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thesynapse

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DOSAGE: The recommended dose is 284 mg inclisiran administered as a single subcutaneous injection: initially, again at 3 months, followed by every 6 months. ♦*Missed doses:* If a planned dose is missed by less than 3 months, inclisiran should be administered and dosing continued according to the patient's original schedule. If a planned dose is missed by more than 3 months, a new dosing schedule should be started – inclisiran should be administered initially, again at 3 months, followed by every 6 months. ♦*Treatment transition from monoclonal antibody PCSK9 inhibitors:* Inclisiran can be administered immediately after the last dose of a monoclonal antibody PCSK9 inhibitor. To maintain LDL-C lowering it is recommended that inclisiran is administered within 2 weeks after the last dose of a monoclonal antibody PCSK9 inhibitor. ♦*Elderly, hepatic impairment, renal impairment:* no dose adjustment is necessary. Inclisiran should be used with caution in patients with hepatic and renal impairment.♦*Paediatric population:* The safety and efficacy of inclisiran in children aged less than 18 years have not yet been established. ♦*Method of administration*: Inclisiran is intended for administration by a healthcare professional via subcutaneous route. Each pre-filled syringe is for single use only.

CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients listed in the SmPC.

WARNINGS/ PRECAUTIONS: ♦*Haemodialysis*: The effect of haemodialysis on inclisiran pharmacokinetics has not been studied. Considering that inclisiran is eliminated renally, haemodialysis should not be performed for at least 72 hours after inclisiran dosing. ♦*Sodium content:* This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

INTERACTIONS: Inclisiran is not an inhibitor or inducer of cytochrome P450 enzymes or common drug transporters. Therefore, inclisiran is not expected to have clinically significant interactions with other medicinal products. Based on the limited data available, clinically meaningful interactions with atorvastatin, rosuvastatin or other statins are not expected.

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Authors

Dr Alfred Grech MD graduated from the University of Malta in 1985. He has been working in Primary Health for these last 30 years. His special interests are molecular biology and epigenetics. As a pastime he cultivates bonsai trees and plays his sax alto. The co-author of the article is Dr Michael Balzan.

Dr Federica Zammit MD is a second year foundation doctor, who graduated from the University of Malta in 2020. She has a special interest in maternal medicine. Ms Isabelle Saliba is the co-author of the article.

Dr Pierre Vassallo MD PhD FACA Artz fur Radiologie specialised in radiology at the Institute of Clinical Radiology at the University of Muenster, Germany and the Memorial Sloan-Kettering Cancer Center, New York, US. He is currently Consultant Radiologist and Managing Director at DaVinci Health, Malta

Issue Guide

TheSynapse

On the Cover: Beyond the COVID-19 pandemic.

Editor-in-Chief: Dr Wilfred Galea
Managing Editor: Dr Ian C Ellul
Sales & circulation Director: Carmen Cachia

Email: mpl@thesynapse.net
Telephone: +356 21453973/4

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MADS Malta Association of Dental Students

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Schicksalsgemeinschaft

An inherent characteristic of the German language, which I believe renders it unique, is the fact that many concepts can be covered by a single compound word.

My expanding waistline constrains me to include a couple of examples relating to food. *Futterneid* means that one realises, after ordering a dish, that what our dinner companion has ordered looks more appetizing and inviting. There is also Kummerspeck which relates to the act of eating in order to find solace and consolation when one is worried, miserable or unfulfilled.

Schicksalsgemeinschaft on the other hand may be translated as community of fate. In my opinion it aptly captures the essence of human evolution. This word has been repeatedly trumpeted in Nazi propaganda; and it has also been courageously advocated by great German leaders. Indeed, this 22-letter word has been echoed by the likes of Angela Merkel and Olaf Scholz, but its significance extends well beyond the German territory.

This community of fate has been championed by some member states, osmotically taken up by others, but resisted by specific ones (such as Poland). The seemingly reluctant assimilation by the latter category has been sweetened by events primarily stemming from the COVID-19 pandemic. I am specifically referring here to the EU's vaccine joint purchase and logistics agreements. Malta has also benefited from this agreement, as evidenced by the political surveys which have been commissioned in view of the upcoming general election.

I am discussing *Schicksalsgemeinschaft* here, because in hindsight, the pandemic has made us aware of our obligations to, and reliance on, a wide network of people, which extends beyond family, friends and tribe. It has also made us aware of the 'invisible' workers who enabled us to survive. Sanitation workers are one example. Indeed, coming to terms with, and expanding, such a community of fate involves a cognitive informational process. It essentially requires the internalization of norms of justice and equity into one's thinking and practice, as antidote to political polarization, and any sclerosis which stems from this.

We discussed briefly the relation between *Schicksalsgemeinschaft* and the pandemic. However, other important areas relating to Sustainable Development Goals, such as climate change, must also be tackled at such a supranational level. Truth be told, we may well edge nearer to such behemoth targets - jotted on paper during conferences by enthusiastic champions - through seemingly small events. As an example, I can mention Greta Thunberg. This Swedish teenager mobilized young people across the globe to speak truth to power about climate change, leading to a butterfly effect.

I wish to conclude this editorial by auguring that such community of fate attempts to bridge the R&D gap relating to medicines in the EU, particularly paediatric medicines and orphan medicines. Let us not forget that we stand on the shoulders of giants!

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DR FEDERICA ZAMMIT & MS ISABELLE SALIBA

Managing Pregnancy
During the Covid-19 Pandemic

ABSTRACT

COVID-19 has impacted the way we manage pregnancy, delivery and the postpartum period. Good obstetric care aims at preventing devastating complications by being knowledgeable on the routes of viral transmission, risk factors, clinical presentation and diagnostic findings. Maternal complications may include C-section, secondary maternal infection, pre-eclampsia, eclampsia, hyperglycaemia and mortality. Neonatal complications are mostly due to preterm delivery. Classifying disease severity allows the patient to be channeled into the appropriate care pathway. This allows a patient-centered approach to timely antenatal follow-up, screening, vaccination, delivery and neonatal care. Patient education and involvement of the mother in decision-making ensures a positive experience.

Keywords: COVID-19, pregnancy, neonate, complications, management

INTRODUCTION

Two years down the line, Malta is still fighting against the pandemic that is COVID-19. First identified in the city of Wuhan in China in December 2019, a strain called SARS-CoV-2 was found responsible for the pathogenicity of COVID-19.[1]

Pregnant women have an equal chance of becoming infected with COVID-19 as the general population. However, its implications on maternal and fetal health may differ.

TRANSMISSION

The main method of transmission of COVID-19 is via respiratory droplets and contact with bodily fluids, especially within the initial 3 days of symptoms. Fomites and the faeco-oral route represent other methods of transmission.

Vertical transmission is uncommon, with the likelihood of neonatal transmission increasing with higher maternal viral load. However, the method of delivery, timing of cord clamping, mode of feeding or maternal contact do not change the likelihood of viral transmission.[2] Vertical transmission may be evidenced by neonatal Immunoglobulin M against SARS-CoV-2.

The incubation time is on average 5-6 days, with some patients developing symptoms within 14 days from exposure.[2] Viral shedding may occur up to 3 days before developing symptoms.[2]

PATHOGENESIS

It is known that pregnancy upregulates Angiotensin-Converting Enzyme 2 (ACE2).[3] Conversely, COVID-19 is associated with inhibition of the anti-inflammatory effects brought about by ACE2, along with enhanced angiotensin II function. Lymphopenia, demonstrated in two thirds of COVID-19 infected patients, can be explained by the inflammatory cascades which destroy these cells.[4] In addition, endothelial damage is partly related to the presence of ACE2 receptors on the endothelial lining to which the coronavirus attaches.

The inflammatory response peaks during the first and third trimesters due to the pro-inflammatory stimulus provided by T Helper 1 cells.[3] Also, the extent of virus elimination as well as maternal and neonatal complications vary with gestational age.

Interestingly, COVID-19 and pre-eclampsia share common features - mainly enhanced angiotensin II function, reduced ACE2 effect and potentiation of complement. This thus explains the increased risk of venous thromboembolism and endothelial cell damage seen in both conditions.

CLINICAL PRESENTATION

Over two thirds of pregnant women lack symptoms.[2] However, the maternal respiratory and cardiovascular adaptations may result in a delayed diagnosis of COVID-19 or increased morbidity.

Around 86% of pregnant women will have mild disease. 9% of pregnant women experience severe disease, with 5% manifesting life-threatening illness.[2] Red flags include tachypnoea, hypoxaemia, pulmonary crackles, stigmata of heart failure, arrhythmias, myocarditis and shock.

Pregnant women with COVID-19 mostly present with fever (40%) and cough (41%).[2] They may also experience myalgias (19%), breathlessness (21%), diarrhoea (8%), lack of taste (14%), lethargy and reduced appetite.[2] Other non-specific manifestations include sore throat, coryza, reduced sense of smell, nausea, vomiting and neurological manifestations such as seizures, encephalopathy and cerebrovascular accidents.[1]

Affected pregnant women may manifest more severe symptomatology than non-pregnant women.[2] However, pregnant women have a lower risk of presenting with fever or myalgia.

Interestingly, while the Omicron variant is known to be more infectious, it manifests milder symptoms when compared to other variants such as the Delta variant.[2]

DIAGNOSIS

COVID-19 is typified by lymphopenia, thrombocytopenia and raised inflammatory markers. Liver enzymes and lactate dehydrogenase may also be elevated. A troponin rise may signify damage to the myocardium.

Viral and rapid antigen tests as well as serology are used to detect infection.[5]

Useful imaging modalities may include Chest X-Ray, Computed Tomography (CT) and pulmonary ultrasound. Chest X-Ray may demonstrate peripheral and lower lung zone opacities. CT may show bilateral ground glass appearance in 83% of gravid women, which may not be apparent until after the fourth day. Ultrasound may show thickened pleura and consolidations.

RISK FACTORS

The following increase the risk of infection and subsequent hospital admission:

- Age ≥35 years
- BMI ≥25kg/m^2
- Asian, Black or ethnic minority groups[6]
- Medical comorbidities present before pregnancy, exemplified by hypertension and diabetes[6]
- Poor socioeconomic background
- Occupations with frequent human interaction
- High viral load and elevated neutrophil-lymphocyte ratio.[2]

COMPLICATIONS

Maternal complications

Affected pregnant women are more likely to develop severe illness, with higher rates of intensive care (ICU) admission. Also, women who experience fever, dyspnoea and pneumonia have poorer maternal and neonatal outcomes.[7]

Infected pregnant women are thus at increased risk for the following:

- 17% risk of preterm delivery - In most cases this is iatrogenic, especially in symptomatic mothers.[2]
- 59% risk of C-Section[2]
- 25% risk of maternal mortality[4]
- Secondary maternal infections
- Pre-eclampsia and eclampsia
- Hyperglycaemia due to stress and antenatal corticosteroids.

Neonatal complications

COVID-19 does not increase the risk of congenital anomalies, stillbirth or neonatal mortality.[2] Effectively, 95% of neonates born to infected mothers are delivered healthy.[2] However, in the presence of maternal infection, 13% of neonates were found to be positive for COVID-19.[7]

The main neonatal risk associated with maternal infection is preterm delivery. This accounts for most of the perinatal morbidity and mortality such as fetal distress, low birthweight and higher rates of ICU admission.

MANAGEMENT

Antenatal Care

Pregnant women should be encouraged to attend their antenatal visits, with appropriate modifications to their visit schedule in cases of quarantine. In the latter cases, women should organize a visit as soon as possible. Patient-centered care calls are also made for quarantined high risk patients, which should be reviewed earlier, since they have a lower threshold for more aggressive management.

Women who had mild, moderate or asymptomatic disease need not be seen more frequently than non-affected patients. Women who suffered severe or critical disease with hospital admission should be followed up more closely, with a fetal ultrasound scan at 14 days following disease resolution, or earlier if the need arises.[2]

Educating women about concerning symptoms and signs, such as abdominal pain or headaches, bleeding, visual disturbances, presyncope, seizures, breathing difficulties and reduced fetal movement, is crucial for them to seek timely medical attention. Nevertheless, other diagnoses such as urinary tract infection and pulmonary embolism must be excluded.

Appropriate screening tools help in classifying disease severity and in guiding appropriate management. Screening should occur at every contact and appropriate questions regarding symptomatology and positive contacts

should be made. This allows patients who are suspected to have COVID-19 or are confirmed cases to be directed to the appropriate care pathway.

Healthcare professionals should be sensitive to the mother's mental wellbeing. With quarantine, loss, financial hardships, limited contact with support services and increased rates of domestic violence, psychological distress may be amplified. Thus, timely referral to support facilities is recommended.

Vaccinations

The importance of taking the recommended vaccines, including the flu vaccine, must be emphasised. In case of COVID-19 infection, women may resume routine vaccines after resolution of illness.[2]

The Malta College of Obstetricians and Gynaecologists is encouraging all pregnant women beyond 12 weeks of gestation to receive the COVID-19 vaccine, including the booster dose, since this is associated with a significant reduction in COVID-19 complications.[8,9] It is also safe for lactating women, as well as those planning a pregnancy since there is no sound evidence that it causes fertility problems.[8]

Despite the Omicron variant being particularly infectious, pregnant women who have received three COVID vaccine doses exhibit an 88% reduction in the rate of hospital admission.[2]

Intrapartum Care

The approach towards labour must be patient-centered and led by a multidisciplinary team. At all times, the woman should be involved in the decision-making process and should not be denied skin-to-skin contact or delayed cord clamping.

COVID-positive women manifesting mild symptoms must present to the Labour Ward once the process of labour has been established, i.e. past the early latent stage of labour, unless the mother's state contraindicates this. Upon admission, parameters should be recorded every hour with continuous cardiotocography (CTG). The latter need not be offered continuously in asymptomatic women.

Cases of uncomplicated recovery from COVID-19 often do not require deviation from conventional labour management. Conversely, complicated recovery requiring hospital admission calls for a modified birth plan and frequent fetal growth monitoring.

Postpartum Care

It must be emphasised that mother and baby should not be separated, unless the mother has severe disease requiring ICU care.[2]

Neonates of suspected or confirmed cases can be tested for COVID-19 within 24 hours after birth, via nasopharyngeal, oropharyngeal or nasal swabs.[10] The test can be repeated 48 hours after birth.[10] A repeat swab is especially important in high risk neonates. These include those born to COVID-positive mothers and those portraying highly suggestive symptoms.

COVID-positive mothers may still breastfeed since the risk of viral transmission is minimal and the benefits of breastfeeding and skin-to-skin contact by far outweigh the risks. However, mothers should be educated on infection control measures that reduce the risk of transmission to their baby. These include hand hygiene, washing of feeding devices, wearing a facemask as well as avoidance of coughing within the baby's proximity.[10,11] Some mothers may also require help in daily neonatal care.

MEDICAL MANAGEMENT OF MATERNAL COVID-19 INFECTION

Symptomatic women should be treated as COVID-positive until infection can be excluded by a swab test. Febrile episodes should also prompt blood cultures to exclude bacterial infection.

The medical care of confirmed cases should be led by a multidisciplinary team with close follow-up by the leading obstetrician, especially if the woman exhibits unstable parameters.

Recording parameters every hour allows for escalation of treatment should the following be noted:

- Increased oxygen requirements
- Worsening tachypnoea
- Decreased urinary output
- Deranged renal function suggestive of acute kidney injury
- Reduced level of consciousness

Foetal heart monitoring is also vital, at intervals determined on a case-by-case basis.

Oxygen Therapy

One should aim for oxygen saturations of 94% to 98%.[2]

Fluid Therapy

Hourly input-output charting is advised, especially in moderate or severe cases. This ensures optimal hydration in preparation for delivery whilst avoiding fluid overload.

Antibiotic Therapy

Antibiotics may be administered in cases of suspected bacterial infection. Treatment must be revised especially in confirmed COVID cases, although antibiotic therapy may still hold if a secondary bacterial infection is suspected.

Venous Thromboembolism Prophylaxis

A comprehensive history quantifies the risk of venous thromboembolism and highlights comorbidities that might contraindicate low molecular weight heparin (LMWH) use.

Thromboembolism prophylaxis may be achieved by administering prophylactic LMWH along with thromboembolic deterrent stockings or pneumatic

compression devices. The latter may be used in isolation when LMWH is contraindicated or if there is a low platelet count. Platelet counts below 50x10^9/L should instigate cessation of aspirin and LMWH until haematology review.[2]

A therapeutic dose of LMWH should be administered in suspected or confirmed cases of venous thromboembolism.

Antenatal Corticosteroids

Corticosteroids are key for women with severe COVID-19 disease, especially those requiring oxygen therapy. A 10-day course is usually administered, although shorter courses terminating on the day of discharge may be prescribed.[1] Steroids in the form of oral prednisolone or intravenous hydrocortisone may be used. Intramuscular dexamethasone may also be used if promotion of fetal lung development is required.

Other Medication

The decision to prescribe Remdesivir in pregnant or lactating women should be led by the multidisciplinary team and is only recommended in situations where the advantages exceed the risks, such as in women receiving oxygen therapy.[2] This is due to uncertainty regarding possible foetal effects.

On the other hand, Tocilizumab may enhance the survival of hypoxic patients with an ongoing inflammatory response who require oxygen therapy.[2] This is through blockade of interleukin-6 receptors.

Planning Delivery

The timing and mode of delivery should be jointly discussed with the mother and the multidisciplinary team, bearing in mind the maternal or foetal factors that may necessitate induction of labour or urgent delivery via a C-section. The obstetrician might also recommend corticosteroids and magnesium sulphate therapy in cases of premature delivery.

CONCLUSION

The COVID-19 pandemic, with all the uncertainties it has brought upon maternal and fetal medicine, has stirred much clinical research on how to adopt a safe practice that allows for optimal maternal and fetal wellbeing. Following updated versions of authorised clinical guidelines is crucial in the planning of good obstetric and neonatal care.

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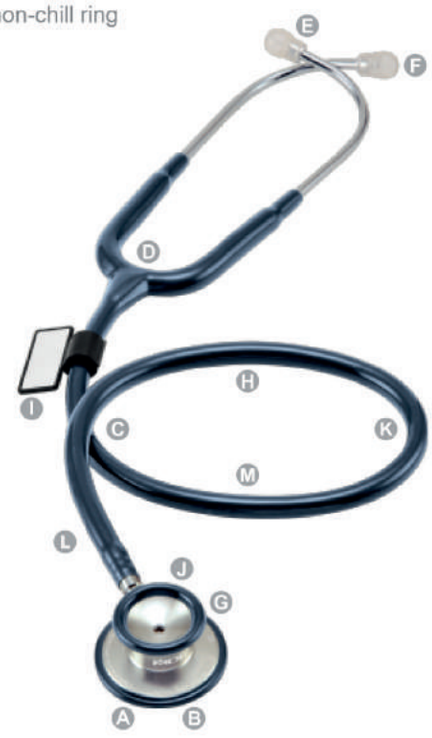

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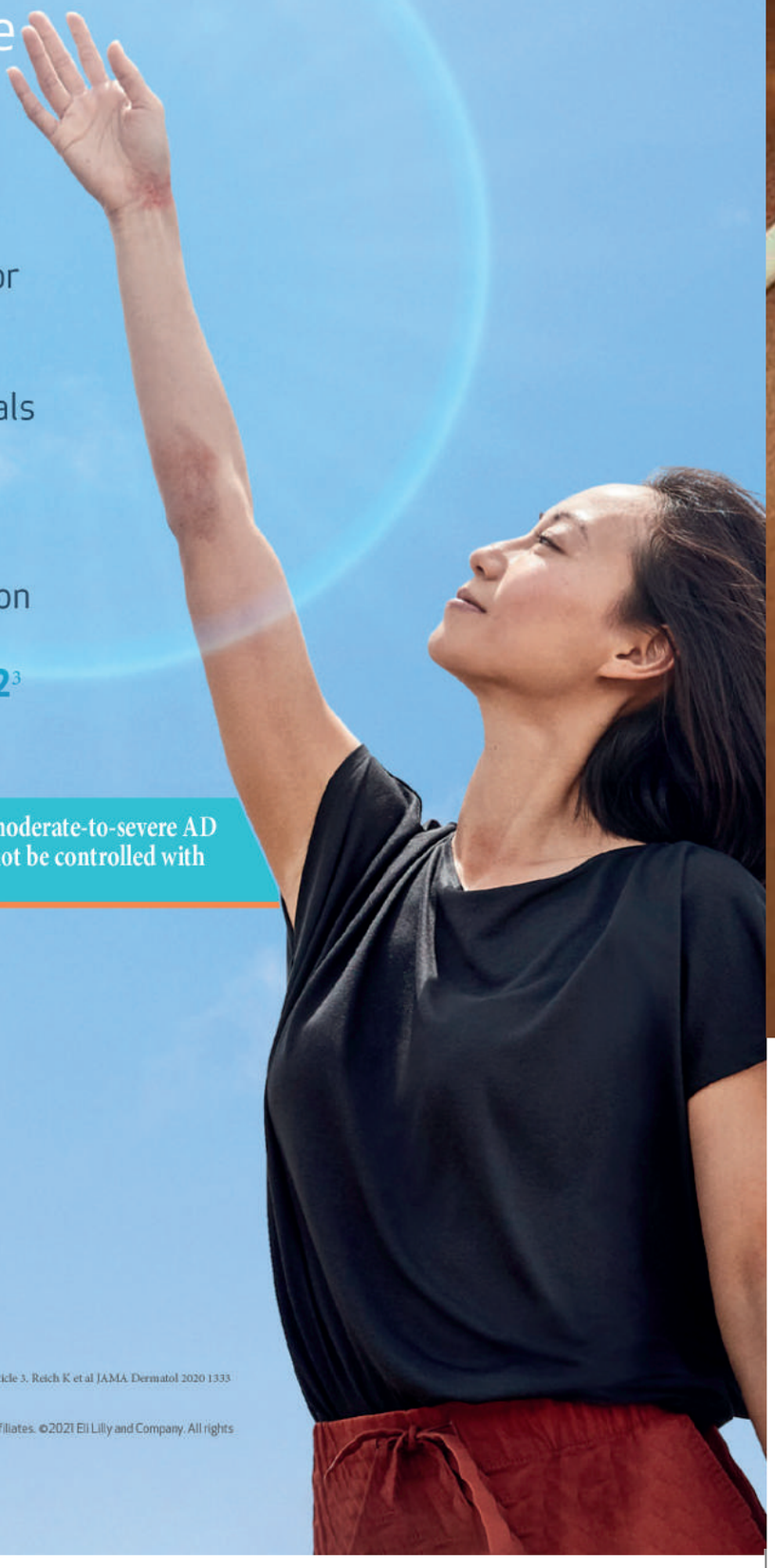

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Taltz, a targeted IL-17A inhibitor with high binding affinity (kd<3 pM) Taltz is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy

* measured as percentage decrease in PASI score from baseline

Undesirable Effects Summary of the safety profile: The most frequently reported adverse drug reactions were injection site reactions (15.5 %) and upper respiratory tract infections (16.4 %) (most frequently nasopharyngitis). Injection site reactions: The most frequent injection site reactions observed were erythema and pain. These reactions were predominantly mild to moderate in severity and did not lead to discontinuation of Taltz. **Infections**: In the placebo-controlled period of the phase III clinical studies in plaque psoriasis in adults, infections were reported in 27.2 % of patients treated with Taltz for up to 12 weeks compared with 22.9 % of patients treated with placebo. The majority of infections were non-serious and mild to moderate in severity, most of which did not necessitate treatment discontinuation. Serious infections occurred in 13 (0.6 %) of patients treated with Taltz and in 3 (0.4 %) of patients treated with placebo. Infection rates observed in psoriatic arthritis and axial spondyloarthritis clinical studies were similar to those observed in the plaque psoriasis studies with the exception of the frequencies of the adverse reactions of influenza and conjunctivitis which were common in patients with psoriatic arthritis. **Paediatric population:** The safety profile observed in children with plaque psoriasis is consistent with the safety profile in adult patients with plaque psoriasis with the exception of the frequencies of conjunctivitis, influenza, and urticaria which were common. Inflammatory bowel disease was also more frequent in paediatric patients, although it was still uncommon. Very common (≥ 1/10): Upper respiratory tract infection, injection site reactions. Common (≥ 1/100 to < 1/10): Tinea infection, herpes simplex (mucocutaneous), oropharyngeal pain, nausea. Laboratory assessment of neutropenia and thrombocytopenia In plaque psoriasis studies, 9% of patients receiving Taltz developed neutropenia. In most cases, theblood neutrophil count was ≥1,000 cells/mm3. Such levels of neutropenia may persist, fluctuate or betransient. 0.1% of patients receiving Taltz developed a neutrophil count <1000 cells/mm3. In general,neutropenia did not require discontinuation of Taltz. 3% of patients exposed to Taltz had a shift froma normal baseline platelet value to <150,000 platelet cells/mm3 to ≥75,000 cells/mm3.Thrombocytopenia may persist, fluctuate or be transient.The frequency of neutropenia and thrombocytopenia in psoriatic arthritis clinical studies is similar tothat observed in the plaque psoriasis studies

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via ADR Reporting, The Medicines Authority , Post-Licensing Directorate, 203 Level 3, Rue D'Argens, GŻR-1368 Gżira; www.medicinesauthority.gov.mt; postlicensing.medicinesauthority@gov.mt

Legal Category POM Marketing Authorisation Numbers and Holder EU/1/15/1085/001, EU/1/15/1085/004. Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands.
Date of Preparation or Last Review June 2020 **Further Information is Available From** Charles de Giorgio Ltd Triq. Kan. Pirrotta B'Kara, BKR 114, Malta

This medicinal product is subject to additional monitoring. To report any suspected adverse reactions associated to this medicine is important.
Taltz, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drug (DMARD) therapies. For full prescribing information please refer to your local country product information.

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DR ALFRED GRECH & DR MICHAEL BALZAN

Epigenetics in Mental Illness

ABSTRACT

Mental illnesses are complex and multifactorial. Nature (genetic factors) is important in their etiology but nurture (environmental factors) via epigenetic mechanisms is being found to be an additional etiological player. Indeed, studies among identical twins show high rates of discordance, especially for stress syndromes and depression. Specifically, aberrant epigenetic regulation is being found to underlie psychiatric disorders. While epigenetic studies of mental illnesses are relatively still in their infancy, further translational research will surely reveal new insights into their pathophysiology, which in turn will help with the discovery of new targets for treatments, biomarkers, patient stratifications and more 'personalized' treatment.

Keywords: DNA methylation, histone modifications, epigenetic biomarkers, epimutations, theranostics

INTRODUCTION

Historically, the word 'epigenetic' was used to describe the phenomenon of cell identity.[1] 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.

Amongst the most studied epigenetic modifications are 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, with DNA methylation being the most stable and histone modifications being more plastic. This fact has enabled the prospect of epigenetic therapy. Indeed, epimutations have been targeted for new drug innovations, and "turning back on" silenced genes represents a prospective advancement in treatment.

Genetic factors (nature) underlie the etiology of most mental disorders. But studying identical twins is showing that there are high rates of discordance, especially when it comes to depression and stress-related syndromes.[2] This implies other etiological mechanisms possibly involving nurture. And since epigenetics is a layer between nature and nurture, this has spurred research into epigenetics of mental illness.

Indeed, early studies of epigenetics in mental diseases are aiming to discover how environmental factors affect the epigenetic processes in brain regions. These will hopefully shed light on the pathophysiology of mental diseases, which when integrated into the clinical setting, will in turn guide new targets for treatment, stratify patients for specific personalized treatment, and diagnosis.

INVESTIGATIONS

The pathophysiological mechanisms of mental illnesses remain relatively limited as several barriers still exist. Specifically, mental illness is the result of aberrations in the functions of the brain, which is the organ in the human body that is least understood. Moreover, the genetic studies, which in themselves are also limited, imply that mental illness is complex and polygenic with many genetic variants. Many of these variants are associated with the non-coding regions of the genome.[3] Model systems are scarce, as is diseased tissue and cell types that can be studied, as will be discussed below.

Nevertheless, in order to gain molecular mechanistic insights, researches are using the following.

Peripheral Blood

Peripheral blood samples are utilised to study epigenetic signatures in neuropsychiatric disorders. For example, Numata et al.[4] used peripheral blood samples to study the DNA methylation state of the NR3C1 gene. They found a hypomethylation signature in depressed patients. The gene encodes for a glucocorticoid receptor. From post-mortem studies, under expression of this receptor in the hippocampus is linked to depression and suicide.

In another study using peripheral blood samples, Maffioletti et al.[5] found aberrant expressions of five microRNAs in the 20 subjects in the depressed arm of the analysis. They suggested that these microRNAs form part of the pathophysiological mechanism in depression. Similarly, another study on microRNA from mononuclear cells using peripheral blood by Fan et al.[6] found five other microRNAs which were up-regulated in patients with depression.

Enatescu et al.[7] analysed changes in plasma microRNA profiles of patients with major depression. They found that after 12 weeks of treatment, some were over-expressed while others were under-expressed. They propose that such studies have the potential to identify and validate microRNAs as biomarkers in depression; also, they can offer new targets for treatment by using anti-microRNAs or microRNAs mimics.

Brain Tissue

Biopsies of patient's brain tissue are invasive and provide little material to work with. Moreover, neurons that are post-mitotic cannot be expanded in vitro. Post-mortem brain samples have their own disadvantages as well. For example, they represent late stages of the mental illness and so do not provide insight of the epigenetic aberrations present in early life. Besides end-stage brain samples will not show the true natural picture of disease progression as patients would have receivedpharmacological treatments, which definitely leave their 'noise' marks. On top of these are effects from fixation methods and storage of the samples.

Despite the above, post-mortem human brain samples have been used in several studies. One such study is that done by Lopez et al.[8] which showed that miR-1202 is expressed differentially in patients with major depressive disorder. This micro-RNA regulates the gene that codes for glutamate metabotropic receptor-4 (GRM4). From their results, they propose that this micro-RNA forms part of the pathophysiology of depression, can predict response to anti-depressant treatment, and is a potential therapeutic target.

Animal Models

Peripheral blood or post-mortem brain tissues have many variables when they are used to study the pathophysiological mechanisms of mental disorders. Amongst them are sex, race, age, living conditions, medication, and time of collection after death. These can greatly impact the results. Using animal models provide a more controlled approach.[9] Other advantages of using animal models are that one can study the effects of pharmacological agents and gene editing, which are not possible when using human patients.

Using mice models, Baubry et al.[10] and O'Connor et al.[11] showed that micro-RNAs can be potential markers of response to anti-depressant treatments. Also, Grayson et al.[12] studied the DNA methylation profiles in adult offsprings of two mouse models of schizophrenia, i) the 'prenatal restraint stress model' and ii) the 'chronic methionine mouse model'. The adult offsprings showed behavioural and epigenetic and other biochemical deficits. These and similar studies on animal models are providing solid evidence that early-life adversity and other environmental factors can mediate long-lasting epigenetic modifications in the brain, which are conducive to mental ill-health.

Cellular Models

Cellular reprogramming is offering another platform to study neuropsychiatric disorders. In their review, Seshadri et al.[13] state that induced pluripotent stem cells (iPSCs) and their neural derivatives are being used to understand schizophrenia. Indeed, the results, namely relating to abnormalities in neurotransmission, neurodevelopment, and oxidative phosphorylation, support those arising from other study designs. Viswanath et al.[14] similarly reviewed cellular models to study bipolar disorders.

One great advantage of the above traditional iPSC technology, when used to model human diseases, is that the induced cells have the whole genome of the donor and this makes them fit to dissect diseases caused by genetic errors. This platform is becoming more valuable when combined with CRISPR/Cas9 gene editing and genome-wide association studies. However, when it comes to studying epigenetics it faces a problem, namely that during the process of reprogramming, the epigenetic memory is erased (epigenetic erasure).[15] Thus, mental illnesses that are epigenetically modified by environmental factors need to be studied by a sister technology called 'transdifferentiation' to generate functional-induced neurons (iNs).[16] Transdifferentiated cells seem to maintain the original epigenetic landscape.[17,18] However, such studies are still in their infancy.

SCHIZOPHRENIA

Studies are revealing that epigenetic modifications are important in the pathophysiological mechanisms of schizophrenia. Here, the main epigenetic mechanisms mostly studied on post-mortem brain tissue and bio-fluids are DNA methylation, histone modifications, and non-coding miRNAs. Amongst the gnes that are being

found to be affected by epigenetic aberrations include those that regulate immune function, neurotransmission and neurodevelopment.[19] It is proposed that some of these epigenetic aberrations are induced through environmental factors which affect brain functions in a patient's life but may also be transmitted across generations (the trans-generational epigenetic inheritance effect).

In the study done by Murata et al.[20] betaine levels in peripheral blood samples were found to be low especially in first-episode schizophrenia patients but also in some cases of chronic schizophrenia. Betaine is a methyl-donor and its under-expression was associated with genome wide hypomethylation. The authors propose that the genome-wide hypomethylation from decreased betaine expression might be a puzzle part of the pathophysiology of schizophrenia.

Another puzzle part might be the role of NR3C1 gene which is a glucocorticoid receptor gene. The gene is a key contributor in the regulation of the hypothalamic-pituitary-adrenal axis. Liu et al.[21] found epigenetic aberrations, specifically DNA hypermethylation of the promoter of this gene. This correlates with other similar findings mentioned below associated with depression, implicating that these mental illnesses might have common biological networks.

There are many other research studies on altered DNA methylation, but also on histone modifications of schizophrenic risk genes. Such studies are in hyperdrive especially those involving the common two histone modifications linked with the active promoters and enhancers of schizophrenic risk genes, specifically H3-trimethyl-Lys4 (H3K4me3) and H3-acetyl-Lys27 (H3K27ac). Amongst the schizophrenic risk genes one finds - RELN, GAD1 and CACNA1C.

MicroRNAs are emerging as important regulators in post-transcriptional gene expression in various human diseases. MicroRNAs have been established as important players in the development of the brain and its neuroplasticity and their aberration are involved in neuropsychiatric diseases including schizophrenia. The study by Santarelli et al.[22] supports the fact that miRNA aberrations are important players in the complex pathophysiological mechanisms of schizophrenia. The authors analysed gene expression in the post-mortem prefrontal dorsolateral cortex. They integrated this gene expression analysis with miRNA expression profiles and found an important gene-miRNA interaction biological network. Specifically they identified aberrations in miR-92a, miR-495, and miR-134, which are important in neurodevelopment and oligodendrocyte functions. The dysregulation of miRNAs have also been detected in peripheral blood mononuclear cells (PBMCs) in schizophrenia. Further research will surely exploit this as a potential of miRNA biomarkers in schizophrenia. Translational research will also exploit and harness miRNA aberrations and their biological networks as new therapeutic targets.

DEPRESSION

Only about 40% of depression is heritable and this points to factors which are not genetic in nature, like stressful life events, especially those that occur in early life. Research on animal models have shown that early-life adversity affects gene expression involving epigenetic mechanisms.[23-25]

Prenatal stress has epigenetic repercussions on the brain. Jensen Peña et al.[26] and O'Donnell et al.[27] showed that maternal stress is associated with decreased expression of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) from the placenta. Normally 11β-HSD2 shields the foetus from glucocorticoids coming from the mother. The suppression of 11β-HSD2 is associated with DNA hypermethylation in the promoter of its gene and thus the protection is absent, rendering the offspring more vulnerable - to stress and depression.

In another animal study, Mueller and Bale[28] identified DNA hypermethylation of the NGF1-A binding region of the glucocorticoid receptor (GR; Nr3c1) in the hypothalamus of offspring of females that were stressed early in the prenatal period. A similar finding of increased DNA methylation at this site was shown in cord blood taken from infants born to human mothers who, during their pregnancy, were depressed or physically abused.[29-31]

In keeping with the above, research has shown that maternal separation and maternal maltreatment also induce epigenetic changes in the brain of animal offspring.[32,33] Some of these epigenetic changes are lasting but others can be partially reversed pharmacologically.[34,35] Epigenetic aberration signatures have also been shown in suicide completers. For example, Labontéet al.[36,37] found aberrant promoter DNA methylation in several genes in the hippocampus of suicide completers; however, other aberrant epigenetic mechanisms, like miRNA and histone modifications, are also involved in suicidal behaviour.[38]

Epigenetic studies have also been carried out to investigate epigenetic signatures following antidepressant treatment. Melas et al.[39] used a genetic rodent model of depression, specifically the 'Flinders Sensitive Line (FSL) one'. They looked into epigenetic changes with regards to the P11 gene in the frontal cortex of the brain. P11 has been implicated in the pathophysiological mechanisms of depression in humans and rodents alike. They found DNA hypermethylation in the promoter of P11 gene, leading to its under-expression. Importantly they also found that giving escitalopram reversed this hypermethylated profile into a hypomethylated one with re-expression of the P11 gene. Treatment with escitalopram also leads to decreased Dnmt1 and Dnmt3a. The latter are two

DNA methyltransferases that, when over-expressed, are responsible for the hypermethylation pattern of the P11 gene in the adult forebrain neurons.

Despite the availability of various anti-depressant treatments, depressed patients may not show good response, even after several different medications have been tried. This is why specific research in epigenomics[40] (together with other –omic studies) is focusing on identifying epigenetic biomarkers that could predict the optimal treatment for particular subtypes of depressed patients.

CONCLUSION

Harnessing the knowledge that is forthcoming from the study of epigenetics in mental illnesses will definitely aid in their theranostics. Prevention-wise, epidrugs and other conventional therapies (like psychotherapy) have the potential to reverse the epigenetic alterations associated with environmentally-induced mental illnesses and help in preventing their transmission to future generations.

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Dr Ian Ellul meets up with **Mr Gordon Caruana Dingli** to shine a light on breast cancer surgery. We then shifted our gaze to the Moon. Mr Caruana Dingli is consultant general and breast surgeon, Head of the St Agatha Breast Unit at Mater Dei Hospital and Chairman of the Department of Surgery.

Halsted, Méliès & Maltese Giants

EDWARD CARUANA DINGLI WAS AN EARLY 20TH CENTURY PROLIFIC MALTESE PAINTER. I HAVE ALWAYS WONDERED WHETHER YOU ARE RELATED TO HIM.

Edward was my grandfather's brother. The artistic streak has touched various family members, including my grandfather Robert who was also an artist, as well as my sister Debbie and her sons, and even my daughter Sarah who is a graphic designer. I also wonder whether the artistic heritage helps me in my work since oncoplastic breast surgery inherently draws from aesthetics.

WHY BECOME A DOCTOR AND LATER ON, DECIDE TO SPECIALISE IN BREAST SURGERY?

My interest in science was kindled when the US landed on the Moon in 1969. I remember staying up late, watching the event on television with my father. My passion for science was also gradually nurtured by the television series Star Trek. I carried my interest in science to school and I have always felt that my father envisaged me graduating as a doctor one day; he was, however, never explicit about this. At University the available courses were also limited back then, and this seems favoured the course of my fate to become a doctor.

I opted for surgery early on because I was always inclined to work with my hands, an aptitude which I had since my childhood days, enjoying building and making things with my hands. My initial training was general surgery, but, after training in the UK, I worked with Mr Charles Swain who influenced me greatly and I am deeply indebted to him. He wanted to improve the care of breast cancer patients and thus, he set up the Breast Clinic in 2000 where all breast cancer cases would be managed by a multidisciplinary team including radiologists, pathologists, oncologists, surgeons and breast care nurses. In 2007 the national breast cancer screening programme was also set up. Time showed the magnitude of the progress we managed to achieve. Suffice it to say that 20 years ago we had the worst results in Europe. Now we have a 5-year survival rate of breast cancer of 87% which is the highest in the EU.

YOU ALSO HELD THE POSITION OF PRESIDENT OF VARIOUS ASSOCIATIONS SUCH AS MAM, ASSOCIATION OF SURGEONS OF MALTA, AS WELL AS THE COMMONWEALTH MEDICAL ASSOCIATION. CAN YOU GIVE SOME MORE DETAIL?

MAM's purpose is two-fold, serving as a trade union, being one of the oldest and most effective ones, as well as an association of doctors. Dr Martin Balzan, the current President, would agree with me in saying that MAM has been instrumental in our evolving healthcare systems, championing healthcare quality measures in a proactive manner.

The Association of Surgeons of Malta is far smaller than MAM. Whilst recognising the importance of training abroad, one of our landmark contributions was the implementation of the local training of our surgeons. The current President is Professor Joseph Galea.

On the other hand, the Commonwealth Medical Association comprises 54 countries who find convergence in the use of English language, and systems of governance and healthcare based on the British system, but differ in size, GDP and health equalities. Great efforts are being done to implement digital innovations to overcome such inequalities.

CAN YOU SINGLE OUT A DEVELOPMENT IN MEDICINE WHICH PROVED TO BE SEMINAL SINCE YOUR GRADUATION IN 1984? MAYBE THE CONCEPT OF 'EVIDENCE-BASED MEDICINE' COINED BY PROF. GORDON GUYATT? THIS WAS TO BE A 'PARADIGM SHIFT', AS HE EXPLAINED IN HIS PIONEERING PAPER OF 1992 AT MCMASTER UNIVERSITY.

I agree. We strive to provide the best care to patients, based on research. Today we also see subspecialisations. We have currently just appointed a hepatobiliary surgeon, for example. Evidence-based practices show that these subspecialisations translate into better results. Screening is also part of the equation leading to better survival rates; in surgery we screen for breast and colonic cancer and aortic aneurysm screening will soon be rolled out. Genetics are another important area which will probably lead to a shift to personalised treatments.

ONE CANNOT BUT REMEMBER HERE THE TRAGIC DEMISE OF NIRVANA AZZOPARDI, A POPULAR TV PRESENTER, WHO DIED OF BREAST CANCER AT THE TENDER AGE OF 40 YEARS IN 2013. NEWSPAPERS REPORTED ALLEGATIONS THAT THIS COULD HAVE STEMMED FROM A MISDIAGNOSIS BY HER OBSTETRICIAN. DO YOU CONSIDER THIS TO BE A WATERSHED MOMENT IN BREAST SCREENING LOCALLY?

Possibly yes, since the female population in Malta became aware that breast cancer affects younger women as well.

IN 1894, DR WILLIAM HALSTED AT THE JOHN HOPKINS HOSPITAL PUBLISHED HIS PIONEERING WORK ON RADICAL MASTECTOMY WHICH WAS CARRIED OUT IRRESPECTIVE OF TUMOUR SIZE, TYPE, OR PATIENT'S AGE. A CENTURY LATER ITS PODIUM PLACEMENT HAS BEEN REPLACED BY BREAST CONSERVATION THERAPY. KEY HERE ARE THE ADVANCES IN RADIOLOGY SUCH AS U/S GUIDED CORE BIOPSIES AND DIGITAL MAMMOGRAPHY. WHAT ELSE?

At that time, medics were not aware that their patients died from breast cancer, primarily from metastasis. Thus, with the conviction that the disease was localised to the breast area, they continued increasing the operation area until they reached radical mastectomy. This operation is notoriously associated with cosmetic disfigurement and limb disability. This was done with the aim of decreasing mortality. In my career I only performed it once for a patient with breast sarcoma.

The greatest evolution in breast cancer stemmed from two things. The first was tamoxifen which is a selective estrogen receptor modulator. The second arose from evidence-based medicine, as you correctly indicated before. An Italian research group conducted a clinical trial in the eighties. They randomised women with a small tumour size into two arms, one undergoing a mastectomy and the other having an excision followed by radiotherapy. The results were equivalent. Further research along the years has shifted the balance, for small tumours, to breast excision followed by adjuvant treatment.

YOU MENTIONED TAMOXIFEN. THE ROAD FROM ITS MARKETING AUTHORISATION IN 1978 TO TRASTUZUMAB TWENTY YEARS LATER WAS LENGTHY AND BUMPY. ARE WE IN FOR A SMOOTHER RIDE?

In our field, the first hormonal therapy was tamoxifen which decreased mortality by 15% and the first biological medicine was trastuzumab which is a monoclonal antibody. Since then there have been newer drugs. In Malta we see 350 new cases of breast cancer yearly, and 60-80 yearly deaths. We see a heavy international R&D investment in this area precisely because research is profit-driven which in turn relies on lengthy treatments which is the case in breast cancer. Screening also helps by detecting the disease at an earlier stage. We are, in fact, seeing a faster market launch of new technologies and medicines, which may well translate in a shift to less invasive ablation interventions, followed by genetic testing and biologicals.

DO YOU RECOMMEND PREVENTIVE MASTECTOMY FOR WOMEN CARRYING THE BRCA1 AND BRCA2 MUTATIONS?

When patients with a family history of breast cancer get referred to us, risk reduction surgery is clearly explained with its inherent limitations and if need be, they are referred for genetic counselling. If the geneticist then agrees that there is a considerable risk, we perform genetic testing to investigate the mutations and then, if indicated and the patient agrees, we proceed with the operation.

SOME TIME AGO I DISCUSSED AT LENGTH THE TOPIC OF SOCIAL DETERMINANTS OF HEALTH WITH PROF. SANDRO GALEA WHO IS DEAN AT THE BOSTON UNIVERSITY SCHOOL OF PUBLIC HEALTH, US. WHAT IS THEIR RELATION TO BREAST CANCER?

You touched an area which is close to my heart. I strongly believe that an investment in better schooling and housing, for example, has a major positive impact on health outcomes. In fact it has been reported in Malta, that for example, people with higher levels of education have higher overall longevity.

YOU CORRECTLY STATED THAT, ACCORDING TO THE OECD'S COUNTRY HEALTH PROFILE 2021 REPORT FOR MALTA, THE 5-YEAR SURVIVAL RATE FOR BREAST CANCER IS HIGHER THAN THE EU AVERAGE (87%). NOTWITHSTANDING THIS, THE MORTALITY RATE IS HIGHER THAN THE EU AVERAGE. IS ACCESS TO DRUGS THE REASON?

I do not think so. If a particular medicine is not available in the NHS, patients get referred to the Community Chest Fund. We certainly need more new treatments in the NHS but this is a political question. As discussed previously,

politicians need to gauge all social determinants of health before investing in a particular area.

IN KEEPING WITH THE ABOVE QUESTION, ACCORDING TO THE EU'S CLINICAL TRIALS REGISTRY THERE ARE ONLY TWO MULTI-CENTRE PHARMACEUTICAL CLINICAL TRIALS WHICH ARE CURRENTLY ONGOING IN MALTA. ON THE OTHER HAND, ESTONIA, HAVING A POPULATION OF 1.3 MILLION, HAS 250 ONGOING TRIALS, IRELAND 509 AND GERMANY 3909. WHAT ARE YOUR VIEWS ABOUT THIS?

I was not aware of this, and it worries me. We know for certain that patients receive better care during clinical trials because there is more dedicated monitoring, since this involves financial investment by the sponsoring company, besides the contribution to medical science. Only a few weeks ago the surgical department entered a series of EU multicentric clinical trials in various aspects of surgery. You are mentioning clinical trials on medicines which relate more to the oncologists. We should definitely do more to attract clinical trials to Malta.

ACTION FOR BREAST CANCER FOUNDATION AND EUROPA DONNA MALTA WROTE TO THE HEALTH AUTHORITIES LAST AUGUST ABOUT THE LONG WAITING TIMES FOR BREAST CANCER SURGERY. DO YOU SHARE THEIR VIEWS?

What they said was true and the reason for this is that our department was operating with a reduced number of anaesthesiologists and nurses due to the opening of the COVID-19 ITUs. However, we managed to reverse this and in October and November 2021 we managed to perform more operations than those performed during the same period in pre-COVID 2019. To do so, we increased operating times with later finishing times and also Sunday lists; Mater Dei hospital only has 20 theatres. We also reverted to leasing operating rooms from the private sector with a view to augment our operating capacity; our surgeons leave Mater Dei hospital during normal working hours to work in the private sector.

YOU RECENTLY PENNED *WE WENT TO THE MOON*, A BOOK WHICH DESCRIBES THE EVENTS LEADING UP TO THE MOON LANDING. IT REMINDS ME OF THE 1902 HALLMARK FILM BY THE INFLUENTIAL FRENCH FILMMAKER GEORGES MÉLIÈS' *LE VOYAGE DANS LA LUNE*, WHICH I HAVE SEEN OVER AND OVER AGAIN. WHY DID YOU DECIDE TO NARRATE THE POWER GAME BETWEEN THE US AND RUSSIA?

In 1969 the US landed on the Moon and since then, I developed an interest in space travel, buying books and reading on the power game, as you correctly stated, between President John Kennedy of the US and Premier Nikita Khrushchev of the Soviet Union. The race to the Moon was the driving force behind this show of superiority, even if this meant spending 4% of the US's annual GDP on this quest.

The book discusses how this pioneering feat moulded Maltese culture. We have shops and even a hotel, named after Kennedy. Kennedy Grove is another example. Why was this related to one specific president? Kennedy was a staunch Catholic, but he was also telegenic with tousled hair and an air of youthful confidence, alongside a beautiful wife; he managed to achieve movie star status. One must consider the political background back then. He was elected President in 1960, just 15 years after WWII ended and space travel was sorely needed to alienate people from the current state of affairs and to project the image of a future technological age.

In the book, I narrate the experience of 50 Maltese people who saw the Moon-landing event; the general feeling was that 'we' (all mankind) went to the Moon (but the US paid for it). The book then proceeds to discuss the press and television coverage of the event, stamps issued to commemorate the landing and the Apollo-inspired art by the British artist Victor Pasmore who lived on our island at the time. I have also decided to include a Times interview with the Moon-walking astronaut Harrison Schmitt in 2009 during his visit to Malta, and the text of Kennedy's Moon speeches.

AT THIS STAGE I WISH TO COMMEMORATE THE LIFE OF PROF. FREDERICK FENECH AND HIS NEPHEW PROF. ALBERT FENECH WHO PASSED AWAY IN 2021. BUT I ALSO WISH TO REMEMBER DR VICTOR CALVAGNA, PAEDIATRIC ONCOLOGIST, AND DR ALBERT BEZZINA, OPHTHALMOLOGIST, WHO GRADUATED WITH YOU BACK IN 1984. THEY ALSO LOST THEIR BATTLES IN 2021. THESE ARE GIANTS ON WHOSE SHOULDERS WE STAND. CAN YOU SHARE YOUR MEMORIES?

I remember Albert Bezzina to be an intelligent and entertaining man. We used to have lengthy discussions on cars and astronomy, with Albert coming up with all sorts of theories. He was an excellent ophthalmologist and a true gentleman. Dr Victor Calvagna was a person of few words but the empathy which he radiated was admirable. His work led to a paradigm shift in the manner in which paediatric oncology patients were treated, with astounding results. I have always admired how he managed to keep serene, having the arduous task to deal with paediatric oncology patients.

ONE LAST QUESTION. WHAT DO YOU THINK OF CME30.EU?

CME30.eu is the future. Online learning saves so much time with respect to commuting and logistics. It is ironic that we realised this because of pandemic-led events. Obviously, meeting face-to-face has its networking advantages, but online learning will be ubiquitous in the future. Also, I must add that the magazine is well-executed.

DR PIERRE VASSALLO

Breast Cancer in Young Women

Breast cancer is the most common cancer in women affecting approximately 1 in 8 individuals worldwide in 2021;[1] it is also the third most common cause of death from cancer in women.[2]

Breast cancer screening programs recommend yearly screening of women starting at 40 years of age unless they are considered higher-than-average risk.[3] Indeed, research studies have shown that screening women starting from 40 years of age with yearly mammograms improves breast cancer survival through early detection and treatment with a resultant decrease in mortality rate of over 40%.[4]

Breast cancer screening in women younger than 40 years of age has so far focussed only on those who have a genetic predisposition, either through carrying the breast cancer genes or due to a strong family history. However, as in women over the age of 40 years, the overwhelming majority of breast cancers in younger women occur in individuals who have no breast cancer gene mutations (90-95%)[5] or without a first-degree relative with breast cancer (89%).[6]

Consequently, breast cancer in younger women is mostly detected solely through clinical findings, which results in late diagnosis and poor treatment outcome. In addition, younger women tend to have more aggressive breast cancers including triple negative cancers and human epidermal growth factor receptor 2 (HER2)-rich tumours. Triple negative cancers are those cancers that test negative for oestrogen, progesterone and Human Epidermal Growth Factor 2 (HER2) receptors on immune histochemical testing.

Historically, triple negative and HER2-positive cancers have been considered more aggressive than oestrogen receptor negative (luminal) cancers. However, luminal cancers are more common than triple negative and HER2-positive breast cancers in young women. In addition, studies comparing breast cancer survival rates over the past four decades have shown that younger women with luminal cancers fare worse that those with triple negative or HER2-positive cancers.[7] This is likely due to developments in breast cancer therapy, particularly adjuvant chemotherapy that have been less successful for luminal cancers. [8]

IMPACT OF PATIENT AGE AND TUMOUR SUBTYPE ON BREAST CANCER PROGNOSIS

Age strongly influences the likelihood of survival. The younger the age at the time of diagnosis the worse the prognosis.

The more aggressive tumour types, such as triple negative breast cancers, are more common in women <40 years old (24.9%) compared to older women (14.6%).[9]

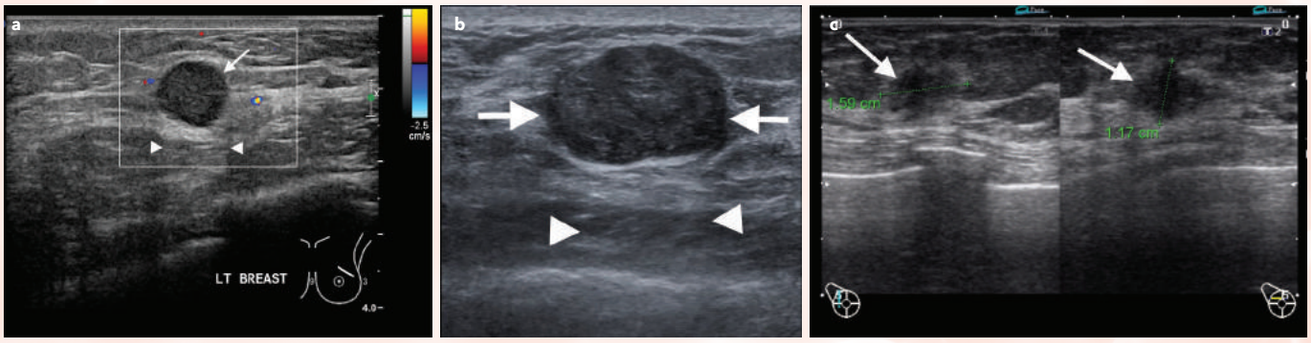

Figure 1: Triple negative breast cancer vs fibroadenoma - US. a. Colour Doppler US image of a triple negative breast cancer showing a rounded well-defined hypoechoic nodule (arrow) and no appreciable internal vascularity. **b.** US image of a fibroadenoma showing a well-defined hypoechoic lesion (arrows) with oval shape and horizontal orientation. A central echogenic line is seen in b that is more indicative of a fibroadenoma. Dorsal enhancement, a.k.a. through transmission, is seen in both a and b (arrowheads). **c.** US image showing an ill-defined nodule (arrows) in the left breast that was confirmed to be invasive ductal carcinoma on US-guided biopsy (Case c courtesy of Dr Roberto Schubert, Radiopaedia.org, rID: 15840).

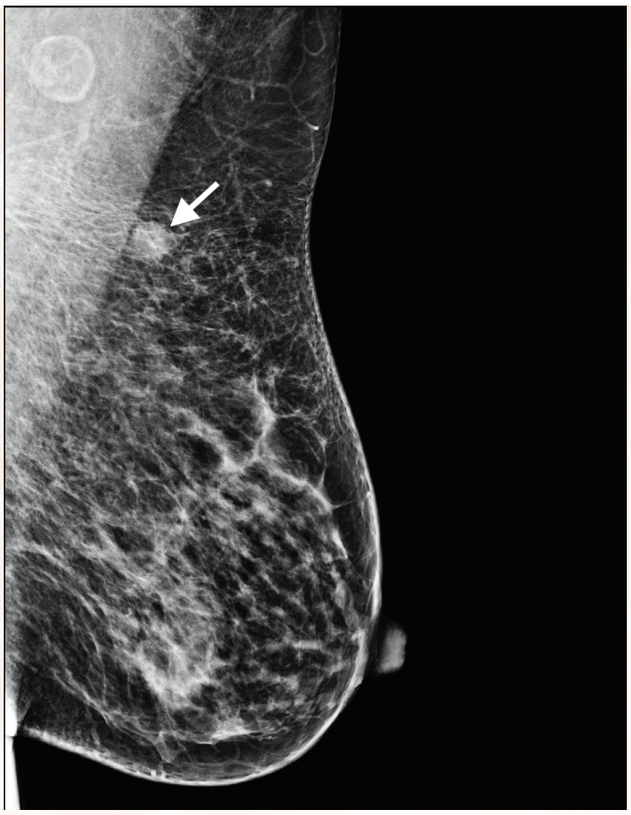

Figure 2: Triple negative breast cancer - mammogram. Left mediolateral oblique mammogram showing the same nodule (arrow) as in 1a in the superior portion of the left breast; this lesion exhibits smooth margins.

IMAGING FINDINGS IN TRIPLE NEGATIVE CANCERS

Ultrasound (US) findings in triple negative cancer may closely mimic those of a fibroadenoma. A subtle feature such as a more rounded appearance may be the only distinguishing US finding that would prompt further investigation (Fig 1a). Fibroadenomas tend to have a more oval shape and a horizontal orientation (Fig 1b). Due to the similar features of both lesions, core biopsy confirmation is required to guide further management. While US is a very valuable tool for the detection of and characterisation of breast nodules particularly in women <30 years of age, subtle features such as described above should prompt further imaging and biopsy. In contrast, ill-defined lesion margins are strongly suggestive of malignant disease (Fig 1c).

Mammograms characteristically show malignant lesions as having irregular lesion margins, but these are often absent in triple negative cancers (Fig 2a). Mammograms are less useful in younger women due to a higher proportion of triple negative cancers in this age group and because these women are more likely to have dense breasts.

Magnetic Resonance Imaging (MRI) has the highest sensitivity for detection of breast cancer in young women, with malignant lesions tending to show higher T2 signal due to more abundant cytoplasm, oedematous stroma, and necrosis (Fig 3a). Ring enhancement on contrast-enhanced T1-weighted images (Fig 3b) and diffusion restriction on Diffusion-Weighted Imaging (DWI) (Fig 3c) are both strong indicators of malignant disease.

Due their rapid growth, triple negative breast cancers are known to present as interval cancers on mammographic screening. Interval cancers are those cancers that grow so rapidly that they may present as sizeable tumours on a mammogram, even though no lesion was present on a previous mammogram performed 12 months earlier or less.

HER2-ENRICHED (HER2-POSTIVE) TUMOURS

HER2-positive tumours comprise 25% of all breast cancers in women <40 years of age.[10] HER2-rich cancers have a higher proliferative index, are more aggressive and are more likely to present with multifocal or multicentric disease and metastases.[11]

HER2-positive tumours are more aggressive when they are hormone-receptor (oestrogen/progesterone-receptor) negative.[12]

HER2-positive tumours are more likely to be associated with ductal carcinoma in situ (DCIS) and hence frequently present with microcalcifications. Digital breast tomosynthesis (or 3D mammography) is useful in assessing the extent of multifocal/multicentric disease in HER2-positive tumours by detecting foci of microcalcification (Figure 4). MRI helps further in establishing the extent of HER2-positive cancers.

Accurate mapping of these tumours is crucial to monitoring the effects of therapy particularly because HER2-positive

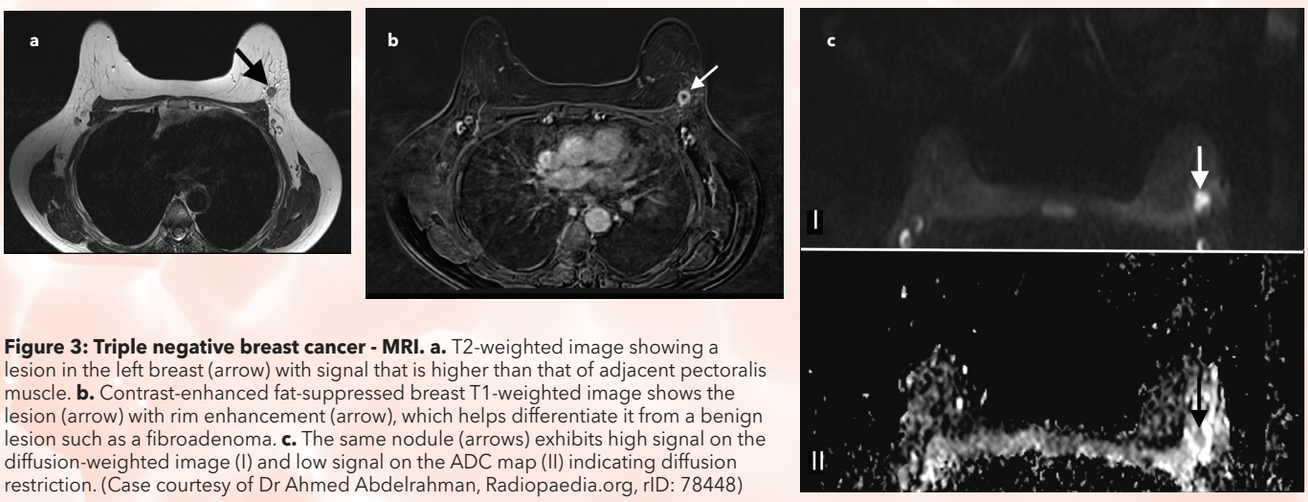

Figure 3: Triple negative breast cancer - MRI. a. T2-weighted image showing a lesion in the left breast (arrow) with signal that is higher than that of adjacent pectoralis muscle. **b.** Contrast-enhanced fat-suppressed breast T1-weighted image shows the lesion (arrow) with rim enhancement (arrow), which helps differentiate it from a benign lesion such as a fibroadenoma. **c.** The same nodule (arrows) exhibits high signal on the diffusion-weighted image (I) and low signal on the ADC map (II) indicating diffusion restriction. (Case courtesy of Dr Ahmed Abdelrahman, Radiopaedia.org, rID: 78448)

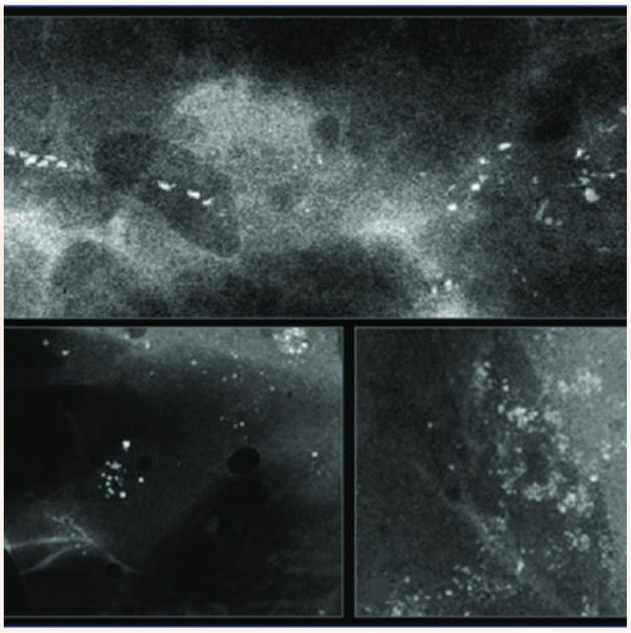

Figure 4: Mammogram showing multiple clusters of microcalcifications; these are related to DCIS that is more common in HER2-postive cancers.

tumours tend to respond well to cytotoxic and monoclonal antibody therapy.[13]

DE NOVO STAGE IV DISEASE AND TUMOUR RECURRENCE RATE

Women <40 years of age are four times more likely to be diagnosed with distant stage breast cancer than those aged 40-69 years[14] due to lack of screening resulting in late diagnosis. This observation is further supported by the increased incidence of de novo stage IV disease over the past four decades in women under 40 years of age;[15] this is likely due to both the aggressiveness of the tumour types seen in this age group and the lack of screening. A full imaging evaluation of all potential sites for extramammary metastatic disease is crucial in this age group.

Regardless of tumour subtype, women <40 years of age have a higher tumour recurrence rate after surgical treatment and a higher mortality rate than older women.[16]

CONCLUSION

Current breast cancer screening programs do not adequately address women younger than forty years of age. While some attention is given to those younger women who are breast cancer gene positive and to those who have a strong family history, none is paid to the remaining women who account for the majority of breast cancer cases in this age group.

It is important to understand the biological characteristics and imaging appearances of early breast cancer in younger women.

The higher incidence of triple negative and HER2-positive breast cancers in this age group leads to poorer outcomes. In addition, younger women with cancers considered to be less aggressive (such as luminal cancer) have shown less improvement in mortality rate that the more aggressive breast cancers in younger women over the past four decades.

Subtle findings on US may raise the level of suspicion and change management. Patients with an assumed benign lesion on US may not return for follow-up for years, potentially resulting in a late-stage cancer diagnosis. Advances in chemotherapy do not overcome the disadvantages of a late-stage diagnosis.[17] Thus, any subtle, atypical findings on US should be aggressively investigated with supplementary imaging (mammography and MRI) and/or imaging-guided biopsy.

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ENTRESTO®(sacubitril/valsartan)

Presentation: Each film-coated tablet of 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. Splitting or crushing of the tablets is not recommended.

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/valsartan is 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/valsartan immediately 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 (Child Pugh 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. Psychiatric disorders: Psychiatric events such as hallucinations, paranoia and sleep disorders, in context of psychotic events, have been associated with sacubitril/valsartan use. If a patient experiences such events, discontinuation of sacubitril/valsartan treatment should be considered.

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 coadministered 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/valsartan is 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. Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists including sacubitril/valsartan. 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 C_{max} 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 C_{max} 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; Entresto 49 mg/51 mg – x28 tablets; Entresto 97 mg/103 mg - x28 & x56 tablets.

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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.

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