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Revolade™ is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) or, as second line treatment, for adult non-splenectomised patients where surgery is contraindicated. **Dosage and administration** REVOLADE dosing must be individualised based on the patient’s platelet counts. The objective of treatment with REVOLADE should not be to normalise platelet counts but to maintain platelet counts above the level for haemorrhagic risk. Measurable elevations in platelet counts take 1-2 weeks. Adults Recommended starting dose: 50 mg once daily. Patients of East Asian ancestry: initiate at 25 mg once daily. Adjust the dose to achieve and maintain a platelet count ≥ 50,000/μl as necessary to reduce the risk for bleeding. Do not exceed 75 mg daily. Clinical haematology and liver tests should be monitored regularly throughout therapy with REVOLADE and the dose regimen of REVOLADE modified based on platelet counts. CBCs should be assessed weekly until a stable platelet count (at least 4 weeks) is achieved and monthly thereafter. **Warnings and precautions** Risk of hepatotoxicity. Thrombotic/Thromboembolic complications. Bleeding following discontinuation of eltrombopag. Bone marrow reticulin formation and risk of bone marrow fibrosis. Malignancies and progression of malignancies. Cataracts. Loss of response to eltrombopag. **Interactions** HMG CoA reductase inhibitors. OATP1B1 and BCRP substrates. Cytochrome P450 substrates. Antacids, dairy products, or other products containing polyvalent cations. **Pregnancy and lactation** REVOLADE is not recommended during pregnancy and in women of childbearing potential not using contraception. It is not known whether eltrombopag / metabolites are excreted in human milk. **Adverse reactions** Pharyngitis, urinary tract infection. Insomnia. Headache. **Overdose** In clinical trials there was one report of overdose where the subject ingested 5000mg of eltrombopag. Reported adverse events included mild rash, transient bradycardia, fatigue and elevated transaminases. Because eltrombopag is not significantly renally excreted and is highly bound to plasma proteins, haemodialysis would not be expected to be an effective method to enhance the elimination of eltrombopag. **Please refer to the REVOLADE full prescribing information before prescribing.** Abridged PI (EPA/R1032010)
In the featured article of the current issue, Dr YT Chen reviews the current approach to treating young women with deep vein thrombosis, which is a significant problem that physicians often encounter. It is very important to be aware of the possible underlying causes, so as not to miss the chance to prevent its recurrence.

There are another three articles that will help us to manage our patients in daily clinical practice. Dr Johnny Chan reviews drug reactions with eosinophilia and systemic symptoms. Professor Leung and Dr CP Kwan have contributed informative updates on the management of gastro-oesophageal reflux disease and irritable bowel syndrome, respectively.

I am certain that you will find this issue interesting, informative and beneficial to your practice.

Pictorial Medical History (4)

Asclepius (in Latin Asculapius) may have been a real person who lived sometime before 1200 BCE. Due to his great deeds, he was elevated to the rank of deity. He and his followers, including Hippocrates and Galen, exerted great influence in the practice of medicine that was to dominate the Western world for nearly 3,000 years.

Homer dedicated a hymn to Asclepius as follows:

“I begin to sing of Asclepius, son of Apollo and healer of sicknesses. In the Dotian plain (in Thessaly, east-central Greece) fair Coronis, daughter of King Phlegyas, bore him, a great joy to man, a soother of cruel pangs. And so hail to you, Lord; in my song I make my prayer to thee.”

Asclepius, holding the Asclepian
(a staff with a single entwined snake)
Roman sculpture in marble, 2nd Century
Pergamon Museum, Berlin, Germany
A 22-year-old college student returned to Hong Kong following a summer break, during which she had traveled and hiked extensively in New Zealand. Two days after her flight, she awoke with swelling and pain in her left calf and thigh, and noticed that the skin of the leg appeared dusky blue in color. Because of these rather alarming symptoms, and the fact that her mother had a blood clot at a young age, she came straight to the emergency room, where noninvasive venous studies showed an extensive deep venous thrombosis (DVT) involving the popliteal, femoral and iliac veins of her left leg.

Question: Should this patient be evaluated for an underlying thrombophilia?

Answer: Yes! This patient shows signs of an underlying thrombophilia or procoagulant state. The long plane flight could have provoked the clot, but since most people who take long flights do not get blood clots, we interpret this as “unprovoked”.

The four main signs of a procoagulant state are:
- Thrombosis at an early age
- Recurrent thromboses
- Thrombosis at an unusual site
- Family history of thrombosis

Review of Procoagulant States

Common risk factors for thrombosis

There are many general risk factors for thrombosis that need to be excluded first in any patient who presents with thrombosis.

1. **Obesity**: Obesity is the single most common entity associated with thrombosis. Over 50% of all patients with venous thrombosis are obese.

2. **Inactivity**: Inactivity contributes to thrombosis risk. Inactivity when traveling is defined as a period of greater than 4 hours without physical activity. A 20-year-old person confined to bed with significant comorbid factors (infection, trauma, etc.) for 2 weeks, has a 20% risk for thrombosis; a 40-year-old person has a 40% risk; and a 60-year-old person, 60% risk.

3. **Pregnancy**: Pregnancy is always a possibility in women of childbearing age. DVT and its sequela, pulmonary embolism, constitute the most common cause of maternal death. The incidence is 1–5/1,000 pregnancies (including postpartum). The risk of thrombosis is 12%–35% in women with previous DVT, and increases to 75% in women with antithrombin deficiency. Aetiologies for venous thrombosis include congenital risk factors, inactivity, and venous stasis. Decreased protein S values (antigen and activity) in pregnancy may contribute, but may also be part of the normal physiology of pregnancy. For example, like DVT in general, pregnancy-associated DVT affects the left leg more often than the right, probably because the left iliac artery is on top of the left iliac vein, and presses down on it. Increased levels of factors VII, VIII and fibrinogen also occur in pregnancy.

4. **Oestrogens/birth control pills**: Oestrogens increase the relative risk for venous thrombosis 3–5-fold, but the absolute risk is much smaller. The presence of factor V Leiden and the prothrombin gene mutation have a strong synergistic effect with oral contraceptives in promoting thrombosis. Women who take third-generation oral contraceptives have a several-fold increased risk of thrombosis.

5. **Post-surgery**: Undergoing surgery increases the risk of thrombosis by 10–30-fold. Previous surgery is the most common risk factor for DVT. The period of relative hypercoagulability can extend for weeks after surgery; on average, post-operative DVT presents over 2 weeks after surgery.

6. **Malignancy**: Thrombosis can be the presenting sign of cancer. The cancers most frequently associated with thrombosis are lung, breast and gastrointestinal cancers, especially pancreatic. Primary brain tumors are also associated with an increased risk of thrombosis.
Inherited procoagulant states

1. Factor V Leiden (Hereditary resistance to activated protein C): A polymorphism in factor V (R506Q), renders it relatively resistant to inactivation by activated protein C. Factor V Leiden is associated with primarily venous thrombosis. It is mostly seen in Caucasians or families where Caucasians have intermarried, among whom it accounts for 40%–60% of defined procoagulant states, 20% of first DVTs, and 5%–10% of the normal population. The presence of factor V Leiden dramatically increases the risk of thrombosis in women who are pregnant or taking oestrogen-containing oral contraceptives. This is important because venous thrombosis is the summation of risk factors, and having factor V Leiden increases an individual’s risk when other circumstances change. Heterozygous individuals have a 7-fold increased risk for thrombosis compared to non-carriers. Oral contraceptive use increases heterozygous women’s risk of venous thrombosis compared to non-carriers. This is the summation of risk factors, and having factor V Leiden increases an individual’s risk when other circumstances change. Heterozygous individuals have a 7-fold increased risk for thrombosis compared to non-carriers.

2. Prothrombin gene mutation: A defect in the prothrombin gene (nt20210 G→A) is present in 2%–4% of Caucasians. By itself, the mutation appears to confer weak hypercoagulability, but it can act synergistically with other hypercoagulable states, especially factor V Leiden. The mechanism is associated with slightly increased plasma levels of prothrombin that result in a hypercoagulable state, with a 2.8-fold increased risk in heterozygous individuals.

3. Homocysteinaemia: The classic genetic disease of elevated homocysteine due to cystathionine β-synthetase deficiency, has long been associated with increased arterial and venous thrombosis. Recently, it has been appreciated that even high-normal or minor elevations of acquired homocysteine are associated with accelerated vascular disease, including venous and arterial thrombosis. The risk increases at levels above 11 μmol/L. The pathogenesis of homocysteinaemia varies. Homocysteine is metabolised by being converted into methionine or cysteine. Thus, defects in the enzymes of homocysteine metabolism lead to abnormally elevated homocysteine levels. Acquired causes more commonly lead to hyperhomocysteine states. Conversion to methionine requires folic acid and vitamin B12, the most potent risk factor being lack of dietary folic acid. More than 90% of Americans do not ingest 400 μg/d of folic acid, and 50% not even 200 μg. In clinical nutrition studies, an intake of 400 μg/d was required to prevent elevation of serum homocysteine. Patients with vitamin B12 deficiency will also have increased homocysteine levels. Patients with increased folate requirements such as those with haemolytic anaemia or psoriasis, will also have elevated homocysteine. The kidney is a major organ in homocysteine metabolism; patients with renal failure will have increased homocysteine levels. High homocysteine is associated with accelerated atherosclerosis.

4. Protein C deficiency: When activated by thrombin, protein C degrades factors V and VIII. Functional deficiency of protein C primarily causes venous thrombosis. The risk of thrombosis ranges from 0.5%–2.5% per year. Protein C deficiencies are found in fewer than 5% of hypercoagulable patients. Protein C deficiency is a serious prothrombotic risk disorder; 75% of heterozygous individuals have a VTE, of which 70% are spontaneous or non-provoked and 30% are provoked by pregnancy, oral contraceptives, inflammation or infection, surgery, trauma, etc. Inherited homozygous protein C deficiency is associated with neonatal purpura fulmans, which is fatal within 3 days of birth if not detected and treated.

5. Protein S deficiency: Protein S is a cofactor for protein C that exists in a form bound to plasma protein (C4b-binding protein) and an unbound form. Deficiencies of total protein S and of unbound protein S (more common) can lead to the hypercoagulable state. Risk of thrombosis may be up to 3.5% per year. Protein S deficiency is primarily associated with venous thrombosis. Protein S deficiency affects fewer than 5% of patients with hypercoagulable states and has an incidence of 1 in 2–5,000. It too is a serious disorder; heterozygotes have an associated 74% likelihood of having a VTE. Functional protein S values are influenced by inflammatory states as a result of the interaction with C4b binding protein.

6. Antithrombin deficiency: Antithrombin inhibits activated clotting factors such as thrombin and Xa. Antithrombin deficiency is primarily associated with venous thrombosis. Antithrombin deficiency is found in fewer than 1% of individuals presenting with DVT. It is a serious risk for VTE, which affects 50% of heterozygous individuals.

7. Dysfibrinogenaemia: In dysfibrinogenaemia, defective fibrinogen forms clots that are difficult for fibrinolytic agents to degrade. Dysfibrinogenaemia can result in both venous and arterial thrombosis. These uncommon entities can be both congenital and acquired. They are not considered serious risk factors for thrombosis.

8. Elevated lipoprotein(a): Elevated lipoprotein(a) is a risk factor for both arterial and venous thrombosis. It is a demonstrated risk factor for heart attacks and stroke; however, the level of venous thrombosis risk has not been established.

Acquired prothrombotic medical states

1. Antiphospholipid antibody syndrome: Antiphospholipid antibodies (APLA) are antibodies directed against certain phospholipid-binding proteins such as prothrombin or β2-glycoprotein I. When detected by a clotting assay, they are known as ‘lupus anticoagulants’. They can also be measured quantitatively in an enzyme-linked immunosorbent assay that contains β2-glycoprotein I or cardiolipin. They are found in a variety of clinical situations, but can be idio-pathic. APLA have to be considered in all patients with VTE, regardless of other medical conditions. Venous thrombosis was the first described manifestation of APLA and still is one of the most clinically predominant.
Overall, retrospective studies show that 31% of patients with APLA have venous thrombosis. Patients with lupus and systemic lupus erythematosus (SLE) have a thrombosis rate of 42%. In patients with infectious and drug-induced APLA, the rate is less than 5%. Patients with APLA are overrepresented among young patients who have DVT. Prospective studies have demonstrated a relative risk for venous thrombosis of 5.3 for patients with SLE who have persistent elevations of IgG anticardiolipin antibody.

There does not appear to be a single mechanism by which APLA increases the risk of venous and arterial thrombosis. These antibodies have been shown to inhibit the functions of proteins C or S, interfere with tenase (factor X activation) and prothrombinase (prothrombin activation), damage the endothelium, activate platelets, or inhibit prostacyclin formation. Besides venous thrombosis, APLA have also been implicated in the aetiology of arterial thrombosis (especially strokes), recurrent miscarriages and immune thrombocytopenia.

2. Disseminated intravascular coagulation: In disseminated intravascular coagulation (DIC), thrombosis arises due to excess thrombin formation. DIC arises in patients with sepsis, cancer, obstetrical emergencies, tissue destruction injuries, and certain coagulation protein deficiency states, for example, homozygous protein C deficiency.

3. Heparin-induced thrombocytopenia and thrombosis syndrome: Heparin-induced thrombocytopenia and thrombosis syndrome can be induced by unfractionated heparin and any low molecular weight heparin (LMWH). In this condition, antibodies arise to the heparin (or LMWH)/platelet factor 4 complex that binds via platelet Fc gamma 2 receptors, thus leading to platelet activation. Patients with this condition have both venous and arterial thrombosis.

4. Inflammatory bowel disease: Patients with inflammatory bowel disease are at increased risk of thrombosis; up to 33% have thrombi present at autopsy. Patients with inflammatory bowel disease complicated by thrombosis usually present with DVT of the lower extremity. Increased risk of visceral vein thrombosis has also been reported, perhaps due to local inflammation. Rarely, large arterial thrombi have also been reported. Patients with inflammatory bowel disease have been reported to have lowered levels of free protein S due to increased levels of C4b-binding protein, which is an acute-phase reactant. Increased levels of inflammatory cytokines such as IL-1 and TNF, may also contribute to the procoagulant state.

5. Myeloproliferative disorders: Thrombosis is the most common cause of death in myeloproliferative syndrome, especially in patients with essential thrombocythaemia (50%) or polycythaemia vera (90%) who have the JAK2 V617F polymorphism. Although many patients will have markedly elevated blood counts, patients with essential thrombocythaemia may have thrombotic complications at platelet counts as mildly elevated as 600,000/µL. The thrombosis can occur in small vessels, perhaps due in part to increased viscosity, or in large vessels. Patients with myeloproliferative syndromes are at increased risk of thrombosis even with relatively normal blood counts, which suggests an intrinsic defect in the blood cells leading to thrombosis. Patients with Budd-Chiari and other visceral vein thrombosis have a high incidence of underlying myeloproliferative syndromes.

6. Nephrotic syndrome: Nephrotic syndrome is associated with an increased incidence of renal vein and other thromboses. Pathogenesis of the hypercoagulable state in nephrotic syndromes is due to loss of natural anticoagulants. Low levels of both antithrombin III and protein S are commonly seen. Patients may also have a concurrent autoimmune disease, such as lupus, that is independently associated with thrombosis.

7. Paroxysmal nocturnal haemoglobinuria (PNH): PNH is a rare haematological disorder that should be considered in patients who present with pancytopenia, hypocellular bone marrow and/or an episode of venous thrombosis. The underlying problem is a mutation in a gene encoding a lipid ‘anchor’ that links membrane proteins with the phospholipid membrane (Figure). Without the lipid anchor membrane proteins are lost. Patients with PNH have approximately 50% risk for developing VTE. This loss of membrane proteins leads to a variety of effects. The loss of red cell membrane proteins (which includes enzymes that inactive complement) renders the erythrocytes more susceptible to lysis. Patients can present with thrombosis at any site. PNH is one of a few hypercoagulable states that classically lead to Budd-Chiari syndrome. Pathogenesis of the thrombosis is not precisely known. The classic “nocturnal haemoglobinuria” is a rare finding. Most patients will have pancytopenia, although rare patients can present with elevated blood counts. Patient will usually have a raised serum lactate dehydrogenase.

Sources
Relieve GERD & leave them to dream

NEW
DEXILANT
dexilansoprazole
90 mg | 45 mg DELAYED RELEASE CAPSULES
Designed to deliver

- Sets a new standard for PPI therapy, with dual releases of active drug to provide significantly extended heartburn control1,2

- Effective across the spectrum of GERD3,4

- Maintain long-term healing and therefore quality of life5,6

- Lifestyle-friendly PPI: once daily, taken with or without food7,8

Dexilant Abbreviated Product Information

Presentation: Dexilant 30mg and 60mg capsules. Indication: Healing of all grades of erosive oesophagitis (EE) for up to 8 weeks, maintenance of healed erosive oesophagitis for up to 6 months, treatment of heartburn associated with nonsymptomatic non-erosive gastroesophageal reflux disease (NURS) for 4 weeks. Dosage and administration: 60mg once daily for up to 6 weeks for healing of EE, 30mg once daily for maintenance of healed EE, 30mg once daily for 4 weeks for symptomatic non-erosive GERD. Dexilant can be taken without regard to food and should be swallowed whole. Contraindication: contraindicated in patients with known hypersensitivity to any component of the formulation. Interaction: paracetamol, simvastatin, digoxin, iron salts, ketocazole, warfarin, tacrolimus. Precaution: gastro malignancy. Adverse reaction: diarrhoea, abdominal pain, nausea, upper respiratory tract infection, vomiting, flatulence.


For further information, consult full prescribing information.

* 98% of patient on Dexilansoprazole 60mg achieved 24-h heartburn-free days9

Takeda
The prevalence of gastro-oesophageal reflux disease (GERD) in Asia is increasing, possibly due to the adoption of more “Westernised” lifestyles. A systematic review of current data showed that 2.5% to 6.7% of Asians report at least weekly symptoms of heartburn and/or acid regurgitation. Not only has the number of patients with symptomatic GERD increased, but we are also witnessing an increase in complications of GERD such as Barrett’s oesophagus, a pre-neoplastic condition, during endoscopy (Figure 1).

Proton pump inhibitors (PPIs) have had a significant impact on the management of acid-related disorders, and are by far the most effective medical therapy for GERD. Consistent evidence confirms the superior efficacy of PPIs compared with histamine-2 receptor antagonists in terms of symptom relief and healing oesophagitis. Most patients therefore require long-term PPIs for oesophageal mucosal healing and/or control of acid reflux symptoms.

Medical Treatment for GERD

Despite their established benefits in GERD therapy, currently available PPIs have limitations. While food is the primary stimulus for proton pump activation, it is generally recommended that a PPI be administered less than 60 minutes before the morning meal, to ensure subsequent daytime reduction in basal and meal-stimulated acid production. Nonetheless, a considerable proportion (20%–30%) of patients do not have adequate relief of symptoms despite daily treatment with PPIs. One reason for an inadequate response to PPIs may relate to sub-optimal pH control. Sachs and coworkers demonstrated that PPIs inhibit only 70% to 80% of activated proton pumps. In addition, proton pumps are continuously regenerated, with the entire population within the parietal cell turned over every 48 hours. As a result, PPIs do not completely suppress acid secretion over a 24-hour period, particularly at a single daily dose. Nocturnal acid breakthrough (intragastric pH <4 for ≥1 continuous hour) therefore occurs in a proportion of patients receiving PPI treatment.

Novel PPIs

Since the clinical efficacy of PPIs correlates with the degree of acid suppression, newer PPIs with prolonged antisecretory effects and an extended plasma half-life may have a therapeutic advantage over existing PPI therapies. Dexlansoprazole MR, the R-enantiomer of lansoprazole, employs dual delayed-release technology to extend the duration of action following once-daily dosing. The formulation produces two distinct releases of drug: 25% of the total dose is released at pH 5.5 in the proximal small intestine within 2 hours of dosing, with the remaining 75% released at pH 6.5 in the distal small intestine several hours later. Dexlansoprazole MR significantly prolongs the duration of active plasma concentrations and the proportion of time with pH above 4 relative to conventional single-release PPI therapy. Unlike PPIs that must be taken before eating, dexlansoprazole can be administered without regard to meals or their timing in most patients. Dexlansoprazole has been shown to effectively control heartburn and heal and maintain healed erosive oesophagitis, preventing relapse, as well as improving work productivity and health-related quality of life. While there are concerns about the
potential for interaction between PPIs and clopidogrel,

concomitant administration of dexlansoprazole and clopidogrel has no clinically important effects on clopidogrel-induced platelet inhibition.

A study in healthy volunteers, also confirmed that dexlansoprazole has less interaction with clopidogrel than esomeprazole or omeprazole.

Future Perspectives on the Treatment of GERD

In addition to PPIs, a new class of acid suppressant, the potassium competitive acid blockers (P-CABs), have been tested in patients with GERD. P-CABs are superior to conventional PPIs because they provide reversible and complete suppression, the potassium competitive blocker, with lansoprazole in animals. J Pharmacol Exp Ther 1999;292:576-583.

In a randomised clinical trial adding leso-gaberan to ongoing PPI therapy had only a small benefit in resolving GERD symptoms. Moreover, the benefits of the new mGluR5 inhibitor (ADX10059) in patients with GERD were marginal, and were associated with considerable adverse events (eg, liver derangement) which may limit its future use. Further research and development is therefore necessary to identify other new medical therapies for GERD.

Conclusion

Successful management of patients with GERD symptoms remains a clinical challenge. Despite the efficacy of existing PPIs, there remain many unmet needs, such as inadequate and poor responses to PPI, nocturnal breakthrough and potential drug interactions with clopidogrel. While new drug targets appear to offer little benefit compared to existing PPI therapy, the availability of a new PPI that provides an extended duration of gastric acid control with a well-defined safety and efficacy profiles may help to address some of these unmet needs.

References

Drug Adverse drug reactions (ADRs) are any noxious, unintended, and undesired effect of drugs that occur at doses used in humans for prophylaxis, diagnosis, or therapy.1 ADRs are frequent in hospital patients, with an estimated incidence of 2% to 6%.2-5 Severe ADRs lead to hospitalisation, prolonged inpatient stay, substantial morbidity, and even death. As the body’s largest organ, the skin is most commonly affected by ADRs, which manifest in diverse patterns.

Drugs reaction with eosinophilia and systemic symptoms (DRESS) is an idiosyncratic, acute, and distinct, drug-induced hypersensitivity reaction that is potentially lethal. Alongside Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and acute generalised exanthematous pustulosis, DRESS is regarded as a severe cutaneous adverse reaction (SCAR). Diagnostic labeling of DRESS has been confusing, with several terms used to describe the same condition (Table 1). Bouquet and coworkers coined the term ‘drug rash with eosinophilia and systemic symptoms’ in 1996,6 and this was widely adopted thereafter. However, given the heterogenous pattern of rashes in DRESS, the definition was subsequently refined to ‘drug reaction with eosinophilia and systemic symptoms’.

The incidence of DRESS has been estimated to be from 1/1,000 to 1/10,000 drug exposures.7 DRESS is characterised by delayed onset, usually 2–6 weeks after initiating the causative agent, and its persistence or aggravation of symptoms despite discontinuing the drug.8 The hallmark of DRESS syndrome is the classical triad of fever, rash and visceral involvement. Lymphadenopathy is typically present. Cutaneous manifestations of DRESS are highly diverse,6,8 common dermatological findings include maculopapular eruption, lichenoid eruption, facial oedema, exfoliative dermatitis and sterile pustules at the head and neck region (Figure 1). Mucositis, cheilitis, vesicles, bullae, purpura and target lesions have also been described.9,10 Visceral involvement is the major cause of morbidity in DRESS. Liver damage, either hepatocellular injury or less commonly cholestasis, occurs in most patients. Isolated asymptomatic hepatomegaly can sometimes be present. In severe cases, fulminant hepatitis and liver failure may result in death or necessitate transplantation. Proteinuria without renal function impairment is the most common renal abnormality.10 Interstitial nephritis is uncommon, but a higher incidence is associated with allopurinol-induced DRESS than other drugs.11 Renal failure requiring dialysis is seldom reported and is related to acute tubular necrosis.12 Cardiac involvement is rare, but potentially fatal. Increased risk of myocarditis and pericarditis have been reported in cases induced by minocycline.10 Lung, pancreas and muscle involvement have also been described. Haematological abnormalities in DRESS patients are consistently observed. Peripheral eosinophilia is frequently detected and present in more than 50% of cases.10 Activated, large lymphocytes are characteristically detected in peripheral blood smears (atypical lymphocytosis). Other associated blood dyscrasias include neutrophilia, lymphopenia, thrombocytopenia and pancytopenia. DRESS syndrome has no pathognomonic histopathological features and the diagnosis does not require histological confirmation. Lichenoid mononuclear infiltrates with vacuolar degeneration of the basal cell layer are often seen. Superficial perivascular lymphocytic infiltrates

Table 1. Synonyms for DRESS syndrome

<table>
<thead>
<tr>
<th>Term (acronym)</th>
<th>Author (year)</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Drug-induced pseudolymphoma</td>
<td>Saltzstein (1959)</td>
<td>40</td>
</tr>
<tr>
<td>Anti-convulsant hypersensitivity syndrome (AHS)</td>
<td>Vittorio (1995)</td>
<td>41</td>
</tr>
<tr>
<td>Drug-induced hypersensitivity syndrome (DIHS); or Hypersensitivity syndrome (HSS)</td>
<td>Callot (1996)</td>
<td>42</td>
</tr>
<tr>
<td>Drug-induced delayed multiorgan hypersensitivity syndrome (DIDMOHS)</td>
<td>Sontheimer (1998)</td>
<td>43</td>
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are another common but non-specific histological finding. Other reported findings include pseudolymphoma, leukocytoclasic or lymphocytic vasculitis.6,13,14

To date, more than 40 drugs have been described in DRESS (Table 2).8 Aromatic anticonvulsants (phenytoin, carbamazepine, phenobarbital), allopurinol, and sulphonamides including dapsone and sulfamethoxazole-trimethoprim (cotrimoxazole), are the most important classes of causative drugs.8,15,16 Lamotrigine, minocycline and anti-retroviral agents (abacavir and nevirapine) are also frequently involved.9,10,17-20

The precise pathogenesis of DRESS has not yet been elucidated; however, viral reactivation has been widely postulated to play a pivotal role, with subsequent stimulated T-cell expansion thought to be pivotal to skin and visceral damage in DRESS.28,29

Table 2. Causative agents in DRESS syndrome8

<table>
<thead>
<tr>
<th>Common</th>
<th>Uncommon</th>
</tr>
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<tbody>
<tr>
<td>Allopurinol</td>
<td>Sodium meglumine iodate</td>
</tr>
<tr>
<td>Aromatic anti-convulsants</td>
<td>Sodium valproate/ Ethosuximide</td>
</tr>
<tr>
<td>(Carbamazepine, Phenytoin, Phenobarbital)</td>
<td>Spironolactone</td>
</tr>
<tr>
<td>Sulphonamides</td>
<td>Streptomycin</td>
</tr>
<tr>
<td>(Sulphasalazine, Salazosulfapyridine, Cotrimoxazole, Dapsone)</td>
<td>Streptomycin</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Anti-retroviral drugs</td>
</tr>
<tr>
<td>Minocycline</td>
<td>(Abacavir, Nevirapine)</td>
</tr>
<tr>
<td>Anti-retroviral agents (abacavir and nevirapine)</td>
<td>Sodium meglumine iodate</td>
</tr>
</tbody>
</table>

There is increasing evidence of genetic predisposition to adverse drug reactions. The association between human leukocyte antigen (HLA) related induced hypogammaglobulinaemia has been hypothesised to permit viral reactivation, with subsequent stimulated T-cell expansion thought to be pivotal to skin and visceral damage in DRESS.28,29

Diagnosing DRESS can be difficult, especially in clinical scenarios without clear-cut drug history. Infectious mononucleosis can mimic DRESS, but a relevant drug history, presence of eosinophilia and involvement of internal organs other than the liver, may aid differential diagnosis. Other possible diagnoses include lymphoma or pseudolymphoma, collagen vascular diseases and serum sickness-like reaction. SJS/TEN, being another form of SCAR, shares certain similarities and overlapping features with DRESS. In DRESS, rashes typically begin with a maculopapular eruption that progresses into erythroderma and exfoliative dermatitis, often with scattered pustules and...
facial oedema. Bullae may occasionally be present due to dermal oedema, but are neither a prominent nor a common feature. These differ from the blistering eruption in SJS/TEN, in which extensive keratinocyte necrosis is typically present.

Early recognition and prompt withdrawal of the causative drug is essential to optimising clinical outcomes. Hospitalisation is recommended to closely monitor vital signs and organ dysfunctions. In mild cases, full recovery of skin and visceral injuries can be achieved by supportive care alone for a few weeks. Nevertheless, blood biochemistry should be monitored regularly on subsequent visits. With a high index of suspicion, appropriate tests should be performed to exclude the uncommon involvement of specific organs, namely pancreas, lungs, heart and muscles, if clinically indicated.

Systemic corticosteroid is the therapeutic mainstay for DRESS. The literature advocates moderate to high doses of systemic corticosteroid when there is central organ involvement. However, any underlying infection should be cautiously sought-out, before commencing systemic corticosteroid. The usual oral corticosteroid dose is prednisolone 40 to 60 mg daily (1 mg/kg/day). Relapse of symptoms is fairly common in DRESS, and rashes, hepatic or renal deterioration are observed upon tapering or abrupt discontinuation of corticosteroid. Consequently, systemic corticosteroid is often gradually tapered-off over 6–8 weeks following initial high dose treatment, to prevent relapse. Other treatment options with reported success in individual cases or series, include pulsed intravenous methylprednisolone, intravenous immunoglobulin G and plasmapheresis, or a combination of these. Other immunosuppressants, including cyclosporine A and cyclophosphamide, have also been reported to be effective in corticosteroid-resistant cases of DRESS. The overall mortality of DRESS syndrome is reported to be 10% to 20%, with most fatalities related to liver failure and myocarditis. Irreversible renal damage requiring long-term dialysis is rare. Owing to the use of high dose systemic corticosteroid, infectious complications are not uncommon during the course of DRESS treatment, and mortality from bacterial sepsis and fungaemia has been reported. DRESS is associated with the development of several autoimmune conditions subsequent to the acute episode. In particular, hypothyroidism resulting from autoimmune thyroiditis can develop months after recovery from the hypersensitivity syndrome. Type 1 diabetes, in which immune-mediated pancreatic islet cell destruction may be implicated, is also associated with DRESS. Systemic lupus erythematosus associated with EBV reactivation has also been described as a complication. Long-term follow-up of DRESS patients is therefore recommended and these autoimmune complications warrant a high index of suspicion.

### References

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Significant symptom relief
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Symptom relapse reduced significantly after treatment period¹

Placebo like tolerability³

References
Update on Irritable Bowel Syndrome

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Introduction

Irritable bowel syndrome (IBS) is a common disorder in Hong Kong. IBS is characterised by abdominal pain associated with abnormal bowel movement without any clinically identifiable structural or biochemical abnormality. Based on Rome I or Rome II criteria, the prevalence of IBS in local epidemiological studies in Hong Kong ranges from 3.6% to 6.6%,1-3 with female preponderance accounting for 57% to 66% of all patients. Disease onset in most patients is before age 60 years and prevalence decreases with age above 60. Breakdown by IBS subtypes indicates that diarrhoea-predominant subtype constitutes 27% of cases, constipation-predominant subtype 17% with the remaining 56% non-specific, or alternating subtype. The Asian Neurogastroenterology and Motility Association (ANMA) recently published a series of consensus statements on IBS.4 This article highlights some of the new findings in IBS.

Pathophysiology

IBS is a multifactorial disorder, in which a variable combination of genetic factors, gut infections, brain/gut interactions, and psychological disturbance can interact in the pathophysiology. Although altered GI motility can be found in IBS patients, it does not always correlate with IBS symptoms. Visceral hypersensitivity plays an important role in the development of symptoms in IBS patients. In any given patient, it is likely that more than one factor might be present.

Acute GI infection is a triggering factor for symptom development in a subset of patients with IBS (post-infectious IBS). Increased intestinal permeability and inflammatory cells and levels of cytokines are observed in such patients, which may subsequently lead to visceral hypersensitivity. In a cohort study of 295 patients from Beijing who were recovering from dysentery,5 the incidence of functional bowel disorders and IBS by Rome II criteria were 22.4% and 8.1%, respectively, compared with incidences of 7.4% and 0.8%, respectively, in the control cohort.

IBS in a proportion of patients is associated with small intestinal bacterial overgrowth (SIBO). A center in the USA reported the prevalence of SIBO in their IBS patients to be 84%, compared with 20% in healthy controls.6 That study defined SIBO based on lactulose hydrogen breath test. Using the same criterion, a study from Korea reported a SIBO prevalence of 48.7% in IBS versus 26.5% in controls.7 Antibiotics might be useful in this group of SIBO patients but unfortunately lactulose or hydrogen breath test are not available in Hong Kong. The relationship between use of proton pump inhibitors and SIBO is controversial.8

Treatment

An effective therapeutic relationship between a physician and the patient is important. A positive diagnosis, listening to the patient’s concerns and patient counseling with explanation of the symptoms and possible mechanism, and reassurance, often help to alleviate patient’s fears that they may have other serious diseases. Physicians should explain the benign prognosis and relapsing/remitting course of the condition as well as the possible association between emotional stress and flare of symptoms. Good education facilitates better patient understanding, acceptance and adaptation to this chronic condition.

The two main food groups that can aggravate IBS symptoms in Caucasian populations are dairy products and cereals.9 Studies from Asia suggest that chili and curry may be possible food triggers for dyspepsia-like upper abdominal pain in IBS patients.10 Lactose

Diagnosis

Since IBS has no characteristic pathophysiologic abnormalities, the diagnosis is mainly based on symptom analysis and simple laboratory tests to rule out common differential diagnoses which include drug induced gastrointestinal (GI) side effects, carcinoma of colon and pancreas, thyrotoxicosis, and inflammatory bowel disease. Bowel-related symptoms consist of abdominal pain, bloating, or other discomfort that is either improved by passing stool or flatus, or is associated with any change in stool form or frequency. The patient’s bowel pattern should not be described by stool frequency alone, but should include the stool type and the specific defaecation symptoms of straining at stool, feeling of incomplete defaecation, and urgency. Early and confident diagnosis of IBS is important to minimise excessive investigations, inappropriate treatment, and unnecessary surgery. Alarming symptoms and signs, such as blood in the stool, pallor, fever, weight loss, nocturnal symptoms, presence of an abdominal mass and age >45 should be looked for and if present, prompted further investigations to look for an organic lesion. Figure 1 shows the ANMA algorithm for IBS management.

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and fructose intolerance are common in Asia, and could be a contributing factor for symptoms, such as bloating, flatulence, and diarrhoea. Recent studies suggest that measuring of serum immunoglobulin G antibodies to food can help to identify specific food intolerance, but the role of these tests in clinical practice is not yet certain.

Drugs

Suggested initial treatments for patients with IBS include various combinations of antispasmodic, laxative, prokinetic, anti-diarrhoeal, and probiotic agents. Intestinal smooth muscle relaxants (eg, Mebeverine, Spasmoden) or anticholinergic agents (eg, Dicyclomine, Hyoscine, Scopolamine, etc.) have been shown to have variable success in pain control especially meal-related symptoms. However these can aggravate constipation and anticholinergic side effects may prevent patients from continued use. Recently, a multi-center European study showed that otilonium bromide (Spasmomen) for 15 weeks is safe, well-tolerated and superior to placebo in reducing the frequency of abdominal pain during treatment, as well as better protecting patients from relapse in the 10 week follow-up period after stopping the drug (Figure 2).

In a large US multi-center study on 1,260 non-consisted IBS patients, rifaximin (non-absorbable antibiotic) 550 mg thrice daily for 2 weeks was better than placebo in achieving adequate relief of global IBS symptoms in the follow-up period up to 6 weeks, supporting the role of SIBO in a subset of IBS patients. However, this drug is very expensive and the long term impact remains unclear. Probiotics may provide another way to try to alter the intestinal microflora, and hopefully to reduce visceral hypersensitivity. A recent meta-analysis suggested that probiotics are effective for improving abdominal pain and flatulence in IBS, with a positive trend for bloating. However, the magnitude of the benefits and the most effective species and strains of probiotic remain to be defined. Low-dose antidepressants, such as tricyclic antidepressants and selective serotonin reuptake inhibitors, can be considered in patients who fail to respond to initial treatment, even in the absence of any overt psychological disorders.

References
Tumor Radioresistance and p53: Focusing on Cancer Stem Cells

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The loss of p53 functions, either through mutations on the p53 gene itself or other factors, has long been associated with decreased radiosensitivity of human tumor cells. For example, patients with recurrent non-small cell lung carcinoma (NSCLC) whose tumors were found with mutations in exons 5-8 of the p53 gene were up to four times less likely to respond to radiotherapy than those patients whose tumors had wild-type p53. Similarly, analysis of glioblastoma multiforme brain tumor (GM) clonogenic cell lines has indicated that the lack of functional p53 was associated with resistance to fractionated irradiation. A closer look at the phenomenon suggests that tumor cells that retain radiation-induced G1 arrest and radiation-induced accumulation of p53 levels are those that show the highest sensitivity to ionizing radiation. Simultaneous detection of bcl-2 over-expression and p53 gene mutations in primary squamous-cell carcinoma of the head and neck (HNSCC) treated with conventional radiotherapy is associated with higher risk of locoregional failure and worse survival within 5 years.

Many such examples have pointed to a mechanism whereby tumor cells have become ionizing radiation-resistant because mutations in their p53 fail to induce cell death by apoptosis, or tumor cells have acquired other anti-apoptosis mechanisms such as when bcl-2 is expressed at high levels. As in normal cells, irradiated tumor cells seem to have the choice between dying by apoptosis and undergoing growth arrest, a process that seems to be dictated by the severity of DNA damage, and type of tissue (see review). When tumor cells lose p53 functions, they revert to growth arrest that give the cells a chance to repair DNA damage, and perhaps die by mitotic catastrophe if the damage cannot be repaired.

The idea that supplementing tumor cells with exogenous p53 by viral vector transduction would increase radiosensitivity, or equivalently, reverse radioresistance, has been tested in both pre-clinical and clinical settings by various groups. Indeed, human prostate cancer cell lines have been shown to become highly sensitive to ionizing radiation upon infection with an adenoviral vector containing the wild-type p53 in a viral dose-dependent manner, which also resulted in induction of G1 cell cycle arrest. Growth of human cervical cancer cells have also been shown to be inhibited by a combination of ionizing radiation and p53 added by viral transduction at a rate that was significantly higher than when the cells were treated by either method alone.

In a clinical study involving patients with advanced nasopharyngeal carcinoma (NPC), 42 subjects who were treated with a combination of adenoviral p53 gene therapy by intratumoral injection and local treatment with radiotherapy showed remarkable complete tumor response rate of 2.73 times higher than those 40 control patients who received radiotherapy alone. In addition, locoregional recurrence observed in follow-ups over a period of 6 years in the combination treatment group was only 2.7% compared to 28% for the group that received radiotherapy alone. Thus, at least for this study treatment of tumors in patients who received both gene therapy and radiation showed not only rapid complete tumor response but also long-term inhibition of local recurrence.

Solid tumors are complex structures involving heterogeneous types of tumor cells, stromal cells that support structure, endothelial cells that are involved in its vasculature, infiltrating immune cells of various kinds that are likely is suppressed state, and a subpopulation of cancer stem cells (CSCs). In particular, the CSCs have caught the attention of many investigators for they seem to be involved in resistance to genotoxic treatments, in the repopulation of the tumor mass, and in distant metastases (see review). Certain studies show that p53 is highly involved in the suppression of CSCs and that perhaps loss of p53 could lead to genetic instability, which in turn results in plasticity, a hallmark of CSCs, of certain phenotypes in the tumor population due to random mutations and clonal evolution. Loss of p53 and deregulation of growth factor signalling pathways are thought be involved in the transformation of adult neural stem cells, and it is suggested treatments involving reactivation of p53 in brain tumor stem cell populations should be explored. In breast cancers, studies show that tumor cells can acquire stem cell properties when p53 functions are lost. As the focus in cancer treatment is turning towards the control of CSCs in which p53 seems to be central in its regulation, it is perhaps time to reconsider the role of p53 gene therapy in combination with conventional treatments in the development of highly effective regimens for various types of solid tumors.

References: