NEWSPAPERPOST

TheSynapse

The Medical Professionals' Network

Issue 06/13

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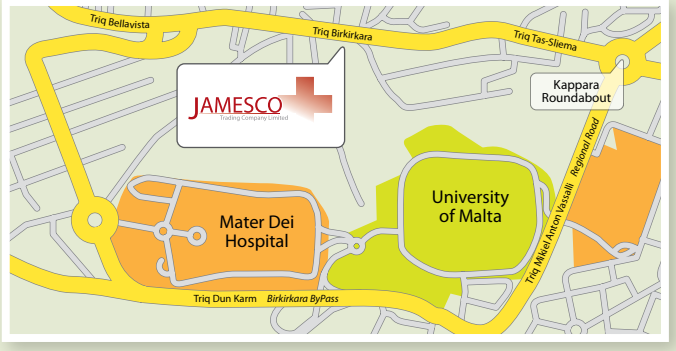


Of white papers, pink cards and Christmas puddings

Last month, the Ministry of Health issued a white paper entitled *Ensuring Your Right to Entitlement Medicines at the Time You Require Them.* Obviously this has been heralded by the degenerating out-of-stock situation of the POYC scheme which has been accompanying us for several years. At the time of penning this editorial, even the flu vaccine which is distributed freely from health centres is out-of-stock! Although there may be many reasons for this, including mismanagement and abuse, ultimately it is always the patient who is forced to bear the cross.

The 61 page document is fraught with literary terms which if minced thoroughly seem to indicate that with respect to the POYC scheme, the Ministry of Health actually means to take the bull by the horns and empower healthcare professionals and patients alike to effectively tackle the problems. However, as always, (and to be seasonal) the proof of the Christmas pudding is in the eating…

I will not waste time to regurgitate what has been said in the document. What I wish to recount is a personal experience which highlights the extent to which a lack of communication between the different entities involved in the supply chain of medicines to patients through the POYC scheme can actually deflate stalwart terms such as *motivation*, *goodwill* and *empowerment*, leading to a general disgruntlement amongst healthcare professionals and patients alike.

A patient of mine had both the pink and yellow cards since she is diabetic and also suffers from other chronic conditions. All her medications were automatically transferred onto her yellow card in June of 2012 with her pink card being revocated in the process. Upon phoning *all* the different entities involved in the supply chain of medicines through the POYC scheme, I was consistently informed that those

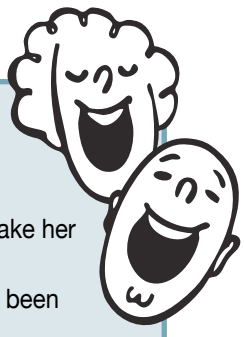
patients who had their pink card revoked were eligible to reapply and attain again the pink card; however the expiry date for this derogation was 31st May 2013. Upon challenging this date, every entity referred me to a mysterious DH circular; nevertheless no-one was able to give me either the DH circular number or a link to it.

It was only through an intervention by the Health Minister, Dr Godfrey Farrugia that this saga finally resolved. Basically, I have received a document which states that previous diabetic pink card holders who opted for a diabetes yellow card before 1st June 2012 can still revert to the pink card. The patients can telephone the Medicines Entitlement Office (Schedule V office), leave their details and after checking is done, an appointment is made for the patient to return the diabetes yellow card. A note stating that the yellow card was returned is given to the patient so that the Social Security Office issues a new pink card. *There is currently no derogation date on this practice.*

I wish to conclude this year's editorial by first of all reiterating the importance of maintaining good communication channels with healthcare professionals. This investment is logically very cost-effective. Secondly I wish to augur you and your loved ones a peaceful Christmas and a New Year filled with *happiness* and *good health* … the only two things which, in my opinion, really matter …

Ian C Ellul

A JOKE A DAY KEEPS THE DOCTOR AWAY



Warm milk is good for you

In a convent in Ireland, the 98-year-old Mother Superior is dying. The nuns gather around her bed trying to make her last journey comfortable. They try to give her warm milk to drink but she refuses it.

One of the nuns takes the glass back to the kitchen. Then, remembering a bottle of Irish whiskey that had been received as a gift last Christmas, she opens it and pours a generous amount into the warm milk.

Back at Mother Superior's bed, the nuns hold the glass to her lips. The frail nun drinks a little, then a little more and before they know it, she has finished the whole glass down to the last drop. As her eyes brighten, the nuns think it would be a good opportunity to have one last talk with their spiritual leader. "Mother," the nuns ask earnestly, "Please give us some of your wisdom before you leave us."

She raises herself up in bed on one elbow, looks at them and says,

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ADVERSE REACTIONS: Common (≥1/100 to <1/10): Nasopharyngitis, insomnia, headache, dry mouth, gastroenteritis, urinary tract infection. Uncommon (≥1/1,000 to <1/100): Rhinitis, cystitis, hyperglycaemia, hypoaesthesia, atrial fibrillation, palpitations, sinus congestion, productive cough, throat irritation, epistaxis, dyspepsia, dental caries, rash, pain in extremity, musculoskeletal chest pain, dysuria, urinary retention, fatigue, asthenia.

LEGAL CATEGORY: POM

PACK SIZES: Single pack containing 30x1 hard capsules, together with one inhaler.

MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom.

MARKETING AUTHORISATION NUMBER: Seebri Breezhaler 44 micrograms inhalation powder, hard capsules - EU/1/12/788/001-006

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 124, Valletta, VLT 1000, Malta. Tel: +356 22883217/21222872

2013-MT-SBB-14-AUG-2013

For information on Seebri Breezhaler dose expression, please refer to full prescribing information.

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Dr Nikolai P Pace MD PhD
is a lecturer and researcher at the Faculty of Medicine and Surgery, University of Malta. His research focuses on the genomics of type 2 diabetes and obesity. The coauthors of this article are Prof Josanne Vassallo and Prof Alex Felice.

Prof. Maurice Cauchi MD MSc PhD DPH FRCPA FRCPath
was Professor of Pathology and Director of Pathology in Malta. He has published several monographs, including Health, Bioethics and the Law. For his services to the Maltese community in Australia he was made Member of the Order of Australia (AM), and given the Medalja għall-Qadi tar-Repubblika by the Maltese Government

Dr Rachel Vella Critien MD
is a second year Foundation trainee, who graduated from the University of Malta in 2012. The case detailed was written during her rotation in Rehabilitation Medicine, a specialty that she is interested in pursuing in the near future.

Prof. Victor Grech MD PhD (Lond) PhD (Malta)
is a consultant paediatrician with a special interest in paediatric cardiology. He is also the creator and editor-in-chief of the journal Images in Paediatric Cardiology (www.impaedcard.com). The co-authors of the article are Dr Clare Vassallo and Prof Ivan Callus.

Massimo Azzopardi
is an independent catering consultant and event specialist with over 20 years experience in delivering successful events, quality catering and bespoke services designed to reach and exceed guest expectations.

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 Hospital, Malta

Dr Patricia De Gabriele MD Dip WH(ICGP) MMCFD
is a specialist in Family Medicine. She is a Senior Lecturer at the UOM within the Faculty of Health Sciences. She has been involved in academia in family medicine for many years. She has been instrumental in the setting up the MCFD Membership examination accredited by the RCGP and in creating an AKT bank for this examination. She is currently a GP trainer. She has delivered training-the-trainers and assessment courses as well as training in AKT writing for family doctors.

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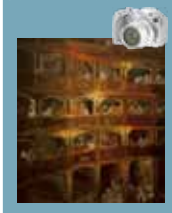

COVER:
Watching as they watch | Oil on canvas 100x100cm
Celia Borg Cardona was born in 1957 and graduated in Pharmacy in 1977. After living the art-v-science debate for several years, art won and Celia has been a professional full time artist for several years. Her works most often depict groups of people, usually as seen from unusual perspectives.

Published by Medical Portals Ltd.
The Professional Services Centre
Guzi Cutajar Street
Dingli, Malta
Email: editor@thesyapse.net
Web: www.thesynapse.net

Editor: Wilfred Galea
Scientific Editor: Ian C Ellul
Administration Manager: Carmen Cachia

Production: Outlook Coop
Printing: Europrint Ltd

The magazine is distributed to all Maltese doctors, pharmacists & dentists, as well as students of the aforementioned professions, with a print run of 3500 copies. Queries on advertisements may be sent to mpl@thesynapse.net

Dr Helen Pulasky in Star Trek: The Next Generation

VICTOR GRECH

Star Trek (ST) has been with us since 1966, and medical doctors have been principal protagonists since the outset. This paper will review Dr Helen Pulaski, an old-fashioned doctor who serves as Chief Medical Officer aboard the Starship ***Enterprise*** in the 24th century (in the second season of ***Star Trek: The Next Generation***).[1] The role was reprised by Diane Muldaur between November 1988 and July 1989.

Interestingly, Muldaur confessed to have "a real interest in medicine as well. […] I always have. I remember as a kid I would pick up Time magazine and read the medical news first. It's always fascinated me - how they can give their time, which is total. […] they weren't making a fortune either. But even today, I don't know how they do what they do".[2]

Dr. Pulaski was a grumpy and curmudgeonly character, as admitted by Muldaur herself, "I'm kind of a pain in the neck".[3] Pulaski replaced another female chief medical officer. This was because the producers wanted a doctor "more in the mould of DeForest Kelley's crusty "Bones" McCoy, [and] devised Dr. Kate Pulaski as a replacement for Dr. Beverly Crusher".[2]

Like McCoy, Pulaski distrusted technology, to the extent that she "never used our transporter […] She's a woman of very strongly held opinions",[4] and this despite the fact that the instantaneous matter transportation device is ubiquitous in the 24th century.[3] She explains that "every time I get into the damn thing, I'm convinced [the transporter will] spread my atoms across the galaxy".[1]

Her old fashioned ways are further evidenced when she prescribes "generous doses of PCS […] Pulaski's chicken soup" as part of a treatment regimen. However, she embraces the futuristic medical technology witnessed in ST. For example, the ship's Chief Engineer is blind from birth and she offers two options: "it's possible to install optical devices which look like normal eyes, and would still give you about the same visual range as the visor. […] There is another option. I can attempt to regenerate your optic nerve, and, with the help of the replicator, fashion normal eyes. You would see like everyone else. […] I've done it twice, in situations". However, she is realistic, continuing "there are risks. I can offer choices, not guarantees".[1]

This is not to say that she is above using old methods, such as a splint, when the "bone knitter" fails to work, since "it's a time honored way to practice medicine: with your head, and your heart, and your hands".[1]

The crew had high opinions of Pulaski and her abilities: "I've never met a more dedicated physician. I would say she has a passion for her work […] consuming dedication".[1] Her skills are legion, as is typical of ST doctors, and include heart surgery and selective memory alteration.[1]

She also acts as the unofficial ship's ethics officer, staunchly standing up for an unknown planetary population on the brink of extinction "I have a problem with that kind of rigidity. It seems callous and even a little cowardly. […] My emotions are involved. […] friend is going to die. That means something". The captain retorts: "Sophistry", and she replies "I'll buy that excuse. We're all jigging madly on the head of a pin anyway".

Muldaur herself favours ST and aptly summarises: "I think the show depicts faith in the future and hope for mankind. […] we all spend all of our days and all of our lives watching horrible things happen, things we're very frustrated about - like drugs - and it all becomes very consuming. Then you see Star Trek and see that indeed we made it and we made it in a positive way and we're out there doing some good. I think that's why Star Trek will continue for years to come".[2] S

These and similar topics will be discussed during the Star Trek Symposium (www.startreksymposium.com) on the 10-11 July 2014 at the Dolmen Hotel.

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No data available for use in patients with severe hepatic impairment. No relevant use in the paediatric population. If a dose is missed, the next dose should be taken at the usual time the next day. **CONTRAINDICATIONS:** Hypersensitivity to the active substance, to lactose or to any of the other excipients. **WARNINGS/PRECAUTIONS:** ***Asthma:*** Onbrez breezhaler is a long acting beta2-adrenergic agonist, which is only indicated for COPD and should not be used in asthma. Long-acting beta2-adrenergic agonists may increase the risk of asthma-related serious adverse events, including asthma-related deaths, when used for the treatment of asthma.***Paradoxical bronchospasm:*** If paradoxical bronchospasm occurs Onbrez Breezhaler should be discontinued immediately and alternative therapy substituted. ***Deterioration of disease:*** Not indicated for treatment of acute episodes of bronchospasm, i.e. as rescue therapy. ***Systemic effects:*** Indacaterol should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension), in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta2-adrenergic agonists. ***Cardiovascular effects:*** Indacaterol may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms, ECG changes. In case such effects occur, treatment may need to be discontinued. ***Hypokalaemia:*** Beta2-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce cardiovascular effects. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment which may increase the susceptibility to cardiac arrhythmias. ***Hyperglycaemia:*** Inhalation of high doses of beta2-adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with Onbrez Breezhaler plasma glucose should be monitored more closely in diabetic patients. During clinical studies, clinically notable changes in blood glucose were generally more frequent by 1 2% on Onbrez Breezhaler at the recommended doses than on placebo. Onbrez Breezhaler has not been investigated in patients with not well controlled diabetes mellitus. ***Pregnancy and Lactation:*** No data available from the use of indacaterol in pregnant women. Onbrez Breezhaler should only be used during pregnancy if the expected benefits outweigh the potential risks. Not known whether indacaterol / metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or discontinue Onbrez Breezhaler therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Immediate hypersensitivity reactions have been reported after administration of Onbrez Breezhaler. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, Onbrez Breezhaler should be discontinued immediately and alternative therapy instituted. I**NTERACTIONS:** Concomitant administration of other sympathomimetic agents may potentiate the undesirable effects of Onbrez Breezhaler. Onbrez Breezhaler should not be used in conjunction with other long-acting beta2-adrenergic agonists or medicinal products containing long-acting beta2-adrenergic agonists.Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta2-adrenergic agonists, therefore use with caution. Indacaterol should not be given together with beta-adrenergic blockers (including eye drops) as these may weaken or antagonise the effect of beta2-adrenergic agonists. Where required, cardioselective beta-adrenergic blockers should be preferred, although they should be administered with caution. Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-gp, does not raise any safety concerns given the safety experience of treatment with Onbrez Breezhaler. Indacaterol has not been shown to cause interactions with co-medications. **ADVERSE REACTIONS:** The most common adverse reactions with Onbrez Breezhaler are: dizziness, nasopharyngitis, upper respiratory tract infection, sinusitis, , headache, , cough, , rhinorrhoea, respiratory tract congestion, muscle spasm, peripheral oedema. Common: Chest Pain, Oropharyngeal pain including throat irritation, Uncommon: Myalgia, Musculoskeletal pain, Pruritis/rash, Paradoxical bronchospasm, tachycardia, palpitations, hypersensitivity, diabetes mellitus and hyperglycaemia ,paraesthesia, atrial fibrillation and non-cardiac chest pain, ischaemic heart disease. Please refer to SmPC for a full list of adverse events for Onbrez Breezhaler. **LEGAL CATEGORY:** POM **PACK SIZES:** Onbrez Breezhaler 150mcg - carton containing 10 or 30 capsules and one Onbrez Breezhaler inhaler. Onbrez Breezhaler 300mcg - carton containing 30 capsules and one Onbrez Breezhaler inhaler **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/09/593/001, 002, 007 **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 124, Valletta, VLT 1000 Malta. Tel: +356 22983217/+35621222872 2013-MT-ONB-09-Sep-2013

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1. Cazzola M, Matera MG. Novel long-acting bronchodilators for COPD and asthma. Br J Pharmacol. 2008;155:291-299.
2. Novartis Europharm Ltd. Onbrez® Breezhaler® Summary of Product Characteristics.

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The genomics of type 2 diabetes – the Maltese contribution

NIKOLAI P PACE
JOSANNE VASSALLO
ALEX E FELICE

Abstract
The genomic revolution has transformed the type 2 diabetes genetic landscape, with many loci reported to have association with disease risk. Such loci exert a weak to modest effect size and are as yet of limited use in risk prediction studies. They also fail to account for robust genotype-phenotype associations. This study aims to address these issues by looking at the quantitative summation of risk alleles and the use of special populations to better define risk and phenotypic associations.

Introduction

Diabetes Mellitus type 2 (T2DM) is a common, etiologically complex chronic disorder that arises from the elaborate interplay between lifestyle factors and various genetic elements. It represents one of the most widespread public health problems in both the developed and developing world. Commonly, the impaired regulation of glucose homeostasis that leads to type 2 diabetes is associated with a cluster of cardio-metabolic risk factors - including abdominal obesity, hypertension and atherogenic dyslipidaemia, which is a chronic subclinical proinflammatory state. These factors combine to determine the development and progression of both microvascular and macrovascular disease that carry a substantial socio-economic burden globally. Central to the development of obesity, insulin resistance and type 2 diabetes is a distinct lifestyle component defined by the overconsumption of calorie-dense food and a lack of physical exercise.

Background

The study of complex disease genetics has undergone a massive revolution over the past decade, driven largely by the completion of the Human Genome and the International HapMap projects.[1] These have provided researchers with innovative insight into population-specific patterns of common human genetic variation. Simultaneously, technological advances have led to the development of DNA microarray platforms. These commercially available 'DNA chips' utilize known linkage disequilibrium patterns to genotype tag polymorphisms and enable the imputation of genotypes at linked loci. Ongoing developments in second-generation sequencing technology have enabled the processing of millions of sequence reads in parallel. These have continued to drive down the cost and timeframes necessary to obtain whole genome and transcriptome datasets which are vital to understanding complex diseases.

Candidate Gene or Genome-Wide Association Studies?

The search for T2DM susceptibility loci has been fraught with complications. The disease is genetically heterogeneous, and strong gene-environment interactions influence its onset and progression. Furthermore, the diagnosis of T2DM hinges on the identification of elevated fasting or post-prandial blood glucose levels that lead to metabolic and microvascular complications. It is highly likely that such a diagnosis masks a tremendous amount of clinical heterogeneity, and that the genetic heterogeneity behind diabetes is as great as its clinical heterogeneity.[2] Hypothesis-driven candidate gene studies have identified a few genetic variants associated with T2DM. These include common variants in peroxisome proliferator-activated receptor γ (PPARγ),[3] the KCNJ11 potassium channel[4] and the transcription factor TCF7L2.[5] Such candidate gene studies are based on selection of loci with a known or inferred biological function which may predispose to disease or the observed phenotype.[6] Nevertheless such *a priori* assumption inherently limits the capacity of candidate gene studies to identify pathways or loci playing previously unsuspected roles in the etiology or pathogenesis of complex diseases.

The genomics revolution and the subsequent introduction of Genome-Wide Association Studies (GWAS) in 2007 has lead to a massive upsurge in the number of T2DM-associated loci. To date, the online catalog of published Genome-Wide Association Studies (www.genome.gov/gwastudies/) lists 43 GWAS that have investigated T2DM as a disease of which 8 GWAS have also investigated fasting blood glucose as a quantitative trait. As larger collections continue to be assembled for meta-analysis by international consortia, new associations with T2DM, fasting blood glucose and fasting insulin continually emerge.[7]

GWAS – a failed promise?

Hundreds of variants identified through GWAS have been associated with complex traits or diseases, including T2DM. In some cases, the identified variants have provided valuable insight into the genetic architecture of disease. However, GWAS-identified variants have a low effect size and consequently confer only slight increments in risk and account for a minor proportion of familial clustering.[8] GWAS-identified associations are estimated to explain only around 10% of the heritability of T2DM. They fail to account for epistasis, epigenetic changes and gene-environment interactions. They are largely restricted to populations of European descent and carry poor discriminatory capacity that limits their use in risk prediction. Furthermore, the transition from genotype to functional physiology is not straightforward. While polymorphisms in promoter or exon regions have predictable biological effects, variants in deep intronic or intergenic regions have probable regulatory roles. GWAS also utilise large cohorts of patients that are often heterogeneous or poorly characterised, thus limiting the association of genotype data with clinical or biochemical phenotypes.

Type 2 Diabetes Genetics and the Maltese Population

The Maltese population has a high predisposition for T2DM. The earliest evidence concerning interest in diabetes in Malta dates back to 1698.[9] The period following the Second World War witnessed an improvement in socio-economic conditions which, despite the introduction of oral hypoglycemic agents, was accompanied by a marked increase in diabetes-specific mortality. The estimated national prevalence for T2DM in 2013 stands at 10.14% and is expected to rise to 11.44% by 2035.[10]

Two studies have investigated the genetics of T2DM in the Maltese population.[11,12] The aims are listed hereunder.

1. Further define the genetic interplay between a carefully selected panel of genes from metabolic and inflammatory pathways and the risk of developing type 2 diabetes in adulthood.
2. To relate the association of defined genetic profiles with biological and clinical endpoints and monocyte gene expression profiles to type 2 diabetes.

These studies were innovative in several key points. A total of 42 genetic variants were selected for genotyping from genes in several metabolic and/or inflammatory pathways that impact on glucose regulation, lipid metabolism, inflammation and insulin resistance. The genetics of the disease was investigated using different comparative populations, including 600 Maltese and 200 Libyan T2DM cases. The Maltese T2DM cases were further subdivided into carefully defined subpopulations of treatment-naïve and high-morbidity groups. A unique collection of two hundred cord blood DNA samples obtained from the Malta BioBank (www.um.edu.mt/biobank/home) was selected as the control reference population. These were carefully selected to be of Maltese ethnicity and to exclude close siblings.

The salient findings of these investigations are the following:

1. The quantitative summation of risk alleles has been associated with significant increases in the risk of developing T2DM (figure1). Nevertheless, when individual cases are considered, risk polymorphisms exerted only a slight-to-modest effect on disease risk. Consequently, risk alleles studied in isolation contribute minimally to disease risk prediction. Equally interesting is the high odds ratios for selected risk alleles reported in these studies, in particular for a common variant in the beta-2 adrenergic receptor (ADRβ2).
2. The recruitment of a carefully-characterised treatment-naïve cohort is a powerful tool in the identification of genotype-phenotype associations. The clinical, anthropometric and biochemical risk factors were, as much as possible and to our knowledge, unaltered by drugs and/or lifestyle change. Too often, published genotype-phenotype associations included larger numbers of less well-characterized subjects that were clinically heterogeneous. Such associations have doubtful pathophysiological relevance, lacked reproducibility or were replicated with disconcordant findings. Drugs commonly used in the management of T2DM, including metformin, statins and aspirin, exert their effects on multiple tissue types through various signaling pathways that could rapidly alter the systemic metabolic and inflammatory profile. Of note, the authors have identified an association between a promoter polymorphism in the melatonin-receptor 1 beta gene (MTNR1β) and total cholesterol and LDL-C levels which has also been reported in other ethnic groups.[13] Other significant genotype-phenotype associations which have been identified include promoter polymorphism in Interleukin-6 with insulin resistance index (HOMA-IR), and an insulin growth factor 1 variant (IGF1) with body weight.
3. Despite the increased effort to recruit treatment-naïve subjects and the aforementioned findings, genotype-phenotype associations still remain considerably deficient. This strongly suggests that while genetic factors contribute to disease risk and onset, the end clinical phenotype is highly variable and is influenced by complex non-genetic factors.
4. Microarray gene expression analysis of peripheral blood leukocytes in T2DM provides an intriguing insight into their role in inflammation and the development and progression of diabetic complications. While there is no clear direct relationship between genetic risk scores and gene expression profiles, bioinformatic approaches have identified differentially expressed genes that have established roles in inflammation, oxidative damage and leukocyte activation.

References may be accessed at thesynapse.net

Acknowledgements

The research work disclosed in this article was funded by the Strategic Educational Pathways Scholarship Scheme – STEPS (Malta) and by institutional funds of the University of Malta. The STEPS scholarship is part-financed by the European Union – European Social Fund (ESF) under Operational Programme II- Cohesion Policy 2007-2013, "Empowering people for More Jobs and a Better Quality of Life"

We acknowledge the invaluable contribution of all the staff and patients at the Diabetes and Endocrine Clinic, Mater Dei Hospital and to the family medicine practitioners who helped in the recruitment of the study cohorts for this project.

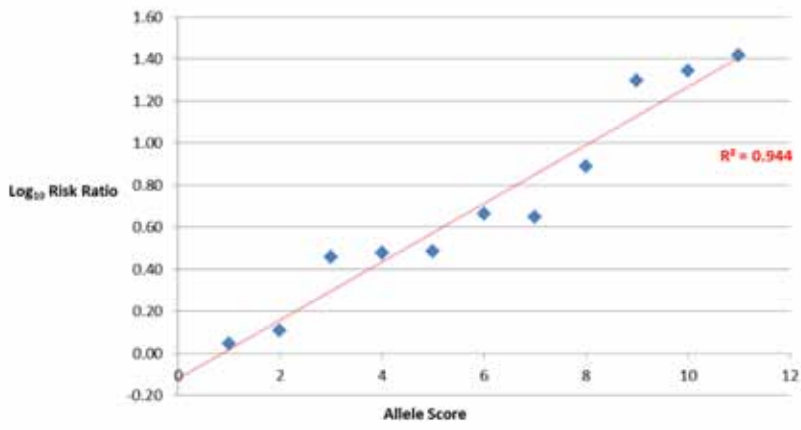

Figure 1. Log10 risk ratio of T2DM in a study meta-analysis vs. increasing number of risk alleles. An unweighted genetic score was constructed by the simple count of risk alleles. This method assumed that each allele exerts equal and additive effects that can be summed. Genetic risk scores identify a gradient of genetic risk in the T2DM population, with individuals at the high end of the genetic risk score distribution having a markedly higher individual risk than those at the lower end of the genetic risk score distribution. The predictive nature of genetic risk scores in this investigation is limited by the cross-sectional study design.

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In patients with a recent low-trauma hip fracture, it is recommended to give the Aclasta infusion two or more weeks after hip fracture repair. **Paget's Disease:** A single intravenous infusion of 5 mg Aclasta. Specific re-treatment data are not available for Paget's disease. Aclasta is administered via a vented infusion line and given at a constant infusion rate. The infusion time must not be less than 15 minutes. Adequate calcium and vitamin D are recommended in association with Aclasta administration. In patients with recent low-trauma hip fracture a loading dose of 50,000 to 125,000 IU of Vitamin D is recommended prior to the first Aclasta infusion. No dose adjustment in patients with creatinine clearance ≥35 mL/min, or in patients with hepatic impairment, or in elderly patients. The safety and efficacy of Aclasta in children and adolescents below 18 years of age has not been established. Re-treatment of Paget's disease: After initial treatment with Aclasta in Paget's disease, an extended remission period is observed in responding patients. Re-treatment consists of an additional intravenous infusion of 5mg Aclasta after an interval of one year or longer from initial treatment in patients who have relapsed. Limited data on re-treatment of Paget's disease are available. Aclasta is essentially sodium-free. **CONTRAINDICATIONS:** ♦ Hypersensitivity to zoledronic acid or to any of the excipients or to any bisphosphonate ♦ hypocalcaemia ♦ pregnancy ♦lactation. **WARNINGS/PRECAUTIONS:** ♦ Serum creatinine should be measured before each Aclasta dose. Aclasta should not be used in patients with creatinine clearance <35 ml/min. Transient increase in serum creatinine may be greater in patients with underlying impaired renal function. Monitoring of serum creatinine should be considered in at-risk patients. ♦ Patients must be appropriately hydrated prior to administration of Aclasta, especially important for the elderly and for patients receiving diuretic therapy. Use with caution in conjunction with medicinal products that can impact renal function. A single dose of Aclasta should not exceed 5mg and the duration of infusion should be at least 15 minutes. ♦ Pre-existing hypocalcaemia and other disturbances of mineral metabolism must be treated by adequate intake of calcium and vitamin D before initiating therapy with Aclasta. It is strongly advised that patients with Paget's disease receive supplemental calcium and vitamin D. Measurement of serum calcium before infusion is recommended for patients with Paget's disease. Severe and occasionally incapacitating bone, joint and/or muscle pain have been infrequently reported with bisphosphonate therapy. ♦ A patient being treated with Zometa should not be treated with Aclasta. ♦ As a precaution against osteonecrosis of the jaw (ONJ) a dental examination with appropriate preventive dentistry should be considered prior to treatment in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene). While on treatment, these patients should avoid invasive dental procedures if possible. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. ♦Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment. During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture. ♦ Aclasta is not recommended in women of childbearing potential. **INTERACTIONS:** ♦Specific drug-drug interaction studies have not been conducted with zoledronic acid. ♦Caution is recommended when Aclasta is used concomitantly with drugs that can significantly impact renal function, such as aminoglycosides and diuretics that can cause dehydration. ♦ In patients with renal impairment, the systemic exposure to concomitant medicinal products that are primarily excreted via the kidney may increase. **ADVERSE REACTIONS:** ♦The incidence of adverse reactions (e.g. fever, myalgia, flu-like symptoms, arthralgia and headache) are greatest with the first infusion and decrease markedly with subsequent infusions. The majority of these reactions occur within the first three days and were mild to moderate and resolved within three days of the event onset. The incidence of these adverse reactions can be reduced with the administration of paracetamol or ibuprofen shortly following Aclasta administration. ♦Very common: Fever. ♦Common: Flu-like symptoms, chills, fatigue, pain, asthenia, malaise, arthralgia, myalgia, bone pain, back pain, pain in extremity, vomiting, nausea, headache, dizziness, atrial fibrillation, hypocalcaemia†, ocular hyperaemia, diarrhoea, increased C-reactive protein, infusion site reactions. ♦Uncommon: Hypertension, flushing, palpitations and others. ♦Not known: Scleritis, orbital inflammation, hypotension, renal impairment, osteonecrosis of the jaw, dehydration secondary to post dose symptoms, hypersensitivity reactions. ♦Rare: Atypical subtrochanteric and diaphyseal femoral fractures† (bisphosphonate class adverse reaction) *† Common in Paget's disease only.* Please refer to SmPC for a full list of adverse events. **LEGAL CATEGORY:** POM. **PACK SIZE:** Aclasta is supplied in packs containing one 100ml bottle **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBER:** EU/1/05/308/001.**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 2013-MT-ACL-5-SEP-2013

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Necrotising fasciitis: a case report

RACHEL VELLA CRITIEN

Abstract

Necrotising fasciitis is a rapidly progressive and potentially life-threatening bacterial infection involving the subcutaneous tissues and fascia which can result in extensive tissue necrosis and severe sepsis. Key factors affecting survival include an early diagnosis, surgical debridement and the appropriate use of antimicrobials. We present a case in a diabetic patient with necrotizing fasciitis of the abdominal wall secondary to a subcutaneous saline infusion, describing the presentation, diagnosis and the successful treatment of this patient.

Introduction

Necrotising fasciitis leads to the development of thrombosis of skin microcirculation, resulting in necrosis of skin and soft tissue, destruction of muscles, and liquefaction of fats. Mortality in several studies has ranged from 22% to 44%, with the truncal region having a higher mortality (44%) than the perineal region (28%) and the extremities (22%).[1]

The case report highlights the importance of a high index of suspicion. In the early stages, the signs can be non-specific and can mimic other non-severe soft tissue infections. Severe pain at onset, out of proportion to the clinical findings, can be an important pointer towards the diagnosis. It shows how the commonly used subcutaneous injections can be a cause of necrotizing fasciitis.

Case presentation

A 69 year old male was noted to have an elevated temperature of 39°C during routine parameters. His past medical history included cerebrovascular accident, type 2 diabetes mellitus, hypertension, atrial fibrillation, hypothyroidism and congestive heart failure.

On initial examination, he was tachypnoeic and hypertensive. Other physical parameters were normal. Left-sided basal crackles were identified on chest auscultation. The values of laboratory parameters were as follows: leucocytes 18.10x10^9/L and C-reactive protein (CRP) 187mg/L. All other laboratory values were within normal range. The first clinical impression was one of hypostatic pneumonia. He was thus started on antibiotics and on a subcutaneous saline infusion.

The clinical status of the patient deteriorated further despite the treatment. The patient started complaining of severe abdominal pain; on palpation, there was generalized tenderness over the right hypochondrium with associated rigidity. There was also a well demarcated area of erythema and induration of the skin localized to the region of insertion of the subcutaneous infusion.

The patient was transferred to a surgical ward for further investigations and management. A computed tomography scan of the abdomen showed inflammatory changes (indicative of an infection) with free gas in the abdominal wall on the right of the mesogastrium (figure 1).

A diagnosis of necrotising fasciitis of the abdominal wall secondary to the subcutaneous infusion was formulated. The patient was transferred to the operating theatre where the abdominal wall was incised and surgical debridement of the infected tissues was performed under local anaesthetic (figure 2). The wound was packed with alginate and left to heal by secondary intention.

Postoperatively the patient was started on intravenous metronidazole and piperacillin/tazobactam. The clinical course of the infection was closely observed by monitoring the patient's vitals including temperature, physiological functions and laboratory parameters. Eventually the leukocyte and C-reactive protein values decreased significantly and the patient's clinical status improved.

Discussion

The hypothesis is that the subcutaneous injection for the saline infusion resulted in a loss of skin integrity with a subsequent bacterial inoculation into the subcutaneous space resulting in damage to the overlying skin. One can suspect that skin contamination contributed to the aetiology.

Several reports link intramuscular injections and intravenous drug abuse to the development of necrotising fasciitis.[2] Other reported aetiologies

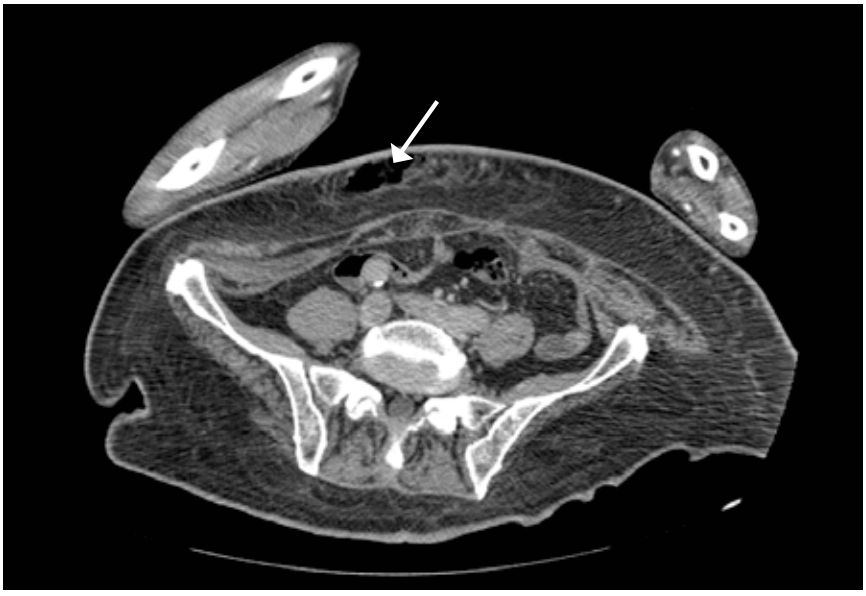

Figure 1. The CT scan of the abdomen showing gases in the abdominal wall (arrow).

include blunt or penetrating trauma and haematogenous spread from a distant site. No literature was found linking subcutaneous saline injections to the development of necrotizing fasciitis.

The patient was a known case of diabetes. His uncontrolled diabetes, as monitored by his glycosylated haemoglobin, resulted in an increased susceptibility to the development of necrotizing fasciitis. Increasing age is another consistent risk factor across several case studies; although the condition can affect any age group.[1] Other recognized risk factors for this condition include immunosuppression and chronic systemic diseases (for example atherosclerosis and renal failure).[3]

This patient presented with the typical early symptoms of necrotizing fasciitis: fever, erythema and out-of-proportion pain on physical examination. Such pain preceded any skin changes. This occurs in the majority of patients (>97.8%) with necrotizing fasciitis.[1] The intensity of the local signs could have also been weakened by the previous antibiotic therapy.

The CT scan was an important tool in this case, allowing the detection of gas tracking along the fascial planes. The radiological data was correlated to the clinical and laboratory results in order to establish the diagnosis of necrotising fasciitis. Despite this, CT scans sometimes do not adequately differentiate between severe cellulitis and necrotizing fasciitis. Magnetic resonance imaging has been reported as having the highest sensitivity (93-100%) for diagnosing necrotizing fasciitis, exhibiting high signal intensity on T2-weighed images.[4]

Other diagnostic procedures for necrotising fasciitis include the LRINEC (Laboratory Risk Indicator for Necrotising Fasciitis) which is a scoring system developed by Wong et al.[5] The C-reactive protein, creatinine, haemoglobin, leukocyte count, serum sodium and glucose are used in this score. A score of 6 'raises the suspicion' and a score of 8 is 'strongly predictive' (table 1). A score of 7 was retrospectively calculated for this patient.

Figure 2. The incision in the lower abdominal wall following surgical debridement

VARIABLES	SCORE
HAEMOGLOBIN	
>13.5	0
11-13.5	1
<11	2
TOTAL WHITE CELL COUNT	
<15	0
15-25	1
>25	2
GLUCOSE	
<10	0
>10	1
C-REACTIVE PROTEIN (mg/dl)	
<150	0
>150	4
SODIUM (mmol/L)	
>135	0
<135	2
CREATININE (µmol/L)	
<141	0
>141	2

Table 1. Laboratory Indicator Necrotising Fasciitis Scoring System (LRNEC)[5]

Conclusion

Subcutaneous injections can represent a local portal of entry for infection that can progress to serious skin infections such as necrotising fasciitis. Necrotising fasciitis should be suspected in every skin infection with fever, signs of systemic toxicity and severe pain.

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MAURICE CAUCHI

Doctors, patients and the social media

A recent article in *Ann Intern Med*[1] highlights issues relating to the possible dangers of doctor-patient interaction through emails, Facebook and other electronic means. Some of the advice given is worth highlighting.

This advice is particularly apt for the younger generations of doctors, who, like others of their age group seem to enjoy a particular facility, fascination and fondness for pocket-sized electronic gadgets which make communications and interactions so easy and so painless.

The State Medical Boards in the US have recently reported several instances of violation of professionalism that led to a major action, including revocation of the licence to practice.

"There are legitimate ways that physicians can engage in social media with patients" Dr Chaudhry, one of the authors of the report commented. As long as there is a pre-established physician-patient relationship, contact with an email, for instance, to make an appointment or send an urgent report is not considered to have untoward consequences.

Social media have their uses, particularly from an educational point of view, directed to an anonymous audience, relating to topics such as health information, vaccines, etc. The report, however warns that what you say and how that is interpreted could be two completely different things. Dr Chaudhy advises: "Pause before posting."

Other issues that physicians should be warned about relate to ensuring confidentiality when information of any kind is posted on Facebook, Twitter, etc, which are widely dispersed among the community. Any information posted there may be read by a large number of persons. There is the possibility of it going viral and confidentiality cannot be assured.

These are some of the 'dont's' stressed in this report:

- Do not start a professional relationship with a person who you know only from an email;
- Do not contact patients through social media;
- Do not befriend patients through social media;
- Use emails or other electronic communications only with established patients and with patient consent;
- When you receive an email from a person who is not your patient, insist that the patient organises a visit with yourself or with another doctor;
- Never text messages relating to medical issues, "not even with established patients, except with extreme caution and consent from the patient."

There is no doubt that advances in social medial have been enormous in recent years, and have caught on like wildfire particularly among the younger generation. Those of us who have reached a certain age might be considered to be living in the age of the dinosaurs if we do not participate in these advances and make use of such gadgets. However, it is well to bear in mind that we must not allow professionalism to suffer in an effort to appear "with it" and connected.

Reference

1 Farnan JM, Snyder Sulmasy L, Worster BK, Chaudhry HJ, Rhyne JA, Arora VM et al. Online medical professionalism: patient and public relationships: policy statement from the American College of Physicians and the Federation of State Medical Boards. Ann Intern Med 2013; 158(8):620-7.

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Vildagliptin is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control. **DOSAGE:** When used as monotherapy, in combination with thiazolidinedione, in combination with metformin and sulphonylurea or in combination with insulin (with or without metformin), the recommended daily dose of vildagliptin is 100mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening. When used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. Galvus can be administered with or without a meal. Doses greater than 100 mg are not recommended. Galvus is not recommended for use in children and adolescents (< 18 years). The safety and efficacy of Galvus in children and adolescents (< 18 years) have not been established. No data are available. The recommended dose for patients with moderate/severe renal impairment is 50mg once daily. If a dose of Galvus is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day. No dose adjustments are necessary in elderly patients (≥ 65 years. The safety and efficacy of vildagliptin as triple oral therapy in combination with metformin and a thiazolidinedione have not been established. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients **WARNINGS / PRECAUTIONS:** Galvus should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.There is limited experience in patients with ESRD on haemodialysis. Therefore Galvus should be used with caution in these patients . Galvus is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST >3x the ULN. Liver function tests should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Should an increase in AST or ALT of 3xULN or greater persist, withdrawal of Galvus therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Galvus. Clinical experience in patients with NYHA functional class III treated with vildagliptin is still limited and results are inconclusive. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Galvus should not be administered during pregnancy or breast-feeding since no studies on the effect on human fertility have been conducted for Galvus. Should be used with caution in patients with renal impairment. Sulphonylureas are known to cause hypoglycaemia. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia. **INTERACTIONS:** Vildagliptin has a low potential for drug interactions. No clinically relevant interactions with other antidiabetics (glyburide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin. As with other oral antidiabetic medicines, the hypoglycaemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics. **ADVERSE REACTIONS:** Rare cases (>1/10,000 to <1/1,000) angioedema, abnormal liver function tests, hepatic dysfunction (including hepatitis). *Monotherapy:* Common (>1/100 to <1/10): dizziness, Uncommon (>1/1,000 to <1/100): headache, constipation, arthralgia, hypoglycaemia, oedema peripheral. Very rare (<1/10,000): URTI, nasopharyngitis. *Combination with metformin:* Common: tremor, headache, dizziness, nausea, hypoglycaemia, hyperhidrosis, asthenia. Uncommon: fatigue. *Combination with sulphonylurea:* Common: tremor, headache, dizziness, asthenia, hypoglycaemia. Uncommon: constipation. Very rare: nasopharyngitis. *Combination with Thiazolidinedione:* Common: weight increase, oedema peripheral. Uncommon: headache, asthenia, hypoglycaemia. *Combination with insulin:* Common: decreased blood glucose, headache, chills, nausea, gastro-oesophageal reflux disease. Uncommon: Diarrhoea. Rare/unclear/frequency not known: urticaria, pancreatitis, hepatitis and abnormal liver function tests (reversible upon discontinuation of the medicinal products), bullous or exfoliative skin lesions. **LEGAL CATEGORY:** POM **PACK SIZES:** 7, 28 tablets **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** UK/0734/0001, 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 22983217 / +356 21222872. 2013-MT- GAL-07-AUG-2013.

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PRESENTATION: Each 50 mg/850 mg film-coated tablet contains 50 mg of vildagliptin and 850 mg metformin hydrochloride. Each 50 mg/1000 mg film-coated tablet contains 50 mg of vildagliptin and 1000 mg metformin hydrochloride. **INDICATIONS:** Eucreas is indicated in the treatment of type 2 diabetes mellitus patients, indicated in the treatment of adult patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone or who are already treated with the combination of vildagliptin and metformin as separate tablets. Eucreas is indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled with metformin and a sulphonylurea. Eucreas is indicated in triple combination therapy with insulin as an adjunct to diet and exercise to improve glycaemic control in adult patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control. **DOSAGE:** The dose of antihyperglycaemic therapy with Eucreas should be individualised on the basis of the patient's current regimen, effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100 mg vildagliptin. Eucreas may be initiated at either the 50 mg/850 mg or 50 mg/1000 mg tablet strength twice daily, one tablet in the morning and the other in the evening. For patients inadequately controlled at their maximal tolerated dose of metformin monotherapy: The starting dose of Eucreas should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) plus the dose of metformin already being taken. For patients switching from co-administration of vildagliptin and metformin as separate tablets: Eucreas should be initiated at the dose of vildagliptin and metformin already being taken. For patients inadequately controlled on dual combination with metformin and a sulphonylurea: The doses of Eucreas should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Eucreas is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin: The dose of Eucreas should provide vildagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. Eucreas should be taken with or just after food to reduce gastrointestinal symptoms associated with metformin. Patients > 65 taking Eucreas should have their renal function monitored regularly. Eucreas is not recommended for use in patients less than 18 years old. For use in renal or hepatic impairment, see contraindications and precautions below or refer to the SmPC for more information. The safety and efficacy of vildagliptin and metformin as triple oral therapy in combination with a thiazolidinedione have not been established. **CONTRAINDICATIONS:** Hypersensitivity to vildagliptin or metformin hydrochloride or to any of the excipients. Diabetic ketoacidosis or diabetic pre-coma. Renal failure or renal dysfunction defined as creatinine clearance < 60 ml/min. Acute conditions with the potential to alter renal function e.g. dehydration, severe infection, shock or intravascular administration of iodinated contrast agents. Acute or chronic disease which may cause tissue hypoxia e.g. cardiac or respiratory failure, recent myocardial infarction, shock, hepatic impairment, acute alcohol intoxication, alcoholism, lactation. **WARNINGS / PRECAUTIONS:** Eucreas is not a substitute for insulin in insulin-requiring patients and should not be used in patients with type 1 diabetes. Due to the risk of lactic acidosis, renal function could be monitored at least once yearly in patients with normal renal function and at least two to four times/year in patients with serum creatinine at the upper limit of normal and in elderly patients. Eucreas is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST >2x the ULN. LFT's should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Should an increase in AST or ALT or 3x ULN or greater persist, withdrawal of Eucreas therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Eucreas. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. As Eucreas contains metformin, treatment should be discontinued 48 hours before elective surgery with general anaesthesia and not usually resumed earlier than 48 hours afterwards. The IV administration of iodinated contrast agents can lead to renal failure. Therefore due to metformin active ingredient, Eucreas should be discontinued prior to or at the time of the test and not reinstituted until 48 hours afterwards and only after renal function has been re-evaluated and found to be normal. Eucreas should not be administered during pregnancy or lactation. Sulphonylureas are known to cause hypoglycaemia. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia. **INTERACTIONS:** Vildagliptin has a low potential for drug interactions. No clinically relevant interactions with other antidiabetics (glyburide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin. Interactions with metformin hydrochloride that are not recommended include alcohol, cationic active substances e.g. cimetidine and intravascular administration of iodinated contrast media. Combinations requiring caution include metformin hydrochloride with medicines tending to produce hyperglycaemic activity e.g. glucocorticoids, beta agonists and diuretics. The dose of antihyperglycaemic medicinal products may need to be adjusted in combination with ACE inhibitors. **ADVERSE REACTIONS:** Rare cases (>1/10,000 to <1/1,000) angioedema, hepatic dysfunction (including hepatitis) have been reported with vildagliptin. *Vildagliptin Monotherapy:* Common (>1/100 to <1/10): dizziness, Uncommon (>1/1,000 to <1/100): headache, constipation, arthralgia, hypoglycaemia, oedema peripheral. Very rare (<1/10,000): URTI, nasopharyngitis. *Metformin monotherapy:* Very common (>1/10) Nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. Common: metallic taste. *Combination vildagliptin with metformin:* Common: tremor, headache, dizziness, nausea, hyperglycaemia. Uncommon: fatigue. *Combination with metformin and sulphonylurea:* Common: hypoglycaemia, dizziness, tremor, hyperhidrosis, asthenia, decreased blood glucose, headache, chills. *Combination with insulin:* Decreased blood glucose, headache, chills, nausea, gastro-oesophageal reflux disease, diarrhoea, flatulence. For a full list of Adverse reactions, please refer to the SmPC. **LEGAL CATEGORY:**POM **PACK SIZES:** 30, 60 film-coated tablets **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBER:** EU/1/07/425/002–003, EU/1/07/425/006-009. **Please refer to Summary of Product Characteristics (SmPC) before prescribing.** Full prescribing information is available upon request from Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel +356 22983217 +356 21222872. 2013-MT-EUC-31-JUL-2013

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Psoriasis

Gabriella Grech

Malta Medical Student Association

Psoriasis is a chronic, persistent, life-long inflammatory disease.[1] Psoriasis is an inflammatory disease presenting with red scales on the skin, most commonly at the elbows and knees. At the moment there is no complete cure for this disease but there are a wide range of therapies which can control it, and the patients can live a normal life.[2] However this brings on the patients an economic burden, which increases in proportion with the severity of the disease.[3]

Management

This disease can be managed efficiently by a large variety of therapies. Studies have shown that there is a low adherence (around 40%) to treatment in this subpopulation. Factors such as efficacy and duration of the treatment are important in the adherence to treatment.[4] Localised psoriasis at the knees and elbows are usually treated with topical corticosteroids or Vitamin D analogues. On the other hand, more severe and extensive psoriasis can be better managed by systemic therapies such as methotrexate or acritretin and/or phototherapy.[5]

Complications

Psoriasis may result in psychosocial disability that is similar to that of patients suffering from diabetes, depression and other chronic illness. Patients may also have a low self-esteem due to shame and embarrassment about their body image and stigmatization.[4] In a survey carried out by Ramsay and O'Reagan[6] about the social and psychological effects of psoriasis, it was found out that most of the patients with psoriasis avoid social activities such as swimming and sports. Half of the patients participating in this survey felt that their sexual relationships where inhibited by this condition and 11% said they were not going to have any children to avoid the risk of their offspring developing this disorder as well.

Conclusion

Due to the complexity of this skin condition and the several effects it has on the patient's health, psoriasis patients should receive regular health assessments to increase the awareness of the condition which would in turn lead to an improvement in their own overall health. This is important as patients with psoriasis have an increased risk of death at a younger age.[7]

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PATRICIA DE GABRIELE

Iron deficiency anaem

Case presentation

A 22 year old female University student attends your GP clinic accompanied by her mother. She complains of progressive lethargy and weakness, making it difficult for her to concentrate on her studies.

On further questioning, she informs you that she has been having heavier regular menses for the past six months. Her last menstrual period was one week ago. During menstruation, she feels very weak and has to stop halfway up a staircase because of shortness of breath. She has been very busy lately finalising her thesis and her mother complains that she is hardly eating anything at home. The patient states that she feels hungry but doesn't have time to eat a proper meal. She also claims that she is only having four to five hours of sleep every day. She has no abdominal upsets and does not complain of any irregularity in her stools.

The patient has no significant past medical history and is not on any regular medications. She does not drink alcohol or smoke. She has not been abroad for the past year.

On examination, her skin, nail beds and conjunctivae are somewhat pale. She has strong peripheral pulses. Blood Pressure is 115/75 mmHg and pulse is regular at 90 bpm. Her chest is clear and examination of her neck is normal. Her BMI is 19.5. Rectal examination is normal.

Investigations carried out

- Full Blood Count
  - Haemoglobin - 8 g/dL
  - Red Cell Count - 4 million/mm^3
  - Haematocrit - 30%
  - Mean Cell Volume (MCV) - 65 fL
  - Mean Corpuscular Haemoglobin Concentration (MCHC) - 25 g/dL
  - Serum ferritin - 5 ng/mL

- Thyroid Function Tests - Normal
- Ultrasound Pelvis - Normal

Iron supplements are prescribed and a review appointment is given in four weeks' time.

Discussion

Generalised weakness, lethargy, dyspnoea and history of heavy blood loss during menstruation accompanied by a haemoglobin level of 8g/dL are all suggestive of anaemia. A mean cell volume (MCV) of 60 fL and a mean corpuscular haemoglobin concentration (MCHC) of 25 g/dL classifies the anaemia as a microcytic, hypochromic anaemia, which is suggestive of iron deficiency. However, this may also be due to a thalassaemic trait. The patient does not have a family history of thalassaemia or its trait; nonetheless a serum ferritin test is required. A level <10ng/mL is indicative of iron deficiency anaemia. Hypothyroidism as a possible cause of lethargy and weakness and cardiac compensation has also been excluded. The history of the patient's complaint helps to shed light on the cause of the iron deficiency. There is evident excessive blood loss in the patient's menses. She is not pregnant as she has had her last menstrual period one week before. Dietary intake of iron seems to be somewhat limited as she "doesn't have time to eat a proper meal".

Chronic disease is unlikely because she has previously been healthy and she is not experiencing a loss of appetite. There doesn't seem to be any signs of gastrointestinal blood loss as her stools are normal and she is not taking any medications such as aspirin or non-steroidals (NSAIDs). Besides, she has no abdominal upsets and so coeliac disease would not be greatly considered at this point. Anxiety or depression should also be considered, given her psycho-social context. Thus, the next step in management in general practice is to control her menorrhagia and at the same time start iron supplementation, as well as follow the patient up to monitor response or otherwise. If the patient does not respond, she would be a candidate for further investigation.

Iron Deficiency Anaemia

Anaemia is a condition in which the number of red blood cells, and thus their oxygen-carrying capacity, is insufficient to meet the physiological needs of the body. Anaemia can also occur if the red blood cells don't contain enough haemoglobin. Specific physiological needs vary with a person's age, gender, altitude, smoking behaviour and different stages of pregnancy. Iron deficiency anaemia is thought to be the most common cause of anaemia globally, but other nutritional deficiencies, including folate, vitamin B_{12} and vitamin A, acute and chronic inflammation, parasitic infections, and inherited or acquired disorders that affect haemoglobin synthesis, red blood cell production or red blood cell survival, can all cause anaemia.[1]

nia in general practice

Haemoglobin concentration alone cannot be used to diagnose iron deficiency anaemia. A serum ferritin level is required, since this is the most sensitive marker of early iron deficiency and is the preferred initial diagnostic test. Serum ferritin level correlates with total iron body stores and a low level can be identified before serum iron is affected. The state of the iron stores can be assessed by considering together the serum ferritin, iron and transferrin; the latter is indirectly measured by the total iron binding capacity. Thus, a full blood count and iron studies are required to establish a diagnosis of iron deficiency anaemia.

Aetiology and epidemiology of Iron Deficiency Anaemia

Iron deficiency anaemia occurs in 2–5% of adult men and post-menopausal women in the developed world.[2] While menstrual blood loss is the commonest cause of iron deficiency anaemia in pre-menopausal women, blood loss from the gastrointestinal tract is the commonest cause in adult men and post-menopausal women.[3] Asymptomatic colonic and gastric carcinoma may present with iron deficiency anaemia and exclusion of these conditions is of prime importance. Malabsorption, most frequently from coeliac disease, poor dietary intake, previous gastrectomy, and NSAID use may also give rise to iron deficiency anaemia.

The balance of iron in humans is tightly controlled and designed to conserve iron for optimal utilisation. The only mechanisms by which the body loses iron are menses, gastrointestinal bleeds or other forms of bleeding but also through the loss of epithelial cells from the skin, gut and genitourinary tract. Normally, the only route through which iron enters the body is by absorption from food or oral supplementation; however iron may also enter the body during blood transfusions or injection of iron complexes. A dietary intake of iron is needed to replace the iron that is lost daily in the stools, urine and through the skin. These basal losses represent approximately 0.9mg of iron per day for an adult male and 0.8 mg per day for an adult female.[4] Iron requirements will be increased with heavy menstrual flow, during pregnancy as well as in infants and adolescents.

There are two distinct types of iron found in food – haem and non-haem iron. Haem iron is a constituent of haemoglobin and myoglobin and so is present in meat, fish, poultry and blood products. Non-haem iron is mainly found in vegetables, cereals, tubers and pulses

There are two distinct types of iron found in food – ***haem*** and ***non-haem iron***. Haem iron is a constituent of haemoglobin and myoglobin and so is present in meat, fish, poultry and blood products. Non-haem iron is mainly found in vegetables, cereals, tubers and pulses. The latter is less easily absorbed by the body and is affected by the presence of enhancing or inhibiting factors. Meat, fish and ascorbic acid-containing products are enhancers of non-haem iron absorption. On the other hand, compounds which inhibit the absorption of both haem and non-haem iron include tannins, phytates and soy protein when it is used as a meat substitute. Phytates are present in wheat and cereals. Tannins are present in tea and to a lesser extent in coffee. However, this inhibitory effect can be counteracted by ascorbic acid. Thus, iron absorption is greatly influence by the constituents of an entire meal.[5]

Thus, iron deficiency may result from ***excessive loss*** or decreased absorption of iron. Excessive loss might take place as ***occult gastrointestinal blood loss*** caused by:

- Aspirin
- NSAID use
- Benign gastric ulceration
- Angiodysplasia
- Uncommon causes such as oesophagitis
- Colonic carcinoma
- Gastric carcinoma
- Other gastrointestinal tract malignancies

Blood loss might not be gastrointestinal in origin. It might be due to:

- Menstruation
- Pregnancy
- Blood donation
- Rarely, haematuria & epistaxis

Decreased absorption of iron may be due to ***inadequate dietary intake*** of iron in certain subpopulations, example, vegetarians and elderly. It may also arise because of unbalanced diets or because of ***malabsorption syndromes***, example:

- Coeliac disease
- Post-gastrectomy
- Gastric Helicobacter pylori colonisation
- Impaired gastric acid secretion
- The use of proton pump inhibitors
- Parasitic infections
- Uncommon causes such as gut resection and bacterial overgrowth
- Chronic inflammation

Management of Iron Deficiency Anaemia

The aim of the treatment of iron deficiency anaemia should be to restore haemoglobin levels and mean cell volume (MCV) to normal values and to replenish body stores, that is, serum ferritin levels are restored to normal limits. If this cannot be achieved, further investigation may be warranted.

Treatment of the underlying cause should prevent further iron loss; nonetheless all patients should have iron supplementation in order to correct anaemia and replenish body stores. This is achieved most simply and cheaply with ferrous sulphate 300 mg twice daily although ferrous gluconate and ferrous fumarate are as effective.[6] These provide 100-120mg of oral elemental iron per day. A liquid preparation is an alternative when tablets are not tolerated. Patients must also be advised to include more iron in their diet. Iron-rich foods include dark-green leafy vegetables, wholegrains, beans, nuts, apricots, prunes, raisins, iron-fortified cereals and meat.

To ensure a healthy, well-balanced diet, foods from all major food groups should be included in the diet. Ascorbic acid enhances iron absorption[7] and should be advised as a dietary intake, in the form of oranges or other citrus fruits, with the iron supplementation. Patients need to be advised to avoid taking iron supplements with tea or coffee, as tannins can form insoluble complexes with iron, reducing its absorption. Oral iron preparations should be taken on an empty stomach, as food may inhibit iron absorption. However, if oral iron causes gastric upset, it can be taken with or shortly after food.[8] Other drugs such as antacids, calcium, oral bisphosphonates and thyroid hormones should be avoided when taking the oral iron as it forms poorly soluble complexes with them, decreasing iron absorption.[8]

Parenteral iron should only be used when there is intolerance to at least two oral preparations or non-compliance. Parenteral iron treatment is expensive and may cause anaphylactic reactions.[8] Besides, the rise in haemoglobin is no quicker than with oral preparations. If parenteral iron is needed, intravenous iron is preferred; iron administered intramuscularly is painful and is also poorly absorbed from muscle.[9]

The haemoglobin concentration should rise by 2 g/dl after 3–4 weeks. Failure to do so is usually due to poor compliance, misdiagnosis, continued blood loss, or malabsorption. Guidelines vary in their recommendations for the duration of iron therapy after the anaemia has been corrected. Some guidelines suggest an additional 3 to 4 months of treatment.[8,10] Others suggest 4 to 6 months[11] whereas others suggest 6 to 12 months.[12] However iron supplementation should be continued for at least three months after correction of anaemia to replenish adequately the iron stores.[6]

Once normalized, the haemoglobin concentration and red cell indices should be monitored at intervals. It is suggested that monitoring should be done three monthly for one year and then after a further year. Additional oral iron should be given if the haemoglobin or MCV fall below normal levels (a ferritin estimation should also be done in doubtful cases). Further investigation is only necessary if the haemoglobin and MCV cannot be maintained in this way.[3]

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‘We have not lost faith, but we have transferred it from God to the medical profession’: Medicine in Mainstream Literature – Part II

Victor Grech
Clare Vassallo
Ivan Callus

The *locus classicus* that, arguably, above all other works, demonstrates the duality of human nature in all of mankind, including in the medical profession, is Robert Louis Stevenson’s *The Strange Case of Dr. Jekyll and Mr. Hyde* (1886) wherein doctors are portrayed as weak and fallible, primarily because of the potential abuse of their special knowledge and abilities.[12] The duality of man’s psyche is the story’s overriding theme, an allegory of mankind’s permanent inner conflict between good and evil through the potential dissociation of a single entity into two opposing selves. The story was recently rewritten by Steven Moffat as *Jekyll* and billed as a modern-day sequel to the original novella.[13]

Jekyll, a medical doctor, is the novel’s protagonist: in late-middle age, intelligent, tall, dignified, wealthy, widely respected and with a good house and a household of loyal servants, the epitome of the Victorian gentleman and the embodiment of all that is good in mankind. Nevertheless, deep down and invisible to all but himself, just like common mortals, Jekyll harbours a dark side with secret passions and vices that he is unable and unwilling to unleash, a sinister force that is also manifest in his name, ‘I kill’ in French. For this reason, he concocts a potion that will bring forward only one (the best) of his two halves. The potion is impartial and favours neither good nor evil, and because Jekyll approaches this unnatural endeavour with ambition and unseemly anticipation, it is the evil half, Mr. Hyde, in the Frankensteinian trope (which will be amplified later) that is manifested at this crucial crossroad. Hyde is described as small, distorted and ugly, and any who see him experience distaste and outright horror.

Jekyll is initially in total control over his metamorphosis into Hyde, but slowly damns himself as he finds that he enjoys slipping into the Hyde alter-ego since it endows him with the liberty to perform iniquity with impunity, a freedom that is derived from Hyde’s untouchability, since he can be made to vanish at will. However, this becomes an addiction and Hyde eventually becomes powerful enough to manifest spontaneously. The completely senseless, unprovoked and callous murder of a member of parliament is the nadir of Hyde’s wickedness and Jekyll finds that he now has to take ever increasing doses of potion in order to remain in the Jekyll persona, living in the fear that as Hyde, he will be caught, prosecuted and executed for murder. Toward the end of the novel, Jekyll runs out of potion and is unable to find the necessary raw materials in order to produce a new supply of potion, and realises that the only way to impede his permanent transformation into Hyde, along with prosecution for murmur and execution, is by suicide, a deed that he actually commits, bringing the story to a close.

Lanyon, a medical doctor, also appears in the story, and is used as a scientific foil for Jekyll. Lanyon is unfortunate in witnessing a Jekyll-Hyde transition, and as a firmly rational man, he simply could not adapt to the

revelation of the Hyde possibility, a monstrous half that is suppressed in all of us. His stricken soul leads his physical body into a rapid decline and death, also a form of suicide. While 'a text like Jekyll and Hyde could be said to be premised on a scientific 'novum,' [...] it is equally overdetermined by Gothic, melodramatic, and imperialist elements' and hence not strictly appertaining to the science fiction genre.[14]

This trope has been frequently reused in science fiction, and for example in ***Darkling*** (1997), the sentient hologram that is the doctor on the starship ***Voyager*** actively endeavours to develop a realistic human personality, and he attempts to accelerate this process by directly grafting character traits that he deems desirable onto his computer subroutines from historic figures, such as Ghandi and Byron.[15] This endeavour fails when the darker and more negative aspects of the historic figures' characters manifest in a literal Jekyll and Hyde manner, with the doctor being intermittently taken over by an evil persona.

A more benign portrayal of the latent duality of human nature and the potential for change is displayed by Dickens in ***A Tale of Two Cities*** (1895), where Manette, a brilliant physician, spends eighteen years as a prisoner in the Bastille. Initially, he is found making shoes in prison in order to distract himself from the harshness of prison life, but transforms himself into a man of distinction after he is rescued.[16]

Tertius Lydgate is yet another doctor, the perfect Aristotelian tragic hero in Eliot's ***Middlemarch*** (1871),[17] who has already been briefly discussed in another essay and whose dilemmas are typical of any doctor's.[18] Lydgate is poor, ambitious and somewhat arrogant and starts off with lofty ideals but falls in love, marries, and rapidly runs into dire financial straits and a potential conflict of interest forcing him to seek more lucrative pastures than provincial Middlemarch, among London's high society, abandoning his high ideals. Even in his role of physician, Lydgate finds himself unable to treat a heart condition or give a prognosis on the case, and indeed, the patient dies shortly after being examined. Moreover, all of the doctors in Middlemarch, that is, Wrench, Toller, Minchin and Sprague, are in their turn depicted as petty and vindictive, jealous of Lydgate and reluctant to embrace new medical advances.

A broader view of the overall ineffectiveness of medicine in mainstream literature is seen in Mary Wollstonecraft Shelley's ***The Last Man*** (1826), wherein Shelley conceived a plot device that would eventually be reused by a string of writers: an apocalyptic plague that threatens to destroy humanity.[19] The medical field appears powerless to help out at all except to provide hospitals for the terminally ill. Similarly and more recently, in Albert Camus' ***La Peste*** (1947), not only are doctors completely incapable of arresting an outbreak of bubonic plague in Algerian Oran, but incredibly, take a considerable period of time to realise that a fatal epidemic is sweeping their city and to organise quarantine measures, and this despite rats dying bizarrely and ***en masse***, followed by large numbers of the populace who come down with obvious signs of bubonic plague. The story is narrated in the first person by Bernard Rieux, a physician in Oran who finds solidarity among the other doctors in Oran, all of whom futilely attempt to control the plague. Camus also emphasises another noteworthy observation in that nature is hostile, or at best indifferent to humanity and suffering.[20]

However, while literature has portrayed medicine overall negatively, the arts have not, and a plethora of paintings have depicted doctors, scientists and students, not only as formal portraits, but also in ***tableaux*** with patients, as reviewed by Ludmilla Jordanova and many others.[21] The intermingling of medicine and the humanities has been further analysed by Evans and others who propose the study of 'Medical Humanities', an interdisciplinary field of medicine which includes the humanities, social science and the arts, along with their application to medical education and practice. The purpose of this endeavour is the improvement in the delivery of healthcare through a better understanding of disease in society, and in the individual, with insights into suffering and the human condition and how culture interacts with individual experience of illness and the way medicine is practised. The thorny issues raised by the ever increasing complexity of medical ethics are also considered.[22]

It is evident that in all of these narratives, doctors are depicted stereotypically, weak and impotent, unable to perform the job for which they have trained, and this is perhaps a parable, an attempt by various authors to chastise us for believing that science may have all of the answers. These are therefore cautionary tales, warning us of our ***hubris***, and leading us to conclude that human ingenuity, as manifested by doctors and scientists, can only go so far in alleviating the human condition. This essay also demonstrates that despite the growing importance of medicine to the human condition, literature has sidelined medicine, somehow rendering doctors impotent and unable to father cures, with stories that tend to be formulaic and repetitive, casting the medical profession in a mediocre light.

This is not the case in science fiction, where doctors are the heroes in many a narrative, and that is the subject of another manuscript. S

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MASSIMO AZZOPARDI

THE caterer FOR YOUR BIG DAY

Whether a long or short invitation list, choosing a caterer for your big day may seem complicated. Here are a few tips to take into consideration before actually shopping around and standing at wedding fairs, only to come back home more confused

Invitation list

Ensure that you have taken into consideration those guests who most probably will not make it to your event, e.g. who are abroad or who are very elderly, and those who will be coming late. This will reduce your food item list by some numbers that can save you on cost. Furthermore, every caterer includes a surplus of food items ordered to ensure availability, so you do not have to be too precise on the number of guests attending.

Location and venue

The location and venue will play an important role on your type of catering and caterer required. Outdoor venues in summer should not be considered for sit-down meals due to unpredictable wind and hot climate. Visiting the venue beforehand at the same time of the day of the event will give you a better idea of how the venue will feel like. If the climate and ambiance is uncomfortable, guests will not enjoy food and service.

Type of cuisine

When you come to selecting the type of food, it is not what you wish that matters, but what the caterer is able to produce! Check out what kind of food the caterer specialise in and request to see their menus. Getting a taste is extremely important; it also prevents any unexpected 'surprises' on your wedding day. If your venue is within a hotel, it would be more practical to consider a seated or buffet type of meal, since this will be their area of specialisation.

The caterer`s kitchen

Do not hesitate to ask to have a look at the kitchen of your caterer. Even if you are not in the same line of business, you will be able to identify any shortcomings that might result to unpleasant situations. Ask to have a look at the service uniforms and do not settle for any basic white shirt and black trousers.

Fresh or frozen foods

This option is debatable and some prefer to opt for fresh food items rather than ready frozen options. Frozen does not mean a lower quality as today the food industry specialises in ready-made frozen foods of a high level. Furthermore, frozen items require less handling therefore carry less food contamination risks.

Refrigerated vehicles

Ask your caterer about his food transportation vehicles` conditions and food compartment temperatures. Most venues have a limited kitchen on site and food is kept in refrigerated vans until served.

Speciality tables

It has become a tradition to include speciality tables at weddings. Consult with the caterer if such tables will be well-manned and strategically positioned to avoid endless queuing with the last guests being left with little or no food options at all.

Desserts

Your caterer will guide you accordingly to his dessert options. However bear in mind that by this time the majority of guests would have left or be leaving. You can keep your dessert list as low as 3 dessert types with more fruit options in summer.

Beverages

Depending on your agreement, beverages need not be purchased from the caterer, but some caterers come with a package price that can save you on opened spirits bottles that cannot be returned if purchased from wines and spirits agents. Another point is that some caterers include an extra charge for the use of ice in drinks which are not purchased from them.

Timings

Keep an accurate time plan for your best man to follow. It is important for your caterer to plan accordingly without the need of being at the venue too early or even worse, too late!

Air-conditioning

The climate of your wedding venue is to be looked into very well. If temperatures are not appropriate when the hall is full of guests, it can have an effect on the quality and presentation of food, especially if it is on buffet style.

Contractual obligations

Take time to look into the contract/ agreement well and if need be ask for legal advise prior to committing yourselves. Look well into how realistic the overtime charges are and what are the other supplementary costs involved. If not otherwise indicated, VAT should always be included in pricing.

Food is arguably the main thing people complain about at events and coincidentally, it's also the largest cost you will pay for your wedding reception. Take sufficient time in advance to look into your catering options and services and although you might be presented with many reasons that involve innovative and creative catering, remember that these might not work for every taste and budget.

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QUIZZES

1. If a previous diabetic pink card holder opted for a diabetic yellow card before 1st June 2012 can the patient revert to the pink card? Yes or no?
(TIP: if you read the editorial you would know)
Send your answers by 10th January to ian.c.ellul@gmail.com
The 5th correct entry will win a Medical Language Translator book published by MMSA.

2. Which famous Star Trek doctor does Dr. Pulasky emulate and in which Star Trek series does this other character appear?
(TIP: if you read Doctor by Doctor: Dr Helen Pulasky in Star Trek: The Next Generation you would know)

Send your answers by 10th January to ian.c.ellul@gmail.com
The 5th correct entry will win a free attendance at the plenary talk followed by the barbeque at the Dolmen Hotel on the 10th of July 2014 during the Star Trek Symposium (www.startreksymposium.com)

Winner of the Day Pass for 1 person at Le Spa by Transforma

Dr Patrick Zahra MD DCH MRCP is the lucky winner of the 'Download the Synapse App & Win' published in Issue 5/13. He won a Day Pass for 1 person at Le Spa by Transforma.

Winner of the Medical Language Translator book published by MMSA

Dr Joseph Cassar Delia is the winner of the Medical Language Translator book published by MMSA. He was the 5th participant who replied correctly to the question, 'According to the Budget document 2014, what new condition will be included in Schedule V?' published in Issue 5/13. The correct answer was Multiple Sclerosis.

Dr Joseph Cassar Delia MD graduated in 1969. He is a specialist in Family Medicine, with private general practice in the south of Malta. Previously he also used to lecture in Anatomy at the UOM.

MARIKA AZZOPARDI

On new medications, market access and Malta's health system

PHARMACEUTICAL RESEARCH-BASED INDUSTRY MALTA ASSOCIATION

INTERVIEW WITH **MARK MALLIA**

The recently announced Malta Budget 2014 included a key health-associated proposal that assured that new medications shall be introduced on the Government Formulary List in the coming year specifically targeting the treatment of multiple sclerosis, ADHD and diabetes. The announcement comes just a few hours prior to an interview with Mark Mallia, a pharmacist and President of PRIMA (Pharmaceutical Research & Development Industry Maltese Association). He shares some invaluable insight and concerns regarding the current situation on medicines and their availability in Malta.

> "As PRIMA our priority mission is market access and we welcome any addition to the Government Formulary List (GFL) of available medications. However the regular access to innovative medications is listed in the EU charter for patients' rights and if our country is to abide with EU legislation, Malta should ascertain that it respects the set timelines by when our patients should have access to such drugs."

Mr. Mallia voices strong concerns over Malta's innovation deficiency in terms of pharmaceutical products. He pinpoints a number of incongruencies in the system.

> "Malta has not and is not abiding with the EU Transparency Directive, (Directive 2013/50/EU) mainly in terms of respecting the time frames within which new products are placed on the GFL (if introduced at all!). Variations are not simply days or weeks, but months and in some cases, years. There are specific conditions for which generic medications were introduced, when the proprietary medication was never introduced. This is unacceptable since it deprives patients of innovative solutions to their health concerns. Then again, some innovative medications are only available to the few who can afford to buy them from the private market."

Mr Mallia adds:

> "We must acknowledge the improvements that have been made to the quality of public health care in Malta, but investing in infrastructure and equipment is not enough. Restricting the introduction of better innovative medicines defeats the whole scope of providing high standard health care."

But isn't it all about costs involved and sustainability? PRIMA has a hands–on approach to this issue.

> "Significant cost increase? Not necessarily. We need to make the system more efficient and sustainable. We need to introduce more accountability on the use of medications, consumables and medical procedures through more defined protocols of use. We need better forecasting and purchasing systems, improved storage and distribution systems and improved market access. If innovative drugs are introduced on the Government Formulary in line with EU regulations, this would result in more competitive pricing for the government through increased availability of products. This would also provide the medical profession with more tailored treatment choices which are very often more cost-effective than older remedies. It would also benefit pricing in the retail market for those patients who might not fit the protocol criteria for the free innovative drugs. This can be achieved by adopting, where appropriate, policies and systems used in the great majority of other healthcare systems in the EU."

Scientific innovation has led to an increased life expectancy and a subsequent significant increase in the elderly population. The interview harnesses on the topic of sustainability of the system.

> "With the common political decision that all health services are to remain 'free' or rather as is the reality, paid for by our taxes, sustainability of the health system will be very difficult to achieve and maintain due to the exponential increase in demand. A sustainability problem, besides limiting availability of new medications, also contributes to out-of-stock situations. This may cause poor control of the patient, which in turn may result in increased use of other health services, such as increased admissions to the general hospital at an overall higher cost."

PRIMA believes that within the current scenario, significant improvements may still be made through the revision of certain policies and practices. Mr. Mallia goes on to explain immediate reforms which may be implemented.

> "PRIMA suggests that the National Formulary should be revised and old medicines which have become obsolete be removed. Cost-saving should be reinvested in innovative drugs to bring the national formulary in line with that of other EU countries.
> Part of the savings achieved from switching originator medicines to generic medicines should be reinvested into innovative medicines".

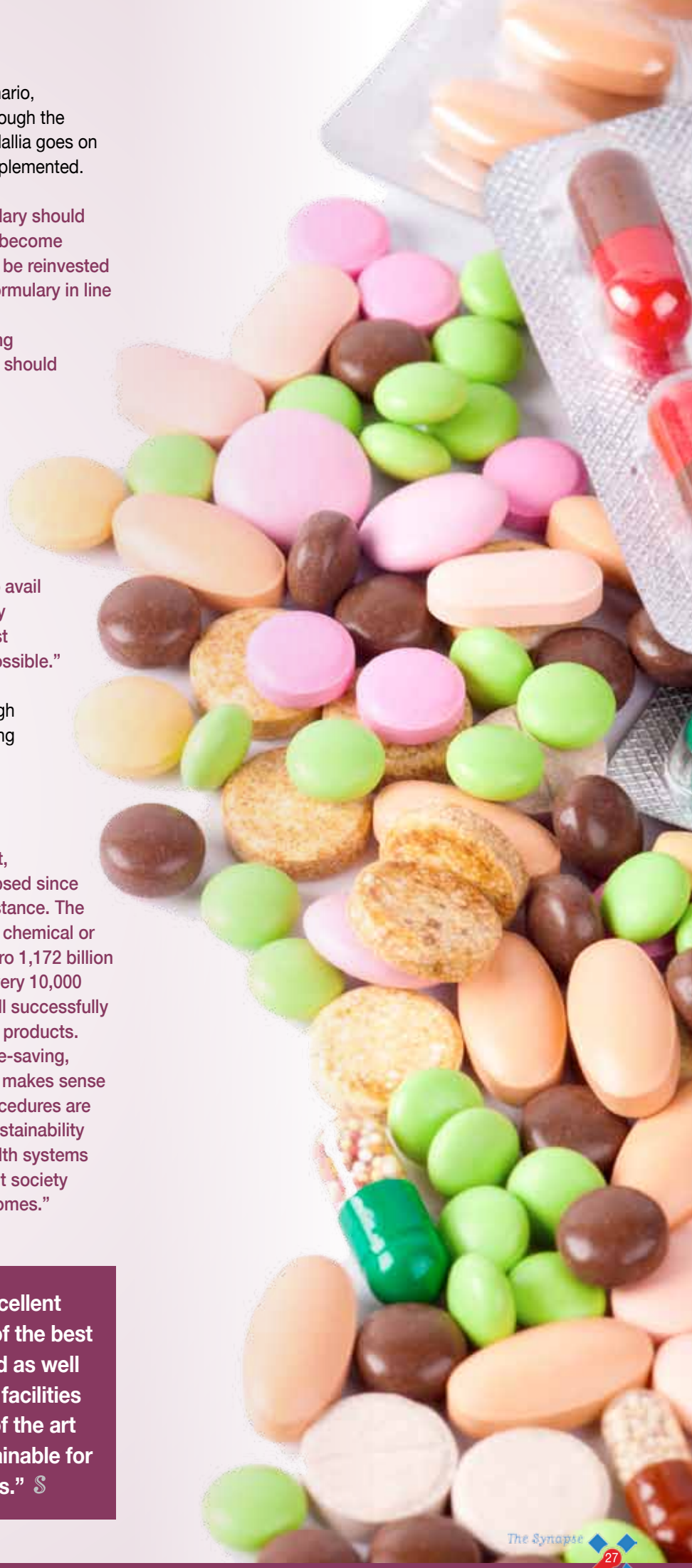
PRIMA estimates that over recent years the Maltese government has saved at least 10 million Euros per year following patent expiration.

> "As a research & development industry, our focus is on ensuring that patients who avail themselves of medicines locally, find ready availability medications which are the most advanced and of the highest standards possible."

Mr. Mallia explains the entire process through which medications end up on the market, staring from the lengthy, costly and risky research and development process conducted by the pharmaceutical companies.

> "By the time a product reaches the market, an average of 12 to 13 years will have elapsed since the initial synthesis of the new active substance. The cost of researching and developing a new chemical or biological entity has been estimated at Euro 1,172 billion in 2012. On average, only one or two of every 10,000 substances synthesized in laboratories will successfully pass all the stages to become marketable products. The invention and introduction of major life-saving, therapeutic, revolutionary treatments only makes sense if market access regulations/laws and procedures are adhered to. This benefits the long-term sustainability and profitability of the industry and of health systems alike, and ensures that investments benefit society through innovative and better health outcomes."

"Our country is blessed with excellent human resources including some of the best medical professionals in the world as well as excellent hospitals and health facilities … we want to be part of a state of the art health system which remains sustainable for present and future generations." S



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Full prescribing information is available from the Malta M.A.H.: Novartis Europharm Ltd., Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. Tel: +35622983217.

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Due to the hydrochlorothiazide component, Exforge HCT is contraindicated for use in patients with anuria and in patients with severe renal impairment (glomerular filtration rate (GFR) <30 ml/min/1.73 m2).Amlodipine dosage recommendations have not been established in patients with mild to moderate hepatic impairment. **CONTRAINDICATIONS:** Known hypersensitivity to the active substances, to other sulfonamides, to dihydropyridine derivatives, or to any of the excipients Second and third trimesters of pregnancyHepatic impairment, biliary cirrhosis or cholestasis Severe renal impairment (creatinine clearance < 30 ml/min) Anuria patients undergoing dialysis, Refractory hypokalaemia, Hyponatraemia, Hypercalcaemia Symptomatic hyperuricaemia. Exforge HCT is contraindicated in patients with severe renal impairment, diabetes, anuria or undergoing dialysis. Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricaemia as well as precipitate gout in susceptible patients. Exforge HCT is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Exforge HCT should be discontinued if hypercalcaemia develops during treatment. Serum levels of calcium should be periodically monitored during treatment with thiazides, Severe hypotension, Shock (including cardiogenic shock), Obstruction of the outflow tract of the left ventricle (e.g. hypertrophic obstructive cardiomyopathy and high grade aortic stenosis), Haemodynamically unstable heart failure after acute myocardial infarction. Exforge HCT should not be used with angiotensin receptor antagonists (ARB) or ACE with aliskiren in patients with diabetes or renal impairment. **WARNINGS/PRECAUTIONS:** The safety and efficacy of amlodipine in hypertensive crisis have not been established. In sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur after initiation of treatment with Exforge HCT. Exforge HCT should be used only after correction of any pre-existing sodium and/or volume depletion. Caution is advised when administering Exforge HCT to patients with renal impairment or systemic lupus erythematosus. Exforge HCT should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney since blood urea and serum creatinine may increase in such patients. Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue, has been reported in patients treated with valsartan. Some of these patients previously experienced angioedema with other medicinal products, including angiotensin-converting enzyme (ACE) inhibitors. Exforge should be discontinued immediately in patients who develop angioedema and should not be re-administered. Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality. Disturbance of serum electrolyte balance (monitoring recommended), glucose tolerance and serum levels of cholesterol, triglycerides and uric acid. Not recommended in patients below 18 years of age and in patients with primary hyperaldosteronism Beta-blocker withdrawal should be gradual. Caution in elderly and in patients with hepatic impairment or biliary obstructive disorders. Caution in patients with heart failure and coronary artery disease. As with all other vasodilators, special caution in patients suffering from aortic or mitral stenosis, significant aortic stenosis that is not high grade If a photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. Not recommended during the first trimester of pregnancy. Avoid use in women planning to become pregnant and while breast-feeding. Caution when driving or using machinery. Patients taking Exforge and driving vehicles or operating machines i should be taken into account that dizziness or weariness may occasionally occur. Amlodipine can have mild or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Treatment with Exforge HCT should only start after correction of hypokalaemia and any coexisting hypomagnesaemia. Thiazide diuretics can precipitate new onset hypokalaemia or exacerbate pre-existing hypokalaemia. Thiazide diuretics should be administered with caution in patients with conditions involving enhanced potassium loss, for example salt losing nephropathies and prerenal (cardiogenic) impairment of kidney function. If hypokalaemia develops during hydrochlorothiazide therapy, Exforge HCT should be discontinued until stable correction of the potassium balance. Thiazide diuretics can precipitate new onset hyponatraemia and hypochloraemic alkalosis or exacerbate pre-existing hyponatraemia. Hyponatraemia, accompanied by neurological symptoms (nausea, progressive disorientation, apathy) has been observed. Treatment with hydrochlorothiazide should only be started after correction of pre-existing hyponatraemia. In case severe or rapid hyponatraemia develops during Exforge HCT therapy, the treatment should be discontinued until normalisation of natraemia. All patients receiving thiazide diuretics should be periodically monitored for imbalances in electrolytes, particularly potassium, sodium and magnesium. Thiazide diuretics may precipitate azotaemia in patients with chronic kidney disease. When Exforge HCT is used in patients with renal impairment, periodic monitoring of serum electrolytes (including potassium), creatinine and uric acid serum levels is recommended. Hydrochlorothiazide has been associated with an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to a week of treatment initiation. Untreated acute-angle closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle closure glaucoma may include a history of sulphonamide or penicillin allergy. The safety of amlodipine in human pregnancy has not been established. Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function. Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality. The concomitant use of ARBs with other agents acting on the RAAS is associated with increase in incidence of hypotension, hyperkalaemia, and changes in renal function. Therefore monitoring of blood pressure, renal function and electrolytes is recommended. **INTERACTIONS:** Monitoring recommended when used concomitantly with lithium. Caution when used concomitantly with drugs that may increase potassium levels. Caution if combined with other antihypertensives, curare derivatives, NSAIDs, corticosteroids, ACTH, amphotericin, carbenoxolone, Penicillin G, salicylic acid derivatives, digoxin, CYP3A4 inhibitors and inducers, antidiabetic agents, allopurinol, probenecid, sulfinpyrazone, pressor amines, amantadine, diazoxide, cytotoxic drugs, anticholinergic agents, methyldopa, cholestyramine, colestipol resins, vitamin D, calcium salts, carbamazepine and ciclosporin, alcohol, anaesthetics and sedatives. Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required. There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g. rifampicin, *Hypericum perforatum*) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers. Co-administration of multiple doses of 10 mg amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine should be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia. Co-administration of rifampicin, ciclosporin or ritonavir may increase the systemic exposure to valsartan. Concomitant administration of thiazide diuretics with substances that also have a blood pressure lowering effect may potentiate orthostatic hypotension. Cisapride may decrease the bioavailability of thiazide-type diuretic. Thiazides may alter glucose tolerance, dose adjustment of the antidiabetic medicinal product may be necessary. Absorption of hydrochlorothiazide is decreased by cholestyramine or colestipol. The hyponatraemic effect of diuretics may be intensified by concomitant administration of medicinal products such as antidepressants, antipsychotics, antiepileptics, etc. Caution is indicated in long-term administration of these medicinal products. Due to the risk of hypokalaemia, hydrochlorothiazide should be administered with caution when associated with medicinal products that could induce *torsades de pointes*, in particular Class Ia and Class III antiarrhythmics and some antipsychotics. Thiazides potentiate the antihypertensive action of other antihypertensive drugs (e.g. guanethidine, methyldopa, beta blockers, vasodilators, calcium channel blockers, ACE inhibitors, ARBs and Direct Renin Inhibitors. Hydrochlorothiazide may reduce the response to pressor amines such as noradrenaline. The clinical significance of this effect is uncertain and not sufficient to preclude their use. Concomitant use of thiazide type diuretics may lead to hypercalcaemia in patients pre-disposed for hypercalcaemia (e.g. hyperparathyroidism, malignancy or vitamin-D-mediated conditions) by increasing tubular calcium reabsorption. Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects. **ADVERSE REACTIONS:** Agranulocytosis, bone marrow depression, Decrease in haemoglobin and in haematocrit, Haemolytic anaemia, Leukopenia, Neutropenia, Thrombocytopenia, sometimes with purpura, Aplastic anaemia, Hypersensitivity, Anorexia, Hypercalcaemia, Hyperglycaemia, Hyperlipidaemia, Hyperuricaemia, Hypochloraemic alkalosis, Hypokalaemia, Hypomagnesaemia, Hyponatraemia, Worsening of diabetic metabolic state, Depression, Insomnia/sleep disturbances, Mood swings, confusion, Coordination abnormal, Dizziness, Dizziness postural, dizziness exertional, Dysgeusia, Extrapyramidal syndrome, Headache, Hypertonia, Lethargy, Paraesthesia, Peripheral neuropathy, neuropathy, Somnolence, Syncope, Tremor, Hypoesthesia, Acute angle-closure glaucoma, visual disturbance, Visual impairment, Tinnitus, Vertigo, Palpitations, Tachycardia, Arrhythmias (including bradycardia, ventricular tachycardia, and atrial fibrillation), Myocardial infarction, Flushing, Hypotension, Orthostatic hypotension, Phlebitis, thrombophlebitis, Vasculitis, Cough, Dyspnoea, Respiratory distress, pulmonary oedema, pneumonitis, Rhinitis, Throat irritation, Abdominal discomfort, abdominal pain upper, Breath odour, Change of bowel habit, Constipation, Decreased appetite, Diarrhoea, Dry mouth, Dyspepsia, Gastritis, Gingival hyperplasia, Nausea, Pancreatitis, Vomiting, Hepatic enzyme elevation, including increase of serum bilirubin, Hepatitis, Intrahepatic cholestasis, jaundice, Alopecia, Angioedema, Cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, Erythema multiforme, Exanthema, Hyperhidrosis, Photosensitivity reaction, Pruritus, Purpura, Rash, Skin discoloration, Urticaria and other forms of rash, Vasculitis necrotising and toxic epidermal necrolysis, Exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, Arthralgia, Back pain, Joint swelling, Muscle spasm, Muscular weakness, Myalgia, Pain in extremity, Ankle swelling, Elevation of serum creatinine, Micturition disorder, Nocturia, Pollakiuria, Renal dysfunction, Renal failure acute, Renal failure and impairment, Impotence, Gynaecomastia, Abasia, gait disturbance, Asthenia, Discomfort, malaise, Fatigue, Non cardiac chest pain, Oedema, Pain, Pyrexia, Lipids increased, Blood urea nitrogen increased, Blood uric acid increased, Glycosuria, Serum potassium decreased, Serum potassium increased, Weight increase, Weight decrease. **LEGAL CATEGORY:** POM **PACK SIZES:** Packs of 28 film-coated tablets **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUHORISATION NUMBER:** Exforge HCT 5 mg/160 mg/12.5 mg - EU/1/09/569/002 Exforge HCT 10 mg/160 mg/12.5 mg - EU/1/09/569/014 **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: +35621222872 2013-MT-EXH-08-Aug-2013

PIERRE VASSALLO

Breast cancer imaging: ductal carcinoma in-situ (DCIS) - Part I

Ductal carcinoma in-situ (DCIS) is a noninvasive malignancy and a potential precursor to invasive cancer at pathologic analysis, DCIS shows proliferation of malignant epithelial cells that line the ducts (at the level of the terminal ductal–lobular unit) (Fig 1) without invasion through the basement membrane The detection rate of DCIS has increased markedly over the past two decades with the advent of breast cancer screening. Early detection and assessment of extent of DCIS is important for planning successful conservative breast surgery. Half the cases of recurrent DCIS are associated with invasive ductal cancer. In addition, 20% of patients with DCIS develop metastases within 10 years of initial diagnosis.

In the following article, we will review the findings of DCIS on mammography and breast ultrasound (US) and also discuss the role of breast Magnetic Resonance Imaging (MRI) for improved detection of DCIS.

Over 90% of cases of DCIS are detected as microcalcifications on mammography. These calcifications are calcified cellular debris or secretions within the intraductal lumen. The uneven calcification of the cellular debris explains the fragmentation and irregular contours of the calcifications.

Figure 2 shows the distinction between linear and rounded microcalcifications that helps distiguish acinar (mostly benign) from ductal (suspicious for malignancy)-type calcifications. Calcifications are extremely variable in size, density and form; they may be amorphous (*morphus* means form in Greek, amorphus means no particular form), pleomorphic (*pleo* is Greek for more or many forms), heterogeneous (mixed density), rounded, coarse (≥5mm) or fine (<5mm). Their distribution may be clustered, linear, or segmental (Fig 3). The diagnostic approach to breast calcifications is to analyze the morphology, distribution and sometimes change over time.

Pleomorphic calcifications distributed in a linear fashion or in a cluster (>5 calcifications in an area of 1cm diameter) should raise enough suspicion to advise biopsy (Fig 4). The presence of amorphous (Fig 5) or rounded calcifications in a linear or clustered distribution may also lead to biopsy, however the level of suspicion is lower in these instances. Dispersed or regional distribution of calcifications in one or both breasts or in multiple foci is usually indicative of benign disease (Fig 6). A segmental distribution of calcifications especially in the absence of pleomorphism is of indeterminate significance; in such situations or when calcifications are scanty in number, a close mammographic follow-up may be justified (Fig 7). Fine linear and branching calcifications, particularly when fragmented, require biopsy (Fig 8).

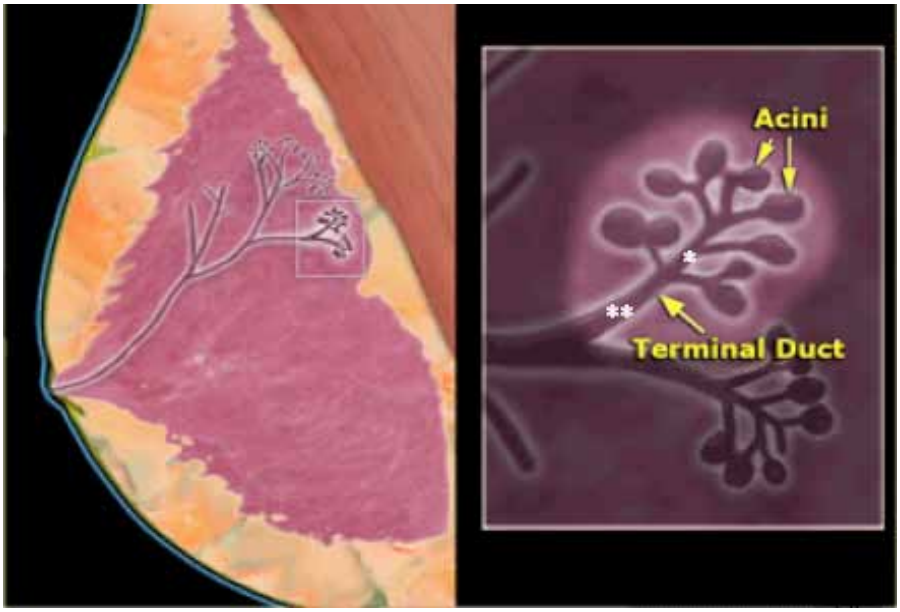

Figure 1. Terminal lobular ductal unit (highlighted) includes the terminal duct with extralobular (**) and intralobular (*) portions and the acini.

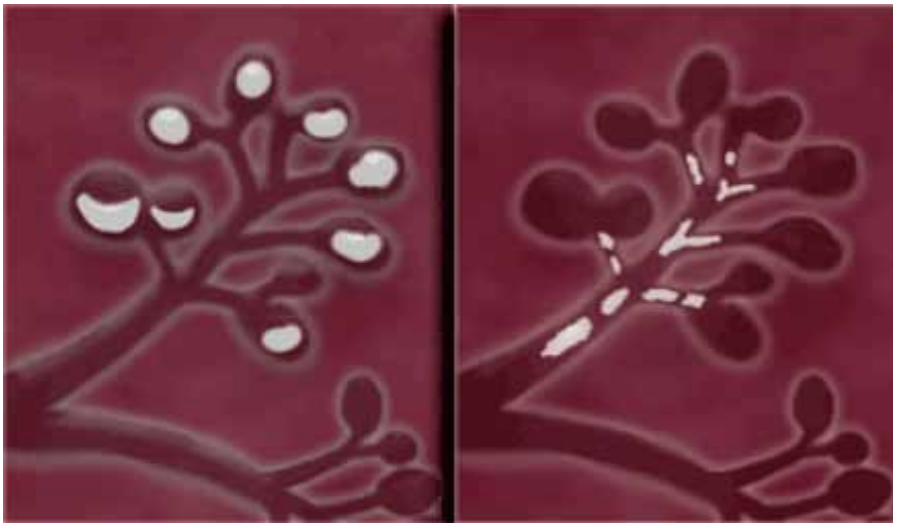

Figure 2. Calcifications may be classified as acinar (round or cresentic) or ductal (elongated, linear distribution).

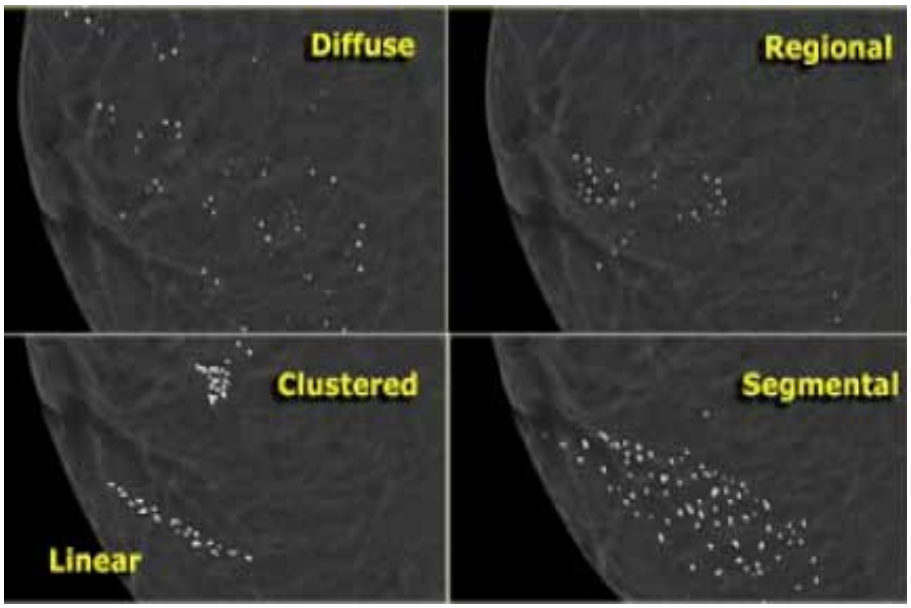

Figure 3. Distribution of calcifications may be diffuse, regional, segmental or clustered/linear.

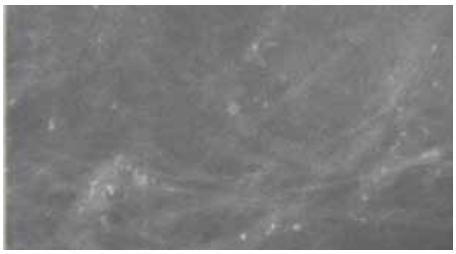

Figure 4. Mammogram showing pleomorphic calcifications in a linear distribution.

Figure 5. Mammogram showing amorphous calcifications in a clustered distribution.

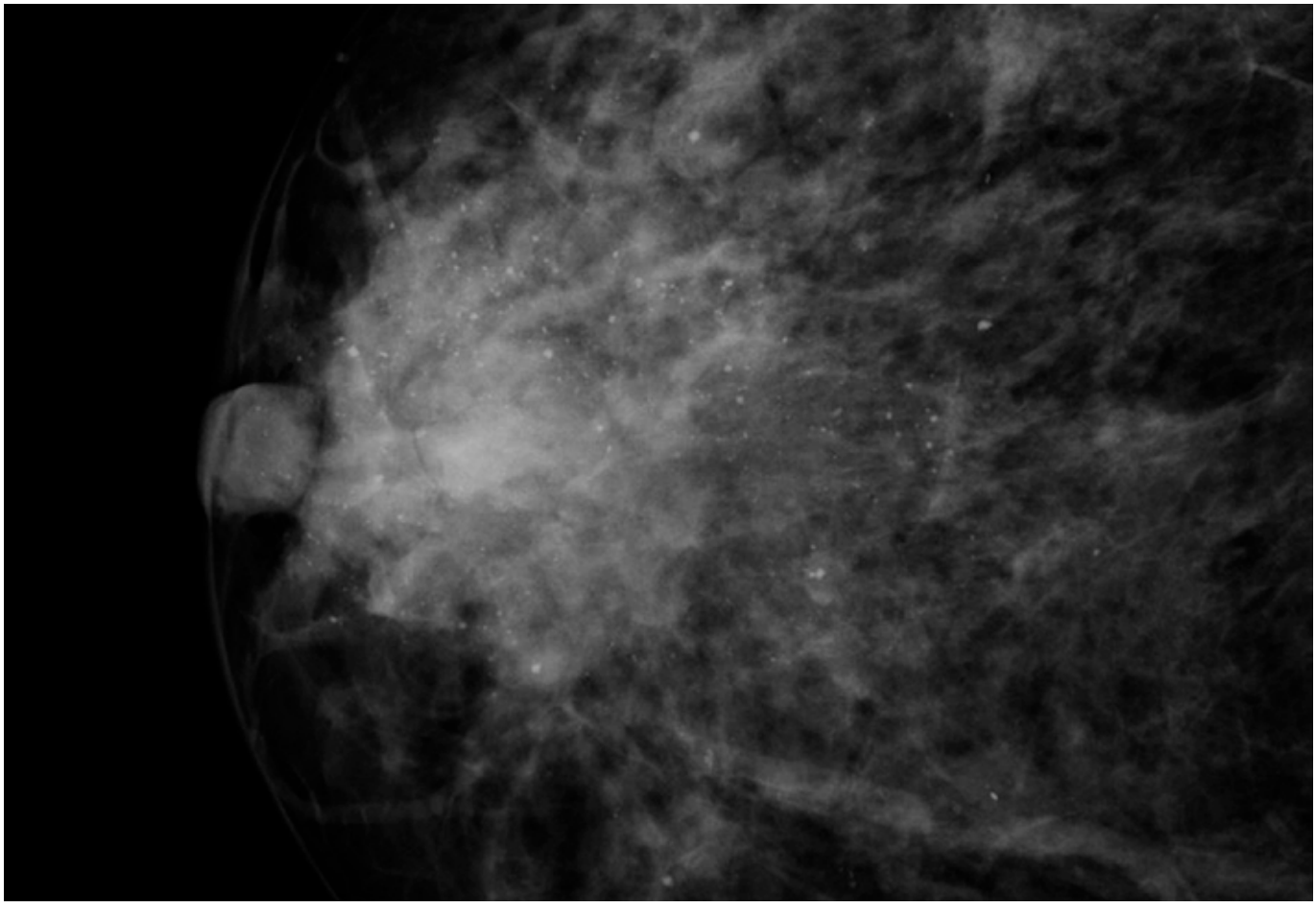

Figure 6. Mammogram showing dispersed calcifications.

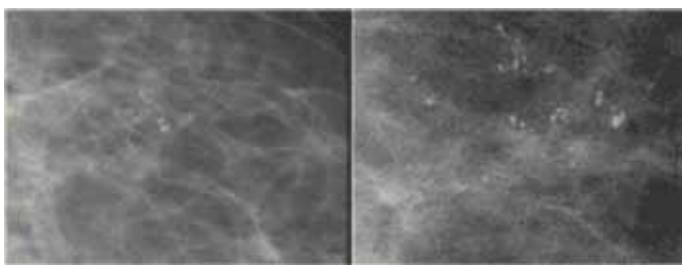

Figure 7. Mammographic follow-up of scanty calcifications; an increase in number of microcalcifications noted after 6 months should herald a biopsy.

Figure 8. Mammogram showing fine linear, branching and fragmented calcifications that are strongly indicative of malignant disease and required biopsy.

to be continued

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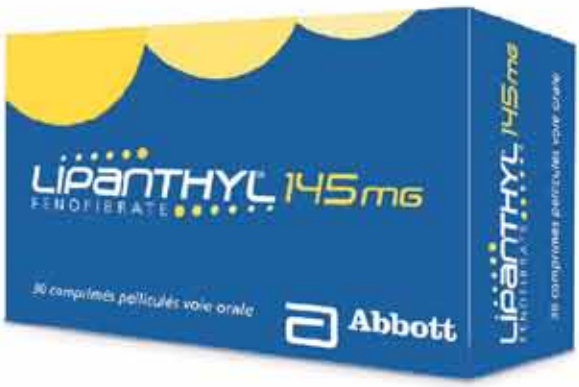

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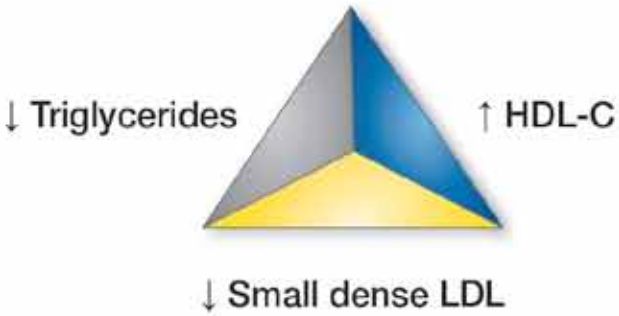

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References:
1. Accord Study Group. *N Eng J Med*. 2010;362:1563-74.
2. Lipanthyl Summary of Product Characteristics.

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