Sato S Hokari R Kurihara C Ueda T Hozumi H Sato H Narimatsu K Okada Y Watanabe C Komoto S Tomita K Kawaguchi A Nagao S Miura S	Dietary lipid and sweetener regulate secretion of glucagon-like peptide-2 (GLP-2) from intestine in a different manner.	Digestive Disease Week 2012	San Diego	2012.5.19-22
Watanabe C Hokari R Kurihara C Ueda T Hozumi H Sato H Narimatsu K Okada Y Sato S Komoto S Tomita K Kawaguchi A Nagao S Miura S	Prevalence of celiac disease in patients with inflammatory bowel disease: A study from Japan.	Digestive Disease Week 2012	San Diego	2012.5.19-22
Okada Y Tsuzuki Y Hokari R Watanabe C Kurihara C Ueda T Hozumi H Sato H Narimatsu K Sato S Komoto S Tomita K Kawaguchi A Nagao S Miura S	A novel vegetable-derived probiotics (VDP) exerts a therapeutic effect on DSS induced colitis possibly mediated by IL-27 producing CD11c+ dendritic cells.	Digestive Disease Week 2012	San Diego	2012.5.19-22
Okada Y Tsuzuki Y Hokari R Watanabe C Kurihara C Ueda T Hozumi H Sato H Narimatsu K Sato S Komoto S Tomita K Kawaguchi A Nagao S Miura S	Trans fatty acids exposure induced expression of proinflammatory cytokines and NK-1R in colonic epithelial cells by phosphorylation of p38.	Digestive Disease Week 2012	San Diego	2012.5.19-22

Higashiyama M Akiba Y Miura S Kaunitz JD	17 ATP-P2Y-Duox2 pathway; a novel antimicrobial duodenal defense mechanism.In: Symposium: Chemosensing and Gut Hormones.	International Ulcer Week 2012, The 14th Meeting of International Conference on Ulcer Research	Tokyo	2012.07.12-13
Hokari R Miura S	Effect of dietary fat on intestinal disorders. In: Symposium: Nutritional Factors (Nutritional aspect) in GI disorders.	JSDE-APAGE Joint Conference. The 3rd Asian-Pacific Topic Conference, Nutritional Related Disorders and Digestive System	Tokyo	2012.11.02-03
Ueda T Hokari R Miura S	Dietary fat exacerbates NSAID-induced mucosal damage in murine small intestine.	JSDE-APAGE Joint Conference. The 3rd Asian-Pacific Topic Conference, Nutritional Related Disorders and Digestive System	Tokyo	2012.11.02-03
Okada Y Tsuzuki Y Ueda T Hozumi H Sato S Hokari R Kurihara C Watanabe C Tomita K Komoto S Kawaguchi A Nagao S Miura S	Trans fatty acids in diet act as precipitating factor of DSS-induced colitis by the up-regulation of macrophage-derived proinflammatory cytokines.	JSDE-APAGE Joint Conference. The 3rd Asian-Pacific Topic Conference, Nutritional Related Disorders and Digestive System	Tokyo	2012.11.02-03
Kurihara C Hokari R Matsunaga H Higashiyama M Ueda T Sato H Narimatsu K Okada Y Watanabe C Tomita K Komoto S Kawaguchi A Nagao S Miura S	Exposure to fatty acid modifies IL-6 mRNA expression in macrophages from small intestine of IBD-mice model.	Asian IBD Symposium Seoul 2012,	Seoul	2012.11.02-03
渡辺知佳子 穂苅量太 高本俊介 富田謙吾 三浦総一郎	本邦におけるセリアック病の実態の臨床調査～炎症性腸疾患患者における合併の可能性について～	第98回日本消化器病学会総会	東京	2012.04.19-21

丸田紘史 因幡健一 和田晃典 岩城智之 寺田尚人 種本理那 高城　健 清水基規 安武優一 佐藤宏和 成松和幸 佐藤伸悟 渡辺知佳子 高本俊介 穂苅量太 川口　淳 永尾重昭 三浦総一郎	当院における下部消化管出血の診断と治療の現況	第83回日本消化器内視鏡学会総会	東京	2012.05.12-13
清水基規 永尾重昭 川口　淳 高城　健 丸田紘史 成松和幸 佐藤宏和 佐藤伸悟 高本俊介 穂苅量太 三浦総一郎	当科における高齢者胃ESDおよびEMR症例の偶発症の現状	第83回日本消化器内視鏡学会総会	東京	2012.05.12-13
三浦総一郎	炎症性腸疾患診療の進歩	第20回日本消化器病学会関東支部教育講演会	大宮	2012.6.17
佐藤宏和 穂苅量太 三浦総一郎	炎症性腸疾患におけるリンパ管新生因子の検討	第35回日本リンパ学会総会	東京	2012.06.29-30
成松和幸 佐藤宏和 東山正明 上田俊秀 渡辺知佳子 高本俊介 冨田謙吾 穂苅量太 三浦総一郎	NSAIDs起因性小腸潰瘍に対するToll-like receptor 2 agonistの抑制効果	第49回日本消化器免疫学会総会	鹿児島	2012.07.05-06

成松和幸 東山正明 佐藤宏和 八月朔日秀明 上田俊秀 佐藤伸悟 渡辺知佳子 栗原千枝 岡田義清 高本俊介 冨田謙吾 穂苅量太 川口　淳 永尾重昭 三浦総一郎	oll-like receptor 2 agonist によるインドメタシン起因性小腸潰瘍の抑制効果。シンポジウム:粘膜上皮修復機転の最前線	第40回日本潰瘍学会総会	東京	2012.07.12-14
佐藤宏和 穂苅量太 成松和幸 上田俊秀 東山正明 渡辺知佳子 高本俊介 冨田謙吾 栗原千枝 岡田義清 川口　淳 永尾重昭 三浦総一郎	炎症性腸疾患におけるリンパ管新生における検討、シンポジウム:IBD診療・治療への更なる挑戦	第30回日本大腸検査学会総会	東京	2012.9.1
鈴木博久 東山正明 緒方　衝 穂苅量太 上田俊秀 佐藤宏和 成松和幸 渡辺知佳子 高本俊介 冨田謙吾 川口　淳 永尾重昭 三浦総一郎	内視鏡検査時の捺印細胞診で治療経過が追えたヒト腸管スピロヘータ症の1例	第30回日本大腸検査学会総会	東京	39691
渡辺知佳子 穂苅量太 三浦総一郎	我が国における炎症性腸疾患とセリアック病の関連について、ワークショップ:アレルギー消化器疾患の実態	第54回日本消化器病学会大会、第20回日本消化器病週間内合同企画 JDDW 2012 Kobe	神戸	2012.10.10-13

穂苅量太 上田俊秀 東山正明 冨田謙吾 岡田義清 栗原千枝 成松和幸 佐藤宏和 渡辺知佳子 高本俊介 川口　淳 永尾重昭 三浦総一郎	腸管炎症における脂肪摂取の影響－ω3系多価不飽和脂肪酸の2面性	第9回日本在宅静脈経腸栄養研究会学術集会	名古屋	2012.10.20
渡辺知佳子 穂苅量太 高本俊介 三浦総一郎	当科におけるセリアック病の実態調査：疾患特異的血清抗体と炎症性腸疾患の関連について、シンポジウム：小腸生理・再生・病態の新たなエビデンス	第50回小腸研究会	京都	2012.11.7
三浦総一郎	炎症性腸疾患の栄養指導（教育講演）	第16回日本病態栄養学会年次学術集会	京都	2013.01.12-13
佐々木智彦 国崎玲子 田中正則 他	クローン病小腸病変の活動性診断における体外式超音波ドプラ法の有用性に関する基礎的検討	第30回日本大腸検査学会総会	東京	2012.9.1
国崎玲子 石毛　崇 田中正則 他	小児期発症クローン病と診断されていたX連鎖リンパ増殖症候群2型（XLP-type 2）の2例	第13回日本小児IBD研究会	大阪	2012.2.10
Ohkubo H Nakajima A et al.	An epidemiologic survey of chronic intestinal pseudo-obstruction (CIPO) and evaluation of the newly proposed diagnostic criteria.	Joint International Neurogastroenterology and Motility Meeting	Bologna, Italy	2012.9.6-8
Kano Y Tsuchiya K Horita N Zheng X Okamoto R Nakamura T Watanabe M	The acquisition of cancer stemness in colon cancer by the Atoh1 protein stabilization.	ISSCR2012	Yokohama	2012.6.14
Yui S Nakamura T Nemoto Y Mizutani T Fukuda M Nozaki K Yamauchi Y Mochiduki W Zheng X Nagaishi T Okamoto R Tsuchiya K Watanabe M	Regeneration of damaged colon epithelium by transplanted colon Lgr5+ stem cells maintained and expanded in vitro.	第10回 幹細胞シンポジウム	淡路島	2012.6.1

Nemoto Y Kanai T Okamoto R, Tsuchiya K Nakamura T Matsumoto S Watanabe M	Colitogenic effector memory CD4+ T cells develop TH1/TH17 mediated interstitial pneumonia independent to intestinal bacterial antigens.	DDW2012	San Diego	2012.5.22
Tsuchiya K Zheng X Kano Y Okamoto R Nakamura T Watanabe M	Flagellin response via TLR5 on basolateral membrane of primary intestinal epithelial cells is regulated by Notch signaling.	DDW2012	San Diego	2012.5.22
Mizutani T Nakamura T Morikawa R Fukuda M Mochizuki W Yamauchi Y Nozaki K Yui S Okamoto R Tsuchiya K Watanabe M	Real-time analysis of p-glycoprotein-mediated drug transport across primary intestinal epitherial cells three-dimensionally cultured in vitro.	DDW2012	San Diego	2012.5.21
Okamoto R Murano T Shimizu H Ito G Tsuchiya K Nakamura T Watanabe M	Notch signaling regulates expression of Gelsolin superfamily genes, Gelsolin and Scinderin, and promotes re-assembly of actin cytoskelton in human intestinal epithelial cells.	DDW2012	San Diego	2012.5.21
Kano Y Tsuchiya K Horita N Zheng X Okamoto R Nakamura T Watanabe M	The acquisition of cancer stemness in colon cancer by the Atoh1 protein stabilization.	DDW2012	San Diego	2012.5.19
Murano T Okamoto R Shimizu H Ito G Tsuchiya K Nakamura T Watanabe M	Hes1 promotes IL-22-Mediated epithelial regeneration through enhancement of STAT3-Dpendent transcription in human intestinal epithelial cells.	DDW2012	San Diego	2012.5.19

社会活動報告

社会活動に関する一覧表

活動者名 (所属施設)	会の名称および講演演題等	会場および新聞名等	活動年月日
清水誠治 (大阪鉄道病院)	第24回浜名湖胃と腸フォーラム「IBDの鑑別診断」	浜松アクトシティ	平成25年9月14日
清水誠治 (大阪鉄道病院)	第277回広島胃と腸疾患研究会「炎症性腸疾患の診断プロセス」	ANAクラウンプラザホテル広島	平成26年1月11日
田中正則 (弘前市立病院)	第10回大久保消化器病理カンファ「消化管病理の基本と適切な生検部位」	新宿パークタワー(新宿)	平成25年4月23日
田中正則 (弘前市立病院)	岩手消化器病理セミナー「炎症性腸疾患の病理診断のコツ」	盛岡グランドホテル(盛岡)	平成25年4月27日
田中正則 (弘前市立病院)	第11回大久保消化器病理カンファ「ステロイド抵抗性・依存性UCの予測」	新宿パークタワー(新宿)	平成25年7月2日
田中正則 (弘前市立病院)	第11回三重IBD研究会「IBDとIBD類縁疾患の病理診断」	津都ホテル(津)	平成25年8月1日
田中正則 (弘前市立病院)	第40回東北大腸疾患研究会「IBDUとIndeterminate Colitis」	アスパム(青森)	平成25年9月14日
田中正則 (弘前市立病院)	第249回木曜会「IBDとIBD類縁疾患の病理診断」	メトロポリタンプラザオフィスタワー(西池袋)	平成25年10月3日
田中正則 (弘前市立病院)	第9回スキルアップ臨床研究会「消化管病理の基礎と生検部位」	青森国際ホテル(青森)	平成25年11月1日
田中正則 (弘前市立病院)	第12回大久保消化器病理カンファ「薬剤性の消化管粘膜障害の病理像」	新宿パークタワー(新宿)	平成25年11月26日
田中正則 (弘前市立病院)	第16回北関東炎症性腸疾患研究会「IBDの生検診断とIBDU」	群馬ロイヤルホテル(前橋)	平成26年2月21日
渡辺　守 (東京医歯大)	非常に強力な抗体製剤、日本での使い過ぎを懸念	NIKKEI MEDICAL	平成25年11月号
渡辺　守 (東京医歯大)	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成果発表会第12回市民公開講座プログラム「炎症性腸疾患の治療をめぐって」	東京医科歯科大学	平成25年8月10日

渡辺　守 （東京医歯大）	消化器疾患のトレンド 腸疾患時代をよみとく	Medhical ASAHI	平成25年4月号
渡辺　守 （東京医歯大）	難病患者訪問診療実施協議会「新しい時代に入った潰瘍性大腸炎治療」	東京都医師会	2013年2月27日
渡辺　守 （東京医歯大）	日経ラジオ社 「ドクターサロン」	日経ラジオ社	2013年2月26日
渡辺　守 （東京医歯大）	医療連載 「患者を生きる」 （計5回の連載）	朝日新聞	2012年12月20日
渡辺　守 （東京医歯大）	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成果発表会第11回市民公開講座プログラム「炎症性腸疾患の治療をめぐって」	名古屋市立大学病院	2012年12月16日
渡辺　守 （東京医歯大）	炎症性腸疾患医療講演会 「潰瘍性大腸炎・クローン病など、潰瘍性大腸炎・クローン病を正しく理解しましょう～生活上での注意点と最新治療について～」	東京都難病相談・支援センター	2012年11月11日
渡辺　守 （東京医歯大）	秋期特集＝主な疾患の話題 潰瘍性大腸炎～QOL改善を目指した治療～	MEDICAMET NEWS	2012年10月15日
渡辺　守 （東京医歯大）	NHK出版生活実用シリーズ 「あなたのためのセレクトレシピ　きょうからスッキリ！快腸レシピ」	NHK出版	2012年10月号
渡辺　守 （東京医歯大）	潰瘍性大腸炎	日本経済新聞夕刊	2012年10月12日
渡辺　守 （東京医歯大）	夕刊フジ 「ニッポン　病院の実力」	夕刊フジ	2012年8月15日
渡辺　守 （東京医歯大）	名古屋IBDセミナー 「新しい時代に入ったIBD～考えておくべきこと～」	名古屋	2012年6月29日
渡辺　守 （東京医歯大）	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成果発表会 「炎症性腸疾患の治療をめぐって」「炎症性腸疾患の治療をめぐって」	ラ・プラス青い森	2012年6月2日

渡辺　守 (東京医歯大)	東京都医師会 「日本医師会生涯教育講座」 IBDからIBSを繙く／IBSからIBDを繙く	東京	2012年6月7日
渡辺　守 (東京医歯大)	幹細胞1個からの再生	代ゼミジャーナル	2012年4月10日
山本 博徳 新畑 博英 佐藤 博之 (自治医大)	第6回 下野IBD研究会	自治医科大学 地域医療情報研修センター第2・3研修室	平成24年7月11日
山本 博徳 新畑 博英 佐藤 博之 (自治医大)	第7回 下野IBD研究会	自治医科大学 地域医療情報研修センター第2・3研修室	平成25年2月6日
松本主之 (九州大)	第65回日本消化器内視鏡学会四国支部例会 「炎症性腸疾患と内視鏡検査:現状と将来」	松山市民文化センター	2012年11月17日
松本主之 (九州大)	第108回日本消化器内視鏡学会中国支部例会 「炎症性腸疾患の小腸・大腸内視鏡所見」	広島国際会議場	2012年7月1日
松本主之 (九州大)	日本消化器病学会中国支部第15回教育講演会 「炎症性腸疾患の診断と治療:最近の話題」	広島国際会議場	2012年5月27日
松井敏幸 (福岡大筑紫病院)	第37回日本大腸肛門病学会九州地方会/第28回九州ストーマリハビリテーション研究会	都久志会館・福岡ガーデンパレス	2012年9月21日
松井敏幸 (福岡大筑紫病院)	IBD(炎症性腸疾患)センター開設記念市民公開講座	JR九州ホール	2012年5月27日
松井敏幸 (福岡大筑紫病院)	潰瘍性大腸炎	九州朝日放送	2012年5月5日
松井敏幸 (福岡大筑紫病院)	IBD(炎症性腸疾患)センター開設記念インタビュー	西日本新聞	2012年4月27日
清水誠治 (大阪鉄道病院)	第3回多摩腸疾患カンファレンス 「炎症性腸疾患の鑑別診断」	パレスホテル立川	2012年4月27日
清水誠治 (大阪鉄道病院)	第2回日胆IBD研究会 「炎症性腸疾患の鑑別診断」	グランドホテルニュー王子	2012年6月29日
清水誠治 (大阪鉄道病院)	鳥取炎症性腸疾患講演会 「炎症性腸疾患の鑑別診断」	ニューオータニ鳥取	2012年7月21日

清水誠治 (大阪鉄道病院)	第4回熊本IBDカンファレンス 「炎症性腸疾患の鑑別診断」	ホテルニューオータニ熊本	2012年9月28日
清水誠治 (大阪鉄道病院)	第2回日立IBDカンファレンス 「炎症性腸疾患の鑑別診断」	ホテル テラス ザ スクエア日立	2012年11月27日
田中正則 (弘前大)	第8回大久保消化器病理カンファランスにて特別講演 「クローン病のマクロとミクロ」	東京	2012年6月26日
田中正則 (弘前大)	第6回診断病理サマーフェストにて教育講演 「IBDの生検病理」	東京	2012年8月25日
小林清典 (北里大東病院)	水戸炎症性腸疾患学術講演会 「炎症性腸疾患の画像診断－IBDを中心に」	水戸市	2012年11月7日
小林清典 (北里大東病院)	第49回神奈川大腸疾患研究会「IBDに対する最近の内科治療の進歩」	横浜市	2012年2月29日

添　付　資　料

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RAPID COMMUNICATION

The 2nd edition of consensus statements for the diagnosis and management of intestinal Behçet's disease: indication of anti-TNFα monoclonal antibodies

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Abstract
Background Clinical evidence regarding intestinal Behçet's disease (BD) management is lacking and intestinal lesions are a poor prognostic factor. In 2007, the Japan consensus statement for diagnosis and management of intestinal BD was developed. Recently, the efficacy of anti-tumor necrosis factor (TNF)α monoclonal antibodies (mAbs), and infliximab (IFX) was reported and adalimumab (ADA) was approved for intestinal BD in Japan. This study renewed consensus-based practice guidelines for diagnosis and treatment of intestinal BD focusing on the indication of anti-TNFα mAbs.
Methods An expert panel of Japanese gastroenterology and rheumatology specialists was involved. Clinical statements for ratings were extracted from the literature, a professional group survey, and by an expert panel discussion, which rated clinical statements on a nine-point scale. After the first round of ratings, a panelist meeting discussed areas of disagreement and clarified areas of uncertainty. The list of clinical statements was revised after the panelist meeting and a second round of ratings was conducted.
Results Fifteen relevant articles were selected. Based on the first edition consensus statement, improved clinical statements regarding indications for anti-TNFα mAbs use were developed. After a two-round modified Delphi approach, the second edition of consensus statements was finalized.
Conclusions In addition to standard therapies in the first edition, anti-TNFα mAbs (ADA and IFX) should be considered as a standard therapy for intestinal BD. Colchicines, thalidomide, other pharmacological therapy,

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endoscopic therapy, and leukocytapheresis were deemed experimental therapies.

Keywords Intestinal Behçet's disease · Anti-TNFα mAb · Consensus statements

Abbreviations

ADA	Adalimumab
BD	Behçet's disease
CRP	C-reactive protein
IFX	Infliximab
mAb	Monoclonal antibody
TNF	Tumor necrosis factor

Introduction

Behçet's disease (BD) is a chronic relapsing disease with multiple organ system involvement characterized clinically by oral and genital aphthae, cutaneous lesions, and ophthalmological, neurological, or gastrointestinal manifestations [1, 2]. Approximately 3–16 % of patients with BD have gastrointestinal tract involvement. Gastrointestinal disease typically affects the ileocecal area, although involvement of the esophagus and small intestine has been reported [3]. The most common gastrointestinal symptoms are abdominal pain, diarrhea, and bleeding. Deep ulcers are responsible for the most common intestinal complications, such as severe bleeding and perforation [4]. Various drugs, such as 5-aminosalicylic acid (5-ASA), systemic corticosteroids, and immunosuppressive agents have been used anecdotally to treat intestinal BD. However, the clinical evidence regarding the management of intestinal BD is very limited. In 2007, the Japanese Inflammatory Bowel Disease Research Group, supported by the Japanese Ministry of Health, Labour and Welfare, proposed consensus statements for the management of intestinal BD for the first time [5]. In this consensus, infliximab (IFX) was described as an optional therapy for intestinal BD. In recent years, accumulating evidence on the efficacy of anti-TNFα agents for the management of Crohn's disease and Behçet's uveitis have encouraged the use of anti-TNFα agents for management of intestinal BD. Although clinical studies with high-quality evidence have not been available, several cases of intestinal BD successfully treated by anti-TNFα agents have been reported [6–14]. These case reports mainly showed clinical efficacy in the short term, although some reports showed mid- and long-term efficacy and improved endoscopic findings [15, 16]. Furthermore, on May 16 2013, adalimumab (ADA) was approved as a therapeutic option for intestinal BD in Japan. Currently, the Research Committee for small bowel inflammation of unknown etiology operated by the Health Labour Sciences Research Grant, titled "Research on Measures for Intractable Diseases", was concerned that the approval of anti-TNFα mAb could dramatically change the therapeutic strategy for intestinal BD. Furthermore, the first edition does not contain information regarding anti-TNFα mAbs and is, therefore, outdated. Therefore, consensus statements for the management of intestinal BD should be adjusted to the current clinical settings, especially regarding the indication of anti-TNFα agents (Table 1).

Methods

An overview of the study

The development of the second edition of consensus statements for the diagnosis and management of intestinal BD consisted of three phases. In brief, in the first phase, literature that reported the efficacy of anti-TNFα monoclonal antibodies (mAbs) in intestinal BD were collected by survey using PubMed with the following key words: "intestine", "Behçet's disease", "anti-TNF", "infliximab" and "adalimumab". In addition, results of a questionnaire-based investigation on the actual treatment situation of intestinal BD by infliximab performed by the Japanese Study Group for a project on Research on Measures for BD operated by the Japanese Ministry of Health, Labour and Welfare in 2012 were referred to. During the second phase, expert panelists discussed areas of disagreement and areas of uncertainty regarding improvements of statements from the first edition and revised some of the clinical statements. During the third phase, the revised clinical statements were rated. Ratings of appropriate methods were developed using a modified Delphi approach, where members of the expert panel rated each part of the statements using a nine-point scale from 9 to 1 (9, strongly agree; 1, strongly disagree). Consensus was defined as a median score of ≥ 7, if the difference between the highest score and lowest score

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Table 1 Consensus statements for the diagnosis and management of intestinal Behçet's disease (second edition), by Research Committee for small bowel inflammation of unknown etiology, and Behçet's Disease Research Committee, Ministry of Health, Labour, and Welfare, Japan

Concept of the second edition of consensus statements

According to increased use of anti-TNFα mAb in inflammatory bowel disease, many cases of intestinal Behçet's disease in which anti-TNFα mAb (infliximab, IFX) showed efficacy also have been reported in Japan. The same tendency was observed in foreign countries that have a high prevalence of Behçet's disease, such as Korea. In 2013, adalimumab, humanized anti-TNFα mAb was approved for intestinal Behçet's disease in Japan. In the second edition, statements have focused on where we should place anti-TNFα mAb for the treatment of intestinal Behçet's disease based on relevant literature and expert panel discussion.[a]

Diagnosis

1. Diagnosis of intestinal Behçet's disease can be made if

   A. There is a typical oval-shaped large ulcer in the terminal ileum, OR

   B. There are ulcerations or inflammation in the small or large intestine, and clinical findings meet the diagnostic criteria of Behçet's disease.[b]

2. Acute appendicitis, infectious enteritis, tuberculosis, Crohn's disease, nonspecific colitis, drug-associated colitis and other diseases that mimic intestinal Behçet's disease should be excluded by clinical findings, radiology, and endoscopy before diagnosis of intestinal Behçet's disease is made.

Assessment of severity

Disease severity should be comprehensively assessed by systemic symptoms (e.g., fever, extra-intestinal manifestations), physical examinations of abdomen (e.g., pain, inflammatory mass, rebound tenderness), depth of ulcers and intestinal complications (e.g., bleeding, stricture, fistula), inflammatory mediators (e.g., CRP, WBC, ESR), and anemia.

Treatment objectives

In the treatment of intestinal Behçet's disease, as well as the improvement of abdominal and extra-intestinal symptoms, the achievement of negative levels of CRP could be desirable. In the long-term prognosis, the prevention of progression to disability and poly-surgery is important.

A. Standard treatment

1. In patients with severe symptoms (i.e., abdominal pain, diarrhea, gastrointestinal bleeding) and complications with deep ulcers confirmed by radiology or endoscopy, corticosteroids should be considered for induction therapy. The initial dose of corticosteroids is 0.5–1 mg/kg per day of prednisolone for l–2 weeks. When clinical improvement is observed, prednisolone should be tapered by 5 mg every week and finally stopped. ADA (approved on May 16, 2013 in Japan) could be considered for induction therapy [160 mg at 0 w, 80 mg at 2 w, 40 mg at 4 w, sub-cutaneously (s.c.)]. In responders, scheduled maintenance therapy should be considered (40 mg s.c. every other week). IFX (not approved yet) could also be considered for induction therapy (5 mg/kg at week 0, 2, and 6). In responders, scheduled maintenance therapy every 8 weeks should be considered. In patients with mild to moderate activity, mesalasine (5-ASA) could be effective for induction therapy. In patients treated with corticosteroids, anti-TNFα mAbs and immunomodulators, infectious disease and neoplasm should be surveyed. After initiation of these therapies, the risk of infectious disease and neoplasm should be monitored continuously.
2. In patients who are induced to clinical remission, 5-ASA and colchicine could be used for maintenance therapy. The optimal dose of 5-ASA for adult patients is 2.25–3 g/day. When sulfasalazine (SASP) is used, the optimal dose is 3–4 g/day.
3. Immunosuppressive agents such as azathioprine (AZA)[c] are indicated when patients are corticosteroid-dependent, corticosteroid-resistant, or anti-TNFα mAb-resistant. The initial dose of AZA is 25–50 mg/day. In patients treated with AZA, adverse effects (e.g., neutropenia and liver dysfunction) should be monitored.
4. Total parenteral nutrition (TPN) is indicated for patients with severe systemic symptoms such as fever and for patients with intestinal complications such as stenosis, fistula, bleeding, and impending perforation. TPN is also indicated for patients who cannot orally intake drugs due to severe oral or upper gastro intestinal lesions. It is usually used for a limited period of time considering the risk of catheter infection and thrombosis. After the patient's condition is improved by TPN, enteral nutrition (EN) could be considered.
5. EN using an elementary diet could be effective for induction therapy. It is indicated in particular for patients with refractory disease, severe activity, and disability such as stricture lesions. When EN is introduced, adherence and quality of life of the patients should be considered.
6. Surgery is indicated for patients in whom improvement is not expected by medications. Patients with severe stricture lesions, perforations, large abscesses, and massive gastrointestinal bleedings have an absolute indication. Patients refractory to medications, and with a low quality of life due to intestinal complications such as fistula, have a relative indication of surgery. Minimum length of resection surgery should be considered.
7. Risk of post-operative recurrence is high in patients with volcano shape deep ulcers and fistulas. Post-operative recurrence often occurs at anastomosis. Although a treatment strategy has not been established that can reduce the risk of post-operative recurrence, considering the high risk of post-operative recurrence and poly surgeries, medication by 5-ASA, immunomodulators, metronidazole, anti-TNFα mAb and EN could be considered for post-operative management.
8. In patients with intestinal Behçet's disease complicated with eye lesions, consultation with ophthalmologists is necessary for their management

B. Optional treatment

- Since there are some case reports showing that spraying of absolute ethanol via endoscope has efficacy for ulcers of intestinal Behçet's, it could be considered in refractory patients.

Table 1 continued

- Expecting the efficacy as an anti-rheumatoid arthritis drug, change from 5-ASA to SASP could be considered in patients with arthritis (especially peripheral arthritis).

The authors state that, (1) most of the consensus statements are based on expert opinions, (2) the consensus statements have not been endorsed by any organizations, (3) the consensus statements need to be prospectively reevaluated, (4) the consensus statements do not cover histopathological diagnosis, and (5) the consensus statements do not have any binding force.

[a] The majority of literature regarding anti-TNFα therapy in intestinal Behçet's disease that is referred to for establishment of the second edition described the efficacy of infliximab. On May 16 2013, ADA was approved for intestinal Behçet's disease. The clinical trial of infliximab in intestinal Behçet's disease is currently in progress in Japan.

[b] Diagnosis of Behçet's disease is according to the Japanese criteria proposed in 2003.

[c] Immunomodulators besides AZA, including 6-mercaptopurine, cyclosporine, tacrolimus and methotrexate could be considered, but consultations with specialists who have sufficient experience are required. When considering the use of these drugs, adverse effects should be monitored.

was <4. For the present study, an expert panel composed of gastroenterologists ($n = 6$), gastrointestinal surgeons ($n = 2$), and rheumatologists ($n = 2$) was established. In addition to the expert panel, a moderator (Hisamatsu, T.) and a professional adviser (Ueno, F.) were involved in the study. The moderator organized discussion by the expert panel and moderated the modified Delphi approach. The moderator searched and reviewed the literature and collected clinical statements. The professional adviser surveyed the process of the modified Delphi approach. The second edition of consensus statements proposed by the expert panel was discussed and then recognized by the Research Committee for small bowel inflammation of unknown etiology operated by a Health Labour Sciences Research Grant, Research on Measures for Intractable Diseases, Japan.

Results

Search for literature on intestinal BD and anti-TNFα mAbs

In the first phase, 15 relevant literature items were collected. This literature included 10 case reports, 3 retrospective analyses of more than one patient in a single institute, 1 letter to the editor, and 1 review article ("Appendix"). To date, no randomized controlled trials of anti-TNFα mAbs for the treatment of intestinal BD have been reported.

Development of the second edition of consensus statement

In the second phase, the expert panel discussed the place of anti-TNFα mAb for the treatment of intestinal BD. Based on the literature found, the clinical experience of experts and results of a questionnaire-based investigation, the expert panel agreed that anti-TNFα mAb treatment should be regarded as a standard therapy for intestinal BD, which was an optional treatment in the first edition. With the recognition of anti-TNFα mAb treatment as a standard therapy, the expert panel also discussed the therapeutic goal of intestinal BD. In the second edition, it was proposed that the achievement of negative levels of C-reactive protein (CRP) levels, in addition to the improvement of clinical symptoms, could be desirable as an objective therapeutic goal. The expert panel also proposed that improvement of long-term prognosis such as reducing the risk of surgery should be set as a final goal in the treatment of intestinal BD. Corticosteroid and anti-TNFα mAb were placed as standard therapies, while the expert panel deemed colchicines, thalidomide, endoscopic therapy, and leukocytapheresis to be experimental therapies.

In the first round of the modified Delphi approach, there were no statements with a median score <7. Although median scores were ≥7, three parts of statements did not obtain consensus because the difference between the highest and lowest score was 4. After discussion by the expert panel, the second round was performed, and then consensus was obtained for all statements. Thus, after a two-round modified Delphi approach, the second edition of consensus statements was finalized.

The authors' stated that limitations of the second edition included (1) most of the consensus statements are based on expert opinions, (2) the consensus statements have not been endorsed by any organizations, (3) the consensus statements need to be prospectively reevaluated, (4) the consensus statements do not cover histopathological diagnosis, and, (5) the consensus statements do not have any binding force.

Discussion

BD involves multiple organs, including the eye, nervous system, skin, genitalia, and gastrointestinal tract. About

3–16 % of patients with BD have gastrointestinal tract involvement [3], while most clinical studies of BD published to date concern the management of mucocutaneous lesions and ophthalmological lesions. However, intestinal BD often causes severe gastrointestinal complications, such as massive bleeding and perforation; therefore, intestinal lesions should be considered a poor prognostic factor. Even in high-prevalence areas such as Japan, Korea, the Middle East, and the Mediterranean region, intestinal BD has been treated empirically because data from the literature regarding management of this condition are scant. The consensus of expert opinion in a high-prevalence area should, therefore, be extremely helpful in daily practice. With this background, the first edition of a consensus for the management of intestinal BD was proposed for the first time in 2007 [5]. However, even after its proposal, conventional therapies have been insufficient for the management of intestinal BD. In the current clinical setting, anti-TNFα mAbs have been used to treat patients with intestinal BD. Reports demonstrating the efficacy of anti-TNFα mAbs for the management of intestinal BD are increasing. Furthermore, ADA was approved for intestinal BD in 2013 after an open-label clinical trial in Japan. With this in mind, it was considered that the first edition of the consensus statement should be updated.

The first edition was established in 2007 by the Japanese Inflammatory Bowel Disease Research Group. In 2011, the Research Committee for small bowel inflammation of unknown etiology was established independently from the Japanese Inflammatory Bowel Disease Research Group. To avoid changes in expert panel members affecting the results, some members of the first edition joined the expert panel of the second edition, which also had discussions with the Behçet's Disease Research Committee as well as the first edition expert panel. Finally, the second edition was evaluated and approved by the Research Committee for small bowel inflammation of unknown etiology composed of experts for gastrointestinal disorders including members of the first edition.

The modified Delphi approach used in the second edition also provided panelists with the opportunity to discuss their judgments between the rating rounds as well as in the first edition. Unfortunately, there is not much evidence for the management of intestinal BD. Therefore, the discussion by the expert panel must make practical consensus statements rather than be a simple rating method. In the process for improving the second edition of the consensus statement, several subjects were discussed. First, the expert panel discussed the validity of the efficacy of anti-TNFα mAb therapy in intestinal BD. To date, no clinical trial for anti-TNFα mAb therapy in intestinal BD with high-quality evidence such as a double-blind, randomized, placebo-controlled trial has been reported. Therefore, the expert panel relied on their clinical experience and clinical case reports. All members agreed that anti-TNFα mAb therapy is effective for intestinal BD. Second, the expert panel discussed where anti-TNFα mAb therapy should be placed in the treatment of intestinal BD. Although anti-TNFα mAb therapy was considered an option therapy in the first edition in 2007 [5], the expert panel recommended anti-TNFα mAb as a standard therapy in the second edition. Third, according to the recommendation of anti-TNFα mAb as a standard therapy, the expert panel discussed whether the goals for medication of intestinal BD should be addressed. The expert panel was concerned about the overuse of anti-TNFα mAb without any objective parameters. Unfortunately, practical clinical activity indexes for intestinal BD (e.g., Crohn's disease activity index for Crohn's disease) have not been established. Endoscopic mucosal healing was also discussed, but it was not agreed on because of the lack of evidence in the literature and an impractical setting. Although evidence that CRP is a practical biomarker to assess disease activity of intestinal BD is insufficient, several reports suggested that CRP could reflect disease activity and disease prognosis [17]. In addition, in Crohn's disease, negative CRP levels are considered a therapeutic goal as well as endoscopic mucosal healing by biologics therapy. In this context, the expert panel proposed "treatment objectives" that were not in the first edition and recommended the monitoring of CRP.

The problems that now confront us are the safety monitoring of anti-TNFα mAb use and the determination of whether anti-TNFα mAb treatment can improve the long-term prognosis of intestinal BD by prospective observation.

Conclusions

The second edition of consensus statements for the diagnosis and management of intestinal BD was established. In the second edition, anti-TNFα mAb treatment was recognized and recommended as a standard therapy for the treatment of intestinal BD.

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Conflict of interest Tadakazu Hisamatsu received a research grant from Ajinomoto Pharmaceuticals CO., LTD. and received lecture fees from Abbvie.

Appendix: literature list of intestinal Behçet's disease and anti-TNFα mAbs treatment

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