Many studies have shown *M. genitalium* to be one of the pathogens responsible for uterine cervicitis [2, 10–13, 15]. However, there are no clinical recommendations for treating *M. genitalium*-positive uterine cervicitis [17]. The study described in the present work investigated the clinical efficacies of various antibiotics against uterine cervicitis caused by *M. genitalium*.

Patients and methods

Study design

This was a retrospective, single-center, study focusing on the period from January 2008 to August 2010. Women patients with *Mycoplasma genitalium*-positive uterine cervicitis received the following antibacterial therapies: azithromycin extended release formulation (AZM-SR) 2 g single dose, azithromycin (AZM) 1 g single dose, clarithromycin (CAM) 400 mg/day for 7 days, CAM 400 mg/day for 14 days, moxifloxacin (MFLX) 400 mg/day for 7 days, MFLX 400 mg/day for 14 days, levofloxacin (LVFX) 500 mg/day for 7 days, LVFX 500 mg/day for 14 days, sitafloxacin (STFX) 200 mg/day for 7 days, or STFX 200 mg/day for 14 days.

Each patient had two visits: a baseline visit (day 1) and an EOS (end of study: 14 days after end of treatment) evaluation visit. PCR-based assay was performed to evaluate the microbiological efficacy of eradication in these patients at the baseline and EOS visits.

The protocol was approved by an institutional review board at Izumi Ladies Clinic, and the study was conducted in compliance with the ethical principles of the Declaration of Helsinki. All patients provided written informed consent before initiating the study procedure.

Patients

The study included women aged 18–42 years with uterine cervicitis diagnosed as *M. genitalium*-positive by PCR-based assay. Patients had discharge from the cervix with clinical symptoms of cervicitis. Two major diagnostic signs characterize cervicitis: (1) a purulent or mucopurulent endocervical exudate visible in the endocervical canal or on an endocervical swab specimen (commonly referred to as "mucopurulent cervicitis" or cervicitis), and (2) sustained endocervical bleeding easily induced by gentle passage of a cotton swab through the cervical os. Either or both signs could be present. Patients had their *M. genitalium* infection confirmed by PCR-based assay, except in those cases with chlamydial and gonococcal infections. We studied a total of 257 women with *M. genitalium*-positive uterine cervicitis.

Sampling procedure

Two cervical swab specimens were obtained from all patients. After the endocervical canal had been cleaned by removing discharge, cotton swabs were inserted and rubbed against the endocervical canal. The first swab was placed into the PCR transport medium to detect *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. A second swab was placed into 0.5 mL of 10 mmol/L Tris–HCl buffer, pH 8.0, including 1 mmol/L EDTA to perform a PCR-based assay to detect *M. genitalium*.

PCR amplification

DNA preparation and PCR amplification using a semi-nested strategy and Southern blot hybridization analysis was performed as previously described. Specimens for which the 300 bp DNA fragment hybridized to the internal probe were regarded as positive for *M. genitalium*. Gonorrhea was excluded by microscopy or a PCR assay. Prevalence of *C. trachomatis* also was determined by testing the cervical swab specimens using a PCR assay.

Detection of *M. genitalium*

To detect *M. genitalium*, a modified version of the published [18] procedure was used. The nucleotide sequences of the *M. genitalium* were made from oligonucleoside of the 140 kDa adhesion protein gene. MgPa-1 was complementary to the coding strand and its sequence was 5′AGT TGATGAAACCTTAACCCCTTGG3′. MgPa-3 was complementary to the noncoding strand and its sequence was 5′CCGTTGAGGGGTTTTCCATTTTTGC3′. These genes were different from those previously reported in the literature [4, 10, 19–22]. Samples were denatured at 95°C for 60 s, and primers were annealed at 52°C for 50 s and extended at 72°C for 50 s. A total of 35 cycles were performed.

Detection of *N. gonorrhoeae* and *C. trachomatis*

Baseline cervical samples were assessed for *N. gonorrhoeae* and *C. trachomatis* by the PCR method (Amplicor® STD-1, Roche Diagnostics K.K., Japan).

Efficacy endpoint

To assess efficacy, the eradication rate was analyzed by PCR-based assay at the EOS evaluation visit in the overall population treated.

Results

Efficacy endpoint

The eradication rates at the EOS visit were 90.5% (19/21) for AZM-SR 2 g single dose, 85.7% (36/42) for AZM 1 g single dose, 65.0% (13/20) for CAM 400 mg/day for 7 days, 85.0% (17/20) for CAM 400 mg/day for 14 days, 90.5% (38/42) for MFLX 400 mg/day for 7 days, 100% (42/42) for MFLX 400 mg/day for 14 days, 54.5% (12/22) for LVFX 500 mg/day for 7 days, 71.4% (15/21) for LVFX 500 mg/day for 14 days, 78.6% (11/14) for STFX 200 mg/day for 7 days, and 92.3% (12/13) for STFX 200 mg/day for 14 days (Table 1).

Safety

All adverse events experienced by the patients during these antibacterial regimens were digestion-related events. The number of AEs increased with the length of the treatment period (Table 2).

Discussion

We examined the antimicrobial efficacies of various antibiotics for *M. genitalium*-positive uterine cervicitis based on the eradication rate at the EOS visit. The eradication assessments were made according to the results of a PCR-based assay.

In most cases, *M. genitalium* infections are asymptomatic [2, 23, 24]. When the diagnosis of *M. genitalium* infection or the detection of *M. genitalium* is delayed, the disease progresses to salpingitis [25] or pelvic inflammatory disease (PID) [26]. The treatment regimens for *M. genitalium* are not mentioned in the literature, even in the guidelines [17]; descriptions of the recommended treatment used for *Mycoplasma* spp. in actual clinical practice are, however. Falk et al. reported that treating *M. genitalium* with tetracyclines (doxycycline and lymecycline) could not be recommended because of low eradication rates. This report indicated that AZM (5-day course: 500 mg the first day and 250 mg for the following 4 days) could be more efficient than tetracyclines [27].

In our study, the eradication rate of *M. genitalium* by AZM-SR 2 g single dose was 90.5% (19/21) and that achieved by AZM 1 g single dose was 85.7% (36/42). Other studies have reported that the eradication rate of *M. genitalium* by AZM 1 g single dose was 84–85% [28–30]. Almost all patients enrolled in these studies were male patients with urethritis. In our study, AZM 1 g single dose yielded the same level of efficacy as these reported data.

A lot of new-generation fluoroquinolones are now available in Japan. Although some fluoroquinolones showed antibacterial activities against *M. genitalium* in

Table 1 Microbiological efficacy (eradication rates)

Regimen	AZM-SR 2 g	AZM 1 g	CAM 400 mg 7 days	CAM 400 mg 14 days	MFLX 400 mg 7 days	MFLX 400 mg 14 days	LVFX 500 mg 7 days	LVFX 500 mg 14 days	STFX 200 mg 7 days	STFX 200 mg 14 days
Number of patients	21	42	20	20	42	42	22	21	14	13
Number of successful microbiological outcomes/total (%)	19/21 (90.5)	36/42 (85.7)	13/20 (65.0)	17/20 (85.0)	38/42 (90.5)	42/42 (100)	12/22 (54.5)	15/21 (71.4)	11/14 (78.6)	12/13 (92.3)

AZM-SR azithromycin extended release formulation, *AZM* azithromycin, *CAM* clarithromycin, *MFLX* moxifloxacin, *LVFX* levofloxacin, *STFX* sitafloxacin

Table 2 Adverse events

Regimen	AZM-SR 2 g	AZM 1 g	CAM 400 mg 7 days	CAM 400 mg 14 days	MFLX 400 mg 7 days	MFLX 400 mg 14 days	LVFX 500 mg 7 days	LVFX 500 mg 14 days	STFX 200 mg 7 days	STFX 200 mg 14 days
Number of patients	21	42	20	20	42	42	22	21	14	13
Number of AEs (%)										
Diarrhea	8 (38.1)	0	0	1 (5.0)	3 (7.1)	4 (9.5)	0	0	1 (7.1)	4 (30.8)
Loose stool	2 (9.5)	1 (2.4)	0	1 (5.0)	3 (7.1)	5 (11.9)	0	2 (14.3)	2 (14.3)	3 (23.1)

AZM-SR azithromycin extended release formulation, *AZM* azithromycin, *CAM* clarithromycin, *MFLX* moxifloxacin, *LVFX* levofloxacin, *STFX* sitafloxacin

Table 3 MICs for isolated pathogens from Japan [32]

Antibiotic	MIC range (mg/L)	MIC 50%	MIC 90%
Sitafloxacin	0.008–0.125	0.063	0.125
Moxifloxacin	0.016–0.25	0.063	0.125
Gatifloxacin	0.031–0.5	0.25	0.25
Levofloxacin	0.125–2	1	2
Ciprofloxacin	0.063–8	4	8
Norfloxacin	1–64	32	64
Minocycline	0.031–0.25	0.125	0.25
Doxycycline	0.063–1	0.125	0.25
Tetracycline	0.063–2	0.125	0.5
Azithromycin	0.0002–250	0.001	0.002
Clarithromycin	0.0005–128	0.004	0.008

MIC minimum inhibitory concentration

vivo (Table 3), the results for the eradication rates achieved with these were lower than expected.

Currently, assays of *N. gonorrhoeae* and *C. trachomatis* are performed using PCR methods that are optimized so that they can be easily conducted by clinics. Mikamo et al. [31] reported that the appropriate method used and time needed to assess the therapeutic efficacy for *C. trachomatis* infectious STD are PCR and three weeks after treatment, respectively. On the other hand, the PCR-based assay of *M. genitalium* is not common nor commercialized, so it needs more time to detect *M. genitalium* than the commercialized assays of *N. gonorrhoeae* and *C. trachomatis*. As *M. genitalium* causes STD or PID, a commercialized assay is needed for early treatment.

The regimen of AZM 1 g is effective for urethritis and cervicitis caused by *C. trachomatis*, and recommended in the guidelines [16]. Single-dose AZM treatment options (AZM-SR 2 g single dose or AZM 1 g single dose) are favorable for the initial treatment for STD if *C. trachomatis* is detected, whatever the result obtained from the *M. genitalium* PCR. If the EOS assessment after AZM treatment finds any remaining *M. genitalium* by PCR or any clinical symptoms, an alternative treatment such as fluoroquinolones is considered. In particular, if female patients may be pregnant, tetracyclines and fluoroquinolones are alternative options or options after confirming that the patient is not pregnant.

There were some clear limitations to our study. Our study is a retrospective study, and the number of patients included meant that statistically significant results were not obtained. A prospective, large-scale clinical study is needed in order to produced such statistically significant results. *M. genitalium* was only detected in the patients by PCR; no other methods were used, such as culture-based confirmation. Our PCR method for *M. genitalium* was not standardized to each site, and a more appropriate method with high sensitivity and high specificity is required.

In our study, *M. genitalium* was eradicated from the uterine cervix in 19 of the 21 (90.5%) patients treated with AZM-SR 2 g single dose, in 38 of the 42 (90.5%) patients treated with MFLX 400 mg/day for 7 days, in 42 of the 42 (100%) patients treated with MFLX 400 mg/day for 14 days, and in 12 of the 13 (92.3%) patients treated with STFX 200 mg/day for 14 days.

In conclusion, AZM-SR 2 g single dose, MFLX 400 mg/day for 14 days, or STFX 200 mg/day for 14 days are each effective treatments for *M. genitalium* infection.

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女性医学分野

15. 骨盤内炎症性疾患

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はじめに

産婦人科領域で問題となる感染症は特異的であり，後遺症としての不妊症など，将来重大な問題点を残すものが含まれている．また，嫌気性菌などの下部生殖器である腟内の常在細菌叢を形成している細菌などが病原体となっていることが多く，宿主側の要因に左右される難治性感染症が増加している．

産婦人科領域感染症は，内性器感染症，外性器感染症，腟炎，子宮頸管炎，尿路感染症，周産期感染症，周術期感染(術後感染)，性感染症(sexually transmitted disease：STD)などに大別される．内性器感染症とは，子宮内感染，子宮付属器炎，骨盤腹膜炎，ダグラス窩膿瘍，子宮傍結合組織炎など内性器およびその結合組織の炎症の総称である．内性器感染症は大部分が上行性感染であり，子宮内感染から子宮付属器炎へ，子宮付属器炎から骨盤腹膜炎へと進展することが一般的である．したがって，今日では骨盤内炎症性疾患(pelvic inflammatory disease：PID)と表現されている．

女性生殖器感染症の多くは，好気性菌などとの複数菌感染症として，嫌気性菌が関与する頻度が高いのが特徴である．

PIDの疾患概念

多くのPIDでは，帯下，下腹部痛，下腹部圧痛，下腹部不快感，時に不正性器出血などを認めるが，発熱を伴わないことも多い[1)2)]．

1．子宮内膜炎

子宮内膜炎は，本来，無菌である子宮内膜に炎症が惹起された状態で，産褥性と非産褥性のものがある．

産褥性は，分娩後，流産後あるいは人工妊娠中絶後にみられるもので，急性の経過をとり，胎盤や卵膜の一部遺残や子宮内操作が誘引となる．上行性で，*Staphylococcus* spp.，*Streptococcus* spp.，*Escherichia coli* などのほか，嫌気性菌との複数菌感染も多い．

非産褥性は，子宮内膜掻爬術，子宮卵管造影，子宮内避妊器具(intrauterine device：IUD)挿入，放射線治療などで急性炎症を起こす．淋菌性子宮内膜炎も急性型である．結核性子宮内膜炎は，結核性腹膜炎などから経卵管的に下行性あるいは血行性に子宮内膜に感染をきたし，ほとんどは慢性型である．子宮留膿症(腫)は，高齢による子宮頸部萎縮，子宮体部への癌浸潤，子宮頸癌に対する放射線治療後の子宮頸部の萎縮などにより，卵管間質部・内子宮口が閉塞し，感染により子宮内腔に膿が貯留したものをい

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う．IUDが長期にわたって留置されたことによって起こった子宮内感染では，嫌気性菌の*Actinomyces* spp.が検出されることがあり注意を要する．

慢性型では，最近は，性感染症に関連するものが注目され，子宮頸部に*Neisseria gonorrhoeae*，*Chlamydia trachomatis*の証明された症例に子宮内膜炎を認めることもある．

原因菌が，好気性菌・嫌気性菌ともに，β-ラクタマーゼ産生菌であることが多い．

2．子宮付属器炎

子宮付属器炎は，内性器の炎症の中で最も頻度の高いもので，卵管炎から隣接する卵巣にも炎症が及びやすい．好気性グラム陰性桿菌，好気性グラム陽性球菌，*N. gonorrhoeae*，嫌気性菌，*C. trachomatis*，*Mycoplasma* spp.(*Mycoplasma genitalium*，*Mycoplasma hominis*など)，*Ureaplasma* spp.(*Ureaplasma parvum*，*Ureaplasma urealyticum*など)，時に真菌(*Candida* spp.)などが原因となり，複数菌感染が多い．腟からの上行性感染が大部分を占める．骨盤内感染巣からの下行性感染としては，虫垂炎などに起因するものが挙げられるが，その頻度は低い．

担癌患者などでは，腸管からのトランスロケーションに起因することもある．また，結核性卵管炎は，血行性感染による．流産，分娩，子宮内清掃術などの子宮内操作，IUD装着，子宮卵管造影後，性交感染などが誘引となる．

原因菌が，好気性菌・嫌気性菌ともに，β-ラクタマーゼ産生菌であることが多い．

3．子宮傍結合組織炎

子宮傍結合組織炎とは，小骨盤腔内の骨盤壁，骨盤底筋膜と骨盤腹膜の間で，子宮，膀胱，直腸などの周囲間隙間を満たす広範囲な結合組織の炎症である．本症は，骨盤内感染とは異なり，腹膜外，特に後腹膜の炎症である．本症は，分娩時の産道損傷ならびに流産，人工妊娠中絶時の頸管裂傷などの外傷，子宮全摘術後，あるいは悪性腫瘍の子宮傍結合組織浸潤が激しい場合などに起こりやすい．また，膀胱，直腸などの近接臓器の炎症から連続的にあるいは血行性に発症することもある．

4．骨盤腹膜炎

骨盤腹膜炎とは，小骨盤腔に位置する壁側腹膜および臓側腹膜に発症する限局性腹膜炎のことである．本症は，子宮内膜炎，子宮付属器炎に引き続いて発症することが多いが，虫垂炎の破裂など消化管破裂に続発することもある．特に，子宮付属器炎は，いったん発症すると周囲組織に進展しやすく，多少なりとも骨盤腹膜炎を併発しているとみなすべきである．

子宮内膜炎のみであれば，子宮内膜の周期性のある年齢の女性では，回復力が早く，高熱などの全身症状はほとんど認められず，主として帯下の訴えがあるのみである．炎症が，子宮内膜を越えて筋層に及んだ子宮内膜筋層炎では帯下などの症状が持続する．高齢者では，しばしば子宮留膿腫，骨盤腹膜炎に発展することがあり，この際には，激しい下腹部痛が出現する[3)4)]．

子宮付属器炎の急性期には，付属器に激痛があり，炎症が進行すると，腹膜刺激症状(骨盤腹膜炎)を認めることもある．内性器感染症では，上行性感染により，骨盤腹膜炎，ダグラス窩膿瘍を認めることもある[3)4)]．

PIDの原因微生物は，好気性グラム陰性桿菌，好気性グラム陽性球菌，*N. gonorrhoeae*，嫌気性菌，*C. trachomatis*，*Mycoplasma* spp.，*Ureaplasma* spp.，時に真菌(*Candida* spp.)などが原因となり，複数菌感染が多い．腟からの上行性感染が大部分を占める．骨盤内感染巣からの下行性感染としては，虫垂炎などに起因するものが挙げられるが，その頻度は低い．担癌患者などでは，腸管からのトランスロケーション

に起因することもある．また，結核性卵管炎は，血行性感染による．流産，分娩，子宮内清掃術などの子宮内操作，IUD 装着，子宮卵管造影後，性交感染などが誘引となる．原因菌が，好気性菌・嫌気性菌ともに，β-ラクタマーゼ産生菌であることが多い[5]．

肝周囲炎(perihepatitis，かつての Fitz-Hugh Curtis syndrome)とは，一般的には，クラミジアや淋菌による子宮頸管炎からの上行性感染により骨盤腹膜炎をきたし，上腹部に及んで肝周囲炎に至ったものと考えられている．本症候群の特徴としては，下腹部痛とそれに伴う右季肋部痛であるが，激しい上腹部痛を初発症状とすることも多いため，内科，外科など他科を初診とすることも多い．したがって，適切な診断・治療が遅れ，患者に不要な苦痛を与えることになりかねない疾患である[6]．

また，抗菌薬による治療に反応しない場合には，真菌性腹膜炎などの深在性真菌症も考えられる[7]．ハイリスク患者で，抗菌薬(≧3 種類，＞連続 7 日)投与後も発熱や炎症所見が持続する場合には，血清診断：β-D-グルカンおよび真菌学的検査(血液培養：末梢静脈血を 1 日 2 回 2 日間連続培養，ほかの部位の監視培養：≧3 カ所［喀痰，ドレーン，創，尿，便など］)を実施して，総合的に判断することが重要である[7]．さらに，必要に応じて，CT などを施行し，ほかの原因を除外すること，膿瘍形成例では穿刺吸引して培養を提出することが必要である．また，視覚異常例では，眼底検査が必須である．

β-D-グルカン陽性またはカンジダ colonization が複数箇所の場合は，真菌症疑い例として経験的治療を行う[7]．真菌性眼内炎症例，中心静脈カテーテル培養陽性で抜去後も 72 時間発熱が持続する場合，新生児でカンジダ尿が検出された場合には，臨床的診断例として標的治療を行う[7]．血液培養陽性例，または膿瘍穿刺液からカンジダ属が証明された場合には，確定診断例として標的治療を行う外科領域で分離される真菌は，ほとんどがカンジダ属である．特に，*Candida albicans* 以外のカンジダ属(non-*albicans Candida*)が増加している[8]．

PID の診断

PID では，嫌気性菌が関与する症例が多いので，培養結果に時間を要することも多く，検体のグラム染色結果は，empiric therapy を行う上で非常に重要な意味をもつ．具体的には，「主体はグラム陽性菌か，グラム陰性菌か」「主体は球菌か，桿菌か」を知ることは，抗菌薬選択の上で非常に有意義な情報となる．また，検査室から，嫌気性菌培養結果が陰性として報告される場合も少なくないので，グラム染色のもつ意義は大きい．

グラム染色標本で，グラム陰性双球菌が認められる場合には，淋菌性子宮内膜炎などを強く疑うことができる場合もある．

検体採取にあたっては，できる限り腟内細菌のコンタミネーションを避けるよう努力する必要がある．子宮付属器炎では，ダグラス窩穿刺の必要性について，患者に十分説明をするなどして，コンタミネーションの少ない良質の検体を提出するよう心がける．

図 1 に PID である子宮および付属器の感染症の病原診断のためのフローチャートを示した．

オフィス診療としての PID 治療

感染巣(遺残胎盤など)や骨盤内膿瘍を認めれば抗菌化学療法施行のもと，内容除去や手術(患側卵管の摘除)，切開排膿を行う．抗菌化学療法は原則として単剤投与で行うが，病態によっては抗菌薬相互の併用療法も採用する．

原因菌決定後の標的治療は，抗菌化学療法の基本は，常在菌叢にあまり影響を与えず，原因

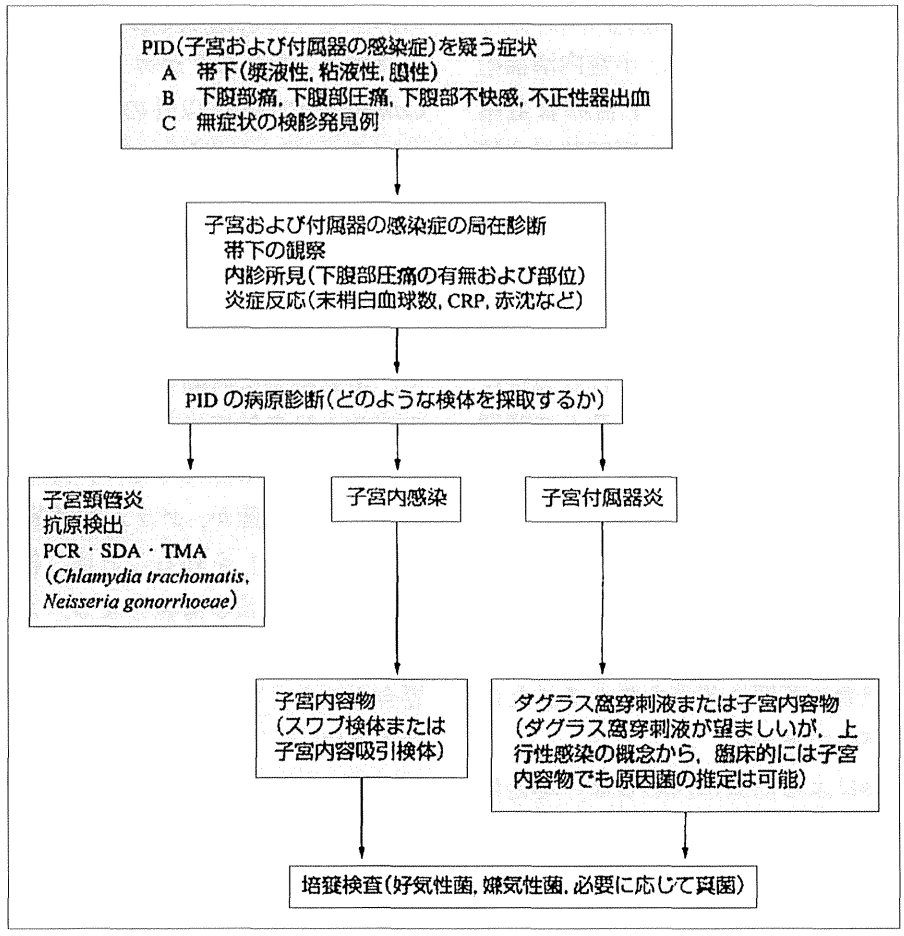

図1 PID診断のためのフローチャート

表1 オフィス診療におけるPIDに対する抗菌化学療法の一例

①アモキシシリン/クラブラン酸カリウム	1回375 mg, 1日3〜4回
②ファロペネム	1回150〜300 mg, 1日3回
③シタフロキサシン	1回50〜100 mg, 1日2回
④メトロニダゾール	1回500 mg, 1日4回

嫌気性菌による感染が主である場合には, 点滴静注治療を行う場合が多い.
③は, 妊娠している女性, 妊娠の可能性のある女性には, 投与しない.
授乳中の女性に③を投与する場合には, 授乳を中止する.
好気性菌などとの複数菌感染症の症例に, ④を投与する場合には, 推定原因菌に感受性を示す薬剤と併用投与する.
①〜③のいずれも, 症状により, クリンダマイシン, ミノサイクリンと併用することもある.

菌のみを攻撃する狭域性抗菌薬投与(培養検査および薬剤感受性検査の施行が前提となる)が望ましい.

メチシリン耐性黄色ブドウ球菌(MRSA)感染症に遭遇した場合には, バンコマイシン, テイコプラニン, アルベカシン, リネゾリド, ダプトマイシンなどの抗MRSA薬を投与する必要があるため, 外来オフィス診察では困難であり

入院治療を勧める.

PIDでは，経口治療がよいか，点滴静注治療がよいかは，臨床症状の程度によって判断する．PIDの急性期では，嫌気性菌にも抗菌力を示す広域スペクトルの抗菌薬が汎用される．一般的に，軽症から中等症では経口治療も可能であるためオフィス診療の適応となる(表1)が，下腹部痛，下腹部圧痛が強く，骨盤腹膜炎，腹膜炎まで進展している症例は重症であり，入院しての点滴静注治療が望ましい.

耐性菌の発現を抑制するため，発熱，下腹部痛，下腹部圧痛などの臨床症状が改善したところで，抗菌薬の投与を中止して経過を観察するのが原則であることはいうまでもない．オフィス診療の対象となる多くのPIDは7日以内の抗菌薬治療で治癒することが多い.

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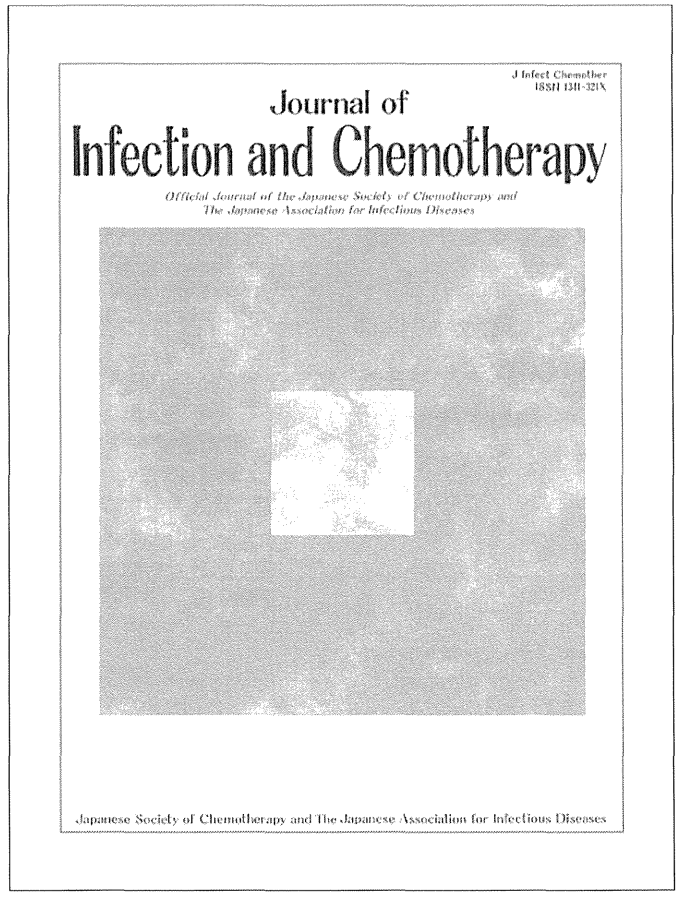
Column　保険診療上の留意点

PIDの診断において，嫌気性菌も含めた原因微生物検索を実施するにあたっては，「腟分泌物」を提出するのではなく，「子宮内容物」「ダグラス窩穿刺液」「腹水」などを提出するよう心がけることが保険診療上も重要である．また，クラミジア・トラコマチスと淋菌の遺伝子学的同時診断法(SDA法やTMA法など)を全症例ルーチンに実施すると査定の対象となるため，症例を見極めて検査を提出することも重要である．保険診療上，淋菌に関して遺伝子診断と培養検査を同時に実施してはならない．オフィス診療の対象となるPIDに対する治療は，7日以内の抗菌薬投与により治癒することが多く，投与期間が長くなる場合には，培養検査の実施などがないと査定の対象となるため注意されたい.



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Original article

Efficacy and safety of intravenous azithromycin followed by oral azithromycin for the treatment of acute pelvic inflammatory disease and perihepatitis in Japanese women

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ABSTRACT

Pelvic inflammatory disease (PID) is mainly caused by ascending infection from the vaginal flora including the sexually transmitted organisms, *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, and lower genital tract endogenous anaerobes, leading to serious consequences including infertility and ectopic pregnancy. To evaluate the efficacy and safety of azithromycin in the treatment of PID that requires initial intravenous therapy, we conducted a multicenter, unblinded, non-comparative phase 3 trial. Intravenous azithromycin (500 mg, once daily) for 1 or 2 days followed by oral azithromycin (250 mg once daily) to complete a total of 7 days treatment was administered to 60 Japanese women with acute PID. The clinical and bacteriological responses were assessed at the end of treatment, and on Days 15 and 29. The most commonly detected baseline causative pathogens were *C. trachomatis* (12 strains), *Prevotella bivia* (10 strains), *Streptococcus agalactiae* (7 strains), *N. gonorrhoeae* and *Peptostreptococcus anaerobius* (6 strains each). The clinical success rate on Day 15 was 94.1% (48/51 subjects including perihepatitis). The clinical efficacy and bacterial eradication rates against *C. trachomatis* and *N. gonorrhoeae* (including 2 quinolone-resistant strains) were both 100%. Common treatment-related adverse events were diarrhoea, injection site pain, and nausea. All adverse events were mild or moderate in severity. Azithromycin intravenous-to-oral switch therapy demonstrated excellent clinical and bacteriological effects for PID caused by various etiologic agents including quinolone-resistant strains and strains with low susceptibility to azithromycin at *in vitro* testing. The therapy was well tolerated in the treatment of PID in Japanese women.

Registration number: NCT00871494.

1. Introduction

Pelvic inflammatory disease (PID) is a common infection and consists of inflammation of the upper female genital tract caused by ascending infection from the endocervix in women in their reproductive years, and it frequently leads to serious consequences including infertility, ectopic pregnancy, and chronic pelvic pain [1–4]. In Japan, there is little epidemiologic data on PID available at the moment [5].

Based on the polymicrobial etiology of PID, antimicrobial therapy should provide broad spectrum coverage of *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, mycoplama, and anaerobic and aerobic bacteria. The initial antimicrobial therapy for PID is usually empirical, and is complicated by the increasing global prevalence of antibiotic resistance, in particular resistance to β-lactams, quinolones and/or macrolides, among the common causative pathogens, especially gonorrhoea in PID [1,2,4]. Owing to the emergence of quinolone-resistant *N. gonorrhoeae* (QRNG), quinolones are no longer recommended for the treatment of PID associated with gonorrhoea [1,2,4].

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1341-321X/

Azithromycin (AZM) is a macrolide antibiotic that has a broad spectrum of antimicrobial activity covering various causative pathogens in PID including *N. gonorrhoeae*, *C. trachomatis*, mycoplama, and endogenous anaerobic and facultative bacteria. Randomized controlled studies demonstrated that intravenous (IV) AZM 500 mg once daily for 1 or 2 days followed by oral AZM 250 mg once daily to complete a total of 7 days treatment produced high clinical success rates, both as monotherapy and combined with metronidazole [6]. AZM regimens are included in the Centers for Disease Control and Prevention (CDC) 2010 sexually transmitted disease (STD) treatment guidelines as alternative regimens for PID [4].

Since an AZM IV formulation was approved in the United States of America in 1997, it has been approved in more than 50 countries except for Japan. We conducted a phase 3 trial of IV AZM followed by oral AZM administration in Japanese adults to evaluate the clinical efficacy and safety for the treatment of PID requiring initial IV therapy in order to obtain regulatory approval.

2. Materials and methods

This study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice Guidelines, the principle of the Declaration of Helsinki and all applicable laws and regulations. The protocol was reviewed and approved by the Institutional Review Boards at participating study sites. All subjects or legally authorized representatives provided a written informed consent form before enrollment.

2.1. Study design

This multicenter, non-randomized, unblinded, non-comparative phase 3 study was designed to investigate the clinical efficacy and safety of AZM IV-to-oral switch therapy in Japanese female subjects with PID. An independent Data Review Committee (DRC) was organized to assure an objective and unified efficacy evaluation based on the clinical conditions and findings from the diagnostic imaging. To all subjects, 500 mg IV AZM was administrated once daily at an infusate concentration of 1 mg/ml over 2 h for 1 or 2 days, followed by 250 mg oral AZM once daily to complete a total of 7 days. Switching from IV-to-oral therapy was determined by the investigators according to the subject's condition.

2.2. Eligibility criteria

Females aged 16 years or older who were given a diagnosis of PID and required initial IV antibacterial therapy were eligible.

PID is defined as follows [4,6]:

(A) Either one or both of the following symptoms should be observed: (a) abdominal pain lower and/or lower abdominal tenderness (tenderness of the uterus or its adnexa); and (b) hypochondrial pain and/or hypochondrial tenderness.
(B) Once the above criterion is satisfied, then 2 of the 5 following conditions should be observed: (a) fever $\geq$ 37 °C (axillary); (b) increased white blood cell (WBC) count (>upper limit of the normal range); (c) raised CRP (>upper limit of the normal range); (d) purulent leucorrhea and purulent discharge that can be confirmed by Douglas puncture and laparoscopy; and (e) pelvic abscess that can be confirmed by ultrasonography.

Peritonitis (including perihepatitis) and Douglas abscess were included in PID as relevant diseases in this study. However, patients with these diseases were not enrolled if they did not meet the criteria for PID.

Exclusion criteria of the study included the following conditions or situations: hypersensitivity to AZM, or any macrolide or ketolide antibiotics, hepatic dysfunction, severe renal dysfunction, severe heart diseases, severe underlying disease or complication, causative pathogens resistant to AZM, pregnancy or lactation in women, immunodeficiency disease, or endometriosis without any infection.

The following concomitant medications during the primary evaluation period (up to Day 15) were prohibited: human immunoglobulin, colony-stimulating factors, corticosteroids, taking an analgesic antipyretic continuously, and other investigated drugs or medical devices.

2.3. Clinical and radiographic assessments

The primary endpoint was clinical response assessed by the DRC at the end of treatment (EOT), and on Days 15 and 29. The clinical response was evaluated as "effective" if both of the following criteria were met: (A) all signs and symptoms associated with PID resolved or improved; and (B) abnormal findings in the parameters in paragraph 2 of the diagnostic criteria, which had been found on Day 1, resolved or improved. The clinical response was evaluated as "ineffective" if any of the following criteria was met: (A) the criteria of "effective" were not satisfied; (B) the treatment failed and other systemic antibiotics were administered; (C) persistent infection or recurrence of infection in the abdominal cavity was confirmed by abdominal ultrasonography, percutaneous drainage, or second surgery; (D) surgical site infection was confirmed after surgery; and (E) death linked to infection of the same area was confirmed. The clinical response was evaluated as "indeterminate" if the above-mentioned criteria were not assessed for various reasons.

We also investigated the reasons for switching from IV-to-oral therapy.

2.4. Bacteriological assessment

The secondary efficacy endpoint was bacteriological response at EOT, and on Days 15 and 29 assessed by the DRC. All subjects provided clinical specimens, which were sent to a central laboratory for culture, and isolated pathogens were tested for susceptibility according to the Clinical and Laboratory Standards Institute procedures at the baseline visit, EOT, on Days 15 and 29. These specimens were also submitted for detection of *C. trachomatis*, *N. gonorrhoeae*, or *Mycoplasma* spp by antigen tests using polymerase chain reaction (PCR), strand displacement amplification, and/or enzyme immunoassays. Antigen tests were performed at baseline and on Days 15 and 29.

Bacteriological response was assessed as "eradication" if the original pathogen was not identified in the specimens, "presumed eradication" if the subject was not producing evaluable specimens from a focus of infection, "persistence" if the original pathogen remained in the specimens, "replacement bacterium" if the original pathogens were eradicated by treatment, and other new pathogens appeared in the same specimen, with symptoms and/or findings of an infection, and "indeterminate" if the above-mentioned criteria were not assessed for various reasons.

2.5. Safety assessment

Safety data were obtained from findings of clinical signs/symptoms, physical examinations, vital signs, and laboratory data up to 29 days. The causality and severity of the adverse events were evaluated by the investigators based on MedDRA terminology.

2.6. Statistical analysis

In accordance with the guideline for clinical evaluation of antimicrobial agents [7], the total target number of patients was determined to be 18. Based on the fact that the bacterial detection rate was estimated to be 30%, the total target number of patients to be included in the study was determined to be 60. The Clinical Per-Protocol Set (CPPS) consisted of all subjects who received at least 1 dose of the study drug, had no significant protocol violations, and underwent the evaluations during the observation period as specified in the protocol. The Bacteriologic Per-Protocol Set (BPPS) consisted of a subset of the CPPS in whom causative pathogens were identified by culture and by antigen tests at baseline. For the primary analysis of the primary endpoint, the efficacy rate based on DRC-evaluated clinical response on Day 15 and its 95% confidence interval (CI) were calculated for the CPPS. For the secondary analysis, the efficacy rate based on DRC-evaluated clinical response at EOT and on Day 29 and the respective 95% CIs were calculated for the CPPS. For the bacteriological response, which was the secondary endpoint, the eradication rate at EOT and on Day 15 and 29 and the respective 95% CIs were calculated for the BPPS. Safety data were analyzed based on all subjects who received at least 1 dose of the study drug and utilized mainly descriptive statistics. In the above analyses, 95% CI for the rates were based on the Clopper-Pearson method.

3. Results

3.1. Subject disposition

This study was performed at 35 medical centers nationwide in Japan from October 2009 to March 2010. A total of 60 subjects were enrolled in the study at 30 sites, and all of them received the study drug. Among them, 50 subjects (83.3%) completed the study, and 10 subjects (16.7%) discontinued the study (Table 1).

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

Details of the primary diagnosis for the subjects are shown in Table 3. Nine subjects were excluded from the CPPS. Of the 9 subjects excluded from the CPPS, 5 subjects did not meet the inclusion criteria, 2 subjects continuously used antipyretic analgesic drugs, 1 subject met any exclusion criteria concerning systemic antimicrobial drugs, and it was impossible to evaluate the drug efficacy in 1 subject. Of 51 subjects in the CPPS, 3 subjects had perihepatitis, 23 subjects had pelvic peritonitis, 16 subjects had adenexitis, and 9 subjects had intrauterine infection.

Among 51 subjects in the CPPS, 20 different species of causative pathogens were isolated at baseline from 36 subjects (70.6%) as shown in Table 4. The most common causative pathogen was *C. trachomatis*, followed by *Prevotella bivia*, *Streptococcus agalactiae*, *Peptostreptococcus anaerobius*, and *N. gonorrhoeae*.

Table 1
Subject disposition.

	Number of subjects
Assigned to treatment	60
Treated	60
Completed	50 (83.3)
Discontinued	10 (16.7)
Deviation from the inclusion criteria	4 (6.7)
Insufficient efficacy	3 (5.0)
Adverse events	3 (5.0)
Lost to follow-up	0

Values represent the number (%) of subjects.

Table 2
Baseline demographic characteristics by analysis set.

Characteristics	FAS ($N = 60$)	CPPS ($N = 51$)	BPPS ($N = 36$)
Age (yr)			
≤19	5 (8.3)	5 (9.8)	5 (13.9)
20–25	10 (16.7)	8 (15.7)	5 (13.9)
26–30	16 (26.7)	13 (25.5)	13 (36.1)
31–35	10 (16.7)	8 (15.7)	2 (5.6)
36–40	7 (11.7)	6 (11.8)	5 (13.9)
≥41	12 (20.0)	11 (21.6)	6 (16.7)
Mean ± SD	32.3 ± 0.0	32.3 ± 10.3	30.8 ± 10.3
Range	16–54	16–54	16–54
Body weight (kg)			
Mean ± SD	52.8 ± 10.2	52.1 ± 8.2	50.8 ± 6.6
Range	38.0–101.0	38.0–81.7	38.0–66.4

Abbreviations: FAS, full analysis set; CPPS, clinical per protocol set; BPPS, bacteriologic per protocol set.
N = number of subjects assigned.
Values represent the number (%) of subjects.

In this study, IV AZM was administered for 1 or 2 days. Of 51 subjects in the CPPS, 12 subjects were given IV AZM for 1 day. The diseases that the 12 subjects had were the following: intrauterine infection (5 subjects); pelvic peritonitis (2 subjects); adnexitis (2 subjects); perihepatitis (1 subject); pelvic peritonitis and adnexitis (1 subject); and pelvic peritonitis, Douglas abscess, and adnexitis (1 subject). For 51 subjects in the CPPS, the average administration period of IV AZM was 1.8 days and that of oral AZM preparation was 5.1 days. The average overall treatment period was 6.9 days. Of 51 subjects in the CPPS, 26 subjects (51.0%) were hospitalized patients. The remaining 25 subjects (49.0%) received outpatient treatment. Among the hospitalized patients, 10 subjects (38.5%) were discharged before or on the day of the first oral dose, and 15 subjects (57.7%) were discharged between the day of the second oral dose and the day following EOT. After discharge, the 25 subjects received outpatient therapy.

3.2. Efficacy

As for the clinical response assessed by the DRC, the efficacy rate of subjects in the CPPS was 94.1% on Day 15 (primary analysis)

Table 3
Details of primary diagnosis.

Primary diagnosis	FAS ($N = 60$)	CPPS ($N = 51$)
Pelvic inflammatory disease	60	51
Perihepatitis, pelvic peritonitis, adnexitis	1 (1.7)	1 (2.0)
Perihepatitis, pelvic peritonitis	1 (1.7)	1 (2.0)
Perihepatitis	1 (1.7)	1 (2.0)
Pelvic peritonitis, Douglas abscess, adnexitis, intrauterine infection	1 (1.7)	1 (2.0)
Pelvic peritonitis, Douglas abscess, adnexitis	2 (3.3)	2 (3.9)
Pelvic peritonitis, Douglas abscess	1 (1.7)	1 (2.0)
Pelvic peritonitis, adnexitis, intrauterine infection	1 (1.7)	1 (2.0)
Pelvic peritonitis, adnexitis	7 (11.7)	6 (11.8)
Pelvic peritonitis, intrauterine infection	1 (1.7)	1 (2.0)
Pelvic peritonitis	11 (18.3)	11 (21.6)
Adnexitis, intrauterine infection	2 (3.3)	2 (3.9)
Adnexitis	15 (25.0)	14 (27.5)
Intrauterine infection	9 (15.0)	9 (17.6)
Not eligible[a]	7 (11.7)	–

Abbreviations: FAS, full analysis set; CPPS, clinical per protocol set.
N = number of subjects.
Values represent the number (%) of subjects.
[a] Subjects with "pelvic abscess," "pelvic peritonitis, adnexitis," "pelvic peritonitis," and "intrauterine infection" who did not meet the inclusion criteria, and other subjects who were not eligible.

Table 4
Baseline causative pathogens identified (CPPS).

Causative pathogen	
Total number of subjects	51 (100)
Total number of subjects with pathogen(s)	36 (70.6)
Number of subjects with a single pathogen	17 (33.3)
N. gonorrhoeae	3
C. trachomatis	6
Coagulase negative *Staphylococcus*	1
S. agalactiae	2
Streptococcus pneumoniae	1
Sphingomonas paucimobilis	1
P. anaerobius	1
P. bivia	2
Number of subjects with 2 or more pathogens	19 (37.3)
N. gonorrhoeae + *P. bivia*	1
C. trachomatis + *M. hominis*	2
C. trachomatis + *P. bivia*	2
C. trachomatis + *Fusobacterium varium*	1
M. hominis + *P. anaerobius*	1
Coagulase negative *Staphylococcus* + *P. bivia*	1
S. agalactiae + *H. influenzae*	1
S. agalactiae + *P. anaerobius*	1
Escherichia coli + *P. bivia*	1
Porphyromonas gingivalis + *Bacteroides ovatus*	1
N. gonorrhoeae + *M. hominis* + *P. anaerobius*	1
N. gonorrhoeae + *S. agalactiae* + *P. bivia*	1
C. trachomatis + Coagulase negative *Staphylococcus* + *S. agalactiae*	1
E. coli + *P. bivia* + *Enterococcus avium*	1
Ureaplasma urealyticum + Coagulase negative *Staphylococcus* + *P. anaerobius* + *Porphyromonas asaccharolytica*	1
Streptococcus constellatus + *P. anaerobius* + *Fusobacterium nucleatum* + *Actinomyces spp.*	1

Abbreviation: CPPS, clinical per protocol set.
Values represent the number (%) of subjects.

(Table 5). High efficacy rates exceeding 90% were achieved at all assessment time points. Of the 12 subjects given IV AZM for 1 day among 51 subjects in the CPPS, the clinical response on Day 15 was classified as ineffective only in 1 subject.

The clinical response by baseline causative pathogen in the BPPS judged by the DRC is shown in Table 6. The clinical efficacy rate on Day 15 was 100% (12/12) for *C. trachomatis*, 100% (6/6) for *N. gonorrhoeae*, and 90.5% (19/21) for anaerobes.

The bacteriological response by baseline causative pathogen in the BPPS judged by the DRC is shown in Table 7. The eradication rate by major causative pathogen on Day 15 was 100% (6/6 strains) for *N. gonorrhoeae*, 100% (11/11 strains) for *C. trachomatis*, 77.8% (7/9 strains) for *P. bivia*, 71.4% (5/7 strains) for *S. agalactiae*, and 83.3% (5/6 strains) for *P. anaerobius*.

For subjects in the BPPS, the clinical and bacteriological responses by AZM susceptibility of baseline pathogens assessed by the DRC are shown in Table 8. Good clinical efficacy and bacterial eradication were achieved regardless of the type and *in vitro* susceptibility of the causative pathogens. AZM IV-to-oral therapy was

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

Assessment time point	Total	Clinical response			Efficacy Rate[a]	95% CI
		Effective	Ineffective	Indeterminate		
End of treatment	51	48 (94.1)	3 (5.9)	0	94.1	(83.8, 98.8)
Day 15	51	48 (94.1)	3 (5.9)	0	94.1	(83.8, 98.8)
Day 29	51	43 (84.3)	3 (5.9)	5 (9.8)	93.5	(82.1, 98.6)

Abbreviations: CPPS, clinical per protocol set; CI, confidence interval.
[a] Efficacy rate = effective/(total − indeterminate) × 100.

Table 6
Clinical response by baseline causative pathogen (Data Review Committee assessment, BPPS).

Pathogen[a]	Clinical response					
	End of treatment		Day 15		Day 29	
	n/*N*	Efficacy rate[b]	*n*/*N*	Efficacy rate[b]	*n*/*N*	Efficacy rate[b]
N. gonorrhoeae	6/6	100	6/6	100	4/4	100
C. trachomatis	12/12	100	12/12	100	11/11	100
M. hominis	3/4	75.0	3/4	75.0	2/3	66.7
U. urealyticum	1/1	100	1/1	100	1/1	100
Coagulase negative *Staphylococcus*	4/4	100	4/4	100	3/3	100
S. pneumoniae	1/1	100	1/1	100	1/1	100
S. agalactiae	6/7	85.7	6/7	85.7	6/7	85.7
S. constellatus	1/1	100	1/1	100	0	–
E. avium	0/1	0	0/1	0	0/1	0
H. influenzae	1/1	100	1/1	100	1/1	100
E. coli	1/2	50.0	1/2	50.0	1/2	50.0
S. paucimobilis	1/1	100	1/1	100	1/1	100
P. anaerobius	5/6	83.3	5/6	83.3	3/4	75.0
B. ovatus	1/1	100	1/1	100	1/1	100
P. bivia	9/10	90.0	9/10	90.0	7/8	87.5
P. asaccharolytica	1/1	100	1/1	100	1/1	100
P. gingivalis	1/1	100	1/1	100	1/1	100
F. varium	1/1	100	1/1	100	1/1	100
F. nucleatum	1/1	100	1/1	100	0	–
Actinomyces spp.	1/1	100	1/1	100	0	–

Abbreviation: BPPS, bacteriologic per protocol set.
n = number of subjects in whom the clinical response was effective.
N = number of assessable subjects excluding subjects in whom the clinical response was indeterminate.
[a] More than 1 pathogen may be isolated in a subject.
[b] Calculated as *n*/*N* × 100.

Table 7
Bacteriological response by baseline causative pathogen (Data Review Committee assessment, BPPS).

Pathogen[a]	Bacteriological response					
	End of treatment		Day 15		Day 29	
	n/*N*	Eradication rate[b]	*n*/*N*	Eradication rate[b]	*n*/*N*	Eradication rate[b]
N. gonorrhoeae[c]	2/2	100	6/6	100	4/4	100
C. trachomatis[c]	8/8	100	11/11	100	11/11	100
M. hominis[c]	0/1	0	2/3	66.7	2/3	66.7
U. urealyticum[c]	0	–	1/1	100	1/1	100
Coagulase negative *Staphylococcus*	4/4	100	2/2	100	3/3	100
S. pneumoniae	1/1	100	1/1	100	1/1	100
S. agalactiae	4/7	57.1	5/7	71.4	5/7	71.4
S. constellatus	1/1	100	1/1	100	0	–
E. avium	0/1	0	0/1	0	0/1	0
H. influenzae	0/1	0	1/1	100	1/1	100
E. coli	1/2	50.0	1/2	50.0	1/2	50.0
S. paucimobilis	1/1	100	1/1	100	1/1	100
P. anaerobius	5/6	83.3	5/6	83.3	3/4	75.0
B. ovatus	1/1	100	1/1	100	1/1	100
P. bivia	8/10	80.0	7/9	77.8	6/8	75.0
P. asaccharolytica	1/1	100	1/1	100	1/1	100
P. gingivalis	1/1	100	1/1	100	1/1	100
F. varium	1/1	100	1/1	100	1/1	100
F. nucleatum	1/1	100	1/1	100	0	–
Actinomyces spp.	1/1	100	1/1	100	0	–

Abbreviation: BPPS, bacteriologic per protocol set.
n = number of causative pathogens assessed as eradication or presumed eradication, and *N* = number of total pathogens − number of pathogens with an indeterminate response.
[a] More than 1 pathogen may be isolated in a subject.
[b] Calculated as eradication rate = *n*/*N* × 100.
[c] For these causative pathogens, the bacteriological response for those identified only by antigen tests was indeterminate at the end of treatment since measurement had not been scheduled (excluding cases where systemic antimicrobial agents were administered).

Table 8
Clinical and bacteriological responses by AZM MIC of baseline causative pathogen (Data Review Committee assessment, BPPS).

Pathogen[a]	MIC	End of treatment		Day 15		Day 29	
		Efficacy rate[b] (%)	Eradication rate[c] (%)	Efficacy rate[b] (%)	Eradication rate[c] (%)	Efficacy rate[b] (%)	Eradication rate[c] (%)
N. gonorrhoeae	MIC = 0.12 μg/ml	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
	MIC = 0.25 μg/ml	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
	MIC unknown	4/4 (100)	0 (–)	4/4 (100)	4/4 (100)	2/2 (100)	2/2 (100)
C. trachomatis	MIC = 0.015 μg/ml	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
	MIC = 0.03 μg/ml	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)	1/1 (100)	1/1 (100)
	MIC = 0.06 μg/ml	3/3 (100)	3/3 (100)	3/3 (100)	3/3 (100)	3/3 (100)	3/3 (100)
	MIC unknown	6/6 (100)	2/2 (100)	6/6 (100)	5/5 (100)	6/6 (100)	6/6 (100)
M. hominis	MIC unknown	3/4 (75.0)	0/1 (0)	3/4 (75.0)	2/3 (66.7)	2/3 (66.7)	2/3 (66.7)
U. urealyticum	MIC unknown	1/1 (100)	0 (–)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
Coagulase negative *Staphylococcus*	MIC = 0.5 μg/ml	3/3 (100)	3/3 (100)	3/3 (100)	1/1 (100)	2/2 (100)	2/2 (100)
	MIC > 64 μg/ml	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
S. pneumoniae	MIC > 64 μg/ml	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
S. agalactiae	MIC = 0.06 μg/ml	2/3 (66.7)	1/3 (33.3)	2/3 (66.7)	2/3 (66.7)	2/3 (66.7)	2/3 (66.7)
	MIC = 0.12 μg/ml	2/2 (100)	1/2 (50.0)	2/2 (100)	2/2 (100)	2/2 (100)	1/2 (50.0)
	MIC = 0.25 μg/ml	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
	MIC > 64 μg/ml	1/1 (100)	1/1 (100)	1/1 (100)	0/1 (0)	1/1 (100)	1/1 (100)
S. constellatus	MIC = 0.06 μg/ml	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	0 (–)	0 (–)
E. avium	MIC > 64 μg/ml	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)
H. influenzae	MIC = 4 μg/ml	1/1 (100)	0/1 (0)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
E. coli	MIC = 4 μg/ml	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
	MIC = 8 μg/ml	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)
S. paucimobilis	MIC = 1 μg/ml	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
P. anaerobius	MIC = 1 μg/ml	2/3 (66.7)	2/3 (66.7)	2/3 (66.7)	2/3 (66.7)	1/2 (50.0)	1/2 (50.0)
	MIC = 2 μg/ml	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
	MIC > 64 μg/ml	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)	1/1 (100)	1/1 (100)
B. ovatus	MIC >64 μg/ml	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
P. bivia	MIC = 2 μg/ml	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
	MIC = 4 μg/ml	3/4 (75.0)	3/4 (75.0)	3/4 (75.0)	3/4 (75.0)	3/4 (75.0)	3/4 (75.0)
	MIC = 16 μg/ml	2/2 (100)	2/2 (100)	2/2 (100)	1/2 (50.0)	2/2 (100)	1/2 (50.0)
	MIC = 64 μg/ml	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	0 (–)	0 (–)
	MIC > 64 μg/ml	2/2 (100)	1/2 (50.0)	2/2 (100)	1/1 (100)	1/1 (100)	1/1 (100)
P. asaccharolytica	MIC = 0.06 μg/ml	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
P. gingivalis	MIC >64 μg/ml	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
F. varium	MIC = 0.5 μg/ml	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
F. nucleatum	MIC = 0.12 μg/ml	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	0 (–)	0 (–)
Actinomyces spp.	MIC unknown	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	0 (–)	0 (–)

Abbreviations: AZM, azithromycin; BPPS, bacteriologic per protocol set.
–: Not available.
[a] More than 1 pathogen may be isolated in a subject.
[b] Efficacy rate = Effective/(Total − Indeterminate) × 100.
[c] Eradication rate = (Eradication + Presumed Eradication)/(Total − Indeterminate) × 100.

effective for PID, on Day 15, even in subjects from whom high-level resistant strains (MIC ≥ 64 mg/ml) were isolated. AZM treatment was also effective in eradicating highly resistant pathogens.

Of 6 strains of *N. gonorrhoeae* identified in the BPPS, 2 strains showed quinolone-resistance judged by their MIC values. As shown in Table 9, good clinical efficacy and bacterial eradication were achieved in these 2 cases as well as improvement of the clinical signs and symptoms. In case 1, the abdominal pain lower and the CRP value improved dramatically. In case 2, the abdominal pain lower and the WBC count also improved dramatically.

For subjects in the CPPS, clinical signs and symptoms tended to improve from EOT onwards, and further improved and/or resolved over time. Body temperature, WBC count, and CRP improved in most subjects after switching to oral therapy. After bacterial infection, WBC starts to increase at an early stage, and CRP starts to increase thereafter [8–10]. Improved levels of CRP were therefore limited at the time of switching to oral therapy (Fig. 1).

Inflammatory findings of the diagnostic radiographic imaging improved after EOT and further improved over the course of treatment in subjects in the CPPS.

For 48 subjects in the CPPS whose clinical response on Day 15 was assessed as effective by the DRC, the reasons for switching from IV-to-oral therapy were "improvement in clinical signs and symptoms (body temperature, WBC count, and CRP)" in 19 subjects (39.6%) and "improvement in clinical symptoms (other than body temperature, WBC count, and CRP; i.e., improvement in abdominal pain lower, lower abdominal tenderness, hypochondrial pain, upper abdominal tenderness, pain upon moving, painful respiration, and fluor vaginalis)" in 29 subjects (60.4%). The descriptive statistics (median, 75th and 90th percentiles) for body temperature, WBC count, and CRP at the time of switching from IV-to-oral therapy are shown in Fig. 1. For body temperature, approximately 75% of the investigators switched from IV-to-oral AZM therapy for subjects with a temperature under 37 °C. Concerning the WBC count and CRP, approximately 75% of the investigators decided to switch to oral therapy for subjects if these parameters were under 8200/mm^3 and 4.5 mg/dl, respectively.

3.3. Safety results

Among the 60 subjects, 17 subjects (28.3%) experienced treatment-related adverse events. All treatment-related adverse events were mild or moderate in severity. Moderate adverse events were diarrhoea (3 subjects), gastroenteritis and urticaria (1 subject each). No serious treatment-related adverse events were reported and no subject discontinued the study due to treatment-related adverse events. Common treatment-related adverse events were diarrhoea (8 subjects, 13.3%), and nausea (3 subjects, 5.0%).

Table 9
Clinical signs and symptoms in 2 PID cases due to quinolone-resistant *N. gonorrhoeae*.

Clinical sign and symptom	Assessment time point				
	Day 1	IV-to-oral	EOT	Day 15	Day 29
Case 1[a]					
Pain, lower abdominal	2+	–	–	–	–
Tenderness, lower abdominal	2+	1+	–	–	–
Pain, upon movement	2+	–	–	–	–
Body temperature (°C)	37.2	36.4	36.6	36.9	36.7
WBC (/mm^3)	9600	3000	3100	3400	4700
CRP (mg/dl)	14.99	9.37	0.76	<0.25	<0.25
Clinical efficacy	–	–	Effective	Effective	Effective
Bacterial Eradication	–	–	Eradicated	Eradicated	Eradicated
Case 2[b]					
Pain, lower abdominal	3+	–	–	1+	–
Tenderness, lower abdominal	3+	1+	–	1+	–
Pain, upon movement	1+	–	–	–	–
Fluor vaginalis	+	–	–	–	–
Abscess	+	+	+	–	–
Body temperature (°C)	37.1	36.3	36.8	35.8	36.4
WBC (/mm^3)	15,600	11,500	6900	7700	5400
CRP (mg/dl)	2.4	1.8	0.1	0.0	0.1
Clinical efficacy	–	–	Effective	Effective	Effective
Bacterial eradication	–	–	Eradicated	Eradicated	Eradicated

Abbreviation: PID, pelvic inflammatory disease; IV, intravenous; EOT, end of treatment; WBC, white blood cell; AZM, azithromycin.
[a] Subject with PID due to quinolone-resistant *N. gonorrhoeae* (ciprofloxacin MIC = 8.0 μg/ml, levofloxacin MIC = 4.0 μg/ml, AZM MIC = 0.12 μg/ml), who was co-infected with *S. agalactiae* and *P. bivia*.
[b] Subject with PID due to quinolone-resistant *N. gonorrhoeae* (ciprofloxacin MIC = 4.0 μg/ml, levofloxacin MIC = 4.0 μg/ml, AZM MIC = 0.25 μg/ml), who had failed to respond to levofloxacin 100 mg 3-times-daily treatment for 6 days.

No clinically significant changes from baseline were seen in systolic blood pressure, diastolic blood pressure, pulse rate, or respiration rate.

4. Discussion

The goals of therapy for PID include the resolution of clinical symptoms and signs, the eradication of pathogens from the genital tract (short-term goals), and the prevention of sequelae including infertility, ectopic pregnancy and chronic pelvic pain (long-term goals). Early and appropriate therapy is important to achieve both good short-term and long-term clinical outcomes [1,2,4]. In this study, AZM IV-to-oral switch therapy demonstrated excellent clinical and bacteriological efficacy for the treatment of PID regardless of the type and *in vitro* susceptibility of causative pathogens. This efficacy result was similar to those reported in 2 previous multinational, randomized, comparative studies [11], and confirmed the beneficial effect of AZM IV-to-oral therapy as monotherapy for the management of PID.

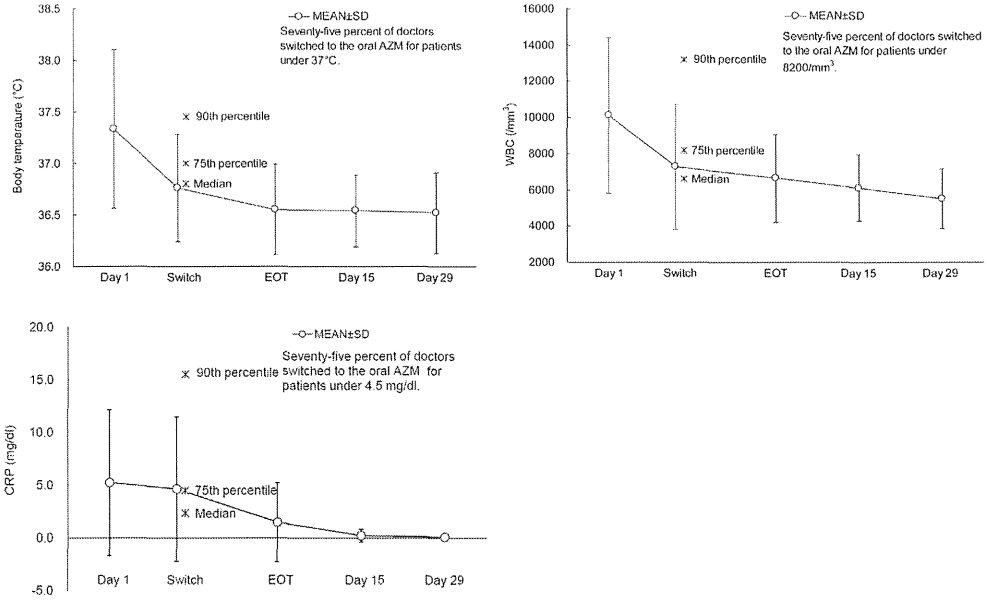

Fig. 1. Time course of body temperature, WBC count, and CRP for subjects in the CPPS. The descriptive statistics (median, 75th and 90th percentiles) of these parameters at the time of switching from IV-to-oral therapy are indicated in the figure. Abbreviation: AZM, azithromycin; EOT, end of treatment; WBC, white blood cell; CPPS, clinical per protocol set; IV, intravenous.

Such excellent clinical efficacy of AZM is due to the anti-inflammatory and immunomodulatory activities both *in vitro* and *in vivo* by inhibiting the production of pro-inflammatory cytokines at the infection sites [12,13]. Studies using a macaque model of *C. trachomatis* infection, and epithelial cells or cervical mononuclear cells from infertile women infected with *C. trachomatis* demonstrated that AZM had an immunomodulatory activity and inhibited the production of pro-inflammatory cytokines such as IL-1, IL-6, IL-8, IL-10, or TNF-α induced by *C. trachomatis* infection, which may have a favorable effect on the clinical outcome of patients with PID by preventing the exacerbation of inflammation, persistence of the infection, and complications such as infertility [14–16].

An increasing global prevalence of antibiotic resistance, in particular resistance to β-lactams, tetracyclines, and/or quinolones, of *N. gonorrhoeae* is of great concern for the antimicrobial regimens used in the treatment of PID [17]. A recent study reported that ciprofloxacin resistance of gonococcal isolates in 2008 was 70.7% and AZM resistance was 0.4% in Japan [18]. The emergence of resistance of *N. gonorrhoeae* to the extended spectrum of cephalosporins (oral cephalosporins mostly) and to AZM was recently reported, which leads to serious concerns about the current recommendations for the treatment of gonococcal infections [19,20].

For the treatment of PID due to gonorrhoea, the CDC 2010 STD treatment guidelines recommend that if the isolate is determined to be QRNG or if the antimicrobial susceptibility cannot be assessed, a parenteral cephalosporin should be used, but if cephalosporin therapy is not feasible, 2 g oral AZM as a single dose should be added to a quinolone-based PID regimen [4].

In this study, 2 QRNG strains were isolated from 2 PID subjects including 1 subject who had failed to respond to levofloxacin 100 mg 3-times-daily treatment for 6 days. The clinical efficacy and bacterial eradication rates were 100% (2/2) for QRNG, indicating the effectiveness of AZM IV-to-oral switch therapy for QRNG. These results indicate a therapeutic efficacy of AZM IV-to-oral therapy for PID caused by QRNG.

Since most subjects showed improvements in body temperature, WBC count, and CRP at the time of switching to oral therapy, and the proportion of subjects with improved clinical signs and symptoms increased, the time when the clinical signs and symptoms improve or tend to improve seems to be a suitable time to switch to oral therapy.

AZM IV-to-oral switch therapy seems to have the advantage of shortening the length of patients' hospitalization. IV-to-oral switch therapy enables early switch to oral therapy as soon as possible after resolution, improvement or a tendency for improvement of the intense abdominal pain lower and inflammatory findings through initial IV therapy, resulting in an early return to normal life and higher cost effectiveness of antimicrobial therapy. Similar beneficial effects of early switching to oral therapy in the treatment of CAP were reported in the studies of transition to oral therapy after an abbreviated course of IV therapy [21–23]. Furthermore, AZM IV-to-oral switch therapy also seems to have the advantage that the dosing regimen is simple (1 dose per day) compared with standard multidrug regimens recommended for the treatment of PID, leading to higher compliance and better clinical efficacy.

AZM IV-to-oral switch therapy was effective and well tolerated in the treatment of PID in Japanese women.

Conflict of interest

H. Mikamo has received a consultant fee and a fee for participation in the Committee from Pfizer Japan Inc. K. Iwasaku has received a fee for participation in the Committee from Pfizer Japan Inc. Y. Yamagishi has received a clinical study grant from Pfizer Japan Inc. M. Matsumizu and M. Nagashima are employees of Pfizer Japan Inc.

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TOPICS トピックス

ヒトパピローマウイルス(HPV)ワクチン(子宮頸癌予防ワクチン)と副反応

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ヒトパピローマウイルス感染症とは

ヒトパピローマウイルス(human papillomavirus, HPV)には100種類以上の型があり，皮膚に疣贅を引き起こす皮膚型と，性器周辺に感染する粘膜型(約40種類)に大別される．粘膜に感染するHPVのうち，少なくとも15種類(16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68型など)が子宮頸癌などの悪性腫瘍症例で検出され，これらは「高リスク型HPV」と呼ばれている．特に子宮頸癌では90%以上でHPVが検出され，約65%は16型または18型である[1]．

高リスク型HPVは性交渉によって感染し，子宮頸癌以外に，中咽頭癌，肛門癌，膣癌，外陰癌，陰茎癌などにも関与している[2]．子宮頸部の細胞に異常がなくても，10~20%の女性がHPVに感染しているという報告もあり，また，海外では性交渉歴のある女性の50~80%が生涯に一度はHPVに感染するとも報告されている[1]．HPVに感染しても，90%以上の場合，2年以内にウイルスは自然に排出されるとされているが，ウイルスが自然排出されず，数年から数十年にわたって持続感染した場合には，癌に進展しうることが報告されている．

低リスク型である6，11型は尖圭コンジローマの原因ウイルスである[3]．また，HPVによる母子感染として若年性再発性呼吸器乳頭腫症があり，本症のほぼ全例にHPV6型，11型が検出される．小児の咽頭・口頭良性腫瘍の原因の第1位であり，嗄声，呼吸困難，気道閉塞をきたし，若年発症ほど予後不良である．罹患者の約半数は，再発のため手術を10回以上必要とすることもある[4]．

ヒトパピローマウイルスワクチン

ヒトパピローマウイルスワクチンには，持続的なHPVの感染や癌になる過程の異常(異形成)を予防する効果が確認されており，これらに引き続いて起こる子宮頸癌を予防することが期待されているワクチンである．

サーバリックス®は2009年10月に厚生労働省から製造販売承認を受けた2価ワクチンである．効果接種回数は1回目の接種を行った1カ月後に2回目を，6カ月後に3回目の接種を行う．ガーダシル®は，2011年7月に販売承認を得た4価のワクチンであり，1回目の接種を行った2カ月後に2回目を，6カ月後に3回目の接種を行う．

2種類のワクチンの概要を**表1**に示す．ワクチンを接種していても，HPV16型，18型以外の高リスク型HPVが原因となる子宮頸癌は原則として予防できないため，必ず子宮頸がん検

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表1　わが国で接種可能なHPVワクチン(2013年8月15日現在)

	サーバリックス	ガーダシル
開発企業	グラクソ・スミスクライン社	メルク社
わが国での製造承認	2009年10月	2011年7月
カバー可能なHPV型	16, 18	6, 11, 16, 18
抗原	L1-VLP(HPVの殻を模倣した蛋白質L1のウイルス様粒子)	L1-VLP (HPVの殻を模倣した蛋白質L1のウイルス様粒子)
アジュバント	AS04	アルミニウム塩
接種対象者	10歳以上の女性	9歳以上の女性
適応疾患(国内承認)	HPV16/18による，子宮頸癌と上皮内腫瘍(CIN2, 3)	HPV16/18による，子宮頸癌と上皮内腫瘍(CIN1-3, AIS)，外陰上皮内腫瘍(VIN1-3)，腟上皮内腫瘍(VaIN1-3)HPV6/11による，尖圭コンジローマ
接種方法	0, 1, 6カ月	0, 2, 6カ月
接種量	1回0.5mL	1回0.5mL
接種経路	筋肉注射	筋肉注射
接種部位	上腕の三角筋部	上腕筋，大腿四頭筋

VLP：virus-like particle(ウイルス様粒子)，CIN：cervical intraepithelial neoplasia(子宮頸部上皮内腫瘍)，ASI：adenocarcinoma *in situ*(上皮内腺癌)，VIN：vulvar intraepithelial neoplasia(外陰上皮内腫瘍)，VaIN：vaginal intraepithelial neoplasia(腟上皮内腫瘍)．

診を受診することが重要である．

ヒトパピローマウイルスワクチンの副反応

現行のわが国の予防接種制度では，薬剤使用後に生ずる生体にとって好ましくない現象(症状や検査値)だけではなく，ワクチン接種後に生体反応として生じてもおかしくない発熱や腫脹などの軽微な反応，あるいはそれを超えた生体反応について，因果関係の有無にかかわらず副反応として報告することとなっている．すなわち，子宮頸がん等ワクチン接種緊急促進事業における副反応報告ではワクチン接種との因果関係にかかわらず，重篤・非重篤，未知・既知の全てについて契約医師には報告義務があるが，薬事法では，副反応によると疑われる場合に自主的に報告することという違いがある[5]．

予防接種法で報告される副反応報告制度では，医療機関などが予防接種による副反応を知ったときは，厚生労働大臣へ報告し，厚生労働大臣は報告の状況について審議会に再報告し，必要に応じて予防接種の適正な実施のために必要な措置を講ずることとなっている．副反応報告にかかわる情報の整理および調査は独立行政法人医薬品医療機器総合機構に委託が可能となっている．**表2**に，わが国で実施されているワクチンの副反応報告件数を示す[6]．

定期の予防接種などによる副反応の報告などの取り扱いにおけるHPVワクチンの報告基準に関する症状(発生までの時間)は，アナフィラキシー(4時間以内)，急性散在性脳脊髄炎(acute disseminated encephalomyelitis, ADEM)(28日)，ギラン・バレー(Guillain-Barré)症候群(28日)，血小板減少性紫斑病(28日)，血管迷走神経反射(失神を伴うもの)(30分)，その他の反応(時間の定義なし)の6項目となっている[7]．2013年3月までの報告のうち，ワクチンとの関係が否定できないとされた報告頻度

表2　各ワクチンの副反応報告状況

ワクチンの種類	副反応の報告*1		重篤*2		企業報告のうち医師が重篤と判断したもの		医療機関報告のうち医師が重篤と判断したもの		接種回数
	件数	発生率	件数	発生率	件数	発生率	件数	発生率	
子宮頸癌予防ワクチン（サーバリックス®）	1,705	245.1	302	43.4	211	30.3	91	13.1	6,957,386
子宮頸癌予防ワクチン（ガーダシル®）	263	155.7	56	33.2	41	24.3	15	8.9	1,688,761
ヒブワクチン	675	63.8	237	22.4	153	14.4	92	8.7	10,591,278
小児用肺炎球菌ワクチン	933	89.1	288	27.5	191	18.2	97	9.3	10,480,144
不活化ポリオワクチン	67	23.8	15	5.3	9	3.2	12	4.3	2,815,142
4種混合ワクチン	15	13.5	4	3.6	2	1.8	10	9.0	1,107,279
日本脳炎ワクチン	63	67.4	24	25.7	11	11.8	13	13.9	934,354
インフルエンザワクチン	387	7.5	121	2.3	74	1.4	53	1.0	51,506,304

発生率は100万接種当たりの発生数．接種回数については，製造販売業者の出荷量からの推計．副反応報告制度は，予防接種との因果関係の有無にかかわらず，接種後に健康状況の変化をきたした症例を収集したもの．
*1：企業からの報告＋医療機関からの報告．
*2：企業報告のうち，医師が重篤と判断したものと，医療機関報告のうち医師が重篤と判断したもの．
（文献6より転載）

は，アナフィラキシーが約96万接種に1回，ギラン・バレー症候群が約430万接種に1回，ADEMが約430万接種に1回，複合性局所疼痛症候群(complex regional pain syndrome, CRPS)が約860万接種に1回の頻度となっている[8]．

HPVワクチン接種後の失神関連の副反応については，サーバリックス®の失神に関連する副反応（意識障害，失神，失神寸前の状態，ショック，神経原性ショック，意識レベルの低下，意識変容状態が含まれる）は783例（発生率10万接種当たり11.25例）で，このうち意識消失のあった症例は544例（発生率10万接種当たり7.82例）と報告されている．同様に，ガーダシル®の失神関連の副反応は297例（発生率10万接種当たり17.6例）で，このうち意識消失のあった症例は210例（発生率10万接種当たり12.4例）と報告されている[9]．HPVワクチンに特徴的と思われるものにCRPSがあるが，これまでに5例が報告されている[10]．

副反応への対策

上述のいずれの報告についても，専門家による検証がなされており，2013年6月14日に開催された専門家会議では，収集された医学的情報をもとにした分析・評価とワクチン接種の有効性との比較検討の結果，HPVワクチンの定期接種を中止するほど副反応のリスクが高いとは評価されず，HPVワクチン接種の積極的な接種勧奨の差し控えが決定されている[11]．

本ワクチン接種後に，注射部位に限局しない痛み，しびれ，脱力などが出現し，長期間持続する例が複数報告されていることを受けて，国は，その病態やワクチンとの関係を調査分析し適切な医療提供をする目的で対応を開始している．すなわち，厚生労働省健康局は“厚生労働科学研究費補助金・慢性の痛み対策研究事業”のなかで，難治性神経因性疼痛の基礎疾患の解