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A PPI with Dual Delayed Release Technology for the management of GERD

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*96% of patient on DEXILANT 60 mg achieved 24-h heartburn-free days\textsuperscript{5}.
Gastro-Esophageal Reflux Disease: Optimizing Proton Pump Inhibitor Therapy to Improve Symptom Control

Introduction

Gastro-esophageal reflux disease (GERD) is a chronic disorder of the upper gastrointestinal tract with associated morbidity and an adverse impact on quality of life. GERD is defined as a “condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications”. The current definition is not only symptom-based and patient-driven, but also encompasses esophageal and extra-esophageal manifestations of the disease. Psychological well-being questionnaires have found that patients with GERD can have a worse quality of life than some patients with menopausal symptoms, peptic ulcer disease, angina or congestive heart failure.

Prevalence estimates show significant geographical variation, with prevalence rates as high as 28% in North America and up to 33% in the Middle East. A population-based survey involving 2,209 individuals from Chinese households in Hong Kong found the GERD prevalence rate to be about 8.9%. The initial management of GERD includes lifestyle modifications and pharmacologic therapy. The therapeutic goals are to control symptoms, heal esophagitis and maintain remission so that morbidity is decreased and quality of life is improved.

According to the recently published ‘Guidelines for the diagnosis and management of GERD’, lifestyle interventions should be part of the management strategy for patients GERD. Medical options for patients failing lifestyle interventions include antacids, histamine-receptor antagonists (HRA), or proton pump inhibitor (PPI) therapy.

A novel treatment option for the management of GERD

Once-daily dexlansoprazole has a dual-delayed release (DDR) formulation, making it attractive for step-down management of patients whose symptoms are well controlled on twice-daily PPIs. DDR technology is designed to provide an initial drug release in the proximal small intestine followed by another drug release at more distal regions of the small intestine several hours later. For this reason, once-daily dexlansoprazole produces two distinct peaks: the first at 1–2 hours and the second at 4–5 hours, post-dose. Current one of the widely used once-daily PPIs, esomeprazole, produces maximum plasma concentrations at approximately 1.6 hours post-dose. While dexlansoprazole may be taken without regard to meals, esomeprazole should be taken 30 minutes before meals to achieve maximum efficacy.

Key words:
Gastro-esophageal reflux disease (GERD) (胃食道反流性疾病), proton pump inhibitor (質子泵抑制劑), dexlansoprazole (右蘭索拉唑), symptom control (症狀控制)
In patients with symptomatic GERD, dexlansoprazole 30 mg was found to be more efficacious than placebo in providing relief from nocturnal heartburn, in reducing GERD-related sleep disturbances and the consequent impairments in work productivity, and in improving sleep quality/quality of life.19

In a phase I, randomized, open-label, crossover study, the average intragastric pH following a single dose of dexlansoprazole was higher than that observed following a single dose of esomeprazole (p<0.001).11 In the first 24 hours after a dose, the mean percentage of time patients’ intragastric pH was above 4 for dexlansoprazole and esomeprazole was 58% and 48%, respectively (p=0.003).11

In the 12–24 hour post-dose period, the mean percentage of time patients on dexlansoprazole had an intragastric pH above 4 was 60% (vs 42% with esomeprazole; p<0.001).11 During this 12–24 hour post-dose period, the average mean intragastric pH was 4.5 for dexlansoprazole, compared with 3.5 for esomeprazole (p<0.001).11 These findings demonstrate that dexlansoprazole may be more effective than once-daily esomeprazole for the control of nighttime symptoms.

Further, a randomized, double-blind trial involving 445 patients showed that 6 months treatment with dexlansoprazole (30 mg or 60 mg) was superior to placebo for maintaining healed erosive esophagitis (p<0.0025).20 Superiority to lansoprazole in healing of erosive esophagitis was also demonstrated in one study, with non-inferiority in another study.21 Adjusted indirect comparisons based on currently available randomized controlled trial data suggested significantly better control of heartburn in patients with non-erosive reflux disease for dexlansoprazole versus esomeprazole. Dexlansoprazole 30 mg was more effective than esomeprazole 20 mg or 40 mg (RR: 2.01, 95% CI: 1.15–3.51; RR: 2.17, 95% CI: 1.39–3.38).22

PPI therapy has been associated with adverse effects such as vitamin and mineral deficiencies, hip fractures and osteoporosis, and increased cardiovascular events in patients using concomitant clopidogrel therapy.8

In 2009, the FDA issued a warning regarding the potential for increased adverse cardiovascular events in concomitant users of PPI and clopidogrel therapy, particularly among users of omeprazole, lansoprazole, and esomeprazole.8 The concern arises from the fact that the anti-platelet activity of clopidogrel requires activation by CYP2C19, the same pathway required for metabolism of some PPIs. This potentially reduces the effectiveness of clopidogrel.23

A randomized, open-label, two-period, crossover study of healthy subjects (N=160) found that the area under the curve for clopidogrel active metabolite decreased significantly with esomeprazole but not with dexlansoprazole or lansoprazole. Similarly, esomeprazole but not dexlansoprazole or lansoprazole significantly reduced the effect of clopidogrel on vasodilator-stimulated phosphoprotein platelet reactivity index.23 Dexlansoprazole does not attenuate the efficacy of clopidogrel.

Common side effects of dexlansoprazole include gas, mild diarrhoea, nausea and vomiting.17 Upper respiratory tract infections may also be observed more frequently in dexlansoprazole-treated patients.20

Pooled data from 4,270 patients receiving dexlansoprazole (30 mg, 60 mg or 90 mg), lansoprazole 30 mg, or placebo showed that the number of patients with at least one treatment-emergent adverse event was higher in placebo and lansoprazole groups than in any dexlansoprazole group. Fewer patients receiving dexlansoprazole discontinued therapy because of an adverse event (p≤0.05 versus placebo).24

PPI is the mainstay of GERD treatment. However, patients report inadequate symptom control with currently available PPIs. Dexlansoprazole, an enantiomer of lansoprazole, is formulated with a unique DDR formulation. It has proven efficacy in symptom control,11 healing of esophagitis12 and maintaining remission20. Clinical data also demonstrate superior effects compared with currently available PPIs.11,21,22

Dexlansoprazole is generally well tolerated.24,25 Importantly, dexlansoprazole may be used concomitantly with clopidogrel without increasing the risk of adverse cardiovascular events.23

References
TKI THERAPY JUST GOT BETTER IN Ph+ CML

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POWER TO REDUCE PROGRESSION AND INCREASE RESPONSE

- Tasigna is the only TKI proven to significantly reduce rates of progression to accelerated phase/blast crisis vs Imatinib
- Fewer CML-related deaths with Tasigna than with Imatinib
- Tasigna produces faster and deeper molecular responses vs Imatinib, thus protecting patients from progression

Non-Hodgkin’s lymphoma (NHL) is the eighth most common malignancy in Hong Kong, with an annual incidence of 800 cases. It is amongst the most treatable, with only 300 deaths annually. The peak age of presentation is 70 years. About 70% of cases are aggressive lymphomas (mostly diffuse large B cell lymphoma [B-DLCL]). The rest are indolent lymphomas comprised of a mixture of entities (follicular lymphoma [FL], marginal zone lymphoma [MZL], mantle cell lymphoma [MCL], small lymphocytic lymphoma [SLL] and mucosa lymphoid tissue associated lymphoma [Maltoma]). About 85% of lymphomas are of B-cell lineage and express the surface marker CD20. The advent of anti-CD20 antibody (rituximab, R) in 1999 vastly improved survivals. For low-risk DLCL, cure rates exceed 90%. For indolent lymphomas, 5-year disease free survival rates >80% are easily achievable. Similar improvements have also been seen in chronic lymphocytic leukemia (CLL), a blood-based version of SLL. Although CLL and FL are less common in Chinese patients due to genetic factors, lifestyle Westernization have led to a steady increase in cases.2-4

Remarkably, almost no new anti-lymphoma chemotherapy has been approved by the US Food and Drug Administration (FDA) over the past 30 years. Until recently, older drugs including cyclophosphamide (C), vincristine (V or O), prednisolone (P), doxorubicin (H) and fludarabine (F) were the mainstay of anti-lymphoma therapy. A randomized trial of FL patients in Italy showed that there was no difference in outcomes comparing R-CVP, R-CHOP and R-F combinations.5 Hence, there has been an unmet need for a new anti-lymphoma agent, with increased activity and an improved side effect profile, to supplement rituximab for both aggressive and indolent lymphomas.

Forward progress is often achieved by considering lessons from the past. The drug bendamustine represents a remarkable example. After the Second World War, the Soviet Union set up a string of Communist-controlled puppet states in Eastern European nations. On 1 May 1949, a “direct election” of screened worker representatives established East Germany, ironically named the German Democratic Republic (GDR). For a host of reasons, the phobic government commissioned the overnight construction of the Berlin Wall on 13 August 1961. The Iron Curtain sealed off Eastern Europe from the world, ceasing all medical and academic exchange, leaving Communist technology and science to evolve on its own. From 1953, in the East German...
ZIMET 3393, invented by W. Ozegowaski and D. Krebs, and first described in 1963 (Zentralinstitut für Mikrobiologie und experimentelle Therapie, ZIMET). Its predecessor was the German drug giant Jena Pharm, and its director Hans Knoll, together with its handpicked executive council members, were collectively responsible for classified decisions on scientific experiments. The most famous were the biochemical manipulations of young East German athletes, who were not allowed to fail in open competition. Numerous medical compounds were also conceptualized and tested. These included ZIMET 3393, which combined active parts of cyclophosphamide, cladribine and butyric acid.

In 2003, the drug was marketed to the rest of the world under the brand name Trenda. In the European Intergroup CLL study, a 2-day infusion of bendamustine outperformed oral chlorambucil in elderly CLL patients (median age, 65 years) with a response rate of 68% versus 39% (p<0.0001) and a progression-free survival of 21.7 months versus 9 months (p<0.0001). The results led to its FDA approval for frontline CLL on 20 March 2008..

References

PRADAXA® (dabigatran etexilate) is indicated for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more risk factors$^1$.

$^1$ Risk factors: previous stroke, transient ischemic attack, or systemic embolism (SEE); left ventricular ejection fraction < 40%; symptomatic heart failure, > New York Heart Association (NYHA) Class 2; age ≥ 75 years; age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension.

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Chronic myeloid leukaemia (CML) is a neoplastic disease of the haematopoietic stem cells. The Philadelphia chromosome, the product of a translocation between chromosomes 9 and 22, is characteristic of CML. The resulting BCR-ABL fusion protein acts as an active kinase and tyrosine kinase inhibitors (TKIs), such as imatinib, can block the tyrosine kinase activity of BCR-ABL.

CML is one of the few malignant diseases triggered by a single oncogene, the BCR-ABL oncogene. This serves as the basis for and efficacy of, molecular targeted therapy in CML. A diagnosis of CML requires evidence of BCR-ABL translocation verified by cytogenetic studies or polymerase chain reaction (PCR) analyses.

The treatment of CML has been revolutionized over the past decade by the introduction of the TKI, imatinib. Haematologic, cytogenetic and molecular techniques are currently used to monitor disease and treatment responses. Achieving a complete cytogenetic response (CCyR) is an important objective of therapy because it is associated with prolonged survival. In patients who achieved CCyR, the BCR-ABL1 transcript levels can be measured to assess molecular residual disease. The results are often expressed as the log_{10} reduction from a standardized value for untreated patients, or more recently using the international scale where 100% is the starting point. It is generally accepted that CCyR corresponds to an approximate 2-log reduction in transcript levels or 1% on the international scale. Major molecular response (MMR) is usually defined as a 3-log reduction in transcript levels or 0.1% on the international scale. Real-time PCR (RT-PCR) is by far the most sensitive method for monitoring BCR-ABL levels during treatment. It can measure the levels of BCR-ABL transcripts in both the peripheral blood and bone marrow. Achieving MMR is regarded as an optimal response to TKI treatment. An optimal treatment response has been associated with the best long-term outcome, which means the life expectancy of the patient is comparable with that of the general population. The rate of progression to AP/BC was also lower with these newer generation TKIs.

Second-generation TKIs, nilotinib and dasatinib, have demonstrated efficacy as frontline therapy for chronic phase CML in phase III studies, in which molecular and cytogenetic responses to either agent were found to be superior to imatinib. The 2013 European Leukaemia-Net (ELN) guideline-recommended first, second and subsequent lines of treatment are summarized in the Table on the next page.

The ENEStnd trial
Nilotinib binds to the inactive conformation of BCR-ABL1, with a 30–50-fold increased binding affinity compared with imatinib. Nilotinib has demonstrated superior efficacy to imatinib in the ENEStnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials) trial.
In this phase III, randomized, open-label, multi-center study, 846 patients with chronic- phase Philadelphia chromosome-positive CML were randomized in a 1:1:1 ratio to receive nilotinib (at a dose of either 300 mg or 400 mg twice daily [BID]) or imatinib (at a dose of 400 mg once daily).

At 12 months, the rates of MMR for nilotinib (44% for the 300 mg dose and 43% for the 400 mg dose) were twice that for imatinib (22%; \( p<0.001 \) for both comparisons). The rates of CCyR by 12 months were also significantly higher for nilotinib (80% for the 300 mg dose and 78% for the 400 mg dose) than for imatinib (65%; \( p<0.001 \) for both comparisons). Significantly longer time to progression to AP or BC were also noted with either the 300 mg or 400 mg of nilotinib BID versus imatinib (\( p=0.01 \) and \( p=0.004 \), respectively).\(^7\)

At the 4-year data cutoff, >86% of patients across the three treatment arms remained in the study. In addition, more patients in the nilotinib arms (76% for the 300 mg dose and 73% for the 400 mg dose) achieved MMR compared with those in the imatinib arm (66%; Figure).

Patients in both nilotinib arms had significantly lower rates of progression to AP/BC on core treatment throughout the study period (including follow-up after discontinuation of treatment) versus patients in the imatinib arm.\(^8\) Including clonal evolution, progression occurred in 3 (1.1%), 5 (1.8%), and 17 (6.0%) patients receiving nilotinib 300 mg BID, nilotinib 400 mg BID, and imatinib, respectively (\( p=0.0009 \) and \( p=0.0085 \) for nilotinib 300 mg BID and nilotinib 400 mg BID vs imatinib, respectively).  

The estimated overall survival rates were similar across all groups at 4 years (94.3% and 96.7% for nilotinib 300 mg and 400 mg, respectively, and 93.3% for imatinib). However, fewer CML-related deaths occurred with nilotinib 300 mg and 400 mg versus imatinib (n=5, 4 and 13, respectively).  

Some commonly reported side effects of nilotinib included skin rash, hyperglycaemia and increased triglyceride levels. Therefore, patients are required to fast for 2 hours before taking nilotinib and 1 hour thereafter.

**Conclusions**

Recent results from the ENESTnd trial confirm the benefits of nilotinib over imatinib, supporting the role of frontline nilotinib therapy in patients with newly diagnosed chronic phase CML. The updated ELN recommendations also recommend nilotinib 300 mg twice daily as one of the first-line treatment options for chronic phase CML.\(^6\)

A complete list of references can be downloaded from [www.SOPHYSICIANSHK.org](http://www.SOPHYSICIANSHK.org)
Abbreviated Prescribing Information

Active ingredients: Micafungin sodium.

Indication and dosage:
1. Esophageal candidiasis: IV infusion. Adult: 150 mg/day.
3. Treatment of patients with candidemia, acute disseminated candidiasis, candida peritonitis and abscesses: IV infusion. 100 mg/day.


Contraindications: Hypersensitivity to any of the components.


References

Abbreviated Prescribing Information


Full prescribing information is available upon request.
Lung cancer is the leading cause of cancer death worldwide, including Hong Kong. About 75% of cases are inoperable upon presentation, largely because of their advanced stage or patients’ poor physical performance status. Systemic therapy is, therefore, the mainstay of treatment for locally advanced or metastatic disease in which surgery is inappropriate. However, the survival rate for inoperable disease is dismal despite platinum-based chemotherapy, which carries the risk of systemic side effects and poor tolerability. Epidermal growth factor receptor – tyrosine kinase inhibitors (EGFR-TKIs) such as gefitinib and erlotinib are a breakthrough in the treatment of advanced lung cancer. The landmark study, iPASS, was the first clinical trial to show that oral targeted therapy is both effective and well tolerated in patients harbouring EGFR mutation. Although EGFR mutation is more commonly found in patients who are Asian, female, non-smokers and with adenocarcinoma histology, only 60% of this enriched population carries the EGFR mutation. The molecular profiling of the remaining population has yet to be elucidated. 

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Similar to EGFR mutations, anaplastic lymphoma kinase (ALK) translocations are also predominantly found in patients with adenocarcinoma but are more common in patients with signet rings, never- or light-smokers, and young patients (median age, 50 years). Unlike the EGFR mutation, the ALK change is a translocation of the gene. ALK translocations are present in approximately 5% of cases of non-small cell lung cancer (NSCLC); notably, they are also found in anaplastic large-cell lymphoma (in which they were originally identified in the 1990s) as well as pediatric neuroblastoma. The identification of the ALK translocation as a potent oncogenic driver in NSCLC in 2007 resulted in development of ALK inhibitors. Crizotinib is the first identified oral small-molecule TKI targeting ALK, MET, and ROS1. In contrast to EGFR status, studies suggest that ALK status is not predictive of chemotherapy response. In the iPASS study, patients harbouring the EGFR mutation showed better response to chemotherapy compared with EGFR mutation-negative patients.

Currently, there are three methods for identification of ALK-positivity: fluorescence in situ hybridization (FISH; Figure 1), immunohistochemistry (IHC; Figure 2) and reverse transcriptase polymerase chain reaction (RT-PCR). Each of these is associated with strengths and weaknesses. FISH is the only test approved by the US Food and Drug Administration (FDA) as the standard method. However, it is labour-intensive (needing interpretation by two qualified personnel) and is associated with false negatives. IHC is widely used, and its detection of ALK-positivity is improving as methods of signal enhancement and more sensitive antibodies are developed. A two-tier screening, comprising an initial IHC screening followed by FISH evaluation of IHC samples scoring 1 to 2, is commonly adopted.

Trials with crizotinib have consistently reported notably high response rates of prolonged duration, often rapidly achieved. In addition, crizotinib is well tolerated and provides symptomatic relief while maintaining quality of life. Accelerated FDA approval of crizotinib was granted based on data from phase I and II trials. Results of the phase III
clinical trial, published in 2013, established the role of crizotinib as an alternative first-line treatment of NSCLC. Platinum-based chemotherapy was traditionally standard treatment.\(^6\) Patients with locally advanced or metastatic ALK-positive lung cancer assigned to receive crizotinib 250 mg twice daily achieved a median progression-free survival of 7.7 months compared with 3.9 months for those receiving standard chemotherapy (hazard ratio 0.49, \(p<0.001\)). The objective response rate was 65% versus 20% favouring crizotinib (\(p<0.001\)). Patients also reported greater symptom reduction and greater improvement in quality of life with crizotinib than with chemotherapy.

Both EGFR mutation and ALK translocation require the presence of adequate tissue in order to be analyzed by immunohistochemical staining or FISH test. In the iPASS study, only 36% of tissue retrieved was adequate for EGFR mutation study. This has significant clinical implications: even if the diagnosis of NSCLC is established by conventional tissue sampling methods, an EGFR TKI cannot be employed as first-line treatment without knowledge of EGFR mutation status.

Recently, endobronchial ultrasound-guided-transbronchial aspiration (EBUS-TBNA) has emerged as a highly diagnostic and safe tissue sampling modality. Its advantage is that almost all locally advanced or metastatic lung cancer patients have mediastinal lymph nodes involved.\(^9\) EBUS-TBNA is a non-surgical technology which can be performed under conscious sedation, and the length-of-stay in hospital can be shortened to one or two days. A tiny ultrasound probe is incorporated at the tip of a designated bronchoscope which allows both endoscopic and ultrasonic visualization simultaneously. The target lymph nodes, which may be situated outside the airway and not normally detected by conventional bronchoscopy, are readily revealed by the ultrasound probe. EBUS-TBNA manages tissue sampling under direct visualization, enabling diagnostic yields of 90% with an extremely high safety profile. Our group recently reported that 95% of tissue obtained is suitable for molecular profiling such as EGFR and/or ALK analysis.\(^10\)

In conclusion, the nomenclature and treatment modalities for lung cancer have evolved over the past 10 years. The previous classification into small cell and non-small cell lung cancer is now considered an oversimplification. The exact cell type and molecular profile of a lung cancer patient constitutes important components directing personalized management. The detection of EGFR and ALK positivity status allows patients the opportunity to achieve a significantly better response rate, safety profile, quality of life and progression-free survival.

**Figure 1.** ALK-positive non-small cell lung cancer as detected by interphase FISH using a dual colour break-apart probe system

![Figure 1](image1.png)

The arrow shows a tumour cell with the typical split red and green and one wild-type yellow fusion signal pattern. ALK, anaplastic lymphoma kinase

**Figure 2.** ALK-positive non-small cell lung cancer as detected by immunohischemistry using the 5A4 clone

![Figure 2](image2.png)

ALK, anaplastic lymphoma kinase

**References**

Introduction

Ever since the late 1950s, with the introduction of amphotericin B-deoxycholate, the development of safer, more effective systemic antifungal agents has been eagerly awaited. The deleterious side effects of amphotericin B had earned it the nickname ‘ampho-terrible’. The introduction of fluconazole in the 1990s and the second-generation triazoles voriconazole and posaconazole in the early-to-mid-2000s were promising developments. The introduction of echinocandins – effective agents with only limited toxicity – represented the fulfillment of this clinical need. This article focuses on one of the echinocandins, micafungin.

Structural characteristics, mechanism of action & pharmacodynamic properties

Echinocandins are cyclic hexapeptides, with an N-linked fatty acyl side chain. Differences in structure, lipophilicity and geometry of the side chain can lead to reduced toxicity and improved anti-Candida activity.1 Micafungin has a 3,5-diphenyl-substituted isoxazole ring side chain, whereas caspofungin has a fatty acid side chain and anidulafungin, a pentyloxycarophenyl moiety. Irrespective of the side chain, all echinocandins non-competitively inhibit 1,3-beta-D-glucan synthase, an enzyme present in, and essential to, the fungal cell wall.2 The result is the weakening of the cell wall structure and osmotic instability of the cell membrane leading to fungal cell lysis and eventual death.2

Micafungin produces a dose-dependent antifungal effect against all clinical and/or laboratory isolates of Candida spp. Combining micafungin with azoles resulted in negligible effects on antifungal activity, while in immunosuppressed mice with disseminated C. glabrata infection, co-administration of micafungin with amphotericin B or liposomal amphotericin B resulted in significant improvements in antifungal activity.9 Large global surveillance studies have shown that there is a low potential for the emergence of micafungin resistance (≥98.8% of Candida spp. are susceptible). Mutations conferring reduced susceptibility to echinocandins have been mapped to the FKS1 and/or FKS2 genes that encode 1,3-beta-D-glucan synthase.9

Micafungin has shown in vitro activity against Candida biofilms, including those resistant to other antifungal agents.

Pharmacokinetic properties

The oral bioavailability of micafungin is poor because of its high molecular weight. For this reason, it is administered intravenously. It is extensively protein bound in plasma (>99%), primarily to albumin.10 The drug is primarily metabolized in the liver and excreted in the feces. The mean terminal elimination half-life is 10–17 hours.11 The clearance of micafungin in children is affected by age, with younger children clearing the drug more rapidly.10 Micafungin is not dialyzable: continuous haemodiafiltration and continuous venovenous haemodialysis had little effect on micafungin pharmacokinetic parameters.11 Micafungin has a low potential to cause drug interaction through inhibition of CYP3A4. However, increased side effects may be expected when administered concomitantly with itraconazole, nifedipine or sirolimus. Concomitant use of micafungin and amphotericin B was associated with a 30% increase in exposure to the latter and therefore close monitoring for renal toxicity is needed.11
**In vitro activities**

To date, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) has not proposed clinical breakpoints (CBP) for micafungin or caspofungin against *Candida* spp.13 The recent 2012 European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines indicate that EUCAST breakpoints remain to be established for micafungin and caspofungin. EUCAST susceptibility breakpoints for anidulafungin against *C. albicans*, *C. glabrata*, *C. krusei* and *C. tropicalis* are <0.03, <0.06, <0.06 and <0.06 mg/L, respectively.6 The US Clinical and Laboratory Standards Institute (CLSI) has established a susceptibility CBP against *Candida* spp. for echinocandins of ≤2 μg/mL.3 However, evidence indicates that clinical isolates of *Candida* spp. showing resistance to echinocandins appear to have minimum inhibitory concentrations (MICs) that are lower than this CLSI CBP and, thus, a lower CBP may be more appropriate.9 A 2011 study indicated that species-specific interpretive criteria for CLSI CBP were generally lower than the initial CLSI CBP for echinocandins of ≤2 mg/mL.4 Against *C. albicans*, *C. tropicalis* and *C. krusei*, proposed CBPs for echinocandins were ≤0.05 (susceptible), 0.50 (intermediate) and ≥1 mg/L (resistant); for *C. parapsilosis*, respective CBPs for echinocandins were ≤2, 4 and ≥8 mg/L; and against *C. glabrata*, respective CBPs for micafungin were ≤0.06, 0.12 and ≥0.25 mg/L, with those for caspofungin and anidulafungin being ≤0.12, 0.25 and ≥0.5 mg/L.4

The SENTRY program is the largest study on *in vitro* susceptibilities of clinical isolates from patients with invasive fungal infections. The latest published study consists of 3,418 clinical isolates collected between 2010 and 2011 from 98 laboratories (34 countries) in North America (1,349 isolates), Europe (1,191 isolates), Latin America (492 isolates) and the Asia-Pacific region (384 isolates).13 All three echinocandins and four azoles (fluconazole, itraconazole, voriconazole and posaconazole) were tested using CLSI broth microdilution methods. Resistance to the echinocandins was distinctly uncommon (overall range, 0.0 to 1.2%) among *C. albicans* (0.0 to 0.6%), *C. tropicalis* (0.0%), *C. parapsilosis* (0.0 to 1.2%), and *C. krusei* isolates (0.0%) from all four geographic regions, using the new CLSI CBP values. Resistance to anidulafungin (3.8%), caspofungin (1.9%), micafungin (1.9%), and the triazoles (5.8% to 13.5%) was most prominent among isolates of *C. glabrata* from the Asia-Pacific region, whereas none of the *C. glabrata* isolates from Latin America were resistant to the echinocandins.13 All echinocandins, as expected, were resistant to Cryptococcus spp., Fusarium, Scedosporium and Mucorales since they all lack 1,3-beta-D-glucan synthase. Forty strains of *Aspergillus fumigatus* were tested in the 2009 SENTRY program and were found to have MIC₉₀ ≤0.008 μg/mL for micafungin, 0.008 μg/mL for anidulafungin and 0.25 μg/mL for caspofungin.14

**Clinical effectiveness**

Multiple large-scale, randomized controlled or non-inferiority trials in adults have been performed to compare normal-dose micafungin (100 mg/d) to high-dose micafungin (150 mg/d), liposomal amphotericin B, fluconazole and caspofungin for invasive candidiasis and esophageal candidiasis, including neutropenic or HIV-infected patients. All study results showed that micafungin given 100 mg/d was as effective as any comparator.12 In a study of a large multinational trial, micafungin 2 mg/kg/d (body weight [BW] ≤40 kg) or 100 mg/d (BW >40 kg) was compared with liposomal amphotericin B 3 mg/kg/d in the treatment of paediatric patients (median age ≤1 year), including neonates, with candidemia or other types of invasive candidiasis. Both treatments were shown to be effective without a statistically significant difference.12 Likewise, studies comparing the use of micafungin 50 mg/d and fluconazole 400 mg/d or itraconazole 5 mg/kg/d as prophylaxis against *Candida* infections in paediatric and adult populations have found that micafungin is as effective as comparators.2

**Summary**

Micafungin is one of the three echinocandins currently available for the treatment of invasive fungal infection. It has been proven to be safe and effective in adult and paediatric populations. It requires no loading dose and has few drug interactions. When compared to the other two echinocandins, it has comparable MICs against different *Candida* species and, perhaps, a lower MIC for *Aspergillus fumigatus*. Moreover, it has been shown to be active against *Candida* in biofilms, which may have important implications for the treatment of catheter-related fungal infections. More studies are warranted to see if this feature can be translated into clinical benefits.

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**References**

Introduction

The novel oral anticoagulants – including the direct thrombin inhibitor dabigatran and the direct Xa inhibitors apixaban, edoxaban and rivaroxaban – are increasingly popular for use in prevention of stroke in non-valvular atrial fibrillation (AF) and prevention and treatment of venous thromboembolism (VTE). Advantages of these agents over warfarin include faster onset and offset of action and predictable anticoagulant effect so that routine coagulation monitoring is not required (Table 1).1-3 However, there is increasing concern about managing patients on these novel agents in the perioperative setting. This article aims to give a brief overview of the perioperative management of patients on novel oral anticoagulants.

Bleeding risk of new anticoagulants

In stroke prevention for patients with non-valvular AF, the rate of overall major bleeding was 3.1–5.6%, which is similar to patients receiving vitamin K antagonists (VKAs).4,5 In the EINSTEIN DVT trial, the rate of major bleeding with rivaroxaban (0.8%) was not significantly different from that observed in the VKA group (1.2%).6 In the EINSTEIN PE study, the rate of major bleeding was 1.1%, which was half that of the VKA group.7 Data on bleeding rate from 7 days prior until 30 days following invasive procedures for patients receiving dabigatran in the RE-LY study has been recently reported.8 This was based on data from over 4,500 patients and over 7,500 procedures and operations. The procedures included the following: pacemaker/defibrillator insertion (10.3%), dental procedures (10.0%), cataract removal (9.3%), colonoscopy (8.6%) and joint replacement (6.2%). There were no significant differences in the rates of peri-procedural major bleeding among patients receiving dabigatran 110 mg (3.8%), dabigatran 150 mg (5.1%) and warfarin (4.6%). Among patients undergoing urgent surgery, major bleeding occurred in 17.8%, 17.7% and 21.6% in the three groups, respectively. No increase was observed in the risk of thromboembolic or bleeding complications among dabigatran-treated compared with warfarin-treated patients, among those who required major or urgent surgical procedures. To date, there are no published data on perioperative outcomes in patients receiving rivaroxaban or apixaban who require surgery or procedures.

Preoperative assessment

The patient’s risk of thromboembolism must be weighed against the risk of perioperative outcomes in patients receiving rivaroxaban or apixaban who require surgery or procedures.

Perioperative Management of Patients on Novel Oral Anticoagulants

<table>
<thead>
<tr>
<th>Key words: novel oral anticoagulants (新型口服抗凝血藥), perioperative management (手術前後的處理), laboratory monitoring (實驗室監察), reversal of bleeding (逆轉出血)</th>
<th>Table 1. Pharmacological characteristics of direct thrombin inhibitors and direct Xa inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td><strong>Rivaroxaban</strong></td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>Thrombin</td>
</tr>
<tr>
<td><strong>Time to peak effect</strong></td>
<td>1 hr</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>12–14 hrs</td>
</tr>
<tr>
<td><strong>Plasma protein binding</strong></td>
<td>34–35%</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Inhibitors of P-glycoprotein transporter</td>
</tr>
<tr>
<td><strong>Renal elimination</strong></td>
<td>80%</td>
</tr>
</tbody>
</table>

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Table 1. Pharmacological characteristics of direct thrombin inhibitors and direct Xa inhibitors
anticoagulants

Timing of discontinuation of perioperative bleeding. To assess thromboembolic risk, the clinician should consider both patient characteristics and the surgical procedure. Patient characteristics are summarized in the commonly adopted CHADS2 score (Congestive heart failure 1 point, hypertension 1 point, age >75 years 1 point, diabetes 1 point, and prior stroke or transient ischemic attack 2 points) for patients with AF, and by underlying thrombophilia severity in patients with VTE. CHADS2 score of 5 or 6, recent stroke, TIA, VTE within 3 months and severe thrombophilia (eg, protein C or protein S deficiency, antiphospholipid antibodies, or multiple abnormalities) are considered high-risk strata. The risk of bleeding can be determined by considering previous bleeding history, advanced age, and liver and renal function of the patient. It should be appreciated that patients with a high risk of thromboembolism often have an increased bleeding risk.

Perioperative management issues

Timing of discontinuation of anticoagulants

<table>
<thead>
<tr>
<th>Drug and dosage</th>
<th>Surgery of low bleeding risk</th>
<th>Surgery of high bleeding risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran: 150 mg BID</td>
<td>Resume 24 hours post-operatively</td>
<td>Resume 48-72 hours post-operatively</td>
</tr>
<tr>
<td>Rivaroxaban: 20 mg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban: 5 mg BID</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

As there is no specific antidote for immediate reversal of the new anticoagulants, planning ahead of the elective surgery or procedure is the rule. If the surgery cannot be delayed, there may be an increased risk of bleeding. The risk of bleeding should be weighed against the urgency of the surgical operation. For urgent surgery, administer oral activated charcoal if dabigatran is ingested within the last 2 hours. Since dabigatran excretion is primarily renal, the time of interruption of dabigatran before elective surgery or invasive procedures depends on the creatinine clearance (CrCl) and the risk of bleeding associated with the surgery (Table 2). The Cockcroft-Gault formula is recommended for calculation of CrCl:

\[
\text{CrCl} = \frac{1.23 \times (140 - \text{age (years)}) \times \text{weight (kg)}}{\text{serum creatinine (μmol/L) \times 0.85 if female}}
\]

For normal renal function and low bleeding risk surgery (including dental surgery), discontinue dabigatran 24 hours (~2 half-lives) before surgery, at which point around 25% of the drug remains active. Rivaroxaban, which is cleared to a lesser degree by the kidneys compared to dabigatran, should be stopped within 1–2 days before the procedure. Some authorities recommend a longer period of discontinuation (eg, 3–4 half-lives).

Resumption of new anticoagulants after surgery

The key factor is whether good hemostasis is achieved postoperatively. Perioperative deterioration of liver and renal function should be considered for either continued usage or need of dose reduction. Do not restart dabigatran if CrCl <30 mL/min and rivaroxaban, if CrCl <15 mL/min. In surgery where haemostasis is satisfactory, it is suggested that dabigatran or rivaroxaban is restarted 24–72 hours post-op depending on the bleeding risk of the surgery (Table 3). For patients at high risk of thromboembolism after high bleeding risk surgery, it is suggested to consider starting a reduced dose of anticoagulant (dabigatran 150 mg once daily, rivaroxaban 10 mg QD and apixaban 2.5 mg BID) on the evening after surgery and on the following postoperative day.

Bridging anticoagulation

The rapid onset and offset of the new oral anticoagulants (Table 1) should obviate the need for perioperative bridging anticoagulation unless the patient is unable to take oral medications, or has undergone gastric resection or is with prolonged ileus, when drug bioavailability is in doubt.

Laboratory monitoring

For emergency surgery, it is useful to determine any residual anticoagulant effect in patients taking dabigatran or rivaroxaban. PT/ International Normalized Ratio (INR) is relatively insensitive to the activity of dabigatran. An APTT >80 seconds at trough is associated with a higher risk of bleeding but it is less sensitive at supra-therapeutic dabigatran levels. The Hemoclot Thrombin Inhibitor assay, which is a dilute thrombin test, allows for quantitative measurement of
dabigatran activity with a reportable range of 50–500 ng/mL. The effect of riva-
xoxaban on PT is reagent-dependent and it shows an even weaker effect on APTT. With the use of rivaroxaban calibrators and controls, chromogenic anti-Xa assay provides peak concentration and trough concentration ranges for clinical use.

**Anaesthetic issues**

Spinal anaesthesia may require complete hemostatic function. The risk of spinal or epidural hematoma may be increased in cases of traumatic or repeated puncture and by the prolongation of used epidural catheters. The European Society of Anaesthesiology suggested the time elapsed from the last dose of anticoagulant to performing a central neuraxial block or catheter removal should be at least 2 half-lives of the drug, ie, 24 hours for dabigatran, 22–26 hours for rivaroxaban and 26–30 hours for apixaban. Anticoagulants should not be recommenced in patients with an epidural or spinal catheter in place. After removal of neuraxial catheters, an interval of at least 4–6 hours should elapse before resuming the first dose of the new oral anticoagulant. Vigilant monitoring for spinal or epidural haematoma is essential in the post-op recovery period and after catheter removal to allow for early detection of neurological deterioration and prompt intervention.

**Acute reversal of bleeding**

To date, direct thrombin inhibitors and Xa inhibitors have no specific antidote. Supportive measures, including fluid resuscitation, blood transfusion, maintenance of diuresis, identification of bleeding source and surgical haemostasis, are essential. For dabigatran, hemofiltration and hemodialysis could be considered because of its relatively low (35%) plasma protein binding. Concerning hemostatic agents, human data are scarce. Reversal of the new oral anticoagulants requires overriding the drug effects on factor IIa or Xa and not just standard factor repletion. Fresh frozen plasma is not likely to be helpful. Efficacy of activated factor VIIa is unclear. Administration of pro-thrombin complex concentrates (PCC) may reverse the effect of dabigatran and rivaroxaban. Lower doses of Factor VIII inhibitor bypass activity (FEIBA) may potentially reverse the effects of dabigatran and rivaroxaban. Administration of 4-factor PCC or FEIBA appears to be a reasonable approach in emergency situations. A catalytically inactive recombinant factor Xa neutralizing direct Xa inhibitors has been recently proposed as a potential antidote. An antibody Fab fragment that binds dabigatran and reverses its anticoagulant activity has also been developed. Further clinical studies are needed to clarify if there is any effective reversal agent for these new anticoagulants.

**Conclusion**

The perioperative management of patients on novel oral anticoagulants is an increasingly common clinical challenge to clinicians. The pharmacokinetics of the new anticoagulants, the thrombosis risk, and the bleeding risk related to both the patient and the surgical procedure, are crucial factors to consider for optimal perioperative care. There is, as yet, no consensus on a standardized protocol of perioperative management. Large multinational registries and further clinical data are required for the development of better evidence-based recommendations.

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  - 65% with Xalkori vs. 20% with chemotherapy (p<0.001)
- Greater overall improvement in quality of life (QoL) vs. chemotherapy (p<0.001)

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