表 1. 咽喉頭炎の鑑別診断(文献1より改変)

	急性の経過をとりやすいもの	慢性の経過をとりやすいもの
非感染性または毒素産生に関係するもの	黄色ブドウ球菌毒素性ショック症候群(TSS) 溶連菌毒素性ショック症候群 川崎病 drug fever 物理化学的刺激 重金属製剤(水銀, ヒ素など)の投与	GERDに伴う咽喉酸逆流症 舌咽神経痛 良性・悪性腫瘍
	ベーチェット病 クローン病 SLE 天疱瘡・類天疱瘡 再発性アフタ性咽喉頭炎(原因不明)	
ウイルス性	ライノウイルス アデノウイルス インフルエンザウイルス パラインフルエンザウイルス エンテロウイルス コロナウイルス EBV サイトメガロウイルス HSV VZV 麻疹ウイルス HIV(急性初期感染期)	HIV(無症候期からエイズ期)
細菌性	連鎖球菌(Aβ, Cβ) 黄色ブドウ球菌 インフルエンザ菌 パラインフルエンザ菌 髄膜炎菌 *Chlamydophlia pneumoniae* *Mycoplasma pneumoniae* ジフテリア菌	
	梅毒トレポネーマ 淋菌 *Chlamydia trachomatis* 結核 放線菌症	
真菌性	*Candida albicans*	

る．普通感冒としてのウイルス感染症が原因である場合が最も多く，次いで細菌感染症が多い．刺激性ガスの吸入や火災に伴う気道熱傷などの物理化学的刺激や，重金属製剤(水銀，ヒ素など)投与も原因となる場合がある．

咽喉頭粘膜の発赤以外にみられる病変として(表2)，A群レンサ球菌，アデノウイルス，伝染性単核球症，単純ヘルペスウイルス(herpes simplex virus；HSV)性咽頭炎・扁桃炎では，咽頭粘膜の発赤，リンパ濾胞の発赤・顆粒状腫脹，咽頭側索や口蓋垂の発赤・腫脹のほか，口蓋扁桃，咽頭後壁，上咽頭に白斑や偽膜を認める．ワンサンアンギーナは口腔内に常在する紡錘状桿菌とスピロヘータ(Borrelia vincentii)が過剰に増殖することによって引き起こされる咽頭炎で，扁桃に白黄色の偽膜とともに上極に境界不整で鋭利な深い潰瘍を形成する．文献的には一側性のことが多いとされるが，筆者の経験では両側性にみられることが少なくない(図2)．局所所見に比べて自覚症状は重くなく，微熱，咽頭痛，口臭を伴うが全身状

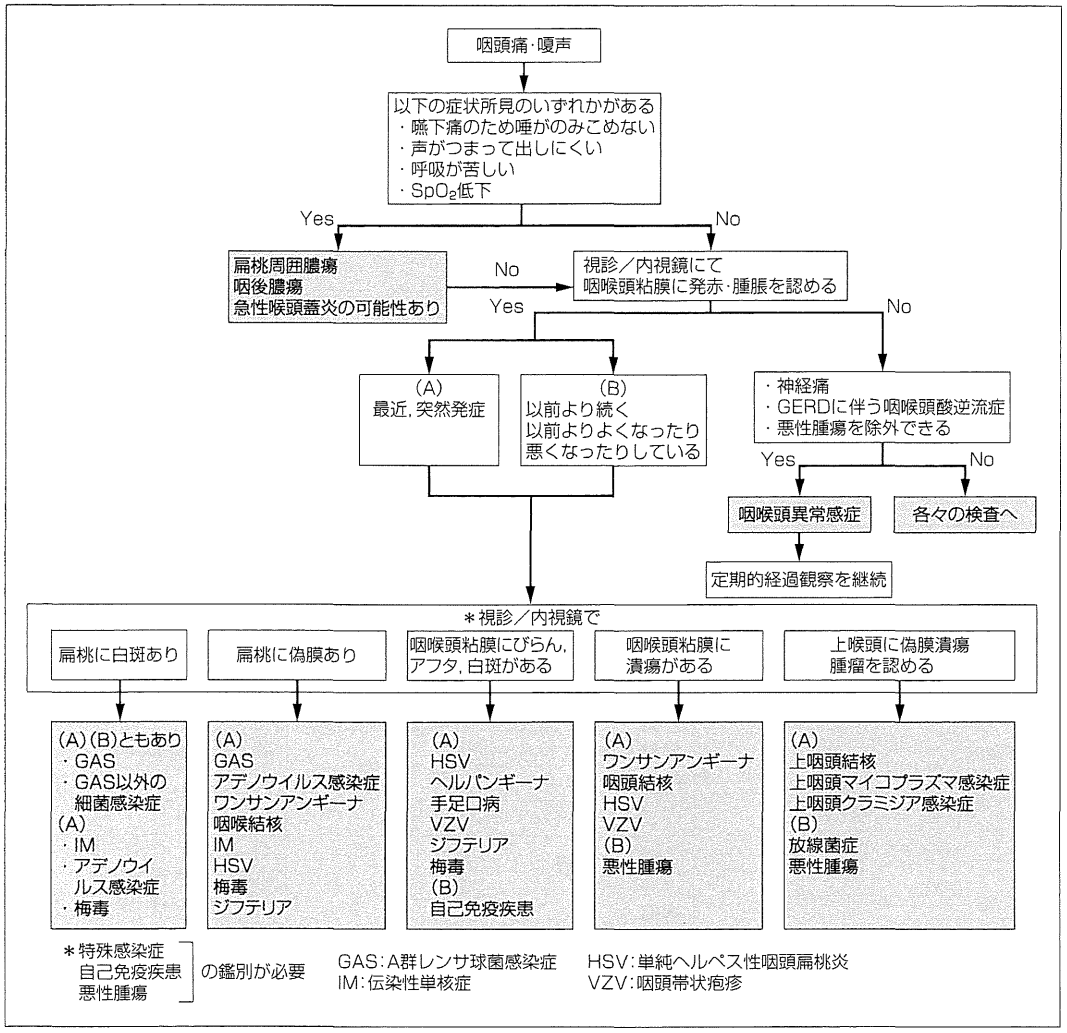


図 1. 咽喉頭炎の診断アルゴリズム(文献 2 より転載)

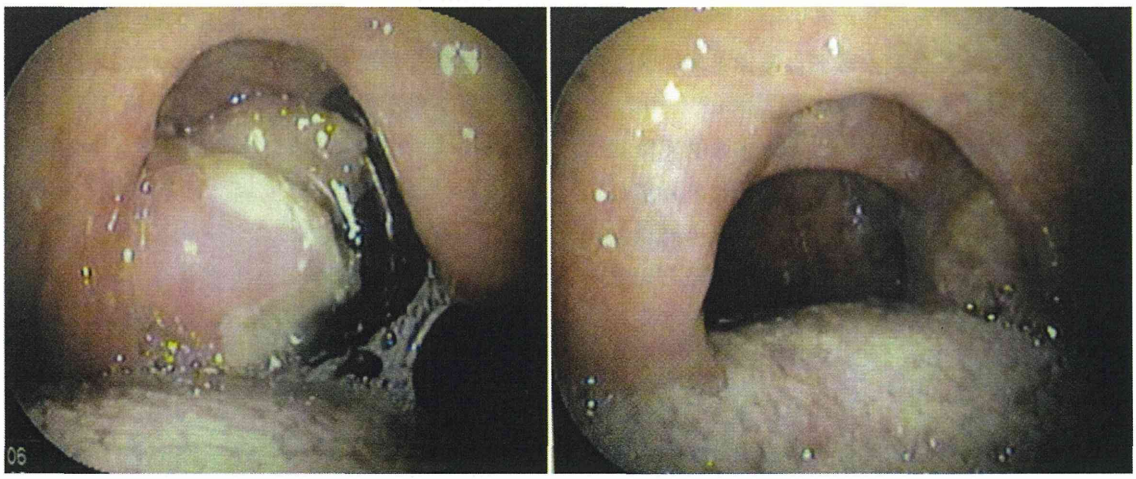
態は良好で，15～30 歳の男性に多い．淋菌は咽頭に無症候性に感染する場合が多いが，時に一般的な急性咽頭炎や扁桃炎で発症する場合がある[3]．

水痘帯状疱疹ウイルス(varicella zoster virus；VZV)の再活性化病変である咽頭帯状疱疹では水疱，アフタ，白苔などが片側性に生じる．三叉神経第 2 枝または第 3 枝と舌咽神経の帯状疱疹では，その領域の咽頭粘膜に集簇して水疱が現れ，破れて不規則な白苔を伴うびらんとなり強い痛みを訴える．三叉神経の帯状疱疹では，同じ神経分布域の顔面や外耳の疱疹がみられる．舌咽神経領域の帯状疱疹では，片側の口蓋扁桃の白い偽膜を伴う発赤腫脹と同側の口蓋に水疱を認める(図 3)[4]．

梅毒，結核，ジフテリアは，それぞれ特徴的な臨床所見を呈する．梅毒では，感染後 3ヶ月頃までの梅毒第 1 期はトレポネーマが侵入した部位に，指頭大までの大きさで暗赤色の軟骨のように硬いしこりが生じ(初期硬結)，数日後には硬結の中央に潰瘍ができる(硬性下疳)．初期硬結・硬性下疳とも痛みがないという特徴がある．感染後 3ヶ月を過ぎた第 2 期では，扁平で若干の隆起があり，青みがかった白または灰色を呈して周囲は薄い赤色の紅暈で囲まれる粘膜斑が生じる．粘膜斑が拡大・融合すると軟口蓋に特徴的な“butterfly appearance”(図 4)[5][6]を呈し，咽頭痛や違和感を訴える．中咽頭結核は口蓋，扁桃，口蓋垂に，初めは粟粒大の結節が生じ，その後潰瘍となり，強い痛みを訴える[7]．肺結核からの二次感染が多い．ジフテリアは，咽頭痛，発熱，全身倦怠感を訴え，灰白色で剝離し難い独特の厚い偽膜が

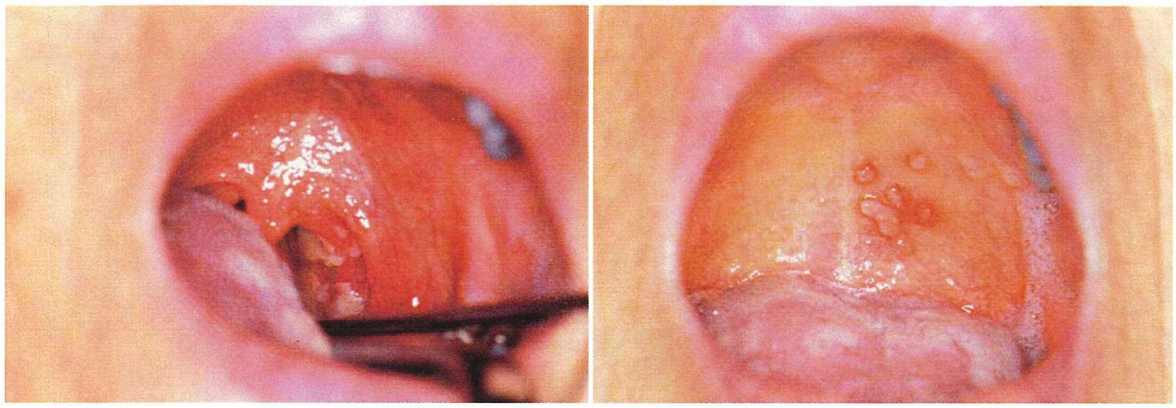
表 2. 臨床症状・所見から推定される原因と臨床診断

咽喉頭粘膜の炎症とともにみられる病変	考えられる原因	臨床診断
口蓋扁桃の膿栓，白斑，偽膜，または潰瘍	A 群レンサ球菌	A 群レンサ球菌性咽頭炎
	A 群レンサ球菌以外の細菌	細菌性咽頭炎
	アデノウイルス	アデノウイルス性咽頭炎
	EBV	伝染性単核球症
	サイトメガロウイルス	伝染性単核球症
	HSV	HSV 咽頭炎・扁桃炎
	VZV	舌咽神経領域の帯状疱疹
	口腔内常在性紡錘状桿菌 およびスピロヘータ(Borrelia vincentii)	ワンサンアンギーナ
	淋菌	淋菌性扁桃炎
	梅毒	第 2 期の咽頭梅毒
	結核	咽頭結核
	ジフテリア	咽頭ジフテリア
咽喉頭のびらん，アフタ，または白斑	HSV	HSV 性咽喉頭炎
	エンテロウイルス	ヘルパンギーナ，手足口病
	コロナウイルス	ヘルパンギーナ，手足口病
	麻疹ウイルス	麻疹
	VZV	三叉神経または舌咽神経領域の帯状疱疹
	梅毒	第 2 期の咽頭梅毒
	結核	咽頭結核
	ジフテリア	咽頭ジフテリア
	自己免疫疾患	ベーチェット病，クローン病，天疱瘡，類天疱瘡など
咽喉頭の潰瘍	梅毒	第 1 期の硬性下疳
	結核	咽頭結核
	悪性腫瘍	扁平上皮癌，悪性リンパ腫など
上咽頭の偽膜，潰瘍，または腫瘤	*C. trachomatis*	上咽頭クラミジア感染症
	M. pneumonia	上咽頭マイコプラズマ感染症
	結核	上咽頭結核
	放線菌	上咽頭放線菌症
	悪性腫瘍	上咽頭癌，悪性リンパ腫など



a．右扁桃所見　　b．左扁桃所見

図 2. ワンサンアンギーナ(23 歳，男性)
両側の扁桃が白黄色の偽膜で覆われ，右扁桃に境界不整で鋭利な深い潰瘍を認めた



a．右扁桃所見　　b．右口蓋の所見

図 3. 舌咽神経領域の咽頭帯状疱疹(59 歳，女性)(文献 4 より転載)
片側の口蓋扁桃の白い偽膜を伴う発赤腫脹と同側の口蓋に水疱を認める

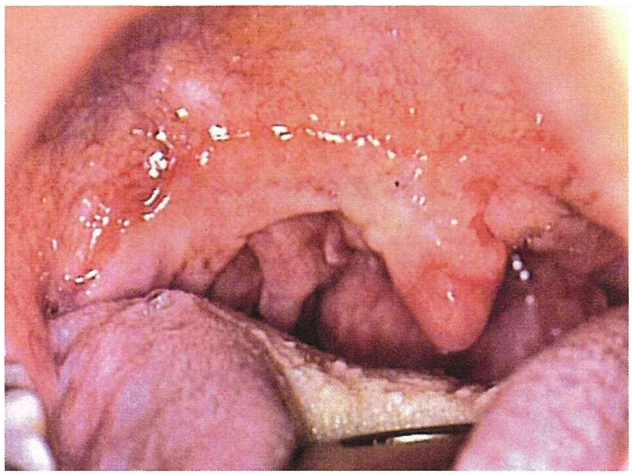


図 4. 梅毒 2 期の咽頭粘膜斑(27 歳，女性)(文献 5 より転載)
粘膜斑が口峡部に沿って弧状に拡大融合して，蝶が羽を広げたような“butterfly appearance”を呈している

口蓋扁桃に生じる．偽膜が喉頭に及ぶと嗄声・犬吠様咳嗽が生じ窒息の危険がある．

エンテロウイルスおよびコロナウイルス感染によるヘルパンギーナと手足口病は，主に乳幼児にアフタを伴う咽頭炎を認める．麻疹では，特徴的な頬粘膜のコプリック斑が現れる前駆期に，コプリック斑様の白斑が口腔咽頭全体に拡大して咽頭痛が生じる場合がある(図 5)[4]．15 歳以上で咽頭病変が著明な場合では，麻疹と思わずに最初に耳鼻咽喉科を受診する可能性があり，注意を要する．

2．慢性咽喉頭炎

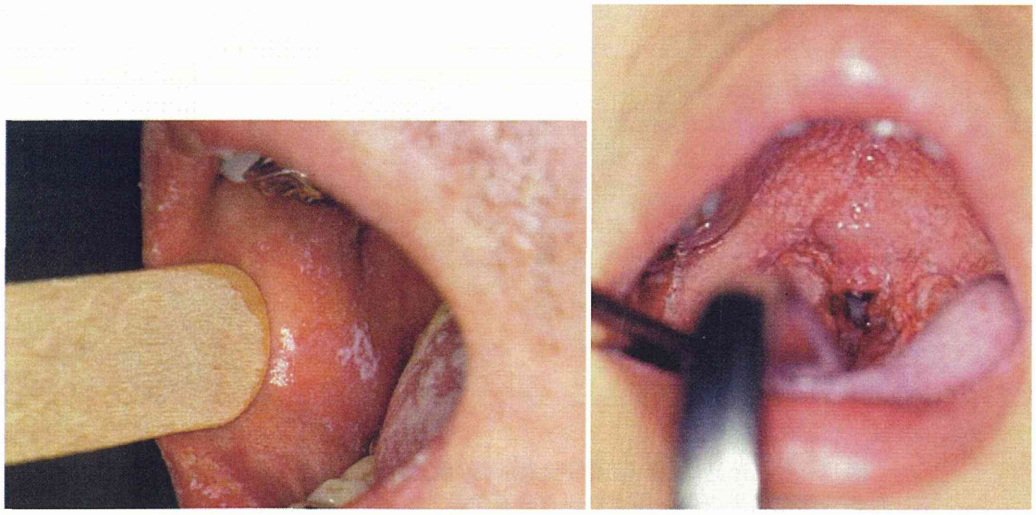
長引く咽頭の不快感，瘙痒感，熱感，後鼻漏感，嚥下時違和感などの咽喉頭異常感，または咳嗽(刺激性の乾性咳嗽が多い)，嗄声，痰，咽頭痛，嚥下痛を訴える．急性咽喉頭炎の遷延化や，喫煙・塵埃・後鼻漏による持続的刺激，逆流性食道炎(GERD)に伴う咽喉頭への酸の逆流などが原因となる．

難治性・再発性に経過する場合には，特殊感染症や自己免疫疾患(ベーチェット病，クローン病，天疱瘡，類天疱瘡など)との鑑別が必要となる．

ヒト免疫不全ウイルス(human immunodeficiency virus；HIV)感染者では，その 40～50％に真菌，細菌，ウイルスなどによる口腔・咽頭の感染症が無症候期以降の比較的早い時期に生じる[8]．特に，HIV 感染を強く示唆するのが口腔・咽喉頭のカンジダ症で，のどの痛みや違和感，嗄声を訴える．HIV 感染者の 8 割ほどを占める 20～40 歳代の男性であれば，積極的に HIV 感染の有無を検査しなければならない．

3．上咽頭炎

咽頭痛，咽頭違和感，後鼻漏，時に耳閉感や鼻汁，鼻閉を訴える．咽頭痛などの咽頭症状を訴えず耳閉感・難聴などの耳症状や，鼻閉・鼻汁などの鼻症状で発症する場合がある．結核，*C. trachomatis*，*M. pneumonia* による上咽頭炎では，特に耳管狭窄症や滲出性中耳炎を合併しやすい．クラミジアは 20 歳前後の感染率が高く，上咽頭の発赤・腫脹またはアデノイドの増大が認められる(図 6)[9]．*M. pneumonia* による上咽頭炎は 20 歳代前半以下，特に年長の学童に多く，発熱，咳嗽，鼻閉といちご状に腫脹したアデノイドを認め



a．33歳，男性にみられら頬粘膜のコプリック斑

b．高熱，咽頭痛，悪心，全身倦怠感を訴えて受診した21歳，女性．口腔咽頭全体に密集して細かく不規則な形の，紅暈を伴う白斑を認めた

図 5. 成人麻疹の咽頭所見(文献4より転載)

る[10]．結核では上咽頭に蒼白な偽膜(図7)[10)~12)]または潰瘍を伴う腫瘤を認める．上咽頭放線菌症は自覚症状に乏しく，悪性腫瘍を疑う腫瘤(図8)を呈する．

検　査

咽喉頭は様々な微生物の侵入門戸であるため，ウイルス，細菌，真菌などあらゆる微生物による多種多様な感染症が生じるが，そのすべての起炎微生物を特定する必要はない．特殊感染症，HSV感染症，ワンサンアンギーナのように一般的な治療が無効であるもの，伝染性単核球症の際のペニ

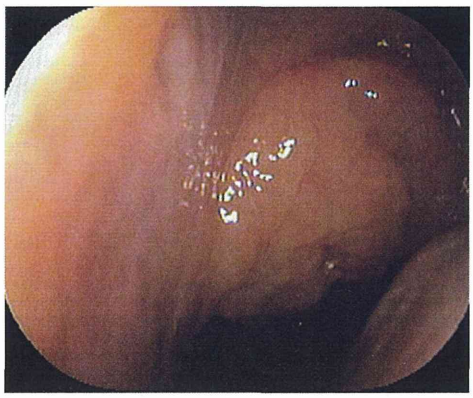
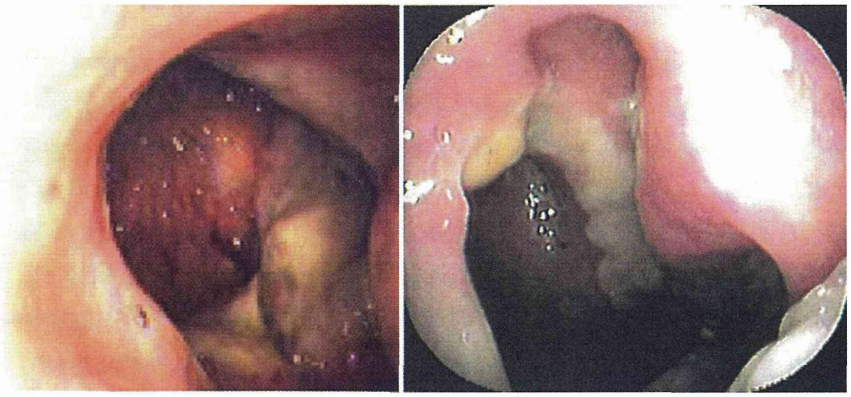


図 6. クラミジアが検出された上咽頭炎
(19歳，女性)(文献9より転載)
右耳の滲出性中耳炎で受診，内視鏡にて上咽頭のアデノイド様腫瘤を認めた



a．29歳，女性．看護師．3週間前からの難治性咽頭痛．左滲出性中耳炎を合併していた(文献11より転載)

b．64歳，女性．1ヶ月前からの難治性上咽頭炎と頸部リンパ節腫脹で紹介された(文献12より転載)

図 7. 上咽頭結核
耳管隆起周囲に蒼白な色調の偽膜を認める

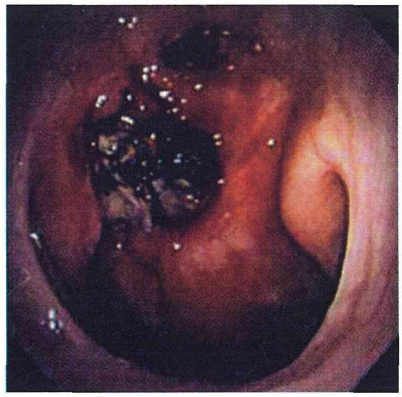


図 8. 上咽頭放線菌症(55歳，男性)(文献10より転載)
痂皮の付着，壊死，潰瘍を伴う腫瘤を認める．悪性腫瘍を疑い行われた上咽頭生検により診断された

表 3. 鑑別すべき原因微生物とその診断に必要な臨床検査

原因微生物	診断に必要な臨床検査
インフルエンザウイルス	病変部スワブのインフルエンザウイルス迅速検査
EBV 初感染(伝染性単核球症)	血清 EBV 抗体価[#1]
アデノウイルス	病変部スワブのアデノウイルス迅速検査
HSV 初感染(HSV 性咽頭炎・扁桃炎)	血清 HSV 抗体価[#1]，病変部スワブのモノクローナル抗体による蛍光抗体法
VZV(帯状疱疹)	血清 VZV 抗体価[#2]，病変部スワブのモノクローナル抗体による蛍光抗体法
サイトメガロウイルス初感染(伝染性単核球症)	血清サイトメガロウイルス抗体価[#1]
麻疹ウイルス	血清麻疹ウイルス抗体価[#1]
風疹ウイルス	血清風疹ウイルス抗体価[#1]
HIV	血清 HIV ウイルス抗体価[#3]
口腔内常在性紡錘状桿菌およびスピロヘータ(ワンサンアンギーナ)	病変部スワブの鏡検と細菌培養検査
A 群レンサ球菌	病変部スワブの A 群レンサ球菌迅速検査 または細菌培養検査(保険収載では同日にどちらか一方のみ可)
淋菌	病変部スワブの核酸増幅検査(SDA，TMA，PCR のいずれかを選択[#4])
C. trachomatis	
M. pneumonia	病変部スワブの核酸増幅検査(PCR)
梅毒	病変部スワブの鏡検(直接法)，梅毒血清反応(RPR および TPHA)
結核	病変部スワブの抗酸菌染色，分離培養，核酸増幅検査(PCR または LAMP)，血清インターフェロン-γ遊離試験(クオンティフェロンなど)
放線菌	組織切片からの硫黄顆粒の検出，またはアクチノミセスを想定した嫌気条件下で保存，培養による．一般培養では同定されにくい
ジフテリア菌	偽膜病変部スワブの塗抹染色，分離培養，PCR
C. albicans	病変部スワブの鏡検，真菌分離培養

[#1]急性期血清からの IgM 抗体の検出，ペア血清での IgG 抗体陽転または抗体価の有意の上昇による
[#2]ペア血清での補体結合反応抗体価，または IgG 抗体価の有意の上昇による
[#3]血清 HIV 抗体のスクリーニング検査を行い，陽性の場合には抗体確認検査または HIV-RNA 定量検査で確定する[13)14)]
[#4]核酸増幅法の SDA(BD プローブテック ET CT/GC®)，TMA(アプティマコンボ 2®)，PCR(コバス 4800 システム CT/NG®)のいずれかを用いる．SDA と TMA は咽頭または上咽頭からスワブを，PCR は咽頭うがい液を採取して検体とする．臨床的に淋菌とクラミジアの判別が難しいこと，同時感染もあることから，診断の際は淋菌とクラミジアの両方を同時に検査する

シリン系・セフェム系など抗菌薬など使用禁忌薬があるもの，そして他者への感染が問題になるものについて鑑別し診断へ導く．表 3[13)14)]に鑑別すべき原因微生物とその診断に必要な臨床検査を挙げる．

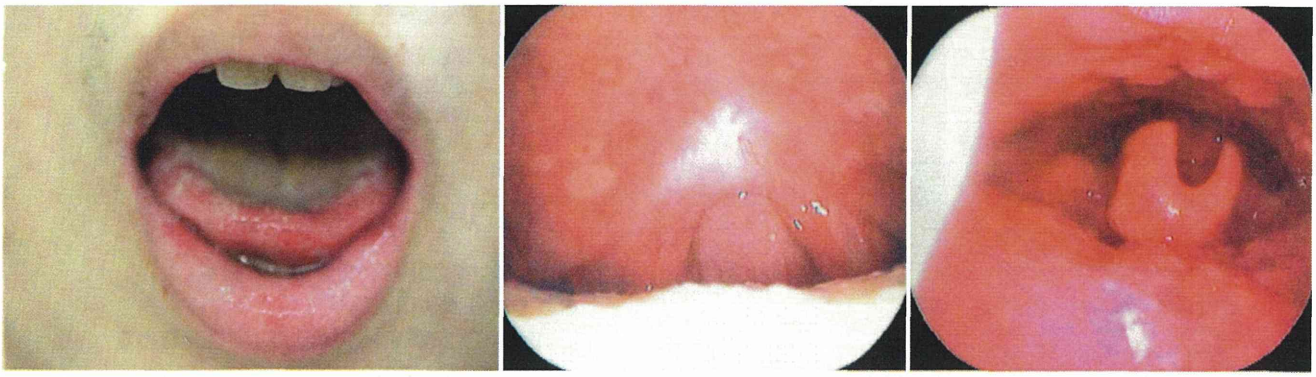
咽喉頭炎例の大半は予後良好であるが，咽頭痛や嗄声を訴えて受診する患者の中に扁桃周囲膿瘍，咽後膿瘍，急性喉頭蓋炎などの，頻度は少ないが適切な対応の遅れが重篤な結果を招くおそれがある緊急疾患や，難治性・反復性に経過する疾患，悪性腫瘍が含まれることを常に念頭に置いて鑑別を勧める必要がある．

症例提示

症例 1：26 歳，男性

主　訴：口内痛，咽頭痛，嚥下困難

経　過：3 週間前から舌と歯齦部内側のひりひりとする痛みと咽頭痛が生じる．1 週間前から痛みが悪化し近医を受診，処方された抗菌薬等を服用したが改善せず摂食困難となり，当科へ紹介入院となった．初診時，下口唇・舌，口蓋から口蓋弓，喉頭蓋(図 9)[2)15)]に複数のアフタを認めアシクロビルの点滴を開始した．同日の血液検査所見は，WBC 14600/ul(好中球 88%，単球 4%，リンパ球



a：舌尖部と下口唇にびらんと複数のアフタを認める　b：口蓋から口狭部に複数のアフタを認める．　c：喉頭蓋舌面，下咽頭粘膜に複数のアフタを認める

図 9. 症例 1 の口腔・咽頭所見(文献 2，15 より転載)

8%)，CRP 13.64 mg/dl，梅毒(−)，HSV-IgM(−)，HSV-IgG(−)，HIV 抗体(−)．問診で，眼・皮膚・消化器症状の有無を確認したところ，前月から間欠的に腹痛と血便があった．入院 2 日目に下痢と血便が始まり，4 日目に行った下部消化管内視鏡検査にてクローン病が疑われ(後に確定診断された)，内科へ転科となった．

＜Point と Pitfall＞咽頭に有痛性のアフタが多発する疾患として，① HSV 咽頭炎，咽頭帯状疱疹，ヘルパンギーナ，手足口病などのウイルス感染症，② ベーチェット病，クローン病，潰瘍性大腸炎，天疱瘡，類天疱瘡などの自己免疫疾患，③ 再発性アフタ性口内炎などの原意不明の咽頭アフタが挙げられる[2)15)]．

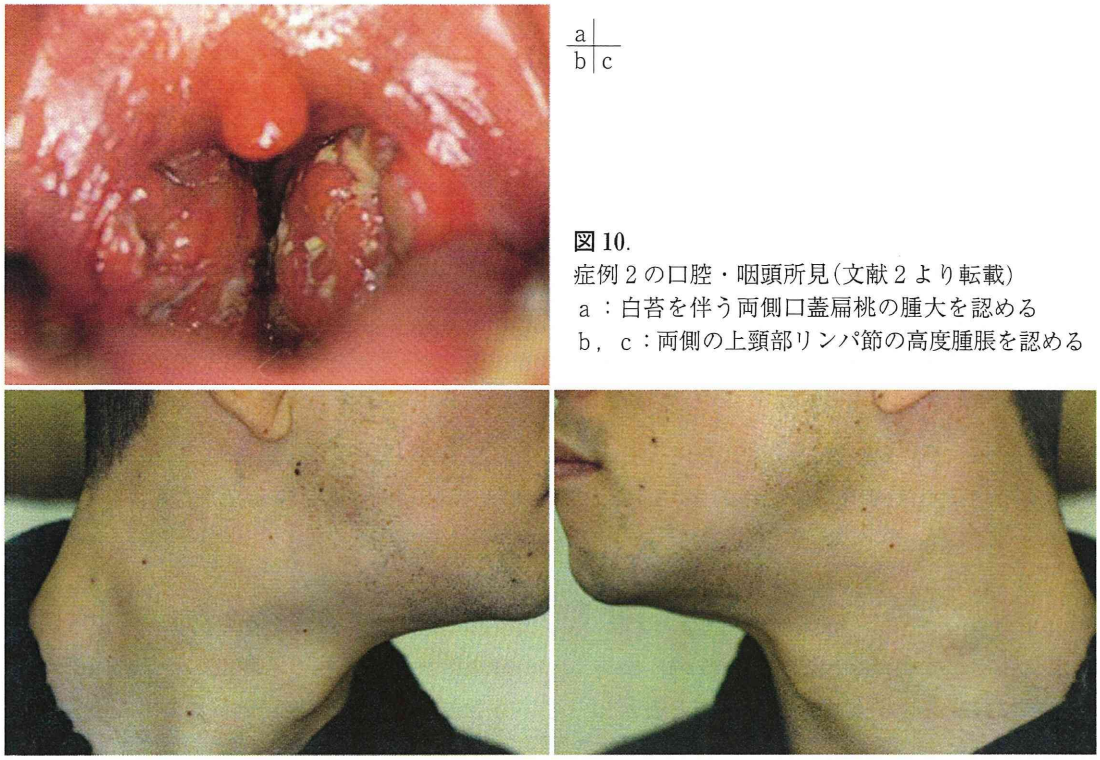
① はほとんどが 1〜2 週間で改善するのに対して，②③ は難治性，再発性に経過する(免疫抑制者や HIV 感染者では ① であっても難治性，再発性に経過する場合がある)．思春期以降の咽頭の多発性アフタでは，頻度は少ないが常に ②③ の可能性を念頭に置いた対応が求められる．HSV 咽頭炎を考え抗ヘルペスウイルス薬を投与しても改善がみられない場合は ②③ を，目のかすみや充血，皮疹，下痢や腹痛，陰部痛がある場合は ② を鑑別しなければならない．臨床所見，経過，生検などから ② が否定されるまでは，ステロイドの全身投与は極力控えるべきと考える．

症例 2：36 歳，男性

主　訴：頸部リンパ節腫脹，難治性の咽頭痛，発疹

経　過：7 週間前から頸部リンパ節腫脹あり，近医内科で血液検査と頸部・胸部・腹部 CT で精査されたが原因が特定されなかった．3 週間前に全身に発疹が，その数日後から扁桃炎が生じて耳鼻科を受診，抗菌薬が処方されたが，扁桃炎・頸部リンパ節腫脹は改善しなかった．2 週前に別の医院でも抗菌薬を処方され，1 週間前に再び体幹と四肢に発疹が生じ扁桃炎も改善しないため，精査目的で紹介となった．初診時，発疹は消失していたが，口蓋扁桃の白苔を伴う発赤，腫脹(図 10-a)[2)]，上咽頭のびまん性発赤，舌扁桃の点状白斑伴う発赤，両側上頸部の高度リンパ節腫脹(図 10-b，c)[2)]を認めた．同日の血液検査所見は，CRP 0.68 mg/dl，LDH 352 IU/l と軽度上昇を認めるほかは，血算・生化学検査で異常はなかった．難治性の経過から初診時に口蓋扁桃から生検を行い，T cell lymphoma と診断された．初診時の EB ウイルス(Epstein-Barr virus；EBV)抗体価は，VCA IgM＜10，VCA IgG 10，EBNA＜10 と EBV 初感染が示唆され，HIV 抗体は陰性であった．扁桃細菌培養では C 群溶連菌 3+，黄色ブドウ球菌 3+が同定された．追加して行った HTLV-1 抗体検査も陰性であった．

＜Point と Pitfall＞経過の長い，または治療に抵抗して遷延する咽頭痛，嚥下痛，嗄声を訴える場合には，上咽頭癌，中咽頭癌，下咽頭癌，喉頭癌，ワルダイエル咽頭輪の悪性リンパ腫，などの悪性疾患を鑑別・除外しなければならない．



a
b c

図 10.
症例 2 の口腔・咽頭所見(文献 2 より転載)
a：白苔を伴う両側口蓋扁桃の腫大を認める
b，c：両側の上頸部リンパ節の高度腫脹を認める

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Original article

Efficacy and safety of metronidazole injection for the treatment of infectious peritonitis, abdominal abscess and pelvic inflammatory diseases in Japan

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ABSTRACT

Although metronidazole (MNZ) has been used worldwide for more than 4 decades as a standard therapy for trichomoniasis, anaerobic and amebic infections, resistance to MNZ is still low. MNZ is available as oral, intravenous, and vaginal formulations, but the intravenous formulation of MNZ has not been approved in Japan. We conducted a phase 3 study to evaluate the efficacy and safety of intravenous MNZ combined with ceftriaxone (CTRX) in Japanese subjects with infectious peritonitis, abdominal abscess or pelvic inflammatory diseases (PIDs) to obtain regulatory approval. A combination of MNZ/CTRX at doses of 500 mg 3 or 4 times a day/1 or 2 g twice a day was administered intravenously to a total of 38 hospitalized subjects. MNZ/CTRX was well tolerated and exhibited excellent clinical and bacteriological efficacy with clinical efficacy rates of 100% (20/20) in infectious peritonitis or abdominal abscess subjects and 90.0% (9/10) in PID subjects, and the eradication rates in infectious peritonitis or abdominal abscess subjects and PID subjects were 100% (16/16) and 100% (4/4), respectively, at the test of cure. MNZ/CTRX was effective in 1 subject in whom a metallo-β-lactamase-producing *Bacteroides fragilis* strain (MIC of MNZ, 2 μg/ml) was identified. The most common treatment-related adverse event was diarrhea (23.7%), followed by nausea (5.3%). No new safety signals were identified. MNZ/CTRX demonstrated excellent efficacy and was well tolerated in Japanese infectious peritonitis, abdominal abscess and PID subjects. This treatment regimen can be useful for anaerobic infections.

Clinical registration number: NCT01473836.

1. Introduction

Metronidazole (MNZ) is a nitroimidazole antimicrobial agent with a potent anti-anaerobic, amebicidal, and antiprotozoal activity. Intravenous (IV) MNZ (MNZ-IV) has been used worldwide for more than 30 years as the standard therapy for the treatment of trichomoniasis, anaerobic and amebic infections [1–5]. Harrison's Principles of Internal Medicine and the Sanford Guide to Antimicrobial Therapy recommend the use of MNZ-IV for the treatment of infections involving commonly encountered anaerobic gram-negative rods [6] and anaerobic infections [7] respectively. The guideline of the Infectious Diseases Society of America (IDSA) for the Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children, the 2010 Sexually transmitted disease treatment guidelines of the Centers for Disease Control and Prevention (CDC), and the IDSA practice guidelines for the diagnosis and management of skin and soft-tissue infections [8–10] also recommended the use of MNZ for various infections.

MNZ-IV has not been developed in Japan. Antimicrobial agents presently used for the treatment of anaerobic infections in Japan are penicillins, β-lactam/β-lactamase inhibitor combination drugs, and some cephalosporins, carbapenams, and clindamycin. However, the emergence of resistance to penicillins, cephalosporins and clindamycin among clinically isolated pathogenic anaerobes has raised great concern [11–13]. In recent years, a high prevalence of resistance to clindamycin has been observed among the *Bacteroides*

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fragilis group and non-*fragilis Bacteroides* spp., which are the most common anaerobes isolated from intra-abdominal infections, as well as *Prevotella* spp., a causative pathogen of aspiration pneumonia [14,15]. Decreased susceptibility and the emergence of resistance to carbapenems among the *B. fragilis* group and non-*fragilis Bacteroides* spp. have also been reported [16].

Although MNZ has been used as a therapeutic drug for infections for longer than 45 years, the rate of resistance to MNZ among anaerobes is still generally low. Therefore, MNZ is still successfully used for the treatment of anaerobic infections caused by *Bacteroides* spp., *Fusobacterium* spp., and *Clostridium* spp [17].

Infectious anaerobic diseases often result in a serious condition and treatment with appropriate antimicrobials is crucial, because patients are highly compromised when the primary disease is severe. It is desirable that MNZ-IV would also be available in Japan for the treatment of severe infectious diseases in hospitalized patients who cannot take oral medication.

We planned this phase 3 study to evaluate the efficacy and safety of MNZ-IV administered at a dose of 500 mg 3 times a day (TID), or 4 times a day (QID) in severe cases, to Japanese adult patients with infectious peritonitis, abdominal abscess or PID in combination with IV ceftriaxone (CTRX).

2. Subjects and methods

This study was conducted in accordance with the International Conference on Harmonisation of Good Clinical Practice Guidelines, the principle of the Declaration of Helsinki, and all applicable laws and regulations at 15 medical centers nationwide in Japan between November 2011 and October 2012. The protocol was reviewed and approved by the Institutional Review Boards of all participating study sites. All subjects provided written informed consent before enrollment.

2.1. Study design

This multicenter, non-randomized, unblinded, non-comparative phase 3 study was designed to investigate the safety and efficacy profile of MNZ-IV in Japanese subjects with infectious peritonitis, abdominal abscess or PID in combination with CTRX. A Data Review Committee (DRC) was organized as an independent organization to perform objective and unified efficacy evaluation based on the clinical condition and diagnostic imaging findings. All subjects received 500 mg MNZ administered by intravenous infusion over 20 min TID (or QID in subjects with refractory or severe infection) for 3–14 days in general. At the investigator's discretion, the duration of treatment could be prolonged for up to 21 days depending on the subject's condition. All subjects received CTRX as a combination drug for the same period as MNZ-IV. CTRX, a 3rd-generation cephalosporin with broad-spectrum activity against aerobic bacteria is widely used in Japan and its efficacy and safety profiles are well established. Overseas textbooks and guidelines recommend MNZ combined with agents that have antibiotic activity against aerobic pathogens, and for infectious peritonitis or abdominal abscess subjects, the target of this study, MNZ combined with 3rd generation cephalosporin antibacterial drugs, because infections caused by anaerobic pathogens, the target diseases of this study, are often mixed infections including aerobic pathogens, and MNZ is not effective against them. Since CTRX can be given to subjects once a day, it is considered useful in terms of decreasing the burden on subjects. We therefore decided to use CTRX as the combined drug. MNZ-IV was studied based on the following: (1) The safety and efficacy of MNZ-IV has been demonstrated; and (2) the development of MNZ-IV was requested by the committee on "Unapproved Drugs and Indications with Unmet Medical Needs" under the Ministry of Health, Labour, and Welfare of Japan, because it is an unapproved drug with high medical needs. As a result of a consultation with the Pharmaceutical and Medical Devices Agency of Japan, the target number of subjects who meet the eligibility criteria and receive the test drugs was set at 30, provided that we could enroll at least 7 subjects in whom bacterial transition could be evaluated with more than 80% probability, since the detection rate of causative pathogens was assumed to be approximately 30%.

2.2. Eligibility criteria

Male and female subjects (for pelvic infections, subjects had to be female) aged 16 years or older who had been diagnosed as having infectious peritonitis, abdominal abscess or PID, required hospitalization, and initial IV antibacterial therapy were eligible.

The diagnostic criteria for infectious peritonitis or abdominal abscess included: confirmed infectious peritonitis or abdominal abscess based on the presence of symptoms and signs of an inflammatory response (fever, increased white blood cell [WBC] count, CRP elevation), imaging findings, and the abdominal signs and symptoms (lower abdominal pain, lower abdominal tenderness, upper abdominal pain, upper abdominal tenderness, abdominal rebound, abdominal guarding, nausea, vomiting, decreased appetite, abdominal distension, diarrhea, constipation, drainage, or abscess), and meeting either of the following criteria: 1) planned (or performed within the previous 24 h) drainage of infective sites; and 2) for postoperative infectious peritonitis or abdominal abscess, confirmed gastrointestinal tract secretion or purulent discharge from an indwelling drain.

The diagnostic criteria for PID and related diseases (endometritis, myometritis, adnexitis, salpingitis, oophoritis, parametritis, pelvic peritonitis, pelvic abscess, Douglas' abscess, perihepatitis, and perihepatic abscess) included: (1) one of the following symptoms should be observed: 1) lower abdominal pain or lower abdominal tenderness; 2) uterus/uterine adnexa pain or uterus/uterine adnexa tenderness; and 3) hypochondrial pain or hypochondrial tenderness; (2) negative for *Chlamydia trachomatis*; (3) once the above criteria are satisfied, one of the following 6 conditions should be observed: 1) fever $\geq$37 °C (axillary); 2) WBC count > upper limit of normal range; 3) CRP > upper limit of normal range; 4) purulent discharge or pus observed by culdocentesis or laparoscopy; 5) pelvic abscess confirmed by ultrasonography; and 6) positive for *Neisseria gonorrhoeae*.

Exclusion criteria included the following: subjects who had undergone surgery for perforation of the digestive tract within 12 h, or who had undergone surgery for perforation of gastroduodenal ulcers within 24 h; subjects with suspected or confirmed simple appendicitis, necrotizing pancreatitis, infectious mononucleosis, non-infectious peritonitis, or non-infectious endometriosis; subjects who did not undergo appropriate drainage; subjects expected to be cured only by the surgical procedures (e.g., drainage) without antimicrobial treatment; subjects who had open abdominal cavity drainage; subjects with hypersensitivity to, intolerance of or another contraindication to MNZ or CTRX or other cephem antibiotics; subjects with alcohol abuse; subjects with severe renal dysfunction; subjects with hepatic dysfunction; subjects with severe underlying disease or other complications; subjects who required additional systemic antibiotics; subjects who had received treatment with systemic antibiotics within 7 days before the study; subjects who had already received MNZ for the disease; subjects whose causative pathogens were insusceptible to MNZ; and pregnant or lactating women.

The following concomitant medications were prohibited up to the test of cure (TOC) assessment: systemic antibiotics (oral, injection); human immunoglobulin; colony-stimulating factor;

corticosteroids; continuous use of analgesic antipyretics; other investigational drugs or medical devices; and anti-malignant tumor agents.

2.3. Clinical and radiologic assessments

The primary efficacy endpoint was the clinical response assessed by the DRC at the end of treatment (EOT) and TOC (1 week after EOT). Clinical efficacy was mainly assessed based on the evaluation of clinical signs and symptoms, body temperature, WBC count, CRP, and diagnostic radiographic imaging findings. The clinical response was evaluated as "effective (cured or improved)" if all of the following criteria were met: (1) resolution (cure) or improvement of all inflammatory and abdominal findings, and/or imaging abnormalities that were observed at the start of the study, at the assessment time point, and (2) treatment with other antibiotics was not required during the study or after the assessment time point. The clinical response was evaluated as "ineffective" if either of the following criteria were met: (1) the requirements for "effective" assessment were not satisfied; or (2) the treatment failed and other systemic antibiotic therapy was applied to treat the target disease. The clinical response was evaluated as "indeterminate" if clinical efficacy assessment was difficult due to missing data or other reasons.

2.4. Bacteriological assessment

The secondary efficacy endpoint was the bacteriological response assessed by the DRC on Day 4, EOT, and TOC. At the baseline visit, all subjects provided clinical specimens (infection sites), which were sent to a central laboratory for culture and the isolated pathogens were tested for susceptibility according to the procedures of the Clinical and Laboratory Standards Institute at baseline, Day 4, EOT, and TOC. The specimens from PID subjects (intrauterine materials, puncture fluid from Douglas' pouch, or a purulent discharge) were also submitted for detection of *C. trachomatis*, *N. gonorrhoeae*, or *Mycoplasma genitalium*, *M. hominis* using antigen tests at baseline, EOT, and TOC.

The bacteriological response was assessed as "eradication" if the original pathogen was not identified in the specimens; "presumed eradication" if evaluable specimens were not obtained from a focus of infection; "colonization" if an organism was isolated from a subject who had no signs or symptoms of infection; "persistence" if the original pathogen remained in the specimens; "presumed persistence" if a culture was difficult or was not done in subjects who were judged to be clinical failures and persistence of the original pathogen was presumed; "replacement bacterium" if the original pathogens were eradicated by treatment but other new pathogens had appeared in the same specimen with symptoms or findings of infection; "superinfection" if a pathogen other than the original pathogens was isolated from a specimen taken while the subject was on therapy and who had signs and symptoms of infection; "recurrence" if the original pathogen was isolated from a specimen culture taken after the TOC visit; and "indeterminate" if a specimen was not assessed according to the above-mentioned criteria for various reasons.

2.5. Safety assessment

Safety data were obtained from the findings of clinical signs/symptoms, physical examinations, vital signs, and laboratory data up to TOC. The causality and severity of the adverse events were evaluated by the investigators (or sub-investigators), based on the MedDRA terminology.

2.6. Statistical analysis

Efficacy analyses were mainly conducted on the Clinical Per Protocol Set (CPPS) and the Bacteriologic Per Protocol Set (BPPS). The CPPS consisted of all subjects in the Full Analysis Set (FAS) who had no significant protocol violations and who underwent the prescribed evaluations during the observation period as specified in the protocol. The BPPS consisted of all subjects in the CPPS in whom causative pathogens were identified by culture and antigen tests at baseline.

The primary endpoint was the clinical efficacy assessed by the DRC at EOT and TOC. As the primary analysis of the primary endpoint, the efficacy rate and its 95% confidence interval (CI) were calculated at the TOC in the CPPS. The efficacy rate and its 95% CI were also calculated for infectious peritonitis or abdominal abscess and for PID.

For analysis of the bacteriological response, the secondary endpoint, assessed by the DRC, the eradication rate and its 95% CI were calculated for the BPPS.

Safety analysis was performed in the "Safety Analysis Set," the population of subjects who received at least 1 dose of the study drug.

3. Results

3.1. Subject disposition

A total of 38 subjects were enrolled at 15 medical centers in Japan and all of them received the study medication. Of these, 6 subjects (15.8%) discontinued the study (Table 1). Among the total of 38 subjects, 23 were diagnosed as having infectious peritonitis or abdominal abscess and 13 with PID. Two subjects were judged to have a disease not included in this study; 1 subject was diagnosed as having lumbar disc herniation by the investigator after enrollment and the other as having suspected PID (non-infectious disease) by the DRC. Since 3 of the 23 infectious peritonitis or abdominal abscess subjects in the FAS were excluded because they had received prohibited concomitant medications (2 subjects) or lacked the minimum 3 days of dosing (1 subject), the CPPS included 20 subjects with infectious peritonitis or abdominal abscess. The

Table 1
Subject disposition and analysis set.

	Total	Diagnosis	
		Infectious peritonitis or abdominal abscess	PID
Subject			
Enrolled and treated	38[a]	23	13
Completed	32[b](84.2)	22 (95.7)	9 (69.2)
Discontinued	6 (15.8)	1 (4.3)	4 (30.8)
Deviation of inclusion criteria	1[c] (2.6)	0	0
Insufficient efficacy	1 (2.6)	0	1 (7.7)
Adverse event	4 (10.5)	1 (4.3)	3 (23.1)
Not related to the study drug	3 (7.9)	0	3 (23.1)
Related to the study drug	1 (2.6)	1 (4.3)	0

Values represent the number (%) of subjects.
PID: pelvic inflammatory disease.
[a] Thirty-eight subjects included 2 subjects who were judged by the Data Review Committee to have a disease not included in the study and who did not have infectious peritonitis, abdominal abscess or PID.
[b] One subject was diagnosed as having suspected PID (non-infectious disease) by the DRC and did not have infectious peritonitis, abdominal abscess or PID.
[c] The subject was diagnosed as having lumbar disc herniation by the investigator after enrollment and did not have infectious peritonitis, abdominal abscess or PID.

BPPS included 17 subjects with infectious peritonitis or abdominal abscess in whom baseline causative pathogens were identified by culture. Since 3 of the 13 PID subjects in the FAS were excluded because they met the exclusion criteria (2 subjects) or lacked the minimum 3 days of dosing (1 subject), the CPPS included 10 subjects with PID. The BPPS included 4 subjects with PID in whom the baseline causative pathogens were identified by culture.

The baseline demographic characteristics of the subjects are summarized in Table 2.

The details of the diagnoses in the CPPS are shown in Table 3. Eleven of 20 infectious peritonitis or abdominal abscess subjects had both abdominal abscess and infectious peritonitis. Among 10 PID subjects, 5 subjects had an abscess.

The average duration of treatment with MNZ-IV was 5.8 days (range: 3–9 days) for infectious peritonitis or abdominal abscess subjects and 8.3 days (range: 5–14 days) for PID subjects in the CPPS. Most subjects received 500 mg of MNZ-IV TID. Only 2 subjects in the CPPS (1 subject with both infectious peritonitis and abdominal abscess and 1 subject with PID) received MNZ-IV QID.

At baseline, 29 causative pathogens were identified in 21 subjects (70.0%) in the CPPS (Table 4). Among infectious peritonitis or abdominal abscess subjects, 9 subjects had mixed infections with anaerobic and aerobic pathogens, 3 subjects had anaerobic infections, and 5 subjects had aerobic infections. For PID subjects, 2 subjects had mixed infections with anaerobic and aerobic pathogens and 2 subjects had aerobic infections. The major causative anaerobic pathogens identified at baseline were *B. fragilis* (5 strains), *Parvimonas micra* and *Bacteroides thetaiotaomicron* (2 strains each) in the CPPS.

Table 2
Demographic characteristics.

Group	FAS	CPPS	BPPS
Infectious peritonitis or abdominal abscess			
Number of subjects	23	20	17
Sex			
Male	14	12	11
Female	9	8	6
Age (years)			
16 – 44	6 (26.1)	6 (30.0)	4 (23.5)
45 – 64	8 (34.8)	8 (40.0)	8 (47.1)
65 – 74	5 (21.7)	4 (20.0)	4 (23.5)
75 – 79	4 (17.4)	2 (10.0)	1 (5.9)
Mean ± SD	55.5 ± 16.3	52.7 ± 15.6	53.6 ± 13.7
Range	25 – 78	25 – 78	25–75
Weight (kg)			
≤45 kg	2 (8.7)	2 (10.0)	1 (5.9)
>45 kg	21 (91.3)	18 (90.0)	16 (94.1)
Mean ± SD	64 ± 14.3	64.4 ± 14.8	65.6 ± 14.9
Range	44.0–108.5	44.0–108.5	45.0–108.5
PID			
Number of subjects	13	10	4
Sex			
Female	13	10	4
Age (years)			
16–19	1 (7.7)	1 (10.0)	0
20–29	1 (7.7)	0	0
30–39	5 (38.5)	4 (40.0)	2 (50.0)
≥40	6 (46.2)	5 (50.0)	2 (50.0)
Mean ± SD	39.4 ± 12.8	41.3 ± 13.2	39.0 ± 1.8
Range	19 – 67	19 – 67	37 – 41
Weight (kg)			
≤45 kg	2 (15.4)	2 (20.0)	0
>45 kg	11 (84.6)	8 (80.0)	4 (100)
Mean ± SD	55.1 ± 13.2	54.5 ± 14.5	63.1 ± 19.3
Range	40.0–90.5	40.0–90.5	45.3–90.5

FAS: full analysis set; CPPS: clinical per protocol set; BPPS: bacteriologic per protocol set; PID: pelvic inflammatory disease.

Table 3
Details of diagnosis in the CPPS.

Diagnosis	Infection site	*N* = 30
Infectious peritonitis or abdominal abscess		20
Abdominal abscess	Appendix, peritoneal cavity, mesentery, sigmoid colon, perihepatic area, ascending colon	6
Abdominal abscess, infectious peritonitis	Appendix, peritoneal cavity, peritoneum, douglas' pouch, small intestine, colon, stomach, others	11
Infectious peritonitis	Peritoneum, small intestine, sigmoid colon, appendix	3
PID		10
Douglas abscess, pelvic peritonitis, tubo-ovarian abscess	Douglas' pouch, pelvic peritoneum, bilateral uterine, adnexia	1
Adnexal abscess, adnexitis, pelvic peritonitis	Right adnexia, pelvic peritoneum	1
Adnexal abscess, pelvic peritonitis	Left adnexia, pelvic peritoneum	1
Adnexitis, endometritis, pelvic peritonitis	Left adnexia, uterus, pelvic peritoneum	1
Adnexitis, intrauterine infection, pelvic peritonitis	Right adnexia, uterus, pelvic peritoneum	1
Adnexitis, pelvic peritonitis	Right adnexia, pelvic peritoneum	1
Pelvic peritonitis	Pelvic peritoneum	2
Adnexitis, right adnexal abscess	Right adnexia	1
Right ovarian abscess	Right ovary	1

Values represent the number of subjects.
CPPS: clinical per protocol set; *N*: number of subjects evaluated; PID: pelvic inflammatory disease.

3.2. Efficacy results

For the clinical response assessed by the DRC in the CPPS (primary endpoint), the overall efficacy rate was 96.7% (95% CI: 82.8%–99.9%) at TOC (primary analysis) and 96.6% (95% CI: 82.2%–99.9%) at EOT (secondary analysis) (Table 5). The efficacy rate was 100% in the subjects with infectious peritonitis or abdominal abscess and 90.0% in the subjects with PID, both at TOC and EOT. The therapy failed only in 1 subject with PID (pelvic peritonitis).

For the clinical response by causative pathogen assessed by the DRC in the BPPS, the efficacy rate was 100% for all pathogens at EOT and TOC.

For the bacteriological response in the BPPS overall assessed by the DRC, the eradication rate was 100% on Day 4, EOT and TOC (Table 6). The eradication rates were also 100% in all subjects with infectious peritonitis or abdominal abscess and PID on Day 4, EOT and TOC (Table 6). The MICs of MNZ against the identified anaerobic pathogens ranged from ≤0.06 to >128 μg/ml (Tables 7 and 8).

Among the 8 subjects with infectious peritonitis or abdominal abscess who had 10 strains of anaerobic pathogens with resistance to other antimicrobials than MNZ and CTRX, the clinical response was assessed as cured or improved, except for 1 subject who was judged as indeterminate at EOT, and the bacteriological response was assessed as eradication or presumed eradication except in 2 subjects who were judged as colonization and indeterminate (1 subject each) (Table 9).

3.3. Safety results

Among 38 subjects, 14 subjects (36.8%) experienced treatment-related adverse events during the entire treatment period. The most common treatment-related adverse event was diarrhea (9 subjects), followed by nausea (2 subjects), and vomiting and abdominal pain upper (1 subject each). The majority of adverse

Table 4
Number of subjects in the CPPS classified by identified pathogen.

Infectious peritonitis or abdominal abscess	
Total number of subjects	20
Total number of subjects in whom pathogens were identified	17 (85.0)
Number of subjects in whom a single pathogen was identified	5 (25.0)
Bacteroides fragilis	2
*Staphylococcus epidermidis**	1
Escherichia coli	2
Number of subjects in whom multiple pathogens were identified	12 (60.0)
2 pathogens identified	
Parvimonas micra + *Escherichia coli*	1
Bacteroides thetaiotaomicron + *Escherichia coli*	1
Bacteroides vulgatus + *Escherichia coli*	1
Enterococcus avium + *Escherichia coli*	1
Escherichia coli + *Morganella morganii*	1
3 pathogens identified	
Bacteroides fragilis + *Streptococcus anginosus* + *Escherichia coli*	1
Bacteroides fragilis + *Streptococcus constellatus* + *Escherichia coli*	1
Bacteroides fragilis + *Enterococcus avium* + *Klebsiella pneumoniae*	1
4 or more pathogens identified	
Eggerthella lenta + *Bacteroides xylanisolvens* + *Escherichia coli* + *Klebsiella oxytoca*	1
Parvimonas micra + *Bacteroides salyersiae* + *Bacteroides thetaiotaomicron* + *Fusobacterium nucleatum* + *Escherichia coli*	1
Clostridium sp. + *Bacteroides ovatus* + *Fusobacterium necrophorum* + *Streptococcus constellatus* + *Escherichia coli*	1
Streptococcus agalactiae + *Streptococcus constellatus* + *Streptococcus oralis* + *Klebsiella pneumoniae* + *Proteus mirabilis* + *Edwardsiella tarda*	1
PID	
Total number of subjects	10
Total number of subjects in whom pathogens were identified	4 (40.0)
Number of subjects in whom a single pathogen was identified	0
Number of subjects in whom multiple pathogens were identified	4 (40.0)
2 pathogens identified	
Fusobacterium nucleatum + *Streptococcus agalactiae*	1
Staphylococus haemolyticus + *Streptococus* group G	1
Streptococcus agalactiae + *Citrobacter koseri*	1
4 pathogens identified	
Gemella morbillorum + *Prevotella intermedia* + *Streptococcus constellatus* + *Streptococcus sanguis*	1

Values represent the number (%) of subjects.
Underlined pathogens are anaerobic bacteria.
*: mutating into obligatory anaerobe.
CPPS: clinical per protocol set; PID: pelvic inflammatory disease.

events occurred within 6 days after starting the treatment, and was mild to moderate in severity. There were no treatment-related adverse events associated with intravenous injection.

One subject discontinued the study because of treatment-related adverse events (atrial fibrillation and sinus tachycardia), which occurred after extubation following ileocecal resection surgery on Day 2. These adverse events were mild and moderate in severity and resolved after discontinuation of the study medication.

There were no deaths or treatment-related serious adverse events reported during the entire period.

4. Discussion

Overall, MNZ-IV combined with CTRX exhibited excellent clinical and bacteriological efficacy for the treatment of infectious peritonitis, abdominal abscess and PID in Japanese subjects.

It is noted that MNZ-IV/CTRX was also effective in 1 subject who had sepsis complicated by infectious peritonitis, indicating the effectiveness of this dosing regimen in the treatment of patients with severe complications of sepsis [18,19].

The combination therapy failed only in 1 subject with PID (pelvic peritonitis) who received MNZ-IV/CTRX for 8 days. Although the spontaneous abdominal pain and tenderness, and the spontaneous pain of the uterus and its appendages improved, tenderness of the uterus and its appendages remained, and a high WBC count (12,600/mm^3) and CRP (8.5 mg/dl) as well as aggravation on computerized tomography and ultrasonic imaging were observed at EOT, the subject discontinued the study. This subject recovered after administration of piperacillin, minocyline, and azithromycin. Since involvement of atypical microorganisms was not confirmed and no baseline causative pathogens were identified, the clinical efficacy in this subject at EOT and TOC was assessed as ineffective.

MNZ is known to have high antimicrobial activity against anaerobes, including those identified in this study [5]. The MICs of MNZ for most anaerobic pathogens identified in this study ranged from ≤0.06 to 2 μg/ml, which may be associated with the high efficacy for infectious peritonitis, abdominal abscess and PID.

Since MNZ has *in vitro* activity against most anaerobes including *Peptostreptococcus* spp., *Porphyromonas* spp., *Eubacterium* spp., *Veillonella* spp., and *Clostridium tetanii*, which were not identified in this study [5,20,21], MNZ-IV may be effective to treat infections caused by these anaerobes. However, it is noted that MNZ is not active *in vitro* against *Actinomyces* spp. or *Propionibacterium acnes* [22,23].

MNZ-IV/CTRX was also effective for mixed infections with anaerobic and aerobic pathogens, which may result due to the antibacterial activity of MNZ on anaerobes and the antibacterial activity of CTRX on aerobes. When it is suspected that patients have mixed infections with anaerobic and aerobic pathogens, it is desirable to use MNZ combined with an antibiotic drug that has antibacterial activity on aerobes as recommended by many therapeutic guidelines.

For the treatment of anaerobic infections, the long-term use of antianaerobic agents including β-lactam/β-lactamase-inhibitor

Table 5
Clinical response assessed by the Data Review Committee (CPPS).

Diagnosis	Visit	*N*	Clinical response				Efficacy rate[a] (%)	95% CI
			Cure (%)	Improved (%)	Ineffective (%)	Ind (%)		
Overall	EOT	30	4 (13.3)	24 (80.0)	1 (3.3)	1 (3.3)	96.6	(82.2–99.9)
	TOC	30	25 (83.3)	4 (13.3)	1 (3.3)	0	96.7	(82.8–99.9)
Infectious peritonitis or abdominal abscess	EOT	20	1 (5.0)	18 (90.0)	0	1 (5.0)	100	(82.4–100.0)
	TOC	20	19 (95.0)	1 (5.0)	0	0	100	(83.2–100)
PID	EOT	10	3 (30.0)	6 (60.0)	1 (10.0)	0	90.0	(55.5–99.7)
	TOC	10	6 (60.0)	3 (30.0)	1 (10.0)	0	90.0	(55.5–99.7)

Values represent the number (%) of subjects.
CPPS: clinical per protocol set; *N*: number of subjects evaluated; Ind: indeterminate; CI: confidence interval; EOT: end of treatment; TOC: test of cure; PID, pelvic inflammatory disease.
[a] Efficacy rate = effective (cure + improved)/(*N* − Ind) × 100.

Table 6
Bacteriological response assessed by the Data Review Committee in the BPPS.

Diagnosis	Visit	n	Bacteriological response									Eradication rate[a] (%)	95% CI
			Era	P Era	Col	Per	P per	Mic	Sup	Rec	Ind		
Overall	Day 4	13	11 (84.6)	2 (15.4)	0	0	0	0	0	0	0	100	75.3–100
	EOT	21	12 (57.1)	6 (28.6)	2 (9.5)	0	0	0	0	0	1 (4.8)	100	83.2–100
	TOC	21	4 (19.0)	17 (81.0)	0	0	0	0	0	0	0	100	83.9–100
Infectious peritonitis or abdominal abscess	Day 4	9	7 (77.8)	2 (22.2)	0	0	0	0	0	0	0	100	66.4–100
	EOT	17	8 (47.1)	6 (35.3)	2 (11.8)	0	0	0	0	0	1 (5.9)	100	79.4–100
	TOC	17	0	17 (100)	0	0	0	0	0	0	0	100	80.5–100
PID	Day 4	4	4 (100)	0	0	0	0	0	0	0	0	100	39.8–100
	EOT	4	4 (100)	0	0	0	0	0	0	0	0	100	39.8–100
	TOC	4	4 (100)	0	0	0	0	0	0	0	0	100	39.8–100

Values represent the number (%) of subjects.
BPPS: bacteriologic per protocol set; n: number of subjects in whom infections were identified; Era: eradication; P Era: presumed eradication; Col: colonization; Per: persistence; P Per: presumed persistence; Mic: microbial substitution; Sup: superinfection; Rec: recurrence of infection; Ind: indeterminate; CI: confidence interval; EOT: end of treatment; TOC: test of cure; PID: pelvic inflammatory disease.
[a] Eradication rate = (Era + P Era + Col)/(n − Ind) × 100.

Table 7
Clinical response by MIC for anaerobic pathogens assessed by the Data Review Committee in the BPPS.

Pathogen	MIC[a] (μg/ml)	Visit	n	Clinical response				Eradication rate[b] (%)
				Cure	Improved	Ineffective	Ind	
Infectious peritonitis or abdominal abscess								
Eggerthella lenta	1/128	EOT	1	0	1 (100)	0	0	100
		TOC	1	1 (100)	0	0	0	100
Parvimonas micra	0.5/≤0.06	EOT	2	0	2 (100)	0	0	100
		TOC	2	2 (100)	0	0	0	100
Clostridium spp.	≤0.06/1	EOT	1	0	1 (100)	0	0	100
		TOC	1	1 (100)	0	0	0	100
Bacteroides fragilis	1/>128	EOT	1	0	1 (100)	0	0	100
		TOC	1	1 (100)	0	0	0	100
	2/4	EOT	1	0	1 (100)	0	0	100
		TOC	1	1 (100)	0	0	0	100
	2/16	EOT	1	0	1 (100)	0	0	100
		TOC	1	1 (100)	0	0	0	100
	2/32	EOT	1	0	1 (100)	0	0	100
		TOC	1	0	1 (100)	0	0	100
	2/64	EOT	1	0	1 (100)	0	0	100
		TOC	1	1 (100)	0	0	0	100
Bacteroides salyersiae	1/32	EOT	1	0	1 (100)	0	0	100
		TOC	1	1 (100)	0	0	0	100
Bacteroides thetaiotaomicron	0.25/128	EOT	1	0	0	0	1 (100)	–
		TOC	1	1 (100)	0	0	0	100
	2/64	EOT	1	0	1 (100)	0	0	100
		TOC	1	1 (100)	0	0	0	100
Bacteroides vulgatus	0.25/>128	EOT	1	1 (100)	0	0	0	100
		TOC	1	1 (100)	0	0	0	100
Bacteroides xylanisolvens	1/32	EOT	1	0	1 (100)	0	0	100
		TOC	1	1 (100)	0	0	0	100
Bacteroides ovatus	2/>128	EOT	1	0	1 (100)	0	0	100
		TOC	1	1 (100)	0	0	0	100
Fusobacterium nucleatum	≤0.06/0.5	EOT	1	0	1 (100)	0	0	100
		TOC	1	1 (100)	0	0	0	100
Fusobacterium necrophorum	NA	EOT	1	0	1 (100)	0	0	100
		TOC	1	1 (100)	0	0	0	100
PID								
Gemella morbillorum	>128/0.5	EOT	1	0	1 (100)	0	0	100
		TOC	1	1 (100)	0	0	0	100
Prevotella intermedia	0.5/≤0.06	EOT	1	0	1 (100)	0	0	100
		TOC	1	1 (100)	0	0	0	100
Fusobacterium nucleatum	≤0.06/1	EOT	1	0	1 (100)	0	0	100
		TOC	1	0	1 (100)	0	0	100

Values represent the number (%) of subjects.
BPPS: bacteriologic per protocol set; n: number of subjects in whom pathogens were identified; Ind: indeterminate; EOT: end of treatment; TOC: test of cure; NA: not applicable; PID: pelvic inflammatory disease.
[a] MIC of MNZ/MIC of CTRX.
[b] Eradication rate = (Cure + Improved)/(n − Ind) × 100.

Table 8
Bacteriological response by MIC for anaerobic pathogens assessed by the Data Review Committee in the BPPS.

Pathogen	MIC[a] (μg/ml)	Visit	*n*	Bacteriological response							Eradication rate[b] (%)
				Era	P Era	Col	Per	P Per	Rec	Ind	
Infectious peritonitis or abdominal abscess											
Eggerthella lenta	1/128	EOT	1	1 (100)	0	0	0	0	0	0	100
		TOC	1	0	1 (100)	0	0	0	0	0	100
Parvimonas micra	0.5/≤0.06	Day 4	1	0	1 (100)	0	0	0	0	0	100
		EOT	2	1 (50.0)	1 (50.0)	0	0	0	0	0	100
		TOC	2	0	2 (100)	0	0	0	0	0	100
Clostridium spp.	≤0.06/1	EOT	1	0	0	0	0	0	0	1 (100)	–
		TOC	1	0	1 (100)	0	0	0	0	0	100
Bacteroides fragilis	1/>128	Day 4	1	1 (100)	0	0	0	0	0	0	100
		EOT	1	1 (100)	0	0	0	0	0	0	100
		TOC	1	0	1 (100)	0	0	0	0	0	100
	2/4	EOT	1	0	1 (100)	0	0	0	0	0	100
		TOC	1	0	1 (100)	0	0	0	0	0	100
	2/16	Day 4	1	1 (100)	0	0	0	0	0	0	100
		EOT	1	1 (100)	0	0	0	0	0	0	100
		TOC	1	0	1 (100)	0	0	0	0	0	100
	2/32	EOT	1	0	0	1 (100)	0	0	0	0	100
		TOC	1	0	1 (100)	0	0	0	0	0	100
	2/64	Day 4	1	1 (100)	0	0	0	0	0	0	100
		EOT	1	1 (100)	0	0	0	0	0	0	100
		TOC	1	0	1 (100)	0	0	0	0	0	100
Bacteroides salyersiae	1/32	Day 4	1	0	1 (100)	0	0	0	0	0	100
		EOT	1	0	1 (100)	0	0	0	0	0	100
		TOC	1	0	1 (100)	0	0	0	0	0	100
Bacteroides thetaiotaomicron	0.25/128	EOT	1	1 (100)	0	0	0	0	0	0	100
		TOC	1	0	1 (100)	0	0	0	0	0	100
	2/64	Day 4	1	0	1 (100)	0	0	0	0	0	100
		EOT	1	0	1 (100)	0	0	0	0	0	100
		TOC	1	0	1 (100)	0	0	0	0	0	100
Bacteroides vulgatus	0.25/>128	Day 4	1	0	1 (100)	0	0	0	0	0	100
		EOT	1	0	1 (100)	0	0	0	0	0	100
		TOC	1	0	1 (100)	0	0	0	0	0	100
Bacteroides xylanisolvens	1/32	EOT	1	1 (100)	0	0	0	0	0	0	100
		TOC	1	0	1 (100)	0	0	0	0	0	100
Bacteroides ovatus	2/>128	EOT	1	0	0	0	0	0	0	1 (100)	–
		TOC	1	0	1 (100)	0	0	0	0	0	100
Fusobacterium nucleatum	≤0.06/0.5	Day 4	1	0	1 (100)	0	0	0	0	0	100
		EOT	1	0	1 (100)	0	0	0	0	0	100
		TOC	1	0	1 (100)	0	0	0	0	0	100
Fusobacterium necrophorum	NA	EOT	1	0	0	0	0	0	0	1 (100)	–
		TOC	1	0	1 (100)	0	0	0	0	0	100
PID											
Gemella morbillorum	>128/0.5	Day 4	1	1 (100)	0	0	0	0	0	0	100
		EOT	1	1 (100)	0	0	0	0	0	0	100
		TOC	1	1 (100)	0	0	0	0	0	0	100
Prevotella intermedia	0.5/≤0.06	Day 4	1	1 (100)	0	0	0	0	0	0	100
		EOT	1	1 (100)	0	0	0	0	0	0	100
		TOC	1	1 (100)	0	0	0	0	0	0	100
Fusobacterium nucleatum	≤0.06/1	Day 4	1	1 (100)	0	0	0	0	0	0	100
		EOT	1	1 (100)	0	0	0	0	0	0	100
		TOC	1	1 (100)	0	0	0	0	0	0	100

Values represent the number (%) of subjects.
BPPS: bacteriologic per protocol set; *n*: number of subjects in whom pathogens were identified; Era: eradication; P Era: presumed eradication; Col: colonization; Per: persistence; P Per: presumed persistence; Rec: recurrence of infection; Ind: indeterminate; EOT: end of treatment; TOC: test of cure; NA: not applicable; PID: pelvic inflammatory disease.
[a] MIC of MNZ/MIC of CTRX.
[b] Eradication rate = (Era + P Era + Col)/(n − Ind) × 100.

combination, carbapenams, moxifloxacin, garenoxacin, and sitafloxacin resulted in the emergence of resistant pathogens and an increased risk for *Clostridium difficile* infection. Increased resistance rates to clindamycin, which is used as an alternative antianaerobic agent, have also been reported among anaerobic pathogens [11–13,16]. Therefore, MNZ-IV/CTRX can be useful to treat anaerobic infections as an antimicrobial therapy that prevents the emergence of drug-resistant strains.

MNZ-IV/CTRX was effective in 1 subject with both infectious peritonitis and abdominal abscess in whom a metallo-β-lactamase-producing *B. fragilis* strain (MIC of MNZ, 2 μg/ml) was identified. Since MNZ shows *in vitro* antimicrobial activity against metallo-β-lactamase-producing carbapenem-resistant strains [24], MNZ may provide a useful option for the treatment of infectious disease involving metallo-β-lactamase-producing anaerobic pathogens.

The emergence rate of MNZ-resistant anaerobes is generally low, but a slight decrease in susceptibility to MNZ among anaerobes including *Bacteroides* spp. has been reported [24,25]. The appropriate use of MNZ is important for the treatment of anaerobic infections to prevent the emergence of MNZ-resistant anaerobes. It is thus desirable to not only administer MNZ, but also various antimicrobial classes equally for anaerobic infections to prevent the excessive use of MNZ. Since clinicians frequently choose clindamycin for anaerobic infections, resistance to clindamycin is a growing

Table 9
Anaerobic pathogens with resistance to antimicrobials other than MNZ and CTRX, MICs, and clinical and bacteriological responses to the pathogens when MNZ-IV combinied with CTRX was administered.

Subject ID	Anaerobic pathogen	MIC of MNZ (μg/ml)	MIC of CTRX (μg/ml)	MIC of other drugs (μg/ml)	Clinical response	Bacteriological response
1	*Bacteroides xylanisolvens*	1	32	Clindamycin: >128 Cefepime: 128 Cefozopran: >64	EOT: Improved TOC: Cure	EOT: Era TOC: P Era
	Eggerthella lenta	1	128	Clindamycin: 0.12 Cefepime: 128 Cefozopran: 32 Sulbactam/Cefoperazone: 64		
2	*Bacteroides vulgatus*	0.25	>128	Clindamycin: >128 Cefepime: >128 Cefozopran: >64 Penicillin G: >128 Ampicillin: >128 Piperacillin: 128	EOT: Cure TOC: Cure	Day 4: P Era EOT: P Era TOC: P Era
3	*Bacteroides thetaiotaomicron*	2	64	Cefepime: >128 Cefozopran: >64	EOT: Improved TOC: Cure	Day 4: P Era EOT: P Era
	Bacteroides salyersiae	1	32	Cefepime: 64 Cefozopran: >64		TOC: P Era
4	*Bacteroides ovatus*	2	>128	Cefepime: >128 Cefozopran: >64 Penicillin G: >128 Ampicillin: >128 Piperacillin: >128	EOT: Improved TOC: Cure	EOT: Ind TOC: P Era
5	*Bacteroides thetaiotaomicron*	0.25	128	Cefepime: >128 Cefozopran: >64	EOT: Ind TOC: Cure	EOT: Era TOC: P Era
6	*Bacteroides fragilis*	2	32	Cefepime: 64 Cefozopran: 64 Penicillin G: 64	EOT: Improved TOC: Improved	EOT: Col TOC: P Era
7	*Bacteroides fragilis*	1	>128	Cefepime: >128 Cefozopran: >64 Penicillin G: >128 Ampicillin: >128 Piperacillin: 128	EOT: Improved TOC: Cure	Day 4: Era EOT: Era TOC: P Era
8	*Bacteroides fragilis*	2	64	Cefepime: 128 Cefozopran: >64 Penicillin G: >128 Ampicillin: >128 Piperacillin: >128	EOT: Improved TOC: Cure	Day 4: Era EOT: Era TOC: P Era

MNZ: metronidazole; CTRX: ceftriaxone; IV: intravenous; EOT: end of treatment; TOC: test of cure; Era: eradication; P Era: presumed eradication; Col: colonization; Ind: indeterminate.

issue in the treatment of anaerobic infections. Similarly, there might be a possibility that the excessive use of MNZ for anaerobic infections may result in an increase in MNZ resistant anaerobes.

In this study, MNZ-IV in combination with CTRX was well tolerated, and demonstrated excellent clinical and bacteriological efficacy in the treatment of hospitalized Japanese subjects with infectious peritonitis, abdominal abscess or PID. These results indicate that MNZ-IV/CTRX therapy can be a reasonable option for the empirical treatment of anaerobic infectious diseases involving antibiotic-resistant organisms in clinical practice.

The use of MNZ is recommended for the treatment of the various anaerobic infections referred to in textbooks and guidelines [7–10,26–31]. However, there has been little information on the efficacy and safety of MNZ-IV in Japanese patients with other anaerobic infections than infectious peritonitis, abdominal abscess, or PID. Therefore, some clinical research will be needed for further evaluation of the efficacy and safety of MNZ-IV in Japanese patients.

Conflict of interest

H. Mikamo has received a consultant fee and a fee for participation in the Committee from Pfizer Japan Inc. M. Matsumizu, Y. Nakazuru, and M. Nagashima are employees of Pfizer Japan Inc.

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Original article

Efficacy and safety of a single oral 150 mg dose of fluconazole for the treatment of vulvovaginal candidiasis in Japan

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ABSTRACT

Vulvovaginal candidiasis is the second most common cause of vaginal infections following bacterial vaginosis. For the treatment of vulvovaginal candidiasis, antifungal agents are used either as topical (vaginal tablets and cream) or oral formulations. A single oral 150 mg dose of fluconazole has been recommended as the standard therapy for uncomplicated, acute vulvovaginal candidiasis in global guidelines; however, in Japan oral fluconazole therapy has not been approved. We conducted a phase 3 study to evaluate the efficacy and safety of a single oral 150 mg dose of fluconazole in Japanese subjects with vulvovaginal candidiasis for regulatory submission. A total of 157 subjects received a single oral 150 mg dose of fluconazole. *Candida* species (104 strains) were identified by fungal culture from 102 subjects at baseline, including *Candida albicans* (100 strains). The efficacy rate for the therapeutic outcome (assessed based on a comprehensive evaluation of the clinical and mycological efficacy in each subject) was 74.7% (74/99) on Day 28 in the modified Intent-To-Treat (m-ITT) population. Concerning the clinical and mycological efficacy on Day 28 in the m-ITT population, the cure, cure or improvement, and eradication rates were 81.6%, 95.9%, and 85.9%, respectively. The most common treatment-related adverse events were diarrhea and nausea (1.9% for each). No clinically significant safety issues were reported. A single oral 150 mg dose of fluconazole demonstrated excellent therapeutic efficacy and was well tolerated in Japanese subjects with vulvovaginal candidiasis.
Clinical registration number: NCT01806623.

1. Introduction

Vulvovaginal candidiasis is an infection of the vulva and/or vagina caused by *Candida* species. Vulvovaginal candidiasis is the second most common cause of vaginal infections after bacterial vaginosis, and is often diagnosed at primary care clinics for obstetrics and gynecology [1–3].

The most common causative pathogen of vulvovaginal candidiasis is *Candida albicans*, followed by *Candida glabrata*, which are part of the indigenous flora of the gastrointestinal tract and skin [1–3]. A positive vaginal culture for *Candida* species is found in approximately 15% of non-pregnant adolescent women, and 30% of pregnant women in Japan, but most women only have *Candida* species in the vagina and are asymptomatic, but are not diagnosed as having candidiasis, and do not require treatment. Treatment is required by approximately 35% of non-pregnant women with vaginal *Candida* species, and 15–30% of pregnant women with vaginal *Candida* species [1]. The infection caused by *Candida* affects 70–75% of women at least once during their lives, and is most common in young women of childbearing age [1–3].

For the treatment of vulvovaginal candidiasis, antifungal agents, either as topical (vaginal tablets and cream) or oral formulations, are used. In European countries and the United States (US), for the treatment of uncomplicated vaginal candidiasis, a single oral 150 mg dose of fluconazole is recommended by the 2010 Sexually

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transmitted disease treatment guidelines of the CDC [3] and the Sanford Guide to Antimicrobial Therapy 2014 [4].

In Japan, oral therapy with antifungal triazoles such as fluconazole has not been approved for vulvovaginal candidiasis, and topical therapies such as vaginal tablets and cream has been clinically used. In accordance with the Diagnosis and Treatment Guidelines for Sexually Transmitted Diseases 2011 in Japan, 100 mg of either clotrimazole, miconazole, isoconazole or oxiconazole is recommended as a daily treatment with vaginal tablets or pessary for uncomplicated acute vulvovaginal candidiasis, which in principle requires daily hospital visits and a vaginal douche prior to administration. For patients who cannot visit the hospital daily, vaginal administration of a weekly dose of 600 mg isoconazole or oxiconazole is recommended after vaginal douche [1]. However, it is difficult for patients to administer vaginal tablets or a pessary, which is painful, by themselves, and therefore it often results in incompliance due to the burden of treatment [5–7].

Fluconazole, a triazole antifungal agent, has clinically been widely used with the indication for deep mycosis as an oral drug (capsules) and injection in Japan since it was launched in 1989. As for the treatment of vulvovaginal candidiasis, a single oral 150 mg dose of fluconazole, if implemented in Japan, would be of clinical significance as a new and satisfactory treatment option providing better dose compliance than topical therapies.

The aim of this study was to investigate the efficacy and safety profile of a single oral 150 mg dose of fluconazole for the treatment of Japanese subjects with vulvovaginal candidiasis for regulatory submission.

2. Subjects and methods

This study was conducted in accordance with the International Conference on Harmonisation of Good Clinical Practice Guidelines, the principle of the Declaration of Helsinki, and all applicable laws and regulations at 10 medical centers nationwide in Japan between March 2013 and November 2013. The protocol was approved by the Institutional Review Boards of all participating study sites. All subjects provided written informed consent before enrollment. The study was conducted in accordance with advice from the Pharmaceuticals and Medical Devices Agency (PMDA) after the appropriateness of the study design, endpoints, analysis set, inclusion criteria, and so on were discussed with the PMDA.

2.1. Study design

This multicenter, open-label, non-comparative phase 3 study was designed to evaluate the efficacy and safety of a single oral 150 mg dose of fluconazole in Japanese subjects with vulvovaginal candidiasis. The target number of subjects was 99 who were in the modified Intent-To-Treat (m-ITT) population and whose therapeutic outcomes on Day 28 would be evaluated as effective or ineffective. All the subjects took 3 fluconazole 50 mg capsules orally only once on the first day of the treatment. The efficacy and safety were evaluated up to Day 28.

2.2. Eligibility criteria

Female Japanese subjects aged 18 years or older (<80 years in principle), who had clinical signs and symptoms of vulvovaginal candidiasis with a total symptom severity scores of 4 or higher, and were positive for *Candida* by fungal culture were eligible. Clinical signs and symptoms were evaluated as follows: (A) symptom severity scores: 0 = no symptoms, 1 = mild, 2 = moderate, and 3 = severe, for vulvovaginal itching, vulvovaginal burning sensation, excoriation of the vulva, vaginal discharge, vulva edema, redness of the vulva, and vaginal redness; and (B) property of vaginal content scores: 0 = normal, 1 = mucoid, 2 = paste-like, and 3 = cottage cheese-like, cheese-like or granular.

Exclusion criteria included the following: a history of hypersensitivity to fluconazole; diabetes; severe renal dysfunction; liver disorder; heart disease or electrolyte abnormality; pregnancy or lactation; serious underlying diseases or complications; possible accompanying trichomonas vaginitis or bacterial vaginosis, vaginitis caused by Chlamydia or Gonococcus, or herpes simplex; chronic vulvovaginal candidiasis; vaginal pH $\geq$ 5.0; the previous use of systemic antifungals within 4 weeks before starting the study medication, or the previous use of local (vulval or intravaginal) antifungals within 2 weeks before starting the study medication; not willing to avoid sexual relations up to 28 days after the dosing; menstruation at enrollment, or next menstruation expected to start within 1 week after the study medication; diagnosis of being immunocompromised.

The following concomitant medications and therapy were prohibited up to Day 28: antifungals, antimicrobials, and antiallergic drugs (oral, injection, topical [vulval or intravaginal] drugs); human immunoglobulin; colony stimulating factor; corticosteroids; vaginal douching after the study medication; and other investigational drugs or medical devices. The use of antimicrobials was allowed for subjects who turned out to have accompanying trichomonas vaginitis, bacterial vaginosis, vaginitis caused by Chlamydia or Gonococcus or herpes simplex after enrollment.

2.3. Assessments

The primary endpoints included therapeutic outcomes determined by investigators on Days 7, 14, 28, and at discontinuation. Primary evaluation was therapeutic outcome on Day 28.

Therapeutic outcome was assessed based on the comprehensive evaluation of clinical and mycological efficacy of each subject according to the criteria shown in Table 1.

2.3.1. Clinical efficacy

Clinical efficacy was assessed based on the evaluation of clinical signs and symptoms (vulvovaginal itching, vulvovaginal burning sensation, excoriation of the vulva, vaginal discharge, vulval edema, redness of the vulva, vaginal redness, property of vaginal content). Clinical efficacy was judged as "cured" or "improved" if the clinical symptoms at the start of treatment had resolved or improved at the assessment time point; "ineffective" if neither the criteria for "cured" nor "improved" were met, or the treatment failed and other antifungals were administered for the treatment of vulvovaginal candidiasis; "indeterminate" if efficacy assessment was difficult or not determined because of missing data or failure to conduct the test, or other antifungals were administered for the treatment of other infections than vulvovaginal candidiasis.

2.3.2. Mycological efficacy

The causative pathogen was identified by vaginal discharge culture before the study medication on Day 1 and on Days 7, 14 and

Table 1
Criteria for determining the therapeutic outcomes.

Clinical efficacy	Mycological efficacy		
	Eradication	Persistent	Indeterminate
Cure	Effective	Ineffective	Indeterminate
Improvement	Ineffective	Ineffective	Indeterminate
Ineffective	Ineffective	Ineffective	Ineffective
Indeterminate	Indeterminate	Ineffective	Indeterminate

28. Mycological response was assessed based on the results of culture. Mycological efficacy was judged as "eradication" if the original pathogen was not identified in the vaginal discharge; "persistence" if the original pathogen remained in the specimens or other antifungals were administered for the treatment of vulvovaginal candidiasis; "indeterminate" if efficacy assessment could not be determined because of a failure to conduct the vaginal discharge culture etc., or other antifungals were administered for the treatment of other infections than vulvovaginal candidiasis.

2.4. Safety assessment

Safety data were obtained from the findings of clinical signs/symptoms, physical examinations, vital signs, and laboratory data up to Day 28. The causality and severity of the adverse events were evaluated by the investigators (or sub-investigators), based on the Medical Dictionary for Regulatory Activities terminology.

2.5. Statistical analysis

Efficacy analyses were mainly conducted of m-ITT subjects with vulvovaginal candidiasis who received the study drug, were positive for *Candida* by culture on Day 1 (before dosing), and whose therapeutic outcome on Day 28 was evaluated as effective or ineffective.

The primary endpoint was the efficacy rate of the therapeutic outcome in the m-ITT population on Day 28, and the efficacy would be confirmed if the lower bound of the 95% confidence interval (CI) of the therapeutic success rate was greater than 38% (pre-specified threshold value).

The safety analysis set was defined as all subjects who received the study drug.

Assuming that the therapeutic success rate in this study would be 54% based on the efficacy results of 2 previous US phase 3 studies, and the lower bound of the 95% CI (threshold value) for the success rate was set to be 38%, which was derived from the mycological eradication rate in meta-analysis literature [8], 99 subjects were needed in the m-ITT population to ensure a statistical power of 90% at a one-sided significance level of 0.025. Assuming that *Candida* was detected in the vulva and/or vagina in 80% of the subjects presenting with such symptoms as vulvovaginal itching and increase in vaginal discharge, 130 subjects were needed to be enrolled.

3. Results

3.1. Subject disposition and demography

In this study, a total of 157 subjects were assigned and all of them received the study drug. Of these, 99 subjects completed the study, and 58 discontinued the study due to the following: (A) not meeting the inclusion criteria in 56 subjects (55 were negative for *Candida* by fungal culture, and 1 had abnormal values for liver function tests, which met the exclusion criteria); (B) voluntary withdrawal from the study in 1 subject; and (C) adverse events not related to the study drug (vulvovaginitis trichomonal) in 1 subject. Of the 157 subjects who received the study medication, 55 were not included in the m-ITT population because they were negative for *Candida* by fungal culture, and the remaining 102 subjects formed the m-ITT population. The safety analysis set included all 157 subjects.

Table 2 summarizes the baseline demographic and other characteristics of the subjects.

At baseline, 104 strains of *Candida* were identified by fungal culture in 102 of 157 subjects: *C. albicans* (100 strains), *Candida parapsilosis* (2 strains), *C. glabrata*, and *Candida* sp. (1 strain each) (multiple strains were identified in 2 subjects). The MIC_{50} and MIC_{90} of fluconazole, oxiconazole, isoconazole, clotrimazole, and miconazole for *C. albicans*, *C. parapsilosis*, and *C. glabrata* isolates are shown in Table 3. Severity scores assigned to each clinical symptom at baseline are summarized in Fig. 1. More than half of the subjects had moderate to severe vulvovaginal itching and vaginal discharge. The property of vaginal content was paste-like, cottage cheese-like, or granular in most subjects.

Table 2
Baseline demographic and other characteristics of subjects with vulvovaginal candidiasis in the m-ITT population.

Variable	m-ITT population (N = 102)
Age (years)	
Mean (SD)	31.9 (8.2)
Range	18–55
Body weight (kg)	
Mean (SD)	53.9 (11.5)
Range	40.0–136.8
Severity of vulvovaginal candidiasis (n (%))	
Mild	11 (10.8)
Moderate	73 (71.6)
Severe	18 (17.6)
Number of occurrence of vulvovaginal candidiasis for the last 1 year (n (%))	
0	80 (78.4)
1 or more	22 (21.6)
1–3	22
1	16
2	4
3	2
4 or more	0

m-ITT, modified intent-to-treat.

3.2. Efficacy results

The rate of "effective" for the therapeutic outcome in the m-ITT population was 33.7% (95% CI: 24.2–44.3%) on Day 7, 54.2% (43.7–64.4%) on Day 14, and 74.7% (65.0–82.9%) on Day 28 (Table 4). Efficacy was confirmed since the lower bound of the 95% CI of the therapeutic success rate on Day 28 (65.0%) was greater than 38% (pre-specified threshold value).

For clinical efficacy in the m-ITT population, the cure rate was 34.8% on Day 7, 57.3% on Day 14, and 81.6% on Day 28. The cure or improvement rate was 100.0% on Day 7, 99.0% on Day 14, and 95.9% on Day 28 (Table 5).

For the mycological efficacy in the m-ITT population, the mycological eradication rate was 95.7% on Day 7, 89.8% on Day 14, and 85.9% on Day 28 (Table 6).

Most subjects whose therapeutic outcomes were assessed as "ineffective" showed "improvement" and "eradication" for clinical and mycological efficacy, respectively (57/61 on Day 7, 33/44 on Day 14, and 10/25 on Day 28). Three subjects had "ineffective" for clinical efficacy and "persistence" for mycological efficacy on Day 28.

Changes in the percentages of subjects with some clinical signs and symptoms are shown in Fig. 2. All the clinical signs and symptoms improved from Day 3.

3.3. Safety results

Among the 157 subjects in the safety analysis set, 12 subjects (7.6%) experienced treatment-related adverse events (Table 7).