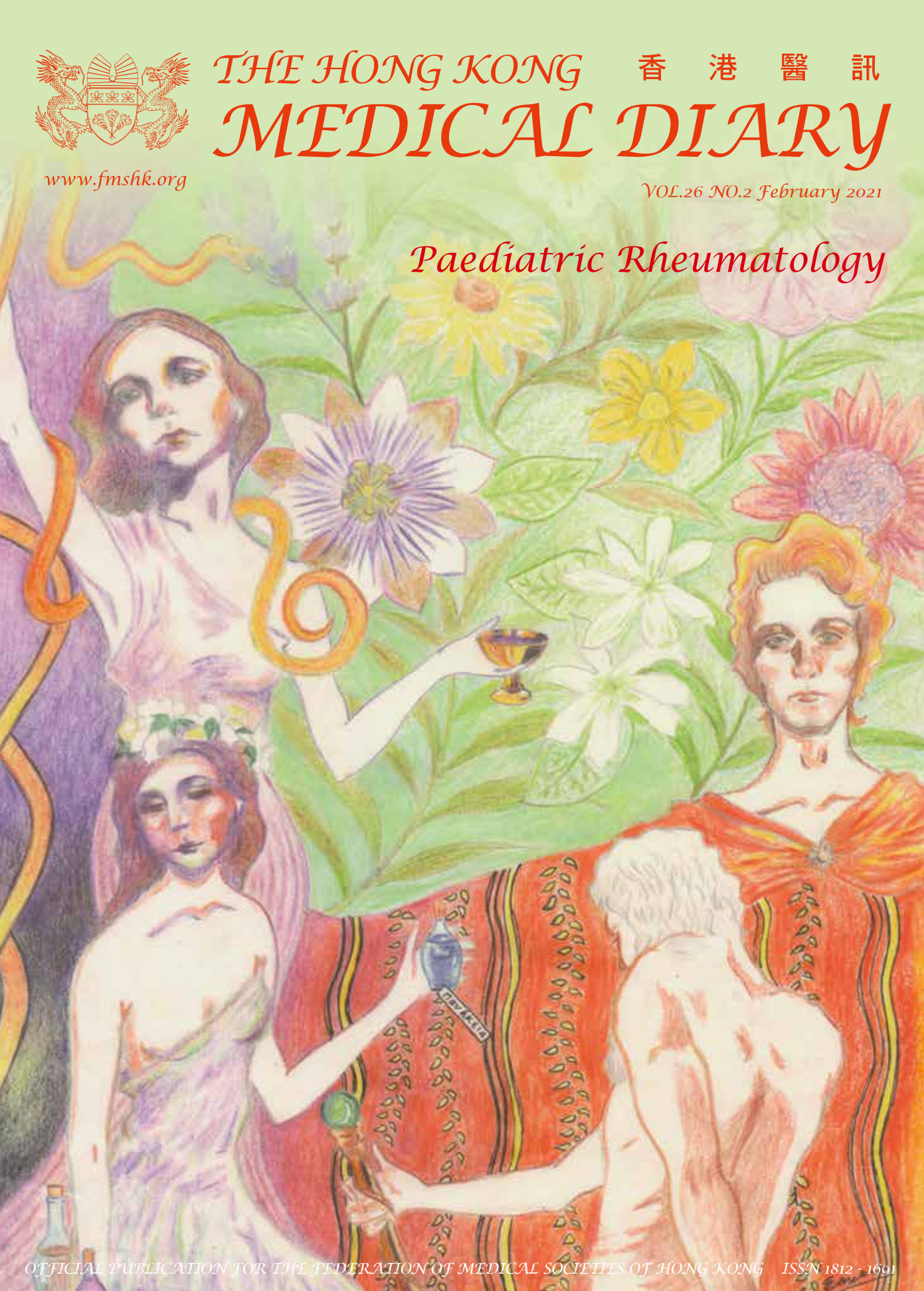
THE HONG KONG 香港醫訊
MEDICAL DIARY
www.fmshk.org
VOL.26 NO.2 February 2021

Paediatric Rheumatology



OFFICIAL PUBLICATION FOR THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG ISSN 1812 - 1691

Benlysta (belimumab)

Subcutaneous Use 200 mg/mL

gsk

The ONE & ONLY approved biologic for SLE treatment

New autoinjector for your patients

When standard therapy is not enough, why not choose BENLYSTA?

- Superior disease activity reduction at week 52[1*†‡]
- Reduced risk of severe SLE flares over 52 weeks[1§]
- Reduction in cumulative steroid dose over weeks 52[2¶]
- Rate of adverse events were similar between BENLYSTA and placebo[1]
- Emerging evidence on organ damage progression[3#]
- Fewer patients experienced renal flares vs standard therapy alone in patients with baseline proteinuria >0.5g/24 hrs[4^]

Physicians should exercise caution when considering the use of BENLYSTA in patients with chronic infections or a history of recurrent infection. Live vaccines should not be given for 30 days before, or concurrently with BENLYSTA[1].

BENLYSTA (belimumab)

Integrated Safety Information

Contraindications:

· Hypersensitivity to the active substance (belimumab) or to any of the excipients of the captioned product.

Warnings and Precautions:

· Not recommended in patients with severe active central nervous system lupus, severe active lupus nephritis, HIV, history of/current hepatitis B or C, hypogammaglobulinaemia (IgG <400mg/dl) or IgA deficiency (IgA <10mg/dl) and patients with a history of major organ transplant or hematopoietic stem/cell/marrow transplant or renal transplant.
· Caution in patients receiving other B cell targeted therapy or cyclophosphamide.
· Administration of BENLYSTA may result in hypersensitivity reactions and infusion reactions which can be severe, and fatal. In the event of a severe reaction, BENLYSTA administration must be interrupted and appropriate medical therapy administered.
· Physicians should exercise caution when considering the use of BENLYSTA in patients with severe or chronic infections or a history of recurrent infection Patients who develop an infection while undergoing treatment with BENLYSTA should be monitored closely and careful consideration given to interrupting immunosuppressant therapy including belimumab until the infection is resolved.
Patients should be monitored for any of these new or worsening symptoms or signs suggestive of progressive multifocal leukoencephalopathy (PML), and if such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until PML has been excluded.
· Live vaccines should not be given for 30 days before, or concurrently with BENLYSTA
· Caution should be exercised when considering belimumab therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy.

The following adverse events have been reported with a frequency of –

Very common (≥1/10): Bacterial infections, e.g. bronchitis, cystitis, Diarrhoea, Nausea
Common (≥1/100 to <1/10): Gastroenteritis viral, Pharyngitis, Nasopharyngitis, Leucopenia, Hypersensitivity reactions, Depression, Insomnia, Migraine, Pain in extremity, Infusion-related reactions, Pyrexia

Abbreviated Prescribing Information

BENLYSTA is a human IgG1λ monoclonal antibody specific for soluble human B Lymphocyte Stimulator protein (BlyS, also referred to as BAFF and TNFSF13B). **Indication:** As add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. positive anti-dsDNA and low complement) despite standard therapy. **Dosage and Administration:** BENLYSTA treatment should be initiated and supervised by a qualified physician experienced in the diagnosis and treatment of SLE. BENLYSTA Solution for injection Recommended dose is 200mg once weekly, administrated subcutaneously. Dosing is not based on weight. If a patient is being transitioned from BENLYSTA intravenous to subcutaneous administration, the first subcutaneous injection should be administrated 1 to 4 weeks after the last intravenous dose. The healthcare professional must provide proper training in subcutaneous technique and education about signs and symptoms of hypersensitivity reactions. A patient may self-inject or the patient caregiver may administrate BENLYSTA after the healthcare professional determines that it is appropriate. BENLYSTA Powder for concentrate for infusion Administered intravenously by infusion; must be reconstituted and diluted before administration. BENLYSTA infusions should be administered by a qualified healthcare professional trained to give infusion therapy. Administration of BENLYSTA may result in severe or life-threatening hypersensitivity reactions and infusion reactions several hours after the infusion has been administered. BENLYSTA should be administered in an environment where resources for managing such reactions are immediately available. Patients should remain under clinical supervision for a prolonged period of time (for several hours), following at least the first 2 infusions, taking into account the possibility of a late onset reaction. BENLYSTA should be infused over a 1-hour period. BENLYSTA must not be administered as an intravenous bolus. The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. The infusion must be discontinued immediately if the patient experiences a potentially life-threatening adverse reaction. **Contraindications:** Hypersensitivity to active substance (belimumab) or any excipients. **Special warnings & Precautions:** Not recommended in patients with severe active central nervous system lupus, severe active lupus nephritis, HIV, history of/current hepatitis B or C, hypogammaglobulinaemia (IgG <400mg/dl) or IgA deficiency (IgA <10mg/dl) and patients with a history of major organ transplant or hematopoietic stem/cell/marrow transplant or renal transplant. Caution in patients receiving other B cell targeted therapy or cyclophosphamide and patients with a history of malignancy or who develop malignancy whilst receiving treatment. Administration of BENLYSTA may result in hypersensitivity reactions and infusion reactions which can be severe, and fatal. In the event of a severe reaction, BENLYSTA administration must be interrupted and appropriate medical therapy administered. Risk of hypersensitivity reactions is greatest with the first two infusions or with the first two subcutaneous injections; however the risk should be considered for every administration. Patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk. Premedication including an antihistamine, with or without antipyretic, may be administered before infusion of BENLYSTA. There is insufficient knowledge to determine whether premedication could diminish the frequency or severity of infusion reactions. In clinical studies, serious infusion and hypersensitivity reactions affected approximately 0.9% of patients, and included anaphylactic reaction, bradycardia, hypotension, angioedema, and dyspnea. Infusion reactions occurred more frequently during the first two infusions and tended to decrease with subsequent infusions. Patients should be advised that hypersensitivity reactions are possible on the day of, or the day after infusion, and be informed of potential signs and symptoms and the possibility of recurrence. Patients should be instructed to seek immediate medical attention if they experience any of these symptoms. The package leaflet should be provided to the patient each time BENLYSTA is administered. Delayed-type, non-acute hypersensitivity reactions have also been observed and included symptoms such as rash, nausea, fatigue, myalgia, headache, and facial oedema. The mechanism of action of BENLYSTA could increase the risk for the development of infections, including opportunistic infections. Severe infections, including fatal cases, have been reported in SLE patients receiving immunosuppressant therapy, including belimumab. Physicians should exercise caution when considering the use of BENLYSTA in patients with severe or chronic infections or a history of recurrent infection. Patients who develop an infection while undergoing treatment with BENLYSTA should be monitored closely and careful consideration given to interrupting immunosuppressant therapy including belimumab until the infection is resolved. The risk of using BENLYSTA in patients with active or latent tuberculosis is unknown. Progressive multifocal leukoencephalopathy (PML) has been reported with BENLYSTA treatment for SLE. Physicians should be particularly alert to symptoms suggestive of PML that patients may not notice (e.g., cognitive, neurological or psychiatric symptoms or signs). Patients should be monitored for any of these new or worsening symptoms or signs, and if such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until PML has been excluded. Live vaccines should not be given for 30 days before, or concurrently with BENLYSTA, as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving BENLYSTA. Because of its mechanism of action, belimumab may interfere with the response to immunisations. However, in a small study evaluating the response to a 23-valent pneumococcal vaccine, overall immune responses to the different serotypes were similar in SLE patients receiving BENLYSTA compared with those receiving standard immunosuppressive treatment at the time of vaccination. Limited data suggest that BENLYSTA does not significantly affect the ability to maintain a protective immune response to immunisations received prior to administration of BENLYSTA. In a substudy, a small group of patients who had previously received either tetanus, pneumococcal or influenza vaccinations were found to maintain protective titres after treatment with BENLYSTA. Immunomodulatory medicinal products, including belimumab, may increase the risk of malignancy. Caution should be exercised when considering belimumab therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy. Patients with malignant neoplasm within the last 5 years have not been studied, with the exception of those with basal or squamous cell cancers of the skin, or cancer of the uterine cervix, that has been fully excised or adequately treated. **Interactions**: No interaction studies have been performed. **Pregnancy and lactation**: Limited data on use in pregnant women. Not to be used unless the potential benefit justifies the potential risk to the foetus. Not known whether BENLYSTA is excreted in human milk or absorbed after ingestion. Maternal IgG is secreted in breast milk so recommended to either discontinue BENLYSTA or breast feeding, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. **Undesirable effects**: See PI for full details. Very common: Bacterial infections, e.g. bronchitis, cystitis, urinary tract infection, Diarrhoea, Nausea. Common: Gastroenteritis viral, Pharyngitis, Nasopharyngitis, Viral upper respiratory tract infection, Leucopenia, Hypersensitivity reactions, Depression, Insomnia, Migraine, Injection site reactions, Pain in extremity, Infusion or injection related systemic reactions, Pyrexia. Uncommon: Anaphylactic reaction, Suicidal ideation, Suicidal behavior, Angioedema, Urticaria, Rash. Rare: Delayed-type, non-acute hypersensitivity reactions. **Overdose:** Limited clinical experience with overdose of BENLYSTA. In case of inadvertent overdose, patients should be carefully observed and supportive care administered, as appropriate. Please read the full prescribing information prior to administration. Full prescribing information is available on request from GlaxoSmithKline Ltd, 23/F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong. Abbreviated Prescribing Information based on PI version: BENLYSTA for infusion -GDS13v2/EMA20160915 and BENLYSTA for injection – GDS15/EMEA/HC/002015/II/0065.

References: 1. Benlysta SC Prescribing Information version GDS15v5. **2.** Zhang F, Bae SC, Bass D, et al. A pivotal phase III, randomised, placebo-controlled study of belimumab in patients with systemic lupus erythematosus located in China, Japan and South Korea. Ann Rheum Dis. 2018;77:355-63. **3.** Urowitz MB, Ohsfeldt RL, Wielage RC, et al. Organ damage in patients treated with belimumab versus standard of care: a propensity score-matched comparative analysis. Ann Rheum Dis. 2019;78(3):372-9. **4.** Stohl W, Schwarting A, Okada M, et al. Efficacy and safety of subcutaneous belimumab in systemic lupus erythematosus: a fifty-two-week randomized, double-blind, placebo-controlled study. Arthritis Rheumatol. 2017;69(5):1016-27.

Remarks: * Defined as positive anti-dsDNA (-30 IU/mL) and low C3 and/or C4 complement. † Standard therapies permitted, alone or in combination: corticosteroids, immunosuppressants, antimalarials, and NSAIDs. ‡ SRI4 improvement at Week 52: 61.4% vs 48.4% (p=0.0006). § 10.6% of patients on BENLYSTA + standard therapy vs 18.2% of patients on placebo + standard therapy had a severe flare over 52 weeks (p<0.0061). ¶ cumulative prednisone dose (or equivalent) over 52 weeks was significantly lower in the BENLYSTA group (4758.1mg) versus placebo (4190.0mg) (P=0.0005). # Patients receiving BENLYSTA were 61% less likely to progress to a higher SDI score over any given year of follow-up compared with patients treated with SoC (HR 0.391; 95% CI 0.253 to 0.605; p<0.001). ^ Fewer patients with baseline proteinuria >0.5 gm/24 hours in the BENLYSTA group (11 of 99) had a renal flare compared with those in the placebo group (13 of 48) (11.1% vs 27.1%; HR 0.40 [95% CI 0.18–0.90]; P=0.0272).

GlaxoSmithKline Limited
23/F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong Tel: (852) 3189 8989 Fax: (852) 3189 8931 hk.gsk.com

PM-HK-BEL-ADVT-190002
Date of preparation: 10/2019

Contents

Scan the QR-code

To read more about The Federation of Medical Societies of Hong Kong

Disclaimer

The Cover Shot

"The concept behind this painting revolves around the Greek gods and goddesses of healing: Apollo, Asclepius, Panacea and Hygieia (from right to left), and around some medicinal flowers including evening primrose, hawthorne and St. John's wort," says Ms Emika Suzuki.

The painting has been hand-drawn by Ms Emika Suzuki, one of our paediatric rheumatology patients, who has a flair for the linguistics and arts. She is currently interning for a magazine.

Ms Emika Suzuki

Dr Roanna YEUNG
MBBS, MRCPCH, FHKAM (Paeds)
Honorary Treasurer, Hong Kong Society for Paediatric Rheumatology

Published by
The Federation of Medical Societies of Hong Kong

The welcome message of the Chinese New Year of Ox

Dr Mario WK CHAK

President
The Federation of Medical Societies of Hong Kong

Dr Mario WK CHAK

送鼠迎牛，庖丁解牛！
祝大家牛年進步！一團和氣！身體健康！

庖 here means the cook. 丁 (Ding) is a person's name. 解 means to dissect something. 牛 is an ox. We use this phrase to indicate that someone can do his work with a kind of magical, skillful craftsmanship just like the cook Ding. Such a person is highly respected by people thanks to his professionalism. Although written many years ago, this proverb 「庖丁解牛」continues to convey words of great wisdom and a moral message today in how to face the challenges of COVID-19.

The pandemic of COVID-19, no doubt, is a threat to humanity, considering the state of emergency declared by the World Health Organization as a result of the rapid spread and severity of the deadly virus across the globe. On the other hand, the COVID-19 pandemic also gives rise to great opportunities in scientific and clinical research, as well as in technological innovation, with the goal of assisting frontline healthcare workers in battles to eradicate the pandemic, and of facilitating the general public to identify ways to prevent and control the rapid spread of the virus.

In an auspicious gesture to welcome the Chinese New Year, I would like to share with you what the Federation has accomplished in the past year.

Due to the COVID-19 pandemic, several projects have been suspended in 2020, namely the charity project for children in need and public talks to the community; but the momentum of advocating and promoting medical care has kept rolling.

With the aim to better gauge the COVID-19 infection situation in Hong Kong and to dig out asymptomatic patients as early as possible to achieve early identification, early isolation and early treatment, and to cut off virus transmission in the community, the Universal Community Testing Programme(UCTP), a virus testing offered to all Hong Kong residents free of charge, was held between 1-14 September 2020 at 141 centres set up in 18 districts. A total of about 1,783,000 people participated in the UCTP and went through the massive testing for COVID-19. Thanks to the support from our member societies and friends, the Federation successfully recruited over 130 healthcare professionals and para-professionals to provide swabbing service to the public. A Federation Team was set up with 67 healthcare professionals and para- professionals to manage the service centre at the Lockhart Road Sports Centre between 1-7 September 2020 and the Hong Kong City Hall between 7-14 September 2020. Over 11,502 tests were done by the Federation Team at the above centres.

During the COVID-19 pandemic, most of our regular events and meetings have been suspended especially in the first half of 2020. Through tremendous efforts, we have transformed our on-site events, courses and seminars into web-based activities successfully. In the second half of year, with the support of member societies and their

members, the Federation organised a number of web-based professional projects/activities, including online certificates courses, symposia, conferences and annual scientific meetings.

As a result of the COVID-19 pandemic, all certificate courses in 2020 were conducted in pre-recorded video format; participants were allowed to watch the videos within three days, with a maximum of 3 times login and access allowed for each video link. It gives a lot of flexibility to the healthcare professionals as they were allowed to continue their learning after a busy workday. Fourteen video courses were held from February to December 2020. The topics during this year ranged diversely and spanned across different disciplines from Cardiology, Allergy, Communication and Swallowing Problems in the Elderly Population, Clinical Cytogenetics and Genetics, Complaint Management, Mental Health, Ophthalmology, Renal Medicine, Respiratory Medicine, Ultrasound Diagnostics of Fetal Anomalies, to Update in Clinical Sleep Medicine and Clinical Toxicology. All were well organised and well attended with encouraging turnout. I would like to profusely thank our healthcare professionals for their robust support.

Owing to the unlimited quotas for enrollment, the total number of participants has increased by 27 percent compared to that of 2019. Over 80 percent of participants preferred to stay with the video format even when the epidermic is over.

One of the services greatly appreciated by our member societies is our meeting- and conference-organising services. In the face of the COVID-19 pandemic, the Federation has extended our services to the organisation of web-based events; for example, webinars, online AGMs, pre-recorded video lectures, and so forth in an effort to support our member societies and medical professionals. We provide support in the 28th annual scientific congress organised by The Hong Kong College of Cardiology and the AGM and scientific meeting of The Hong Kong Society of Child Neurology and Developmental Paediatrians. All these cyber meetings were well attended by members and fellow professionals.

For the Hong Kong Medical Diary, apart from the usual monthly issue on different specialties and subspecialties, a special issue on COVID-19 was published in January 2021 to highlight hot topics related to immunity, intensive care, new treatment and vaccine of COVID-19.

Finally, I would like to thank, for your great efforts and staunch support in the year 2020, our Officers, EXCO members, Foundation directors, council members and staff of the secretarial board. We could not have succeeded without your collaboration. Riding on your continued support for and contribution to the Federation, we are confident in further excelling in the forthcoming Chinese New Year of the Ox.

We look forward to working alongside you all in the near future.

Once again, on behalf of the Federation, I wish you and your family all the best, and may you all have a happy, healthy, wealthy and prosperous Chinese New Year of the Ox.

SANDOZ BIOSIMILARS

More than a decade of experience

Pioneer Leader in Biosimilars

- With **EIGHT marketed products** and a strong pipeline in **Oncology and Immunology**[1]
- Driving worldwide recognition of biosimilars as safe and effective medicines
- Repeatedly innovating to break new ground[1], launched the first biosimilar in:

2006	2009	2015
Omnitrope® Somatropin 3.3mg/ml	Omnitrope® Somatropin 3.3mg/ml	ZARZIO® filgrastim

World-class Expertise

In development, manufacturing and delivery of biosimilars to the healthcare community and patients

ANALYTICAL | CLINICAL | MANUFACTURING | REGULATORY

Unparalleled Heritage Longer than Any Other Company

- Biotechnology experience dating back to the 1940s[1]
- **Over 20 years** of experience in biosimilar development[1]

References: 1. Data on file.

SANDOZ A Novartis Division

Novartis Pharmaceuticals (HK) Ltd
7/F, Citi Tower, One Bay East, 83 Hoi Bun Road, Kwun Tong, Kowloon, Hong Kong
Tel: (852) 2882 5222 Fax: (852) 2577 0274

03-2020-HK-COMB-PRL-646/2-V1

Editorial

Dr Winnie Kwai-yu CHAN

President
Hong Kong Society for Paediatric Rheumatology

Editor

Dr Winnie Kwai-yu CHAN

Our Society is excited to take this opportunity to share with the readers of the Hong Kong Medical Diary an update on various diseases in Paediatric Rheumatology. We hope to raise our colleagues' awareness of rheumatic diseases in children through these snapshot articles. These problems are common in the adult population, and they could inflict children too. The presentations may be subtle, and the diagnosis may be challenging to arrive at initially. Without a high index of suspicion, the window of opportunity to treat may be missed.

Paediatric Rheumatology is one of the newest and least populated paediatric subspecialties, coming slowly to the attention of medical professionals after the Second World War. Along with the realisation that rheumatic diseases in children are distinct, the burgeoning of new technology, and the advent of modern medications, the organisation of Paediatric Rheumatology as a subspecialty blossomed since the 1970s[1]. At present, Paediatric Rheumatology is a developed subspecialty in many countries and continues to thrive with the support from two large international networks, the Paediatric Rheumatology Collaborative Study Group (PRCSG) and the Paediatric Rheumatology International Trials Organisation (PRINTO)[2].

In this issue, members of our Society will try to cover a wide variety of rheumatic diseases in childhood. "Joint pain" is a common complaint in children. Often, the discomfort may not be arising from genuine arthritis, and the patient may not be able to give a consistent history. Acute arthritis can be disabling and is not merely an orthopaedic problem. Dr SY Kong will discuss the clinical approach to this common encounter. Differential diagnosis and management aspects are addressed. Ten CME questions have been set, and our readers can quickly get a full mark after reading her article. Juvenile Idiopathic Arthritis (JIA) is the most familiar rheumatic disease worldwide. The diagnosis embraces several clinical entities. Dr Roanna Yeung will discuss one of the most typical JIA subtypes that we frequently encounter in our Rheumatology clinics - enthesitis-related arthritis (ERA). This category is unique in children, and interestingly is related to various chronic arthritis types in the adult population. ERA is a challenging subtype of JIA to many paediatric rheumatologists. With the advancement in technology, biologics have become a cornerstone in the management of children with rheumatic disease. Dr Assunta Ho will give a brief account on the biologic DMARDs used in children with JIA. Possible complications, side effects and safety concerns are discussed.

ANCA-vasculitis, on the other hand, is a relatively rare rheumatic disease in children. It may present acutely as an organ-threatening scenario. High level of suspicion with prompt treatment is life-saving. Dr Grace Chiang will lead us through this challenging topic and highlight the critical issues. Comparing with ANCA-vasculitis, systemic lupus erythematosus (SLE) is relatively more common, and differs from its adult counterpart in several ways. Childhood-onset SLE carries a poorer prognosis than adults. The impact on growth and puberty could cause severe morbidity. Adherence to medical treatment during the adolescent period is a universal challenge. A brief overview of this topic, and short notes on various management approach will be highlighted in the "Overview of Childhood-onset Systemic Lupus Erythematosus".

Life is always exciting and fascinating. Dr Karen Lau, a paediatrician full of artistic ability, will lead us to explore the City's weekend markets, where you can find fine works of art, painting, drawing, crafts, and a lot more. It is an excellent way to immerse in the local culture. "Small shops with big ideas" is the theme of these weekend markets and likewise despite our Society being a small subspecialty, we are dedicated to improving the health care of children with rheumatic disease.

References

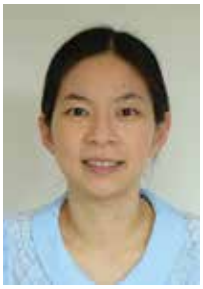
1. Schaller, Jane G. "The history of pediatric rheumatology." Pediatric research 58.5 (2005): 997.
2. Ruperto, Nicolino, and Alberto Martini. "Networking in paediatrics: the example of the Paediatric Rheumatology International Trials Organisation (PRINTO)." Archives of disease in childhood 96.6 (2011): 596-601.

Acute Arthritis in Children

Dr KONG Sum-yi

MBChB, MRCPCH, FHKAM, FHKCPaed

Honorary Secretary, Hong Kong Society for Paediatric Rheumatology



Dr KONG Sum-yi

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 28 February 2021.

INTRODUCTION

Musculoskeletal pain is a common complaint in the child and the adolescent. Not all patients with complaints of "joint pain" have pathology at the joint (articular vs non-articular musculoskeletal pain) and not all patients having articular joint pain (arthralgia) have arthritis (inflammatory vs non-inflammatory joint pain). This article will focus on acute inflammatory arthritic conditions in children.

DEFINITION

Arthritis is defined as swelling within a joint, or limitation in the range of joint movement associated with joint pain or tenderness[1].

GENERAL APPROACH

Pattern recognition is of utmost importance during clinical evaluation to differentiate among the various conditions. History taking should cover the onset and duration of symptoms, site and pattern of joint involvement, precipitating factors, fever, any antecedent illness and systemic review of associated complaints. Chronic arthritis can present as sudden onset of painful and swollen joints. Such abrupt presentation may be mistaken as acute arthritis due to trauma or infection. Morning stiffness is a frequent complaint in the adult patient with rheumatoid arthritis, manifested as soreness and restriction in movement upon awakening. It is believed to be the result of fluid accumulation within the inflamed tissue during sleep. It eases up after the joints are used for a while. It is a cardinal sign of inflammatory arthritis; however, it may be difficult to get this bit of information in young children.

Physical assessment should involve both focused joint assessment and systemic clinical examinations. Positive systemic signs are informative in arriving at the diagnosis. Pediatric Gait Arms Legs and Spine (pGALS) is a useful screening tool for children's musculoskeletal system[2]. It provides a fundamental skill for general practitioners to detect early sign(s) of joint disease in children. It has been validated in school-aged children and in the setting of general paediatrics.

DIFFERENTIAL DIAGNOSIS OF ACUTE ARTHRITIS

The differential diagnosis can be categorised according to whether the pathological process has arisen from an inflammatory versus non-inflammatory origin. Inflammatory arthritis can be caused by an infective agent or as a result of an immune-mediated reaction. The causes are summarised in Table 1.

Table 1: Differential diagnoses of musculoskeletal pain in children (Summarised from Singh S, Mehra S. Approach to polyarthritis. Indian J Pediatr. 2010 Sep; 77 (9): 1005-10 Prabhu AS, Balan S. Approach to a child with monoarthritis. Indian J Pediatr. 2010 Sep 77 (9) 997-1004)

Arthritis (inflammatory articular joint pain)	**Infectious arthritis:** - Septic arthritis - Viral arthritis: Parvovirus B19, hepatitis viruses, rubella, HIV, EBV, VZV, Mumps, CMV, HSV, adenovirus, coxsackieviruses, alphaviruses, Chikungunya virus - Lyme disease **Non-infectious arthritis:** - Idiopathic: transient synovitis - Post-infectious / Reactive arthritis: acute rheumatic fever, post-streptococcal reactive arthritis, preceding episode of respiratory, gastrointestinal or genitourinary infection - Rheumatological conditions: juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), juvenile dermatomyositis (JDM), Behçet disease - Systemic vasculitides: Kawasaki disease (KD), Henoch-Schonlein purpura (HSP) - Neoplastic: leukaemia - Miscellaneous: serum sickness, sarcoidosis
Non-inflammatory articular joint pain	Trauma: accidental, non-accidental Haematological: acute haemarthrosis Osteonecrosis: Legg-Calvé-Perthes disease Osteochondrosis: Osgood Schlatter disease Idiopathic/ unclassified: Slipped capital femoral epiphysis
Non-articular musculoskeletal pain	Idiopathic: Growing pain, fibromyalgia, etc Neoplasm: leukaemia, osteosarcoma, osteoid osteoma Vaso-occlusive pain in sickle cell disease

Septic Arthritis

Septic arthritis is a more common musculoskeletal infection than osteomyelitis. It happens at any age with a peak before the age of 6 years. The majority (~ 80%) involves joints of the lower limb with hip and knee being the most common sites. Up to 10% of cases have more than one joint involvement. It presents acutely in 2 to 5 days with high fever, constitutional symptoms (e.g., irritability, poor feeding) and severe continuous arthralgia. Clinically there will be significant periarticular symptoms with effusion and limited range of movement. Inflammatory markers are usually raised, and a normal C-reactive protein (CRP) carries an excellent negative predictive value (87%) for septic arthritis[3]. Increased joint space in the plain radiograph is usually not sensitive nor useful at the initial stage. Ultrasound (USG) is sensitive in detecting effusion and is used to assist in synovial fluid aspiration. Magnetic resonance imaging (MRI) gives additional information for joint destruction and changes of osteomyelitis. Diagnosis is confirmed via a positive culture from the synovial fluid analysis. Prompt treatment is crucial to minimise long-term damage to the bones and joint. Surgical drainage and lavage for decompression and removal of inflammatory debris can be performed to preserve synovium and collagen matrix. Antibiotics covering S. aureus (the most common pathogens in children) should be initiated empirically and subsequent choice of agents is directed by pathogens isolated. Duration of antibiotic treatment is usually two to three weeks. Complications rate are high in those with delayed diagnosis (duration of symptoms more than 4 to 7 days), deep joint involvement (e.g. hip and shoulder), young age (infants less than one year old, particularly neonates)[4,5,6].

Transient Synovitis

Transient synovitis is one of the commonest non-infectious acute arthritis in children usually seen in age 3 to 8 years old with the hip being the commonest site of involvement. It presents as limping gait in the absence of high fever. Weight bearing can still be possible, and half of them have preceding upper respiratory tract infection. The exact cause is unknown, and the pathology shows non-specific synovitis. It is important to exclude septic arthritis as their treatment and outcome are different. The presence of high fever, non-weight bearing, erythrocyte sedimentation rate of > or = 40 mm/hour, white cell counts > 12,000 cells/mL (> 12 x 10^9/L) predict a higher probability of septic arthritis vis-a-vis transient synovitis[7,8]. Management includes non-steroidal anti-inflammatory drugs (NSAID), bed rest and hip traction. Follow-up radiograph at six months is suggested as 1.5% of these patients develop Legg-Calvé-Perthes disease.

Reactive Arthritis

Reactive arthritis or post-infection arthritis is an inflammatory joint condition triggered by gastrointestinal infection (e.g. *Yersinia, Salmonella, Shigella, Campylobacter*) or genitourinary infection (Chlamydia trachomatis) without evidence of septic process at the joint. The reactive arthritis may be associated with conjunctivitis, uveitis, rash, and urethritis. If obtained, synovial fluid white cell count usually is < 50,000 cells/mL. Prevalence and worse prognosis are seen associated with HLA-B27, but the exact mechanism is unknown. Initial treatment would be pain control by NSAID. Refractory cases may require consideration of glucocorticoids (either intraarticular or systemic). The prognosis is generally good, and the arthritis usually resolves without any sequela in 97 to 99 per cent of cases.

Post-streptococcal Arthritis

Group A beta-haemolytic Streptococcus is well-known in causing several post-infectious, non-suppurative immune-mediated diseases. Acute rheumatic fever and post-streptococcal arthritis are two of these diseases which may present with arthritis in the early course. Arthritis typically occurs 7-10 days after the streptococcus infection, or the patient may have a preceding sore throat. The knees, ankles, hips and wrists are commonly involved. The arthritis is not migratory, and other features of Jone's Criteria for Acute Rheumatic fever is absent. The joint pain may persist and recur. A raised ASOT or positive streptococcus culture helps in making the diagnosis. These patients may need monitoring for any carditis.

Lyme Disease-related Arthritis

Borrelia burgdorferi, the spirochete causing Lyme disease, is spread by tick (*Ixodes spp*) found in the temperate zone of the northern hemisphere. Symptoms begin with an influenza-like illness day to weeks following a tick bite with or without associated arthralgia. Erythema migrans, an enlarging warm painless erythematous rash, may follow. Neuroborreliosis with facial nerve palsy and aseptic meningitis may develop weeks to months later following the infection. Arthritis, commonly intermittent monoarthritis, can occur months to years following the tick bite. Acute Lyme arthritis can be treated with oral doxycycline at 4.4 mg/kg/day, amoxicillin at 50 mg/kg/day or cefuroxime at 30 mg/kg/day for 10 to 14 days. Managing Lyme arthritis is sometimes difficult as the characteristic clinical features are only seen in 40-70% of patients and the serology test is at times difficult to interpret given its high incidence of false positivity.

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is a common form of acute arthritis with a chronic course in children diagnosed at the age younger than 16 years with symptoms lasting for more than six weeks. It is further sub-classified into six categories depending on the pattern of involvement and systemic features[1]. The categories are systemic JIA, polyarticular JIA (rheumatoid factor positive or negative), oligoarticular JIA (persistent or extended), enthesitis-related arthritis (ERA), psoriatic arthritis and undifferentiated arthritis. Serology testing in JIA helps to classify the different types of JIA. RF positivity is mostly seen in the polyarticular course and may mimic rheumatoid arthritis of the adult. Positive antinuclear factor (ANF) is associated with risk of uveitis; HLA-B27 positivity is related to ERA and spondyloarthropathy. The prognosis and treatment considerations depend on the disease categories.

Systemic onset JIA is a distinct type of JIA. It frequently presents as extra-articular symptoms with high swing fever in a quotidian pattern, evanescent erythematous rash, and lymphadenopathy. Macrophage activation syndrome is a severe complication in, particularly systemic-onset JIA.

CONCLUSION

Musculoskeletal pain in children comprises a wide range of conditions from benign and transient to chronic and malignant. Pattern recognition from detailed history and comprehensive clinical assessment is required to decide on optimal investigation plan and treatment regimen.

References

1. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, He X, Maldonado-Cocco J, Orozco-Alcala J, Prieur AM, Suarez-Almazor ME, Woo P; International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004 Feb;31(2):390-2.
2. Foster, H.E., Jandial, S. pGALS – paediatric Gait Arms Legs and Spine: a simple examination of the musculoskeletal system. Pediatr Rheumatol 2013;11: 44.
3. Levine MJ, McGuire KJ, McGowan KL, Flynn JM. Assessment of the test characteristics of C-reactive protein for septic arthritis in children. J Pediatr Orthop. 2003 May-Jun;23(3):373-7.
4. Lunseth PA, Heiple KG. Prognosis in septic arthritis of the hip in children. Clin Orthop Relat Res. 1979 Mar-Apr;(139):81-5.
5. Li Y, Zhou Q, Liu Y, Chen W, Li J, Yuan Z, Yong B, Xu H. Delayed treatment of septic arthritis in the neonate: A review of 52 cases. Medicine (Baltimore). 2016 Dec;95(51):e5682
6. Sukswai P, Kovitvanitcha D, Thumkunanon V, Chotpitayasunondh T, Sangtawesin V, Jeerathanyasakun Y. Acute hematogenous osteomyelitis and septic arthritis in children: clinical characteristics and outcomes study. J Med Assoc Thai. 2011 Aug;94 Suppl 3:S209-16.
7. Kocher MS, Zurakowski D, Kasser JR: Differentiating between septic arthritis and transient synovitis of the hip in children: An evidence-based clinical prediction algorithm. J Bone Joint Surg Am 1999; 81:1662.
8. Luhmann, Scott J.; Jones, Angela; Schootman, Mario; Gordon, J. Eric; Schoenecker, Perry L.; and Luhmann, Jan D., ,Differentiation between septic arthritis and transient synovitis of the hip in children with clinical prediction algorithms. The Journal of Bone and Joint Surgery 2004; 86: 956-962.

Radiology Quiz

Radiology Quiz

Dr Leanne Han-qing CHIN

MBBS, FRCR

Dr Leanne Han-qing CHIN

Case history:

A 16-year-old boy with good past health presented to the General Out-Patient Clinic for persistent pain and weakness of his left arm **for two weeks**, despite having sought treatment from a bonesetter. He volunteered a history of **left sided** shoulder injury one month ago during sudden deceleration of a bus ride whilst holding onto a handrail. Physical examination revealed mild tenderness with limited left arm abduction, and limited internal and external rotation. X-ray of the left shoulder is shown here.

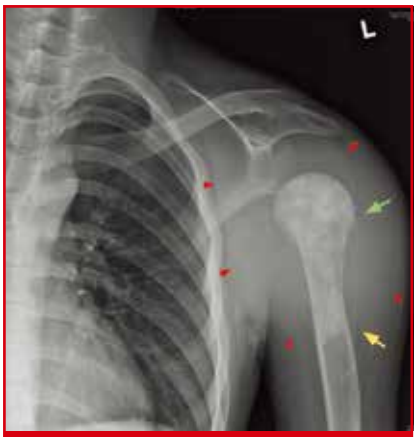


Fig 1. X-ray left shoulder (AP view)

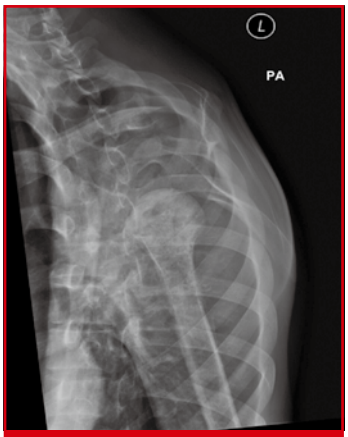


Fig 2. X-ray left shoulder (transcapular view)

Questions

1. Is the shoulder alignment normal?
2. Is the bone normal?
3. What specific abnormal periosteal reactions are seen?
4. What are the possible differential diagnoses?
5. What is the next step of management?

(See P.32 for answers)

MCHK CME Programme Self-assessment Questions

Please read the article entitled "Acute Arthritis in Children" by Dr KONG Sum-yi 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 28 February 2021. 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. **Painful joint conditions in children are always inflammatory in origin.**
2. **Morning stiffness is a sign of inflammatory arthritis.**
3. **pGALS is a screening tool used in musculoskeletal assessment in children.**
4. **Acute arthritis in children requires antibiotic treatment when associated with fever.**
5. **Acute arthritis with positive ASOT is always acute rheumatic fever.**
6. **Lyme disease is common in Hong Kong.**
7. **Tics are the vector for transmission of Lyme disease.**
8. **Post-streptococcal infection can cause arthritis without carditis.**
9. **Defining the categories of juvenile idiopathic arthritis is vital in treatment planning.**
10. **Arthritis may not be the presenting features in systemic-onset JIA.**

ANSWER SHEET FOR FEBRUARY 2021

Please return the completed answer sheet to the Federation Secretariat on or before 28 February 2021 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Acute Arthritis in Children

Dr KONG Sum-yi

MBChB, MRCPCH, FHKAM, FHKCPaed

Honorary Secretary, Hong Kong Society for Paediatric Rheumatology

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Name (block letters):_____ HKMA No.: _____ CDSHK No.: _____

HKID No.: __ __ - __ __ __ __ X X (X) HKDU No.: _____ HKAM No.: _____

Contact Tel No.:_____ MCHK No. / DCHK No.: _____(must fill in)

Answers to January 2021 Issue

COVID-19 Re-infection, Two Contrasting Cases, and Many More to Come

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

REDEFINING EXPECTATIONS
For Those At Risk Of Cardiovascular Events

15% reduction in MACE
HR (95% CI), 0.85 (0.78-0.93)
(Primary composite endpoint)[1,2,‡]

Reduction in:		Hazard Ratio (95% CI)
Non-fatal MI[†,§]	14%	0.86 (0.77, 0.96)
Fatal / Non-fatal Ischemic stroke[†,§]	27%	0.73 (0.57, 0.93)
UA requiring hospitalization[†,§]	39%	0.61 (0.41, 0.92)

15% reduction in All-Cause Mortality[†,§]
HR (95% CI), 0.85 (0.73, 0.98)
(Secondary endpoint)[1,2]

Label update for prevention of CV events in established cardiovascular disease patients*‖

Safety Data[1]:
Adverse events include nasopharyngitis, injection site reactions, influenza, urinary tract infection, diarrhea, bronchitis, myalgia, muscle spasms, sinusitis, cough, contusion and musculoskeletal pain, which were reported in at least 2% of PRALUENT®-treated patients, and more frequently than in placebo-treated patients.

* PRALUENT® is indicated to reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease. PRALUENT® is also indicated as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia to reduce low-density lipoprotein cholesterol (LDL-C).
† Statistical testing performed outside hierarchy; therefore not considered statistically significant.
‡ Primary composite endpoint of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization.
§ Major secondary end points (HR, 95% CI), in order of hierarchical testing, include any coronary heart disease event (0.88, 0.81-0.95), major coronary heart disease event (0.88, 0.80-0.96), any cardiovascular event (0.87, 0.81-0.94), composite of death from any cause, nonfatal myocardial infarction, or nonfatal ischemic stroke (0.86, 0.79-0.93), death from coronary heart disease (0.92, 0.76-1.1), the hierarchical analysis was stopped after the first nonsignificant P value was observed, in accordance with the hierarchical testing plan), death from cardiovascular causes (0.88, 0.74-1.05) and death from any cause (0.85, 0.73-0.98). To adjust for multiplicity, the results of the main secondary end points were to be tested in hierarchical fashion in the sequence listed above if the risk of the composite primary end point was found to be significantly lower in the alirocumab group than in the placebo group.

Study Design[1,2]
ODYSSEY OUTCOMES is a multicenter, randomized, double-blind, placebo-controlled trial involving 18,924 patients who had an acute coronary syndrome 1 to 12 months earlier, had a low-density lipoprotein (LDL) cholesterol level of at least 70 mg per deciliter (1.8 mmol per liter), a non–high-density lipoprotein cholesterol level of at least 100 mg per deciliter (2.6 mmol per liter), or an apolipoprotein B level of at least 80 mg per deciliter, and were receiving statin therapy at a high-intensity dose or at the maximum tolerated dose. Patients were randomly assigned to receive alirocumab subcutaneously at a dose of 75 mg (9462 patients) or matching placebo (9462 patients) every 2 weeks. The dose of alirocumab was adjusted under blinded conditions to target an LDL cholesterol level of 25 to 50 mg per deciliter (0.6 to 1.3 mmol per liter).
MACE=major adverse cardiovascular events. MI=myocardial infarction. UA=unstable angina. PCSK9=Proprotein convertase subtilisin/kexin type 9. CVD=cardiovascular disease. HeFH=Heterozygous Familial Hypercholesterolemia.

Reference:
1. Praluent® Prescribing Information. Mar 2020. 2. Schwartz GG, et al. N Engl J Med. 2018;379:2097-2107.

Presentation: Alirocumab solution for injection. Indications: Prevention of Cardiovascular Events: Reduce risk of myocardial infarction, stroke and unstable angina requiring hospitalization in adults with established cardiovascular disease. Primary Hyperlipidemia: As an adjunct to diet, alone or in combination with other lipid-lowering therapies, for the treatment of adults with primary hyperlipidemia to reduce LDL-C. Dosage: 75 mg once every 2 weeks administered subcutaneously. An alternative starting dosage for patients who prefer less frequent dosing is 300 mg once every 4 weeks. If the LDL-C response is inadequate, the dosage may be increased to the maximum dosage of 150 mg administered every 2 weeks. Contraindications: History of serious hypersensitivity reaction to alirocumab. Precautions: Hypersensitivity reactions. Pregnancy and Lactation: There are no available data on use of alirocumab in pregnant women to inform a drug-associated risk. There is no information regarding the presence of alirocumab in human milk, the effects on the breastfed infant, or the effects on milk production. Undesirable effects: Nasopharyngitis, injection site reactions, influenza, urinary tract infection, diarrhea, bronchitis, myalgia, muscle spasms, sinusitis, cough, contusion, musculoskeletal pain, flu-like illness, angioedema. For other undesirable effects, please refer to the full prescribing information. Preparation: 1 x 75mg/ml prefilled pen, 1 x 150mg/ml prefilled pen. Legal Classification: Part 1, First & Third Schedules Poison Full prescribing information is available upon request.
API-HK-ALI-20.07

MAT-HK-2000222-1.0-10/2020 4IC_1332

SANOFI
Sanofi Hong Kong Limited
1/F & Section 212 on 2/F, AXA SOUTHSIDE,
38 WONG CHUK HANG ROAD, WONG CHUK HANG, HONG KONG
http://www.sanofi.hk/

Praluent®
alirocumab

Aptamil 白金版

Allecure Pepti Syneo 舒敏配方

95% users agreed with improvement in allergy symptoms#

- Most recommended by HCPs for CMPA management*
- Most pleasant taste*

For more information: 3509 2008 1000days@nutricia.com.hk

CMPA: cow's milk protein allergy
* According to 2019 survey conducted by Kantar HK Market Research Company. Respondents are healthcare professionals. Sample size (n=59).
\# According to survey conducted by Kantar HK Market Research company. Respondents are users recommended by HCPs. Sample size (n=61). Aug 2020.

Formula for special medical purposes. Use under medical supervision.

For HCP use only, not for distribution to the general public

Understanding Enthesitis-related Arthritis

Dr Roanna Hoi-man YEUNG

MBBS, FHKCPaed, FHKAM

Honorary Treasurer, Hong Kong Society for Paediatric Rheumatology

Dr Roanna Hoi-man YEUNG

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children. In the Caucasian population, the incidence of JIA is 16-150 per 100,000[1]. It refers to a heterogeneous group of arthritis with onset in the paediatric age group before the 16th birthday, running a chronic course of more than six weeks, with other known medical causes excluded. The latest accepted classification of JIA was published by the International League of Associations for Rheumatology (ILAR) in 1997, which was further revised in 2001. Under this classification system, JIA is divided into seven mutually exclusive subgroups: systemic arthritis, oligoarthritis (persistent and extended forms), rheumatoid factor-positive polyarthritis, rheumatoid factor-negative polyarthritis, psoriatic arthritis, enthesitis-related arthritis (ERA) and undifferentiated arthritis[2]. The ILAR definition of ERA is outlined in table 1.

Table 1. Definition of ERA from International League of Associations for Rheumatology (ILAR), 2004. Excerpted from Petty RE et al[2]

Enthesitis-related arthritis (ERA) is defined as:

- Arthritis and enthesitis, OR
- Arthritis or enthesitis, with at least two of the following: sacroiliac joint tenderness and/or inflammatory spinal pain, presence of HLA B27, the onset of arthritis in a male over 6 years old, family history of at least one first degree relative with ankylosing spondylitis, ERA, or inflammatory-bowel disease-associated sacroiliitis
- Acute symptomatic anterior uveitis

The exclusion criteria are: the presence of psoriasis or a history of psoriasis inpatient or a first-degree relative, presence of rheumatoid factor IgM on at least two occasions that are at least 3 months apart, or presence of systemic arthritis.

EPIDEMIOLOGY

Incidence of ERA varies worldwide. In general, it is quoted that 10-20% of JIA patients have ERA[3]. However, it has been noted that in patients of Asian descent, particularly in Chinese, ERA remains to be the most common subtype. A retrospective review in Taiwan reported that ERA was the single largest category with an incidence close to 40%[4]. A recently-published Singaporean JIA registry also found ERA to be the most common JIA subtype accounting for 33% of all their JIA patients[5]. A Canadian study involving patients from multiple ethnic descents also confirms this fact[6]. As one would expect, after going through the ILAR definition, male preponderance is observed in ERA, with the proportion as high as 80%[4]. Older age of onset is also observed in ERA patients, and a recently published series found the mean age of onset or diagnosis to be 10-15 years of age[7].

HLA B27 POSITIVITY

HLA B27 positivity is also observed in the majority of ERA patients. A Polish study found HLA B27 positivity in around one-third of all JIA patients, and 71% of ERA patients had HLA B27 positivity[8]. The aforementioned Taiwanese study found an exceedingly high percentage of 97% of ERA patients being HLA B27-positive[4]. It is also useful to note that HLA B27 can also be found in a significant proportion of patients with juvenile psoriatic arthritis though less than that of ERA. The importance of HLA B27, apart from aiding diagnosis of ERA, also lies in its prediction of a more chronic clinical course[9].

CLINICAL PRESENTATION AND DIAGNOSIS

ERA is hallmarked by the presence of arthritis, enthesitis and anterior uveitis. The pattern of arthritis in ERA is typically oligoarticular, asymmetrical and predominantly affecting the large joints of the lower limbs. The most commonly affected joints are the hips, knees and ankles. Axial disease is also common in ERA, with up to 50% ERA patients having evidence of clinical or radiographic sacroiliac disease. Axial disease is typically not present at the initial diagnosis of ERA but develops as the disease progresses. By 5 years after disease onset, up to 92% of ERA patients were found to have symptomatic axial disease involvement[10].

Enthesitis is present in around 60-80% of ERA patients. Enthesis is the connection between a tendon, ligament or joint capsule and bone. The most common sites for enthesitis in ERA patients are at the lower limbs, notably the insertion of the patellar ligament at the inferior pole, the insertion of the plantar fascia at the calcaneus, and the insertion of the tendon Achilles at the calcaneus[11].

Extra-articular manifestations in ERA may occur before the onset of articular symptoms. The most important extra-articular manifestation to watch out for is acute symptomatic anterior uveitis. This uveitis is painful, as opposed to the asymptomatic nature of the uveitis that occurs in ANA-positive JIA patients. Incidence of anterior uveitis in ERA patients was observed to be 5-10%[7].

There is no single confirmatory test for the diagnosis of ERA. Peripheral arthritis and enthesitis may be

elicited on physical examination. Axial arthritis may be indicated by the presence of inflammatory back pain (insidious onset lower back pain at age less than 40 years, that improves with exercise and associated with more than thirty minutes of morning stiffness, or alternating buttock pain)[12]. ILAR defines sacroiliitis as the presence of tenderness on direct compression over the sacroiliac joint[2]. The modified Schober's test or Patrick's test may also be used to look for any lumbro-sacral involvement. However, in detecting axial involvement by physical examination, one study quoted only 23% sensitivity and 68% specificity[13]. Another study also reported that 21% of children with radiographic evidence of sacroiliitis were clinically silent[14].

Traditionally, X-rays have been used to detect sacroiliitis. The typical signs one could find on X-rays are blurring of the joint margins, sclerosis, erosions and ankylosis. Radiographic sacroiliitis was recognised as part of the diagnostic criteria for adult ankylosing spondylitis back in 1961[15]. However, given these radiographic signs represent already-established structural changes; the detection of these radiographic changes may delay the diagnosis of axial disease by years. Would MRI be a more sensitive tool in detecting sacroiliitis? In adults, MRI of the sacroiliac joints has been shown to reveal early disease process ahead of structural changes in adult spondyloarthropathy with symptoms, using the STIR (Short T1 Inversion Recovery) sequencing. Whole-body MRI has also been proposed to assess early axial skeletal disease in adults[16]. The Assessment in SpondyloArthritis International Society (ASAS) has put forward diagnostic criteria for "positive MRI sacroiliitis" which emphasises on the presence of bone oedema and osteitis to diagnosis the presence of active sacroiliitis[17]. Timely detection and treatment of sacroiliitis are important to prevert structural damage and future functional morbidities.

Blood test for the HLA B27 allele is helpful for the diagnosis of ERA, but the absence of HLA B27 allele does not oppose the diagnosis. Serum inflammatory markers C-reactive protein and erythrocyte sedimentation rate may be elevated, but a normal value does not exclude the presence of active disease. Rheumatoid factor and antinuclear factor are negative in ERA patients.

MANAGEMENT

Management of ERA, as with all forms of chronic arthritis, is multidisciplinary. One must not undermine the importance of physical therapy and occupational therapy as well as the long-term management of the psychosocial aspects of the disease. The medical treatment of ERA is largely based on that of adult ankylosing spondyloarthropathy and other forms of JIA. Non-steroidal anti-inflammatory drugs (NSAIDs), conventional disease-modifying anti-rheumatic drugs (DMARDs) and biologic DMARDs are the mainstays of treatment.

NSAIDs remain the first-line drug for JIA patients, including those with ERA. It can be used as monotherapy, or in conjunction with DMARDs. Commonly-used NSAIDs include ibuprofen, indomethacin, naproxen and diclofenac. In older children, one may consider the use of COX-2 inhibitors such as etoricoxib. The use of NSAIDs as monotherapy is not recommended for more than two months. If the disease remains active, one may consider the use of intra-articular steroid injection and a short course of bridging oral steroids while a trial with DMARD is used.

Methotrexate is one of the well-established DMARDs in treating JIA. It is an anti-metabolite that inhibits enzymes involved in purine metabolism. The usual methotrexate dose is 10-15 mg/m^2 once a week administered orally or by subcutaneous injection. Common side effects include gastrointestinal upset, oral ulcers, deranged liver function and cytopenias. The bioavailability and side effect profile of subcutaneous methotrexate has shown to be better than the oral form. Methotrexate has been shown to be efficacious in treating peripheral arthritis, but not for sacroiliitis and enthesitis.

Sulphasalazine is another common DMARD for use in ERA. The drug is broken down by intestinal bacteria into sulphapyridine and 5-aminosalicylic acid, which in turn act as immunosuppressants and anti-inflammatory drugs in addition to their anti-microbial properties. The usual dose of sulphasalazine is 30-60 mg/kg/day taken orally, and the dose is usually titrated over weeks. Side effects include gastrointestinal upset, bone marrow suppression, skin rash, Stevens-Johnson syndrome and deranged liver function. Sulphasalazine has been shown to achieve remission in small open-label trials. In a 26-week double-blinded trial of thirty-three ERA patients randomised to either sulphasalazine or placebo, there were significant improvements in physicians' and patients' efficacy assessments, but not in active joint counts, tender enthesis, anterior spinal flexion, morning stiffness, or pain visual analogue scales[18].

Biologic DMARDs have been proven effective in treating not only arthritis but also enthesitis and axial disease in adult spondyloarthritis. As of now, TNF-agents etanercept and adalimumab and T-cell co-stimulation inhibitor abatacept have been approved for use in non-systemic JIA. Several prospective trials have been conducted internationally for the use of etanercept and adalimumab in ERA patients with most trials focusing on etanercept, a reasonable choice as etanercept was the first anti-TNF agent approved for use in JIA. These trials have produced promising results showing improvements in active joint counts, enthesis, low back pain, patient/parent/physician global assessments, and reduction of inflammatory markers. Improvement has been shown to sustain till week 52 in a multicentre trial for adalimumab. Serious adverse effects were observed in ≤ 6% of patients, mostly being serious infections[19-22].

Etanercept is a chimeric fusion protein that binds to the TNF receptor, thereby blocking it. It has been approved by the FDA for use in patients with ERA and psoriatic arthritis at 12 years of age or above, as well as polyarticular JIA patients at two years of age or above. The usual dosage is 0.4 mg/kg (max dose 25 mg) twice a week, or 0.8 mg/kg (max dose 50 mg) once a week by subcutaneous injection. Adalimumab is a fully-humanised monoclonal antibody to the

TNF receptor. It has been approved by the FDA for use in ERA patients at six years of age or older, and polyarticular JIA patients at two years of age or older. It is usually prescribed as fixed dosing of 10 mg for 10 kg to < 15 kg, 20 mg for 15 kg to < 30 kg and 40 mg for ≥ 30 kg, every other week, administered subcutaneously. Both Etanercept and Adalimumab can be used as monotherapy or in combination with methotrexate. Main side effects of biologic DMARDs include infections, in particular, tuberculosis infection. Other side effects include allergic reactions and a potential risk for malignancy, in particular lymphoma[23]. Therefore, prior to the start of an anti-TNF agent, one must screen for the presence of active or latent tuberculosis infection, and continue to monitor for any possible tuberculosis infections throughout the treatment. A consensus statement has been published just recently by the JIA Workgroup of the Hong Kong Society for Paediatric Rheumatology regarding the use of biologic DMARDs[24].

CONCLUSION

Enthesitis-related arthritis is a subcategory of juvenile idiopathic arthritis that is characterised by its HLA B27 association and axial involvement. MRI STIR sequence may facilitate earlier detection of axial disease. Current treatment of ERA includes the use of non-medical modalities as well as medical treatment using NSAIDs, conventional DMARDs and promising biologic DMARDs.

References

1. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet. 2007 Mar 3;369(9563):767-778. doi: 10.1016/S0140-6736(07)60363-8. PMID: 17336654.
2. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, He X, Maldonado-Cocco J, Orozco-Alcala J, Prieur AM, Suarez-Almazor ME, Woo P; International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004 Feb;31(2):390-2. PMID: 14760812.
3. Giancane G, Consolaro A, Lanni S, Davì S, Schiappapietra B, Ravelli A. Juvenile Idiopathic Arthritis: Diagnosis and Treatment. Rheumatol Ther. 2016 Dec;3(2):187-207. doi: 10.1007/s40744-016-0040-4. Epub 2016 Aug 12. PMID: 27747582; PMCID: PMC5127964.
4. Shih YJ, Yang YH, Lin CY, Chang CL, Chiang BL. Enthesitis-related arthritis is the most common category of juvenile idiopathic arthritis in Taiwan and presents persistent active disease. Pediatr Rheumatol Online J. 2019 Aug 23;17(1):58. doi: 10.1186/s12969-019-0363-0. PMID: 31443722; PMCID: PMC6708211.
5. Tanya M, Teh KL, Das L, Hoh SF, Gao X, Arkachaisri T. Juvenile idiopathic arthritis in Southeast Asia: the Singapore experience over two decades. Clin Rheumatol. 2020 Nov;39(11):3455-3464. doi: 10.1007/s10067-020-05081-9. Epub 2020 May 16. PMID: 32418038.
6. Saurenmann RK, Rose JB, Tyrrell P, Feldman BM, Laxer RM, Schneider R, Silverman ED. Epidemiology of juvenile idiopathic arthritis in a multiethnic cohort: ethnicity as a risk factor. Arthritis Rheum. 2007 Jun;56(6):1974-84. doi: 10.1002/art.22709. PMID: 17530723.
7. Mistry RR, Patro P, Agarwal V, Misra DP. Enthesitis-related arthritis: current perspectives. Open Access Rheumatol. 2019 Jan 25;11:19-31. doi: 10.2147/OARRR.S163677. PMID: 30774484; PMCID: PMC6354696.
8. Żuber Z, Turowska-Heydel D, Sobczyk M, Chudek J. Prevalence of HLA-B27 antigen in patients with juvenile idiopathic arthritis. Reumatologia. 2015;53(3):125-30. doi: 10.5114/reum.2015.53133. Epub 2015 Aug 7. PMID: 27407238; PMCID: PMC4847302.
9. Berntson L, Nordal E, Aalto K, Peltoniemi S, Herlin T, Zak M, Nielsen S, Rygg M; Nordic Study Group of Paediatric Rheumatology. HLA-B27 predicts a more chronic disease course in an 8-year followup cohort of patients with juvenile idiopathic arthritis. J Rheumatol. 2013 May;40(5):725-31. doi: 10.3899/jrheum.121257. Epub 2013 Apr 1. PMID: 23547219.
10. Burgos-Vargas R, Clark P. Axial involvement in the seronegative enthesopathy and arthropathy syndrome and its progression to ankylosing spondylitis. J Rheumatol. 1989 Feb;16(2):192-7. PMID: 2526221.
11. Weiss PF, Klink AJ, Behrens EM, Sherry DD, Finkel TH, Feudtner C, Keren R. Enthesitis in an inception cohort of enthesitis-related arthritis. Arthritis Care Res (Hoboken). 2011 Sep;63(9):1307-12. doi: 10.1002/acr.20508. PMID: 21618453.
12. Lassiter W, Allam AE. Inflammatory Back Pain. 2020 Jun 22. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan–. PMID: 30969575.
13. Lin C, MacKenzie JD, Courtier JL, Gu JT, Milojevic D. Magnetic resonance imaging findings in juvenile spondyloarthropathy and effects of treatment observed on subsequent imaging. Pediatr Rheumatol Online J. 2014 Jul 11;12:25. doi: 10.1186/1546-0096-12-25. PMID: 25067925; PMCID: PMC4110533.
14. Stoll ML, Bhore R, Dempsey-Robertson M, Punaro M. Spondyloarthritis in a pediatric population: risk factors for sacroiliitis. J Rheumatol. 2010 Nov;37(11):2402-8. doi: 10.3899/jrheum.100014. Epub 2010 Aug 3. PMID: 20682668; PMCID: PMC3093157.
15. Kellgren JH. Diagnostic criteria for population studies. Bull Rheum Dis. 1962 Nov;13:291-2. PMID: 14031789.
16. Bennett AN, Marzo-Ortega H, Rehman A, Emery P, McGonagle D; Leeds Spondyloarthropathy Group. The evidence for whole-spine MRI in the assessment of axial spondyloarthropathy. Rheumatology (Oxford). 2010 Mar;49(3):426-32. doi: 10.1093/rheumatology/kep427. Epub 2010 Jan 11. PMID: 20064871.
17. Banegas Illescas ME, López Menéndez C, Rozas Rodríguez ML, Fernández Quintero RM. Nuevos criterios ASAS para el diagnóstico de espondiloartritis. Diagnóstico de sacroileítis por resonancia magnética [New ASAS criteria for the diagnosis of spondyloarthritis: diagnosing sacroiliitis by magnetic resonance imaging]. Radiologia. 2014 Jan-Feb;56(1):7-15. Spanish. doi: 10.1016/j.rx.2013.05.004. Epub 2013 Oct 9. PMID: 24119715.
18. Burgos-Vargas R, Vázquez-Mellado J, Pacheco-Tena C, Hernández-Garduño A, Goycochea-Robles MV. A 26 week randomised, double blind, placebo controlled exploratory study of sulfasalazine in juvenile onset spondyloarthropathies. Ann Rheum Dis. 2002 Oct;61(10):941-2. doi: 10.1136/ard.61.10.941. PMID: 12228171; PMCID: PMC1753917.
19. Horneff G, Burgos-Vargas R, Constantin T, et al. Efficacy and safety of open-label Etanercept on extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis and psoriatic arthritis: part 1 (week 12) of the CLIPPER study. Ann Rheum Dis. 2014;73(6):1114–1122.
20. Horneff G, Foeldvari I, Minden K, et al. Efficacy and safety of Etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. Arthritis Rheumatol. 2015;67(8):2240–2249.
21. Burgos-Vargas R, Tse SML, Horneff G, et al. A randomized, double-blind, placebo-controlled multicenter study of Adalimumab in pediatric patients with enthesitis-related arthritis. Arthritis Care Res. 2015;67(11):1503–1512.
22. Alexeeva EI, Namazova-Baranova LS, Bzarova TM, et al. Predictors of the response to Etanercept in patients with juvenile idiopathic arthritis without systemic manifestations within 12 months: results of an open-label, prospective study conducted at the national scientific and practical center of children's health, Russia. Pediatr Rheumatol Online J. 2017;15(1):51.
23. Diak P, Siegel J, La Grenade L, Choi L, Lemery S, McMahon A. Tumor necrosis factor alpha blockers and malignancy in children: forty-eight cases reported to the Food and Drug Administration. Arthritis Rheum. 2010 Aug;62(8):2517-24. doi: 10.1002/art.27511. PMID: 20506368.
24. Ho ACH, Wong SN, Leung LCK, Chan WKY, Chong PCY, Tse NKC, Yeung RHM, Kong SY, Lee KP. Biological disease-modifying anti-rheumatic drugs in juvenile idiopathic arthritis of polyarticular course, enthesitis-related arthritis, and psoriatic arthritis: a consensus statement. Hong Kong Med J. 2020 Feb;26(1):56-65. doi: 10.12809/hkmj198195. PMID: 32077861.

HUMIRA®
adalimumab
destination you™

A *Future* built on TRUST

With *20 years* of clinical trial experience starting with RA[1]

Currently used by more than *1,000,000 patients* worldwide and with *15 indications* in Hong Kong[2,3]

Building *success* through science[4]
... more than 300 clinical trial publications[4]
... more than 180 open label extension publications[4]

Reference: 1. Burmester GR, Mease P, Dijkmans BA, et al. Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory d iseases. Ann Rheum Dis. 2009;68(12):1863-1869. 2. Data on file, AbbVie Inc. Humira patients currently treated worldwide Q2 2018. 3. Hong Kong Humira Prescribing Information, version May 2018 4. A literature search strategy was designed to find Adalimumab publications parsed out by study type: Open Label Extensions (OLE), Meta-analysis, Observational / Registry Studies, and Randomized Controlled Trial (RCTs). Four databases in the ACS STN command language platform were used: Medline: 1946 to 17 Jul 18, Embase: 1947 to 17 Jul 18, Biosis: 1926 to 18 Jul 18 and HCAPLUS (Chemical Abstracts Plus): 1907 – 17 Jul 18.

HUMIRA® abbreviated prescribing information

Presentation: For pre-filled syringe and pre-filled pen presentation adalimumab 40mg/0.4mL solution for injection. **Indications and Dosage:** *Adult* Rheumatoid Arthritis 40 mg SC as a single dose EOW, use with MTX. In monotherapy patient who experience decrease in response may benefit from an increase in dosage to 40 mg SC Every Week or 80 mg SC EOW. *Adult* Ankylosing Spondylitis, Axial Spondyloarthritis without radiographic evidence of AS and Psoriatic Arthritis 40 mg SC as a single dose EOW. *Adult* Crohn's Disease 80 mg at week 0, followed by 40 mg SC at week 2 as induction, then 40 mg SC EOW. If need for a more rapid response, the regimen 160 mg SC at week 0 and 80 mg SC at week 2 can be used with the awareness of the higher risk for adverse events during induction. Patients who experience decrease in their response to Humira 40 mg SC EOW may benefit from an increase to 40 mg SC Every Week or 80 mg SC EOW. *Adult* Ulcerative Colitis 160 mg SC at week 0 and 80 mg SC at week 2 as induction treatment, then 40 mg SC EOW. Patients who experience decrease in their response to 40 mg SC EOW may benefit from an increase to 40 mg SC Every Week or 80 mg SC EOW. *Adult* Psoriasis 80 mg SC at week 0, followed by 40 mg SC EOW starting 1 week after the initial dose. If patients experience insufficient response beyond 16 weeks, may benefit from an increase to 40 mg Every Week or 80 mg EOW. If adequate response is achieved with 40 mg Every Week or 80 mg EOW, dosage can be subsequently be reduced to 40 mg EOW. *Adult* Hidradenitis Suppurativa 160 mg SC on day 1 and 80 mg SC on day 15, followed by 40 mg SC or 80 mg EOW from day 29. *Adult* Uveitis 80mg SC at week 0, followed by 40mg SC EOW from week 1. *Paediatric* Polyarticular Juvenile Idiopathic Arthritis children 2 yr and older, 10kg to <30kg 20 mg SC EOW; ≥30kg 40 mg SC EOW. *Paediatric* Enthesitis- Related Arthritis children 6 yr and older, 15kg to <30kg 20 mg SC EOW; ≥30kg 40 mg SC EOW. *Paediatric* Crohn's Disease adolescent and children 6-17 yr <40kg 40 mg SC at week 0, followed by 20 mg SC at week 2 as induction. If need for a more rapid response, the regimen 80 mg SC at week 0 and 40 mg at week 2, can be used with the awareness of the higher risk for adverse event during induction, then 20 mg SC EOW as maintenance. If patients experience insufficient response, may benefit from an increase to 20 mg Every Week; ≥40kg 80 mg SC at week 0, followed by 40 mg SC at week 2 as induction. If need for a more rapid response, the regimen 160 mg SC at week 0 and 80 mg SC at week 2, can be used with the awareness of the higher risk for adverse event during induction, then 40mg SC EOW as maintenance; if experience insufficient response, may benefit from an increase to 40mg Every Week or 80 mg EOW. *Paediatric* Plaque Psoriasis children 4 yr and older, 15kg to <30kg initially 20 mg SC at week 0 and 1, followed by 20 mg SC EOW; ≥30kg initially 40 mg SC at week 0 and 1, followed by 40 mg SC EOW. *Adolescent* Hidradenitis Suppurativa 12 yr and older >30kg 80 mg SC at week 0 and 40 mg EOW from week 1. If experience insufficient response, an increase to 40 mg SC Every Week or 80 mg SC EOW may be considered. *Paediatric* Uveitis children 2 yr and older <30kg 20 mg SC EOW in combination with MTX; a loading dose of 40 mg may be considered 1 week before start of maintenance therapy; ≥30kg 40 mg SC EOW in combination with MTX; a loading dose of 80 mg may be considered 1 week before start of maintenance therapy. **Contraindications:** Patients with known hypersensitivity to adalimumab or any of its excipients. Patients with active tuberculosis or other severe infections. Patients with moderate to severe heart failure (NYHA class III/IV). **Precautions:** As with other TNF-α inhibitor, monitoring closely for infections including tuberculosis before, during and after treatment; Carriers of HBV as reactivation; Pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; History of lymphoma or malignancy; Worsening of CHF; Women of child-bearing potential; Pregnancy; Elderly > 65 yr; Vaccinations. **Interactions:** other biologic DMARDs or TNF antagonists, live vaccines. **Undesirable effects:** Respiratory tract, systemic, intestinal, skin and soft tissue, ear, oral, reproductive tract, urinary tract, fungal and joint infections; benign neoplasm; skin cancer excluding melanoma; leukopenia; anemia; thrombocytopenia; leucocytosis; hypersensitivity, allergies; increased lipids; hypokalaemia; increased uric acid; blood sodium abnormal; hypocalcaemia; hyperglycemia; hypophosphatemia; dehydration; mood alterations; anxiety; anxiety, insomnia; headache; paraesthesias; migraine; nerve root compression; visual impairment; conjunctivitis; blepharitis; eye swelling; vertigo; tachycardia; hypertension; flushing; haematoma; cough; asthma; dyspnoea; abdominal pain; nausea & vomiting; GI hemorrhage; dyspepsia; gastroesophageal reflux disease; sicca syndrome; elevated liver enzymes; rash; pruritus; urticarial; bruising; dermatitis; onychoclasis; hyperhidrosis; musculoskeletal pain; muscle spasms; haematuria; renal impairment; injection site reaction; chest pain; edema; coagulation and bleeding disorders; autoantibody tests positive; increased blood lactate dehydrogenase; impaired healing. **Full local prescribing information is available upon request.**

API.HK.HUO.1118

HK-HUM-200019 30 MAY 2020

For Healthcare Professional Use Only
Adverse event should be reported to AbbVie pharmacovigilance team at drugsafety.pv@Abbvie.com

AbbVie Limited
Unit 2405 - 08, 24/F, AIA Tower, 183 Electric Road, North Point, Hong Kong Tel: 3467 8888 Fax: 2219 7397

abbvie

Overview of Biologics in Juvenile Idiopathic Arthritis

Dr Assunta Chi-hang HO

MBChB, MRCPCH, FHKCPaed, FHKAM

Vice President, Hong Kong Society for Paediatric Rheumatology

Dr Assunta Chi-hang HO

INTRODUCTION

Up until the past two decades, conventional disease-modifying anti-rheumatic agents (cDMARDs) had been the cornerstone treatment for patients with Juvenile Idiopathic Arthritis (JIA). With their long track record and good safety profile, cDMARDs have remained important even in the present day. However, cDMARDs are not always effective. About 10 to 30% of patients would be refractory to these drugs, especially those with the polyarticular course (pcJIA). The roles of cDMARDs are even more limited in systemic arthritis (SJIA) and the axial involvement in enthesitis-related arthritis (ERA).

Since the beginning of the new millennium, there has been a big leap in the translation of the knowledge on the underlying inflammatory mechanism to the development of new therapeutic agents. These drugs, termed biologic DMARDs (bDMARDs), are highly effective, bringing the much-needed relief to many of the children suffering from JIA.

WHAT ARE "BIOLOGICS"?

Biologics are chemicals produced by the molecular method, sometimes derivatives of a living organism. They target several pro-inflammatory cytokines and pathways that mediate the progression of arthritis, namely tumour necrosis factor, interleukin 6, interleukin 1 and T cell co-stimulation. They are usually indicated in patients with persistently active disease or not tolerating cDAMRDs[1].

TUMOUR NECROSIS FACTOR INHIBITORS (TNF INHIBITORS, ANTI-TNF)

Anti-TNF was the very first biological product licenced for use in inflammatory arthritis 20 years ago. Nowadays, among the many preparations available, etanercept and adalimumab are the two approved for use in JIA. According to a UK biologic registry, TNF inhibitors are the most frequently prescribed bDMARDs in JIA[2].

Etanercept is a dimeric fusion protein that functions as a soluble TNF receptor, preventing the binding of the cytokine to its membrane bound receptor. It has been shown to be effective in pcJIA patients who were refractory to NSAIDs and methotrexate. In a randomised withdrawal trial, use of etanercept was associated with a significantly lower risk of arthritis flare as compared to the placebo arm[3]. Efficacy of etanercept in other subtypes, namely oligoarticular, ERA and psoriatic arthritis (PsA), has also been confirmed[4,5].

Adalimumab is a fully humanised monoclonal antibody against TNF. In pcJIA patients refractory to cDMARDS including methotrexate, it was demonstrated that the use of adalimumab led to significantly fewer arthritis flare[6]. The use of adalimumab in persistently active ERA was subsequently assessed in a randomised controlled trial, which showed a significant reduction in the number of active joints in the treatment arm[7].

Indication

Etanercept and adalimumab are indicated for use in pcJIA (≥ 2 years of age), ERA (etanercept ≥ 12 years of age, adalimumab ≥ 6 years of age) and PsA (etanercept ≥ 6 years of age). For patients with concomitant inflammatory bowel disease or JIA-associated uveitis, adalimumab is preferred as there has been some concern over the possible role of etanercept in flares of these extra-articular manifestations.

Side Effects

Common side effects include injection site reactions and minor infections. The use is also associated with opportunistic infection and increased risk of severe infection. Other potential adverse effects reported include demyelination and autoimmunity.

T CELL CO-STIMULATION INHIBITOR

Abatacept is a T cell co-stimulation modulator. It prevents the binding of T cell onto the CD 80 and 86 ligands of the antigen-presenting cell, thereby interfering the subsequent inflammatory cascade. A trial published in 2008 has confirmed the effectiveness of abatacept in JIA patients aged 6 years or older[8]. Abatacept serves as an option for pcJIA children who do not respond adequately to, or not tolerating, TNF inhibitors.

Indication

Abatacept is approved in pcJIA aged six years or above who fail to respond to DMARDs, including anti-TNF.

Side Effects

The side effect profile is similar to other biologics, including local injection reaction (if it is administered via subcutaneous route) and minor infection. Again, the concern for severe and opportunistic infection warrants careful screening and monitoring.

ANTI-INTERLEUKIN 6 INHIBITOR (IL 6 INHIBITOR, ANTI-IL 6)

Tocilizumab is a humanised monoclonal antibody against IL 6. Studies have confirmed the efficacy of tocilizumab in both pcJIA and SJIA. For pcJIA, the use of tocilizumab is associated with a significantly lower chance of arthritis flares[9]. In SJIA, IL 6 is pivotal in the inflammatory process and is responsible for symptoms such as fever, arthritis and thrombocytosis. Therapeutic intervention using tocilizumab offers satisfactory control for both systemic and arthritic manifestations[10].

Indication

Tocilizumab can be used in SJIA and pcJIA who are aged two years or above if the disease is refractory.

Side Effects

In general, most of the side effects are mild, such as local injection reaction and minor infection. It can also cause other adverse effects e.g. cytopenia (neutropenia and thrombocytopenia), raised transaminases, and hyperlipidaemia. Patient-based screening and close surveillance should be carefully performed before and during treatment.

INTERLEUKIN 1 INHIBITOR (IL 1 INHIBITORS, ANTI-IL 1)

SJIA is a unique entity, characterised by marked systemic inflammation and the propensity to develop into Macrophage Activation Syndrome (MAS), a hyperinflammatory state. The pro-inflammatory cytokines IL 6 and IL 1 family are involved in the pathogenesis. Like tocilizumab, IL 1 blockade results in significant symptom improvement in SJIA. Furthermore, there is increasing evidence to support that a window of opportunity does exist. In other words, early target treatment may prevent the subsequent onset of arthritis, which is often difficult to treat[11].

Anakinra, an IL 1 receptor antagonist, has been widely used in the U.S. and European countries. Recent studies demonstrated that, when used as first-line monotherapy, many could achieve a long-lasting remission, even without using any corticosteroids[12].

Canakinumab is a long-acting monoclonal antibody against IL 1β. Patients using this drug demonstrated good response and were much less likely to experience disease flare[13].

Indication

Canakinumab is approved for SJIA patients aged two years or above. Anakinra is approved in European countries by the European Medicines Agency (EMA).

Side Effects

From post-marketing data, the side effect profile of both anti-IL 1 is similar to other biologics. Even though IL 1 and IL 6 inhibitors are effective in managing SJIA, MAS is still observed among those receiving these drugs. Furthermore, the presentations of a MAS episode may be altered [14].

SAFETY CONCERN: INFECTION

Emergence of infection is a genuine concern. The risk is further augmented as many of these patients would have exposed to other DMARDs and glucocorticoid. Findings of different nation-wide registries suggested that JIA patients receiving biologics are at an increased risk of severe infections[15,16]. In a recent multinational pharmacovigilance initiative, about 17% of infections were adjudicated as opportunistic. Varicella-zoster, tuberculosis (TB), papilloma, candida and pneumocystis are among the list[17].

TB reactivation is of particular concern as TNF is one of the key cytokines in intracellular killing of Mycobacterium species and in granuloma formation. Screening for latent TB should be performed and treated prior to biologic therapy.

In adult RA patients, biologics are associated with reactivation of hepatitis B or C infection. With the well-established HBV vaccination programme, the incidence of hepatitis B in children is low. Nevertheless, it is still recommended to screen for carrier state before treatment begins.

Patients should be offered appropriate advice on vaccination, e.g. if they need catch-up pneumococcal vaccine, the seasonal influenza vaccine, as well as to follow the local vaccination guidelines. Live vaccine should not be given while receiving bDMARDs.

SAFETY CONCERN: MALIGNANCY

The concern for incidental malignancy stemmed after FDA issued a box warning in 2008 regarding the development of malignancies in children receiving TNF inhibitors[18]. With more long term information now available, it is reassuring that no strong association with malignancy has been found[19].

One thing worth mentioning is that most of the long-term safety data were derived from anti-TNF. Nevertheless, post-marketing data and real-life experiences of other biologics suggest the safety profiles are comparable. International collaborations are of utmost importance in ongoing data collection.

TAKING CARE OF CHILDREN USING bDMARDs

The use of bDMARDs is becoming more often in children. Healthcare workers of different disciplines may be involved in caring for them. Here is a summary of the suggested care before and during bDMARDs treatment.

Screening Before Starting bDMARDs

- Efforts should be made to screen for pre-existing infections or any active infection, including latent tuberculosis and hepatitis B or C carrier state.
- Efforts should also be made to screen for any systemic conditions that render using bDMARDs contraindicated. Examples include immunodeficiency states, history of demyelinating diseases, low functional status, congestive heart failure of grade 3 or 4 of the New York Heart Association. Raised transaminase of ≥ 1.5 times of baseline and cytopenia, especially neutropenia and thrombocytopenia, are also considered contraindications for starting anti-IL 6.

Monitoring While Receiving bDMARDs

- Conscientious general care should be given, including injection site inspection, early assessment during infection or febrile illnesses, withholding bDMARDs and prompt referral if necessary. Appropriate advice on vaccination should be offered.
- Meticulous physical examination is a must. Further investigation may be required according to individual risk profiles.
- Regular blood tests are part of standard of care, including complete blood count with differentials, renal and liver functions and others as appropriate (e.g. lipid profile while using IL 6 inhibitors).

CONCLUSION

We see in the past few decades an explosion in promising treatment options for JIA. Drugs in the pipeline are ever-increasing. For example, Tofacitinib, a Janus Kinase Inhibitor, is recently approved by the FDA in treating pcJIA. Hopefully, the lives of JIA patients would be much brighter than ever.

Table 1: Summary of bDMARDs in JIA / Adapted from US Food and Drug Administration. http://www.accessdata.fda.gov and summarised by author.

bDMARDs	Class	Indication*	Dose and frequency#
Etanercept	Dimeric fusion protein that functions as soluble TNFα receptor	pcJIA: ≥ 2 years ERA or PsA: ≥ 12 years	0.8 mg/kg/dose sc weekly (max 50mg/dose), or 0.4 mg/kg/dose sc twice weekly (max 25mg/dose)
Adalimumab	Fully humanised anti TNF α monoclonal antibody	pcJIA: ≥ 2 years ERA: ≥ 6 years	10 to < 15 kg: 10 mg sc q2weeks 15 to < 30 kg: 20 mg sc q2weeks ≥ 30 kg: 40 mg sc q2weeks
Abatacept	T cell co-stimulation inhibitor	pcJIA ≥ 6 years	**Intravenous:** < 75 kg: 10 mg/kg/dose 75-100 kg: 750 mg/dose > 100 kg: 1g/dose At day 0, 14 and 29, then q4weeks **Subcutaneous:** 10 to < 25 kg: 50 mg weekly 25 to < 50 kg: 87.5 mg weekly ≥ 50 kg: 125 mg weekly
Tocilizumab	Anti IL 6 monoclonal antibody	pcJIA, SJIA: ≥ 2 years	**pcJIA** **intravenous:** < 30 kg: 10 mg/kg/dose q4weeks ≥ 30 kg: 8 mg/kg/dose q4weeks **subcutaneous:** < 30 kg: 162 mg q3weeks ≥ 30 kg: 162 mg q2weeks **SJIA** **intraveneous:** < 30 kg: 12 mg/kg q2weeks ≥ 30 kg: 8 mg/kg q2weeks **subcutaneous:** < 30 kg: 162 mg q2weeks ≥ 30 kg: 162 mg weekly
Anakinra	Recombinant IL 1 receptor antagonist	SJIA ≥ 8 months, weight at least 10kg (EMA recommendations)	< 50 kg: start at 1-2 mg/kg/dose sc daily ≥ 50 kg: 100 mg sc daily
Canakinumab	Humanised anti IL 1β monoclonal antibody	SJIA: ≥ 2 years	≥ 7.5kg: 4mg/kg/dose sc q4weeks (max 300mg)

*persistently active disease despite adequate use of cDMARDs, or signs of cDMARDs intolerance
dose adjustment may be required according to individual's characteristics
pcJIA: polyarticular course JIA. ERA: enthesitis- related arthritis, SJIA: systemic onset JIA. EMA: European Medicines Agency

References

1. National Institue for Health and Care Excellence. Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis. Technology appraisal guidance. 16 Dec 2015. nice.org.uk/guidance/ta373.
2. Kearsley-Fleet L, Davies R, Baildam E et al. Factors associated with choice of biologic among children with Juvenile Idiopathic Arthritis: results from two UK paediatric biologic registers. Rheumatology 2016;55:1556-65.
3. Lovell DJ, Giannini EH, Reiff A et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. N Engl J Med 2000;342:763-9.
4. Horneff G, Burgos-Vargas R, Constantin T et al. Efficacy and safety of open-label etanercept on extended oligoarticular juvenile idiopathic arthritis, extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis and psoriatic arthritis: part 1(week 12) of the CLIPPER study. Ann Rheum Dis 2014;73:1114-22.

5. Horneff G, Foeldvari I, Minden K et al. Efficacy and safety of etanercept in patients with the enthesitis related arthritis category of juvenile idiopathic arthritis. Arthritis Rheumatol 2015;67(8):2240-9.
6. Lovell DJ, Ruperto N, Goodman S et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl Med 2008;359(8):810-20.
7. Burgos-Vargas R, Tse SM, Horneff G et al. A randomised, double blind, placebo controlled multicenter study of adalimumab in pediatric patients with enthesitis related arthritis. Arthritis care Res (Hoboken) 2015;67(11):1503-12.
8. Ruperto N, Lovell DJ, Quartier P et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double blind placebo controlled withdrawal trial. Lancet 2008;372(9636):383-91.
9. Brunner HI, Ruperto N, Zuber Z et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double blind withdrawal trial. Ann Rheum Dis 2015;74(6):1110-7.
10. De Benedetti F, Brunner HI, Ruperto N et al. Randomised trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med 2012;367(25):2385-95.
11. Kessel C, Hedrich CM, Foell D. Innately adaptive of truly autoimmune: is there something unique about systemic juvenile idiopathic arthritis? Arthritis Rheumatol 2020;72(2):210-219.
12. Ter Haar NM, van Dijkhuizen P, Swart JF et al. Treatment to target using recombinant interleukin 1 receptor antagonist as first line monotherapy in new onset systemic juvenile idiopathic arthritis: results from a five year follow up study. Arthritis Rheumatol 2019;71(7):1163-73.
13. Ruperto N, Brunner HI, Quartier P et al. Two randomised trials of canakinumab in systemic juvenile idiopathic arthritis. N Engl J Med 2012;367(25):2396-406.
14. Schulert GS, Minoia F, Bohnsack J et al. Effect of biologic therapy on clinical and laboratory features of macrophage activation syndrome associated with systemic juvenile idiopathic arthritis. Arthritis Care Res (Hoboken) 2018;70(3):409-19.
15. Becker I, Horneff G. Risk of serious infection in juvenile idiopathic arthritis patients associated with tumor necrosis factor inhibitors and disease activity in the German biologics in pediatric rheumatology registry. Arthritis Care Res (Hoboken) 2017;69(4):552-60.
16. Lee WJ, Lee TA, Suda KJ et al. Risk of serious bacterial infection associated with tumor necrosis factor-alpha inhibitors in children with juvenile idiopathic arthritis. Rheumatology (Oxford) 2018;57(2):273-282.
17. Giancane G, Swart JF, Castagnola E et al. Opportunistic infections in immunosuppressed patients with juvenile idiopathic arthritis: analysis by the Pharmachild Safety Adjudication Committee. Arthritis Res Ther 22,71(2020).
18. Diak P, Siegel J, La Grenade L et al. Tumor necrosis factor alpha blockers and malignancy in children: forty-eight cases reported to the Food and Drug Administration . Arthritis Rheum 2010;62(8):2517-24.
19. Swart J, Giancane G, Horneff G et al. Pharmacovigilance in juvenile idiopathic arthritis patients treated with biologic or synthetic drugs: combined data of more than 15000 patients from Pharmachild and national registries. Arthritis Res Ther. 2018;20(1):285.

A Review of ANCA-associated Vasculitis (AAV) in Children

Dr Grace PK CHIANG

MSc, MBChB, MRCPCH, FHKAM (Paediatrics)
Specialist in Paediatrics
Council Member, Hong Kong Society for Paediatric Rheumatology

Dr Grace PK CHIANG

INTRODUCTION

Vasculitis is defined as inflammation of the blood vessels with infiltration of vessel walls by granulocytes or mononuclear cells. Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare autoimmune condition that affects small-sized vessels (i.e. arterioles, capillaries, intraparenchymal arteries, venules and some veins) predominantly. AAVs include three disease phenotypes: granulomatosis with polyangiitis (GPA; formerly known as Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA; formerly known as Churg-Strauss syndrome). Patients with EGPA carry distinct clinical phenotype and disease course. It is extremely rare in the paediatric population. This article, therefore, focuses more on MPA and GPA and has reviewed briefly on the presentation and treatment of EGPA.

CLASSIFICATION CRITERIA

In 1990, the American College of Rheumatology (ACR) published criteria for the classification of seven most prevalent forms (adult-onset) of systemic vasculitis, including GPA and EGPA.[1,2] At that point in time, MPA was not a well-known condition and was not included within the criteria. The ACR criteria, therefore, offer limited value in differentiating GPA from MPA. Along with the advances in the understanding of ANCA and with more widespread use of the latest diagnostic and imaging techniques, a multidisciplinary group of clinicians and pathologists was called, and an international conference, the Chapel Hill Consensus Conference (CHCC) was convened in North Carolina in 1994 focusing on the goals of reaching consensus on the names for a few common systemic vasculitides and of redefining vasculitis syndromes by the size of blood vessels and immunopathology of lesions.[3] The CHCC nomenclature system was revised in 2012.[4] The addition of a subcategory of AAV and the elimination of eponyms from the AAV nomenclature in this revised version has acknowledged the essential pathogenic role of ANCA in MPA, GPA and EGPA. The updated nomenclature is more reflective of the underlying pathogenesis and clinical characteristics.

In 2006, the paediatric vasculitis working group, Paediatric Rheumatology European Society (PReS) proposed the primary classification criteria of vasculitis in children, which were subsequently endorsed by the European League against Rheumatism (EULAR).[5] This set of criteria also supported the usage of the dimensions of predominantly affected vessels as the basis of classification. In 2008, the Paediatric Rheumatology International Trials Organization (PRINTO) validated the EULAR-endorsed criteria and provided definitions for the classification criteria of four of the paediatric vasculitides, among which, GPA was the only vasculitis among the AAVs that was defined.[6] (Table 1) The EULAR/PRINTO/PReS joint criteria have improved the sensitivity of detecting paediatric GPA to 93% (from 83% by ACR criteria for GPA). In recent years, there have been attempts at reclassifying AAV according to ANCA serotype instead of phenotype. These attempts were driven by the increasing evidence of a stronger correlation between genetic polymorphisms with ANCA serotypes than with the clinical phenotypes of GPA and MPA.[7]

Table 1. EULAR/PRINTO/PReS criteria for granulomatosis with polyangiitis (GPA, Wegener's).
Excerpted from Ruperto N, Özen S, Pistorio A, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener Granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. Ann Rheum Dis 2010;69:798-806.

A patient is said to have GPA when three of the following six criteria are present:	
Criterion	**Descriptors**
Upper airway involvement	Chronic purulent or bloody nasal discharge, or recurrent epistaxis/crusts/granulomata Nasal septal perforation or saddle-nose deformity Chronic or recurrent sinus inflammation
Pulmonary involvement	Chest X-ray or CT scan showing the presence of nodules, cavities, or fixed infiltrates.
Renal involvement	Proteinuria > 0.3 g/24 hours or greater than 30mmol/mg of urine albumin/creatinine ratio on a spot morning sample Hematuria or red blood cell casts: > 5 red blood cells per high-power field or red blood cell casts in urinary sediment or > 2+ on the dipstick. Necrotising pauci-immune glomerulonephritis
Granulomatous inflammation	Granulomatous inflammation within the wall of an artery or in perivascular or extravascular area of artery or arteriole
Laryngo trachea bronchial stenosis	Subglottic, tracheal, or bronchial stenosis
ANCA	ANCA positivity by immunofluorescence of by ELISA (MPO/p or PR3/c ANCA)

EULAR, European League Against Rheumatism; GPA, Granulomatosis with polyangiitis; PRINTO, Pediatric Rheumatology International Trials Organization; PReS, Pediatric Rheumatology European Society.

PATHOGENESIS

In the past two decades, benchtop experiments have established the pathogenic role of ANCA in AAV. Both environmental and genetic factors are found to be contributory to the onset of the autoimmunity.[7] The targeted antigens by ANCA in AAV are MPO and PR3. They are cytoplasmic antigens situated within the granules of neutrophils. After priming by the external factors such as infections, environmental exposure to a toxic substance such as silica, or other factors causing disturbance of the innate or adaptive immunity, the primed neutrophils will display the target antigens (MPO or PR3) on their surface membranes. The binding of circulating ANCA to the surface antigens would then end in excessive activation of neutrophils, which then become more adhesive to endothelial cells of the vascular wall. At the identical time, the release of reactive oxygen species (ROS) and lytic enzymes from the 'excited' neutrophils will directly cause damage to the endothelial cells. A NETosis process (an extrusion of the neutrophil extracellular traps, NETs) was also found to be a key player within the self-perpetuating cycle of ANCA-neutrophil excitation. Neutrophil extracellular traps (NETs) are formed by the release of chromatin and granular contents to the extracellular space. The NETs can cause vascular endothelial cell injuries directly. Concomitantly, their components, including PR3 and MPO, are recognised by dendritic cells, and subsequently T cells and plasma cells, which then results in a regeneration of neutrophil hyper-activation, inflammation and vasculitis.

Alternative complement pathway activation is also believed to be involved in the autoimmune activity.[8] During active disease, an increase in the anti-angiogenic factors sFlt1 (soluble fms-like tyrosine kinase 1) can be observed in patients with PR3-AAV. C5a is found to be a significant driver of sFlt1 release by the monocytes. Animal models have also confirmed the role of C5a/C5aR interactions in the pathogenesis of MPO-ANCA GN.[9]

A genetic contribution to AAV has been extensively studied. Recent genome-wide studies have confirmed the presence of single nucleotide polymorphisms in *HLA-DPB* region on chromosome 6 of patients with PR3-AAV. A weaker association of *HLA-DQ* polymorphism with MPO-AAV was also found. There have also been observed associations of genetic variants within *SERPINA1, PRTN3* with PR3-AAV and *CTLA4* with MPO-AAV respectively.[10] These observations support a strong genetic background of AAV.

EPIDEMIOLOGY

AAVs are rare diseases. They are more frequently reported in adults with both genders being almost equally affected. The incidence of PR3-AAV and MPO-AAV varies worldwide. PR3-AAV is more common in the northern part of the world, while MPO-AAV is found more commonly in southern Europe and Asia. The annual incidence rates of AAV in Europe are reported to be in the range of 13-20 cases per million.[11] The data in the paediatric population are scarce. The annual incidence ranges from 0.5 to 6.39 cases per million children.[12] Unlike adults, AAV in children occurs more frequently in the female. The disease occurs in the second decade of life and is very rare in young children. GPA is the most common form of AAV in children. EGPA only accounts for about 2% of all cases of paediatric vasculitis from an extensive database (ARChiVe study). [13]

CLINICAL FEATURES

AAV is a systemic disease involving different organs and systems. The Birmingham Vasculitis Activity Score (BVAS v. 3) and the paediatric version modified from BVAS (PVAS) summarises the systems that can be involved in any kind of systemic vasculitis.[14] Not uncommonly, patients with AAV present with constitutional symptoms including fatigue, weight loss and fever at disease onset. The triad of upper and lower respiratory tract inflammation and renal disease is characteristic of childhood GPA and MPA. Patients with GPA, especially those with positive PR3-ANCA, are more prone to destructive lesions in the upper airway. These patients may suffer from destructive sinusitis, which can result in saddle-nose or nasal septum deformity. Cavitating and nodular lung lesions on CXR or CT thorax are more common in GPA or AAV with positive PR3-ANCA, in contrast to MPA patients who usually demonstrate patchy infiltrations or fibrosing lesions as the pulmonary manifestations. In patients with EGPA, a history of asthma or wheezing attack and eosinophilic pleural effusions are the representative features in the respiratory system. Pulmonary haemorrhage is a severe complication and can be an expression of the pulmonary-renal syndrome, which is a potentially life-threatening condition complicating MPA and GPA. The kidney is the other organ that is commonly affected in both GPA and MPA but less in EGPA. The key histological feature of renal biopsy is pauci-immune, necrotising and crescentic glomerulonephritis (GN). Granulomatous inflammation may be found in renal tissues of patients with GPA and EGPA but is absent in patients with MPA.(Table 2) Comparing to adults, paediatric patients with AAV tend to have less myalgia and peripheral neuropathy. AAVs are often severe and potentially organ- or even life-threatening diseases. However, limited forms and localised diseases exist. For example, GPA patients can have isolated upper airway diseases with positive PR3-ANCA and histological proof of granulomatous inflammation. Patients with limited or localised diseases can be managed with less toxic immunosuppressive medications.

INVESTIGATIVE FINDINGS

As in adult patients, paediatric patients with AAV usually have positive ANCA in blood tests. Currently, a two-step approach is adopted in most laboratories. Indirect immunofluorescence (IIF) is used to screen for ANCAs. Either a perinuclear pattern (pANCA) for MPO-ANCA or a cytoplasmic pattern (cANCA) for PR3-ANCA can be found in ANCA-positive AAV patients. The IIF would then be followed by enzyme-linked immunosorbent assay (ELISA) to detect the antibodies directed explicitly against MPO or PR3. In 2017, the 1999 international consensus on testing of ANCAs in GPA and MPA was revised.[15] It has recommended to

Table 2. Similarities and differences between the three ANCA-associated vasculitis. Excerpted from Pagnoux. Updates in ANCA-associated vasculitis. Eur J Rheumatol 2016;3:122-33.

	Microscopic polyangiitis (MPA)	Granulomatosis with polyangiitis (GPA)	Eosinophilic granulomatosis with polyangiitis (EGPA)
Clinical features			
ENT	Not destructive, not granulomatous	Frequent: destructive sinusitis, saddle-nose deformity, nasal septum deformity, crusting rhinitis, otitis media	Not destructive, allergic rhinitis, sinus polyposis
Lung	Fibrosing lesions, alveolar haemorrhage	Cavitating lesions, lung nodules, bronchial and/or subglottic stenosis, alveolar haemorrhage	Eosinophilic pleural effusions, transient patchy infiltration
Asthma	No	No	Yes
Kidney involvement	Very frequent, necrotising glomerulonephritis, more fibrosis and C3 deposition, no granuloma in histology	Frequent, necrotising glomerulonephritis, granuloma may be found in histology	Not frequent, necrotising glomerulonephritis, granuloma including eosinophils may be found in histology
Peripheral neuropathy (Mononeuritis multiplex)	Possible	Possible	Frequent
Chest X-ray +/- CT thorax +/- CT sinus	For alveolar haemorrhage (ground-glass opacities)	For alveolar haemorrhage (ground-glass opacities), lung nodules, cavities, subglottic and/or bronchial stenosis. CT for erosive sinusitis, pseudotumor	For transient lung infiltrates, CT for non-erosive sinusitis, polyps
ANCA	> 50%, Mainly MPO-ANCA	> 80%, Mainly PR3-ANCA	20-30%, Mainly MPO-ANCA

ENT, ear, nose, throat; C3, complement 3; CT, computerised tomography; ANCA, anti-neutrophil cytoplasmic antibodies; MPO, myeloperoxidase; PR3, proteinase 3

replace IIF with high-quality antigen-specific assays for PR3 and MPO as the laboratory technology has advanced and high-quality immunoassays have become broadly available. The categorical need for IIF is diminishing. In a paediatric series, PR3-ANCA are positive in 67% in patients with GPA, and MPO-ANCA are positive in 55% of patients with MPA.[12] ANCA positivity is found in about 25% of paediatric EGPA patients. Other blood tests are not specific for AAV. The inflammatory markers may be elevated, but they can be normal in limited or localised diseases. Mild anaemia or thrombocytosis in active disease states are also common.

Out of the concern for commonly associated pulmonary involvement in AAV, a chest X-ray should be performed in all patients with AAV. A follow-up by a CT thorax should be ordered in case of abnormal CXR findings or if the clinical concern for lung involvement remains despite a normal CXR. Pulmonary function tests should be done, including the diffusing capacity of the lung for carbon monoxide (DLCO), in patients with suspected pulmonary haemorrhage.

TREATMENT

The treatment of AAV is structured in a sequential approach comprising remission-induction and remission-maintenance phases. The drug of choice in each phase is governed by the stage and severity of the disease and the extent of organ involvement. There is a lack of controlled trials in paediatric AAV. The treatment is, therefore, based on adult data. The Single Hub and Access point for Paediatric Rheumatology in Europe (SHARE) initiative developed consensus-based guidelines for the management of rare vasculitides in children.[16] It is recommended in the guidelines that the EULAR recommendations on adult-onset AAV (2013) can be used for paediatric GPA or MPA.

The CYLCOPOS study has established a foundation for the treatment of AAV with pulse cyclophosphamide (CYC) during the induction phase.[17] In recent years, studies (RITUXVAS and RAVE) have proven non-inferiority of Rituximab, an anti-CD20 monoclonal antibody and B-cell depleting agent, in comparison to CYC in inducing remission in AAV patients.[18-20] The option of Rituximab should be offered as the first-line treatment in patients when CYC is contraindicated or not preferred by patients and their families. RTX is also found to be a successful agent in inducing remission of relapsing disease (RITAZAREM).[21] Systemic steroid is the cornerstone of therapy in the induction phase. In severe disease, patients may be started first on intravenous pulse methylprednisolone. Regarding the remission-maintenance phase, azathioprine poses the strongest evidence as an effective agent.[22] The alternative choices are methotrexate (MTX), mycophenolate mofetil (MMF) and leflunomide (LEF). The MAINRITSAN studies have found that RTX is superior to AZA in maintaining remission after patients have successfully been induced into remission by either CYC or RTX.[23-25] The results are especially promising in patients with positive PR3-ANCA, who are more prone to relapsing disease. On the other hand, BEVAS trial on another biologic, the belimumab, a human IgG1γ monoclonal antibody directed against soluble B lymphocyte stimulator (BLyS), is found to be not useful in reducing the risk of relapse of GPA or MPA when it was used as an adjunctive therapy during the maintenance phase.[26]

There is no strong evidence regarding the use of plasmapheresis in AAV. The PEXIVAS study on patients with severe AAV, defined by eGFR < 50 ml/min/1.73m^2 BSA or diffuse pulmonary haemorrhage, did not show a beneficial effect of plasmapharesis in terms of reduction of incidence of death or end-stage renal disease after a follow-up for seven years.[27] Patients with AAV often required high dose and prolonged steroid therapy. In view of the concern for toxicity and complications of steroid treatment, studies on adopting

low-dose steroid regimen (LoVAS and TAPIR)[28,29] and a phase III trial on replacing steroid with a C5aR antagonist are on-going with the hope of generating a new era of minimal-steroid AAV treatment strategy.[30] The EGPA treatment recommendations are less robust due to the lack of randomised trials. The treatment is often inferred from GPA/MPA trials. Unique to EGPA is the potential role of interleukin-5 (IL-5) blockade, which reduces blood and airway eosinophils. Wechsler et al. performed an RCT on the use of Mepolizumab and found that the treatment group achieved more accrued weeks of remission at 52 weeks and a higher percentage of patients in remission at weeks 36 and 48 after randomisation.[31] When clinical benefit was defined post-hoc, close to 90% of patients with EGPA experienced benefit from Mepolizumab.[32]

OUTCOME

The largest paediatric AAV cohort to date, the ARChiVe (A Registry for Childhood Vasculitis: e-entry), evaluated the early outcomes of 105 children with AAV.[33] The study has found that 42% of the patients achieved remission (defined as PVAS of 0 on < 0.2 mg/kg/day prednisone or equivalent) at 12 months, and 61% had inactive disease at 12 months. In the same cohort, despite treatment, 63% of patients experienced damage to various organ systems by 12 months which is early in their disease course. The outcome remains unfavourable despite the advance of diagnosis and treatment of AAV in both adult and children.

CONCLUSION

Significant progress has been made in our understanding of pathogenesis, diagnosis and medical treatment of AAV. However, there remain a lot of unanswered questions, especially in paediatric patients, where RCT data are lacking. In view of the rarity of this disease, the inclusion of children in adult studies may be considered. Systemic vasculitis, including AAV, is a complex disease with high mortality and morbidity due to the disease itself and its treatment. A multidisciplinary approach in managing AAV is of paramount importance in achieving better control of the disease and of organ damage, as well as in minimising the impact on the quality of life of these young patients.

References

1. Leavitt RY, Fauci AS, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 1990;33:1101-7.
2. Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990;33:1091-100.
3. Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides Proposal of an International Consensus Conference. Arthritis Rheuma 1994; 37:187-192.
4. Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised International Chapel Hill consensus conference nomenclature of vasculitides. Arthritis Rheum 2013;65:1-11.
5. Ozen S, Ruperto N, Dilon MJ, et al. EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides. Ann Rheum Dis. 2006;65:936-41.
6. Ozen S, Pistorio A, Lusan SM, et al. EULAR/PRINTO/PReS criteria for Henoch Scholein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: final classification criteria. Ann Rheum Dis. 2010;69:798-806.
7. Kronbichler A, Lee KH, Denicolòo S, et al. Immunopathogenesis of ANCA-associated vasculitis. Int. J. Mol. Sci. 2020;21,7319.
8. Brilland B, Garnier AS, Chevailler A, et al. Complement alternative pathway in ANCA-associated vasculitis: Two decades from bench to bedside. Autoimmunity reviews 2020;19:102424. https//di.org/10.1016/j.autrev.2019.102424.
9. Xiao H, Dairaghi DJ, Powers JP, et al. C5a receptor (CD88) blockade protects against MPO-ANCA GN. J Am Soc Nephrol. 2014;25:225-231.
10. Lyons PA, Rayner TF, Trivedi S, et al. Genetically distinct subsets within ANCA-associated vasculitis. N Engl J Med 2012;367:214-23.
11. Watts RA, Robson J. Introduction, epidemiology and classification of vasculitis. Best practice & Research Clinical Rheumatology 2018;32:3-20.
12. Sacri AS, Chambaraud T, Ranchin B, et al. Clinical characteristics and outcomes of childhood-onset ANCA-associated vasculitis: a French nationwide study. Nephrol Dial Transplant 2015;30:104-12.
13. Cabral DA, Canter DL, Muscal E. Comparing presenting clinical features in 48 children with microscopic polyangiitis to 183 children who have granulomatosis with polyangiitis (Wegener's): An ARChiVe Cohort Study. Arthritis Rheumatol. 2016;68:2514-26.
14. Dolezalova P, PKuehne FE, Ozen S, et al. Disease activity assessment in childhood vasculitis: development and preliminary validation of the Paediatric Vasculitis Activity Score (PVAS). Ann Rheum Dis 2013;72:1628-1633.
15. Bossuyt X, Tervaert JWC, Arimura Y, et al. Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. Nat Rev Rheumatol. 2017;13:683-692.
16. De Graeff N, Groot N, Brogan P, et al. European consensus-based recommendations for the diagnosis and treatment of rare paediatric vasculitides – the SHARE initiative. Rheumatology 2019;58:656-671.
17. De Groot K, Harper L, Jayne DR, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med. 2009;150(10):670-80.
18. Jones RB, Cohen Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010;363(3):211-20.
19. Jones RB, Ruruta S, Tervaert JW, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis:2-year results of a randomized trial. Ann Rheum Dis. 2015;74(6):1178-82.
20. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2013;363(3):221-32.
21. Smith RM, Jones RB, Specks U, et al. Rituximab as therapy to induce remission after relapse in ANCA-associated vasculitis. Ann Rheum Dis 2020;79:1243-1249.
22. Walsh M, Faurschou M, Berden A, et al. Long-term follow-up of cyclophosphamide compared with Azathioprine for initial maintenance therapy in ANCA-assocaited vasculitis. Clin J Am Soc Nephrol. 2014;9(9):1571-6.
23. Guillevin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med. 2014;371(19):1771-80.
24. Charles P, Terrier B, Perrodeau E, et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicenter, randomized controlled, phase III trial (MAINRITSAN2). Ann Rheum Dis. 2018;77(8):1143-9.
25. Charles P, Perrodeau E, Samson M, et al. Long-term Rituximab use to maintain remission of anti-neutrophil cytoplasmic antibody-associated vasculitis. Ann Intern Med. 2020;173:179-187.
26. Jayne D, Blockmans D, Luqmani R, et al. Efficacy and safety of belimumab and Azathioprine for maintenance of remission in anti-neutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled study. Arthritis Rheumatol. 2019;71(6):952-63.
27. Walsh M, Merkel PA, Peh CA, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. N Engl J Med. 2020;382(&): 622-631.
28. Furuta S, Sugiyama T, Umibe T, et al. Low-dose glucocorticoids plus Rituximab versus high-dose glucocorticoids plus Rituximab for remission induction in ANCA-associated vasculitis (LoVAS): protocol for a multicenter, open-label, randomized controlled trial. BMJ Open 2017;7:e018748.doi:10.1136/bmjopen-2017-018748.
29. Krischer J. The assessment of prednisone in remission trial (TAPIR) – patient centric approach (TAPIR). https://clinicaltrials.gov/ct2/show/NCT01933724.
30. Merkel P, Jayne DR, Wang C, et al. Evaluation of the safety and efficacy of Avacopan, a C5a receptor inhibitor, in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis treated concomitantly with rituximab or cyclophosphamide/azathioprine: protocol for a randomized, double-blind, active-controlled, phase 3 trial. JMIR Res Protoc 2020;9(4):e16664.doi:10.2196/16664.
31. Wechsler ME, Akuthota P, Jayne D, et al. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. N Engl J Med. 2017;376(20):1921-1932.
32. Steinfeld J, Bradford ES, Brown J, et al. Evaluation of clinical benefit from treatment with Mepolizumab for eosinophilic granulomatosis with polyangiitis. J Allergy Clin Immunol. 2019;143(6):2170-2177.
33. Morishita KA, Moorthy LN, Lubieniecka JM, et al. Early outcomes in children with anti-neutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2017;69:1470-1479.

THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG
香 港 醫 學 組 織 聯 會

Location: **4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wan Chai, Hong Kong**

ROOM RENTAL PROMOTION
Book now & get FREE 2 hours

FMSHK Member Societies are offered 2 hours FREE rental exclusively.
(Applicable to societies who haven't used the rental service before)

Suitable for Meeting / Seminar / Press Conference / Personal Gathering

Well Equipped for Rental:
Sound system : microphones /
Notebook with LCD projector /
42" TV / Broadband Internet & wifi /
Refreshment Ordering, Drinks Ordering /
Printing & Photocopy Services

Multi Function Room I

Lecture Hall

Council Chamber

For enquiry and booking, please contact the Secretariat at 2527 8898.
http://www.fmshk.org/rental

THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG

香 港 醫 學 組 織 聯 會

Application for Booking Meeting Rooms and Facilities

Name of Applicant: _____ Position Held: _____
(in block letters)

Organization: _____
(in full name)

Address: _____

Tel: _____ Fax: _____

Category of Hirer (Please tick):

☐ Member of the Federation of Medical Societies of Hong Kong

☐ Non-Member of the Federation of Medical Societies of Hong Kong

Purpose for Room Reservation: _____

Venue	Date	Time		**FOR OFFICIAL USE ONLY**	
		From	To	**Charge per hour**	**Amount of hire charges**
Multifunction Room I (15 persons)					
Council Chamber (20 persons)					
Lecture Hall (100 persons)					

Equipment	Date	Time		**FOR OFFICIAL USE ONLY**	
		From	To	**Charge per session**	**Amount of hire charges**
LCD Projector (with Screen)				**$500**	
Microphone system				**$50 per hour, minimum 2 hours**	
Laser-pointer				**FREE**	
				Total Amount:	

_____ _____ _____

Date Signature Company Chop

Duke of Windsor Social Service Building, 4/F, 15 Hennessy Road, Hong Kong
Tel: (852) 2527 8898 Fax: (852) 2865 0345 Homepage: www..fmshk.org E-mail: info@fmshk.org

Overview of Childhood-onset Systemic Lupus Erythematosus

Dr Winnie Kwai-yu CHAN

MBBS, FRCPCH, FHKCPaed, FHKAM

President, Hong Kong Society for Paediatric Rheumatology

Dr Winnie Kwai-yu CHAN

INTRODUCTION

Systemic lupus erythematosus is a prototype of autoimmune disease affecting any organ in the body. It is a disease in which chronic inflammation, antibody production and complement immune-complex deposition cause tissue damage and organ failure. Childhood-onset systemic lupus erythematosus (cSLE) is fundamentally the same disease as the adult counterpart (aSLE); however, they differ in several aspects, including the severity of disease and long-term prognosis.

EPIDEMIOLOGY

Ten to twenty percent of all SLE patients developed the disease during childhood[1]. The peak age of childhood presentation is 12-13 years of age. It is rare before five years old. World-widely the prevalence is around 1.9-25.7 per 100,000 children and the incidence varies between 0.36-2.5 per 100,000 children-years[2]. Asian, African, indigenous North American and Hispanic ancestry are more frequently affected than those of the European origin.

PATHOGENESIS

The aetiology of SLE remains unknown. Like many other autoimmune diseases, the interactions of genetic, immunologic and environmental factors play the pivotal roles in the pathogenesis. Along with the advances in Genome-Wide Association Studies (GWAS), several common alleles which may increase the risk of lupus development have been identified in adult patients. More than 30 genes causing a monogenic form of childhood-onset SLE have also been described. These genetic defects are rare. These genetic defects mainly involve the complement systems, interferon pathway, and abnormal B cell development[3].

CLINICAL PRESENTATION

The clinical presentations of cSLE are diverse. Systemic features such as pyrexia of unknown origin, weight loss and fatigue are common. The typical malar rash may not be present, and the dermatological features may be subtle. Haematological disease, neuropsychiatric SLE (NPSLE), nephritis, seizures and lymphadenopathy are more common in cSLE than in aSLE[4,5]. Childhood-onset SLE tends to be more severe at presentation and more likely to involve the kidneys and central nervous system than aSLE. The former is more likely to have an abrupt onset and aggressive course[6,7].

Hematological abnormalities including anaemia, leucopenia, lymphopenia and thrombocytopenia are common. These patients may present as isolated immune-mediated thrombocytopenia (ITP) or autoimmune haemolytic anaemia (AIHA) months to years before the disease evolves into frank lupus. Regular monitoring of the serological markers, the complements, and other organ involvement may help to reveal the ultimate diagnosis.

Lupus nephritis and NPSLE may be the first clinical presentations in cSLE without any musculocutaneous hint. Lupus nephritis is classified similarly to its adult counterpart. The severe forms of lupus nephritis, ISN/RPS (2004) class III or IV are a common histological finding, and affected children usually present clinically as nephrotic syndrome[8]. Recurrent relapse of lupus nephritis is one of the significant risk factors for progressive renal failure in lupus patients.

Neuropsychiatric symptoms in cSLE are diverse and more challenging to diagnose. The prevalence of NPSLE may be underestimated as features like mood changes, headache, and cognitive impairment may be too subtle to diagnose and differentiate from drug effect.

It has been estimated that around 10% of cSLE present with non-classical manifestations which mainly affect the pulmonary, gastrointestinal and cardiac systems. These presentations can be life-threatening. These patients may not fulfil the diagnostic criteria of American College of Rheumatology (ACR) at its presentation, and appropriate treatment may be delayed if clinicians failed to aware of the diagnosis[9].

DIAGNOSIS

There are three diagnostic criteria for systemic lupus erythematosus. The first one was established by the American College of Rheumatology (ACR), and was last revised in 1997, followed by the Systemic Lupus International Collaborating Clinic (SLICC) group classification criteria published in 2012 and the most recent European League Against Rheumatism (EULAR) criteria established in 2019 for aSLE. These criteria help make the diagnosis; however, in children, a single manifestation may predominate in the early course of the disease before additional features that meet the diagnostic criteria are revealed. The SLICC criteria have been validated for cSLE and carry a higher sensitivity and lower specificity than the ACR criteria[10].

TREATMENT

Studies in cSLE are generally non-randomised. Most recommendations have been extrapolated from the results of clinical trials in the adult populations and consensus from experts. In general, corticosteroid is the mainstay of treatment. In severe disease, pulse methylprednisolone at 10-30 mg/kg (maximum of 1,000 mg/dose) intravenous daily for 3-5 doses followed by oral prednisolone at 1-2 mg/kg/day (maximum 60 mg daily) according to the severity of organ involvement. Equivalent dose of alternative preparation of corticosteroid such as dexamethasone, which offers better oral absorption and CNS penetration than prednisolone, can be considered in some patients. Some authors preferred to use weekly pulse methylprednisolone while keeping a medium-to-low dose oral prednisolone at 10-20 mg daily during the acute phase[11,12] as pulse methylprednisolone, but not the usual-dose prednisolone, has been shown to eliminate the interferon-alpha gene expression signature in SLE[13]. However, it is not clear whether this practice will improve patients' outcomes. There is no absolute rule on steroid tapering. In general, one can reduce 10-20% of the dose in a 1-2 weekly interval based on clinical improvement. Steroid complications are well-known. The cushingoid appearance and striae are of significant concerns to teenage girls.

For decades, cyclophosphamide, given either as an infusion or oral form, has been used as adjuvant therapy in severe lupus disease. Before the NIH IV, cyclophosphamide protocol, oral cyclophosphamide at 2-3 mg/kg (maximum 100 mg) daily for 12 weeks is a common regimen for treatment of lupus nephritis in children[8]. The NIH infusion protocol using a high dose at 500-1,000 mg/m^2 monthly for six doses as induction[11,12] offers the advantage of providing better hydration and allows the use of Mesna to minimise cyclophosphamide-induced haemorrhage cystitis. The infusion route may help to ensure drug compliance. In the recent decade, the Euro-Lupus Nephritis Trial using a lower standard dose of cyclophosphamide at 500 mg infusion once every two weeks for six doses showed equal effectiveness and less serious complication[14]. Gonadotoxicity of cyclophosphamide is a major concern in young patients. GnRH analogue, like triptorelin, can be given before or after the dose of IV cyclophosphamide as an ovarian protection agent[15]. Sperm cryopreservation for future assisted reproductive technologies in post-pubertal males could be considered before cyclophosphamide therapy. However, in life- or organ-threatening scenarios, the window for reproductive intervention is narrow.

Mycophenolic acid (MPA), a reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), is an alternative to cyclophosphamide to treat moderate to severe lupus disease in paediatrics. It is a favourable option when there are concerns on future malignancies, infertility and other severe cyclophosphamide complications. Studies in adults have shown that mycophenolate mofetil (MMF) showed a non-inferior efficacy as compared with cyclophosphamide in the control of severe lupus nephritis[16]. MMF is usually given at a dose of 600 mg/m^2 per oral twice daily, not to exceed 1 gm per day in most Asian adult patients, however, children can tolerate a higher dose as compared with the adult counterpart.[11,12,17]. Side effects include gastrointestinal symptoms, cytopenia, hypogammaglobulinemia, opportunistic infections and teratogenicity. Mycophenolate sodium is the enteric-coated salt form of MPA and may have fewer gastrointestinal side effects. Clinicians have to be aware of the dosage difference between these two preparations. As most active lupus patients are female at reproductive ages, advice on contraception and possible teratogenicity of MPA should be provided.

Rituximab (RTX) is an anti-CD 20 monoclonal antibody targeting on B cells, but not plasma cells. It is licensed for adult rheumatoid arthritis, granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). Nevertheless, it is commonly used as rescue therapy in SLE patients resistant to usual treatment. A recent systemic review on the efficacy and safety of Rituximab in paediatric SLE showed that most literature data available are reports on case series[18]. There is acceptable evidence to suggest that Rituximab may improve the renal, neuropsychiatric and haematological disease of cSLE and may offer a steroid-sparing effect. The overall safety profile was acceptable in children[18]. The doses and duration of Rituximab vary. The most common regimen is RTX at 375 mg/m^2/week. The number of doses per course varies from 2 to 4, and the number of courses ranges from 1 to 12. RTX at 750 mg/m^2 (maximum 1 gm) given as two doses 14 days apart is also a common practice. Rituximab administration may result in severe infusion reactions, and hepatitis B reactivation; hence a careful selection of patients, screening of hepatitis status and IGRA for latent tuberculosis should be performed before its use[18].

After the initial induction phase, either azathioprine at 2-3 kg (maximum 150 mg) or MMF is the drug of choice for maintenance therapy. Given the long-term gonadotoxicity of cyclophosphamide, the original NIH protocol of intravenous cyclophosphamide every three months is seldom used nowadays. Azathioprine is a purine antimetabolite. It is metabolised to 6-mercaptopurine (6-MP) after ingestion. Both thiopurine methyltransferase (TPMT) and nudix hydrolase (NUDT 15) are enzymes that metabolise azathioprine. Genotyping of TPMT and NUDT 15 helps to predict the potential toxicity of thiopurine drugs and allows dose adjustment on an individual basis.

Short-term outcome may improve with intensive immunosuppressive agents. The long-term prognosis is affected by the number of disease relapses. Nephritic relapses can occur in 35% of initial responders and is a significant risk factor in the development of end-stage renal disease in lupus patients. Combination therapy using MPA and calcineurin inhibitors (CNI) such as cyclosporine A or tacrolimus serves as an option to induce remission and to prevent frequent relapses. However, the long-term nephrotoxicity of CNI is another concern[19].

Belimumab, a fully humanised monoclonal antibody which inhabits B lymphocytes stimulator (BLyS), was approved by the FDA and European Medicines Agency for the treatment of SLE in adults with moderate disease activity. Recently the FDA also approved its

use in cSLE between 5-17 years of age. A recent phase 2 randomised placebo-controlled double-blinded study evaluating the safety of belimumab at 10 mg/kg showed that belimumab had a benefit-risk profile in cSLE that was consistent with adult studies[20]. However, patients with active and severe lupus nephritis, CNS lupus or using systemic prednisolone > 1.5 mg/kg/day had been excluded in this study. More data are needed to guide clinicians on the use of this new biologic.

As in the adult patient, hydroxychloroquine at a dose of 5 mg/kg with regular ophthalmological assessment is also recommended for children with SLE. Other adjuvant therapies, including oral aspirin to avoid thrombotic phenomenon, calcium and vitamin D supplement to prevent osteoporosis, appropriate vaccinations and advice on contraception are all essential management issues.

LONG TERM PROGNOSIS

Childhood-onset SLE tends to be more aggressive. The risk of organ damage is related to the number of relapses, organ involvement and the side effects of drugs, especially steroid-induced cataract, avascular necrosis of hips and growth failure[21]. Depression can be a manifestation of active NPSLE, the side effect of medications or the impact of lupus itself[22]. Negative emotions can affect patients' daily activity, school performance, peer relationships and treatment adherence. All these psychosocial issues should not be overlooked in long-term management.

CONCLUSION

Childhood-onset SLE is a complex and severe disease. Although there are many similarities to the adult disease, the many unique features of cSLE warrant the support of a multidisciplinary team.

References

1. Kamphuis S, Silverman ED. Prevalence and burden of pediatric-onset systemic lupus erythematosus. Nature Reviews Rheumatology. 2010; 6(9):538.
2. Pineles D, Valente A, Warren B, Peterson MG, Lehman TJ, Moorthy LN. Worldwide incidence and prevalence of pediatric onset systemic lupus erythematosus. Lupus. 2011; 20 (11):1187-92.
3. Demirkaya E, Sahin S, Romano M, Zhou Q, Aksentijevich I. New Horizons in the Genetic Etiology of Systemic Lupus Erythematosus and Lupus-Like Disease: Monogenic Lupus and Beyond. Journal of Clinical Medicine. 2020; 9(3):712.
4. Wu CY, Li CF, Wu QJ, Xu JH, Jiang LD, Gong L, Wu FQ, Gu JR, Zhao JL, Li MT, Zhao Y. Chinese systemic lupus erythematosus treatment and research group registry IX: clinical features and survival of childhood-onset systemic lupus erythematosus in China. Chinese Medical Journal. 2017; 130(11):1276.
5. Aggarwal A, Srivastava P. Childhood onset systemic lupus erythematosus: how is it different from adult SLE? International Journal of rheumatic diseases. 2015;18(2):182-91.
6. Bundhun PK, Kumari A, Huang F. Differences in clinical features observed between childhood-onset versus adult-onset systemic lupus erythematosus: a systematic review and meta-analysis. Medicine. 2017;96 (37).
7. Mina R, Brunner HI. Update on differences between childhood-onset and adult-onset systemic lupus erythematosus. Arthritis research & therapy. 2013;15(4) :218.
8. Wong SN, Tse KC, Lee TL, Lee KW, Chim S, Lee KP, Chu RW, Chan W, Fong KW, Hui J, Li SP. Lupus nephritis in Chinese children–a territory-wide cohort study in Hong Kong. Pediatric Nephrology. 2006; 21(8):1104-12.
9. Huggins JL, Holland MJ, Brunner HI. Organ involvement other than lupus nephritis in childhood-onset systemic lupus erythematosus. Lupus. 2016; 25(8):857-63.
10. Dahlström Ö, Sjöwall C. The diagnostic accuracies of the 2012 SLICC criteria and the proposed EULAR/ACR criteria for systemic lupus erythematosus classification are comparable. Lupus. 2019; 28(6):778-82.
11. Mina R, Von Scheven E, Ardoin SP, Eberhard BA, Punaro M, Ilowite N, Hsu J, Klein-Gitelman M, Moorthy LN, Muscal E, Radhakrishna SM. Consensus treatment plans for induction therapy of newly diagnosed proliferative lupus nephritis in juvenile systemic lupus erythematosus. Arthritis care & research. 2012; 64(3):375-83.
12. Groot N, De Graeff N, Avcin T, Bader-Meunier B, Brogan P, Dolezalova P, Feldman B, Kone-Paut I, Lahdenne P, Marks SD, McCann L. European evidence-based recommendations for diagnosis and treatment of childhood-onset systemic lupus erythematosus: the SHARE initiative. Annals of the rheumatic diseases. 2017; 76(11):1788-96.
13. Guiducci C, Gong M, Xu Z, Gill M, Chaussabel D, Meeker T, Chan JH, Wright T, Punaro M, Bolland S, Soumelis V. TLR recognition of self nucleic acids hampers glucocorticoid activity in Lupus. Nature. 2010; 465(7300):937-41.
14. D'cruz DP, Houssiau FA. The Euro-Lupus Nephritis Trial: the development of the sequential treatment protocol. Lupus. 2009;18(10):875-7.
15. Brunner HI, Silva CA, Reiff A, Higgins GC, Imundo L, Williams CB, Wallace CA, Aikawa NE, Nelson S, Klein-Gitelman MS, Rose SR. Randomized, double-blind, dose-escalation trial of triptorelin for ovary protection in childhood-onset systemic lupus erythematosus. Arthritis & Rheumatology. 2015;67(5):1377-85.
16. Ginzler EM, Dooley MA, Aranow C, Kim MY, Buyon J, Merrill JT, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. N Engl J Med. 2005; 353: 2219–28
17. Paredes A. Can mycophenolate mofetil substitute cyclophosphamide treatment of pediatric lupus nephritis?. Pediatric Nephrology. 2007;22(8):1077-82.
18. Mahmoud I, Jellouli M, Boukhris I, Charfi R, Tekaya AB, Saidane O, Ferjani M, Hammi Y, Trabelsi S, Khalfallah N, Tekaya R. Efficacy and safety of Rituximab in the management of pediatric systemic lupus erythematosus: a systematic review. The Journal of pediatrics. 2017; 187:213-9.
19. Bertsias GK, Tektonidou M, Amoura Z, Aringer M, Bajema I, Berden JH, et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis. 2012; 71:1771–82.
20. Brunner HI, Abud-Mendoza C, Viola DO, Penades IC, Levy D, Anton J, Calderon JE, Chasnyk VG, Ferrandiz MA, Keltsev V, Gastanaga ME. Safety and efficacy of intravenous Belimumab in children with systemic lupus erythematosus: results from a randomised, placebo-controlled trial. Annals of the Rheumatic Diseases. 2020;79(10):1340-8.
21. Sit JK, Chan WK. Risk factors for damage in childhood-onset systemic lupus erythematosus in Asians: a case-control study. Pediatric Rheumatology. 2018 1;16(1):56.
22. Kohut SA, Williams TS, Jayanthikumar J, Landolt-Marticorena C, Lefebvre A, Silverman E, Levy DM. Depressive symptoms are prevalent in childhood-onset systemic lupus erythematosus (cSLE). Lupus. 2013;22(7):712-20.

Certificate Course in

Ophthalmology 2021 *(Video Lectures)*

Jointly organised by

The Federation of Medical Societies of Hong Kong

The Hong Kong Ophthalmological Society

Objectives:

This course aims to provide an overview and update on the diagnosis and management of common and important eye diseases. After attending the course, attendees will learn how to deal with common ophthalmic conditions and when to refer patients to ophthalmologists.

Date	Topics	Speakers
24 Feb, 2021	Cataract and Cataract Surgery Update	Dr. CHAN Chung Yan, Tommy *FHKAM (Ophthalmology)*
	Refractive Errors, Presbyopia and Refractive Surgeries	
3 Mar, 2021	Corneal and External Eye Diseases	Dr. CHOY Nga Kwan, Bonnie *FHKAM (Ophthalmology)*
	Glaucoma and Glaucoma Surgery Update	Dr. WONG Ka Wai, Jasper *FHKAM (Ophthalmology)*
10 Mar, 2021	Neuro-Ophthalmology	Dr. HO Wing Lau *FHKAM (Ophthalmology)*
	Squint, Paediatric Ophthalmology	Dr. YAM Cheuk Sing, Jason *FHKAM (Ophthalmology)*
17 Mar, 2021	Update in Orbital Diseases and Oculoplastic Surgery	Dr. KWOK Sze Wai, Jeremy John *FHKAM (Ophthalmology)*
	Red Eyes, Ocular Trauma and Emergencies	Dr. LEE Allie *FHKAM (Ophthalmology)*
24 Mar, 2021	Retinal Detachment and Diabetic Retinopathy	Dr. LUK Oi Jing, Fiona *FHKAM (Ophthalmology)*
	Common Macular Diseases and Treatment	Dr. LAI Hiu Ping, Frank *FHKAM (Ophthalmology)*
31 Mar, 2021	Ophthalmic Imaging	Dr. MOHAMED Shaheeda *FHKAM (Ophthalmology)*
	Use of Laser in Ophthalmology	Dr. SEE LEUNG Wing Yun, Joy *FHKAM (Ophthalmology)*

Date : 24 February & 3, 10, 17, 24, 31 March, 2021 (Wednesday)
Duration of session: 1.5 hours (6 sessions)
Time : 7:00 pm – 8:30 pm
Course Feature: Video lectures (with Q&A platform for participants to post the questions)
Quiz for doctors: To tie in with the CME requirements for video lectures, DOCTORS are required to complete a quiz after the completion of each lecture
Language Media : Cantonese (Supplemented with English)
Course Fee : HK$1,000 (6 sessions)
Certificate : Awarded to participants with a minimum attendance of 70% (4 out of 6 sessions)
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898 Fax : 2865 0345 Email : vienna.lam@fmshk.org

CME / CNE Accreditation in application
Online Application from website: http://www.fmshk.org

City Exploration: The Weekend Markets

Dr Karen LAU
MBBS(HKU), MRCPCH, FHKC Paed, FHKAM (Paed), DCH (International), DCH (HK)

Dr Karen LAU

It has been a tough time for most of us in the past year, as the pandemic has left us with quite a confined life. Yet there are still some enlightening and peaceful moments during this COVID-19 period. When the global transport and delivery services are being hindered, people start to explore more on local produce. Being a regular weekend market visitor and a market booth owner myself, I find that more and more people begin to take notice of the different types of weekend markets around the city.

Fig. 1. A booth in the weekend market. (Photo from personal collection)

These weekend markets are variably located: at the corner of a narrow street strewn with wall graffiti in Sai Ying Pun; inside cultural preserved buildings in Shek Kip Mei and Tsuen Wan; along the new hipster area in Sham Shui Po; within the café clusters in Mid-level; along with the seashore areas in Sai Kung and Stanley. Sometimes you can see groups of friends and families looking at small booths with interest. These are booths selling products made by mostly freelance locals. Weekend markets carry quite a long history in our city. In recent years, they have become more popular. If you are interested in handmade products, small-sized artworks, locally produced food or self-designed clothings, you can discover surprises at these places.

It may not be easy to get information about weekend markets, as some of them are of tiny scale. I would like to list out some interesting ones here, as a summary and a humble recommendation.

JCCAC (Jockey Club Creative Art Centre)

JCCAC should be the pioneer of the weekend market, and up till now, it is still one of the best quality markets selling handmade products. They hold a market every three months. Each time the market attracts lots of locals with quite a crowd!
Address: 30 Pak Tin Street, Shek Kip Mei
Website: www.jccac.org.hk

The Mills

Being a landmark revitalisation project itself, The Mills supports small local handcrafts businesses. Apart from weekend markets, The Mills also often offers some pop-up stores for a few months selling works by various talented local artists.
Address: 45 Pak Tin Par Street, Tsuen Wan
Website: www.themills.com.hk

Fig. 2. The weekend markets. (Photos excepted from www.jccac.org.hk, www.themills.com.hk, https://www.facebook.com/niceplaceto/, https://www.jtia.hk/)

A Nice Place To

This market is my favourite. It is located at the inner corner of Artlane in Sai Ying Pun. Two passionate youngsters have rented a two-floor shop to hold exhibitions and to organise weekend handcrafts markets. Everything is true-heartedly selected, and I always end up spending a bit too much here.
Address: 2 Chung Ching Street, Sai Ying Pun
Website: https://www.facebook.com/niceplaceto/

Jao Tsung-I Academy

The historic building itself is impressive enough; not many people know there are frequent weekend markets being hold. It is definitely a good idea to spend a day there taking a few nice pictures and shopping around during market days.
Address: 800 Castle Peak Road, Lai Chi Kok
Website: https://www.jtia.hk/

There are simply too many places to recommend to you; our city is full of vibracy and creativity.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	1	* Facebook Live HKMA-HKS&H CME Programme 2019-2020 Topic: Updates on Acute Stroke Management 2	3	* Facebook Live Chronic Pain Management - Online 4	5	6
7	8	* Facebook Live Safety & Efficacy of Corticosteroids for Asthma Treatment - Online 9	* The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed 10	11	12	13
14	15	16	17	* Facebook Live Leading the Shift in Paradigm in T2D Treatments: Cardio-Protection with Glucose-Lowering Drug - Online 18	19	20
21	* Intravenous Iron: A Framework for Changing the Management of Iron Deficiency Anemia 22	* Facebook Live HKMA-GHK CME Programme Topic: 1) CA lung; 2) Lung Nodules and Ground Glass Opacities; how should we manage them? * Certificate Course on Childhood Arthritis and Rheumatic Disease I (Video Lectures) 23	* Certificate Course in Ophthalmology 2021(Video Lectures) 24	* Facebook Live Hemorrhoids…..A Common Disease and Effective Treatment Options - Online * FMSHK Executive Committee Meeting * FMSHK Council Meeting 25	* Facebook Live Non-Surgical Treatment of Benign Thyroid Nodule - Online 26	27
28						

Date / Time	Function	Enquiry / Remarks
2 TUE 1:00 PM	**Facebook Live** **HKMA-HKS&H CME Programme 2019-2020** **Topic: Updates on Acute Stroke Management** Organiser: Hong Kong Medical Association Hong Kong Sanatorium & Hospital; Speaker: Dr Patrick Chung-ki LI	HKMA CME Department 2527 8452 1 CME Point
4 THU 2:00 PM	**Facebook Live** **Chronic Pain Management - Online** Organiser: HKMA - Kowloon East Community Network; Speaker: Dr Timmy Chi-wing CHAN	Miss Antonia LEE 3108 2514 1 CME Point
9 TUE 2:00 PM	**Facebook Live** **Safety & Efficacy of Corticosteroids for Asthma Treatment - Online** Organiser: HKMA - Kowloon West Community Network; Speaker: Dr WONG King-ying	Miss Antonia LEE 3108 2514 1 CME Point
10 WED 7:30 AM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed** **Organiser: Hong Kong Neurosurgical Society** Speaker(s): Dr Ryan Pak-to YUEN; Chairman: Dr Danny Tat-ming CHAN; Venue: Conference Room, F2, Department of Neurosurgery, Queen Elizabeth Hospital; or via Zoom meeting	1.5 points College of Surgeons of Hong Kong Enquiry: Dr Calvin MAK Tel: 2595 6456 Fax: 2965 4061
18 THU 2:00 PM	**Facebook Live** **Leading the Shift in Paradigm in T2D Treatments: Cardio-Protection with Glucose-Lowering Drug - Online** Organiser: HKMA-New Territories West Community Network; Speaker: Dr LAU Chun-leung	Miss Antonia LEE 3108 2514 1 CME Point
22 MON 7-8 PM	**Intravenous Iron: A Framework for Changing the Management of Iron Deficiency Anemia** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Raymond Siu-ming WONG	Ms Cordelia WU 2527 8898
23 TUE 2:00 PM	**Facebook Live** **HKMA-GHK CME Programme** **Topic:** **1) CA lung;** **2) Lung Nodules and Ground Glass Opacities; how should we manage them?** Organiser: Hong Kong Medical Association Gleneagles Hong Kong Hospital; Speaker: Dr WAN Chi-kin, Dr Alan SIHOE	HKMA CME Department 2527 8452 1 CME Point
7:00 PM	**Certificate Course on Childhood Arthritis and Rheumatic Disease I (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr SY KONG	Ms Vienna LAM Tel: 2527 8898
24 WED 7:00 PM	**Certificate Course in Ophthalmology 2021(Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong	Ms Vienna LAM Tel: 2527 8898
25 THU 2:00 PM	**Facebook Live** **Hemorrhoids…..A Common Disease and Effective Treatment Options - Online** Organiser: HKMA-HK East Community Network; Speaker: Dr NG Ka-kin;	Ms Candice TONG 3108 2513 1 CME Point
7:00 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
8:00 PM	**FMSHK Council 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
26 FRI 2:00 PM	**Facebook Live** **Non-Surgical Treatment of Benign Thyroid Nodule - Online** Organiser: HKMA-YTM Community Network; Speaker: Dr Daisy Mei-yee KAN	Ms Candice TONG 3108 2513 1 CME Point

Answers to Radiology Quiz

Answers:

1. No. There is anterior dislocation of the left shoulder. Additional inferior subluxation of the left humerus is evident with the presence of abnormal surrounding soft tissue density extending into the left subacromial space (red arrows in Fig 1.)

2. No. Abnormal ill-defined mixed lytic-sclerotic permeative appearance of the left proximal humerus with a broad zone of transition is noted. Cortical irregularity and destruction is evident. Abnormal periosteal reactions are also present. The internal matrix appears amorphous and cloud-like, suggesting the presence of an osteoid matrix. No pathological fracture is evident.

3. 1. Codman triangle (yellow arrow in Fig 1.)
   2. Sunburst appearance (green arrow in Fig 1.)

   These types of periosteal reactions are often associated with aggressive bony lesions.

4. Aggressive bony lesions/processes in the adolescent age group include:

   1. Osteosarcoma
   2. Ewing's sarcoma
   3. Bony metastasis
   4. Osteomyelitis (if clinical features suggest infection)

5. In this case, the likely diagnosis by plain film findings is in favour of osteosarcoma. Early referral to the Orthopaedics team with further workup is recommended.

   Staging of bone malignancy involves
   - Local staging by MRI to map out the bone marrow and soft tissue involvement: and
   - Distant staging by CT thorax and bone scan,

   Definitive diagnosis is achieved by histopathology, prior to which the treating surgeon should be consulted to plan the biopsy track in order to reduce the chance of seeding.

Dr Leanne Han-qing CHIN
MBBS, FRCR

Certificate Course for Doctors, Nurses and Healthcare professionals interested in Paediatric Rheumatology

- **Course No. C359**
- **CME/CNE Course**

Certificate Course on

Childhood Arthritis and Rheumatic Disease I

(Video Lectures)

Jointly organised by

The Federation of Medical Societies of Hong Kong

Hong Kong Society for Paediatric Rheumatology

Objectives:

To promote the public awareness of rheumatic diseases in children and to update the recent advancement and management of this group of patients.

Date	Topics	Speakers
23 Feb, 2021	Children with Musculoskeletal Complaint and Arthritis Mimics	Dr SY Kong Associate Consultant, Department of Paediatrics, KWH Hong Kong Society for Paediatric Rheumatology
2 Mar, 2021	Children with Juvenile Idiopathic Arthritis	Dr Roanna Yeung Associate Consultant, Department of Paediatrics, QEH Hong Kong Society for Paediatric Rheumatology
9 Mar, 2021	Living with Juvenile Idiopathic Arthritis	Dr Assunta Ho Associate Consultant, Department of Paediatrics, PWH Hong Kong Society for Paediatric Rheumatology Dr Andrea Leung Senior Physiotherapist, Physiotherapy Department, QEH Hong Kong Society for Paediatric Rheumatology
16 Mar, 2021	Cutaneous Manifestations of Paediatric Rheumatic Disease	Dr David Luk Consultant, Department of Paediatrics and Adolescent Medicine, UCH Hong Kong Society for Paediatric Rheumatology
23 Mar, 2021	Myositis and Dermatomyositis in Children – A Distinct Entity from Adult	Dr Grace Chiang Associate Consultant, Department of Paediatrics and Adolescent Medicine, AHNH Hong Kong Society for Paediatric Rheumatology
30 Mar, 2021	Medications Used in Paediatric Rheumatology	Dr Celeste Ewig Senior Lecturer, School of Pharmacy, the Chinese University of Hong Kong Hong Kong Society for Paediatric Rheumatology

Date : 23 February & 2, 9, 16, 23, 30 March, 2021 (Tuesday)
Duration of session: 1.5 hours (6 sessions)
Time : 7:00 pm – 8:30 pm
Course Feature: Video lectures (with Q&A platform for participants to post the questions)
Quiz for doctors: To tie in with the CME requirements for video lectures, DOCTORS are required to complete a quiz after the completion of each lecture
Language Media : Cantonese (Lecture 1-5) ; English (Lecture 6)
Course Fee : HK$1,000 (6 sessions)
Certificate : Awarded to participants with a minimum attendance of 70% (4 out of 6 sessions)
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898 Fax : 2865 0345 Email : vienna.lam@fmshk.org

CME / CNE Accreditation in application
Online Application from website: http://www.fmshk.org

SPORICIDAL DISINFECTANTS POWERED BY CHLORINE DIOXIDE, EFFECTIVE AGAINST SARS-CoV-2[1]

MEDICAL SURFACE DISINFECTION

Ensuring all medical surfaces receive effective disinfection is key in preventing healthcare-associated infections (HAIs).

SARS-CoV-2 has been shown to survive on inanimate surfaces for 4 to 7 days[2].

SPORICIDAL SURFACE DISINFECTANTS

HIGH LEVEL DISINFECTION OF MEDICAL SURFACES FOR THE PREVENTION OF OUTBREAKS IN HOSPITALS & CLINICS

JET

FOR NEAR PATIENT SURFACES SUCH AS MATTRESSES, BED RAILS, IV POLES AND PATIENT MONITORING EQUIPMENT IN A CONTACT TIME OF 1 MINUTE.

FUSE

FOR LARGE SURFACE AREAS SUCH AS FLOORS AND WALLS, IN A CONTACT TIME OF 5 MINUTES.

cache™

BROUGHT TO YOU BY TRISTEL

GET IN TOUCH FOR A DEMONSTRATION & PRODUCT INFORMATION

OFFICE/WHATSAPP: **2895 6968** - EMAIL **customerservicehk@tristel.com**

FUSE refers to Tristel Fuse for Surfaces JET refers to JET (Cache).

[1]A representative sample of Tristel chlorine dioxide at 20 parts per million (ppm) was tested by a United States Biosafety Category 3 laboratory in accordance with EN 14476:2013+A2:2019.

[2]A. W. H. Chin et al., "Stability of SARS-CoV-2 in different environmental conditions," The Lancet Microbe, vol. 1, no. 1, p. e10, 2020, doi: 10.1016/s2666-5247(20)30003-3.