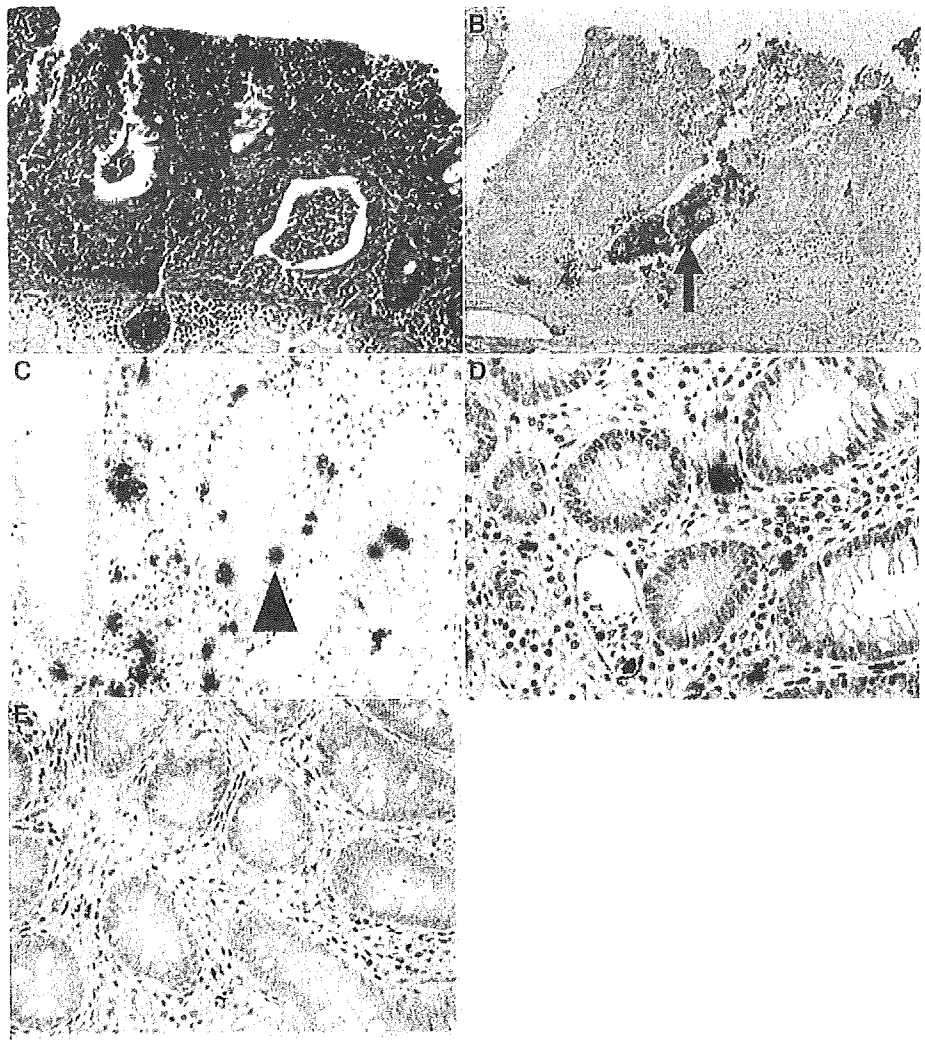

FIGURE 4. Expression of HNP 1–3 in the tissue of patients with active UC or CD and in normal colon tissue. (A) HE staining of colon tissues from patients with UC. (B,C) Immunohistochemical staining demonstrated extensive HNP 1–3 expression in the colon tissues of patients with UC. Many HNP 1–3-positive cells were observed in the crypt abscesses (B: arrow) and in neutrophils that had migrated into the epithelial layers (C: arrowhead). In addition, an ulcer lesion observed in the colon sample stained positive for HNP 1–3. (D,E) Although small numbers of neutrophils in the blood vessels and submucosal tissues were positive for HNP 1–3, epithelial cells in colon samples from patients with inflamed CD or normal subjects were not positive for HNP 1–3. Original magnification: 100× (A,B) and 200× (C–E).

the level of HNP 1–3 had a high discriminatory power for estimating the efficacy of treatment in patients with UC.

DISCUSSION

We identified 27 proteins that showed significant differences in the serum protein profiles of patients with UC compared with those of healthy controls using SELDI-TOF/MS analysis. Of these proteins, 3 signals around 3400 m/z were confirmed to correspond to HNP 1, 2, and 3. In addition, we observed an increase in HNP 1–3 plasma levels in patients with active-phase UC compared with that seen in patients with remission-phase UC or CD; these levels were higher in the plasma of UC patients who showed better therapeutic outcomes than in samples from nonresponder patients.

Several studies have suggested that the development of IBD requires the interaction of genetic factors with both specific luminal bacterial antigens and environmental triggers that break the mucosal barrier.[16–18] Although the principle treatment for IBD is the suppression of inflammation, treatment strategies for the 2 diseases, UC and CD, are somewhat different. Whereas these differences may address the different biomarkers of the 2 conditions, a specific biomarker for IBD remains unknown. To discover a biomarker of UC, we

TABLE 3. Characteristics of Patients with Active UC in the Responder Group and Nonresponder Group

	Responder	Nonresponder	*P*-value
Number	8	7	
Gender (M/F)	5/3	5/2	0.7
Age (yr)	33.5 ± 13.8 [14–50]	42.3 ± 19.8 [16–68]	0.4
CRP (mg/dl)	1.7 ± 1.7	3.3 ± 4.5	0.4
WBC (cells/ul)	12714 ± 4604	7657 ± 3423	*0.04*
Platelets × 10^4/ul	40.4 ± 7.4	36.2 ± 11.1	0.3
HNP 1–3 (ng/ml)	273.0 ± 224.8	84.6 ± 26.5	*0.002*
Type of UC			
Pancolitis/Left-side colitis	7/1	5/2	0.6
UCDAI score	9.4 ± 4.6	8.6 ± 1.9	0.7
Duration	6.7 ± 6.5 [1–19]	5.7 ± 5.1 [2–16]	0.8

Data are shown as the means ± SD [ranges]. Statistical significance was determined using a Mann-Whitney *U*-test or Fisher's exact test, as appropriate. UC, ulcerative colitis; UCDAI, Ulcerative Colitis Disease Activity Index.

employed ProteinChip technology. The likelihood of finding reliable tumor markers by analyzing tissue may be higher than in analyses of serum[12]; malignant cells may produce proteins that are useful biomarkers. In nonmalignant diseases, such as UC, protein profiling of serum or plasma may be more informative than that of tissue samples. Additionally, fluid samples, such as serum, are easier to obtain than tissue samples. Thus, we used serum samples to identify new biomarkers for UC.

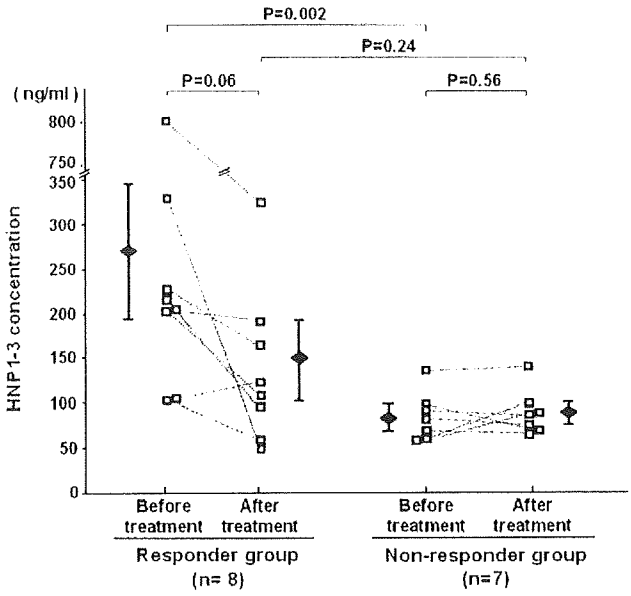

FIGURE 5. HNP 1–3 levels in the responder and nonresponder groups before treatment predicted therapeutic outcomes in UC patients; changes in the HNP 1–3 levels in UC patients in response to treatment are presented. The mean concentration of HNP 1–3 in the responder group before treatment was significantly higher than that seen in the nonresponder group, which indicates that HNP 1–3 levels may be an effective predictor of therapeutic outcomes. HNP 1–3 levels tended to decrease after treatment in the responder group, whereas no changes were observed for the nonresponder group. Patients whose plasma was not obtained after treatment were excluded from analysis.

Defensins are one of the most extensive peptide families of naturally occurring antibiotics. These peptides exhibit microbicidal activities against Gram-positive and Gram-negative bacteria, mycobacteria, fungi, and certain enveloped viruses. HNP 1–3 are part of the α-defensin family and components of the innate immune response. HNP 1–3 are synthesized by neutrophil precursor cells and released at inflammatory sites by mature circulating neutrophils.[9,19] The expression of HNP 1–3 has been observed in epithelial cells of the ileum and colon in patients with active UC or CD.[20] Whether neutrophils within inflamed colon tissue express HNP 1–3 in IBDs, however, is not known. In this study, we demonstrated that the colon mucosal tissue of patients with active UC or CD displayed minimal immunoreactivity for HNP 1–3, whereas the infiltrating neutrophils were stained strongly. These results indicate that HNP 1–3 were secreted from neutrophils, leading to increased plasma levels in patients with UC. High concentrations of HNP 1–3 can be cytotoxic for epithelial cells due to cytolysis and can induce apical conduction in Cl^- secretory epithelia.[21,22] Thus, whereas HNP 1–3 have antibacterial activities in the early phase of UC, they also may injure the colon if they are overexpressed by infiltrating neutrophils. High concentrations of HNP 1–3 may adversely affect colon tissues in UC patients, potentially contributing to diarrhea.[23] HNP 1–3 are secreted from the azurophilic granules of neutrophils following stimulation with IL-8.[24] Epithelial-derived IL-8 is thought to mediate neutrophil migration and infiltration during the inflammatory process of UC.[25,26] IL-8 mRNA levels are

significantly higher in UC patients with crypt abscesses.[27] Although HNP 1–3 have been reported to be expressed by surface enterocytes in the mucosa of patients with active IBD,[28] we observed only minimal staining of the colonic surface mucosa from patients with active UC using anti-HNP 1–3 antibodies. Moreover, Caco-2 and HT-29 cells, 2 colon epithelial cell lines, do not express HNP 1–3 (data not shown). Therefore, we hypothesized that HNP 1–3 are expressed by neutrophils following stimulation with IL-8, which suggested a correlation between the IL-8 and HNP 1–3 levels. We did not, however, observe a correlation between the IL-8 and HNP 1–3 levels in the plasma from active UC patients, and there was no association between the disease activity score and plasma IL-8 concentrations (data not shown). These results indicate that HNP 1–3 expression may be affected by other factors and HNP 1–3 values appear to be more useful to measure clinical UC disease activity than IL-8 levels.

Neutrophils are critical cellular mediators of the inflammation observed in UC. Neutrophils increase in number and display augmented activation during active-phase UC, but not inactive-phase UC.[28] Neutrophils extensively infiltrate colon tissue in patients with UC, and can be detected in the inflamed mucosa during even the early stages of inflammation.[29,30] Platelets are also important in the pathophysiology of UC.[31] Cytapheresis therapy (including LCAP) in combination with steroid therapy can be an effective treatment option for patients with active UC.[32] LCAP may remove and modulate both leukocytes and platelets, thereby altering the expression of proinflammatory cytokines.[33,34] The effect of LCAP on HNP 1–3 levels, however, has not been examined, and further studies are needed to determine whether HNP 1–3 levels decrease in response to LCAP. In addition, we showed that HNP 1–3 levels in the plasma were higher in patients with active UC than in those with infectious colitis, and HNP 1–3 levels were similar between patients with infectious colitis and healthy controls. In contrast, it was reported that HNP 1–3 levels in patients with severe infectious diseases, such as sepsis, were higher than those in healthy controls.[35] The disease severity of the enrolled patients with infectious colitis in this study may have affected our results. Cytapheresis therapy, however, may not be effective for severe infectious diseases, including infectious colitis, and high concentrations of HNP 1–3 in patients with active UC may be associated with disease characteristics. Further examination, including cases of infectious colitis with sepsis, will be necessary.

As previously reported, we found that several inflammatory makers, including the CRP level, WBC, and platelet count, decreased after treatment. Changes in these inflammatory markers did not predict the treatment outcome of patients with UC, whereas plasma levels of HNP 1–3 correlated with UC disease activity and predicted the therapeutic outcome. There were no correlations between plasma HNP 1–3 levels and inflammatory markers, such as platelet counts and CRP levels. These results may suggest that high levels of HNP 1–3 independently indicate the activity of disease and the feasible treatment outcome in patients with UC. However, there is a limitation in the use of HNP 1–3 measurement as a biomarker; low levels of HNP 1–3 in colitis patients did not diagnose whether they had nonresponder UC or active CD. Therefore, low levels of HNP 1–3 in colitis patients should be assessed by clinical symptoms, stool for bacterial examination, and endoscopic and radiographic examination of the gastrointestinal tract for diagnosis. Other proteins and peptides that were detected by SELDI/TOF-MS in this study are now under investigation and may serve as additional biomarkers for the assessment of IBD, especially in nonresponder UC patients.

The levels of HNP 1–3 in tumor tissue and serum were reported to increase in patients with CRC.[12] It was also reported that plasma HNP 1–3 concentrations determined using ELISA increased in Duke's stages C and D, but not in A or B compared to healthy controls.[14] In contrast, we showed that HNP 1–3 concentrations in CRC patients at Duke's stage A were higher than those seen in patients with inactive UC and healthy controls. Although HNP 1–3 concentrations in CRC patients at Duke's stage A seem to be similar between our study and a previous study[14] (100.8 ± 27.6 versus 105.4± 80.6 ng/mL, respectively), the concentrations in the healthy controls were different between the 2 studies (77.5 ±16.5 versus 96.6 ± 36.2 ng/mL). In addition, Albrethsen et al[14] mentioned that in addition to Duke's C and D, HNP 1–3 expression in CRC tissues at Duke's A and B was higher than in normal tissue by SELDI ProteinChip. It is controversial whether the increased HNP 1–3 in tumors is localized to cancer cells or to neutrophilic leukocytes. There is the possibility that the plasma HNP 1–3 levels will increase in patients with CRC at Duke's stage A and that HNP 1–3 concentration is a potential marker for the assessment of CRC patients with advanced disease.[12,14] In addition, these results indicate that HNP 1–3 levels may not be able to distinguish between active UC and colon cancer. In the clinical setting, however, UC can typically be distinguished from colon cancer by various clinical features, such as diarrhea, fever, and colonoscopic findings. On the other hand, colon cancer commonly occurs in patients with UC, especially those who have suffered from the disease for a long period of time; such colon cancers are difficult to detect using colonoscopy. HNP 1–3 levels may help to signal the occurrence of colon cancer in UC patients when high concentrations of HNP 1–3 are detected in the absence of active colitis; these patients should be extensively examined, including total colonoscopy and random biopsies.

In conclusion, we used SELDI-TOF/MS to perform serum protein profiling and determined that HNP 1–3 levels increase in patients with active-phase of UC. We also con-

firmed that HNP 1–3 are predictive markers for UC treatment outcomes. Although these markers may not distinguish UC from CRC, HNP 1–3 are useful markers for the differential diagnosis of patients with IBD.

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Long-term prospective pilot study with tranilast for the prevention of stricture progression in patients with Crohn's disease

Nobuhide Oshitani, Hirokazu Yamagami, Kenji Watanabe, et al.

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Long-term prospective pilot study with tranilast for the prevention of stricture progression in patients with Crohn's disease

Fibrosis and strictures are common and irreversible complications of Crohn's disease that potentially necessitate bowel resection. Tranilast, N-(3',4'-dimethoxycinnamoyl) anthranilic acid, inhibits keloid scar formation through the inhibition of production of metalloproteinases and tissue inhibitor of metalloproteinase-1 from neutrophils.[1] Please check the phrase "inhibition of ... neutrophils" is OK Tranilast has been shown to inhibit fibrosis in various experimental models.[2–4] Randomised, double-blind, placebo-controlled studies have shown substantial inhibition by tranilast of restenosis of coronary arteries.[5–7] A case report has demonstrated the efficacy of long-term administration of tranilast in inflammatory endobronchial stenosis.[8]

Between June 2001 and July 2005, 24 patients with quiescent Crohn's disease with non-symptomatic intestinal strictures were recruited. Baseline intestinal stricture was evaluated by small bowel barium enteroclysis, or Gastrografin® (Schering Aktiengesellschaft, Berlin, Germany) enteroclysis under endoscopic examination using a digital caliper (Digimatic® Caliper, Mitutoyo Corporation, Kawasaki, Japan). Patients were allocated using a random number table to receive tranilast 200 mg (2 tablets) after every meal, three times daily (tranilast group) or to a control group that did not receive the agent, and followed up prospectively. The primary endpoint was whether or not there was development of symptomatic stricture requiring hydrostatic balloon dilatation of the stricture or requiring surgical resection, which was quantified as the cumulative non-symptomatic stricture rate. The secondary endpoint used in this study was the diameter of the stricture, which was measured at the time of recruitment (basal diameter) and at the time of development of symptomatic stricture or at the latest follow-up (final diameter). Change in diameter during the follow-up period was assessed using the equation (final diameter-basal diameter/basal diameter) 100/month. The change in diameter was compared between groups (% change/month)

There was no significant difference in clinical backgrounds between the tranilast group and the control group (table 1). One patient in the tranilast group withdrew because of a reduced white blood cell count. During the observation period, one patient in the tranilast group and two in the control group received infliximab infusion, and two tranilast and one control patient had been taking oral prednisolone. Six tranilast and seven control patients had been taking immunomodulators (azathioprine or mercaptopurine there were no significant differences between groups for these factors.

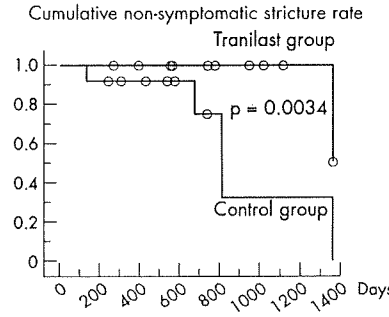

Figure 1 Cumulative non-symptomatic stricture rate with and without oral tranilast administration. Patients taking tranilast had a significantly higher non-symptomatic stricture rate compared with those not receiving this agent. The median observation period for the tranilast group was 782 (25th percentile 558, 75th percentile 1093) days, with a period of 559 (366, 738) days in the control group.

Hydrostatic balloon dilatation was done in one patient in the tranilast group and in five patients in the control group owing to the development of symptomatic stricture (fig 1, p = 0.0034). The median basal diameter of the stricture was 6.40 mm (25th percentile 4.25, 75th percentile 6.70) in the tranilast group and 6.35 mm (5.50, 7.25) in the control group (p = 0.3837). At follow-up, the diameter of the stricture was 5.60 mm (4.25, 11.23) in the tranilast group and 5.05 mm (4.30, 7.10) in the control group (p = 0.1769). Change in diameter during the follow-up period was 0.48% per month (–0.63, 3.18) in the tranilast group, compared with –0.86% per month (–2.11, 0.88) in the control group (p = 0.2740).

We found a preventive effect of tranilast on the development of symptomatic intestinal stricture in patients with Crohn's disease. Since there is no established effective medical therapy for intestinal stricture in Crohn's disease, long-term tranilast administration

Table 1 Clinical background of the patients

Characteristic	Tranilast group (n = 12)	Control group (n = 12)	p Value
Median age, years (25th and 75th percentile)	35.0 (26.5, 40.5)	37.5 (33.5, 46.5)	0.1183
Male/female	7/5	9/3	0.6650
Median disease duration, years (25th and 75th percentile)	7.3 (4.7, 10.5)	11.5 (6.5, 13.5)	0.2122
Location of the disease			
Ileitis	3	7	0.0892
Colitis	4	0	
Ileocolitis	5	5	
Behaviour of the disease			
Stricturing	7	4	>0.9999
Penetrating	5	5	
Location of stricture			
Ileum	7	8	>0.9999
Colon	5	4	

Differences between groups were analysed by one-way analysis of variance with Bonferroni's correction. χ^2 analysis was used for table analysis, and Fisher's exact test with Yates' correction was used. The cumulative non-symptomatic stricture rate was assessed by the life-table method employing Log rank (Mantel–Cox) analysis. P values less than 0.05 were considered significant.

has potential as a therapeutic modality for the prevention of the development of intestinal stricture in patients with Crohn's disease.

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This study was approved by the ethical committee of Osaka City University and informed consent was obtained from all the patients.

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Competing interests: None declared.

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Ⅷ.　研究成果の刊行物

案

一目でわかるIBD

炎症性腸疾患を診療されている先生方へ

難治性炎症性腸管障害に関する調査研究班（渡辺班）

目次

発刊にあたって

厚生労働科学研究費補助金 難治性疾患克服研究事業
難治性炎症性腸管障害に関する調査研究班
研究代表者: **渡辺 守**
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作成にあたって

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旭川医科大学 消化器内科

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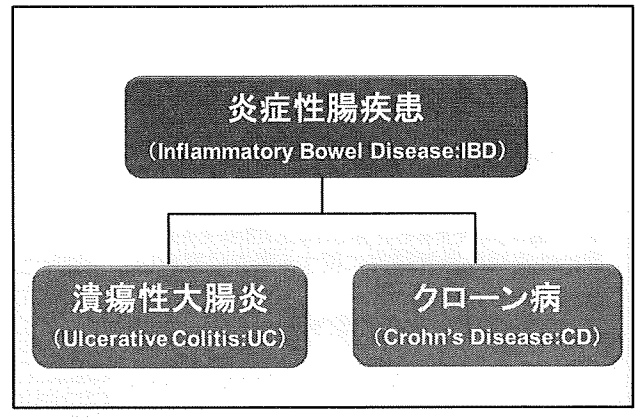
炎症性腸疾患

概念

腸の炎症性疾患には特発性の潰瘍性大腸炎やクローン病のほか、細菌・寄生虫・ウイルス・真菌の感染による感染性腸炎、薬剤・化学物質などに起因する薬剤性腸炎、放射線による放射線照射性腸炎、虚血性腸炎、閉塞性腸炎などの多くの疾患があり、これらすべてを含むものが広義の炎症性腸疾患（Inflammatory Bowel Disease：IBD）である。

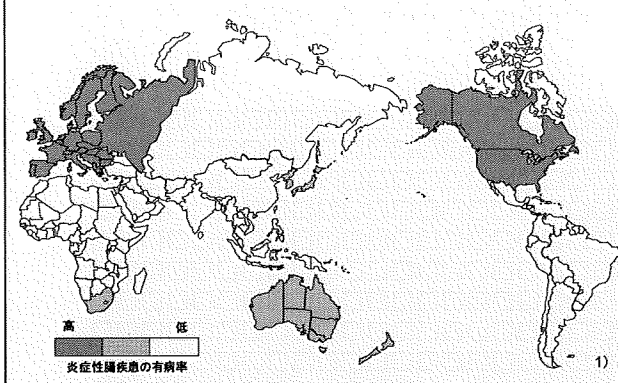
一方、狭義には特発性（idiopathic）炎症性腸疾患として、潰瘍性大腸炎（Ulcerative Colitis：UC）とクローン病（Crohn's Disease：CD）の両疾患を指す。今日、IBDの用語は狭義の意味に用いられる。



疫学

潰瘍性大腸炎とクローン病は欧米で多くみられる。本邦では1970年代までは稀な疾患とされていたが、1970年代以降急激に増加している。しかしながら、1991年の統計による罹患率は欧米に比べ低率である。特定疾患登録・受給患者数の増加からみると、現在の罹患率はこれより高いと推定される。

炎症性腸疾患の分布



1)

炎症性腸疾患罹患率の国際比較

国	地域	潰瘍性大腸炎		クローン病	
		年	罹患率	年	罹患率
デンマーク	全国	1981-92	13.2	1981-92	4.6
スウェーデン	Upsala	1977-83	11.5	1965-83	6.1
英国	Cardiff	1978-87	6.3	1981-85	8.3
オランダ	Leiden	1979-83	6.8	—	—
米国	Minnesota	1984-93	8.3	1984-93	6.9
カナダ	Manitoba	1987-96	15.6	1987-96	15.6
韓国	Seoul	1995-97	1.2	—	—
日本	全国	1991	1.95	1991	0.51

2)

本邦における年齢調整有病率の推移

年度	潰瘍性大腸炎	クローン病
2003年	54.1	16.3
2004年	54.1	18.2
2005年	63.6	21.2
2006年	66.5	23.0

※人口10万人あたり

・衛生行政報告例による特定疾患医療受給者証所持者数に対し、電子化された臨床個人調査票の提出率が85%を越える県（UC：26府県、CD：27府県）について算出。

3)

4

潰瘍性大腸炎

定義

主として粘膜を侵し、しばしばびらんや潰瘍を形成する大腸の原因不明のびまん性非特異性炎症である。WHOのCouncil for International Organization of Medical Science（CIOMS）医科学国際組織委員会で定められた名称と概念は、つぎの通りである。（1973）

特発性大腸炎　idiopathic proctocolitis

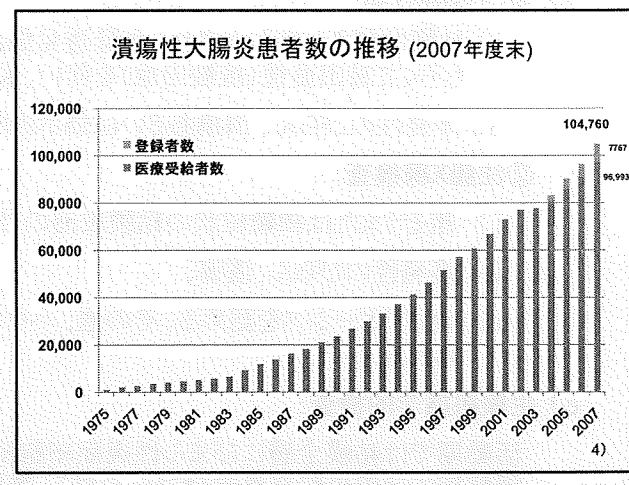
（訳）主として粘膜と粘膜下層をおかす、大腸とくに直腸の特発性、非特異性の炎症性疾患。30歳以下の成人に多いが、小児や50歳以上の年齢層にもみられる。原因は不明で、免疫病理学的機序や心理学的要因の関与が考えられている。通常血性下痢と種々の程度の全身症状を示す。長期にわたり、かつ大腸全体をおかす場合には悪性化の傾向がある。

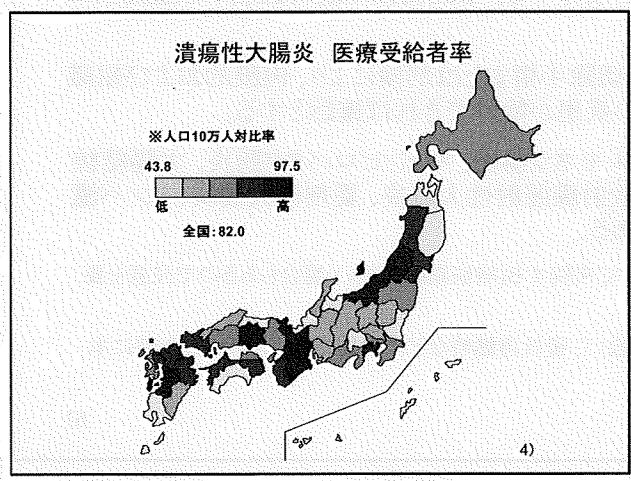
疫学

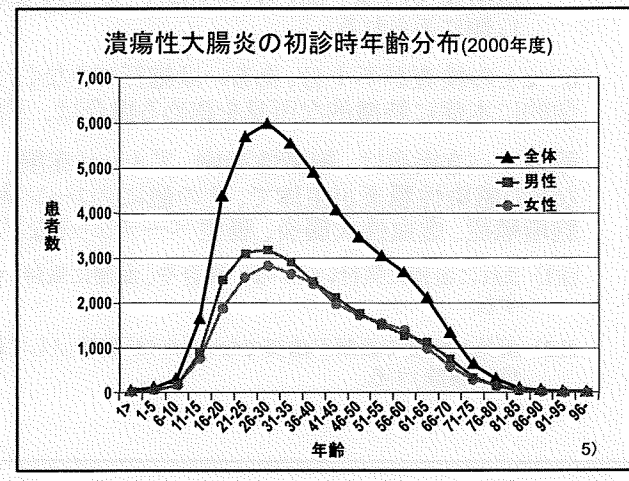
潰瘍性大腸炎は、特定疾患に指定されているため、医療受給者証および登録者証の交付件数から患者数をみると、2007年度末には医療受給者証交付件数は96,993名、登録者証交付件数は7,767名が登録されている。合算すると10万人を超える疾患となるとともに、毎年患者数は5千名程度増加している。

本邦の人口10万人に対する有病率は、1991年の全国疫学調査時は18.12であったが、2006年度の県別年齢調整有病率は40.7～85.2であり、地域によって差があるものの明らかな増加が認められる。

潰瘍性大腸炎の疫学的特徴として、性差はみられず、診断時年齢は男女ともに26～30歳にピークがみられる。







5

診断－潰瘍性大腸炎－

診断の手順

慢性の粘血・血便などがあり本症が疑われるときには、放射線照射歴、抗生剤服用歴、海外渡航歴などを聴取するとともに、細菌学的・寄生虫学的検査を行って感染性腸炎を除外する。次に直腸あるいはS状結腸内視鏡検査を行って本症に特徴的な腸病変を確認する。このさい、生検を併用する。

これだけの検査で多くは診断が可能であるが、必要に応じて注腸X線検査や全大腸内視鏡検査などを行って、腸病変の性状や程度、罹患範囲などを検査し、同時に他の疾患を除外する。

6)

診断基準

次のａ）のほか、ｂ）のうち1項目、およびｃ）を満たし、下記の疾患が除外できれば確診となる。

ａ）臨床症状：持続性または反復性の粘血・血便、あるいはその既往がある。

ｂ）①内視鏡検査：

ｉ）粘膜はびまん性おかされ、血管透見像は消失し、粗ぞうまたは細顆粒状を呈する。さらに、もろくて易出血性（接触出血）を伴い、粘血膿性の分泌物が付着しているか、

ii）多発性のびらん、潰瘍あるいは偽ポリポーシスを認める。

②注腸X線検査：

ｉ） 粗ぞうまたは細顆粒状の粘膜表面のびまん性変化、

ii）多発性のびらん、潰瘍、

iii）偽ポリポーシスを認める。その他、ハウストラの消失（鉛管像）や腸管の狭小・短縮が認められる。

ｃ）生検組織学的検査：

活動期では粘膜全層にびまん性炎症細胞浸潤、陰窩膿瘍、高度な杯細胞減少が認められる。緩解期では腺の配列異常（蛇行・分岐）、萎縮が残存する。上記変化は通常直腸から連続性に口側にみられる。

ｂ）ｃ）の検査が不十分、あるいは施行できなくとも、切除手術または剖検により、肉眼的および組織学的に本症に特徴的な所見を認める場合は、下記の疾患が除外できれば確診とする。

除外すべき疾患は、細菌性赤痢、アメーバ赤痢、サルモネラ腸炎、キャンピロバクタ腸炎、大腸結核などの感染性腸炎が主体で、その他にクローン病、放射線照射性大腸炎、薬剤性大腸炎、リンパ濾胞増殖症、虚血性大腸炎、腸型ベーチェットなどがある。

注1）まれに血便に気付いていない場合や、血便に気付いてすぐ来院する(病悩期間が短い)場合もあるので注意を要する。

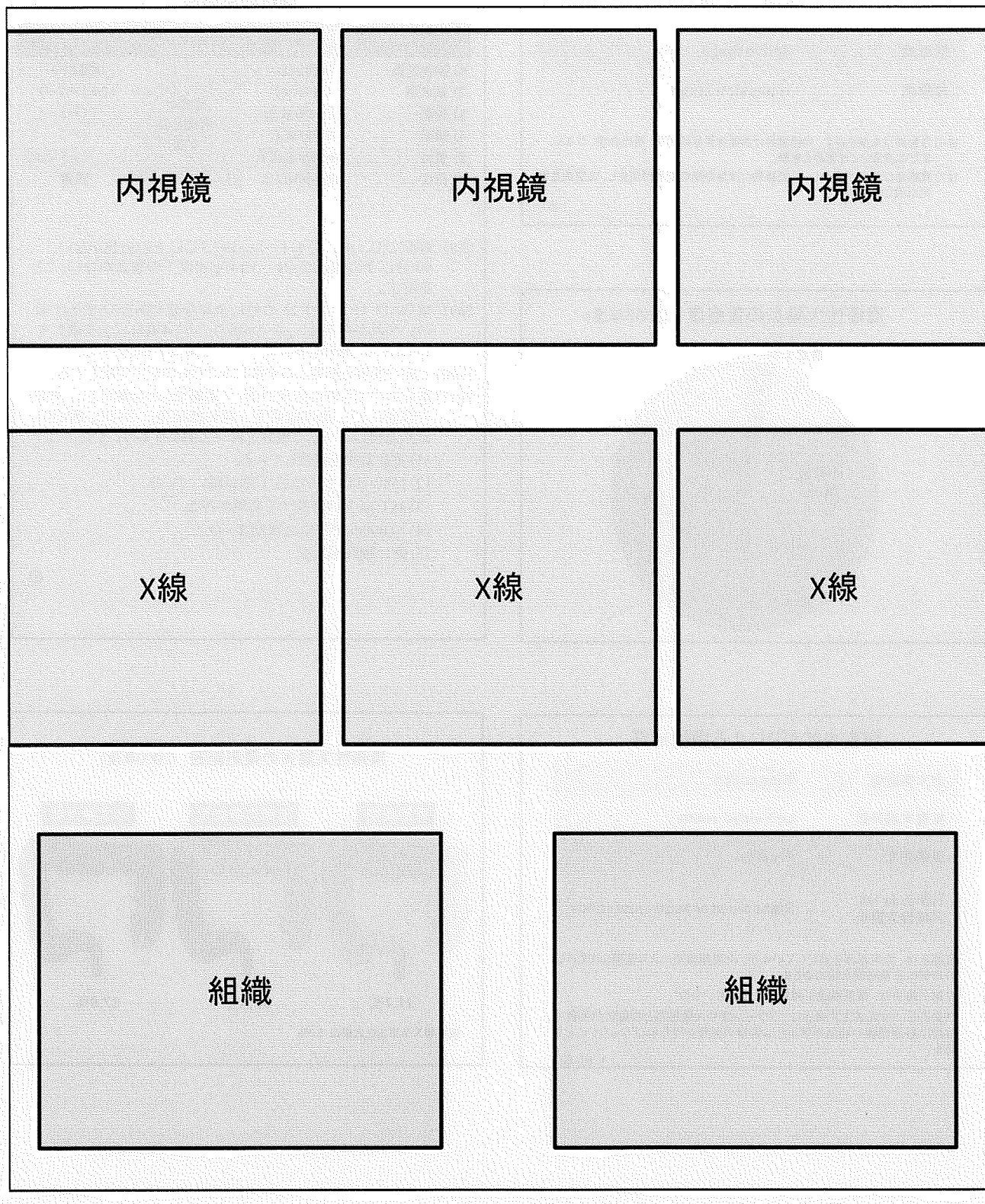
注2）所見が軽度で診断が確実でないものは「疑診」として取り扱い、後日再燃時などに明確な所見が得られた時に本症と「確診」する。

6)

診断－潰瘍性大腸炎－

内視鏡・X線像・組織像

炎症性腸疾患内視鏡アトラスを参照
炎症性腸疾患内視鏡アトラス作成プロジェクト：難治性炎症性腸管障害に関する調査研究班（日比班）2008年2月発行



病態の分類－潰瘍性大腸炎－

病期の分類

活動期	active stage
寛解期	remission stage

注6) 活動期は血便を訴え、内視鏡的に血管透見像の消失、易出血性、びらん、または潰瘍などを認める状態。

注7) 寛解期は血便が消失し、内視鏡的には活動期の所見が消失し、血管透見像が出現した状態。

6)

臨床的重症度

	重症 severe	中等症 moderate	軽症 mild
1) 排便回数	6回以上	重症と軽症との中間	4回以下
2) 顕血便	(＋＋＋)		(＋)～(－)
3) 発熱	37.5℃以上		(－)
4) 頻脈	90/分以上		(－)
5) 貧血	Hb10g/dl以下		(－)
6) 赤沈	30mm/h以上		正常

注8) 軽症の3), 4), 5)の(－)とは37.5℃以上の発熱がない、90/分以上の頻脈がない、Hb10g/dl以下の貧血がない、ことを示す。

注9) 重症とは1) および2) の他に全身症状である3) または4) のいずれかを満たし、かつ6項目のうち4項目以上を満たすものとする。軽症は6項目すべてを満たすものとする。

注10) 上記の重症と軽症との中間にあたるものを中等症とする。

注11) 重症の中でも特に症状が激しく重篤なものを激症とし、発症の経過により、急性激症型と再燃激症型に分ける。激症の診断基準は以下の5項目を統べて満たすものとする。

(1) 重症基準を満たしている。

(2) 15回/日以上の血性下痢が続いている。

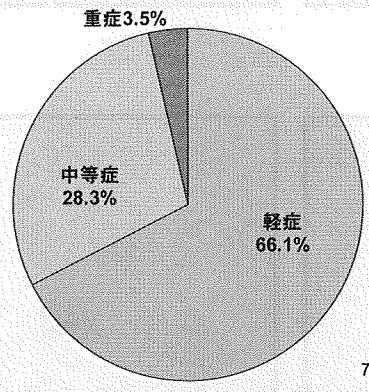
(3) 38℃以上の持続する高熱がある。

(4) 10,000mm^{3}の白血球増多がある。

(5) 強い腹痛がある。

6)

潰瘍性大腸炎の重症度 (2005年度)



7)

病変の拡がりによる病型分類

全大腸炎型	Total colitis
左側大腸炎型	Left-sided colitis
直腸炎型	Proctitis
右側あるいは区域性大腸炎	Right-sided or segmental colitis

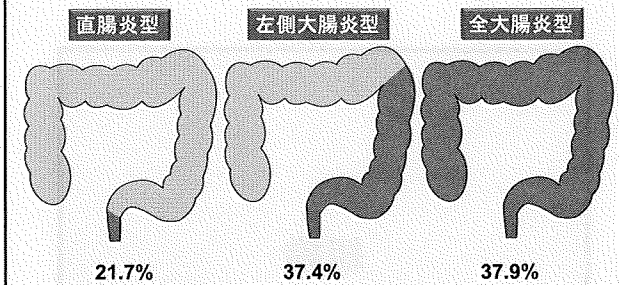
直腸炎は、診断基準を満たしているが、内視鏡検査により直腸S状部(Rs)の口側に正常粘膜を認めるもの。

左側大腸炎は、罹患範囲が脾彎曲を超えないもの*。

右側あるいは区域性大腸炎は、クローン病や大腸結核との鑑別が困難で、診断は経過観察や切除手術または剖検の結果を待たねばならないこともある。

＊:8), 6)

潰瘍性大腸炎の罹患範囲 (2000年度)



※右側又は区域性大腸炎:3.0%

5)

病態の分類－潰瘍性大腸炎－

臨床経過による分類

再燃緩解型	relapse-remitting type
慢性持続型	chronic continuous type
急性激症型(急性電撃型)	acute fulminating type
初回発作型	one attack only

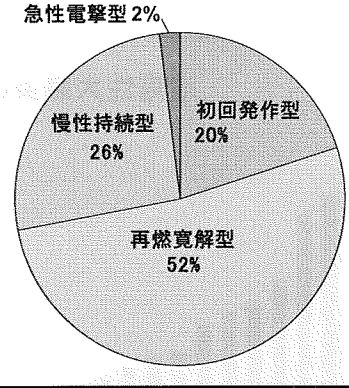
慢性持続型は初回発作より6カ月以上活動期にあるもの。

急性激症型(急性電撃型)はきわめて激烈な症状で発症し、中毒性巨大結腸症，穿孔，敗血症などの合併症を伴うことが多く、予後がきわめて不良なもの。

初回発作型は発作が1回だけのもの。しかし将来再燃をきたし、再燃緩解型となる可能性が大きい。

6)

潰瘍性大腸炎の臨床経過(2000年度)



5)

活動期内視鏡所見による分類

炎症性腸疾患内視鏡アトラスを参照

炎症性腸疾患内視鏡アトラス作成プロジェクト:難治性炎症性腸管障害に関する調査研究班(日比班) 2008年2月 発行

炎症	内視鏡所見
軽度 Mild	血管透見像消失 粘膜細顆粒状 発赤、少横色点
中等度 moderate	粘膜粗ぞう、びらん、小潰瘍 易出血性(接触出血) 粘血膿性分泌物付着 その他の活動性炎症所見
強度 severe	広汎な潰瘍 著明な自然出血

注12) 内視鏡的に観察した範囲で最も所見の強いところで診断する。内視鏡検査は前処置なしで短時間で施行し、必ずしも全大腸を観察する必要はない。

6)

寛解
内視鏡写真

軽度
内視鏡写真

中等度
内視鏡写真

強度
内視鏡写真

難治性潰瘍性大腸炎の定義

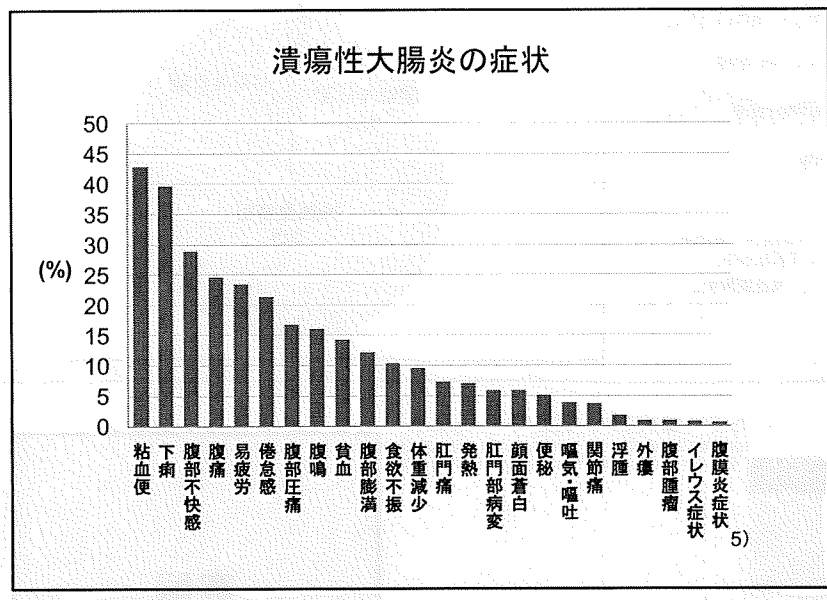
厳密なステロイド療法にありながら、次のいずれかの条件を満たすもの

(1)プレドニゾロン1-1.5mg/kg/日の1-2週間投与で効果がない
(ステロイド抵抗例)

(2)ステロイド漸減中の再燃
(ステロイド依存例)

9)

臨床像－潰瘍性大腸炎－



潰瘍性大腸炎の腸管外合併症

成長障害(小児)	5(8%*)	血管系疾患	10(0.7%)	呼吸器疾患	24(1.7%)
肝胆道系疾患	66(4.6%)	血栓性静脈炎	5	喘息	8
細胆管炎	1	バージャー病	1	肺結核	8
脂肪肝	11	動脈血栓症	1	その他	8
肝硬変	2	その他	3	悪性疾患	11(0.8%)
胆汁性肝硬変	0	皮膚粘膜系合併症	80(5.5%)	子宮癌	0
硬化性胆管炎	4	虹彩炎・結膜炎	14	胃癌	2
胆管癌	1	角膜潰瘍	1	乳癌	1
肝線維症	0	口腔内ｱﾌﾀ・ﾓﾘﾆｱ症	2	肺癌	0
慢性活動性肝炎	8	皮膚発疹	14	膵癌	1
胆石症	10	結節性紅斑	5	悪性リンパ腫	2
膵炎・高ｱﾐﾗｰｾﾞ血症	14	壊疽性膿皮症	5	その他	5
その他	15	紫斑病	0	その他の疾患	83(5.8%)
泌尿・生殖系合併症	36(2.5%)	陰部潰瘍	0	高血圧	16
尿路結石	22	その他	39	糖尿病	8
閉塞性水腎症	1	血液疾患	64(4.4%)	アミロイドーシス	2
腎炎	5	鉄欠乏性貧血	55	胃・十二指腸潰瘍	15
ネフローゼ	1	溶血性貧血	1	精神・神経障害	14
その他	7	その他	8	SMON	1
筋骨格系合併症	56(3.9%)	膠原病	8(0.6%)	内分泌疾患	8
強直性脊椎症	2	SLE	0	心疾患	8
仙骨腸骨炎	1	RA	2	ベーチェット病	0
こん棒状指	1	大動脈炎症候群	3	その他	11
関節炎・関節症	23	慢性甲状腺炎	1		
その他	29	その他	2		

＊成長障害は小児例数に対する%。その他は総症例に対する%。
※潰瘍性大腸炎1433例に対して、腸管外合併症は300例(20.9%)に認められた 10)

臨床像 －潰瘍性大腸炎-

腸管合併症

中毒性
巨大結腸症

大腸癌

腸管外合併症

壊死性膿皮症など

原発性硬化性
胆管炎など

11

内科的治療 -潰瘍性大腸炎-

治療

潰瘍性大腸炎治療指針改訂案[1)]、エビデンスとコンセンサスを統合した潰瘍性大腸炎の診療ガイドライン[2)]を参照

1)松本譽之:難治性炎症性腸管障害に関する調査研究班(渡辺班)平成20年度研究報告書別冊
2)プロジェクト研究グループ:難治性炎症性腸管障害に関する調査研究班(日比班)2006年1月発行

潰瘍性大腸炎は、再燃と寛解を繰り返し、長期に渡って治療を要する疾患である。現状本疾患を完治させる治療方法がないため、治療の目的は、活動期には炎症を速やかに抑え、早期に寛解導入を図るとともに、寛解期には再燃を防ぎ、より長く寛解を維持させることで患者のQOLを向上させることにある。

治療原則

- **重症例やある程度の全身障害を伴う中等症例に対しては、入院のうえ、脱水、電解質異常(特に低カリウム血症)、貧血、低蛋白血症、栄養障害などに対する対策が必要である。**
- **劇症型は極めて予後不良であるので、内科と外科の協力のもとに強力な治療を行い、短期間の間に手術の要、不要を決定する。**
- **小児例では、成長障害などに配慮した治療が必要であり、薬用量等については、小児治療指針を参照されたい。また、手術法など外科治療の詳細については、外科治療指針を参照されたい。**

11)

薬物療法

薬物療法は、主として重症度と罹患範囲に応じて薬剤を選択する。寛解導入後も、再燃を予防するため維持療法を行う。治療継続中に急性増悪を起こした場合や維持療法中に再燃を起こした場合には、前回の活動期と同一の治療法が奏功しないことや、より重症化することが多いので、これらの点を参考にして治療法を考慮する。重症例、難治例は専門医に相談することが望ましい。

潰瘍性大腸炎の治療

軽症	中等症	重症	劇症
直腸炎型 ・ペンタサ・サラゾピリン ・サラゾピリン坐剤・リンデロン坐剤 ・ペンタサ注腸・ステロイド注腸 (プレドネマ・ステロネマ) 単独または併用 **左側大腸炎型・全大腸炎型** ・ペンタサ・サラゾピリン ・ペンタサ注腸・ステロイド注腸 (経口剤との併用)	軽症治療に準じる ・ステロイドp.o. (炎症反応時追加)	原則入院, 全身管理 ・ステロイドp.o./i.v. 必要に応じ ・血球成分除去療法 (セルソーバ、アダカラム) ・サンディミュン持続静注※ ・プログラフp.o. ・手術	絶食・経静脈的栄養補給 ・強力静注療法 ・プレドニゾロン動注療法 必要に応じ ・血球成分除去療法 (セルソーバ、アダカラム) ・サンディミュン持続静注※ ・手術

寛解維持
・ペンタサ・サラゾピリン
・ペンタサ注腸
単独または併用
・免疫調節剤
(ステロイド依存例・抵抗例)

難治例
ステロイド依存例
・免疫調節剤(イムラン・アザニン/ロイケリン※)
ステロイド抵抗例
・血球成分除去療法(セルソーバ、アダカラム)
・サンディミュン持続静注※
・プログラフp.o.
無効例・QOL低下例
・手術

※保険非適応

基準薬ペンタサ錠投与のポイント

*1. 寛解導入療法としてペンタサ®錠は国内外の報告より高用量の効果が高いことから、1日4.0g投与が望ましい。
*2. 寛解維持療法としてコンプライアンスを改善するためにペンタサ®錠1日2.0gを1～2回に分けて投与してもよい。
*3. ペンタサ®経口投与とペンタサ®注腸を併用する場合には、経口4.0gと注腸1.0gの併用が望ましい。

11)