Bowel Disorders" (Suzuki Group) 2019 Joint Research Report], 5-16, 2020.

FY2019 Guidelines for the treatment of Crohn's Disease (internal medicine)

Treatment During the Active Phase
(nutritional therapy, pharmacotherapy, or a combination of both, depending on the condition and acceptability)

Mild to moderate	Moderate to severe	Severe (When the disease is serious or has severe complications)
Drug Treatment ・Budesonide ・5-ASA preparation Pentasa® granules/tablets, Salazopyrinic® tablets (colorectal lesions) **Nutrition Therapy (Enteral Nutrition Therapy)** Nutritional therapy if acceptable As an enteral nutrient, ・Component Nutrient (Elental®) ・Digestive nutrients (e.g., twin-line®) Use as the first choice ※ A semi-digestive nutrient may be used if the acceptability of patients is low ※ If response is inadequate, it is equivalent to moderate to severe disease	**Drug therapy** ・Oral steroids (prednisolone) ・Antimicrobials (e.g., metronidazole*, ciprofloxacin*) ※ When it is difficult to reduce or withdraw steroids: azathioprine, 6-MP* ※ Failure/intolerance of usual treatment such as steroid/nutrition therapy: infliximab, adalimumab, ustekinumab, vedolizumab **Nutrition Therapy (Enteral Nutrition Therapy)** ・Component Nutrient (Elental®) ・Digestive nutrients (e.g., twin-line®) Use as the first choice ※ A semi-digestive nutrient may be used if the acceptability of patients is low **Combination of cytapheresis** ・Granulocyte adsorption therapy (adacolumn®) ※ Indications for patients who are not adequately responding or intolerant to conventional treatment and who have symptoms caused by colorectal lesions	After considering the indications for surgical treatment, the following Practice internal medicine **Drug Treatment** ・Steroid oral or intravenous ・Infliximab adalimumab ustekinumab vedolizumab (usually refractory) **Nutritional Therapy** ・Enteral nutrition ・Fasting and total parenteral nutrition (when complications and severity are particularly high) ※ To enteral nutrition if complications improve ※ Infliximab, adalimumab, ustekinumab vedolizumab may be combined use if it is in the absence of gastrointestinal obstruction or abscesses

*: Not currently included in indications
※ (Principles of Treatment) Be aware of the responsiveness to medical treatment and the side effects or complications caused by drugs, hear the opinions of experts if necessary, and avoid mistakes in the timing of surgical treatment, etc. Refer to the Research Report for more information on the dosage and treatment regimens, as well as pediatric and surgical treatments.

Diagnostic Criteria and Treatment Guidelines for Ulcerative Colitis and Crohn's Disease. FY2019 Revised (March 31, 2020)
Policy Research Project for Intractable Diseases, etc. "Survey Research on Intractable Inflammatory Bowel Disorders" (Suzuki Group) 2019 Joint Research Report], 29-36, 2020.

FY2019 Guidelines for the treatment of Crohn's Disease (internal medicine)

Maintenance Therapy	Treatment of anal lesions	Treatment of stenosis/fistula	Prevention of postoperative recurrence

Drug Treatment
• Budesonide
• 5-ASA preparation
  • Pentasa® granules/tablets
  • Salazopyrinic® tablets (colorectal lesions)
• Azathioprine
• 6-MP*
• Infliximab, adalimumab, ustekinumab, vedoliaumab (if the induction of these medication lead to remission)
Enteral Nutrition Therapy at Home
・Elental®, twin-line®, etc. are used as the first choice
※ If the acceptability of patients is low, a semi-digestive nutrient may be used
※ Consider home parenteral nutrition in patients with short bowel syndrome and other nutritional difficulties
	First consider to the indications for Surgical Treatment
	drainage, sheet drainage, etc.
	For Medical Treatment
	・Anal fistula/perianal abscess
	metronidazole*, antimicrobial/ ntibiotics
	Infliximab, adalimumab
	・Anal fissure, anal ulcer:
	medical treatment according to the intestinal lesion
	・Anal stenosis: Transanal dilation
		[Stenosis]
		・**First consider to the indications for Surgical Treatment**
		・Endoscopic balloon dilation when the inflammation subsides and the ulcer disappears or shrinks with medical treatment
		[Fistula]
		・**First consider to the indications for Surgical Treatment**
		・As medical treatment (external fistula)
		infliximab
		adalimumab
		azathioprine
			Follow maintenance therapy
			Drug Treatment
			・5-ASA preparation
			Pentasa® granules/tablets
			Salazopyrinic® tablets (colorectal lesions)
			・Azathioprine
			・6-MP*
			Nutrition Therapy
			・Enteral nutrition
			※ Combination with drug therapy is acceptable

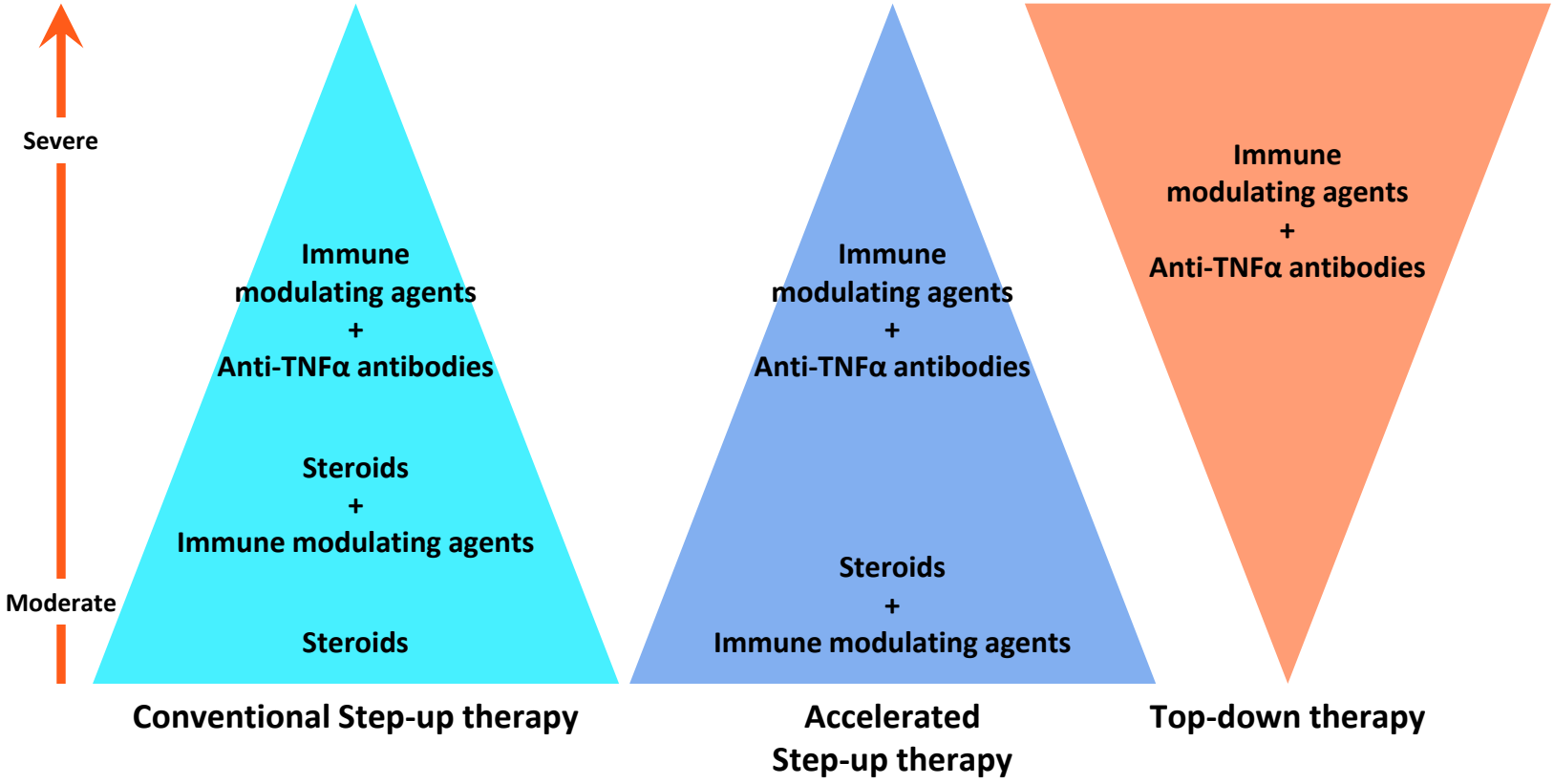
*: Not currently included in indications

※ (Principles of Treatment) Be aware of the responsiveness to medical treatment and the side effects or complications caused by drugs, hear the opinions of experts if necessary, and avoid mistakes in the timing of surgical treatment, etc. Refer to the Research Report for more information on the dosage and treatment regimens, as well as pediatric and surgical treatments.

Diagnostic Criteria and Treatment Guidelines for Ulcerative Colitis and Crohn's Disease. FY2019 Revised (March 31, 2020)
Policy Research Project for Intractable Diseases, etc. "Survey Research on Intractable Inflammatory Bowel Disorders" (Suzuki Group) 2019 Joint Research Report], 29-36, 2020.

Treatment strategies for Crohn's Disease

Depending on the degree of disease progression, an intensified treatment approach is chosen



Reproduced from Gut., Ordás I et al, 60(12):1754-63, 2011
With permission from BMJ Publishing Group Ltd.

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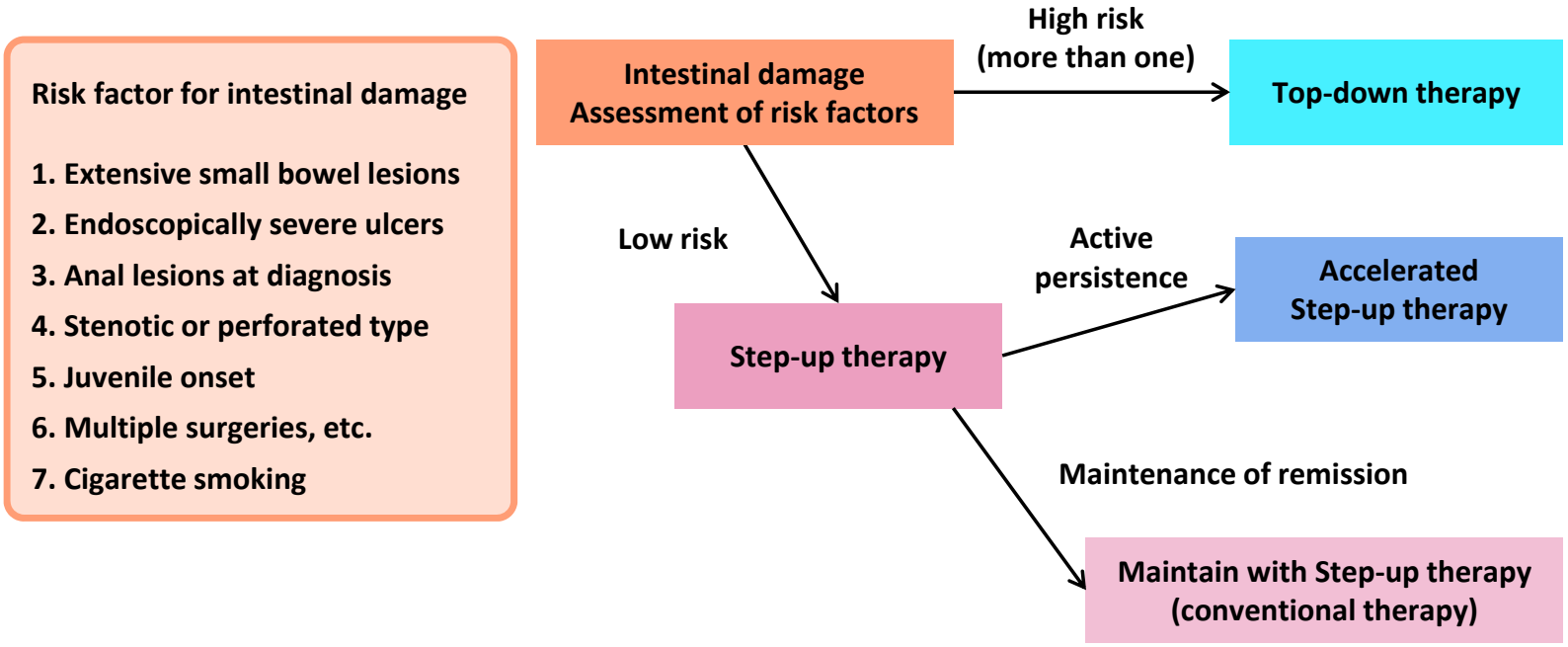
Strategies for the treatment of Crohn's Disease according to risk factors for intestinal damage

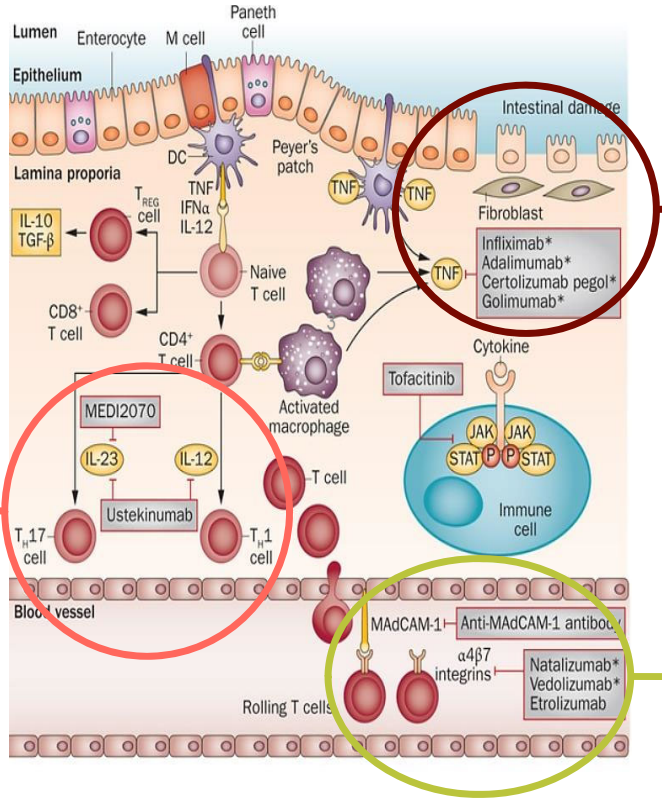
Depending on the degree of disease progression, an intensified treatment approach is chosen



Eiko Saito: Team-based medical care: IBD clinical practice visual text (supervised by Toshifumi Hibi), 103-107, Yodosha, 2016.

Biologic site of actions

There are several mechanistic approaches to the different etiologies of inflammatory bowel disease



TNFα-inhibitors block systemic inflammation a central cytokine leading to multiple downstream events[1,2]

Ustekinumab blocks inflammation produced through IL12/23[1]

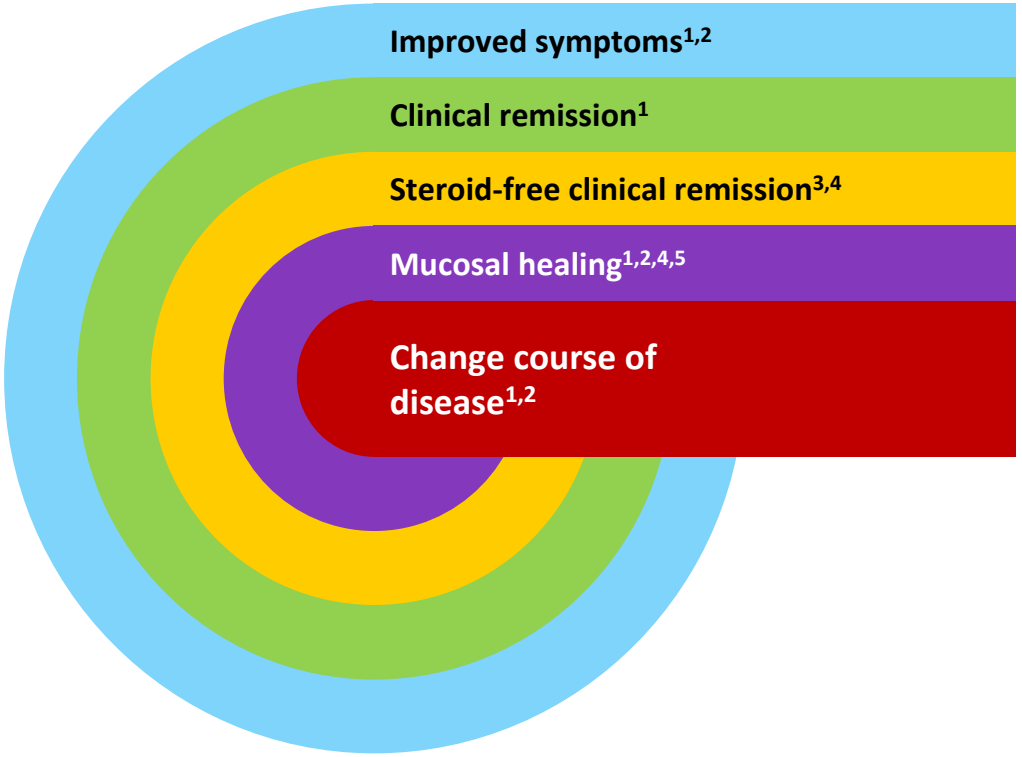
Vedolizumab blocks migration of lymphocytes into the gut via α4β7 integrins[1]

Danese S et al. Nat Rev Gastroenterol Hepatol. 2015;12:537-45

Tracey D et al. Pharmacol Ther. 2008;117:244-79

Treatment goals in inflammatory bowel disease (IBD) are evolving

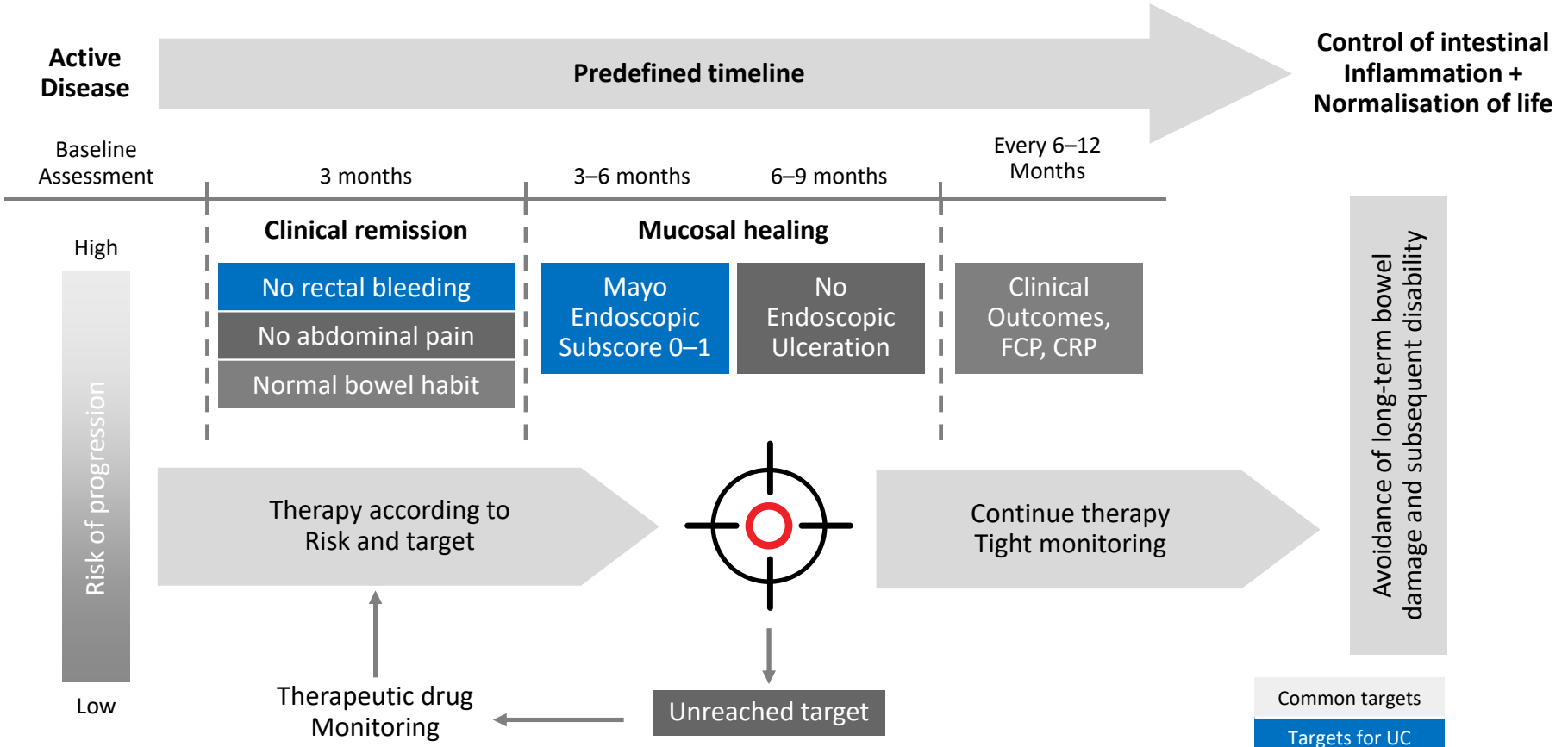
- Historically, treatment was aimed at achieving symptom control
- Treating only symptoms has not changed the natural course of the disease
- In the absence of therapies able to provide 'healing,' this was acceptable
- Newer therapies have changed treatment goals for IBD and can avoid long-term complications
- Treatment of IBD is moving towards more robust targets
- Therapeutic strategy is changing from a clinically driven to a target-driven approach



1. Peyrin-Biroulet L, et al. *Am J Gastroenterol.* 2015;110:1324-38; 2. Sandborn WJ, et al. *J Crohns Colitis.* 2014;8:927-35;
3. Colombel JF, et al. *N Engl J Med.* 2010;362:1383-95; 4. Colombel JF, et al. *J Crohns Colitis.* 2010;4:S10; 5. Baert FJ, et al. *Gastroenterology.* 2010;138:463-8

UC and CD should be tightly monitored and treated to target

Periodic assessment of disease activity and modification of treatment to achieve treatment goals



CD, Crohn's disease; CRP, C-reactive protein; FCP, faecal calprotectin; UC, ulcerative colitis

Adapted from Le Berre C, et al. Clin Gastroenterol Hepatol. 2020; 18: 14-23

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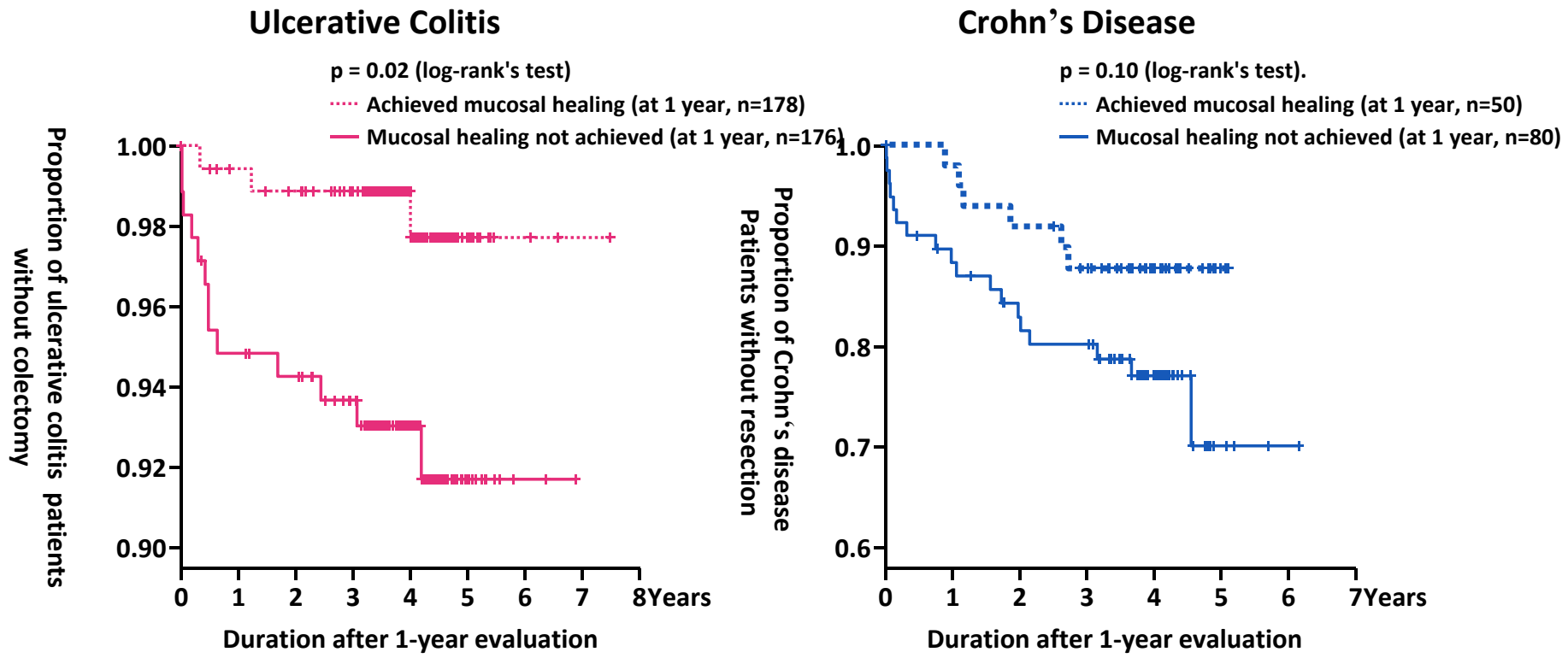
Mucosal healing is associated with reduced risk of surgery in UC and CD

Achieving early endoscopic improvement is important in improving outcomes



[Mucosal healing]. Endoscopic score of 0 (normal) or 1 (mild redness, granular mucosa).

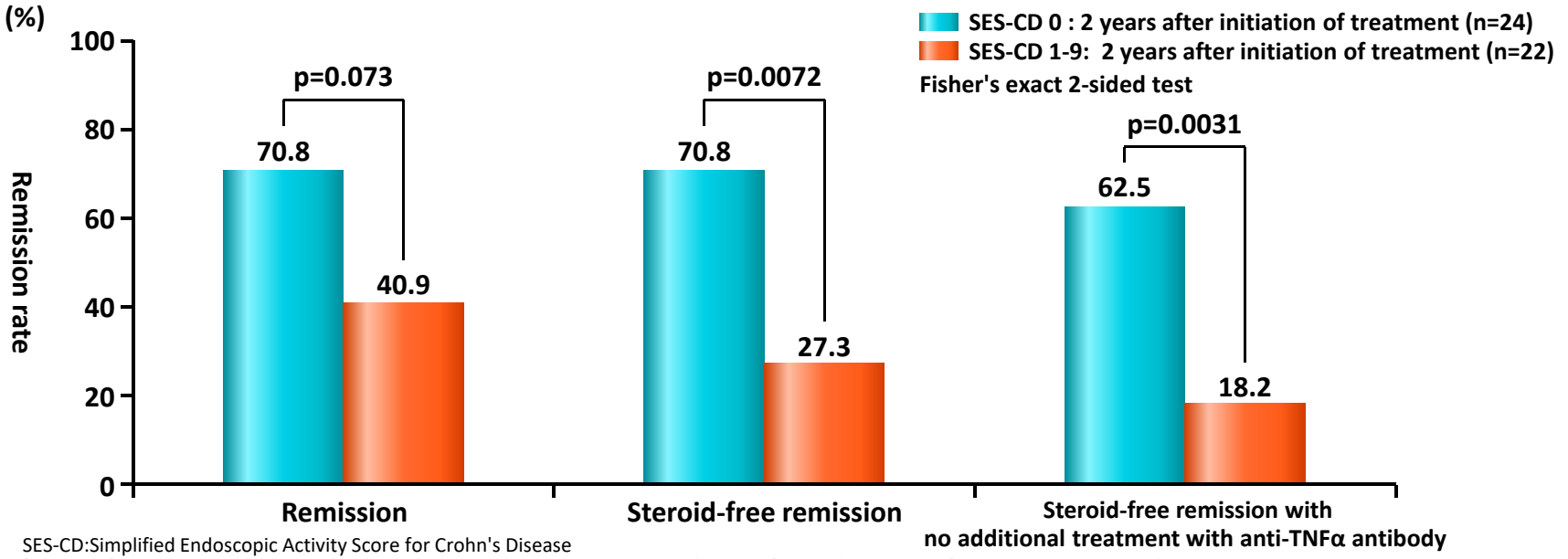
Subjects and Methods : We included 354 patients with ulcerative colitis and 141 patients with Crohn's disease who underwent endoscopy 1 year after the start of treatment, and examined the colectomy rate (ulcerative colitis)/resection rate (Crohn's disease) according to whether or not they achieved mucosal healing 1 year after the start of treatment.

Frøslie KF, et al.: Gastroenterology 2007;133(2):412-422.

GASTROENTEROLOGY

Mucosal healing can predict sustained clinical remission in Crohn's Disease

Achieving early endoscopic improvement is important in improving outcomes



SES-CD:Simplified Endoscopic Activity Score for Crohn's Disease
[Remission] CDAI(Crohn's Disease Activity Index) <150 or HBI (Harvey-Bradshaw index) score<3 [steroid-free remission] without administration of steroids and in remission
[Steroid-free remission and no additional treatment with anti-TNFα antibody]. In remission without administration of steroids and anti-TNFα antibodies

Subjects and Methods : 133 patients with newly diagnosed or untreated Crohn's disease were randomly assigned to the azathioprine (AZA) 2.5mg/kg plus infliximab (IFX) group [IFX 5mg/kg three times. Repeated doses can be given at relapse (on demand) and at 8-week intervals after January 2006] or the steroid group (AZA can be given at relapse. IFX can be given in patients with failed AZA) and followed up prospectively for 2 years. Of this study, 49 patients (26 in the combined AZA+IFX group and 23 in the steroids group) who were evaluated for SES-CD at 2 years were followed up for an additional 2 years to determine SES-CD scores 2 years after treatment initiation and remission rates 3-4 years after treatment initiation.

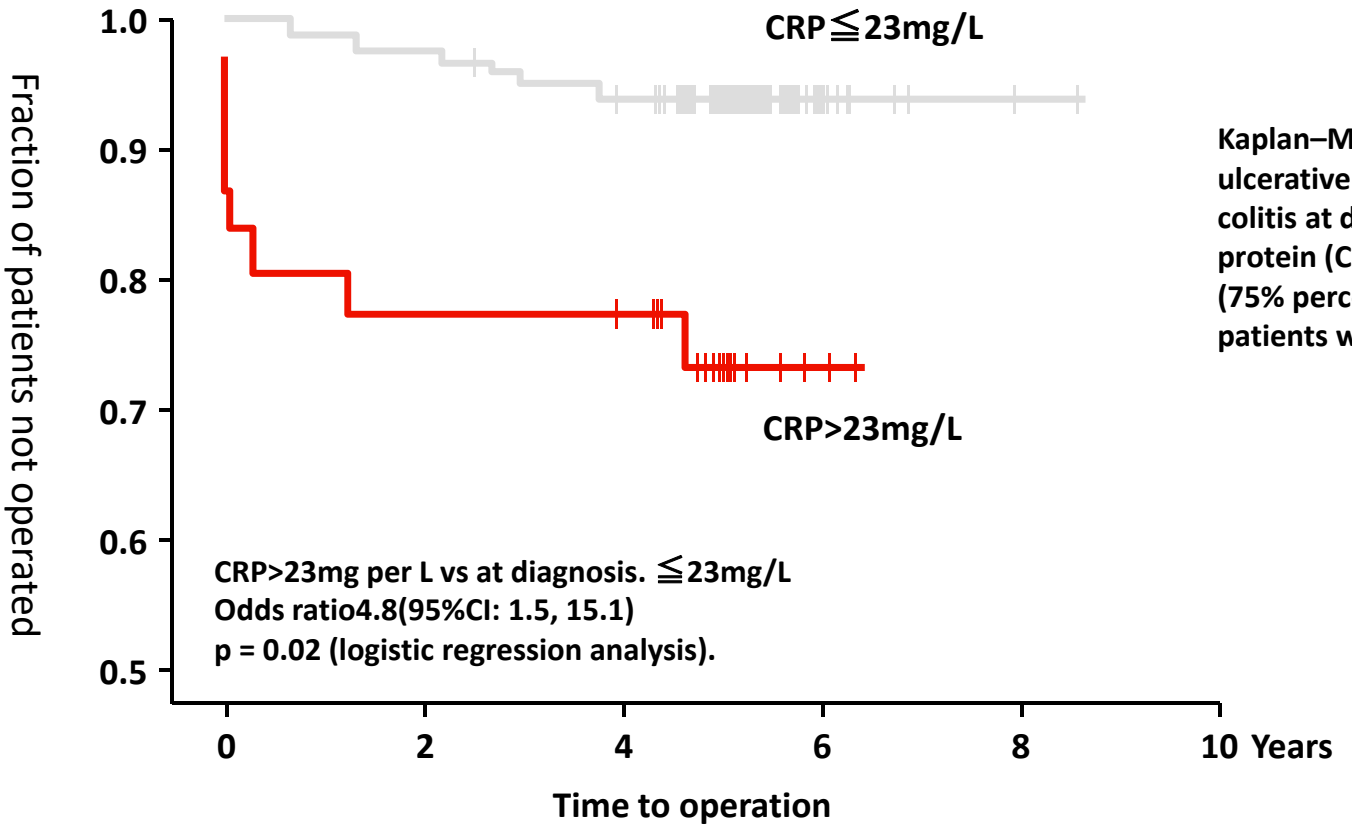
※ Dosage and administration of azathioprine in Japan: In general, for adults and children, the daily dose of azathioprine equivalent to 1-2mg/kg (usually 50-100mg for adults) is orally administered.
※ Dosage and administration of infliximab in Japan: In general, as infliximab (genetical recombination), 5mg per kg of body weight is administered as a single dose by intravenous infusion. Abatacept is re-administered 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. If the effect is diminished after 6 weeks of treatment, the dose may be increased or the dosing interval may be shortened. When the dose is increased, a dose of 10mg per kilogram of body weight can be used as a single dose. If the dosing interval is shortened, a dose of 5mg per kilogram of body weight may be given at a minimum of 4 weeks apart.

Baert F, et al.: Gastroenterology 2010;138(2) 463-468. (drawing)

GASTROENTEROLOGY

Predictors of surgery (CRP) in Ulcerative Colitis (total colitis type)

Reducing CRP leads to improved outcomes



Kaplan–Meier plot of patients with ulcerative colitis with extensive colitis at diagnosis and C-reactive protein (CRP) levels above 23 mg/l (75% percentile) at diagnosis and patients with lower CRP levels

Subjects and Methods : 129 patients with ulcerative colitis (all colitis types) enrolled in the Norwegian Cohort Study of Inflammatory Bowel Disease, IBSEN(Inflammatory Bowel disease in South-Eastern Norway, with a diagnosis/suspicion of inflammatory bowel disease between January 1, 1990, and December 31, 1993, were followed up at 1 and 5 years after diagnosis to investigate rates of no colectomy among patients with ulcerative colitis (all colitis types) by CRP level at diagnosis.

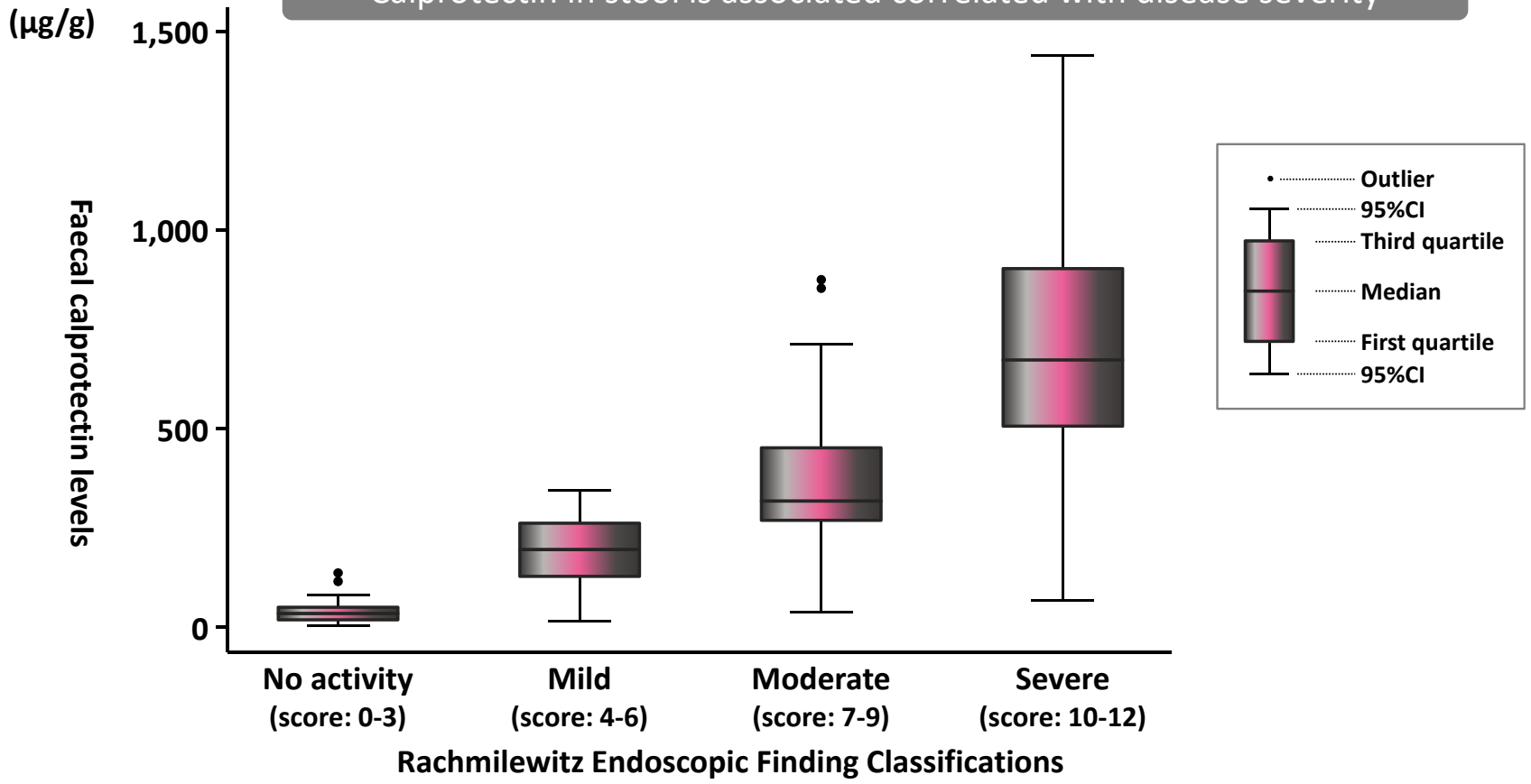
CRP: C-reactive protein

Henriksen M, et al.: Gut 2008;57(11):1518-1523.

GASTROENTEROLOGY

Relationship between fecal calprotectin levels and endoscopic findings in patients with Ulcerative Colitis

Calprotectin in stool is associated correlated with disease severity

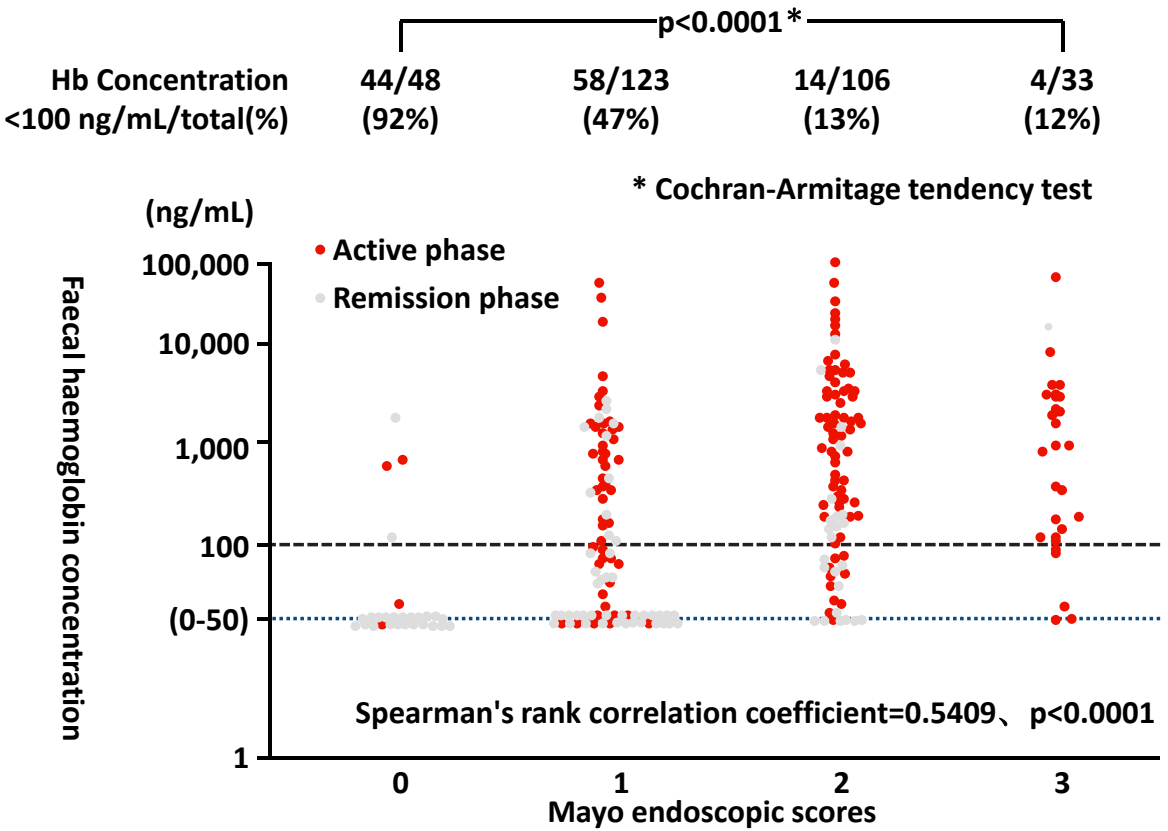


Subjects and Methods : Relationships between endoscopic findings (assessed by Endoscopic Activity Index of Rachmilewitz) and fecal calprotectin (quantified by ELISA) were determined in 115 patients with ulcerative colitis who underwent endoscopy with biopsy at disease duration >3 months and had a stool sample collected 1-3 days prior to endoscopy.

Schoepfer AM, et al.: Inflamm Bowel Dis 2009;15(12):1851-1858. | GASTROENTEROLOGY

Relationship between fecal hemoglobin levels and endoscopic findings in patients with Ulcerative Colitis

Occult blood in stool is associated with disease severity



Subjects and Methods :The correlations between fecal Hb levels and endoscopic findings (Mayo endoscopic scores) were examined by immunological fecal occult blood assay (FIT) in 152 patients with ulcerative colitis who underwent colonoscopy between January 2006 and August 2011.

Nakarai A, et al.: Am J Gastroenterol 2013;108(1):83-89.

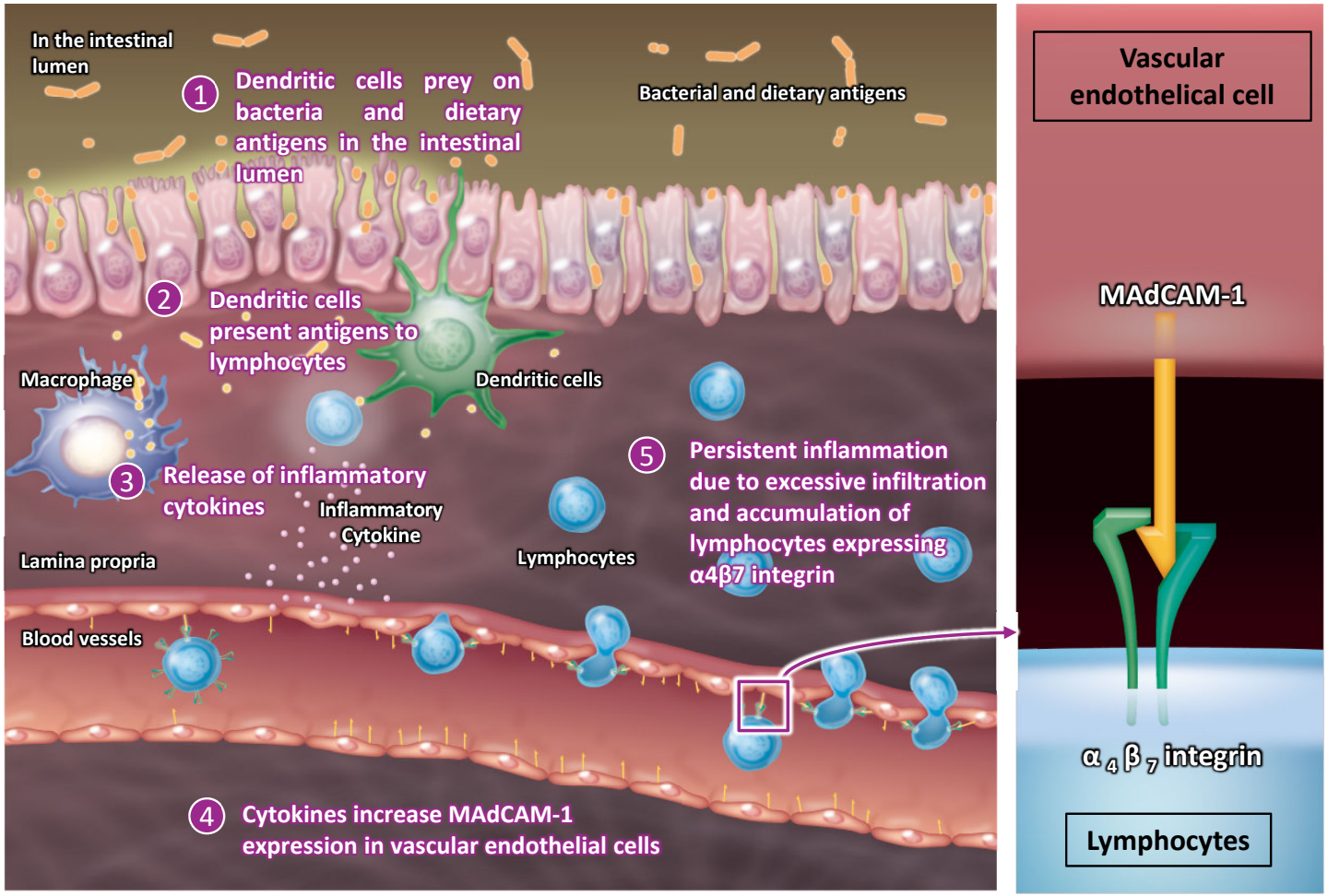
GASTROENTEROLOGY

Today’s Topics

1. Takeda's GI Therapeutic Area and Inflammatory Bowel Disease (IBD) Initiatives
2. What is IBD?: Epidemiology, Etiology, and Symptoms
3. Diagnosis and Treatment for IBD
4. **Vedolizumab**

Pathology of Inflammatory Bowel Disease (IBD)

Interactions between integrins and adhesion molecules influence the pathology of inflammatory bowel disease

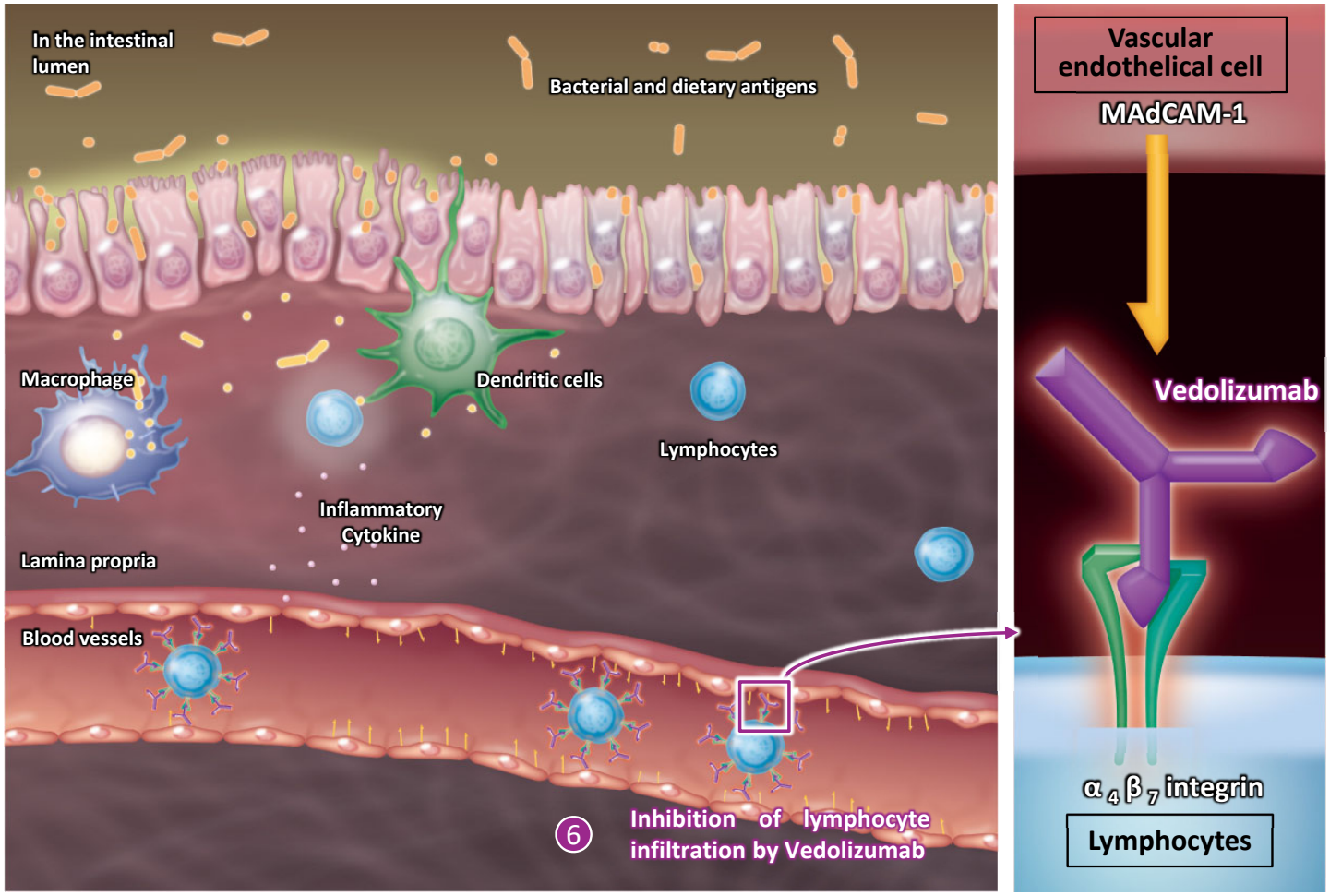


Supervision: Professor Akira Andoh, Department of Gastroenterology, Internal Medicine, Shiga University of Medical Science

GASTROENTEROLOGY

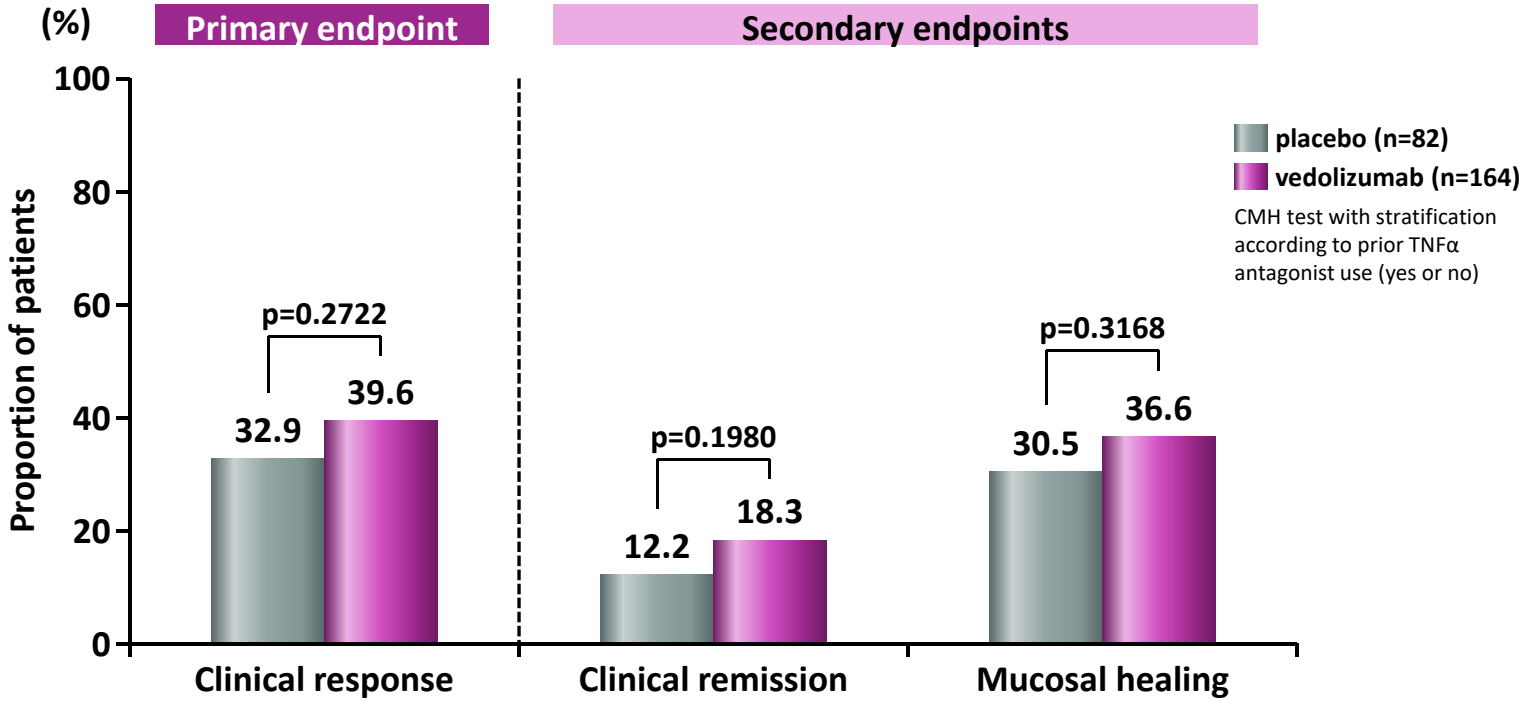
Mechanism of action of Vedolizumab

Vedolizumab suppresses excessive lymphocytic infiltrates in the intestinal mucosa



Supervision: Professor Akira Andoh, Department of Gastroenterology, Internal Medicine, Shiga University of Medical Science

Japanese Phase 3 (CCT-101) for Ulcerative Colitis: Efficacy in Induction at Week 10



CMH test: Cochran-Mantel-Haenszel test

【Clinical response】 The following 2 conditions were fulfilled;

- Decrease of the complete Mayo score by ≥3 points and by ≥30% from baseline
- Decrease of the subscore of rectal bleeding by ≥1 point from baseline, or ≤1 in the subscore of rectal bleeding

【Clinical remission】 ≤2 in the complete Mayo score and ≤1 in all subscores

【Mucosal healing】 ≤1 in the subscore for findings on endoscopy in the complete Mayo score

Subjects : 292 patients with moderate to severe ulcerative colitis who experienced prior treatment failure with at least one of the corticosteroid, immunomodulator or TNFα antagonist.

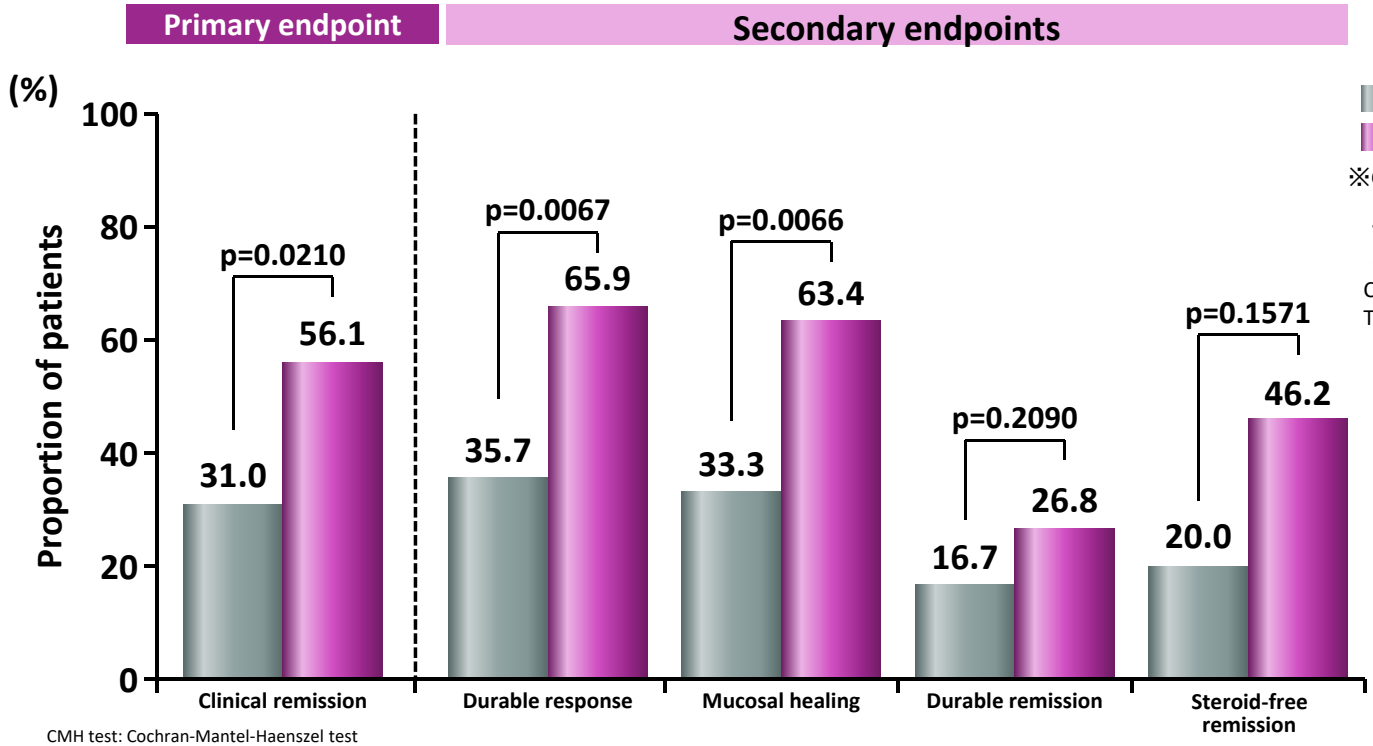
Method : Subjects were randomized 1:2 to the placebo or vedolizumab group, and received the placebo or 300 mg of vedolizumab with intravenous infusion at Weeks 0, 2, and 6 in a double-blinded manner.

Evaluation data at the time of approval review/ Motoya S, et al.: PLoS One 2019;14（2）:e0212989.
This study was conducted by Takeda Pharmaceutical Company Ltd.
Five of the authors of this paper are employees of Takeda Pharmaceutical Company Limited.
The authors of this paper include those who have received research grants from Takeda Pharmaceutical Company Limited.

ENT:2007-5-011

GASTROENTEROLOGY

Japanese Phase 3 (CCT-101) for Ulcerative Colitis: Efficacy in Maintenance at Week 60



CMH test: Cochran-Mantel-Haenszel test
【Clinical remission】 ≤2 in the complete Mayo score and ≤1 in all subscores
【Clinical response】 The following 2 conditions were fulfilled;
- Decrease of the complete Mayo score by ≥3 points and by ≥30% from baseline
- Decrease of the subscore of rectal bleeding by ≥1 point from baseline, or ≤1 in the subscore of rectal bleeding

【Durable remission】 Clinical remission was observed both at Week 10 and Week 60
【Corticosteroid-free remission】 Clinical remission without corticosteroid at Week 60, though a corticosteroid was used at the first dose of the study drug

Subjects : 292 patients with moderate to severe ulcerative colitis who experienced prior treatment failure with at least one of the corticosteroid, immunomodulator or TNFα antagonist.
Method : Subjects showing a clinical response to vedolizumab at Week 10 were enrolled into the maintenance phase at Week 14 and were randomized 1:1 to the placebo or vedolizumab group to receive the placebo or 300 mg of vedolizumab with intravenous infusion at Weeks 14, 22, 30, 38, 46, and 54 in a double-blinded manner.

Evaluation data at the time of approval review/ Motoya S, et al.: PLoS One 2019;14（2）:e0212989.
This study was conducted by Takeda Pharmaceutical Company Ltd.
Five of the authors of this paper are employees of Takeda Pharmaceutical Company Limited.
The authors of this paper include those who have received research grants from Takeda Pharmaceutical Company Limited.

ENT:2007-5-017

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Japanese Phase 3 (CCT-101) for Ulcerative Colitis: Safety in Induction

	Number of subjects (%)			
	Cohort 1		Cohort 2	vedolizumab total (N=210)
	placebo (N=82)	vedolizumab (N=164)	vedolizumab (N=46)	
All adverse events	43(52.4)	82(50.0)	33(71.7)	115(54.8)
Causal relationship with the investigational drug				
Not related	31(37.8)	65(39.6)	26(56.5)	91(43.3)
Related	12(14.6)	17(10.4)	7(15.2)	24(11.4)
Intensity of adverse events				
Mild	32(39.0)	58(35.4)	22(47.8)	80(38.1)
Moderate	10(12.2)	23(14.0)	7(15.2)	30(14.3)
Severe	1(1.2)	1(0.6)	4(8.7)	5(2.4)
Adverse events leading to study drug discontinuation	2(2.4)	8(4.9)	6(13.0)	14(6.7)
Serious adverse events	4(4.9)	10(6.1)	6(13.0)	16(7.6)
Causal relationship with the investigational drug				
Not related	2(2.4)	9(5.5)	5(10.9)	14(6.7)
Related	2(2.4)	1(0.6)	1(2.2)	2(1.0)
Serious Adverse Events Leading to Discontinuation of Study Drug	1(1.2)	7(4.3)	4(8.7)	11(5.2)
Death	0	0	0	0

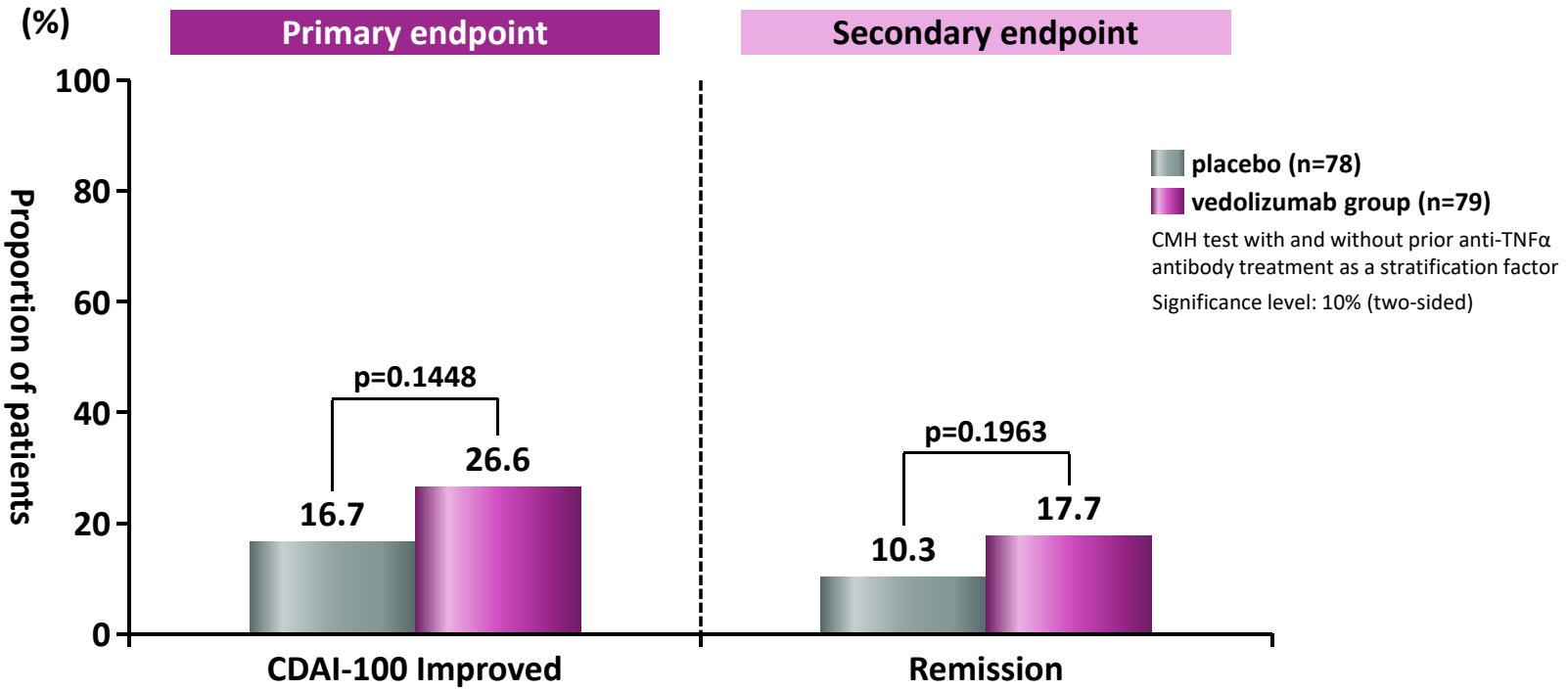
CTD 2.7.6.9 Table 2.7.6.9-17

Japanese Phase 3 (CCT-101) for Ulcerative Colitis: Safety in Maintenance

	Randomized in maintenance setting (%)	
	placebo (N=42)	vedolizumab (N=41)
All adverse events	33(78.6)	36(87.8)
Causal relationship with the investigational drug		
Not related	27(64.3)	32(78.0)
Related	6(14.3)	4(9.8)
Intensity of adverse events		
Mild	23(54.8)	30(73.2)
Moderate	8(19.0)	4(9.8)
Severe	2(4.8)	2(4.9)
Adverse events leading to study drug discontinuation	6(14.3)	2(4.9)
Serious adverse events	3(7.1)	4(9.8)
Causal relationship with the investigational drug		
Not related	3(7.1)	3(7.3)
Related	0	1(2.4)
Serious Adverse Events Leading to Discontinuation of Study Drug	2(4.8)	1(2.4)
Death	0	0

CTD 2.7.6.9 Table 2.7.6.9-44

Japanese Phase 3 (CCT-001) for Crohn's Disease: Efficacy in Induction at Week 10



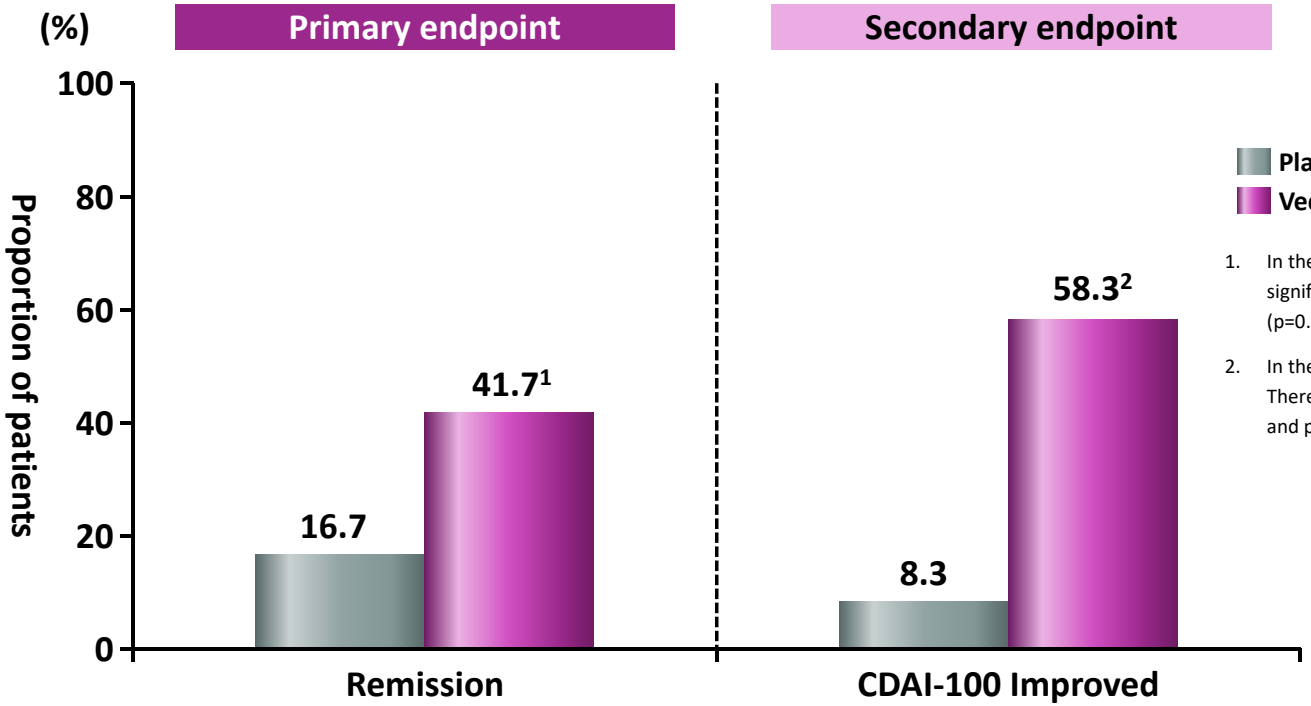
[Improving CDAI-100]. CDAI scores decreased by more than 100 points from baseline
[Remission] CDAI scores of 150 or less

Subjects : 157 patients with moderate or severe Crohn's disease who had a history of treatment failure for at least one of the corticosteroids, immunomodulators, or anti-TNFα antibodies
Methods : Subjects were randomized 1:1 to receive placebo or vedolizumab 300mg and received double-blind intravenous infusions at weeks 0, 2, and 6.

Results of Japanese phase III clinical studies of vedolizumab in patients with Crohn's disease (internal data, evaluation data at approval review)
Watanabe K, et al.: J Gastroenterol 2020; 55(3): 291-306.

GASTROENTEROLOGY

Japanese Phase 3 (CCT-001) for Crohn's Disease: Efficacy in Maintenance at Week 60



1. In the test performed for reference, There was no statistically significant difference between the vedolizumab and placebo groups. (p=0.1779, Pearson's chi-square test)
2. In the test performed for reference, There was a statistically significant difference between the vedolizumab and placebo groups. (p=0.0094, Pearson's chi-square test)

[Remission] CDAI scores of 150 or less
[Improving CDAI-100] CDAI scores decreased by more than 100 points from baseline

Subjects : 157 patients with moderate or severe Crohn's disease who had a history of treatment failure for at least one of the corticosteroids, immunomodulators, or anti-TNFα antibodies
Methods : In the induction period, patients with improved CDAI-70 at Week 10 in the vedolizumab group were enrolled in the maintenance phase at Week 14 and were assigned a 1:1 ratio to the placebo group or the vedolizumab 300-mg group.
They were randomized, double-blind, to receive study drug by intravenous infusion every 8 weeks from week 14 to week 54.

Results of Japanese phase III clinical studies of vedolizumab in patients with Crohn's disease (internal data, evaluation data at approval review)
Watanabe K, et al.: J Gastroenterol 2020; 55(3): 291-306.

GASTROENTEROLOGY

Japanese Phase 3 (CCT-001) for Crohn's Disease: Safety in Induction

	placebo (n=78)	vedolizumab (n=79)
All adverse events	42 (53.8)	49 (62.0)
Causal relationship with the investigational drug[1)]		
Not related	31 (39.7)	39 (49.4)
Related	11 (14.1)	10 (12.7)
Intensity of adverse events[2)]		
Mild	24 (30.8)	37 (46.8)
Moderate	15 (19.2)	11 (13.9)
Severe	3 (3.8)	1 (1.3)
Adverse events leading to study drug discontinuation	12 (15.4)	3 (3.8)
Serious adverse events	10 (12.8)	8 (10.1)
Causal relationship with the investigational drug[1)]		
Not related	6 (7.7)	7 (8.9)
Related	4 (5.1)	1 (1.3)
Serious Adverse Events Leading to Discontinuation of Study Drug	8 (10.3)	1 (1.3)
Death	0	0

Numbers are number of examples, % in parentheses
1) In the event of an AE that was "related" or "unrelated" to the investigational product in the same subject, the event was counted as one subject in the "related" category.
2) Multiple AEs in the same subject were counted as one subject in the highest AE category.

In-house data

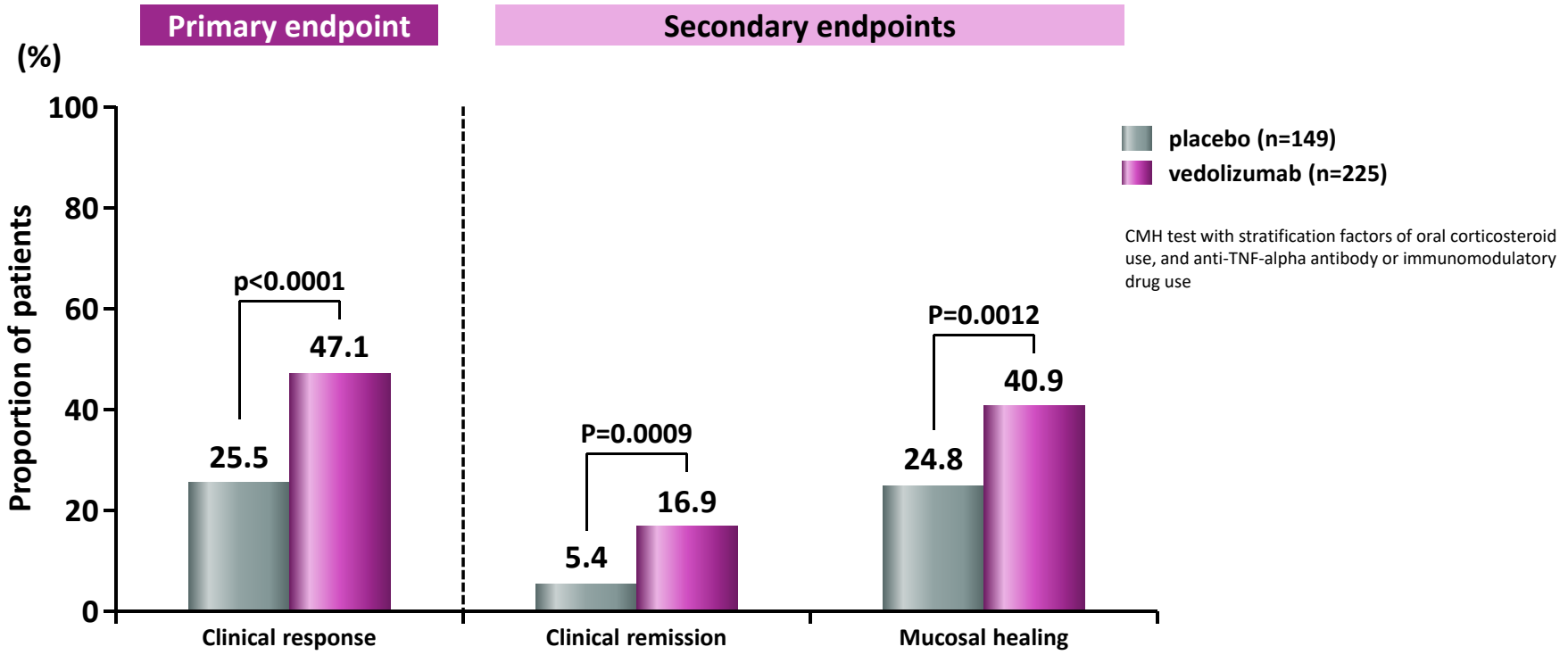
Japanese Phase 3 (CCT-001) for Crohn's Disease: Safety in Maintenance

	Randomized in maintenance period		
	placebo (n=12)	vedolizumab (n=12)	placebo continued cases (n=17)
All adverse events	10 (83.3)	9 (75.0)	12 (70.6)
Causal relationship with the investigational drug[1)]			
Not related	9 (75.0)	7 (58.3)	12 (70.6)
Related	1 (8.3)	2 (16.7)	0
Intensity of adverse events[2)]			
Mild	7 (58.3)	6 (50.0)	9 (52.9)
Moderate	3 (25.0)	3 (25.0)	3 (17.6)
Severe	0	0	0
Adverse events leading to study drug discontinuation	4 (33.3)	2 (16.7)	2 (11.8)
Serious adverse events	4 (33.3)	2 (16.7)	2 (11.8)
Causal relationship with the investigational drug[1)]			
Not related	4 (33.3)	1 (8.3)	2 (11.8)
Related	0	1 (8.3)	0
Serious Adverse Events Leading to Discontinuation of Study Drug	4 (33.3)	2 (16.7)	1 (5.9)
Death	0	0	0

Numbers are number of examples, % in parentheses
1) In the event of an AE that was "related" or "unrelated" to the investigational product in the same subject, the event was counted as one subject in the "related" category.
2) Multiple AEs in the same subject were counted as one subject in the highest AE category.

In-house data

Global Phase 3 (C13006: GEMINI 1) for Ulcerative Colitis: Efficacy in Induction at Week 6



CMH test: Cochran-Mantel-Haenszel test

【Clinical response】 The following 2 conditions were fulfilled;

- Decrease of the complete Mayo score by ≥3 points and by ≥30% from baseline
- Decrease of the subscore of rectal bleeding by ≥1 point from baseline, or ≤1 in the subscore of rectal bleeding

【Clinical remission】 ≤2 in the complete Mayo score and ≤1 in all subscores

【Mucosal healing】 ≤1 in the subscore for findings on endoscopy in the complete Mayo score

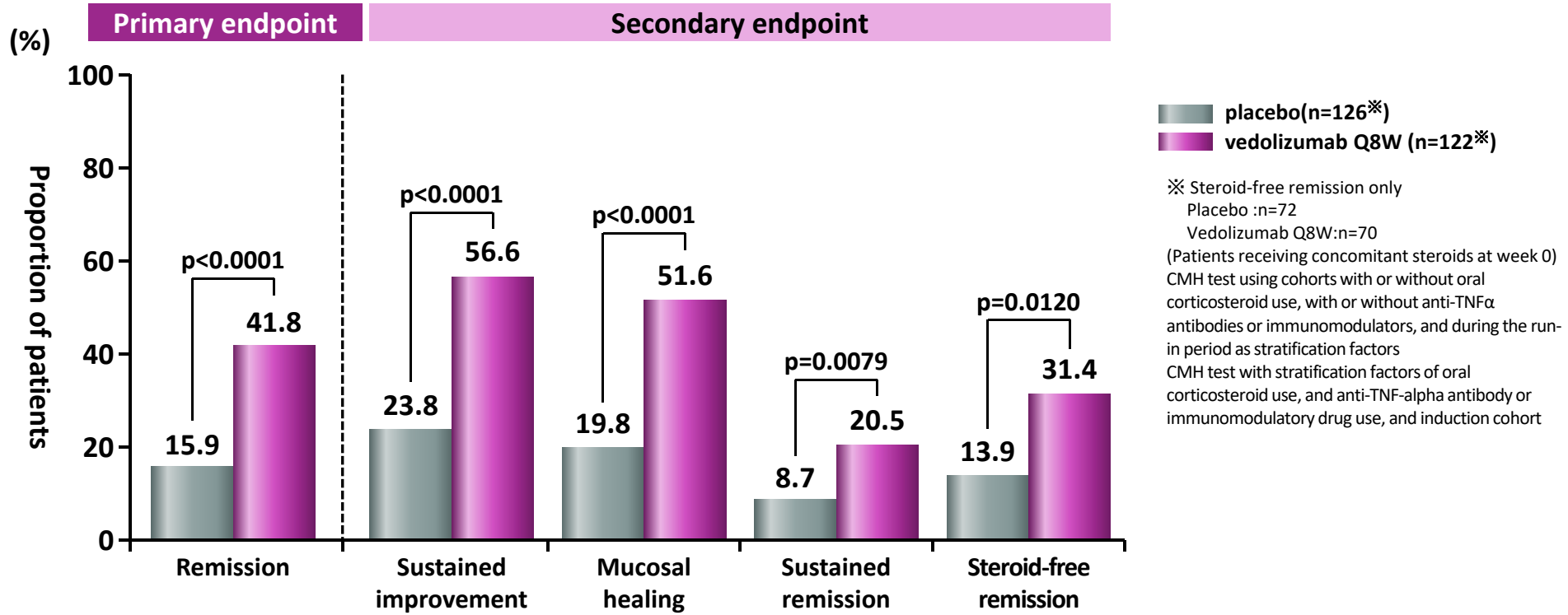
Subjects : 895 patients with moderate to severe ulcerative colitis who experienced prior treatment failure with at least one of the corticosteroid, immunomodulator or TNFα antagonist.

Method : The patients randomized to the placebo group or vedolizumab 300mg group in a 2:3 ratio received intravenous infusion of the double blind study drug at weeks 0 and 2.

Results of foreign phase III clinical studies in patients with ulcerative colitis treated with vedolizumab (internal data, evaluation data at the time of approval review)
Feagan BG, et al.: N Engl J Med 2013;369(8):699-710.

GASTROENTEROLOGY

Global Phase 3 (C13006: GEMINI 1) for Ulcerative Colitis: Efficacy in Maintenance at Week 52



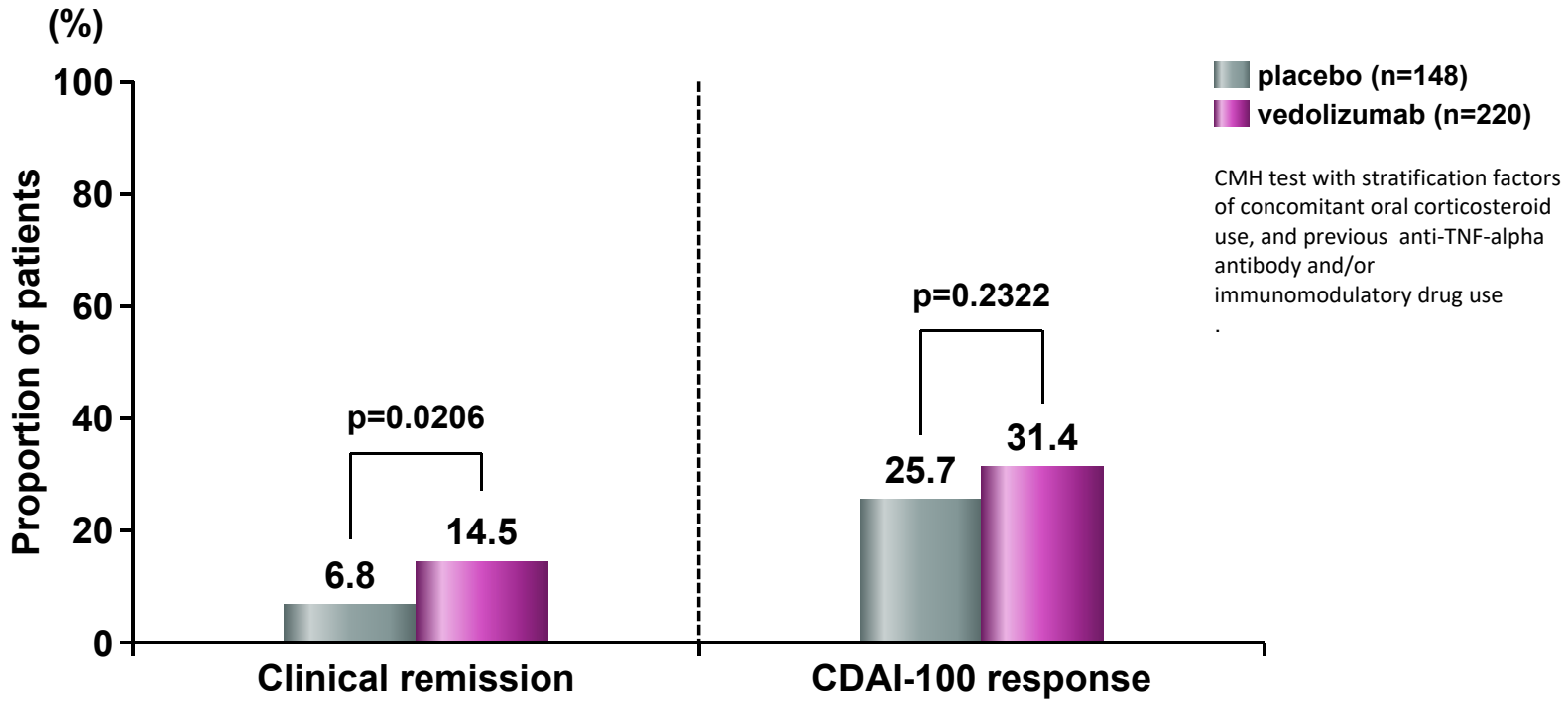
[Remission] Complete Mayo score ≦ 2 and all subscores ≦ 1
[Improvement] When both of the following conditions are met
・ Complete Mayo score decreases by 3 points or more from baseline, decrease by 30% or more, decrease by 1 point or more from baseline in hematochezia sub-score, or 1 point or less in hematochezia sub-score
[Sustained improvement] Improvement at both 6 and 52 weeks, [Mucosal healing] Mucosal finding subscore of complete Mayo score ≦1, [Sustained remission] Remission at both 6 and 52 weeks
[Steroid-free remission]. Adrenocortical steroids were used at baseline (week 0), but corticosteroids were discontinued at week 52, and the patient was in remission.

Subjects : 895 patients with moderate or severe ulcerative colitis who had a history of treatment failure for at least one of the corticosteroids, immunomodulators, or anti-TNFα antibodies
Methods : Subjects who received vedolizumab in the run-in phase and improved at week 6 were randomized 1:1:1 to receive placebo (every 4 weeks), vedolizumab 300mg every 4 weeks (Q4W), or every 8 weeks (Q8W) and received study drug by double-blind intravenous infusion.

Results of foreign phase III clinical studies in patients with ulcerative colitis treated with vedolizumab (internal data, evaluation data at the time of approval review)
Feagan BG, et al.: N Engl J Med 2013;369(8):699-710.

GASTROENTEROLOGY

Global Phase 3 (C13007: GEMINI 2) for Crohn's Disease: Efficacy in Induction at Week 6



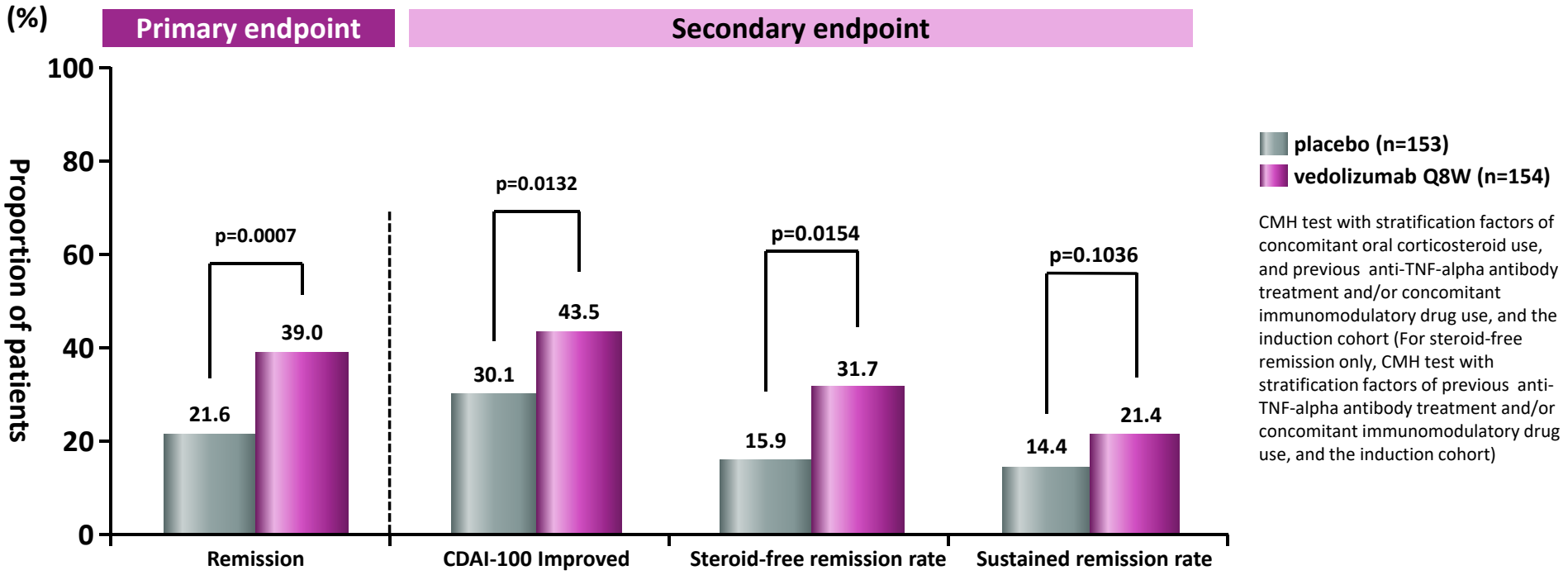
Cochran-Mantel-Haenszel test
[Clinical remission] CDAI score of ≤150
[CDAI-100 response] Decrease in CDAI score by ≥100 points from baseline

Patients : 1,115 patients with moderate to severe Crohn's disease experiencing prior treatment failure with at least one of the following: corticosteroids, immunomodulators, or TNFα antagonists
Method : The patients randomized to receive placebo or vedolizumab 300 mg in a 2:3 ratio received the study drug by intravenous infusion at Weeks 0 and 2 in a double-blind manner.

Results of foreign phase III clinical studies in patients with ulcerative colitis treated with vedolizumab (internal data, evaluation data at the time of approval review)
Feagan BG, et al.: N Engl J Med 2013;369(8):699-710.

GASTROENTEROLOGY

Global Phase 3 (C13007: GEMINI 2) for Crohn's Disease: Efficacy in Maintenance at Week 6



CMH test with stratification factors of concomitant oral corticosteroid use, and previous anti-TNF-alpha antibody treatment and/or concomitant immunomodulatory drug use, and the induction cohort (For steroid-free remission only, CMH test with stratification factors of previous anti-TNF-alpha antibody treatment and/or concomitant immunomodulatory drug use, and the induction cohort)

Cochran-Mantel-Haenszel test
[Clinical remission] CDAI score of ≤150
[CDAI-100 response] Decrease in CDAI score by ≥100 points from baseline

Patients : 1,115 patients with moderate to severe Crohn's disease experiencing prior treatment failure with at least one of the following: corticosteroids, immunomodulators, or TNFα antagonists
Method : Vedolizumab-treated patients in the induction phase who demonstrated a CDAI-70 response at Week 6 were randomized to the placebo group, the vedolizumab 300 mg Q4W group, or the vedolizumab 300 mg Q8W group in a 1:1:1 ratio and received intravenous infusion of the double-blind study drug.

Results of foreign phase III clinical studies in patients with ulcerative colitis treated with vedolizumab (internal data, evaluation data at the time of approval review)
Feagan BG, et al.: N Engl J Med 2013;369(8):699-710.

Integrated Safety Data from GEMINI and Phase 2 studies in UC and CD (1)

- Exposure-adjusted incidence rates of infections were lower with vedolizumab exposure than with placebo
- Exposure-adjusted incidence rates of serious infections were similar in both vedolizumab and placebo treatment groups
- No cases of PML have been reported

Exposure-adjusted incidence rates of AEs in the overall safety population: infections

Adverse event	UC				CD				UC and CD			
	placebo (n=149)		vedolizumab (n=1,107)		placebo (n=355)		vedolizumab (n=1,723)		placebo (n=504)		vedolizumab (n=2,830)	
	Pts	Pts/100 PY (95% CI)	Pts	Pts/100 PY (95% CI)	Pts	Pts/100 PY (95% CI)	Pts	Pts/100 PY (95% CI)	Pts	Pts/100 PY (95% CI)	Pts	Pts/100 PY (95% CI)
Any infection	46	71. 9 (49.7-94.1)	625	56.8 (51.2-62.3)	93	89.7 (70.5-108.9)	981	68.6 (63.4-73.9)	139	**82.9 (68.3-97.5)**	1,606	**63.5 (59.6-67.3)**
Any serious infection or infestation	4	5.0 (0.1-10.0)	54	2.7 (1.9-3.4)	4	3.0 (0.1-6.0)	145	5.6 (4.6-6.5)	8	**3.8 (1.2-6.4)**	199	**4.3 (3.7-4.9)**

AE, adverse event; CD, Crohn's disease; CI, confidence interval; pts, number of patients with event; PML, progressive multifocal leukoencephalopathy; PY, person-year; UC, ulcerative colitis

Colombel JF, et al. *Gut*. 2017;66:839-851. Adapted from Tables 4 and 5.

The study was conducted with the funding of Millennium Pharmaceuticals (currently Takeda Pharmaceutical Co., Ltd.).
The authors of this paper include five company employees and those who have received consultant charges from the company.

GLO/VED/2017-00048. December 2017

Integrated Safety Data from GEMINI and Phase 2 studies in UC and CD (2)

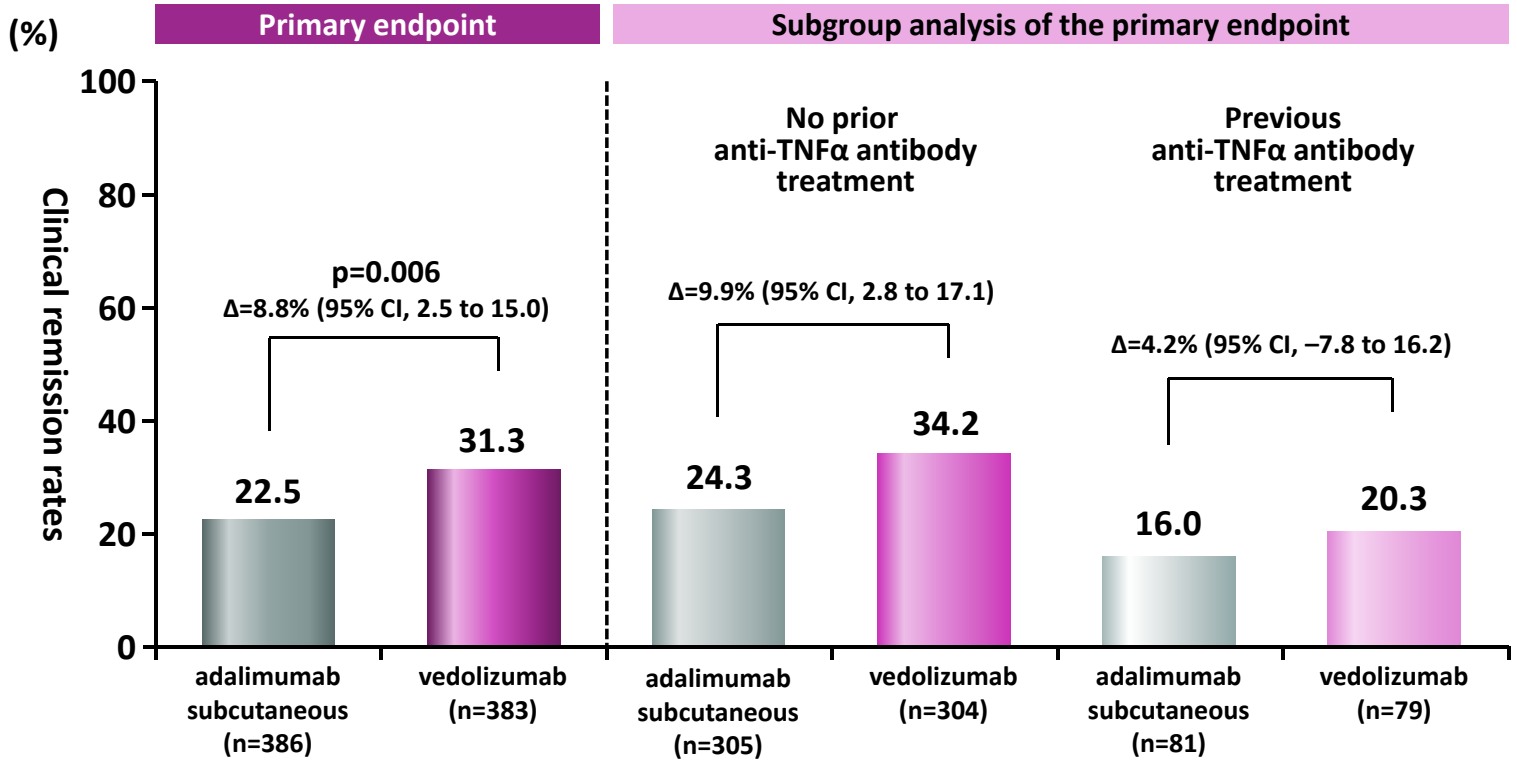
Exposure-adjusted incidence rates of AEs in the overall safety population: most common AEs

Adverse event	UC				CD				UC and CD			
	placebo (n=149)		vedolizumab (n=1,107)		placebo (n=355)		vedolizumab (n=1,723)		placebo (n=504)		vedolizumab (n=2,830)	
	Pts	Pts/100 PY (95% CI)	Pts	Pts/100 PY (95% CI)	Pts	Pts/100 PY (95% CI)	Pts	Pts/100 PY (95% CI)	Pts	Pts/100 PY (95% CI)	Pts	Pts/100 PY (95% CI)
Common AEs (≥15 pts/100 PY in any patient group)												
Nasopharyngitis	11	13.9 (5.5-22.4)	226	13.1 (11.3-14.9)	18	14.1 (7.5-20.8)	315	13.8 (12.2-15.4)	29	14.1 (8.8-19.3)	541	13.5 (12.3-14.7)
Abdominal pain	10	13.2 (4.9-21.5)	138	7.3 (6.0-8.5)	31	25.3 (16.4-34.2)	367	16.0 (14.3-17.7)	41	20.7 (14.3-27.1)	505	12.1 (11.0-13.2)
Headache	13	17.1 (7.5-26.7)	172	9.6 (8.0-11.1)	34	27.9 (18.1-37.8)	299	13.0 (11.4-14.6)	47	23.7 (16.7-30.8)	471	11.5 (10.4-12.6)
Arthralgia	10	13.0 (4.9-21.2)	151	8.2 (6.8-9.5)	29	23.1 (14.6-31.5)	314	13.7 (12.1-15.3)	39	19.3 (13.2-25.4)	465	11.2 (10.1-12.3)
Upper respiratory tract infection	23	30.7 (17.7-43.7)	159	8.6 (7.2-10.0)	44	37.2 (25.8-48.6)	175	7.0 (5.9-8.0)	24	11.6 (6.9-16.3)	334	7.7 (6.8-8.5)
Pyrexia	5	6.3 (0.7-11.8)	78	3.9 (3.0-4.8)	30	23.8 (15.1-32.6)	232	9.4 (8.2-10.7)	35	17.0 (11.3-22.8)	310	7.0 (6.2-7.8)
Exacerbation of CD	N/A	N/A	N/A	N/A	57	47.3 (34.4-60.2)	486	20.4 (18.5-22.4)	57	47.3 (34.4-60.2)	N/A	N/A
Exacerbation of UC	29	38.2 (24.2-52.1)	290	15.5 (13.6-17.4)	N/A	N/A	N/A	N/A	29	38.2 (24.2-52.1)	N/A	N/A

AE, adverse event; CD, Crohn's disease; CI, confidence interval; N/A, not applicable; pts, number of patients with event; PY, person-year; UC, ulcerative colitis

Colombel JF, et al. *Gut*. 2017;66:839-851. Adapted from Table 3.

Global Phase 3b (VARSITY) for Ulcerative Colitis: Efficacy at Week 52



CMH test with or without concomitant oral corticosteroids and with or without prior anti-TNFα antibody treatment as stratification factors

[Clinical remission] Complete Mayo score ≦ 2 and all subscores ≦ 1

Subjects : 769 patients with moderate-to-severe ulcerative colitis who had not received prior anti-TNFα antibody treatment (treatment failure with conventional treatment) or who had previously failed anti-TNFα antibody treatment

Methods : Subjects were randomized to receive intravenous vedolizumab or subcutaneous adalimumab; subjects in the vedolizumab administration group received intravenous vedolizumab 300mg at weeks 0, 2, 6, and every 8 weeks thereafter; and subjects in the adalimumab subcutaneous infusion group received adalimumab 160mg at week 0, 80mg at week 2, and then 40mg subcutaneously every 2 weeks.

Sands BE, et al.: N Engl J Med. 2019;381(13):1215-1226.

GASTROENTEROLOGY

Global Phase 3b (VARSITY) for Ulcerative Colitis : Safety (1)

■ Major adverse events (occurred in 2 or more subjects in any group)

System organ class Preferred Term	Adalimumab subcutaneous (n=386)	Vedolizumab (n=383)	Total (n=769)
Cases of Adverse reactions	86 (22.3)	65 (17.0)	151 (19.6)
Blood and lymphatic system disorders	5 (1.3)	2 (0.5)	7 (0.9)
Anaemia	4 (1.0)	0	4 (0.5)
Lymphopenia	0	2 (0.5)	2 (0.3)
Gastrointestinal disorders	13 (3.4)	15 (3.9)	28 (3.6)
Ulcerative colitis	9 (2.3)	7 (1.8)	16 (2.1)
Abdominal pain	2 (0.5)	2 (0.5)	4 (0.5)
Constipation	0	2 (0.5)	2 (0.3)
Nausea	1 (0.3)	3 (0.8)	4 (0.5)
General disorders and administration site conditions	20 (5.2)	5 (1.3)	25 (3.3)
Asthenia	2 (0.5)	0	2 (0.3)
Fatigue	2 (0.5)	0	2 (0.3)
Pyrexia	1 (0.3)	3 (0.8)	4 (0.5)
Injection site erythema	6 (1.6)	0	6 (0.8)
Injection site pruritus	5 (1.3)	0	5 (0.7)
Injection site reaction	4 (1.0)	1 (0.3)	5 (0.7)
Injection site swelling	2 (0.5)	0	2 (0.3)
Infections and infestations	15 (3.9)	12 (3.1)	27 (3.5)
Oral herpes	2 (0.5)	0	2 (0.3)
Tonsillitis	2 (0.5)	0	2 (0.3)
Upper respiratory tract infection	1 (0.3)	5 (1.3)	6 (0.8)
Urinary tract infection	2 (0.5)	0	2 (0.3)

Numbers are number of examples, and in parentheses are % event names: MedDRA/J ver. 21.0

Sands BE, et al.: N Engl J Med. 2019;381(13):1215-1226. / In-house data

Global Phase 3b (VARSITY) for Ulcerative Colitis : Safety (2)

■ Major adverse events (occurred in 2 subjects in any group)

System organ class Preferred Term	Adalimumab subcutaneous (n=386)	Vedolizumab (n=383)	Total (n=769)
Laboratory tests	12 (3.1)	8 (2.1)	20 (2.6)
Calprotectin stool increased	2 (0.5)	1 (0.3)	3 (0.4)
Blood creatine phosphokinase increased	2 (0.5)	1 (0.3)	3 (0.4)
Musculoskeletal and connective tissue disorders	6 (1.6)	10 (2.6)	16 (2.1)
Arthralgia	5 (1.3)	6 (1.6)	11 (1.4)
Joint swelling	2 (0.5)	0	2 (0.3)
Myalgia	0	5 (1.3)	5 (0.7)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (0.5)	0	2 (0.3)
Colorectal adenoma	2 (0.5)	0	2 (0.3)
Nervous system disorders	5 (1.3)	10 (2.6)	15 (2.0)
Headache	3 (0.8)	3 (0.8)	6 (0.8)
Dizziness	0	2 (0.5)	2 (0.3)
Respiratory, thoracic and mediastinal disorders	5 (1.3)	3 (0.8)	8 (1.0)
Cough	0	2 (0.5)	2 (0.3)
Skin and subcutaneous tissue disorders	24 (6.2)	13 (3.4)	37 (4.8)
Acne	3 (0.8)	3 (0.8)	6 (0.8)
Dermatitis	2 (0.5)	1 (0.3)	3 (0.4)
Erythema	4 (1.0)	2 (0.5)	6 (0.8)
Pruritus	5 (1.3)	0	5 (0.7)
Psoriasis	3 (0.8)	0	3 (0.4)
Papular rash	2 (0.5)	1 (0.3)	3 (0.4)
Vascular disorders	1 (0.3)	4 (1.0)	5 (0.7)
Hypertension	0	3 (0.8)	3 (0.4)

Numbers are number of examples, and in parentheses are % event names: MedDRA/J ver. 21.0

Sands BE, et al.: N Engl J Med. 2019;381(13):1215-1226. / In-house data

Real World Effectiveness from the VICTORY Consortium

Comparative effectiveness between VDZ and anti-TNFα in CD and UC*

Propensity score methods allow estimation of population-average treatment effects

VDZ-treated patients had numerically higher rates of clinical remission, steroid-free remission, and significantly higher rates of endoscopic healing (including in CD patients with colonic involvement)

	CD		UC	
	VDZ (n=269)	Anti-TNFα (n=269)	VDZ (n=167)	Anti-TNFα (n=167)
Clinical remission	38%	34%	54%	37%
	HR: 1.27 95% CI, 0.91-1.78		HR: 1.54 95% CI, 1.08-2.18	
Steroid-free remission	26%	18%	50%	42%
	HR: 1.75 95% CI, 0.90-3.43		HR: 1.73 95% CI, 1.10-2.73	
Endoscopic healing	50%	41%	49%	38%
	HR: 1.67 95% CI, 1.13-2.47		HR: 1.43 95% CI, 0.79-2.60	

Shading indicates statistical significance (95% CI did not cross 1.0.)

*After adjusting for concomitant steroid use, concomitant immunomodulator use, and number of anti-TNFα used.

CI, confidence interval; CD, Crohn's disease; HR, hazard ratio; TNFα, tumor necrosis factor alpha; UC, ulcerative colitis; VDZ, vedolizumab

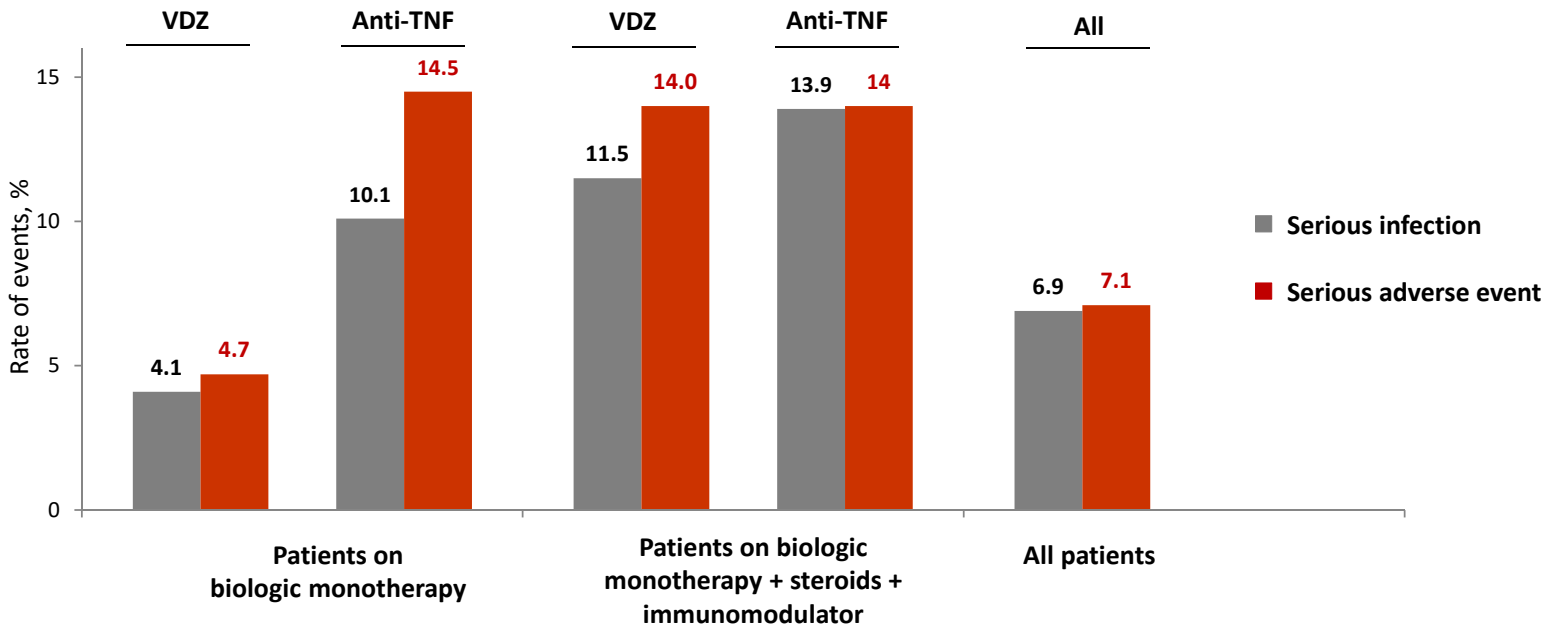
Bohm M, et al. *J Crohns Colitis*. 2018;12(S1):S018; Faleck D, et al. *J Crohns Colitis*. 2018;12(S1):S019.

Real World Safety from the VICTORY Consortium

Rates of serious infection and serious adverse events by therapy combination

Of 1,768 patients in the IBD consortium, 872 were matched in the propensity analysis (538 with CD and 334 with UC)

Patients on concomitant immunosuppressive therapy were more likely to experience a serious infection or serious adverse event



CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis; VDZ, vedolizumab.

Lukin D, et al. *J Crohns Colitis*. 2018;12(S1):S036.

Thank you

Better Health, Brighter Future