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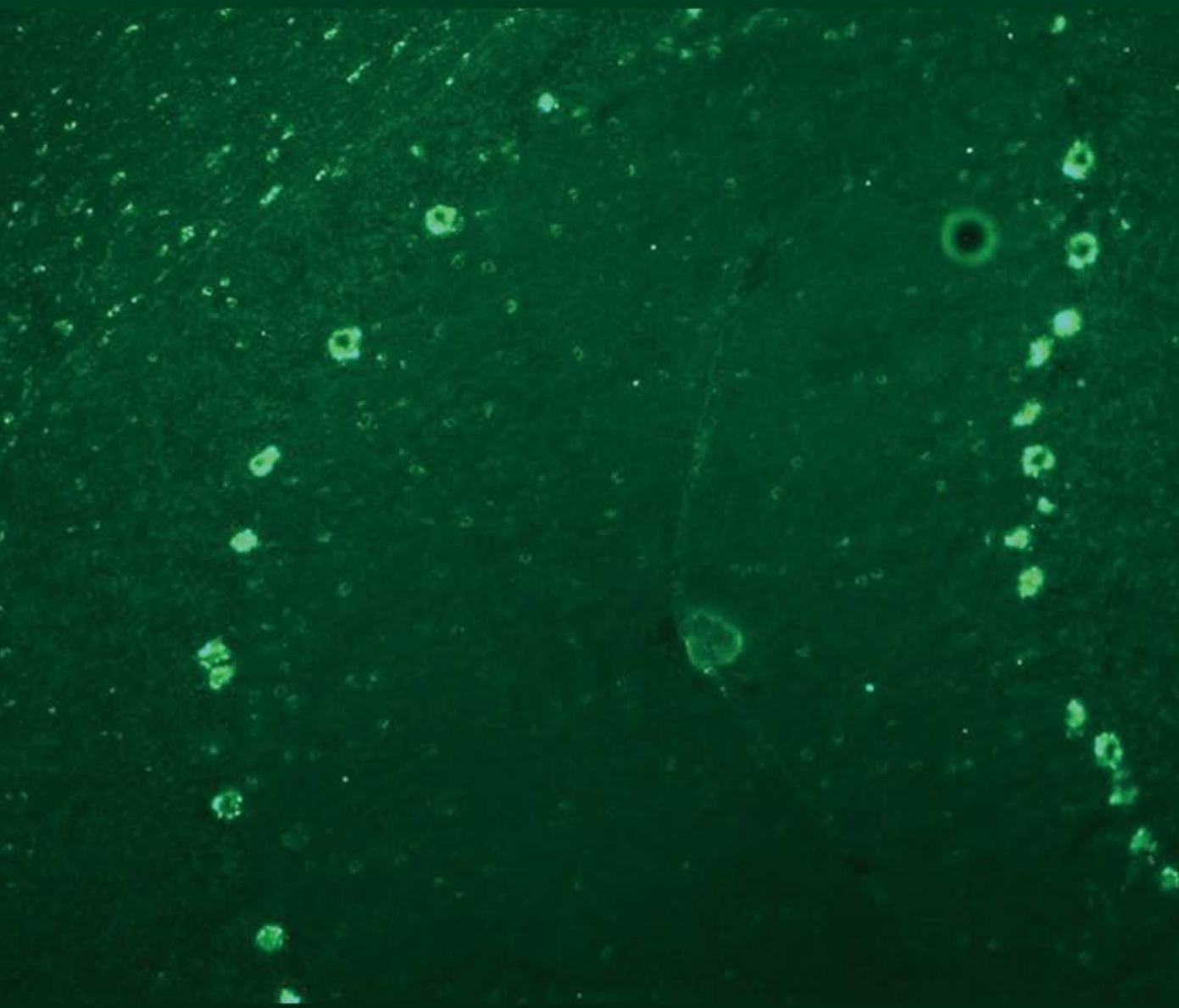
Neuroimmunology



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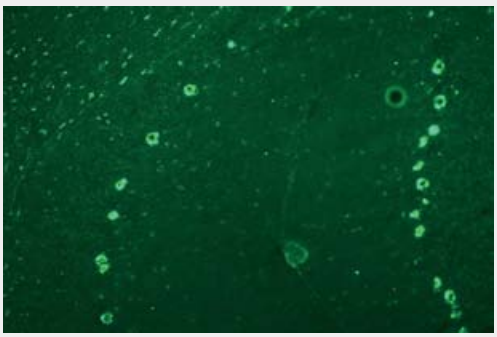

A 72-year-old woman presented with subacute unsteady gait which progressed over two weeks. Examination revealed hyporeflexia and failed tandem walking which deteriorated two weeks later to severe cerebellar ataxia. MRI brain, CSF, gynaecological examination , tumour markers, mammogram and CT thorax, abdomen and pelvis were unremarkable. Immunofluoresence using monkey cerebellum detected Purkinje cell antibody type 1 (PCA-1/anti-Yo) in serum. F18 PET scan revealed a hypermetabolic site over the left breast. Biopsy confirmed a well-differentiated adenocarcinoma. Despite mastectomy, chemotherapy, tamoxifen and pulse steroid followed by prednisolone and azathioprine , she progressed over 10 weeks to severe pancerebellar ataxia and dysphagia requiring tube feeding.

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Neuroimmunology

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Editor

Dr Koon-ho CHAN

Increasing numbers of immune-mediated neurological disorders affecting patients of all ages are recognised in recent years, which is clinically important as they are potentially amenable to immunotherapy. Autoimmune encephalitis has now been better characterised with increasing numbers of autoantibodies discovered, the detection of which greatly facilitates the diagnosis and distinction of common differential diagnoses such as viral encephalitis. The clinical features and presentations of these patients are diverse and clinicians of various specialties including family physicians, neurologists, psychiatrists as well as specialists of infectious diseases and intensive care need to be alerted to their possibilities. In addition, prompt diagnosis of autoimmune encephalitis also provides opportunities of early detection and treatment of underlying neoplasms in paraneoplastic cases.

The classical organ-specific autoimmune neurological disorder, autoimmune myasthenia gravis (MG), is an important disease to diagnose. It is potentially life-threatening and long-term prognosis should be optimistic in most patients with appropriate treatments. The understanding of the pathogenic AChR autoantibodies and subsequent detection of autoantibodies against muscle-specific kinase (MuSK), low density lipoprotein receptor related protein 4 (Lrp4) and agrin in serum of MG patients seronegative for AChR autoantibodies are good examples of the importance of autoantibodies research in diagnosis, understanding of pathophysiological mechanisms and treatment of autoantibody-mediated autoimmune disorders.

Guillain-Barre syndrome (GBS) requires a high index of suspicion for early diagnosis which is clinically important as this acute form of polyradiculoneuropathy can cause life-threatening or severely disabling neurological deficits rapidly. The recognition of various anti-ganglioside antibodies promotes the understanding of different forms of GBS, especially the axonal form and Miller Fisher syndrome, and facilitates diagnosis. Meticulous supportive care frequently requiring intensive care and prompt specific immunotherapy optimises recovery and prognosis.

For central nervous system inflammatory demyelinating disorders (CNS IDD) typified by classical multiple sclerosis (CMS) and neuromyelitis optica (NMO), tremendous advancements in the understanding of their pathogenesis and pathophysiological mechanisms are available in the past decade. The discovery of aquaporin-4 (AQP4) autoantibodies, a specific serum biomarker for NMO and related spectrum disorders (NMOSD), confirms that NMO/NMOSD are distinct from CMS, and strongly suggests that NMO is an autoimmune disease targeting the astrocytic APQ4 water channel. Despite uncertainties about the exact pathogenesis and pathophysiological mechanisms of CMS, there is a dramatic increase in the number of disease modifying therapies (DMT) available for CMS patients in the last 10-12 years. The choice and safe use of these DMT need much knowledge and careful monitoring for possible side effects.

In this issue of the Hong Kong Medical Diary with the Medical Bulletin focusing on neuroimmunology, my colleagues and I briefly review on autoimmune encephalitis, MG, GBS, CMS and NMO/NMOSD. However, many other neuroimmunological disorders are not mentioned in this issue including vasculitis of the CNS, IgG4 related pachymeningitis, other CNS IDD such as acute disseminated encephalomyelitis (ADEM), chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy with or without conduction block, paraproteinaemic neuropathies, vasculitic neuropathies, Lambert-Eaton myasthenic syndrome and inflammatory myopathies.

Clinicians of all specialties should be aware of the diverse group of immune-mediated neurological disorders. Their prompt diagnosis with a high index of suspicion and facilitation by detection of autoantibodies can lead to early initiation of appropriate immunotherapy and supportive/intensive care resulting in optimal recovery and prognosis.

Autoimmune encephalitis

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 March 2017.

Introduction

Autoimmune encephalitis is characterised by brain inflammation associated with autoantibodies which results in a rapidly progressive encephalopathy. Early reports were based on discovery of neural antibodies in patients with paraneoplastic syndromes. In the recent 10 years, new autoantibodies have been discovered, broadening the spectrum of autoimmune encephalitis to include non-paraneoplastic syndromes. Patients with autoimmune encephalitis often present with fever and rapidly progressive encephalopathy resembling viral encephalitis. Some patients may first present to psychiatrists due to neuropsychiatric symptoms. Recognition of the entity of autoimmune encephalitis, a treatable condition, is important and has reshaped our concepts on the treatment and supportive therapy of encephalitis of previously unknown aetiology which were considered futile in the past.[1,2]

Antibodies and target antigens

Antibodies targeting neuronal intracellular proteins

In the 1980's and 1990's, antibodies directed to neuronal intracellular proteins were discovered in patients with specific paraneoplastic syndromes.[3] Examples include anti-Hu associated with limbic encephalitis, encephalomyelitis and sensory neuronopathy in patients with small cell lung carcinoma (SCLC) and anti-Ri associated with opsoclonus/myoclonus in patients with breast cancer (Table 1). These antibodies are highly predictive of cancer and their production is likely induced by neoantigens that emerge as a neoplasm evolves. These antibodies serve as markers of autoimmunity and anti-tumour immunity, and pathologies are due to aggressive cytotoxic T-cell response which is generally poorly responsive to immunotherapy.

Antibodies targeting neuronal cell surface and synaptic proteins

More recently, autoantibodies directed against the neuronal cell surface or synapse have been described. Because these antibodies interact with cell surface proteins, they can alter the structure or function of these proteins and are thus directly pathogenic. Examples include anti-NMDA receptor and anti-LGI1 (Table 2). The resulting syndromes can be severe, but often respond to immunotherapy with marked recovery.

Table 1. Examples of antibodies targeting neuronal intracellular proteins

Autoantibody	Neurologic syndrome	Associated tumour
ANNA-1 (anti-Hu)	Limbic encephalitis, cerebellar degeneration, myelopathy, radiculopathy, neuropathies	SCLC, rarely thymoma
ANNA-2 (anti-Ri)	Brainstem syndrome (opsoclonus/myoclonus), cerebellar syndrome, myelopathy, neuropathy, seizures	Lung, breast, ovarian
Anti-Ma	Cerebellar/brainstem syndromes, limbic encephalitis, polyneuropathy	Breast, Lung, GI tract, non-Hodgkin's lymphoma, germ cell, renal
Anti-Ta	Limbic encephalitis, cerebellar/ brainstem syndrome, polyneuropathy	Testicular or extragonadal germ cell, breast, lung, non-Hodgkin's lymphoma, ovary
Anti-Yo	Cerebellar dysfunction, peripheral neuropathy	Ovarian, breast

Abbreviations: ANNA=anti-neuronal nuclear antibody

Table 2. Examples of antibodies targeting neuronal cell surface proteins.

Autoantibody	Neurologic syndrome	Associated tumour
Anti-NMDA receptor	Anti-NMDA receptor encephalitis	Ovarian teratoma (10-45%), infrequently carcinoma
Anti-AMPA receptor	Limbic encephalitis, psychiatric symptoms	Lung, breast, thymoma (70%)
Anti-GABAb receptor	Limbic encephalitis, prominent seizures	Lung, neuroendocrine (50%)
Anti-LGI1	Limbic encephalitis, hyponatraemia, faciobrachial tonic seizures	Thymoma (<10%)
Anti-Caspr2	Morvan syndrome, neuromyotonia	Thymoma (0-40%)

Abbreviations: NMDA=N-methyl-D-aspartate, AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid, GABAb=γ-amino-butyric acid B, LGI1=leucine-rich, glioma-inactivated 1, Caspr2=contactin-associated protein-like 2.

Specific syndromes of autoimmune encephalitis

The definitive diagnosis of autoimmune encephalitis rests on identification of the autoantibody and

response to immunotherapy. Symptoms caused by different autoantibodies often overlap, and multifocal involvement of the neuroaxis is common. Nevertheless, specific syndromes exist which may allow for early diagnosis and initiation of treatment based on the clinical features before antibody results are available.

Anti-NMDA receptor encephalitis

Since its first description in 2007 in 12 women with ovarian teratomas, anti-NMDA receptor encephalitis is now considered to be the most common autoimmune encephalitis.[4] It is characterised by CSF IgG antibodies against the GluN1 subunit of the NMDA receptor. It occurs more commonly in young adults, predominantly women, but can occur in patients of all ages. It may be paraneoplastic, in which case ovarian teratoma is the most frequently associated tumour which is found in about a third of adult patients, but can occur without underlying tumour particularly in children and men.

Clinical features consist of a prodrome with headache and fever, followed by rapidly evolving cognitive, behavioural and psychiatric manifestations such as memory deficits, labile mood, agitation, anxiety, and psychosis. Abnormal movements then ensue, with orofacial dyskinesias, chorea, athetosis, rigidity and stereotyped movements. As symptoms progress, patients develop reduced consciousness, seizures, and autonomic dysregulation.

Brain MRI is normal in 66% of patients, with the remainder showing nonspecific cortical or subcortical FLAIR/T2W abnormalities. About 50% of patients respond to first line immunotherapies (intravenous immunoglobulin, steroids, or plasma exchange), with the remainder requiring second line therapies such as rituximab and cyclophosphamide.[5] Relapses occur in about 20% of patients and respond to immunotherapy. Tumour removal should be performed in paraneoplastic cases, and recurrent tumours should be searched for in patients who relapse.

Limbic encephalitis

Limbic encephalitis is characterised by subacute onset and rapid progression of memory deficits, seizures or psychiatric symptoms. CSF often shows mild to moderate lymphocytic pleocytosis, with oligoclonal bands present in about 50% of patients. MRI often shows increased FLAIR/T2W signals in the medial aspect of the temporal lobes.

Detection of autoantibodies is important as it affects treatment and prognosis. Those with onconeuronal antibodies such as anti-Hu and anti-Ma2 almost always have an underlying cancer and are much less responsive to immunotherapy. Conversely, patients with antibodies to cell surface antigens respond better. The three neuronal cell surface antibodies most often associated with limbic encephalitis are anti-LGI1, anti-GABAbR, and anti-AMPAR.

Patients with anti-LGI1 are predominantly middle age or elderly men. Approximately 60% of patients have hyponatraemia and some patients have myoclonic-like jerks in the face, arms or legs known as faciobrachial dystonic or tonic seizures.[6] A significant proportion of patients experience rapid eye movement sleep disturbance. Some patients have a more protracted course over a few months with confusion and cognitive decline, thus resembling a rapidly progressive dementia rather than subacute encephalitis. Anti-LGI1 is rarely associated with tumour and when it does, this is usually a thymoma.

Patients with anti-GABAbR have features of limbic encephalitis with early and frequent seizures. About 50% of patients have small cell lung carcinoma (SCLC) or neuroendocrine tumours. Unlike SCLC patients with anti-Hu, these patients have a better response to immunotherapy.

Patients with anti-AMPAR have features of limbic encephalitis, but may present with purely psychiatric features with confusion, agitation and aggressive behaviour. About 65% of patients have an underlying tumour (mainly SCLC, thymoma). The syndrome is responsive to immunotherapy, but has a tendency to relapse despite tumour removal.

Morvan's syndrome

This syndrome is characterised by symptoms of encephalitis such as amnesia, confusion, hallucinations, sleep and autonomic dysregulation, together with peripheral nerve hyperexcitability or neuromyotonia. Patients have anti-Caspr2 antibodies, which were previously classified as antibodies against the voltage-gated potassium channel complex (VGKC). Some patients have underlying thymomas. Immunotherapy is usually effective.

Progressive encephalomyelitis with rigidity and myoclonus (PERM)

This is a syndrome affecting the brainstem and spinal cord, resulting in ocular movement deficits, cranial nerve paresis, encephalopathy and autonomic dysregulation; hyperekplexia is a frequent symptom. Associated antibodies include antibodies to the neuronal cell surface proteins glycine receptor (GlyR) and dipeptidyl-peptidase-like protein-6 (DPPX), and the onconeuronal antibody ANNA2 (anti-Ri).

Bickerstaff's brainstem encephalitis

This disorder is characterised by subacute onset of progressive impairment of consciousness associated with ataxia, ophthalmoplegia, bilateral facial palsy, bulbar palsy and positive Babinski's sign. Generalised limb weakness may occur, which overlaps with features of Guillain-Barre syndrome. IgG anti-GQ1b antibodies are highly specific for this disorder (and the related Miller Fisher syndrome).

Overlapping syndromes

Overlapping syndromes consist of anti-NMDAR encephalitis and a demyelinating disorder. Patients with a demyelinating disorder and atypical features such as dyskinesias or prominent psychiatric features, or patients with anti-NMDAR encephalitis with atypical features such as optic neuritis or demyelination on MRI should be screened for coexisting disorders, and need testing for anti-aquaporin 4 (anti-AQP4) and anti-myelin oligodendrocyte glycoprotein (anti-MOG).

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Steroid-responsive encephalitis/encephalopathy associated with autoimmune thyroiditis

Previously known as Hashimoto encephalitis, this disorder is considered in patients who develop encephalopathy with seizures, myoclonus, hallucinations or stroke-like episodes, subclinical or mildly overt thyroid disease (usually hypothyroidism), presence of serum thyroid antibodies (thyroid peroxidase, thyroglobulin) and exclusion of well characterised neuronal antibodies in serum and CSF. The underlying pathogenic mechanism is unclear, and serum thyroid antibodies are unlikely to be pathogenic as these antibodies are also found in some healthy individuals. This is a diagnosis by exclusion, and a trial of steroid therapy can be given.

Diagnosis

General clinical features that suggest possible autoimmune encephalitis include:[7]

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits, altered mental status, or psychiatric symptoms
2. At least one of:
   - New neurological signs suggestive of CNS lesions
   - Seizures not explained by a previously known seizure disorder
   - CSF pleocytosis (white cell count of more than five cells per mm^3)
   - MRI features suggestive of encephalitis
3. Reasonable exclusion of alternative causes, e.g. CNS infections, septic/metabolic encephalopathies, drug toxicity, epileptic disorders.

It is worth noting that a normal CSF study does not rule out autoimmune encephalitis. This is especially true for patients with anti-LGI1 where 59% do not have CSF pleocytosis.[8] Similarly, patients with autoimmune encephalitis may have normal MRI brain.

Antibody testing

Identification of autoantibody is important as it establishes the diagnosis of autoimmune encephalitis, and has an impact on further investigation for cancer detection and prognosis. Some autoantibodies are better detected in CSF (e.g. anti-AMPA receptor, anti-GABAb receptor, anti-NMDA receptor) while others can be detected in the serum (e.g. anti-LGI1, anti-Caspr2). Therefore, both CSF and serum should be sent for antibody testing. Serum antibody titres are not reliable biomarkers of disease activity and should not be used solely to guide treatment decisions.

Suspected autoimmune encephalitis with no autoantibody identified

In patients with clinical features suggestive of autoimmune encephalitis but no detectable autoantibody in serum and CSF, and after exclusion of other causes, a trial of immunosuppression with steroids, IVIG or plasma exchange should be considered, and clinical response monitored.

Evaluation of cancer where appropriate

Neoplasms associated with autoimmunity are usually in their early and limited stages, and may be difficult to detect on conventional imaging. Evaluation with whole body PET/CT is helpful in detecting these cancers. In patients with antibodies highly associated with underlying tumours, if the initial tumour screening is negative, repeat screening at 3-6 months followed by screening at 6 monthly intervals for 4 years is recommended.[9]

Treatment

Treatment strategy of autoimmune encephalitis is based on experience in the treatment of other autoimmune disorders; data from randomised controlled trials are lacking. The general principle is to maximise reversibility and to maintain this reversibility using long-term immunosuppression. First line therapies include corticosteroids, IVIG and/or plasma exchange. Clinical response should be monitored, and benefits from the first line treatment justify consideration of maintenance immunosuppressants such as azathioprine and mycophenolate mofetil. Second line therapies such as rituximab and cyclophosphamide can be considered in patients with suboptimal response to first line therapies. For paraneoplastic disorders where a cancer is identified, the tumour should be removed entirely if possible. Patients should continue to be monitored after recovery for signs of relapses.

Conclusion

The discovery of neural antibodies and the resulting encephalitis syndromes has expanded our understanding of the roles of neuronal cell surface proteins in shaping our memory, learning and behaviour. It has also led to a paradigm change in the diagnosis and treatment of encephalitis that were previously of unknown causes. Undoubtedly, new neural antigens will be identified, expanding the clinical spectrum of autoimmune encephalitis. Elucidation of the underlying pathogenic mechanisms will shed light on how our brain works, and open up new possibilities in therapeutic strategies of neurological disorders.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Autoimmune encephalitis" by Dr Shirley Yin-yu PANG and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 March 2017. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. Early in the disease course, autoimmune encephalitis often resembles viral encephalitis, with fever and a rapidly progressive encephalopathy.
2. Psychiatric manifestations are extremely rare in autoimmune encephalitis.
3. Antibodies directed to intracellular neuronal proteins are highly predictive of underlying malignancy.
4. Antibodies directed to cell surface proteins are directly pathogenic, and the resulting syndromes often respond to immunotherapy.
5. Anti-NMDA receptor encephalitis occurs most commonly in men and children.
6. Some patients with autoimmune limbic encephalitis may not have an underlying tumour.
7. A negative serum anti-NMDA receptor antibody effectively excludes the possibility of anti-NMDA receptor encephalitis.
8. Cerebral spinal fluid analysis can be normal in autoimmune encephalitis.
9. If no known autoantibodies could be identified in serum and CSF samples of patients with clinical features suggestive of autoimmune encephalitis, immunotherapy is never indicated.
10. Patients with anti-neuronal nuclear antibodies should be screened for malignancy, and repeat screening after an initial negative screen is warranted.

ANSWER SHEET FOR MARCH 2017

Please return the completed answer sheet to the Federation Secretariat on or before 31 March 2017 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Autoimmune encephalitis

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Answers to February 2017 Issue

Update on endovascular therapy for acute ischaemic stroke

1. F 2. F 3. T 4. F 5. F 6. F 7. F 8. T 9. T 10. F

Autoimmune Myasthenia Gravis

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Introduction

Autoimmune myasthenia gravis (MG) is an antibody-mediated autoimmune disorder affecting the neuromuscular junction (NMJ) and is characterised by skeletal muscle weakness and fatigability[1, 2]. The NMJ consists of 1) presynaptic motor nerve terminal, 2) synaptic cleft and 3) postsynaptic muscle membrane which contains the acetylcholine receptor (AChR). Neuromuscular transmission occurs when a neuronal action potential enters the motor nerve ending and triggers the release of acetylcholine. The acetylcholine diffuses across the synaptic cleft and binds to the AChR on the postsynaptic membrane causing a depolarisation (endplate potential), which in turn generates a muscle fibre action potential. In MG, disruption of this neuromuscular transmission by autoantibodies targeting different antigens in the NMJ results in variable muscle weakness.

The reported annual incidence of MG is in the range of 2 to 30 per million, and the prevalence is ranging from 80 to 130 per million[3-6]. Overall the incidence and prevalence rates have been increasing over the years, partly due to increased awareness of the disease and improved diagnostic tests and treatment[1, 2, 4]. A local study in 1992 showed an estimated incidence of 4 per million and a prevalence of about 60 per million[7], and these rates would likely be higher by now. MG has a bimodal incidence pattern, with a peak in early adulthood 30-40 years of age and an increasing incidence with age after 50 years[1-3, 8].

Autoimmunity in myasthenia gravis

About 70-85% of MG patients are characterised by seropositivity of acetylcholine receptor autoantibodies (AChR Ab) [1, 2, 9]. AChR Ab is directly pathogenic in MG via complement activation causing 1) damage to the postsynaptic muscle membrane, 2) cross-linking and internalisation of the surface AChR (antigenic modulation) and 3) blockage of the acetylcholine by attaching to the binding site of the AChR[1, 2, 9, 10].

In 30-40% of MG patients without detectable AChR Ab, there is seropositivity of muscle-specific kinase autoantibodies (MuSK Ab) comprising about 4% of all MG cases[2, 9]. MuSK Ab is also directly pathogenic but act differently compared to AChR Ab. It reduces the postsynaptic density of AChR and impairs the AChR alignment at the NMJ. Low density lipoprotein receptor related protein 4 autoantibodies (Lrp4 Ab) are detected in a portion of MG patients who are seronegative for both AChR Ab and MuSK Ab[11]. Overall LRP4 Ab is detected in 1-5% of all MG patients[11, 12] but a commercial test is not yet available. LRP4 Ab is directly pathogenic by inhibiting the LRP4-agrin interaction and thereby disrupting the AChR clustering on the postsynaptic membrane. While AChR-MG, MuSK-MG and LRP4-MG are considered distinct disorders, there have been case reports about coexistence of these antibodies in a few patients.

Agrin antibodies have been recently identified as a specific marker for MG but their pathogenic role is unknown[13, 14]. There are also other antibodies detected in MG patients with less certain pathogenic or diagnostic roles including antibodies against cortactin, titin, ryanodine receptor, collagen Q and voltage-gated potassium channel $K_V1.4$ [1, 9].

In addition, MG patients, in particular early-onset and ocular subgroups, have increased risks of other autoimmune disorders[1]. The frequency of a second autoimmune disease is 15% in MG patients[15]. Autoimmune thyroiditis is the most common, followed by systemic lupus erythematosus and rheumatoid arthritis[15].

Thymic pathology

Many MG patients have an abnormality of the thymus gland. Different thymic pathologies may lead to the development of different MG subtypes e.g. thymic hyperplasia is reported in up to 80% patients with early-onset MG but occurs much less commonly in late-onset, ocular, and seronegative disease[1, 16]. Inflammatory, neoplastic and age-related changes of the thymus are probably responsible for early-onset MG, thymomatous MG and late-onset MG respectively[16]. On the other hand, the thymus is probably unaffected in MuSK-MG patients[16].

Clinical presentation and subtypes

1. Generalised vs ocular MG

While 85% of all MG patients initially present with ocular symptoms (ptosis and diplopia), most of them later develop generalised MG (GMG) that affects a combination of muscle groups on top of ocular weakness, including the limbs, neck and oropharyngeal muscles[8]. If the patients have only ocular symptoms for 2 years after onset, they are unlikely to develop GMG later[17]. 17% of MG patients have pure ocular involvement throughout their disease course and are

classified as ocular MG (OMG) [8]. The proportion of OMG is reported to be higher in Chinese populations[18,19]. In GMG, patterns of muscle involvement are variable among patients and the symptoms can differ significantly. Common symptoms include dysarthria, dysphagia, dysphonia, masticatory weakness, drooling, limb weakness, dyspnoea, weakness in neck flexion and extension. Characteristically the weakness in MG is fatigable and worsens with exertion. The limb weakness is usually symmetrical and more severe in the proximal muscles, whereas the extraocular muscle weakness including ptosis is commonly asymmetrical.

2. Early-onset vs late-onset AChR-MG (non-thymomatous)

Although there is no consensus on the cutoff age, the usual definition of late-onset MG is symptom onset after the age of 50[1, 20-22]. In early-onset MG, women are affected three times more frequently then men and about 50-80% have thymic follicular hyperplasia[2, 4, 20, 23]. The response to thymectomy is usually good. For late-onset MG, the incidence is higher in men and thymic hyperplasia occurs rarely[1, 20]. While it has been postulated that occult thymomas not seen on imaging or microscopically might be present, the response to thymectomy is often poor[1, 2].

3. MuSK-MG and LRP4-MG

MuSK-MG is usually reported in adults and rarely in children[24]. It has a marked female predominance with more frequent occurrence of MG crises[25]. The weakness mainly affects the bulbar, facial, tongue, neck and respiratory muscles, and less commonly affects the limbs[25]. Fluctuation in weakness is less common than AChR-MG and muscle atrophy may occur. Thymic pathology is exceedingly rare[1]. Long-term outcomes are similar to those of patients with AChR-MG[25].

Unlike MuSK-MG, LRP4-MG patients tend to have ocular or mild generalised symptoms and rarely develop MG crisis[11, 12]. Thymomas are also not reported and thymic hyperplasia is rare[1, 9].

4. Thymomatous MG

Thymomas are found in 10-15% of MG patients[1]. The vast majority of patients with thymomatous MG are seropositive for AChR Ab and have GMG. About 30% of thymoma patients develop MG and another 15% have AChR Ab without symptoms of MG[9]. Outcomes of MG in patients with thymoma have not been shown to be worse[26, 27] but post-thymectomy survival could be affected by the tumour factors e.g. stage of the tumour and completeness of resection[28].

5. Seronegative MG

With the discovery of the pathogenic autoantibodies, seronegative MG is now defined as MG without detectable AChR Ab, MuSK Ab or LRP4 Ab. It includes MG patients with antibodies to other undefined antigens, low-affinity antibodies to known antigenic targets, or low concentrations of antibodies not detectable by conventional assays. Treatment responses of these patients are considered similar to most other MG patients.

Diagnosis and management

A diagnosis of MG is suspected based on clinical presentation with typical ocular symptoms or other muscle weakness with fatigability and fluctuations. It is then confirmed by at least one supportive test and exclusion of alternative diagnoses causing the symptoms e.g. myopathies, thyroid eye diseases, etc. The following three supportive tests are commonly used: 1) serum AChR Ab level, 2) repetitive nerve stimulation looking for decremental response of motor action potential, and 3) bedside double-blinded edrophonium test with a measurable objective endpoint e.g. ptosis. Depending on availability and expertise, one may also consider serum MuSK Ab test and single-fibre electromyography if previous tests are inconclusive. A computed tomography scan or magnetic resonance imaging of the chest should be performed in all patients with MG to look for thymomas.

While MG is one of the most well-defined organ-specific autoimmune diseases, there are limited randomised controlled trials (RCTs) to guide the management. Nevertheless, many of the treatments are generally accepted as the standard of care. The advances in treatment especially immunomodulating therapies have led to improvements in prognosis for MG patients in recent years[8, 27]. Here, a summary of treatment approaches will be presented based on available evidence, recent national guidelines[29-31] and local experience.

Pyridostigmine, an acetylcholinesterase inhibitor, should be the initial treatment in all MG patients. It improves weakness in MG by increasing the amount of acetylcholine available at the NMJ. Dosage is adjusted aiming for a balance between maximal symptomatic improvement and side effects. Commonly used regimes range from 60-360mg daily in 2 to 5 divided doses. Side effects include abdominal cramps and diarrhoea (30%), hypersalivation (6%), increased sweating (4%) and bradycardia or atrioventricular block (1%) [32]. Antimuscarinic agents e.g. propantheline or antimotility agents e.g. loperamide are commonly used to counteract the side effects.

Immunosuppressive therapies

Regardless of the subtypes, in MG patients with significant symptoms despite the use of acetylcholinesterase inhibitor, immunosuppressive (IS) therapies should be considered. Corticosteroids, commonly prednisolone or prednisone, remain the most frequently used immunosuppressive agent in MG. A retrospective cohort has reported up to 80% of patients improve markedly with corticosteroids[33] and the improvement can usually be observed within 2-6 weeks. The usual starting dose is 5-10mg prednisolone daily and it can be titrated up to 0.5-1mg/kg daily.

An alternative IS agent should be used alone if corticosteroids are contraindicated, or in combination with corticosteroids if high-dose (>10-15mg daily) or prolonged use of corticosteroids is required, or when the response to corticosteroids is suboptimal. Although evidence from RCTs is also limited, azathioprine is generally considered another first-line IS agent in

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conjunction with corticosteroids. As an initial treatment, azathioprine is less effective in improving muscle power than prednisolone[34], but its adjunctive use with prednisolone is associated with less treatment failure, lower steroid dose, longer remissions and less side effects[35]. The usual dosage ranges from 1-3mg/kg daily. Clinical improvement is delayed and it may take 6-15 months to take effect. Adverse effects include reversible lymphopenia, derangement in liver function tests and opportunistic infections. Rare cases of haematological malignancies have also been reported. Regular monitoring with blood tests is recommended. Other IS agents that can be used in MG when azathioprine fails include mycophenolate mofetil, cyclosporine, tacrolimus and methotrexate. Again the evidence for their use in MG is limited, but they, especially MMF and cyclosporine, are often used as second-line IS therapies.

There is also growing evidence that rituximab, a monoclonal IgG1 which depletes B-cells by targeting the CD20 antigen, is effective in MG. Although no RCT has been performed, a recent meta-analysis that included 168 MG patients (>80% of which are refractory to standard IS therapies) has shown an overall response rate to rituximab of more than 80%, regardless of AChR Ab or MuSK Ab status[36]. Adverse effects were reported in 7 patients (4.2%), including 4 patients with infection, 2 with prolonged B-cell depletion and one developed heart failure after the third infusion of rituximab[36]. In general, rituximab is reserved for refractory cases where patients do not respond to (usually steroids and two other IS agents with optimal dosage and duration) or cannot tolerate conventional IS therapies. Its role as an induction therapy in patients with aggressive disease with frequent MG crises is unclear.

Thymectomy

Thymectomy has long been advocated as an integral part of treatment in non-thymomatous MG but only until recently was its efficacy confirmed in RCT[37]. It was shown that thymectomy in non-thymomatous GMG patients aged 18-60 years with disease duration less than 3 years, compared to prednisolone alone, was associated with 1) reduction of disease severity over a 3 year period, 2) lower daily steroid requirement, 3) fewer patients requiring azathioprine, and 4) fewer hospitalisations for exacerbations[37]. Therefore, it is generally recommended for early-onset AChR-MG patients. The benefits of thymectomy in late-onset or elderly MG patients are not well-established. Most guidelines do not recommend thymectomy in patients with MuSK-MG, LRP4-MG or OMG.

For all MG patients with thymomas, surgical excision should be performed along with removal of all thymus tissue. Although it might not improve the MG control in this group of patients, it is important as an oncological treatment to prevent local growth or even distant metastases. Adjuvant therapy such as radiotherapy may be required in cases of high grade thymoma or incomplete resection.

In any case, although thymectomy should be performed early, it is not urgent and should only be performed when patients are stable with satisfactory symptom control.

MG crisis

MG crisis is generally defined as severe weakness in GMG patients that requires airway protection or assisted ventilation[38-41]. It is potentially life threatening and typically occurs within the first 2 years from diagnosis[38]. Apart from ventilatory support (invasive or non-invasive) and treatment of the precipitating cause (e.g. infections, medications), prompt initiation of immunomodulating therapies is vital for improving the survival and outcomes in MG crises. These include intravenous immunoglobulin (IVIG) and plasmapheresis (PLEX), which are usually considered equally effective and the choice depends on individual factors e.g. availability and patients' tolerance. At the same time, IS therapies should be titrated to the optimal dose quickly to ensure a sustained symptom improvement and control.

Long-term outcome

With modern treatment strategies and advances of efficacious IS therapies, the prognosis for MG patients is good. Activities of the daily living of MG patients are usually not or only mildly affected and life expectancy is not reduced[1]. In our recent retrospective study, 78% of patients had good clinical outcomes as defined by the Myasthenia Gravis Foundation of America postintervention status (MGFA-PIS) of either remission or minimal manifestation, while another 19.5% had an improved PIS[27]. This finding is similar to a large retrospective cohort of 1976 MG patients reported by Grob et al[8]. We also showed that use of azathioprine is an independent predictor of good outcome[27], suggesting the importance of the use of IS therapies in MG.

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Dermatological Quiz

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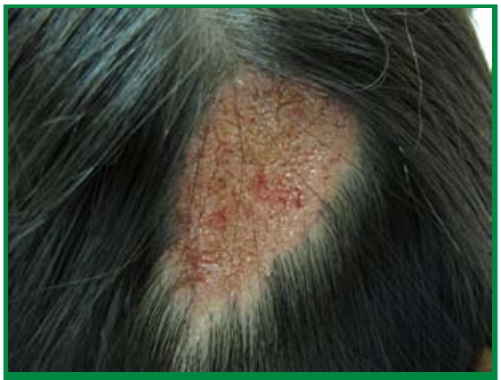

Fig.1: Warty mass protruding from scalp

This 10-year-old girl complained of a yellowish, rough surface, warty mass protruding out at the scalp. According to her parents, the lesion was present since birth and seemed increasing in size slowly. The lesion was almost asymptomatic except with some itch occasionally. It was around 8mm in length, a pale yellow warty plaque without hair on the scalp (Fig. 1). There was no ulcer or erosion on the lesion.

Questions

1. What is the diagnosis of the skin lesion?
2. What is the underlying pathology?
3. How do you manage this girl?

(See P.37 for answers)

Guillain–Barré syndrome: a brief review

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BACKGROUND

Guillain–Barré syndrome (GBS) is the acute neuropathy characterised by flaccid paralysis with high cerebrospinal fluid (CSF) protein but normal CSF cell count first described by Guillain, Barré and Strohl[1]. GBS has been referred as Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP) historically. However, several variants including Acute Motor Axonal Neuropathy (AMAN), Acute Sensorimotor Axonal Neuropathy (AMSAN) and Miller Fisher Syndrome (MFS) have been embraced under the entity of GBS. The disease process is mainly a monophasic immune-mediated polyneuropathy. GBS can cause severe disability and even death. This review is aimed to introduce some of the essential features of this neuroimmunological disease.

PATHOGENESIS

GBS can be considered pathologically as an autoimmune disease in which the immunological target is the peripheral neuronal myelin. Lymphocytes and monocytes infiltrate the peripheral and cranial nerves[2]. Myelin breakdown is observed in both motor and sensory nerves with myelin retraction at the nodes of Ranvier. Severe demyelination can lead to secondary axonal loss. These are the basis of demyelinating features found in electrophysiological studies. Axonal components can also be the principal target of autoimmunity, resulting in axonal variants of GBS. Precipitating events such as gastroenteritis or respiratory infections may trigger GBS despite this part of the clinical history may not be able to be recalled[3]. The mechanism is proposed to have resulted from immunological responses to a preceding infection that provokes immune responses against peripheral nerve components by molecular mimicry. Campylobacter jejuni infection is a well-known precipitant of GBS[4]. Other viral infections such as Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Human immunodeficiency virus (HIV), and Zika virus have also been related to GBS. Flu vaccination has attracted public concern on whether it can lead to the complication of GBS. In 1976, a swine influenza vaccination programme in the United States was associated with a small increased risk of GBS. The increased risk was approximately 1 in 100,000 people who had received the H1N1 vaccine[5]. The link between GBS and influenza vaccination in other years is unclear. Locally, the patient information leaflet on potential GBS complications and screening checklist including a history of GBS before injection is included in the seasonal influenza vaccination programme[6]. It is important to note that the risk of contracting GBS after getting the influenza infection is probably higher than after receiving the vaccine. Besides, prevention of the morbidity and mortality and of influenza infections in the susceptible patient groups may outweigh the small risk of GBS.

CLINICAL FEATURES

The incidence of GBS is about 2 in 100, 000 annually worldwide[7]. Local data suggests that the incidence is about 0.44 per 100, 000[8]. For AIDP, the most preferential variant, classically shows symmetrical ascending limb weakness with hyporeflexia or areflexia. The weakness can range from mild gait difficulty to complete paralysis of all limbs. Facial diplegia and bulbar muscle weakness are possible. Paresthesia can also occur, but can be relatively mild. Respiratory failure requiring ventilatory support is also common. Autonomic failure can manifest as dramatic fluctuations in heart rate and blood pressure, urinary retention, orthostatic hypotension, anhidrosis, etc. The respiratory and autonomic complications can be causes of sudden death and may require intensive care[9].

GBS can progress with clinical deterioration over a period of few weeks, usually reaching the nadir up to one month after onset and then improves slowly in the neurological state. Disease progression beyond eight weeks after onset or polyphasic deterioration should lead to consideration of alternative diagnoses such as Chronic Inflammatory Demyelinating Polyneuropathy (CIDP).

INVESTIGATIONS

The key investigation of GBS is the nerve conduction study (NCS). It typically shows features demyelinating features in the case of AIDP. Various authorities have published electrophysiological criteria to define demyelinating polyneuropathy[10]. In the early course of disease, the NCS may have false negative or equivocal results with features not reaching the electrodiagnostic criteria of demyelinating neuropathy. NCS should be repeated later if GBS is suspected.

CSF examination is another investigation to support the diagnosis of GBS. Typically, the CSF in GBS shows an elevated protein level with normal leukocyte count, a condition known as albuminocytologic dissociation. However, in the early course of disease for up to two weeks, the CSF protein can be normal. Hence, this is not a requisite for the diagnosis of GBS[11].

GBS VARIANTS

Besides AIDP, there are other variants of GBS. Miller Fisher syndrome (MFS) is characterised by a triad of ophthalmoplegia, ataxia, and areflexia, though all three components may not be present concomitantly. Serology is helpful in confirming the diagnosis as antiganglioside antibodies of Anti-GQ1b can be positive in MFS. AMAN and AMSAN are typified by axonal neuropathy affecting the motor component and sensory plus motor components respectively. Clinical features and NCS are needed to differentiate these variants.

TREATMENT OF GBS

Intravenous immunoglobulin (IVIG) and plasma exchange (PE) are the mainstream of therapy in GBS. Both IVIG and PE are of equal effectiveness in treatment of GBS and they are aimed at hastening the neurological recovery[12]. The choice mainly depends on their availability and tolerability of the individual patient. IVIG is generally given at a course of 0.4 gram/kg per day for five days. Usual adverse effects including infusion reaction of rash, hypotension, fever, etc. IgA deficient patients can have anaphylaxis. PE is generally given for four to six sessions over around two weeks' time. Venous access with a temporary central venous catheter may be required in some patients. Albumin is usually used as a replacement fluid in PE. Adverse effects of PE include haemodynamical disturbance, infections and complications related to the establishment of the central catheter. Though both treatments are effective, there has been no evidence to suggest concomitant combination of the two treatments and hence is not recommended.

Close monitoring of physiological vital signs is important. The cardiac rhythm and blood pressure requires meticulous monitoring. Respiratory failure may require temporary non-invasive ventilation or even prolonged mechanical ventilation with tracheostomy. A nasogastric tube for feeding is sometimes indicated. Because GBS patients may remain paralytic in bed for weeks, vigilance against complications such as hospital acquired infections, pressure sores and deep vein thrombosis is essential.

CONCLUSIONS

Though GBS is considered as a monophasic disease with slow recovery, the prognosis is still guarded despite immunomodulating therapies and intensive care. About 25% of patients result in respiratory failure requiring ventilation; death occurs in up to 15%; and persistent disability in about 20%. Because of its rapidly deteriorating and potential life threatening course, prompt diagnosis and initiation of treatment and monitoring may improve the outcome of GBS patients.

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Jointly organised by

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Objectives:

- To promote mediation skills in healthcare sector
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- To understand the concept of mediation, win-win and interest-based resolution
- To communicate better with patients and their families

Date	Topics	Speakers
1 Mar	Mediation & Healthcare	Dr. CHOO Kah-lin 俞佳琳醫生 Consultant (Medicine) Accredited Mediator
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15 Mar	Listening Skills & Use of Body Language	Dr. WAI Ka-chung Abraham 衛家聰醫生 Associate Consultant (Emergency Medicine) Accredited Mediator
22 Mar	Perception Check, Paraphrasing & Summarizing Skills	Dr. TSOI Chun-hing Ludwig 蔡振興醫生 Senior Medical Officer Accredited Mediator
29 Mar	Reframing & Facilitative Skills	Dr. ONG Kim-lian 王金蓮醫生 Consultant (Emergency Medicine) Accredited Mediator
5 Apr	Negotiation Skills & Empowerment	Dr. WAI Ka-chung Abraham 衛家聰醫生 Associate Consultant (Emergency Medicine) Accredited Mediator

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* Defined as a decrease of at least 1 point on the EDSS from a baseline EDSS score that was sustained for at least 6 months;
† 55% (n=215) of patients who entered the extension did not receive LEMTRADA retreatment RRMS=relapsing-remitting multiple sclerosis; MS=multiple sclerosis; IFNβ-1a SC=subcutaneous interferon beta-1a; ARR=annualised relapse rate; DMT=disease modifying therapy; MOA=mechanism of action

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Aubagio® Abbreviated Prescribing Information

Presentation: Teriflunomide film-coated tablet. **Indication:** Treatment of adult patients with relapsing remitting multiple sclerosis. **Dosage:** 14mg once daily. **Contraindications:** Hypersensitivity to the active substance or excipients. Severe hepatic impairment (Child-Pugh class C). Pregnancy and lactation. Patients with severe immunodeficiency states, e.g. AIDS. Patients with significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia. Patients with severe active infection. Patients with severe renal impairment undergoing dialysis. Patients with severe hypoproteinaemia, e.g. nephrotic syndrome. Precautions: Blood pressure, ALG/SGPT and complete blood cell counts should be monitored before and during treatment. Liver enzymes should be assessed before initiation of therapy - every 2 weeks during the first 6 months of treatment, and every 8 weeks thereafter or as indicated by clinical signs and symptoms such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. Patients who consume substantial quantity of alcohol. Patients who develop serious infection during treatment. Patients who had a history of interstitial lung disease. Patients with pre-existing anaemia, leucopenia, and /or thrombocytopenia as well as in patients with impaired bone marrow function or those at risk of bone marrow suppression. Use of live attenuated vaccines. Co-administration of teriflunomide with leflunomide. Co-administration with antineoplastic or immunosuppressive therapies. Patients with galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. **Drug interactions:** Rifampicin and other known potent CYP and transporter inducers such as carbamazepine, phenobarbital, phenytoin and St John's Wort. Cholestyramine or activated charcoal. Medicinal products metabolised by CYP2C8, such as repaglinide, paclitaxel, pioglitazone or rosiglitazone. Oral contraceptives. Medicinal products metabolised by CYP1A2 (such as duloxetin, alosetron, theophylline and tizanidine). Warfarin. Organic anion transporter 3 (OAT3) substrates such as cefaclor, benzylpenicillin, ciprofloxacin, indometacin, ketoprofen, furosemide, cimetidine, methotrexate, zidovudine. BCRP and /or organic anion transporting polypeptide B1 and B3 (OATP1B1/B3) substrates such as methotrexate, topotecan, sulfasalazine, daunorubicin, doxorubicin, statins, nateglinide, repaglinide, rifampicin. Undesirable Effects: Influenza, upper respiratory tract infection, urinary tract infection, bronchitis, sinusitis, pharyngitis, cystitis, gastroenteritis viral, oral herpes, tooth infection, laryngitis, tinea pedis. Neutropenia, anaemia, mild allergic reactions, anxiety, paraesthesia, sciatica, carpal tunnel syndrome, hypertension, diarrhoea, nausea, abdominal pain upper, vomiting, toothache, alopecia, rash, acne, musculoskeletal pain, myalgia, pollakiuria, menorrhagia, pain, elevation of hepatic enzymes, weight decrease, neutrophil count decrease, white blood cell count decrease. ***For uncommon, rare and very rare undesirable effects, please refer to the full prescribing information.*** **Preparations:** 14mg x 28's. ***Full prescribing information is available upon request.*** API-HK-TER-15.05

Lemtrada® Abbreviated Prescribing Information

Presentation: Alemtuzumab concentrate for solution for infusion. **Indication:** Treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features. **Dosage:** 12mg/day administered by intravenous infusion over 4 hours for 2 treatment courses. ***Initial treatment course:*** 12mg/day for 5 consecutive days. ***Second treatment course:*** 12mg/day for 3 consecutive days administered 12 months after the initial treatment course. Patients should be pre-treated with corticosteroids immediately prior to administration on each of the first 3 days of any treatment course. Safety follow-up should be performed until 48 months after the last infusion. **Contraindications:** Hypersensitivity to the active substance or excipients. Human Immunodeficiency Virus (HIV) infection. Precautions: Patients with previous autoimmune conditions other than multiple sclerosis. Serious events of Immune Thrombocytopenic Purpura (ITP) have been reported; complete blood counts with differential should be obtained prior to initiation of treatment and at monthly intervals thereafter until 48 months after the last infusion. Serum creatinine levels, urinalysis with microscopy and thyroid function tests, such as thyroid stimulating hormone levels, should be obtained prior to initiation of treatment and every 3 months thereafter until 48 months following the last infusion. Infusion-associated Reactions (IARs). Infections. Patients with pre-existing and/or an on-going malignancy. Women of childbearing potential should use effective contraceptive measures during treatment and for 4 months following treatment. Immunization with live viral vaccines should be avoided. Patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies for VZV. **Drug interactions:** No formal drug interaction studies have been conducted. In a controlled clinical trial in MS patients recently treated with beta interferon and glatiramer acetate were required to discontinue treatment 28 days before initiating treatment. Undesirable Effects: Respiratory tract infection, urinary tract infection, herpes zoster, gastroenteritis, oral herpes, oral candidiasis, vulvovaginal candidiasis, influenza, ear infection, lymphopenia, leukopenia, lymphadenopathy, cytokine release syndrome, Basedow's disease, hyperthyroidism, autoimmune thyroiditis, hypothyroidism, goitre, anti-thyroid antibody positive, insomnia, anxiety, headache, MS relapse, dizziness, hypoaesthesia, paraesthesia, tremor, dysgeusia, blurred vision, vertigo, tachycardia, bradycardia, palpitations, flushing, hypotension, hypertension, dyspnoea, cough, epistaxis, oropharyngeal pain, nausea, abdominal pain, vomiting, diarrhea, dyspepsia, stomatitis, urticaria, rash, pruritus, generalised rash, erythema, ecchymosis, alopecia, hyperhidrosis, acne, myalgia, muscle weakness, arthralgia, back pain, pain in extremity, muscle spasms, neck pain, proteinuria, haematuria, menorrhagia, irregular menstruation, pyrexia, fatigue, chest discomfort, chills, pain, oedema peripheral, asthenia, influenza-like illness, malaise, infusion site pain, contusion. ***For uncommon, rare and very rare undesirable effects, please refer to the full prescribing information.*** **Preparations:** 12mg/1.2ml x 1 vial. ***Full prescribing information is available upon request.*** API-HK-ALE-16.08

Multiple Sclerosis

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Central nervous system inflammatory demyelinating disorders (CNS IDD)

CNS IDD are idiopathic disorders characterised by monophasic or recurrent attacks of inflammatory demyelination of the central nervous system (CNS). CNS IDD include classical multiple sclerosis (CMS), neuromyelitis optica spectrum disorders (NMOSD), single attack or recurrent acute disseminated encephalomyelitis (ADEM), acute myelitis (AM), optic neuritis (ON) and brainstem encephalitis (BE)[1,2]. It is important to recognise that certain systemic inflammatory and vasculitic diorders such as systemic lupus erythematosis, and infections such as herpes simplex virus and syphilitc infection can lead to attacks of cerebral inflammation, AM and ON. These causes of CNS inflammation must be excluded before the diagnosis of CNS IDD is made.

Classical Multiple Sclerosis

Classical multiple sclerosis (CMS) is the prototypical CNS IDD. Females are affected more than males in a ratio of ~ 3:1, and the mean onset age is ~ 29 years. Paediatric MS patients are well recognised and clinical onsets after the age of 50 years are uncommon. MS is more common among Caucasians compared to Asians and Africans. In the Caucasian populations, CMS is the commonest non-traumatic cause of permanent neurological disability among young subjects[1]. In view of its potentially disabling nature and the availability of treatments for acute attacks and disease-modifying therapies (DMT) for long-term disease control, early diagnosis and appropriate treatment are essential.

Clinical Features

The majority of patients have an initial clinical course of recurrent attacks of acute neuroinflammation affecting the optic nerves, spinal cord, cerebral hemispheres, brainstem and cerebellum which resolves by itself or with recovery hastened by treatment (typically pulse steroid), ascribed as relapsing remitting disease (RRMS). However, a significant proportion of patients with RRMS develop into secondary progressive disease (SPMS) 2 decades or more later, characterised by irreversible deterioration of neurological functions with or without acute attacks of neuroinflammation. Common presenting symtpoms include visual blurring and field loss from optic neuritis, monoparesis or hemiparesis with sensory symptoms from hemispheric involvement, paraparesis with sensory level and sphincter disturbance from myelitis, ataxia from cerebellum involvement and focal limb weakness, sensory symptoms with ataxia and bulbar symptoms (e.g. diplopia, facial sensory loss or pain, facial weakness and dysphagia) from brainstem involvement. Acute aphasia, cognitive impairment and even psychosis with or without cortical signs are uncommon presenting features of relapse[1].

A wide range of chronic symptoms and disabilities are seen in CMS typically in patients with severe disease in the chronic and/or advanced stage which include fatigue and pain, severe spasticity and paraplegia, urinary and bowel incontinence and retention, cerebellar ataxia, oscillopsia, dysphagia, dysarthria, cognitive impairment and impotence. Secondary depression is common[1].

Aetiologies

The underlying aetiology of CMS is uncertain. Both environmental and genetic factors contribute. A number of micro-organisms including herpes viruses and chlamydia have been proposed to be aetiologically related but no consensus is obtained. Recently, evidence supports that vitamin D deficiency probably increases the risk of developing CMS, and is associated with a higher risk of relapse in CMS patients[3]. Most recently, obesity is suggested to promote brain inflammation and increase risk of CMS[4].

Immunopathogenesis and Pathologies

In CMS, the cerebral hemispheres, optic nerves, brainstem, cerebellum and spinal cord are affected; the majority (~90%) of patients have oligoclonal bands (OCB) in cerebrospinal fluid (CSF) [1]. MS is a chronic immune-mediated disorder of the CNS characterised by inflammatory demyelination, axonal injury and cortical demyelination in the early phase, and chronic demyelination, progressive axonal degeneration and loss, cerebral atrophy and gliosis in the chronic phase[1,2]. Various immune cells are shown to be important in its pathophysiologies including Th1, Th17, cytotoxic T cells and more recently B cells. Impaired homeostasis between effector T and B cells with regulatory T and B cells are recently shown to be important. The classical hypothesis proposes that circulating autoreactive T cells migrate into the CNS by crossing the blood-brain-barrier and then initiate acute inflammation leading to relapse (acute attack). Brain and spinal cord atrophy due to both grey matter and white matter volume loss are common in advanced CMS that correlates with irreversible disabilities including cognitive impairment, motor weakness and immobility[1].

Diagnosis

Currently there is no serological or radiological biomarker that can confirm a diagnosis of CMS. Diagnosis is suggested by clinical features raising suspicion of recurrent inflammation affecting different sites of the CNS at different time points with exclusion of other conditions that can mimic CMS (dissemination in space and dissemination in time). Magnetic resonance imaging (MRI) facilitates the diagnosis of CMS but it is important to remember that fulfillment of neuroradiological diagnostic criteria for CMS is not equivalent to confirmation of CMS. Other neurological disorders such as vasculitic syndrome, neuroborreliosis, neuromyelitis optica spectrum disorders and CNS lymphoma can mimic CMS and fulfil the diagnostic criteria[1,5].

The recent MAGNIMS criteria propose that 2 or more of the 5 areas should be affected for dissemination in space to support a diagnosis of CMS. These 5 areas are one or more optic nerve lesions, 3 or more periventricular lesions, one or more cortical or juxtacortical lesions, one or more infratentorial lesions and one or more spinal cord lesions[5]. Dissemination in time is supported by detection of lesions of different ages in a single MRI scan (simultaneous asymptomatic gadolinium-enhancing and non-enhancing lesions) or detection of one or more new T2W or gadolinium enhancing lesions in a follow-up scan some time interval later.

Treatment

Acute Attacks

Aute attacks of neuroinflammation in CMS should be treated with intravenous pulse methylprednisolone (IVMP) if the symptoms and neurological impairment are judged to be significant, such as gait impairment, need of assistance for walking, ataxia, visual impairment or loss, dysphagia and diplopia. The dosing regime is 500-1000 mg daily for 3-5 days[1]. Patients who do not have significant improvement 2 weeks after pulse steroid should receive plasmapheresis[6]. A study of 153 patients with CNS IDD treated with plasmapheresis reported 90 (59%) developed moderate to marked functional neurological improvement within 6 months after treatment[7]. Shorter disease durations, preserved deep tendon reflexes, RRMS, lower EDSS score at last follow-up and presence of ring-enhancing lesions and/or mass effect on MRI were factors associated with beneficial responses to plasmapheresis. Furthermore, plasmapheresis was also less effective for RRMS patients who subsequently developed SPMS[7].

Long-term disease modifying therapies (DMT)

In general, DMT should be recommended to relapsing MS patients (RRMS or SPMS patients with on-going relapses) with active disease aiming to 1) prevent/reduce clinical relapse, 2) suppress/reduce subclinical disease activity to minimise CNS inflammation and subsequent injury, 3) prevent or reduce accumulation of disability from incompletely-recovered relapses and 4) prevent or slow development of SPMS resulting in irreversible disabilities. In most clinical settings, disease activity is assessed by clinical relapse and conventional MRI monitoring of new/enlarging T2W lesions and contrast-enhancing T1W lesions (subclinical disease activity).

First-line DMT

Glatiramer acetate (subcutaneous injection), beta-interferon (subcutaneous and intramuscular injection), oral dimethyl fumarate (DMF) and teriflunomide are approved first-line DMT[8,9]. They are partially effective drugs shown in randomised controlled trials to reduce the relapse rate by ~30-50% in RRMS patients compared to placebo with acceptable side effects profile. Beta-interferon has an anti-inflammatory effect and modulates T cell functions. It reduces the relapse rate by ~ 30-35% and may slow disability accumulation. Flu-like symptoms are common side effects and the liver function test shall be monitored as some patients may develop severe elevation of parenchymal liver enzymes necessitating dose reduction or stoppage of therapy. It should be avoided during pregnancy as increased risks of small birth weight and abortion are reported[8].

Teriflunomide is a reversible inhibitor of mitochondrial enzyme dihydroorotate dehydrogenase, hence inhibits proliferation of stimulated T and B cells. Teriflunomide reduces the relapse rate, slows disability progression and improves MRI parameters in RRMS compared to placebo. Its efficacy is comparable to beta-interferon. Common side effects include hair-thinning and elevated parenchymal enzymes. Risk of teratogenicity is a serious issue. Due to its long half-life, elimination can be accelerated by cholestyramine or activated charcoal given as an 11-day course before conception[9].

DMF is a fumaric acid ester and is available as an enteric-coated microtablet, BG-12. It is thought to act by activation of Nrf-2 pathway. BG-12 reduces the relapse rate, disability progression and MRI disease activity in RRMS patients without superiority to GA. Common side effects include flushing, diarrhoea, nausea and abdominal pain. It may cause lymphopenia and the lymphocyte count should be regularly monitored. Prolonged severe lymphopenia should alert the clinician of the need of therapy cessation as its potential risk for progressive multifocal leukoencephalopathy (PML, a rare but potentially life-threatening and commonly disabling complication due to opportunistic infection by JCV of oligodendrocytes) is uncertain. Teratogenicity is shown in animal studies, hence a washout period of 1 month is recommended before conception[9].

In Hong Kong, beta-interferon is funded by the Hospital Authority (HA) as the first-line DMT for RRMS since 2012 whereas DMF and teriflunomide are just approved by HA as other choices of first-line DMT especially for patients who cannot tolerate injection therapy.

Second-line DMT

Fingolimod, a sphingosine-1 phosphate (S1P) analogue, binds to the S1P receptor and leads to reduced number of S1P receptors on the surface of lymphocytes. This leads to trapping of lymphocytes in lymph nodes and hence peripheral blood lymphopenia. It acts in RRMS possibly by reducing lymphocytes available for migration into CNS. Fingolimod reduces the relapse rate, slows disability progression and reduces MRI disease activity in RRMS compared to placebo and is superior to weekly beta-interferon[9]. Side effects include varicella zoster virus (VZV) infection, bradycardia and heart block, hypertension, macular oedema and deranged liver function test. Patients seronegative for

VZV immunoglobulin G should receive VZV vaccine before fingolimod therapy, and all patients need hourly blood pressure and pulse rate monitoring for 6 hours upon initiation of therapy. A few patients developed PML with fingolimod therapy and is judged to be likely related to fingolimod. Lymphocyte count and liver function test should be regularly monitored and cessation of therapy needs to be considered with prolonged severe lymphopenia[8]. Fingolimod is potentially teratogenic and strict contraception must be practised during therapy. Fingolimod is approved in the US as first-line DMT for RRMS, but is recommended as a second-line drug in Hong Kong following European guidelines.

Natalizumab is a humanised monoclonal antibody against the alpha-4 integrin (VLA4) on leucocytes (mainly lymphocytes), which prevents binding of VLA-4 to vascular cell adhesion molecule (VCAM1) on endothelial cells, hence prevents lymphocyte migration to the CNS. Monthly intravenous infusions of natalizumab effectively reduce the relapse rate of RRMS patients by 68% compared to placebo, and also slows disability progression. It is one of the most effective DMT for RRMS and is generally recommended for patients who fail to respond satisfactorily to first-line DMT[8,9]. However, risk of PML limits its use in RRMS. The risk of PML with natalizumab therapy depends on the duration of therapy, JCV antibody status and previous use of immunosuppressants. The risk is about 1.2% for JCV antibody +ve RRMS patients with previous use of immunosuppressants and natalizumab therapy for more than 24 months[10]. Prolonged use is possible especially for JCV antibody negative patients as the risk of PML is extremely low.

Alemtuzumab is a humanizsed monoclonal antibody against CD52 on the surface of lymphocytes, monocytes, macrophages, eosinophils and NK cells. Infusion of alemtuzumab leads to rapid and prolonged lymphocyte depletion, followed by lymphocyte repopulation. Two yearly courses of alemtuzumab (12 mg daily for 5 days, then 12 mg daily for 3 days a year later) lead to a significant reduction of the relapse rate, disability progression and disease activity on MRI, as well as sustained reduction in disability[11]. It is approved for relapsing MS patients as second- or third-line DMT. Most recent evidence suggests that ~ 60% of RRMS patients remain free of disease activity 5 years after the two yearly courses of therapy. PML has not been reported for use of alemtuzumab in CMS patients, but important secondary autoimmune disorders are known complications; most commonly autoimmune thyroid disorders (Graves' disease, ~25-30%), immune thrombocytopenia (3%), Goodpasture syndrome (0.5%) and autoimmune haemolytic anaemia and autoimmune neutropenia[11]. Hence RRMS patients treated with alemtuzumab needs monthly monitoring of complete blood count and liver/renal function tests for 4 years after the last dose.

Other approved or developing DMT

Rituximab (anti-CD20 monoclonal antibody) is shown to reduce the relapse rate in a proportion of RRMS patients). Daclizumab (anti-CD25 monoclonal antibody) is approved for relapsing MS in mid 2016. Ocrelizumab (another anti-CD20 monoclonal antibody) is shown in randomized controlled trials to be beneficial in relapsing MS[12] and primary progressive multiple sclerosis (PPMS) patients (the first agent shown to be effective in PPMS)[13] but needs confirmation. Most recently, metformin and pioglitazone were shown to reduce inflammatory activity in CMS patients with the metabolic syndrome[14].

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Neuromyelitis Optica and Neuromyelitis Optica Spectrum Disorders

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Neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorders (NMOSD)

Neuromyelitis optica (NMO), also known as Devic's disease, is a CNS IDD characterizsed clinically by optic neuritis (ON) and acute myelitis (AM) typically longitudinally extensive transverse myelitis (LETM)[1,2]. The predominant form is relapsing NMO with recurrent attacks of ON and AM that can occur months or years apart[1-3]. NMO has been considered as a subtype of multiple sclerosis (MS) until in 2004 when a specific serological biomarker for NMO, NMO-IgG, was discovered. NMO-IgG targets the most abundant water channel of the CNS, aquaporin-4 (AQP4)[7,8]. NMO-IgG or AQP4 autoantibodies (AQP4 Ab) are initially detected by indirect immunofluorescence (IIF) with composite mouse tissues containing cerebellum, stomach and kidney in the serum of 73% of NMO patients[7]. Using cell-based immunofluorescence assay, AQP4 Ab are detected in ~70-78% of NMO but not in classical multiple sclerosis (CMS) patients[3]. Detection of AQP4 Ab facilitates early diagnosis of NMO and is especially useful in patients with the first attack of CNS inflammatory demyelination.

Detection of AQP4 Ab also facilitates diagnosis of patients with limited/restricted forms of NMO including idiopathic single or recurrent 1) LETM without ON, 2) simultaneous bilateral ON without AM, 3) brainstem encephalitis (BE), 4) AM with BE without ON and 5) ON with BE without AM[2]. The detection of AQP4 Ab in the sera of some of these patients confirms that a proportion of these patients have limited/restricted forms of NMO within the NMO spectrum disorders (NMOSD).

The distinction between NMO/NMOSD and CMS can be difficult especially in the early stages. An early diagnosis of NMO/NMOSD is important as frequent relapses and disabilities commonly occur early[2]. Commonly used disease modifying drugs for RRMS such as β-interferon, fingolimod and natalizumab can be harmful in NMO/NMOSD[3,4,9]. The detection of AQP4 Ab greatly facilitatesd early distinction of NMO/NMOSD from CMS; hence, early initiation of appropriate immunosuppression for NMO/NMOSD patients.

Epidemiology of neuromyelitis optica

NMO affects patients of almost all ages with a reported median onset age of 4.4 years for paediatric patients and a median onset age of 35-45 years for adult patients[2-4]. The predominant form, relapsing NMO (80-90%), affects females 3-9 times more frequently than males[2-4]. NMO is more common among non-Caucasians including Africans, Brazilians and Asians in whom NMO accounts for 15-57 % of CNS IDD. The highest proportion of NMO was reported in East Asians among whom NMO contributes up to 48% of CNS IDD[2,3]. CMS is more common than NMO among Caucasians in whom NMO accounts for as low as 1.5% of CNS IDD with a CMS:NMO ratio of 43:1 (Bizzoco et al., 2009)[2,3] whereas our hospital-based study suggests that a CMS:NMOSD ratio of 1.9:1 in Hong Kong Chinese[4].

Clinical and neuroradiological characteristics of NMO/NMOSD

Neurological manifestations of NMOSD

Acute myelitis typically presents with severe bilateral lower limb numbness, paresthesia and weakness from thoracic myelitis and similar symptoms affecting four limbs from cervical myelitis with a sensory level. Sphincter disturbance commonly presents as urinary retention, lower abdominal distension and pain, and overflow incontinence that may require catheterisation. Upper cervical myelitis is potentially serious as complicating diaphragmatic weakness and respiratory insufficiency may be life-threateining and require ventilator support. Paroxysmal painful spasm, radicular pain and electric sensation of the trunk and limbs upon neck flexion (Lhermitte's sign) are additional features of AM. The classical AM in NMO is severe complete LETM[2].

Optic neuritis (ON) in NMO/NMOSD typically presents with acute or subacute visual blurring, visual impairment/loss, pain on eye movement, central scotoma, and in severe attack or in chronic stage after repeated attacks, blindness and optic atrophy[2]. ON in NMO/NMOSD can be bilateral or unilateral, and simultaneous bilateral ON or recurrent ON in rapid successions is more suggestive of NMO/NMOSD[2,3]. Visual outcome of NMO patients is unfavourable as blindness develops in at least one eye in 60% of patients with relapsing disease and 22% of monophasic disease in the long-term with the mean follow-up duration being 17 years and 8 years for relapsing and monophasic disease respectively[2]. Optical coherence tomography reveals a thinner retinal fibre layer in NMO/NMOSD than in CMS suggestive of more extensive axonal injury[3].

Brain involvement in NMO/NMOSD

Brain involvements in NMO/NMOSD are increasingly recognised. Brainstem lesions typically continuous with high cervical myelitis are recognised on MRI and confirmed on histological examination of post-mortem brain tissues[5,6,10,11]. NMO patients with lesions

in the hypophysis and hypothalamus present with endocrinopathies and hypothalamic dysfunctions including hyperphagia with weight gain, amenorrhoea, galactorrhoea, diabetes insipidus, and hypothyroidism[2]. Pittock et al. reported up to 60% of NMO patients had evidence of cerebral lesions on MRI. Importantly ~10% of NMO patients have cerebral MRI abnormalities typical of CMS (usually asymptomatic), and 8% of patients, mostly children, had diencephalic, brainstem and cerebral lesions atypical for CMS[10]. Mayo Clinic investigators also noticed a pattern of MRI abnormalities involving the hypothalamus and brain tissues surrounding the third and fourth ventricles (periependymal regions) in 6 out of 89 NMO and 2 out of 31 relapsing LETM patients that were characteristic of NMO/NMOSD[10,11]. Patients with lesions in the area postrema of the dorsal medulla commonly present with refractory hiccups, nausea and vomiting to gastroenterologists[12]. A recent report summarises the NMOSD-typical brain lesions patterns as 1) lesions involving the dorsal medulla especially the area postrema, 2) periependymal surfaces of the 4th ventricle in the brainstem/cerebellum, 3) lesions involving the hypothalamus, thalamus or periependymal surface of the 3rd ventricle, 4) large confluent, unilateral or bilateral subcortical or deep white matter lesions, 5) long, diffuse, heterogeneous or oedematous corpus callosum lesions and 6) long corticospinal tract lesions contiguously involving the internal capsule and cerebral peduncle[6].

Brain involvement in Hong Kong Chinese NMO/NMOSD patients

Our study revealed that 59% of Hong Kong Chinese NMO/NMOSD patients had brain involvements and 56% had MRI brain abnormalities, with 6% of patients having MRI brain abnormalities fulfilling the Barkhof's criteria for CMS. Importantly, the brain involvements in local NMO/NMOSD patients tend to be symptomatic as 32% of patients had clinical manifestations of brain involvement, especially BE with florid bulbar symptoms and signs from severe brainstem dysfunction in 24%, and as initial clinical presentation in 18%. MRI abnormalities were detected most frequently in the brainstem (44% of all patients), followed by the hemispheric periventricular white matter (21%), deep white matter (21%), corpus callosum (12%), thalamus (3%), hypothalamus (3%) , internal capsule (3%), periaqueductal grey matter (3%), and regions around the 3rd and 4th ventricles (3%) [5].

Immunopathogenesis and pathologies of NMO/NMOSD

Typical spinal cord lesions of NMO/NMOSD patients exhibit necrosis in both the grey and white matter, infiltrating leucocytes (macrophages, neutrophils and eosinophils, and lymphocytes), activated microglia, demyelination, axonal loss, thickened hyalinised vessel walls with deposits of IgG, IgM and products of complement activation in a characteristic vasculocentric rim and rosette pattern[2,3,13], reflecting severe damage from complement-mediated inflammation and astrocytic cytotoxicity. Another type of lesion characterised by AQP4 loss without astrocyte loss, vacuolated myelin, inflammation, oedema, astrocytosis but without demyelination or necrosis is observed in the spinal cord and medullary tegmentum extending into the area postrema[12,13]. AQP4 is markedly reduced/lost in lesions of all stages in NMO/NMOSD but preserved or increased in active lesions of CMS patients[3,12,13].

Immunopathogenesis

NMO/NMOSD seropositive for AQP4 Ab is likely due to the underlying autoimmunity against AQP4. The cause of AQP4 autoimmunity is uncertain. Current evidence suggests that AQP4 Ab are directly pathogenic. Potential pathophysiological mechanisms include complement activation, antibody-dependent cellular cytotoxicity, infiltration and degranulation of neutrophils and eosinophils, astrocytic activation with release of inflammatory cytokines and chemokines, and oligodendrocyte injury/loss via glutamate excitotoxicity leading to demyelination[3].

Diagnosis

The 2006 Wingerchuk diagnostic criteria for NMO require the presence of 1) myelitis, 2) optic neuritis and at least 2 of the supportive criteria[18]:

a. MRI evidence of a contiguous spinal cord lesion (T2W hyperintensity) extending over 3 or more vertebral segments longitudinally in the context of AM
b. initial MRI brain at onset of disease is not diagnostic of CMS
c. seropositivity for AQP4 Ab

In 2015, new diagnostic criteria were proposed with consideration of brain involvement in which all NMO and related disorders were unified as neuromyelitis optica spectrum disorders (NMOSD)[19]. In the new criteria, NMOSD were divided into AQP4 Ab +ve or AQP4 Ab –ve; and the diagnosis of AQP4 Ab +ve NMOSD requires one or more core clinical characteristics which include 1) ON, 2) AM, 3) acute area postrema syndrome, 4) acute brainstem syndrome, 5) symptomatic narcolepsy or acute diencephalic syndrome with NMOSD-typical MRI diencephalic lesions, and 6) symptomatic cerebral syndrome with NMOSD-typical brain lesions, with seropositivity for AQP4 Ab. The diagnosis of AQP4 Ab-negative NMOSD requires 2 or more of the 6 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements: a) at least 1 core clinical characteristic must be ON, AM with LETM or area postrema syndrome, b) dissemination in space (2 or more core clinical characteristics), and c) fulfillment of additional MRI requirements as applicable, and exclusion of alternative diagnoses[19]. General consensus for acceptance of the new criteria awaits confirmation.

The clinical, neuroradiological, serological and histopathological differences between CMS and NMO are summarised in Table 1.

Treatment

Acute attacks

Acute attacks of neuroinflammation in NMO/NMOSD are treated with intravenous pulse methylprednisolone, typically 1gm daily for 5 days[14]. This may hasten and enhance recovery of vision and neurological functions. A randomised controlled cross-over study and other studies have shown efficacy of plasmaspheresis (7

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A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year. or - Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI. **Dosage: Adults:** One 0.5 mg capsule taken orally once daily. **Children and adolescents:** Not intended for use (not studied in this population). **Special patient populations:** No dosage adjustment needed for renal impairment, mild to moderate hepatic impairment or elderly patients (caution as experience is limited). Caution in patients with hepatic impairment. Gilenya should be used with caution in diabetic patients. **Contraindications:** Known immunodeficiency syndrome. Patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies). Severe active infections, active chronic infections (hepatitis, tuberculosis). Known active malignancies. Severe liver impairment (Child-Pugh class C). Hypersensitivity to the active substance or to any of the excipients. Warnings/Precautions: ECG to be performed in all patients prior to the first dose and at the end of the 6-hour first-dose observation period. Heart rate and blood pressure to be monitored hourly during the 6-hour observation period. Same recommendation applies after an interruption of one day or more during the first 2 weeks of treatment, or for more than 7 days during week 3 and 4 of treatment; or after an interruption for more than 2 weeks after the first month of treatment. If post-dose bradyarrhythmia-related symptoms occur, or new onset of second-degree or higher grade atrioventricular (AV) block, or the heart rate at 6 hours post-dose is the lowest value post-dose or is <45 bpm, the patient should be observed until the symptoms or findings have resolved, and appropriate management should be initiated as necessary. Patients should be monitored overnight if ECG at 6 hours shows QTc ≥500 msec. If a patient requires pharmacological intervention during the first dose observation period, overnight monitoring should be instituted and the first dose monitoring strategy should be repeated for the second dose of Gilenya. ◆Gilenya should not be used in patients with second degree or higher AV block, sick-sinus syndrome or sino-atrial heart block due to the risk of serious cardiac rhythm disturbances. Gilenya should also not be used in patients with known ischemic heart disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension or severe untreated sleep apnea, since significant bradycardia may not be well tolerated in these patients. ◆Gilenya should not be used in patients with significant QT prolongation (QTc >470 msec (women) or >450 msec (men)) or in patients with relevant risk factors for QT prolongation (e.g. hypokalemia or congenital QT prolongation). ◆In patients with a history of recurrent syncope or symptomatic bradycardia, use of Gilenya should be based on an overall benefit-risk assessment. ◆If treatment is being considered in patients with the aforementioned risk factors, pre-treatment consultation with a cardiologist is required to determine the most appropriate monitoring (should last overnight) for treatment initiation. ◆Gilenya should generally not be initiated in patients on concurrent therapy with beta-blockers, heart rate lowering calcium channel blockers or other substances that may decrease heart rate (limited experience is available and this may be associated with severe bradycardia and heart block). If treatment with Gilenya is being considered, advice should be sought from a cardiologist regarding switching to a non-heart rate lowering drug or appropriate monitoring (should last overnight) for treatment initiation. ◆After the first dose, the heart rate decrease starts within an hour and is maximal within 6 hours. Heart rate returns to baseline within 1 month of chronic dosing. ◆Anti-neoplastic, immunomodulatory or immunosuppressive therapies should not be co-administered due to the risk of additive immune system effects.Specific decisions as to the dosage and duration of treatment with corticosteroids should be based on clinical judgment. Short courses of corticosteroids can be used in combination with Gilenya. ◆Patients without a healthcare professional confirmed history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV prior to treatment initiation. VZV vaccination is recommended in antibody-negative patients and initiation of treatment should be postponed for 1 month to allow the vaccination to take full effect. ◆Infection: Lymphocyte count is decreased during Gilenya therapy and up to 2 months after stopping Gilenya therapy. Before initiating treatment with Gilenya, a recent complete blood count (i.e. within 6 months or after discontinuation of prior therapy) should be available. Initiation of treatment with Gilenya should be delayed in patients with severe active infection until resolution. Effective diagnostic and therapeutic strategies should be used in patients with symptoms of infection while on therapy and up to two months after discontinuation. Consider discontinuing therapy if a serious infection develops, and re-evaluate benefit-risk before restarting therapy. Isolated cases of cryptococcal meningitis have been reported in the post-marketing setting. Patients with symptoms and signs consistent with cryptococcal meningitis should undergo prompt diagnostic evaluation. If diagnosed, fingolimod should be suspended and appropriate treatment should be initiated. A multidisciplinary consultation (i.e. infectious disease specialist) should be undertaken if re-initiation of fingolimod is warranted. ◆Macular edema: Patients with history of uveitis and patients with diabetes mellitus are particularly at risk of developing macular edema. An ophthalmic examination is recommended 3 to 4 months after Gilenya therapy initiation and also before and regularly during Gilenya therapy in patients at risk. Discontinuing therapy should be considered if macular edema develops. ◆Recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with Gilenya. A liver function test is recommended in patients who develop symptoms of hepatic dysfunction. Therapy should be discontinued if significant liver injury is confirmed. ◆Posterior reversible encephalopathy syndrome (PRES): Discontinue Gilenya treatment, if PRES is suspected. ◆Caution is required when switching patients from natalizumab or teriflunomide to Gilenya due to the long half-life of natalizumab or teriflunomide. Initiating treatment with Gilenya after alemtuzumab is not recommended unless the benefits clearly outweigh the risks. ◆Very rare cases of T-wave inversion have been reported in patients treated with fingolimod. In case of T-wave inversion, the prescriber should ensure that there are no associated myocardial ischaemia signs or symptoms. If myocardial ischaemia is suspected, it is recommended to seek advice from a cardiologist. ◆Cases of progressive multifocal leukoencephalopathy (PML) have been reported in the post-marketing setting. Vigilance for clinical symptoms or MRI findings suggestive of PML is warranted. If PML is suspected, Gilenya treatment should be suspended until PML has been excluded. ◆Basal cell carcinoma (BCC) has been reported in patients receiving Gilenya. Vigilance for skin lesions is warranted. **Pregnancy:** Not recommended. Adequate contraceptive measures are recommended in women of childbearing potential. **Breast-feeding:** Not recommended. **Interactions:** Concomitant use is not recommended with Class Ia (e.g. quinidine, disopyramide) and Class III (e.g. amiodarone, sotalol) anti-arrhythmic drugs. ◆At treatment initiation concomitant use with beta-blockers, heart rate lowering calcium channel blockers (e.g. verapamil, diltiazem or ivabradine) or other drugs that may lower heart rate (e.g. digoxin) is not recommended. ◆Caution is required in concomitant use with anti-neoplastic, immune-modulating or immunosuppressive therapies (including corticosteroids) during, and for up to 2 months after stopping Gilenya treatment. ◆Caution is required when switching therapy from drugs with a long-acting immune effect such as natalizumab, teriflunomide or mitoxantrone. ◆Concomitant use is not recommended with live attenuated vaccines; other vaccines may have reduced efficiency during and for up to 2 months after stopping Gilenya therapy. **Adverse reactions: Very common (≥10%):** Influenza, sinusitis, headache, cough, diarrhea, back pain, hepatic enzymes increased. **Common (≥1 to <10%):** Herpes viral infections, bronchitis, tinea versicolor, lymphopenia, leucopenia, basal cell carcinoma, depression, dizziness, migraine, vision blurred, bradycardia, atrioventricular block, hypertension, dyspnea, eczema, alopecia, pruritus, asthenia, blood triglycerides increased. **Uncommon (≥0.1 to <1%):** Pneumonia, depressed mood, macular edema, nausea, neutrophil count decreased **Rare (≥0.01 to <0.1%):** Lymphoma, posterior reversible encephalopathy syndrome. **Very rare (<0.01%):** T-wave inversion. Not known (cannot be estimated from the available data): Progressive multifocal leukoencephalopathy (PML), cryptococcal infections, peripheral oedema, hypersensitivity reactions (including rash, urticaria and angioedema upon treatment initiation), **Packs and prices:** 28's **Legal classification:** P1S1S3 Ref: EMA Mar 2016 (CDS 0743s/0761s/0767s)

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sessions over 14 days) for CNS IDD patients who do not have significant clinical improvements 2 weeks after pulse steroid[14,15]. About 40-59% of patients who have no significant neurological improvement with pulse steroid improve with plasmapheresis[2,3,14,15]. Plasmapheresis was also reported to be effective as a rescue therapy for steroid-unresponsive acute attacks of NMO in Asian patients . Patients who cannot tolerate plasmapheresis may be treated with intravenous immunoglobulins (IVIg) (0.4 gm/kg/day for 5 days) [14].

Prophylaxis against relapses

Once NMO/NMOSD is diagnosed, prompt initiation of immunosuppressants to achieve long-term immunosuppression to prevent relapse of CNS inflammatory attack is crucial[2,3,14]. Early, frequent and severe relapses are common and bear high risk of severe attack-related disabilities and even mortality. The optimal immunosuppressive agents for NMOSD are uncertain and treatment is based on data from small series of patients[2,3,14].

Azathioprine with corticosteroids

Azathioprine and oral prednisolone are commonly used for long-term prophylaxis against relapse in NMOSD[2,3,16]. The 6-mercaptopurine (6-MP) analogue, azathioprine, suppresses lymphocyte proliferation and activation, and possesses anti-inflammatory action. The annualised relapse rate (ARR) decreased from the pre-treatment 2.2 to post-treatment 0.52 over a median duration of 22 months in a series of 99 patients[16]. Azathioprine is started at 25-50 mg daily and gradually increased to 2-3 mg/kg daily. As azathioprine is slow in onset of action and may take 6 months for effect, oral prednisolone is usually initiated at 1 mg/kg daily to achieve more rapid onset of immunosuppression. Prednisolone dose is gradually tailed down to minimal maintanence dose (15 mg daily or less) or off if possible with onset of azathioprine action.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) reversibly inhibits T and B lymphocyte proliferation. Jacob et al. studied 24 NMO/NMOSD patients (7 treatment naïve) treated with MMF (median dose 2000 mg per day) and reported that with a median treatment duration of 27 months, the ARR decreased from the pre-treatment 1.3 to post-treatment 0.09. In addition, disabilities were stabilised or decreased in 22 patients (91%) and one died of disease complication, but 6 (25%) noted adverse effects including headache, constipation, easy bruising, anxiety, hair loss, diarrhoea and abdominal pain, and low white blood cell counts that required discontinuation during MMF treatment. Another study reported the annualised severe relapse rate decreased from 1.01 to 0.06 with MMF therapy[3,14].

Chimeric CD20 monoclonal antibody

Rituximab, a monoclonal antibody against CD20+ B cells can be used for relapse prophylaxis in NMO/NMOSD. The first report on 8 NMO patients refractory to azathioprine and corticosteroids suggests that a course of rituximab (4 consecutive weekly intravenous infusion) every 6 months leads to remission. Rituximab is in general reserved for NMO/NMOSD patients refractory to azathioprine and corticosteroids, and other immunosuppressants such as MMF[2,14]. However, its use as first-line disease-modifying drugs (DMD) in NMO/NMOSD is not uncommon, especially with aggressive disease[3]. A study of 25 NMO patients (23 refractory to other medications) treated with rituximab reported that at a median follow-up of 19 months, the posttreatment ARR was lower than pre-treatment (0 versus 1.7) and disability scores were stabilised in 80% of patients. Unfortunately, 28% of patients had infusion-related adverse effects and 20% developed infections that could have been related to immunosuppression. Two patients died, one from brainstem relapse and one likely from septicaemia[3,14]. Another study reported that induction therapy 375 mg/m^2 once weekly for 4 weeks or 1000 mg intravenously twice with a 2-week interval between followed by maintenance therapy (375 mg/m^2 whenever the frequency of reemerging CD27+ memory B cells was more than 0.05% in peripheral blood mononuclear cells by flow cytometry) resulted in consistent and sustained efficacy over 24 months with good tolerability. Among 30 NMO patients studied, 28 showed marked reduction in the relapse rate while on rituximab; the relapse rate was reduced by 88%, 70% patients became relapse-free over 24 months, and disability improved or stabilised in 97% patients[3]. 1000 mg intravenously twice with a 2-week interval every 6 months is increasingly used as the maintenance therapy for convenience especially when routine monitoring of CD27+ memory B cells is not available.[3]

Disease modifying drugs for refractory NMO/NMOSD

Azathioprine, MMF and rituximab are the three most commonly used DMD for NMO/NMOSD. Agents that may be used for patients who do not respond satisfactorily to them alone or in combination with oral steroids include methotrexate, cyclosporine A, mitoxantrone, IL-6 receptor blockade by tocilizumab, inhibition of complement activation by eculizumab, depletion of CD19+ plasmablasts by anti-CD19 monoclonal antibody[3]. The details of these newer DMD are beyond discussion in this review.

Table 1. Clinical, neuroradiological, serological and histopathological characteristics of neuromyelitis optica and classical multiple sclerosis

	NMO	CMS
Mean onset age (in years)	~40-45	~20-30
F:M	9:1	~3:1
Relapsing-remitting course	predominant	predominant (at onset)
Severe clinical attack	usual	less common
LETM	common	rare
Associated autoimmune diseases	common	rare
Respiratory insufficiency/ failure	~20%	rare
MRI cord lesions	≥3 vs, affect central GM	≤1 vs, affect lateral & posterior WM
MRI brain lesions	~60%	>90%
CSF OCB +ve	~20%	~90%
Serum AQP4 autoantibodies	~60-90%	absent
Associated autoantibodies	common	rare
Histopathology of lesions	AQP4 loss in lesions of all stages, perivascular deposition of IgG, IgM, C9neo, thickened hyalinised vessels	↑ or ↔ AQP4 in active lesions, heterogeneous

↑ = increased; ↔ = preserved

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Federation Visit to Nanjing

The Federation was cordially invited to attend the 2017 Annual Scientific Meeting of the Chinese Medical Association on 13-18 January 2017. Dr Mario CHAK, President of the Federation of Medical Societies of Hong Kong (FMSHK), together with the Deputy Honourary Secretary Dr C.K. NG attended the meeting at the Purple Palace Conference Center in Nanjing. Speakers of the meeting include Dr. Ketan DESAI, President of World Medical Association (WMA) as well as representatives from USA, UK, Thailand, Pakistan, Russia, Sri Lanka, Burma and India etc. In addition, the delegation visited Gulou Hospital and Yuhuatai Community Health Service Center. It was a successful visit and we would like to express our sincere gratitude to the CMA for their invitation and kind hospitality.

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Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
			1	★ Use of Drugs for Sedation, neuroprotection and for Increasing Wakefulness and Smartness in the Clinic 2	★ Joint Surgical Symposium - Problem of Voice Prosthesis 3	4
5	6	★ HKMA Kowloon West Community Network – Cervical Cancer Prevention: We Can Do More for Female Health and Well-being ★ FMSHK Officers' Meeting ★ HKMA Council Meeting 7	★ Hong Kong Neurosurgical Society Monthly Academic Meeting –3D printing in Neurosurgery ★ HKMA Central, Western & Southern Community Network - Holistic Approach of HPV Prevention: Improving Female Life 8	★ HKMA New Territories West Community Network - Training Course on Dementia for Primary Care Doctors (Session 1) - Early Clinical Diagnosis of Dementia – Core Clinical Features and Diagnostic Criteria ★ HKMA Kowloon East Community Network - Updates on Treatments for Diabesity 9	10	★ 12th International Symposium on Healthy Aging "Wellness and Longevity: From Science to Service" ★ "Fronties of Integrative Medicine – Clinical Challenges and Future Directions" Confrence ★ Refresher Course for Health Care Providers 2016/2017 ★ MPS Workshop - Mastering Your Risk 11
★ 12th International Symposium on Healthy Aging "Wellness and Longevity: From Science to Service" ★ Nipple Sparing Mastectomy Cadaveric Workshop ★ "Fronties of Integrative Medicine – Clinical Challenges and Future Directions" Confrence ★ Organ Donation Promotion Walk 2017 12	13	★ HKMA Yau Tsim Mong Community Network - Doctor, Are My Rashes Psoriasis? 14	★ HKMA Shatin Doctors Network - Approach to Osteoporosis in Primary Care Setting ★ MPS Workshop - Mastering Professional Interactions 15	★ HKMA KECN, HKCFP & UCH - Certificate Course for GPs 2017 (Session 1): Continence Management Update 16	17	18
19	20	★ HKMA Kowloon West Community Network – Management of Irritable Bowel Syndrome: An Update ★ HKMA Tai Po Community Network - Three Non-drug Pillars in Dementia Management ★ MPS Workshop - Achieving Safer and Reliable Practice 21	★ HKMA Central, Western & Southern Community Network - Updates on Presbyopia ("Lo Fa") Treatment 22	★ HKMA New Territories West Community Network - Training Course on Dementia for Primary Care Doctors (Session 2) - Drug Treatment – Strategic Pharmacological Intervention for Dementia ★ MPS Workshop - Mastering Difficult Interactions with Patients ★ FMSHK Executive Committee Meeting 23	★ HKMA Kowloon City Community Network - Role of DPP IV Inhibitors in the Context of Latest Trials 24	★ MPS Workshop - Achieving Safer and Reliable Practice 25
★ HKMA Football Day 26	27	★ MPS Workshop - Mastering Adverse Outcomes 28	★ RSCP Golf Tournament 2017 29	★ HKMA Hong Kong East Community Network - Clinical Experience with a Breakthrough Treatment in Heart Failure 30	★ HKMA Yau Tsim Mong Community Network - Option of Oral Anti-diabetic Agent for a Better CV Outcome 31	


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Date / Time	Function	Enquiry / Remarks
2 THU 1:00 PM	**Use of Drugs for Sedation, neuroprotection and for Increasing Wakefulness and Smartness in the Clinic** Organiser: Hong Kong Medical Association; Speaker: Prof. TANG Siu Wa; Venue: Ballroom, Level 7, Cordis Hotel, Mongkok	HKMA CME Dept. Tel: 2527 8452 1 CME Point
3 FRI 8:00 AM - 9:00 AM	**Joint Surgical Symposium - Problem of Voice Prosthesis** Organiser: Department of Surgery, The University of Hong Kong & Hong Kong Sanatorium & Hospital; Chairman: Dr. HO Chung-Wai, Ambrose; Speaker: Professor William WEI, Dr. CHAN Yu-Wai; Venue: Hong Kong Sanatorium & Hospital	Department of Surgery, Hong Kong Sanatorium & Hospital Tel: 2835 8698 Fax: 2892 7511 1 CME Point (Active)
7 TUE 1:00 PM	**HKMA Kowloon West Community Network – Cervical Cancer Prevention: We Can Do More for Female Health and Well-being** Organiser: HKMA Kowloon West Community Network; Chairman: Dr. LAM Ngam, Raymond; Speaker: Dr. YAU Pui Kei, Stephanie; Venue: Panda Hotel, 3 Tsuen Wah Street, Tsuen Wan, N.T	Mr. Ziv WONG Tel: 2527 8285 1 CME Point
8:00 PM	**FMSHK Officers' Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Gallop, 2/F, Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
9:00 PM	**HKMA Council Meeting** Organiser: The Hong Kong Medical Association; Chairman: Dr. CHOI Kin; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Ms. Christine WONG Tel: 2527 8285
8 WED 7:30 AM	**Hong Kong Neurosurgical Society Monthly Academic Meeting –3D printing in Neurosurgery** Organisation: Hong Kong Neurosurgical Society; Chairman: Dr TSE Tat Shing; Speaker: Dr CHAN Nok Lun; Venue: Seminar Room, G/F, Block A, Queen Elizabeth Hospital	Dr. LEE Wing Yan, Michael Tel: 2595 6456 Fax: 2965 4061 1.5 points College of Surgeons of Hong Kong
1:00 PM	**HKMA Central, Western & Southern Community Network - Holistic Approach of HPV Prevention: Improving Female Life** Organiser: HKMA Central, Western & Southern Community Network; Chairman: Dr. TSANG Chun Au; Speaker: Dr. ONG Yeu Theng, Charas; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	Mr. Ziv WONG Tel: 2527 8285 1 CME Point
9 THU 1:00 PM	**HKMA New Territories West Community Network - Training Course on Dementia for Primary Care Doctors (Session 1) - Early Clinical Diagnosis of Dementia – Core Clinical Features and Diagnostic Criteria** Organiser: The HKMA New Territories West Community Network & Institute of Alzheimer's Education of Hong Kong Alzheimer's Disease Association; Chairman: Dr. CHUNG Siu Kwan, Ivan; Speaker: Dr. CHAN Chun Chung, Ray; Venue: Lingnan Chinese Restaurant, 1/F, Lingnan University Amenities Building, Tuen Mun, N.T.	Mr. Ziv WONG Tel: 2527 8285 1.5 CME Points
1:00 PM	**HKMA Kowloon East Community Network - Updates on Treatments for Diabesity** Organiser: HKMA-Kowloon East Community Network; Chairman: Dr. AU Ka Kui, Gary; Speaker: Dr. CHEUNG Fu Keung; Venue: Lei Garden Restaurant, Shop No. L5-8, apm, Kwun Tong, No. 418 Kwun Tong Road, Kwun Tong, Kowloon	Mr. Ziv WONG Tel: 2527 8285 1.5 CME Points
11 SAT 9:00 AM - 5:00 PM *(12)*	**12th International Symposium on Healthy Aging "Wellness and Longevity: From Science to Service"** Organiser: Research Centre of Heart, Brain, Hormone & Healthy Aging, Li Ka Shing Faculty of Medicine, HKU; Chairman: Dr Joseph SK Kwan & Dr Cora SW Lai, HKU; Venue: 3/F, Ballroom, Sheraton Hong Kong Hotel & Towers	Phoebe Chow Tel: 3917 9866 Fax: 2816 5258
2:30 PM - 5:45 PM	**"Fronties of Integrative Medicine – Clinical Challenges and Future Directions" Confrence** Organiser: Hong Kong Association for Integration of Chinese-Western Medicine; Chairman: Dr Yu Chau Leung and Prof. Bian Zhaoxiang; Venue: SCM, Hong Kong Baptist University	Miss YC Yeung Tel: 3119 1858 Fax: 2301 2414
2:15 PM	**Refresher Course for Health Care Providers 2016/2017** Organiser: Hong Kong Medical Association; HK College of Family Physicians; HA-Our Lady of Maryknoll Hospital; Speaker: Dr. LEUNG Hoi Sze; Venue: Training Room II, 1/F, OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin, Kowloon	Ms. Clara TSANG Tel: 2354 2440 2 CME Points
2:30 PM	**MPS Workshop - Mastering Your Risk** Organiser: The Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. CHENG Ngai Shing, Justin; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	HKMA CME Dept. Tel: 2527 8452 2.5 CME Points
12 SUN 8:00 AM -17:00 PM	**Nipple Sparing Mastectomy Cadaveric Workshop** Organisation: Hong Kog Society of Breast Surgeons; Chairman: Dr Sharon Chan and Dr Polly Cheung; Speaker: Professor Shawna C Willey, Dr Polly Cheung, Dr Sharon Chan, Dr Vivian Lee, Dr George Li, Dr Raymond Ng, Dr. Marcus Ying;Venue: Li Ka Shing Faculty of Medicine, 21 Sassoon Rd, Pokfulam, HK	Ms Veronica Chan Tel: 6776 3350 Fax: 2524 9372
8:45 AM - 5:15 PM	**"Fronties of Integrative Medicine – Clinical Challenges and Future Directions" Confrence** Organiser: Hong Kong Association for Integration of Chinese-Western Medicine; Chairman: Dr Yu Chau Leung and Prof. Bian Zhaoxiang; Venue: Tsang Chan Sik Yue Auditorium, Hong Kong Baptist University	Miss YC Yeung Tel: 3119 1858 Fax: 2301 2414
10:00 AM	**Organ Donation Promotion Walk 2017** Organiser: The Hong Kong Medical Association & The Hong Kong Society of Transplantation; Venue: Pak Tam Chung, Sai Kung, N.T.	Miss Kayin LEE Tel: 2527 8285
14 TUE 1:00 PM	**HKMA Yau Tsim Mong Community Network - Doctor, Are My Rashes Psoriasis?** Organiser: HKMA Yau Tsim Mong Community Network; Chairman: Dr. CHAN Wai Keung, Ricky; Speaker: Dr. LEE Tze Yuen; Venue: Pearl Ballroom, Level 2, Eaton, Hong Kong, 380 Nathan Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
15 WED 1:00 PM	**HKMA Shatin Doctors Network - Approach to Osteoporosis in Primary Care Setting** Organiser: HKMA Shatin Doctors Network; Chairman: Dr. MAK Wing Kin; Speaker: Dr. TING Zhao Wei, Rose; Venue: Star Seafood Floating Restaurant, 55-57 Tai Chung Kiu Road, Shatin, N.T.	Ms. Agnes TSE Tel: 2529 8265 / 2529 8931 1 CME Point
6:30 PM	**MPS Workshop - Mastering Professional Interactions** Organiser: The Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. LEE Wai Hung, Danny; Venue: Eaton, Hong Kong, 380 Nathan Road, Kowloon	HKMA CME Dept. Tel: 2527 8452 2.5 CME Points

Date / Time	Function	Enquiry / Remarks
16 THU 1:00 PM	**HKMA KECN, HKCFP & UCH - Certificate Course for GPs 2017 (Session 1): Continence Management Update** Organiser: HKMA Kowloon East Community Network & Hong Kong College of Family Physicians & United Christian Hospital; Chairman: Dr. SHA Kwok Yiu, Edmund; Speaker: Dr. LEUNG Man Fuk; Venue: Lecture Theatre, G/F, Block K, United Christian Hospital, (UCH), 130 Hip Wo Street, Kwun Tong, Kowloon	Ms. Polly TAI / Ms. Cordy WONG Tel: 3949 3430 (Ms. TAI)/3949 3087 (Ms. WONG) 1 CME Point
21 TUE 1:00 PM	**HKMA Kowloon West Community Network – Management of Irritable Bowel Syndrome: An Update** Organiser: HKMA Kowloon West Community Network; Chairman: Dr. LEUNG Kin Nin, Kenneth; Speaker: Dr. FUNG Tang Tat, Konrad; Venue: Panda Hotel, 3 Tsuen Wah Street, Tsuen Wan, N.T	Mr. Ziv WONG Tel: 2527 8285 1 CME Point
1:45 PM	**HKMA Tai Po Community Network - Three Non-drug Pillars in Dementia Management** Organiser: HKMA Tai Po Community Network; Chairman: Dr. CHOW Chun Kwan, John; Speaker: Dr. CHAN Chun Chung, Ray; Venue: Chiuchow Garden Restaurant (潮江春), Shop 001-003, 1/F, Uptown Plaza, No. 9 Nam Wan Road, Tai Po, N.T.	Ms. Candice TONG Tel: 2527 8285 1 CME Point
6:30 PM	**MPS Workshop - Achieving Safer and Reliable Practice** Organiser: The Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. CHENG Ngai Shing, Justin; Venue: Eaton, Hong Kong, 380 Nathan Road, Kowloon	HKMA CME Dept. Tel: 2527 8452 2.5 CME Points
22 WED 1:00 PM	**HKMA Central, Western & Southern Community Network - Updates on Presbyopia ("Lo Fa") Treatment** Organiser: HKMA Central, Western & Southern Community Network; Chairman: Dr. LAW Yim Kwai; Speaker: Dr. YUEN, Leonard Hsu; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	Mr. Ziv WONG Tel: 2527 8285 1 CME Point
23 THU 1:00 PM	**HKMA New Territories West Community Network - Training Course on Dementia for Primary Care Doctors (Session 2) - Drug Treatment – Strategic Pharmacological Intervention for Dementia** Organiser: The HKMA New Territories West Community Network & Institute of Alzheimer's Education of Hong Kong Alzheimer's Disease Association; Chairman: Dr. CHEUNG Kwok Wai, Alvin; Speaker: Dr. CHAN Chun Chung, Ray; Venue: Lingnan Chinese Restaurant, 1/F, Lingnan University Amenities Building, Tuen Mun, Tuen Mun, N.T.	Mr. Ziv WONG Tel: 2527 8285 1.5 CME Points
6:30 PM	**MPS Workshop - Mastering Difficult Interactions with Patients** Organiser: The Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. FUNG Shu Yan, Anthony; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	HKMA CME Dept. Tel: 2527 8452 2.5 CME Points
8:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
24 FRI 1:00 PM	**HKMA Kowloon City Community Network - Role of DPP IV Inhibitors in the Context of Latest Trials** Organiser: HKMA Kowloon City Community Network; Chairman: Dr. CHIN Chu Wah; Speaker: Dr. CHAN Wing Bun; Venue: Spotlight Recreation Club, 4/F., Screen World, Site 8, Whampoa Garden, Hunghom, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
25 SAT 2:30 PM	**MPS Workshop - Achieving Safer and Reliable Practice** Organiser: The Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. CHENG Ngai Shing, Justin; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	HKMA CME Dept. Tel: 2527 8452 2.5 CME Points
26 SUN 12:00 NOON	**HKMA Football Day** Organiser: The Hong Kong Medical Association; Chairman: Dr. CHAN Chi Wing, Timmy; Dr. CHAN Hau Ngai, Kingsley; Venue: Stanley Ho Sports Centre	Miss Ada SIU/ Mr. Ian KWA Tel: 2527 8285
28 TUE 6:30 PM	**MPS Workshop - Mastering Adverse Outcomes** Organiser: The Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. HUNG Chi Wan, Emily; Venue: Eaton, Hong Kong, 380 Nathan Road, Kowloon	HKMA CME Dept. Tel: 2527 8452 2.5 CME Points
29 WED 1:00 PM	**RSCP Golf Tournament 2017** Organiser: The Hong Kong Medical Association; Chairman: Dr. HOU Lee Tsun, Laurence; Dr. CHUNG Ka Leung, Stephen; Venue: Eden Course, Hong Kong Golf Club	Miss Ada SIU/ Mr. Ian KWA Tel: 2527 8285
30 THU 1:00 PM	**HKMA Hong Kong East Community Network - Clinical Experience with a Breakthrough Treatment in Heart Failure** Organiser: HKMA Hong Kong East Community Network; Chairman: Dr. AU YEUNG Shiu Hing; Speaker: Dr. WONG Bun Lap, Bernard; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Ms. Candice TONG Tel: 2527 8285 1 CME Point
31 FRI 1:00 PM	**HKMA Yau Tsim Mong Community Network - Option of Oral Anti-diabetic Agent for a Better CV Outcome** Organiser: HKMA Yau Tsim Mong Community Network; Chairman: Dr. CHENG Kai Chi, Thomas; Speaker: Dr. Enoch WU; Venue: Diamond Ballroom, Level B1, Eaton, Hong Kong, 380 Nathan Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point

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Indication
TECFIDERA [dimethyl fumarate] is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis.

Reduced Relapse Rates

DEFINE[a]

Risk of Relapse
49%

Relative reduction [Hazard ratio] vs. Placebo (95% CI) at 2 years (0.51 (0.40–0.66); P<0.001)[1]

Annualized Relapse Rate
53%

Relative reduction [Rate ratio] vs. Placebo (95% CI) at 2 years (0.47 (0.37–0.61); P<0.001)[1]

Delayed Disability Progression

DEFINE[a]

Risk of Disability Progression
38%

Relative risk reduction vs placebo at 2 years; (Hazard ratio, 0.62; 95% CI, 0.44 to 0.87; P=0.005)[1]

Reduced Brain Lesions

DEFINE[a]

Mean number of new or newly enlarging T2 lesions
Placebo **16.5**
Tecfidera **3.2**
85%

Relative reduction vs placebo at 2 years; (Lesion mean ratio (95% CI); 0.15 (0.10, 0.23); P<0.0001)[1,2]

Mean number of new T1 lesions
Placebo **5.7**
Tecfidera **2.0**
72%

Relative reduction vs placebo at 2 years; (Lesion mean ratio (95% CI); 0.28 (0.20, 0.39); P<0.0001)[1,2]

Mean number of Gd+ lesions
Placebo **1.8**
Tecfidera **0.1**
90%

Relative odds reduction vs placebo at 2 years; (Odds ratio (95% CI); 0.10 (0.05,0.22); P<0.0001)[1,2]

a. Study design: randomized, double-blind, placebo-controlled phase 3 study. The 1237 patients (age 18 to 56 years) with relapsing-remitting multiple sclerosis were randomly assigned to receive oral BG-12 at a dose of 240mg twice daily, BG-12 at a dose of 240mg three times daily, or placebo. The primary end point was the proportion of patients who had a relapse by 2 years.[1]

TECFIDERA ABBREVIATED PRESCRIBING INFORMATION (HONG KONG)

NAME OF THE MEDICINAL PRODUCT: Tecfidera 120 mg gastro-resistant hard capsules and Tecfidera 240 mg gastro-resistant hard capsules. THERAPEUTIC INDICATIONS: Tecfidera is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis. POSOLOGY AND METHOD OF ADMINISTRATION: Treatment should be initiated under supervision of a physician experienced in the treatment of the disease. Posology: The starting dose is 120 mg twice a day. After 7 days, the dose is increased to the recommended dose of 240 mg twice a day. Temporary dose reduction to 120 mg twice a day may reduce the occurrence of flushing and gastrointestinal adverse reactions. Within 1 month, the recommended dose of 240 mg twice a day should be resumed. Tecfidera should be taken with food. For those patients who may experience flushing or gastrointestinal adverse reactions, taking Tecfidera with food may improve tolerability. Elderly: Clinical studies of Tecfidera had limited exposure to patients aged 55 years and above, and did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. Based on the mode of action of the active substance there are no theoretical reasons for any requirement for dose adjustments in the elderly. Renal and hepatic impairment: Tecfidera has not been studied in patients with renal or hepatic impairment. Based on clinical pharmacology studies, no dose adjustments are needed. Caution should be used when treating patients with severe renal or severe hepatic impairment. Paediatric population: The safety and efficacy of Tecfidera in children and adolescents aged 10 to 18 years have not been established. No data are available. There is no relevant use of Tecfidera in children aged less than 10 years for the indication of relapsing remitting multiple sclerosis. Method of administration: For oral use. The capsule or its contents should not be crushed, divided, dissolved, sucked or chewed as the enteric-coating of the microtablets prevents irritant effects on the gut. CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients. SPECIAL WARNING AND PRECAUTIONS FOR USE: Blood/laboratory tests, Prolonged moderate to severe lymphopenia, MR imaging, Progressive Multifocal Leukoencephalopathy (PML), Prior treatment with immunosuppressive or immunomodulating therapies, Severe renal and hepatic impairment, Severe active gastrointestinal disease, Flushing, Infections INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION: Tecfidera has not been studied in combination with anti-neoplastic or immunosuppressive therapies and caution should, therefore, be used during concomitant administration. In multiple sclerosis clinical studies, the concomitant treatment of relapses with a short course of intravenous corticosteroids was not associated with a clinically relevant increase of infection. Vaccination during treatment with Tecfidera has not been studied. It is not known whether treatment with Tecfidera might reduce the effectiveness of some vaccines. Live vaccines might carry an increased risk of clinical infection and should not be given to patients treated with Tecfidera unless, in exceptional cases, this potential risk is considered to be outweighed by the risk to the individual of not vaccinating. During treatment with Tecfidera, simultaneous use of other fumaric acid derivatives (topical or systemic) should be avoided. In humans, dimethyl fumarate is extensively metabolised by esterases before it reaches the systemic circulation and further metabolism occurs through the tricarboxylic acid cycle, with no involvement of the cytochrome P450 (CYP) system. Potential drug interaction risks were not identified from in vitro CYP-inhibition and induction studies, a p-glycoprotein study, or studies of the protein binding of dimethyl fumarate and monomethyl fumarate (a primary metabolite of dimethyl fumarate). Commonly used medicinal products in patients with multiple sclerosis, intramuscular interferon beta 1a and glatiramer acetate, were clinically tested for potential interactions with dimethyl fumarate and did not alter the pharmacokinetic profile of dimethyl fumarate. Administration of 325 mg (or equivalent) non enteric coated acetylsalicylic acid, 30 minutes prior to Tecfidera, over 4 days of dosing, did not alter the pharmacokinetic profile of Tecfidera and reduced the occurrence and severity of flushing in a healthy volunteer study. However, long term use of acetylsalicylic acid is not recommended for the management of flushing. Potential risks associated with acetylsalicylic acid therapy should be considered prior to co-administration with Tecfidera. Concurrent therapy with nephrotoxic medicinal products (such as aminoglycosides, diuretics, NSAIDs or lithium) may increase the potential of renal adverse reactions (e.g. proteinuria) in patients taking Tecfidera. Consumption of moderate amounts of alcohol did not alter exposure to Tecfidera and was not associated with an increase in adverse reactions. Consumption of large quantities of undiluted strong alcoholic drinks (more than 30% alcohol by volume) may lead to increased dissolution rates of Tecfidera and, therefore, may increase the frequency of gastrointestinal adverse reactions. In vitro CYP induction studies did not demonstrate an interaction between Tecfidera and oral contraceptives. In vivo interaction studies have not been performed with oral contraceptives. Even though an interaction is not expected, non hormonal contraceptive measures should be considered with Tecfidera. Paediatric population: Interaction studies have only been performed in adults. FERTILITY, PREGNANCY AND LACTATION: Pregnancy: There are no or limited amount of data from the use of dimethyl fumarate in pregnant women. Animal studies have shown reproductive toxicity. Tecfidera is not recommended during pregnancy and in women of childbearing potential not using appropriate contraception. Tecfidera should be used during pregnancy only if clearly needed and if the potential benefit justifies the potential risk to the foetus. Breast-feeding: It is unknown whether dimethyl fumarate or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue Tecfidera therapy. The benefit of breast-feeding for the child and the benefit of therapy for the woman should be taken into account. Fertility: There are no data on the effects of Tecfidera on human fertility. Data from preclinical studies do not suggest that dimethyl fumarate would be associated with an increased risk of reduced fertility. UNDESIRABLE EFFECTS: Flushing, diarrhea, nausea, abdominal pain upper, abdominal pain, ketones measured in urine, gastroenteritis, lymphopenia, leucopenia, burning sensation, hot flush, vomiting, dyspepsia, gastritis, gastrointestinal disorder, pruritus, rash, erythema, proteinuria, feeling hot, albumin urine present, aspartate aminotransferase increased, alanine aminotransferase increased, white blood cell count decreased, hypersensitivity. DATE OF REVISION OF THE TEXT: February 2016

Please refer to full prescribing information before prescribing.
(Ref. PI 2016_02 version)

References
1. Gold R, et al. N Engl J Med. 2012 Sep 20;367(12):1098-107; 2. TECFIDERA Prescribing Information. Feb 2016. UCB Pharma (Hong Kong) Ltd.

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388 Kwun Tong Road, Kwun Tong, Hong Kong
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Answers to Dermatological Quiz

Answer:

1. Sebaceous naevus
   The diagnosis is sebaceous naevus and can often be reached from its characteristic features clinically. It occurs equally in males and females and is usually noted at birth or in the early infantile stage. It is commonly found in the scalp but also on the face or neck and sometimes on the trunk and upper limbs. At birth, it presents as a solitary hairless yellow or tan patch. In adolescence, the lesion becomes more verrucous. The differential diagnoses include epidermal naevus, wart, seborrhoeic keratosis and aplasia cutis congenita.

2. Sebaceous naevus is benign and also known as organoid naevus which is not only a malformation of the sebaceous gland but a hamartoma including the entire skin malformation of epidermis, follicles, sebaceous and apocrine glands to varying degrees.

3. Most Sebaceous Naevi remain unchanged throughout life and do not cause any problem. So regular monitoring for any change of the lesion remains the standard approach of management. With time, another tumour may grow within the lesion. The most common one is trichoblastoma, others include trichilemmona, infundibular cyst, sebaceoma, eccrine poroma, and syringocystadenoma papilliferum. Previously, basal cell carcinoma and other carcinoma were alleged to develop in 10%. However, recent studies suggested that such malignant transformation appears to be closer to 1%. Therefore, biopsy is needed for any change in the sebaceous naevus and complete excision may be warranted in case of malignant change.

Dr Chi-keung KWAN
MBBS(HK), MRCP(UK), FHKCP, FHKAM(Med)
Specialist in Dermatology and Venereology

*By intent-to-treat analysis, virologic response of HBeAg- patients (n=375) and HBeAg+ patients (n=266) are 75% and 58% respectively at week 384. Total 14 hepatocellular carcinomas were found during the study period. The incidence rate of serious drug-related adverse events was 1.2% (n=7) among patients (n=585) who entered the open-label phases.[1]

† HBV DNA <69 IU/ml.

‡ Missing=excluded/addition of emtricitabine included

CHB=chronic hepatitis B; HBeAg=hepatitis B e-antigen; HBV=hepatitis B virus

Reference: 1. Marcellin P, Gane E, Flisiak R, et al. Long Term Treatment with Tenofovir Disoproxil Fumarate for Chronic Hepatitis B Infection is Safe and Well Tolerated and Associated with Durable Virologic Response with no Detectable Resistance 8 Year Results from Two Phase 3 Trials (QR-229). The Liver Meeting 2014: American Association for the Study of Liver Diseases (AASLD); 2014 November 7-11, 2014; Boston, MA, USA.

VIREAD Abbreviated Prescribing Information (Version: HK-OCT14-US-OCT13)

Presentation: Film-coated tablet containing 300 mg of tenofovir disoproxil fumarate (TDF). **Indications:** 1. Treatment of chronic hepatitis B (CHB) in adults. 2. In combination with other antiretroviral medicinal products for treatment of HIV-1 infected adults and pediatric patients 12 years of age and older. **Dosage:** Adults: One tablet once daily taken orally, without regard to food. **Pediatric patients:** CHB: Not recommended; HIV-1: One tablet once daily taken orally, without regard to food for patients ≥ 12 years of age and ≥35 kg. Elderly: Insufficient data to make dose recommendations for patients >65 years. The dosing interval of VIREAD should be adjusted in patients with baseline creatinine clearance <50 mL/min. **Warnings and Precautions:** Lactic acidosis/severe hepatomegaly with steatosis; severe exacerbation of hepatitis after discontinuation of anti-HBV treatment; new onset or worsening renal impairment; coadministration with products containing TDF or adefovir dipivoxil; patients coinfected with HIV-1 and HBV; decreases in bone mineral density; mineralization defects; fat redistribution; immune reconstitution syndrome; early virologic failure. **Interactions & Side effects:** refer to Package Insert. **Before prescribing, please consult full prescribing information which is available upon request.**

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