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thesynapse

THE MEDICAL PROFESSIONALS' NETWORK

Can
Bronchial Carcinoma
be ascribed to Asbestos Exposure for Industrial Disease Compensation Purposes?

CME for Real Heroes

Getting to Grips with SPMS - Expert View

Doctors for the Environment - Malta

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ENTRESTO® (sacubitril/valsartan) **Presentation**: Each film-coated tabletof Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg contains sacubitril and valsartan respectively (as sacubitril valsartan sodium salt complex). **Indications:** In adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction. **Dosage & administration**:The recommended starting dose of Entresto is one tablet of 49 mg/51 mg twice daily, doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient. In patients not currently taking an ACE inhibitor or an ARB, or taking low doses of these medicinal products, a starting dose of 24 mg/26 mg twice daily and slow dose titration (doubling every 3-4 weeks) are recommended. A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg, moderate or severe renal impairment (use with caution in severe renal impairment) and moderate hepatic impairment. Do not co-administer with an ACE inhibitor or an ARB. Do not start treatment for at least 36 hours after discontinuing ACE inhibitor therapy. Entresto may be administered with or without food. The tablets must be swallowed with a glass of water. **Contraindications**: Hypersensitivity to the active substances or to any of the excipients. Concomitant use with ACE inhibitors. Do not administer until 36 hours after discontinuing ACE inhibitor therapy. Known history of angioedema related to previous ACE inhibitor or ARB therapy. Hereditary or idiopathic angioedema. Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). Severe hepatic impairment, biliary cirrhosis and cholestasis. Second and third trimester of pregnancy. **Warnings/Precautions**: Dual blockade of the renin angiotensin-aldosterone system (RAAS): Combination with an ACE inhibitor is contraindicated due to the increased risk of angioedema. Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with sacubitril/valsartan is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan. Combination of Entresto with direct renin inhibitors such as aliskiren is not recommended. Entresto should not be co-administered with another ARB containing medicinal product. Hypotension: Treatment should not be initiated unless SBP is ≥100 mmHg. Patients with SBP <100 mmHg were not studied. Cases of symptomatic hypotension have been reported in patients treated with sacubitril/valsartan during clinical studies, especially in patients ≥65 years old, patients with renal disease and patients with low SBP (<112 mmHg).Blood pressure should be monitored routinely when initiating or during dose titration with sacubitril/valsartan. If hypotension occurs, temporary down-titration or discontinuation of sacubitril/valsartanis recommended. Impaired or worsening renal function: Limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m2). There is no experience in patients with end-stage renal disease and use of sacubitril/valsartan is not recommended. Use of sacubitril/valsartan may be associated with decreased renal function, and down-titration should be considered in these patients. Impaired renal function: Patients with mild-moderate renal function are more at risk of developing hypotension while patients with severe renal impairment may be at a greater risk of hypotension. sacubitril/valsartan is not recommended in patients with end-stage renal disease. Hyperkalaemia: Treatment should not be initiated if the serum potassium level is >5.4 mmol/l. Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists. If clinically significant hyperkalaemia occurs, consider adjustment of concomitant medicinal products or temporary down-titration or discontinuation . If serum potassium level is >5.4 mmol/l discontinuation should be considered. Angioedema: Angioedema has been reported with sacubitril/valsartan. If angioedema occurs, discontinue sacubitril/valsartanimmediately and provide appropriate therapy and monitoring until complete and sustained resolution of signs and symptoms has occurred. It must not be re administered. Patients with a prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if Entresto is used in these patients. Black patients have an increased susceptibility to develop angioedema. Patients with renal artery stenosis: Caution is required and monitoring of renal function is recommended. Patients with NYHA functional classification IV: Caution should be exercised due to limited clinical experience in this population. Patients with hepatic impairment: There is limited clinical experience in patients with moderate hepatic impairment (ChildPugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Caution is therefore recommended in these patients. B-type natriuretic peptide (BNP): BNP is not a suitable biomarker of heart failure in patients treated with sacubitril/valsartan because it is a neprilysin substrate. **Interactions**: Contraindicated with ACE inhibitors, 36 hours washout is required. Use with aliskiren contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). Should not be co-administered with another ARB. Use with caution when co-administering sacubitril/valsartan with statins or PDE5 inhibitors. No clinically relevant interaction was observed when simvastatin and sacubitril/valsartan were co-administered. Monitoring serum potassium is recommended if sacubitril/valsartanis co-administered with potassium-sparing diuretics or substances containing potassium (such as heparin). Monitoring renal function is recommended when initiating or modifying treatment in patients on sacubitril/valsartan who are taking NSAIDs concomitantly. Interactions between sacubitril/valsartan and lithium have not been investigated. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. Co-administration of sacubitril/valsartan and furosemide reduced Cmax and AUC of furosemide by 50% and 28%, respectively, with reduced urinary excretion of sodium. Co-administration of nitroglycerin and sacubitril/valsartan was associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitroglycerine alone, no dose adjustment is required. Co administration of sacubitril/valsartan with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) may increase the systemic exposure of LBQ657 or valsartan. Appropriate care should be exercised. Co-administration of sacubitril/valsartan with metformin reduced both Cmax and AUC of metformin by 23%. When initiating therapy with sacubitril/valsartan in patients receiving metformin, the clinical status of the patient should be evaluated. Fertility, pregnancy and lactation: The use of sacubitril/valsartan is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy. It is not known whether sacubitril/valsartan is excreted in human milk, but components were excreted in the milk of rats. Entresto is not recommended during breastfeeding. A decision should be made whether to abstain from breast feeding or to discontinue Entresto while breast feeding, taking into account the importance of sacubitril/valsartan to the mother. **Undesirable effects**: Very common (≥1/10): Hyperkalaemia, hypotension, renal impairment. Common (≥1/100 to <1/10): Anaemia, hypokalaemia, hypoglycaemia, dizziness, headache, syncope, vertigo, orthostatic hypotension, cough, diarrhoea, nausea, gastritis, renal failure, acute renal failure, fatigue, asthenia. Uncommon (≥1/1,000 to <1/100): Hypersensitivity, postural dizziness, pruritis, rash, angioedema. **Packs sizes**: Entresto 24 mg/26 mg–x28 tablets; Entresto49 mg/51 mg –x28 tablets; Entresto 97 mg/103 mg-x28 & x56 tablets. **Legal classification**: POM. Marketing Authorisation Holder: Novartis Europharm Ltd, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland. Marketing Authorisation Numbers: Entresto 24 mg/26 mg film coated tablets EU/1/15/1058/001; Entresto 49 mg/51 mg film coated tablets EU/1/15/1058/002-004; Entresto 97 mg/103 mg film coated tablets EU/1/15/1058/005-007. Please refer to the Summary of Product Characteristics (SmPC) before prescribing. Full Prescribing Information is available on request from Novartis Pharma Services Inc., Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel: +356 21222872. 2020-MT-ENT-25-JUN-2020

References: 1. Seferovic PM, Ponikowski P, Anker SD, et al. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of The Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2019;21(10):1169-1186. 2. Claggett B, Packer M, McMurray JJV, et al; for the PARADIGM-HF Investigators. Estimating the long-term treatment benefits of sacubitril-valsartan. *N Engl J Med.* 2015;373(23):2289-2290. 3. Lewis EF, Claggett BL, McMurray JJV, et al. Health-realted quality of life outcomes in PARADIGM-HF. *Circ Heart Fail.* 2017; 10(8):e003430. 4. ENTRESTO Summary of product characteristics. European Medicines Agency website. http://www.ema.europa.eu. Accessed 2020.

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Entresto® sacubitril/valsartan

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Issue Guide

06 Getting to Grips with SPMS – Expert View

07 Can Bronchial Carcinoma be ascribed to Asbestos Exposure for Industrial Disease Compensation Purposes?

08 Cancer Epigenetics and its Clinical Applications

10 Doctors for the Environment - Malta

12 MMSA & MPSA Corner

13 CME for Real Heroes

14 Smoking in the 21st century

18 Cervical Cancer

20 Imaging Back Pain

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NINLARO™
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EXTEND EFFICACY. EXTEND THEIR POSSIBILITIES.

NINLARO™ (ixazomib) is the first and only oral proteasome inhibitor approved for treatment of patients with multiple myeloma who have received at least 1 prior therapy[1]

Superior PFS with NINLARO+len/dex vs placebo+len/dex[1*]

- ~6-month improvement in median PFS (20.6 vs 14.7 months; HR=0.742; P=0.012)[1†]

Safety profile that was sustainable for most patients[2]

- The most frequently reported (20%) adverse reactions with NINLARO+len/dex were diarrhea, rash,[§] constipation, neutropenia,[‖] thrombocytopenia,[‖] anemia, fatigue, nausea, peripheral edema, peripheral neuropathy,[¶] back pain, vomiting, upper respiratory tract infection, nasopharyngitis, and insomnia[2]

Simplicity of oral administration[1]

INDICATION: NINLARO in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.[1]

† Results of the pivotal phase 3 trial TOURMALINE-MM1—a global, randomized, double-blind, placebo-controlled clinical trial designed to evaluate the superiority of once-weekly oral NINLARO+len/dex over placebo+len/dex in 722 adult patients with relapsed/refractory multiple myeloma. Primary and final statistical analysis of PFS occurred at a median of 14.7 months' follow-up. Additional analyses of safety and overall survival were conducted at a median of 23 months' follow-up.[2]

‡ At the primary and final analysis of 14.7 months' median follow-up.[1]

‖ Represents multiple MedDRA-preferred terms.[2]

¶ Data based on standardized MedDRA query, incorporating pooled preferred terms or multiple preferred terms. Thrombocytopenia incorporates preferred terms of thrombocytopenia and decreased platelet count. Neutropenia incorporates preferred terms of neutropenia and decreased neutrophil count.[2]

Data based on the high-level term peripheral neuropathies not elsewhere classified, excluding neuritis; preferred terms included peripheral neuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy.[2]

len/dex=lenalidomide and dexamethasone; PFS=progression-free survival.

For additional information, please see Summary of Product Characteristics.

REFERENCES: 1. NINLARO [summary of product characteristics]. Taastrup, Denmark: Takeda Pharma A/S; 2019.
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Vaccination
Quo Vadis?

Evidence has it that the multi-organ effect of Sars-CoV-2 is primarily attributed to hypercytokinemia, especially in the elderly & immunocompromised. Malta has suffered the brunt of this. According to the European Centre for Disease Prevention and Control, as of 30 September 2020, the 14-day cumulative number of Covid-19 deaths per 100,000 was 3.6 for Malta, topping the EU/EEA charts. If Covid-19 excess deaths were factored in, Malta would possibly fare better; nonetheless Malta is facing a serious problem stemming from the ingrained laissez-faire attitude of the general public.

We also have not fully comprehended this +ve-sense RNA virus including immunogenicity-related issues. The frequency of re-infections is unknown ... whether the presence of antibody changes susceptibility to subsequent infection or how long antibody protection lasts are not clearly understood. Further to this, the long-term sequelae are still unknown and only time will tell …

It seems that the only hope relies on the SARS-Cov-2 vaccine. Quite possibly by Q1 of 2021 specific categories of people, including the vulnerable and selected groups of frontliners, would have access to the vaccine and in the ensuing months, offered to rest of the Maltese population in a staggered risk-based approach. Cornerstone to this is the premise that one should vaccinate with a view to prevent Covid-19 excess deaths and mitigate long term negative economic impacts. However, one must realise that the achilles heel may well be the supply of raw materials, such as glass vials. And before one begins to rub hands with glee, no-one really knows whether one shot will be enough or if boosters will be required, especially in the pediatric cohort. Let us not forget that there is a good proportion of children who are immunologically naïve to the seasonal influenza and other vaccines which have been purported to prime the immune system for SARS-Cov-2. At the other end of the spectrum we have the elderly. Will the proposed vaccine be effective in the elderly with their aged immune systems and co-morbidities? According to the CDC, people aged 30-39 years have a 4x death rate compared to the 18-29 age cohort and this rises to 630x death rate for those above 85 years of age [unadjusted rate ratios].

Against this backdrop each and every person living in the Northern hemisphere is faced with the question as to whether one should have the influenza vaccine for the upcoming Winter season. We will most probably not have such a dilemma next year since my guess is that any SARS-Cov-2 vaccine will incorporate the seasonal flu vaccine. It may be the fact that the Northern hemisphere, including Malta, may experience less cases of influenza cases during the upcoming Winter. This may not stem solely from the swiss cheese model of risk mitigation i.e. mask-wearing, social distancing, hygiene and rapid testing. There has been, in fact, a lower incidence of influenza during the Winter season between May and October in the Southern Hemisphere which could well translate into fewer cases being imported to the Northern Hemisphere.

Let us not lower our guard. We as care givers have a social and moral obligation to become vaccinated and promote such practice. Policy makers on the other hand need to implement systems ***and enforce*** them with a view to safeguard the general population, especially the most vulnerable patients. Much is at stake …

Dr Josanne Aquilina discusses the management of Secondary Progressive Multiple Sclerosis with Dr Ian Ellul.

Getting to Grips with SPMS

WHAT IS MULTIPLE SCLEROSIS AND MORE SPECIFICALLY, SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS?

Multiple Sclerosis (MS) is an immune mediated inflammatory demyelinating disease of the Central Nervous System. It is characterized, as its name implies, by multifocal plaques of demyelination, disseminated in space and in time.

MS is highly heterogeneous and can be classified into different types depending on the pattern and nature of the course of the disease. The Clinically Isolated Syndrome (CIS) represents the first clinical attack of the disease. Approximately 90% of MS patients have a relapsing and remitting course with clear and distinct attacks with full or incomplete recovery in between. These are classified as Relapsing Remitting Multiple Sclerosis (RRMS) where there is no apparent progression of the disease during the periods of remission. The other 10% would have a progressive course characterized by worsening neurological function from onset, and such deterioration progresses gradually. These are classified as Primary Progressive Multiple Sclerosis (PPMS). When RRMS patients demonstrate continued and progressive deterioration without remissions, they become classified as Secondary Progressive Multiple Sclerosis (SPMS). The transition from RRMS to SPMS is very variable and may take 10 to 20 years from disease onset.

HOW DO YOU DIAGNOSE MS?

MS is the commonest demyelinating disease of the CNS and can start at a young age. The diagnosis is based on the clinical presentation, and corroborated by investigations with Magnetic Resonance Imaging of the brain and spinal cord, cerebrospinal fluid analysis and sometimes evoked potentials. Specific criteria of dissemination in space and in time must be satisfied.

WHAT IS THE PREVALENCE OF MS IN MALTA?

There are approximately 400 patients suffering from MS in Malta. These would include all the types described earlier.

HOW DOES MALTA COMPARE TO OTHER COUNTRIES IN RELATION TO THE PREVALENCE OF MS?

It is well known that the prevalence of MS is higher in the northern countries and many theories have been hypothesized to explain this, including sun exposure and vitamin D levels, environmental factors as well as genetic factors.

SINCE THE MAJORITY OF MS PATIENTS SUFFER FROM RRMS, WHAT ARE THE KEY SIGNS AND SYMPTOMS THAT INDICATE A POSSIBLE TRANSITION FROM RRMS TO SPMS?

The symptoms during the periods of remission after each relapse would, as the disease progresses, not return to baseline values but worsen over time. Furthermore, the remission periods decrease in duration, meaning that the frequency of the flare-ups increases gradually. This will result in progressive deterioration. The transition period is not always clearly identifiable and the diagnosis may sometimes be made in retrospect.

WHAT ARE THE CURRENT TREATMENTS FOR RRMS & SPMS?

There are different disease modifying treatments for RRMS. Approximately 25 years ago the beta interferons were introduced, followed by glatiramer acetate which is an immunomodulating drug comprising synthetic polypeptides. These are injectables with subcutaneous or intramuscular administration. Eventually oral agents were introduced, including fingolimod and dimethyl fumarate, both having immunomodulatory and anti-inflammatory properties. Fingolimod is a sphingosine-1-phosphate receptor modulator which sequestrates the lymphocytes in the lymph nodes. Other oral therapies introduced include teriflunomide and cladribine. Infusion therapies such as Natalizumab, Ocrelizumab and Alemtuzamab are used for highly active disease, under specialist supervision.

Treatment for SPMS is more limited. Siponimod which, similar to fingolimod, is also a sphingosine-1-phosphate receptor modulator, is currently the only licensed treatment available for SPMS with evidence of disease activity.

HOW DOES SPMS IMPACT THE LIVES OF PATIENTS AND THEIR FAMILIES?

As the disease progresses, patients become more dependent on families and/or carers due to the ensuing mobility issues. This translates into an added socio-economic burden on the family, community services and rehabilitation institutions.

SINCE SPMS IS A PROGRESSIVE DISEASE, HOW SHOULD PATIENTS KEEP TRACK OF THEIR PROGRESSION?

Patients should monitor their mobility and cognitive functions and possibly write them in a journal. These should then be discussed with the neurologist who would then determine the progression status of the disease.

ARE THERE ANY SUPPORT GROUPS THAT AN MS PATIENT CAN GET SUPPORT FROM?

There is the Multiple Sclerosis society of Malta, **http://www.msmalta.org.mt/**

HOW IS THE SARS-COV-2 PANDEMIC AFFECTING MS PATIENTS?

The risks inherent to the pandemic increase proportionally with the degree of vulnerability of patients. This stems from both the disease progression which can result in mobility issues, as well as the treatment of MS itself.

PROF. ALBERT CILIA-VINCENTI

Can Bronchial Carcinoma

be ascribed to Asbestos Exposure for Industrial Disease Compensation Purposes?

In the early 1990s I received an invitation to join the *UK Register of Expert Witnesses*, a publication put together by lawyers for lawyers. I accepted and stipulated breast and cervical cancer and asbestos-related disease as the areas I would advise on in medico-legal litigation and that I was prepared to act on behalf of patients. I had breast and cervical neoplasia publications to back me up and working in Winchester had provided good experience of asbestos-related deaths. Many deaths of former workers in British Rail's workshops in Eastleigh and in the Portsmouth Naval Dockyard, where they had been exposed to asbestos, ended up with our Winchester Coroner and in our autopsy room.

I learnt later that our Coroner had put my name forward to the *UK Register of Expert Witnesses*. He and the Hampshire Constabulary had also asked me to be put forward to act as Home Office Pathologist for Hampshire, but I declined this. I wasn't interested in forensic (crime) pathology and I wished to concentrate on hospital surgical and medical pathology, and not spending a lot of time in Court.

Shortly before returning to Malta in 1995, solicitors in Bristol acting on behalf of the widow of a deceased demolition worker, asked me to review his case. He had made a statement, before he died, claiming he had been heavily exposed to asbestos dust. However, his Bristol Royal Infirmary autopsy report had certified he died from a disseminated bronchial small cell carcinoma. The Bristol Coroner, after questioning the pathologist concerned, therefore concluded that the cause of death was not ascribable to industrial disease, but to a cancer caused by smoking. His widow was therefore not entitled to compensation.

I asked the solicitors to send me the autopsy pathology paraffin blocks from the Bristol hospital because my initial direct request had been ignored. When the blocks arrived and sections cut and stained, there was fortunately enough to go on to try and reverse the Bristol pathology opinion and the Bristol Coroner's judgement.

There is agreement between North American and UK Courts as to which diseases are ascribable to asbestos exposure and the pathological criteria necessary to arrive at such a conclusion of industrial disease. Asbestos exposure is not only an aetiological factor for mesothelioma but also for bronchial carcinoma. But most asbestos-exposed workers have been smokers, so how does one ascribe a bronchial carcinoma to asbestos in a worker who has been a smoker?

The pathological guidelines, which the people at Bristol seemed unaware of, are quite clear. Bronchial carcinoma in a worker who's been a smoker can be ascribed to asbestos exposure if pathological proof of substantial asbestos exposure can be demonstrated. How?

Pathological proof of substantial asbestos dust exposure consists of demonstration of *asbestosis* in lung parenchyma away from the carcinoma, preferably in the other lung. Proving asbestosis means the presence of *frequent asbestos bodies* in the histological sections together with *diffuse pulmonary fibrosis*.

Some months after I returned permanently to Malta the Bristol solicitors acting for the widow thanked me for my report, ascribing her husband's bronchial carcinoma to his substantial asbestos dust exposure, and also passed on the widow's thanks for having subsequently been granted her husband's industrial disease compensation.

DR ALFRED GRECH & DR MICHAEL BALZAN

Cancer Epigenetics and its Clinical Applications

ABSTRACT

Epigenetics is defined as 'somatically inheritable changes that are not accompanied by alterations in DNA sequence'. DNA methylation, histone modifications and non-coding RNAs are all epigenetic mechanisms. Epigenetic aberrations (or epimutations) have been found to be responsible for carcinogenesis. The research of these epimutations is providing a platform for their application in cancer diagnosis, prognosis and therapeutics.

INTRODUCTION

What causes cancer? One of the most frequent answers to this question is that 'it's in our genes', but what does that mean? The wealth of literature demonstrating that damaged genes are a cause of cancer is irrefutable. However, in recent years, a growing body of research has suggested that epigenetics also plays a critical role in this disease.[1]

Historically, the word 'epigenetic' was used to describe the phenomenon of cell identity.[2] Our bodies exhibit a great diversity in cell identity, with over 200 different cell types all depending on one genome. This variation is regulated by a system of biochemical alterations of DNA and histone proteins, which give DNA its structure. Together, these modifications are termed the epigenome.

Epigenetic modifications include DNA methylation, histone modifications and RNA epigenetics. Epigenetic modifications have importance in gene transcription, but they do not actually modify the coding sequence of the gene itself. While these alterations are heritable, there is also the possibility of reversing them; a fact that has enabled the prospect of epigenetic therapy in cancer treatment. Indeed, epimutations have therefore been targeted for new drug innovations, and "turning back on" silenced genes represents a crucial advancement in treating different forms of cancer.[3]

EPIMUTATIONS IN CANCER

DNA methylation

DNA methylation is a type of epigenetic modification that has been extensively studied in mammals. In normal cells, it ensures the correct regulation of gene expression and stable gene silencing. DNA methylation is closely linked with histone modifications, and their interaction is fundamental in controlling genome functioning by altering chromatin architecture. Generally, the methylation pattern is maintained by DNA methyltransferases. In various cancer types, DNA methylation has been shown to silence a wide range of genes, with inactivation of certain tumour-suppressor genes occurring as a consequence of hypermethylation within the promoter regions.[4]

Histone modifications

In normal cells, histone modifications systematically coordinate and oversee cellular processes such as DNA repair, DNA replication and gene transcription. In recent years, research attention on histone modifications has intensified, leading to the detection and categorisation of many histone-modifying protein complexes and molecules. Changes in these complexes are thought to disturb the configuration and levels of histone marks, and so disrupt the regulation of chromatin-based processes, eventually resulting in oncogenic transformation and cancer development.[5]

RNA epigenetics

Several studies have shown that microRNAs (miRNAs) can also have clinical relevance as biomarkers to indicate the presence of a pathology and also the genetic link, progression or stage of the cancer.[6]

It is known that epigenetic factors are involved in aberrations of the miRNome (that is, the complete set of miRNAs for a certain genome) which are seen in cancer. It is also known that a group of miRNAs known as epi-miRNAs can directly target effectors of the epigenetic machinery, including DNA methyltransferases, histone deacetylases (HDACs), and polycomb repressive complex genes. Epi-miRNAs can also indirectly affect the expression of tumour suppressor genes, whose expression is controlled by epigenetic factors.

Such epigenetic–miRNA interaction results in a new layer of complexity in gene regulation, opening up new avenues in the understanding of human cancerogenesis and in the achievement of new cancer treatments.[7]

EPIGENETIC THERAPY OF CANCER

In a race against precious time, epigenetic therapy emerged as a treatment option when it was discovered that the epigenetic alterations that occur in cancer are reversible in nature. In fact, one of the main aims of epigenetic therapy is to reverse the epigenetic modifications that occur in cancer, therefore leading to the restoration of a healthy and normal epigenome. In recent years, drug development on this front has focused on DNA methyltransferases, HDACs, histone acetyltransferase (HATs) and miRNA-based therapeutic strategies.[8]

DNA methyltransferase inhibitors

Drugs such as the DNA methyltransferase inhibitors azacitidine[9] and decitabine[10] have, for instance, been found to target the inverted methylation pattern of cancer cells. It was shown that these hypomethylating agents not only inhibit all three types of DNA methyltransferases (DNMT1, DNMT3a, and DNMT3b), but they are also effective when used in low dosage. Indeed, both azacitidine and decitabine have been used in the treatment of patients with acute myeloid leukaemia, chronic myelomonocytic leukaemia and higher-risk myelodysplastic syndromes, who are unable to be considered for more intensive treatments such as induction chemotherapy or stem cell transplantation.[11]

HDAC inhibitors

In addition to DNA methyltransferase inhibitors, a few HDAC inhibitors have been approved by the FDA, including vorinostat, panobinostat and romidepsin. Besides the histone of interest, these HDAC inhibitors are known to alter the acetylation state of many proteins. Additional research at the molecular level of patient response is therefore needed to improve the effectiveness of these inhibitors as cancer treatment. Nonetheless, both vorinostat and romidepsin have been used in the treatment of cutaneous T-cell lymphoma.[12,13] Similarly, panobinostat has been used as a therapeutic option for multiple myeloma, although its use has been restricted due to its adverse event profile.[14]

HAT inhibitors

HAT inhibitors are other pharmaceutical targets in cancer research. Lunasin, for example, is a soybean-derived polypeptide which has been found to bind to deacetylated histones competing with HATs, and in doing so, switching off transcription. Such an epigenetic mechanism therefore suggests that this polypeptide can affect regulatory pathways involving chromatin changes that could be important to carcinogenic pathways. Wan et al. (2017) argue that lunasin could therefore be effective against cancers that involve chromatin modifications.[15]

Similarly, the natural product HAT inhibitors anacardic acid[16] and garcinol[17] have been shown to sensitise cancerous cells to irradiation. In mice, garcinol inhibited proliferation of breast cancer cells and also suppressed colon carcinogenesis.[18,19] Curcumin, which is another HAT inhibitor, is currently in clinical trials as a therapeutic agent and combination therapy, however its biological effect is not only due to its HAT inhibition.[20]

miRNA-based therapeutic strategies

Epigenetic therapies also include miRNA-based therapeutic strategies. In general, miRNAs are a feasible therapeutic tool because they can regulate key cellular processes by also simultaneously regulating several targets. Currently, there are two strategies for the treatment of cancer using RNAi-based therapy: (a) the 'sandwich RNAi inhibition' strategy and (b) the 'multiplex RNAi inhibition' strategy.[21,22] In the former strategy, multiple agents are used to target a specific molecular defect connected to cancer pathogenesis. In the latter strategy, on the other hand, it is the various molecular defects which accumulate in the multistep pathway of a specific cancer that are targeted.

In murine models for example, Xue et al. (2014) found that delivery of miR-34a and K-ras siRNA into a lung cancer model resulted in significant tumour regression.[23] Similarly, Yuan et al. (2014) found that siRNA-mediated inhibition of KRAS, in addition to RAF or PI3K combinations, could impair KRAS-mutant colorectal cancer in xenograft models.[24]

In human studies, while some miRNA candidates have failed, others have shown potential. In the first human trial of its kind, a technology termed "TargomiR" exhibited promising results in patients with malignant pleural mesothelioma and non-small cell lung cancer.[25] In this technology, miRNA mimics are delivered by targeted bacterial minicells. In addition, there is a new miRNA drug candidate called RGLS5579 that targets miR-10b which has potential in patients diagnosed with glioblastoma multiforme – one of the most aggressive forms of brain cancer.[26,27] In glioblastomas, miR-10b is over-expressed and is an oncogenic miRNA. Overall, these studies suggest a feasible future for miRNA drugs in cancers with no effective treatments.

CONCLUSION

It is clear that epigenetic therapeutics has a promising future for cancer treatment. Nevertheless, we still need to fully comprehend the complex system of interactions between the human genome and epigenome, transcriptome and proteome. Looking into the future, if the potential for epigenetic therapy is fulfilled, it will definitely open an exciting new avenue for personalised cancer treatment medicines.

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PROF. MAURICE CAUCHI

Doctors for the Environment

Malta

Most of us are now aware of the dangers resulting from climate change, which include a whole raft of medical conditions. Most of us also feel impotent in doing something about this situation, hoping that our elected politicians would deal with the problems that we, and particularly our children, will be facing in the not too distant future.

The medical profession is still considered to be one of the most respected professions in Malta, and while this may be considered flattering, it imposes certain obligations on us.

Without any doubt, as emphasized by the WHO, climate change is 'the defining issue' of our time. Scientists have emphasized the catastrophic scenario that we can expect if we don't take action to redress the issue.

We, as medical professionals, are also well aware that prevention is the crucial motto, advising our patients to do everything in their power to take all possible measures to prevent the emergence of medical disease and its complications.

While individually one may feel powerless, there is strength in unity. A novel association, 'Doctors for the Environment Australia (DEA)' was created in Australia in 2002, aimed "to utilise the skills of members of the medical profession to address the ill health resulting from damage to the natural environment at local, national and global levels" (http://dea.org.au). It is now a thriving organisation, and it uses its influence to lobby government and politicians on the need to appreciate the gravity of the situation.

They point out that '*Political ideology has proved to be the greatest obstacle to DEA's ability to reduce the health hazards of climate change*'.

Although these hazards become obvious, and include droughts, deluges, and rising sea levels which will eventually affect our lives, there seem to be resistance in certain quarters to appreciate that an unsustainable doctrine of continuous economic growth might be incompatible with life on earth in the long run.

It is also my impression that the Maltese public seem to be on the whole rather apathetic towards appreciating the challenges we are faced with.

It is a false premise do dismiss the action of the few nations as having little impact on the final outcome, on the assumption that small nations can have a minimal impact on world scenarios. It is a fact that nearly 50% of global change results from those nations which are not considered to belong to the highest polluters on earth.

Likewise, it is a mistake to dismiss the actions of groups of individuals, even a prominent group like the medical profession. It is a case of thinking globally and acting locally, and this holds for all nations and all individuals on earth.

My strong recommendation is for the medical profession in Malta to follow the lead of DEA and organise themselves, perhaps within the Maltese Medical Association, with the specific aim of forming a group, 'Doctors for the Environment - Malta' to advise and promote our views relating to dangers to health resulting from global warming.

SLOW DOWN SPMS WITH ACTIVE DISEASE. IT'S TIME FOR MAYZENT®[1]

SPMS = Secondary Progressive Multiple Sclerosis

MAYZENT is the first and only oral treatment specifically indicated for SPMS with active disease [1,2 *†]

Start MAYZENT at the first signs of progression [1,2]

CDP=confirmed disability progression; CI=confidence interval; Gd+=gadolinium-enhancing; HR=hazard ratio; MOA=mechanism of action.

*EXPAND was a randomized, double-blind, placebo-controlled, Phase III study with a broad range of 1651 patients with SPMS over 24 months, followed by an optional open-label extension. †In a subgroup analysis In EXPAND, SPMS with active disease was defined as patients with relapse in the 2 years prior to the study and/or presence of T1 Gd+ lesions at baseline.[1]

Mayzent®

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

PRESENTATION:

- 0.25mg film-coated tablets: each film-coated contains siponimod fumaric acid (equivalent to 0.25 mg siponimod).
- 2mg film-coated tablets: each film-coated tablet contains siponimod fumaric acid (equivalent to 2 mg siponimod).

INDICATION: Mayzent is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.

DOSAGE: Treatment should be initiated and supervised by a physician experience in the management of multiple sclerosis. Mayzent is for oral use. It should be taken with or without food and the tablets should be swallowed whole with water. ♦ *Treatment initiation*: Treatment has to be started with a titration pack that lasts for 5 days. Treatment starts with 0.25 mg once daily on days 1 and 2, followed by once-daily doses of 0.5 mg on day 3, 0.75 mg on day 4, and 1.25 mg on day 5, to reach the patient's prescribed maintenance dose of siponimod starting on day 6. During the first 6 days of treatment initiation the recommended daily dose should be taken once daily in the morning with or without food. ♦ *Special populations*: ♦ *Elderly*: Siponimod has not been studied in patients aged 65 years and above. Clinical studies included patients up to the age of 61 years. Siponimod should be used with caution in the elderly due to insufficient data on safety and efficacy. ♦ *Renal impairment*: Based on clinical pharmacology studies, no dose adjustment is needed in patients with renal impairment. ♦ *Hepatic impairment*: Siponimod must not be used in patients with severe hepatic impairment (Child-Pugh class C). Although no dose adjustment is needed in patients with mild or moderate hepatic impairment, caution should be exercised when initiating treatment in these patients. ♦ *Paediatric population*: The safety and efficacy of siponimod in children and adolescents aged 0 to 18 years have not yet been established. No data are available.

CONTRAINDICATIONS: ♦Hypersensitivity to the active substance or to peanut, soya or any of the excipients, ♦ Immunodeficiency syndrome, ♦ History of progressive multifocal leukoencephalopathy or cryptococcal meningitis, ♦ Active malignancies, ♦ Severe liver impairment, ♦ Patients who in the previous 6 months had: myocardial infarction, unstable angina pectoris, stroke/transient ischaemic attach, decompensated heart failure, ♦ Patients with a history of second-degree Mobitz type II atrioventricular block, sino-atrial heart block or sick-sinus syndrome, if they do not wear a pacemaker, ♦ Patients homozygous for CYP2C9*3 genotype, ♦ During pregnancy and in women of childbearing potential not using effective contraception.

WARNINGS/ PRECAUTIONS: ♦ *Effects on ability to drive and use machines*: Siponimod has no or negligible influence on the ability to drive and use machines. However, dizziness may occasionally occur when initiating therapy with siponimod. Therefore, patients should not drive or use machines during the first day of treatment initiation with siponimod. ♦ *Infections*: the immune system effects of siponimod may increase the risk of infections. Before initiating treatment, a recent complete blood count (within last 6 months or after discontinuation of prior therapy) should be available. Assessments of CBC are also recommended periodically during treatment. Initiation of treatment should be delayed in patients with severe active infection until resolution. Patients should be instructed to report symptoms of infection to their physician promptly. Suspension of treatment with siponimod should be considered if a patient develops a serious infection. ♦ *Vaccination*: A full course of vaccination with varicella vaccine is recommended for antibody negative patients prior to commencing treatment with siponimod, following which initiation of treatment should be postponed for 1 month to allow the full effect of vaccination to occur. The use of live attenuated vaccines should be avoided while patients are taking siponimod and for 4 weeks after stopping treatment. Vaccinations may be less effective if administered during siponimod treatment. Discontinuation of treatment 1 week prior to planned vaccination until 4 weeks after is recommended. When stopping siponimod therapy for vaccination, the possible return of disease activity should be considered. ♦ *Macular oedema*: Siponimod therapy should not be initiated in patients with macular oedema until resolution. Siponimod should be used with caution in patients with a history of diabetes mellitus, uveitis or underlying/co-existing retinal disease due to a potential increase in the risk of macular oedema. It is recommended that these patients should undergo an ophthalmological evaluation prior to initiating therapy and regularly while receiving siponimod therapy to detect macular oedema. Continuation of siponimod therapy in patients with macular oedema has not been evaluated. It is recommended that siponimod be discontinued if a patient develops macular oedema. A decision on whether or not siponimod should be re-initiated after resolution needs to take into account the potential benefits and risks for the individual patient. ♦ *Bradyarrhythmia*: As a precautionary measure, patients with the following cardiac conditions should be observed for a period of 6 hours after the first dose of siponimod for signs and symptoms of bradycardia:sinus bradycardia (heart rate <55 bpm), history of first- or second-degree [Mobitz type I] AV block, history of myocardial infarction, or history of heart failure (patients with NYHA class I and II). In these patients, it is recommended that an electrocardiogram (ECG) is obtained prior to dosing and at the end of the observation period. Due to the risk of serious cardiac rhythm disturbances or significant bradycardia, siponimod should not be used in patients with: history of symptomatic bradycardia or recurrent syncope, uncontrolled hypertension, or severe untreated sleep apnoea. In such patients, treatment with siponimod should be considered only if the anticipated benefits outweigh the potential risks, and advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring strategy. ♦ *Liver function*: recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with siponimod. ♦ *Cutaneous neoplasms*: Patients treated with siponimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy. ♦ *Unexpected neurological or psychiatric symptoms/signs*: should a patient on siponimod treatment develop any unexpected neurological or psychiatric symptoms/signs or accelerated neurological deterioration, a complete physical and neurological examination should promptly be scheduled and MRI should be considered. ♦ *Prior treatment with immunosuppressive or immune-modulating therapies*: caution should be exercised during concominant administration of any of these medicinal products is stopped. ♦ *Blood pressure effects*: Blood pressure should be regularly monitored during treatment with siponimod. ♦ *CYP2C9 genotype*: Before initiation of treatment with siponimod, patients should be genotyped for CYP2C9 to determine their CYP2C9 metaboliser status. Patients homozygous for CYP2C9*3 should not be treated with siponimod. ♦ *Stopping siponimod therapy*: Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of another S1P receptor modulator. The possibility of severe exacerbation of disease after stopping siponimod treatment should be considered. Patients should be observed for relevant signs of possible severe exacerbation or return of high disease activity upon siponimod discontinuation and appropriate treatment should be instituted as required. After siponimod therapy has been stopped, siponimod remains in the blood for up to 10 days. Starting other therapies during this interval will result in concomitant exposure to siponimod. ♦ *Interference with haematological testing*: Since siponimod reduces blood lymphocyte counts via re-distribution in secondary lymphoid organs, peripheral blood lymphocyte counts cannot be utilised to evaluate the lymphocyte subset status of a patient treated with siponimod. ♦ *Excipients*: The tablets contain soya lecithin. Patients who are hypersensitive to peanut or soya should not take siponimod. The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

INTERACTIONS: ♦ *Antineoplastic, immune-modulating or immunosuppressive therapies*: Siponimod has not been studied in combination with antineoplastic, immune-modulating or immunosuppressive therapies. Caution should be exercised during concomitant administration due to the risk of additive immune effects during such therapy and in the weeks after administration of any of these medicinal products is stopped. ♦ *Anti-arrhythmic medicinal products, QT-prolonging medicinal products, medicinal products that may decrease heart rate*: During treatment initiation siponimod should not be concomitantly used in patients receiving class Ia (e.g. quinidine, procainamide) or class III (e.g. amiodarone, sotalol) anti-arrhythmic medicinal products, QT-prolonging medicinal products with known arrhythmogenic properties, heart-rate-lowering calcium channel blockers (such as verapamil or diltiazem) or other substances that may decrease heart rate (e.g. ivabradine or digoxin) because of the potential additive effects on heart rate. If treatment with siponimod is considered, advice from a cardiologist should be sought regarding the switch to non-heart-rate-lowering medicinal products or appropriate monitoring for treatment initiation. ♦ Beta blockers: Caution should be exercised when siponimod is initiated in patients receiving beta blockers due to the additive effects on lowering heart rate. Beta blocker treatment can be initiated in patients receiving stable doses of siponimod. ♦ *Vaccination*: The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided during siponimod treatment and for up to 4 weeks after treatment. During and for up to 4 weeks after treatment with siponimod vaccinations may be less effective. The efficacy of vaccination is not considered to be compromised if siponimod treatment is paused 1 week prior to vaccination until 4 weeks after. ♦ *CYP2C9 and CYP3A4 inhibitors*: Because of a significant increase in exposure to siponimod, concomitant use of siponimod and medicinal products that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition is not recommended. This concomitant drug regimen can consist of a moderate CYP2C9/CYP3A4 dual inhibitor (e.g. fluconazole) or a moderate CYP2C9 inhibitor in combination with a separate moderate or strong CYP3A4 inhibitor. ♦ *CYP2C9 and CYP3A4 inducers*: Siponimod may be combined with most types of CYP2C9 and CYP3A4 inducers. ♦ *Oral contraceptives*: Co-administration with siponimod did not reveal clinically relevant effects on the pharmacokinetics and pharmacodynamics of the combined ethinylestradiol and levonorgestrel oral contraceptive. Therefore the efficacy of the investigated oral contraceptive was maintained under siponimod treatment. No interaction studies have been performed with oral contraceptives containing other progestagens, however an effect of siponimod on the efficacy of oral contraceptives is not expected.

PREGNANCY, LACTATION AND FERTILITY: ♦ *Women of childbearing potential/Contraception in females*: Siponimod is contraindicated in women of childbearing potential not using effective contraception. Before initiation of treatment in women of childbearing potential a negative pregnancy test result must be available and counselling should be provided regarding serious risk to the foetus. Women of childbearing potential must use effective contraception during treatment and for at least ten days following the last dose of siponimod ♦ *Pregnancy*: Siponimod is contraindicated in pregnancy. Siponimod should be stopped at least 10 days before a pregnancy is planned. If a woman becomes pregnant while on treatment, siponimod must be discontinued. ♦ *Lactation*: Siponimod should not be used during breast-feeding. ♦ *Fertility*: The effect of siponimod on human fertility has not been evaluated.

ADVERSE REACTIONS: ***Very Common*** (≥1/10): Headache, Hypertension, Liver function test increase. ***Common*** (≥1/100 to <1/10): Herpes zoster, Melanocytic naevus, lyphopenia, dizziness, seizure, tremor, macular oedema, bradycardia, atrioventricular block (frist and second degree), nausea, diarrhoea, pain in extremity, oedema peripheral, asthenia, pulmonary function test decreased.

LEGAL CATEGORY: POM

PACK SIZES: 0.25mg: Titration packs of 12 film-coated tablets, Packs of 120 film-coated tablets.2mg: Packs of 28 film-coated tablets

MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland.

MARKETING AUTHORISATION NUMBERS: Mayzent 0.25 mg film-coated tablets: EU/1/19/1414/001-002. Mayzent 2 mg film-coated tablets: EU/1/19/1414/003

Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 4, Marsa MRS 1000 Malta. Tel +356 21222872.

2020-MT-MAY-13-Jan-2020

References: 1. Novartis Europharm Ltd. Mayzent Summary of Product Characteristics. **2.** Kappos L, Bar-Or A, Cree BAC, et al; for the EXPAND Clinical Investigators. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet.* 2018;391(10127):1263-1273.

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Celebrating World Pharmacist Day

TAMARA ATTARD

World Pharmacist Day is celebrated globally on 25 September, so as to create awareness about pharmacists and their role in improving the health and quality of life of the patient. This year's theme was 'Transforming Global Health'. MPSA in collaboration with the Department of Pharmacy at the University of Malta organized an online webinar, with speakers from different areas of the pharmaceutical sector. The webinar was introduced by the Head of the Pharmacy Department, Prof. Lilian M. Azzopardi and Ms Martina Fitzgerald, President of MPSA. This was followed by Prof. Anthony Serracino Inglott's reflections on the pharmaceutical workforce development. The role of the pharmacist in clinical and community pharmacy were highlighted by Dr Sephorah Falzon and Dr Elena Marie Mifsud, respectively. This was followed by a discussion on pharmacy expectations and experiences moderated by Dr Maresca Attard Pizzuto with the participation of Dr Francesca Wirth and third year pharmacy students Ms Raquel Formosa and Mr Jean Claude Calleja. Reflections from pharmaceutical technologist Mr Jake Pace on analytical science, Dr Timothy Scicluna on regulatory sciences and Mr Clint Muscat on the pharmaceutical industry followed.

Another panel, which was moderated by Dr Nicolette Sammut Bartolo, discussed the future of pharmacy and pharmaceutical research. The panel members were Dr Janis Vella Szijj and pharmacy students Ms Julia Micallef, a fifth year student and Ms Tamara Attard, a second year student.

The webinar which was also streamed on Facebook was concluded by Prof. Azzopardi and Ms Fitzgerald. Through this webinar, one could get a good overview of how all the different areas within the pharmaceutical sector come together, for the benefit of the patient.

Source: //www.facebook.com/watch/?v=328316401777979

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  Consultant in Endocrinology and Diabetes

DR MOSES CAMILLERI

Smoking
in the 21st century

INTRODUCTION

Jean Nicot de Villemain (1530 – 1600) was a French diplomat who became famous for introducing tobacco to France. Little could he imagine the immense upheaval he would bring to future generations. Up until the early 1900's, smoking cigarettes was made to look glamorous and even had health benefits attributed to it.

However, the link between smoking and respiratory diseases had been established back in the early 1900s in studies by European and American doctors but this remained a taboo up until the 1950s.[1] As time went

by, the evidence linking smoking as the cause of disease continued to accumulate and, what was a controversy in the 1960s and 1970s, turned into outright condemnation in the 1980s. Although the medical profession had more knowledge about the harm caused by smoking, the general public was less informed because cigarette manufacturers were doing their best to cast doubt on how true these "allegations" were. Mass legal action instituted in the 1990s led to the Master Settlement Agreement in 1998 with US courts condemning major US cigarette companies to pay huge sums of money to the US government over a period of 25 years to compensate for some of the damage and expenses incurred in caring for the millions of people suffering ill health directly caused by smoking over the years.[2]

Over the past couple of decades, regulations to control tobacco use have fallen short of outright prohibition. With current knowledge of the harm caused by smoking, this would be a sensible thing to do. But experience has taught us that prohibition, while reducing use of a substance in the general population, does not really stop those who are intent on using the prohibited substance from doing so.[3,4] Legislation to control tobacco use aims at reducing harm to smokers and protect non-smokers from exposure to exhaled secondary smoke. It is surprising that, the Manufacture, Presentation and Sale of Tobacco and Related Products Regulations (S.L. 315.10), enacted under the Tobacco (Smoking Control) Act (Cap. 315) , actually identifies the addictive properties of nicotine and defines "addictiveness as the pharmacological potential of a substance to cause addiction", which is described as "a state which affects an individual's ability to control his or her behaviour, typically by instilling a reward or a relief from withdrawal symptoms, or both." By 2016, Maltese legislation with regards to smoking control was updated to reflect EU law. The law specifies measures to control not only concentration of nicotine in cigarettes but, probably of more importance, the law describes which cancerogenic substances are allowed. Surprisingly, the law permits use of chemicals that are known to make the smoker sick and possibly sick enough to die! Keeping up with the times, the same legislation S.L. 315.10 confirms that smokeless tobacco is illegal in Malta and also defines and describes electronic cigarettes.

This brings me to the subject of smoking other than conventional cigarettes. Probably most people assume that smoking is the act of putting a tobacco-filled cigarette to one's mouth and lighting it up. The process of burning tobacco reaches a temperature as high as 650°C where chemicals that are known to be cancerogenic tend to be more harmful to the lung tissue of the smoker. However, tobacco can also be smoked without burning (combusted or heat-not-burn/HNB) by using a battery-operated device to power a heating

element, which when in contact with tobacco, heats rather than burns the tobacco. This mode of nicotine delivery system (the polite way to refer to smoking) heats up tobacco to a temperature of 300 to 350°C, generating a vapour that is inhaled by the smoker. At the lower temperature, the cancerogenic chemicals in tobacco are thought to be less harmful to the smoker.

The latest fad in smoking is the use of what are known as electronic cigarettes. Like combusted cigarettes, electronic cigarettes are battery-operated but instead of heating tobacco, a solution is heated to generate a vapour inhaled by the smoker. This is referred to as vaping.

Appearing on the market towards the end of the 20th century, the first electronic cigarettes were patented in 2003 and appeared in China in 2004, in Europe two years later and the US in 2007. The prevalence of electronic cigarettes in the general population is 3.5 to 5.5%, but prevalence studies indicate it is a fad that has mostly engaged young people and adolescents. Some US studies indicate rates as high as 46% in this cohort. Most people who use electronic cigarettes also smoke conventional cigarettes at some stage during their smoking career. Studies indicate that electronic cigarettes might serve as a gateway for the use of conventional cigarettes. Among factors contributing to the prevalence of e-cigarette use cited by young people is the exposure to robust advertising campaigns, the ability to customize devices, flavours, nicotine content, peer use, enjoyment, and curiosity.[5,6] This prompted US authorities earlier this year to limit the flavours that could be included in electronic solutions (e-solutions, e-liquid, or e-juice). This was done to reduce the appeal that smoking flavoured e-cigarettes might have to younger users.

A major influence contributing significantly to favourably change the perception towards e-cigarettes in the general population but also in the medical

community, was a 2014 study, which sought to estimate the harm of nicotine-containing products through modelling techniques. It concluded that conventional smoking was 20 times more harmful than vaping e-cigarettes.[7] The UK Public Health took this up and started advertising the use of e-cigarettes, which it said were "at least 95% less harmful than cigarettes". This study has been contested with claims that advances in technology allows bigger power generation resulting in more vapour production and exposure of the user and bystanders to more, possibly harmful chemicals, and the ever increasing variety of flavours made up of chemicals that might be considered safe to eat but with as yet unknown consequences when inhaled. Another advancement has been the development of protonated nicotine which allows higher concentrations of nicotine to be inhaled without causing throat irritation, with the consequence of higher addiction to nicotine.[8]

With the current understanding, should smokers be encouraged to change to vaping to improve their health? Unfortunately, there are different thoughts on this. A study in 2017 followed vapers who smoked e-cigarettes exclusively for 3.5 years and found no detriment to their health, even when investigated extensively. The study does highlight that 3.5 years is a short period of time to follow up for possible harm.[9] The World Health Organization remains uncommitted as to whether e-cigarettes should be advocated, neither as a means of smoking cessation nor as a means of harm reduction.[10]

As to second-hand smoke exposure, studies comparing vapour generated by e-cigarettes and that by conventional ones, indicate that the latter generate more particles and stay around for longer periods of time.[11] Yet it is well known that the belief that e-cigarettes generate only a water vapour is certainly a misconception. Studies indicate particles in e-cigarette generated vapour to be cancerogenic, harmful to the unborn and a source of indoor pollution.[12]

Of concern with the use of e-cigarettes has been the observation of a newly identified lung disease referred to as e-cigarette and vapour product use-associated lung disease (EVALI). First noticed in early 2017 in the US, some cases have also been reported in Europe. Patients complain of a cough, chest pain and shortness of breath. While some patients improve with no need for hospital care, others are not so lucky. By mid-January 2020, 2,668 hospitalized EVALI cases were reported in the US and nearly half the patients required intensive care to treat respiratory failure. Sixty died. Most patients were younger than 35 years old. While the exact cause of EVALI is still being investigated, it is well documented that all patients presenting with this condition had been vaping in the three months before getting sick. It has been confirmed that this condition is not an infective but rather an inflammatory process that causes lung injury. Of interest is the presence of tetrahydrocannabinol (THC) which is the active ingredient in marijuana (cannabis), in up to 80% of e-solutions that had been used by patients presenting with this condition. In up to half of the implicated e-solutions, another component found was vitamin E acetate (VEA). This is an additive that started being used in e-solutions as a cutting agent to thicken the solution. While VEA is considered safe to eat, it seems that its safety profile significantly changes when inhaled as a vapour. In such a scenario the Food and Drug Administration (FDA) in the US could only strongly advise e-cigarette users to avoid use of vaping products that were spiked with THC and to buy e-solutions only

from reliable sources. It seems vapers are heeding this advice as new cases of EVALI have dropped since October 2019.[13,14]

A new challenge with the ever-increasing number of vapers, is the further risk that comes with spiking of e-solutions with dangerous drugs of abuse.

Of concern is the presence of psychedelic substances and opioids such as fentanyl (at least 50 times stronger than heroin) in e-solutions. While not yet a widespread problem, it is envisaged that this new mode of drug administration could present itself as a new challenge to services caring for people who use drugs.[14] It is important that users of e-cigarettes are made aware of the dangers involved when buying e-solutions from sources that are not certified as required by The Manufacture, Presentation and Sale of Tobacco and Related Products Regulations (S.L. 315.10), enacted under the Tobacco (Smoking Control) Act (Cap. 315). The aforementioned Regulations stipulate that electronic cigarettes are subject to a number of safeguards (e.g. maximum concentration of nicotine of 20 mg/ml, maximum single use cartridge size of 2 ml) and requirements (e.g. notification to the competent authority prior to placing on the market, reporting of ingredients, inclusion of an information leaflet, and specific rules on advertising).

Vapers who intentionally want to use drugs of abuse administered by utilizing an e-cigarette, should be aware of the dangers involved and ensure safer use by following harm reduction guidelines such as starting off with lower doses, not mixing drugs and avoid as much as possible use of such substances when on their own. Help to address one's drug use is available. Sedqa may be contacted on helpline 179, 24 hours a day and 2388 5110 during office hours.

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Cervical Cancer:
The Importance of Screening and Vaccination

KEYWORDS: Cervical Cancer, Cervical Screening Programme, HPV (Human Papilloma Virus), HPV Vaccination

ABSTRACT

Cervical cancer is the fourth most common cancer in women worldwide and it is the most common cancer in women aged 15 to 44 years. The national cervical screening programme was introduced in Malta in 2016, aiming to increase the detection rate of pre-malignant, low- and high-grade cervical disease. The Human Papilloma Virus (HPV) is the main cause of cervical cancer and with the HPV vaccine as part of the national immunization programme, we have a strong and useful weapon in the prevention of infection with this virus.

CERVICAL CANCER

Cervical cancer originates at the transformation zone which surrounds the opening of the cervix leading into the endocervical canal (Figure 1). The ectocervix is a layer of squamous cells on the outer surface of the cervix whilst the endocervix consists of mucus producing glandular columnar cells making up the inner surface of the cervix. If cells from the ectocervix become cancerous it will lead to a squamous cell carcinoma, which is the most common type of cervical cancer. The glandular cells of the endocervix can also become cancerous, leading to an adenocarcinoma of the cervix.[1] Less commonly, cervical cancers have features of both squamous cell carcinomas and adenocarcinomas. These are called adenosquamous carcinomas or mixed carcinomas.

Cervical cancer can be detected at a pre-malignant stage due to presence of dyskaryotic atypical cells within the squamous epithelium, better known as cervical intra-epithelial neoplasia (CIN) or cervical dysplasia. CIN is a histological diagnosis and depends on the extent of invasion. CIN I refers to mild dysplasia whereby atypical cells are found only in the lower 1/3 of the epithelium. CIN II refers to moderate dysplasia with atypical cells found in the lower 2/3 of epithelium. CIN III refers to carcinoma in situ, where atypical cells occupy the full thickness of the epithelium. In CIN III the cells are similar to malignant lesions but show no invasion beyond the epithelial basement membrane.[3]

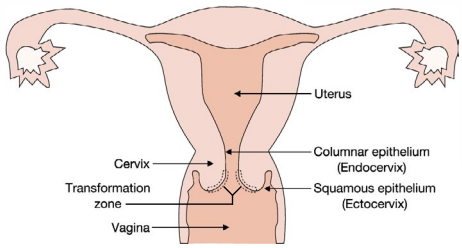

Figure 1: Female Reproductive System[2]

Cervical cancer is the commonest type of cancer in women under the age of 35 years in developed countries. It is the fourth most common cancer in women worldwide and the second most common in low- and middle-income countries.[4] It has an overall 65% five-year survival and is thus a major cause of morbidity and mortality from cancer.[3] Cervical cancer isn't always obvious and may not cause any symptoms until it's reached an advanced stage. In most cases, vaginal bleeding is the first noticeable symptom. The most common symptoms of cervical cancer include intermenstrual, postcoital or postmenopausal bleeding. Cervical cancer may also be associated with vaginal discharge, dyspareunia or pelvic pain.[5]

RISK FACTORS

The major cause of cervical cancers is Human Papilloma Virus (HPV). There are over 130 strains of HPV with the majority being harmless, causing genital warts, and some others being associated with cervical cancer.[3] HPV types 16 and 18 are responsible for around 70% cervical cancer cases.[6] HPV18 is mainly a risk factor for the development of adenocarcinoma whereas HPV16 is associated with both squamous cell and adenocarcinoma. Other high-risk strains include HPV type 13, 31, 33.[3] For most people, the immune system clears the HPV infection spontaneously within 2 years. In cases of persistent infection, especially with a high-risk type of HPV there is a higher risk of developing CIN leading to cervical cancer.[6] The risk is even higher in women who have other sexually transmitted infections alongside of HPV, especially Herpes Simplex Type 2 virus.

Other risk factors include:

- Immunodeficiency
- Smoking
- Taking the oral contraceptive pill for more than five years
- High parity[6]
- Becoming sexually active at a younger age (especially <18 years).[7]

PREVENTION AND EARLY DETECTION

Regular cervical screening can detect CIN changes and is a simple and effective way to pick up cervical cell changes. The cervical screening test was independently invented in

the 1920s by Drs Georgios Papanikolaou and Aurel Babeș and named after Papanikolaou. The German virologist, Prof. Harald zur Hausen discovered the link between HPV and cervical cancer and was awarded the Nobel Prize for Physiology and Medicine in 2008 for this discovery.

Conventional Papanicolaou (PAP) smears can give false results due to inadequate sampling and slide preparation, and errors in laboratory detection and interpretation. On the other hand liquid-based cervical cytology has been developed to improve the diagnostic reliability of the test. Cervical cells are rinsed in a liquid based medium, which prevents false results due to blood or other potentially obscuring materials. Liquid-based cytology also allows for additional testing for HPV from the same sample in high risk cases.[8]

An abnormal cervical screening test result does not mean cancer. Most abnormal results are due to signs of HPV, the presence of treatable precancerous cells (CIN), or both, rather than cancer itself.[6]

With an abnormal smear result, the next investigation in line would be colposcopy +/- biopsy. This procedure also allows for staining with acetic acid and Lugol's iodine which help detect abnormal cells, as well as biopsies of the cervix. CIN I commonly regresses spontaneously but if left untreated CIN II and III will usually develop into cervical cancer over a period of 10 years, therefore detection and treatment are crucial. CIN can be treated by doing a large loop excision of the transformation zone using cutting diathermy under local anaesthetic. Established cervical cancer requires further investigation to determine FIGO classification and histology for staging. Treatment ranges from cone biopsy to radical hysterectomy +/- radiotherapy and chemotherapy.[3]

Practising safer sex by using barrier methods like condoms will reduce the risk of getting HPV and passing it on but is not 100% effective. There are now vaccines available to prevent HPV infection. HPV vaccination provides safe, effective, and lasting protection against the HPV infections that most commonly cause cancer. These vaccines do not protect against all kinds of HPV, therefore one still needs to take part in cervical screening, even if vaccinated.[6]
The vaccines available are Gardasil 9 (recombinant HPV nonavalent vaccine, Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) and Cervarix (recombinant HPV bivalent vaccine, Types 16 and 18). Both vaccines are recommended from the age of 9 years.[9]

Between the ages of 9 and 14, the vaccine is given in 2 doses spaced 6 months apart. After the age of 14, the course is of 3 doses, with the first 2 doses given 1 month apart and the third dose given 5 months after the second dose. In Malta, HPV vaccination is part of the National Immunisation Schedule and is given free of charge to girls born from 2000 onwards on reaching their 12th birthday.[9] Previously girls were vaccinated with Cervarix but in recent months Gardasil 9 started being administered. The earlier the vaccination, the better the response, since increasing age is linked to more persistent infection. Previous HPV infection does not provide immunity to future infection and it is not yet known whether the vaccine offers lifelong protection. Males have the potential to be HPV carriers, therefore it may be advisable to offer them the HPV vaccine as well. In keeping with this, since September 2019 the UK has extended its vaccination programme to include twelve-year-old boys.[6] This is a key factor in stopping spread of vaccine-preventable diseases and hopefully Malta will take on board free male HPV vaccination through the National Immunisation Schedule sooner rather than later.

MALTA'S SCREENING PROGRAMME

Women aged twenty-five to forty-nine years are offered screening every three years and those aged fifty to sixty-four years are offered screening every five years.[10] The national screening programme has been in place since 2016 but many females were aware of the importance of cervical screening long before that. Unfortunately, the national screening programme is very poorly attended with less than 30% attendance rate. It is important to note that this is not representative of the females who are actually getting screened since several opt to get screened privately. Ideally the data from the screening programme and private gynaecologists is merged to get a clear idea of how many people are aware of cervical cancer and the need for screening. Until then, medical professionals are encouraged to promote screening to help combat cervical cancer as it is a preventable disease.

ACKNOWLEDGEMENTS

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DR PIERRE VASSALLO

Imaging Back Pain
Part 2

INTRODUCTION

The first part of this series that appeared in the last issue of The Synapse Journal presented the mechanisms of discogenic back pain. This second article will discuss the **osseous** causes of back pain, their mechanisms and MR imaging findings. The osseous causes of back pain that will be discussed will include metabolic, infections and neoplastic diseases.

A. VERTEBRAL ENDPLATE

Damage to the vertebral endplate is a frequent cause of low back pain.

The vertebral endplate is composed of two layers: a layer of hyaline cartilage that abuts the intervertebral disk and a layer of cortical bone (subchondral plate) that separates the hyaline cartilage from the vertebral marrow. A network of blood vessels crosses these two layers to transfer nutrients between the vertebral marrow and the intervertebral disk (Fig 1). The endplate is thinnest centrally, while cervical endplates are thinner than lumbar ones.

Degenerative Endplate Disease

The vertebral MR findings seen as a result of degenerative disk disease were first described by Modic et al in 1988.[1] The MR grading system developed by Modic has been widely used to report the stage of endplate damage.

Modic type 1 changes include areas in the vertebral body adjacent to the endplate that are hypointense on T1-weighted images and hyperintense on T2-weighted and STIR images (Fig 2). Foci of contrast enhancement may be present within these areas on contrast-enhanced T1-weighted images. These foci represent an inflammatory reaction related to the release of interleukin-1-beta, an inflammatory mediator; this results in fibrosis, angiogenesis, and neurogenesis. These mechanisms induce nociceptive pain.

There are three theories as to how Modic changes occur. The first theory suggests that microfractures resulting from trauma to a normal endplate or to an endplate weakened by age induces an inflammatory response in the adjacent bone marrow. The second theory is that trauma results in microfractures that allow permeation of nucleus pulposus into the vertebral medulla that stimulates the inflammatory change. The third theory is that a transient bacteraemia with low-virulence bacterial strains occurs. These colonise and proliferate in the bone marrow adjacent to the vertebral endplate resulting in an immune response with inflammatory change. This explains why in addition to NSAIDs, physiotherapy and even antibiotics have been prescribed for the treatment of pain related to Modic type 1 changes.

Modic type 2 changes are represented by areas of hyperintensity on both T1- and T2-weighted images in the bone marrow adjacent to the endplates (Fig 3); the hyperintensity is suppressed on fat-suppressed images such as STIR. The increased signal on T1-weighted images is the result of deposition of fatty yellow marrow and is not related to any inflammatory processes. This explains why Modic type 2 changes are less likely to cause pain than type 1 changes.

Type 1 changes normally transition to type 2 changes. However, type 2 changes may revert to type 1 changes. Activation of inflammatory mechanisms within areas of type 2 change are speculated to induce conversion of fatty marrow to red marrow with re-activation of inflammatory mechanisms.

Modic type 3 changes are described as areas of hypointensity on both T1- and T2-weighted images in the bone marrow adjacent to the endplates (Fig 4). Type 3 changes are due to sclerosis and are not associated with stimulation of the inflammatory cascade, neurogenesis or angiogenesis. Type 3 changes are therefore less likely to cause back pain than type 1.

Modic type 1, 2 and 3 changes are considered to represent a continuum of the same process starting with acute inflammation and ending with sclerosis. Mixed types including type 1 and 2 or type 2 and 3 may also be observed.

B. OSTEOMYELITIS-DISCITIS

Osteomyelitis-discitis is an inflammatory process caused by infection of the disk that extends to adjacent vertebral bodies; this is why discitis is seen in the two contiguous vertebral bodies. The vertebra body changes include areas of low signal on T1-weighted images and high signal on T2-weighted and STIR images with enhancement on contrast-enhanced T1-weighted images (Fig 5). The high T2 and low T1 signal is due to bone marrow oedema. Contrast enhancement is due to leakage of intravascular contrast material from damaged vessels into the interstitial spaces within the bone marrow.

Inflammatory change and infected disk material may break into the ventral epidural space resulting in mechanical and chemical processes that are similar to an acute herniated disk. These processes include neurological impingement and nociceptor stimulation due to release of inflammatory mediators resulting in acute back pain. Angiogenesis and fibrosis caused by infection lead to the increased presence of inflammatory cytokines and fibrotic mechanical stress on the disk and nerve roots.

Acute pain can be a patient's only presenting symptom before laboratory data suggestive of infection or fever are acquired.

Immune-mediated inflammatory responses may persist after treatment of the infection, leading to prolonged symptoms despite resolution of the infection.

Most cases of osteomyelitis-discitis arise from haematogenous spread of infection from remote infected foci. Some cases are caused by direct instrumentation or by continuous spread from superficial foci of infection (e.g. pressure sores).

Standard treatment for osteomyelitis-discitis usually involves administration of parenteral antibiotics. However, bacterial colonies may survive in a biofilm environment, which shields them from antibiotic treatment. Surgical drainage and debridement may be required for persistent foci of infection.

C. BONE METASTASES

Bone is the preferential site of metastasis from cancers most notably breast, prostate, lung, renal and thyroid cancers. Most bony metastases appear low signal on T1-weighted images, high signal on T2-weighted and STIR images and show enhancement on contrast enhanced T1-weighted images (Fig 6).

One of the classic findings that helps distinguish metastatic disease from benign disease is involvement of the pedicles, laminae, spinous and transverse processes, and adjacent soft tissues. This is less common in benign diseases but may occur in osteomyelitis. Dynamic-contrast-enhanced MR imaging has also been reported to help with hypervascular bone metastases, which show increased blood flow, volume, and vascular permeability.

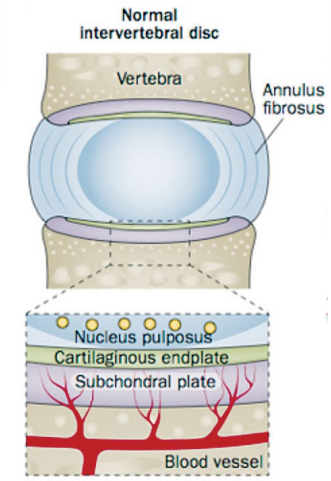

Figure 1: The vertebral endplate is composed of two layers, the hyaline cartilage layer contacts the intervertebral disk, while the cortical bone or subchondral plate contacts the vertebral marrow. Perforating vessels traverse the endplate to transport vital nutrients from the bone marrow to the intervertebral disk.

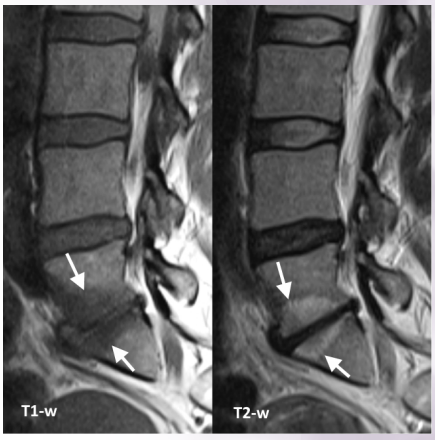

Figure 2: Modic type 1 changes are seen in the vertebral bodies abutting L5/S1 intervertebral disk; these appear hypointense on T1w images and hyperintense on T2w images (arrows).

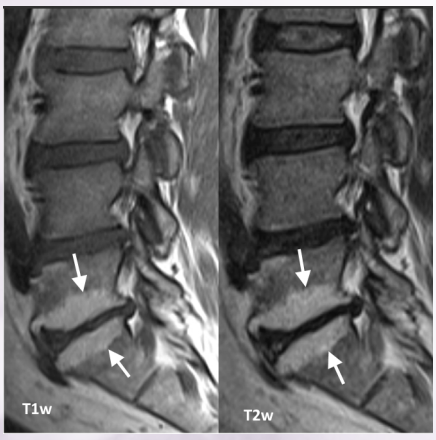

Figure 3: Modic type 2 changes are seen as areas of hyperintensity in the bone marrow adjacent to the endplate on both T1w and T2w images (arrows).

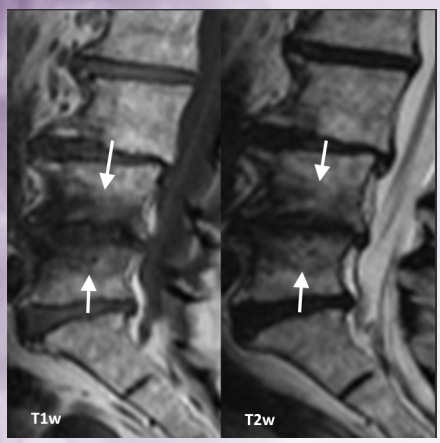

Figure 4: Modic type 3 changes are described when the bone marrow adjacent to the endplate is hypointense on both T1w and T2w images (arrows).

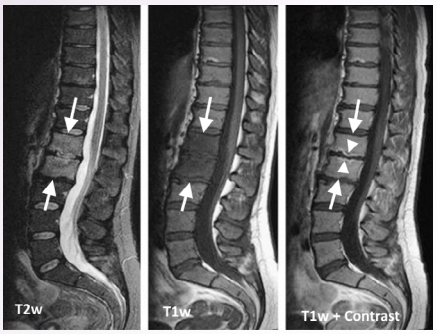

Figure 5: Osteomyelitis-Discitis seen at L1-2 level (arrows) with high T2 signal on the T2w image due to bone marrow oedema. Loss of bone marrow fat signal is seen on the T1w images. There is diffuse enhancement throughout both L1 and L2 vertebral bodies seen on the contrast enhanced T1w images; this is due to damaged and leaking vessels caused by osteomyelitis. Note that enhancement is particularly evident in the involved endplates (arrowheads).

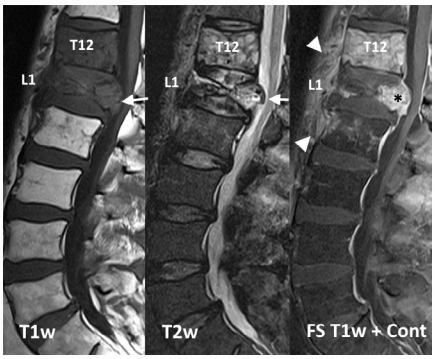

Figure 6: Bone Metastases are seen in T12 and L1 vertebral bodies. These show low signal on the T1w image and high signal on T2w image due to bone marrow oedema. Marked enhancement is seen on the fat-suppressed contrast-enhanced T1w image. Note that a burst fracture of L1 has resulted in protrusion of bone fragments and tumour into the spinal canal (*) with impingement on the spinal cord. Also note contrast enhancement (arrowheads) in the pre-spinal soft tissues that is likely related to the fracture and leaking damaged vessels.

Direct compression of the neurological and musculoskeletal structures by the tumour or associated fractures causes neuropathic pain, while the release of many chemical mediators of pain such as proinflammatory cytokines stimulate nociceptors of the periosteum and bone marrow that induce the nociceptive pain.[2]

Cancer-induced bone pain is the most common consequence of bone metastases, and the treatment options available vary from surgical intervention to drug treatment depending on the patients' symptoms, prognosis, and general state of health.

Surgical treatment is indicated in addition to palliative treatment with corticosteroids when tumor metastasis or fractures result in vertebral compression. Among surgical procedures, nerve destruction such as spinal cordotomy may be indicated in patients who are resistant to palliative drug treatment.

Radiation therapy and kyphoplasty with radiofrequency ablation may also be used to obtain pain relief and induce ossification of osteolytic lesions, which stabilizes the bone and also desensitizes the innervated portions.[2] Among the pharmacological treatments, NSAIDs are effective in pain relief because of their blockage of inflammation induced by cyclooxygenase-2.[3]

The next and last part of this series on the mechanisms of back pain will deal with spinal fractures and osteonecrosis, facet joint disease and paraspinal/ myofascial disease. Treatment options will be discussed based on each pain mechanism.

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The required dose of each component of AirBuFo Forspiro is individual and should be adjusted to the severity of the disease during initial and maintenance treatment. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Reassess patients regularly, to maintain an optimal dose of budesonide/formoterol. See SPC for long-term control. **A. AirBuFo Forspiro maintenance therapy:** Take as regular maintenance treatment, even when asymptomatic, with a separate rapid-acting bronchodilator as rescue. **B. AirBuFo Forspiro maintenance and reliever therapy:** Take as regular maintenance treatment and as needed in response to symptoms. Consider for patients with: • inadequate asthma control and in frequent need of reliever therapy • asthma exacerbations in the past requiring medical intervention. **Patients should be advised to have their separate rapid-acting bronchodilator available for rescue use at all times in maintenance and/or AirBuFo Forspiro in maintenance and reliever therapy.** A. Maintenance therapy: Recommended doses: Adults (18 years and older): 1-2 inhalations twice daily. Some patients may require up to a max. of 4 inhalations twice daily. Adolescents (12 – 17 years): 1-2 inhalations twice daily. Titration to the lowest effective dose could include AirBuFo Forspiro given once daily, when in the opinion of the prescriber, a long-acting bronchodilator in combination with an inhaled corticosteroid would be required to maintain control. Increasing use of a separate rapid-acting bronchodilator indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy. Children under 12 years: Not recommended. B. Maintenance and reliever therapy: Recommended doses: Adults and adolescents (12 years and older): 2 inhalations per day, given either as one inhalation in the morning and evening or as 2 inhalations in either the morning or evening. For some patients a maintenance dose of 2 inhalations twice daily may be appropriate. Patients should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. Not more than 6 inhalations should be taken on any single occasion. A total daily dose of more than 8 inhalations is not normally needed; however, a total daily dose of up to 12 inhalations could be used for a limited period. Patients using more than 8 inhalations daily should be strongly recommended to seek medical advice, for reassessment and reconsideration of their maintenance therapy. Children under 12 years: Not recommended. COPD: Recommended doses: Adults: 2 inhalations twice daily. Hepatic and renal impairment: No data. Method of administration: See SPC and PIL for illustrations and description. **Contraindications:** Hypersensitivity to the active substances or the excipient. **Warnings and Precautions for Use:** Contains lactose monohydrate: 5.4 mg per metered dose and 4.4 mg per delivered dose. Taper dose when treatment is discontinued and don't stop abruptly. Continue treatment but seek medical advice if asthma symptoms remain uncontrolled, worsen or serious adverse events occur. Sudden and progressive deterioration in asthma control or COPD can be life threatening and medical assessment and change in treatment may be needed urgently. Do not initiate AirBuFo Forspiro during asthma exacerbation, worsening or deterioration. In paradoxical bronchospasm, discontinue immediately and initiate alternative treatment. No data on prophylactic use e.g. in exercise. See SPC for possible systemic effects (less likely to occur than with oral corticosteroids). During long term treatment consider effect on bone density. Check adrenal function if necessary, especially if changing from oral corticosteroids to inhaler or in high doses. Consider additional systemic corticosteroid if needed. A lower systemic steroid action may result in allergic or arthritic symptoms. Rinse mouth out with water after use, to minimise risk of oropharyngeal candida infection. Caution in thyrotoxicosis, phaeochromocytoma, diabetes mellitus, untreated hypokalaemia, hypertrophic obstructive cardiomyopathy, idiopathic sub-valvular aortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disorders (ischaemic heart disease, tachyarrhythmias or severe heart failure), in patients with prolongation of QTc interval. Re-evaluate necessity in active or quiescent pulmonary tuberculosis, fungal and viral airway infections. Evaluate reason if visual disturbances develop. Monitor height of children. Caution as an increase in incidence of pneumonia in COPD patients receiving inhaled corticosteroids has been observed. **Interactions: Avoid:** Potent inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone, cobicistat and HIV protease inhibitors). Beta-adrenergic blockers can weaken or inhibit the effect of formoterol. Don't give together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons. **Caution:** Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine) and tricyclic antidepressants can prolong the QTc-interval and increase the risk of ventricular arrhythmias. L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards beta2 sympathomimetics. Concomitant treatment with monoamine oxidase inhibitors, including agents with similar properties such as furazolidone and procarbazine, may precipitate hypertensive reactions. There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons. Concomitant use of other beta-adrenergic or anticholinergic medicinal products can have a potentially additive bronchodilating effect. Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides. Hypokalaemia may result from beta2-agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, corticosteroids and diuretics. **Pregnancy and Lactation:** Pregnancy: only use when the benefits outweigh the potential risks. The lowest effective dose of budesonide needed to maintain adequate asthma control should be used. Breast-feeding: Only consider if the expected benefit to the mother is greater than any possible risk to the child. **Ability to Drive and Use Machinery:** No or negligible influence. **Undesirable Effects:** Common: Candida infections in the oropharynx; Pneumonia (in COPD patients); Headache; Tremor; Palpitations; Mild irritation in the throat; Coughing; Hoarseness. Refer to the SPC for other undesirable effects. **Marketing Authorisation Holder:** Rowex Ltd., Bantry, Co. Cork. **Marketing Authorisation Number:** PA0711/284/001. Further information and SPC are available from: Rowex Ltd., Bantry, Co. Cork. Freephone: 1800 304 400 Fax: 027 50417 E-mail: rowex@rowa-pharma.ie **Legal Category:** Subject to medical prescription. **Date of Preparation:** July 2019 Adverse events should be reported. Reporting forms and information can be found on the HPRA website (www.hpra.ie) or by emailing medsafety@hpra.ie or by emailing Rowex pv@rowa-pharma.ie