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103年10月 第131期

新一代oxazolidinones：tedizolid phosphate (sivextro®)

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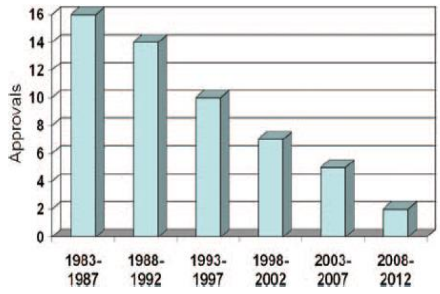
一、前言

近20年來，細菌抗生素的抗藥性日益增長，但在抗生素的研發卻越趨緩慢(圖一)，自1998年來，僅有14個全身性抗生素被FDA核可，而在新機轉的抗生素研發更是屈指可數(圖二)。



圖一、自1983年來，每五年被FDA核可的抗生素數量趨勢圖。(1)

本院ADR通報專線 #2165 或 線上通報

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任何醫療人員發現懷疑因藥物引起的不良反應時，請即通報本院ADR小組。

Antibacterial	Year Approved	Novel Mechanism?
Rifapentine[b]	1998	No
Quinupristin/dalfopristin[c]	1999	No
Moxifloxacin	1999	No
Gatifloxacin[d]	1999	No
Linezolid	2000	Yes
Cefditoren pivoxil	2001	No
Ertapenem	2001	No
Gemifloxacin[d]	2003	No
Daptomycin	2003	Yes
Telithromycin[d]	2004	No
Tigecycline[e]	2005	Yes
Doripenem	2007	No
Telavancin	2009	Yes
Ceftaroline fosamil	2010	No

[a] Rifaxamin (Food and Drug Administration [FDA] approved in 2004) and fidaxomicin (FDA approved in 2011) are not systemically absorbed, and so are not included on this list.
[b] Antituberculous agent.
[c] Infrequently used due to adverse event profile.
[d] Withdrawn from market due to adverse event profile.
[e] Label warning regarding possible excess mortality.

圖二、美國FDA核准的系統性抗生素1998~2013。(1)

2014年，在急性細菌性皮膚與皮膚組織感染(acute bacterial skin and skin structure infections，ABSSSIs)的抗生素發展上，是突破的一年， 2014年5月23日FDA核准dalbavancin (dalvance®)上市、2014年6月20日FDA核准

本期要目

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tedizolid（sivextro®)上市、2014年8月6日FDA核准oritavancin(orbactiv®)上市，新的抗生素的研發，不啻讓我們面對後抗藥性時代，能有更多的治療選擇。

Tedizolid是新一代oxazolidinone抗生素(前一代為linezolid[zyvox®]），FDA 取證兩篇人數共1,315人的臨床研究(ESTABLISH-1 [4]、ESTABLISH-2[5])，認為tedizolid有不劣於linezolid的治療效果，核准tedizolid用於*staphylococci*（包含MRSA)導致的急性細菌性皮膚與皮膚組織感染。

Tedizolid距第一代oxazolidinones核可上市，已過了14個寒暑，本文將介紹tedizolid的藥物特性與臨床應用，並和前一代oxazolidinones做比較，供讀者參考。

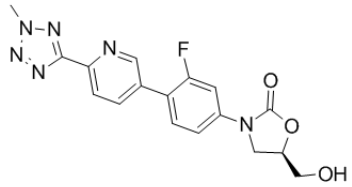
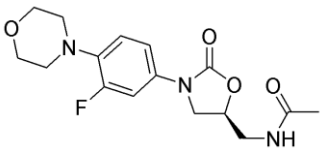
二、Tedizolid藥物特性

Tedizolid phosphate為 tedizolid的前驅藥，作用機轉、抗菌光譜、藥物動力學均和linezolid相似，tedizolid作用在細菌50S次單元核醣體上的P位，抑制細菌蛋白質的生合成。與其他蛋白質生成的抗生素相比，tedizolid在蛋白質生成的更上游阻斷合成，使tedizolid可以使用在對其他抗生素產生抗藥性的具敏感菌種上。抗菌光譜部分，tedizolid對*streptococci*、*enterococci*和*staphylococci*具有抑菌效果(Kisgen, 2014)。成人常用劑量為200mg口服或靜脈輸注，每天一次; 小於18歲的族群因安全性和有效性尚未建立，目前並無建議劑量。在靜脈輸注上，tedizolid只可用0.9%生理食鹽水泡製，且須持續輸注超過一小時，不可以靜脈推注。

在療程上，tedizolid具有較短療程的優點，治療急性細菌性皮膚與皮膚組織感染建議療程為六日。Tedizolid具有很好的生體可用率(91%)，當感染症已得到適當的控制，tedizolid具有口服劑型可以做轉換，可以減少醫療費用。

tedizolid常見的副作用有噁心、嘔吐、腹瀉、頭痛、眩暈等，此外，tedizolid仍有骨髓抑制、血小板低下、貧血的問題，尤其是使用在白血球低下的病人須特別小心與警慎。如同linezolid，tedizolid為弱效的單胺氧化酶抑制劑(Monoamine oxidase inhibitors , MAOIs)，與影響serotonin濃度的藥物(表二)併用仍須注意serotonin syndrome發生的可能。

Tedizolid與linezolid的詳細比較請見表一。

	Tedizolid	**linezolid**
分類	oxazolidinones	
懷孕分級	C級	
結構		
劑型	200mg tablets / IV	600mg tablet / IV 100mg / 5mL oral suspension
成人參考劑量	200mg PO / IV QD 劑量不須依肝腎功能調整	600mg PO / IV Q12H 劑量不須依肝腎功能調整
口服可用率	91%, 與食物併服無影響	100%, 與食物併服無影響
蛋白質結合率	70-90 %	31%
平均血漿半衰期	12小時	5 小時
T max	3小時	1.3 小時
CSF / Blood (%)	無資料	60 – 70 %, 可在CSF達到治療劑量(AAC 50:3971, 2006)
分布體積	67-80 L (Vss)	40-50 L (Vss)
CYP 450交互作用	無	無
副作用 (常見)	**Gastrointestinal** : Diarrhea (4%), Nausea (8%), Vomiting (3%) **Neurologic**: Dizziness (2%), Headache (6%)	**Gastrointestinal**: Diarrhea (8.2% ~8.3%), Nausea (5.1% ~ 6.6%), Vomiting (2% ~ 4.3%) **Neurologic**: Headache (5.7%~ 8.8%)
副作用 (嚴重)	**Cardiovascular**: Tachycardia (< 2%) **Gastrointestinal**: Clostridium difficile colitis (<2%) **Hematologic**: Anemia(<2%), Neutropenia (0.5%), Thrombocytopenia(<2%) **Neurologic**: Peripheral nerve disease (1.2%) **Ophthalmic**: Disorder of optic nerve (0.3%)	**Endocrine metabolic**: Lactic acidosis **Gastrointestinal**: Clostridium difficile diarrhea **Hematologic**: Anemia (0.4%~ 7.1%), Neutropenia(1.1%),Thrombocytopenia(0.7~3%) **Hepatic**: Injury of liver **Neurologic**: Peripheral neuropathy, Seizure **Ophthalmic**: Disorder of optic nerve **Other**: Serotonin syndrome

表一、Tedizolid與linezolid比較[2][3]

機轉	藥物
增加serotonin合成	-Tryptophan
增加serotonin釋放	-Amphetamines & Amphetamine derivatives -Cocaine -MDMA (Ecstasy) -Levodopa & Carbidopa-levodopa
損害神經突觸對serotonin的再吸收	-Cocaine -MDMA (Ecstasy) -Meperidine -Tramadol -Pentazocine -Selective serotonin reuptake inhibitors (SSRIs) -Serotonin-norepinephrine reuptake inhibitors (SNRIs) -Dopamine-norepinephrine reuptake inhibitors (DNRIs) -Serotonin modulators -Tricyclic antidepressants (TCAs) -St. John's wort (Hypericum perforatum) -5-HT3 receptor antagonists -Metoclopramide -Valproate -Carbamazepine -Dextromethorphan -Cyclobenzaprine
抑制serotonin代謝	-Monoamine oxidase inhibitors (MAOIs) 包含: phenelzine, tranylcypromine, isocarboxazid, moclobemide, selegiline, rasagiline, linezolid, tedizolid, procarbazine
直接serotonin致效劑	-Buspirone -Triptans -Ergot derivatives -Fentanyl -Lysergic acid diethylamide (LSD)
增加神經突觸對serotonin的敏感度	-Lithium

表二、可能造成serotonin syndrome的藥物[6]

三、臨床應用與相關研究

急性細菌性皮膚與皮膚組織感染，包含蜂窩性組織炎(cellulitis)、丹毒(erysipelas)、表皮膿瘍(cutaneous abscesses)等，若不妥善加以治療，可能會有致命的危險。在皮膚與皮膚組織常見的致病菌多為*streptococci*和*staphylococci*，許多對*streptococci*和*staphylococci*具敏感性的抗生素在皮膚與皮膚組織有著很好的藥物濃度，但在抗藥性日益高漲的情況下，特別是抗藥性金黃色葡萄球菌(methicillin-

resistant *staphylococcus aureus*, MRSA,常見治療MRSA的抗生素請參閱表三)，使得我們的抗生素的選用面臨挑戰，tedizolid即為我們面對這場戰爭的新生力軍。

Tedizolid應用在急性細菌性皮膚與皮膚組織感染的根據主要來自兩篇臨床研究：ESTABLISH-1與ESTABLISH-2。

ESTABLISH-1為隨機分派、雙盲、多中心、非劣性的phase 3臨床試驗，收納667位懷疑或確診為葛蘭氏陽性菌造成的急性細菌性皮膚與皮膚組織感染的成人，比較口服tedizolid的六日療程，是否不劣於口服linezolid的十日療程(noninferiority margin : -10%)，主要療效指標(primary efficacy outcome)為早期臨床反應(比較投藥後48-72小時，傷口面積與體溫是否有得到控制)，結果發現兩組在主要療效指標並無顯著差異(difference 0.1% [95% CI : -6.1%~ 6.2%])，詳細結果請參閱圖三。

ESTABLISH-2同為隨機分派、雙盲、多中心、非劣性的phase 3臨床試驗，收納666位懷疑或確診為葛蘭氏陽性菌造成的急性細菌性皮膚與皮膚組織感染的成人，比較靜脈輸注tedizolid的六日療程，是否不劣於靜脈輸注linezolid的十日療程(noninferiority margin : -10%)，主要療效指標(primary efficacy outcome)為早期臨床反應(比較投藥後48-72小時，傷口面積比基準值減少20%以上)，同樣發現兩組在主要療效指標並無顯著差異(tedizolid vs linezolid : 283人 [85%] vs 276人[83%] ,difference 2.6%, 95% CI : –3.0 - 8.2)，但有著較少的腸胃道不良反應(tedizolid vs linezolid : 52人[16%] vs 67人[20%])，詳細結果請參閱圖四、圖五。綜合ESTABLISH-1與ESTABLISH-2可以發現，tedizolid在療效部分不劣於linezolid，而藥物不良反應並不多於linezolid。

	Tedizolid Phosphate 200 mg Once Daily No. (%) [95% CI]	Linezolid 600 mg Twice Daily No. (%) [95% CI]	Absolute % Difference (95% CI)
Clinical Response			
No., ITT population	332	335	
Response at 48 to 72 hours (ITT)	264 (79.5) [74.8 to 83.7]	266 (79.4) [74.7 to 83.6]	0.1 [–6.1 to 6.2]
Response at EOT (ITT)	230 (69.3) [64.0 to 74.2]	241 (71.9) [66.8 to 76.7]	–2.6 [–9.6 to 4.2]
No., CE population	273	286	
Response at EOT (CE)	219 (80.2) [80.0 to 84.8]	232 (81.1) [76.1 to 85.5]	–0.9 (–7.7 to 5.4)
Investigator assessment of clinical response at PTE[a]			
No., ITT population	332	335	
Clinical success at PTE	284 (85.5) [81.3 to 89.1]	288 (86) [81.8 to 89.5]	–0.5 (–5.8 to 4.9)
No., CE population	279	280	
Clinical success at PTE	264 (94.6) [91.3 to 97.0]	267 (95.4) [92.2 to 97.5]	–0.8 (–4.6 to 3.0)

Abbreviations: CE, clinically evaluable; CI, confidence interval; EOT, end of therapy; ITT, intent-to-treat; PTE, post-therapy evaluation.

[a] For the investigator's assessment of clinical response, clinical success was defined as meeting these 3 criteria: (1) resolution or near resolution of most disease-specific signs and symptoms; (2) absence or near resolution of systemic signs of infection (lymphadenopathy, fever, >10% immature neutrophils, abnormal white blood cell count), if present at baseline; and (3) no new signs, symptoms, or complications attributable to the ABSSSIs so no further antibiotic therapy was required for the treatment of the primary lesion.

圖三、ESTABLISH-1 臨床療效 (9)

	Tedizolid phosphate (n=332)	Linezolid (n=334)	Difference (95% CI)
48–72 hours*	304 (92%)	302 (90%)	1·2% (–3·3 to 5·6)
Day 7*	309 (93%)	308 (92%)	0·9% (–3·2 to 4·9)
End of treatment (day 11)†	304 (92%)	301 (90%)	1·4% (–3·0 to 5·9)
Post-therapy assessment (7–14 days after end of treatment)†	292 (88%)	293 (88%)	0·3% (–4·8 to 5·3)
Late follow-up (18–25 days after end of treatment)‡	262/268 (98%)	266/269 (99%)	–1·1% (–3·8 to 1·3)

Data are n (%), unless otherwise indicated. ABSSSI=acute bacterial skin and skin-structure infection. *Clinical success defined as improvement in overall clinical status of ABSSSI compatible with continuation of study drug. †Clinical success defined as resolution or near resolution of disease-specific signs and symptoms, absence or near resolution of baseline systemic signs of infection, and no further antibiotic treatment required for treatment of primary ABSSSI lesion. ‡Clinical success defined as no new signs or symptoms of primary ABSSSI after post-therapy assessment. Only assessed in patients who were clinically evaluable and deemed clinical successes at post-therapy assessment.

圖四、ESTABLISH-2 臨床治療成功率 (5)

	藥名	常用劑量(成人)
口服	Clindamycin	300 to 450 mg PO TID
	Trimethoprim-sulfamethoxazole	1 DS tab PO BID
	Doxycycline	100 mg PO BID
	Minocycline	200 mg orally ST, then 100 mg PO BID
	Linezolid	600 mg PO BID
	Tedizolid	200 mg PO QD
針劑	Vancomycin	15 to 20 mg/kg/dose Q8~12H, not to exceed 2 g per dose
	Daptomycin	4 mg/kg IV QD (Skin and soft tissue infection) 6 mg/kg IV QD (Bacteremia)
	Ceftaroline	600 mg IV Q12H
	Linezolid	600 mg IV BID
	Tedizolid (for skin and soft tissue infection)	200 mg IV QD
	Telavancin	10 mg/kg QD
	Dalbavancin (for skin and soft tissue infection)	1 g IV on day 1, then 500 mg IV on day 8
	Oritavancin (for skin and soft tissue infection)	single dose regiment : 1200 mg ST

表三、對抗methicillin-resistant *staphylococcus aureus* (MRSA)的抗生素選擇[7]

	Tedizolid phosphate (n=331)	Linezolid (n=327)	Difference (95% CI)
Patients with at least one serious treatment-emergent adverse event*	7 (2%)	9 (3%)	−0·6 (−3·3 to 1·9)
Any treatment-emergent adverse event†	148 (45%)	141 (43%)	1·6 (−6·0 to 9·2)
Nausea	26 (8%)	36 (11%)	−3·2 (−7·8 to 1·3)
Headache	20 (6%)	22 (7%)	−0·7 (−4·6 to 3·2)
Abscess	14 (4%)	10 (3%)	1·2 (−1·8 to 4·3)
Diarrhoea	11 (3%)	17 (5%)	−1·9 (−5·2 to 1·3)
Vomiting	10 (3%)	17 (5%)	−2·2 (−5·5 to 0·9)
Cellulitis	9 (3%)	6 (2%)	0·9 (−1·6 to 3·5)
Fatigue	8 (2%)	7 (2%)	0·3 (−2·2 to 2·8)
Dizziness	4 (1%)	7 (2%)	−0·9 (−3·3 to 1·2)
Vulvovaginal mycotic infection	2 (<1%)	7 (2%)	−1·5 (−3·8 to 0·3)
Infusion-site reactions	5 (2%)	7 (2%)	−0·6 (−3·0 to 1·6)
Any drug-related treatment-emergent adverse event‡	68 (21%)	81 (25%)	−4·2 (−10·6 to 2·2)

Data are n (%), unless otherwise indicated. *Serious treatment-emergent adverse events in the tedizolid group (n=1 patient each; none deemed related to study drug): myocardial infarction leading to death (in an elderly man with extensive medical history of coronary heart disease), *Escherichia* sp urinary tract infection, pneumonia and staphylococcal bacteraemia, septic shock, diabetes mellitus, hypertension, nephrolithiasis. Serious treatment-emergent adverse events in the linezolid group (n=1 patient each, unless otherwise indicated): tuberculous meningitis leading to death (in a 33-year old woman on day 14 of the study), anaphylactic reaction (deemed related to study drug), acute coronary syndrome, acute myocardial infarction, cellulitis (n=2), bacterial urinary tract infection, increased blood glucose, superficial thrombophlebitis. †Only treatment-emergent adverse events taking place in 2% or more of patients in either treatment group are shown. ‡Possibly, probably, or definitely related to study treatment.

圖五、ESTABLISH-2 藥物治療副作用發生率 [5]

四、結論

Tedizolid與linezolid相比，有著較強的效價與較突出的藥物動力學性質，治療療程比linezolid更短且頻次降低為每日一次，造成腸胃道副作用與血小板低下(thrombocytopenia)的機率也較低(參閱表一)。雖然tedizolid在安全性部分因使用經驗不足，須待未來更多的研究證實，但就目前的研究資料來看，tedizolid是個可以合理取代linezolid的新一代oxazolidinones藥物。相信不久的將來在台灣上市後，臨床工作者在面對抗藥性金黃色葡萄球菌引起的急性細菌性皮膚與皮膚組織感染，能有多一項抗菌武器供選擇。

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