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thesynapse

THE MEDICAL PROFESSIONALS' NETWORK

Postmenopausal Bleeding

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Role of Hop Extract in Menopause

Cervical Cyto/Histological Nomenclature

Staging Cancer of the Uterine Cervix

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Presentation: Each film-coated tablet of Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg contains sacubitril and valsartan respectively (as sacubitril valsartan sodium salt complex).

Indications: In adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

Dosage & administration: The recommended starting dose of Entresto is one tablet of 49 mg/51 mg twice daily, doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient. In patients not currently taking an ACE inhibitor or an ARB, or taking low doses of these medicinal products, a starting dose of 24 mg/26 mg twice daily and slow dose titration (doubling every 3 - 4 weeks) are recommended. A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg, moderate or severe renal impairment (use with caution in severe renal impairment) and moderate hepatic impairment. Do not co-administer with an ACE inhibitor or an ARB. Do not start treatment for at least 36 hours after discontinuing ACE inhibitor therapy. Entresto may be administered with or without food. The tablets must be swallowed with a glass of water. Splitting or crushing of the tablets is not recommended.

Contraindications: Hypersensitivity to the active substances or to any of the excipients. Concomitant use with ACE inhibitors. Do not administer until 36 hours after discontinuing ACE inhibitor therapy. Known history of angioedema related to previous ACE inhibitor or ARB therapy. Hereditary or idiopathic angioedema. Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m²). Severe hepatic impairment, biliary cirrhosis and cholestasis. Second and third trimester of pregnancy.

Warnings/Precautions: Dual blockade of the renin angiotensin-aldosterone system (RAAS): Combination with an ACE inhibitor is contraindicated due to the increased risk of angioedema. Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with sacubitril/valsartan is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan. Combination of Entresto with direct renin inhibitors such as aliskiren is not recommended. Entresto should not be co administered with another ARB containing medicinal product. Hypotension: Treatment should not be initiated unless SBP is ≥100 mmHg. Patients with SBP <100 mmHg were not studied. Cases of symptomatic hypotension have been reported in patients treated with sacubitril/valsartan during clinical studies, especially in patients ≥65 years old, patients with renal disease and patients with low SBP (<112 mmHg). Blood pressure should be monitored routinely when initiating or during dose titration with sacubitril/valsartan. If hypotension occurs, temporary down-titration or discontinuation of sacubitril/valsartan is recommended. Impaired or worsening renal function: Limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m²). There is no experience in patients with end-stage renal disease and use of sacubitril/valsartan is not recommended. Use of sacubitril/valsartan may be associated with decreased renal function, and down-titration should be considered in these patients. Impaired renal function: Patients with mild-moderate renal function are more at risk of developing hypotension while patients with severe renal impairment may be at a greater risk of hypotension. sacubitril/valsartan is not recommended in patients with end-stage renal disease. Hyperkalaemia: Treatment should not be initiated if the serum potassium level is >5.4 mmol/l. Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists. If clinically significant hyperkalaemia occurs, consider adjustment of concomitant medicinal products or temporary down-titration or discontinuation . If serum potassium level is >5.4 mmol/l discontinuation should be considered. Angioedema: Angioedema has been reported with sacubitril/valsartan. If angioedema occurs, discontinue sacubitril/valsartan immediately and provide appropriate therapy and monitoring until complete and sustained resolution of signs and symptoms has occurred. It must not be re administered. Patients with a prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if Entresto is used in these patients. Black patients have an increased susceptibility to develop angioedema. Patients with renal artery stenosis: Caution is required and monitoring of renal function is recommended. Patients with NYHA functional classification IV: Caution should be exercised due to limited clinical experience in this population. Patients with hepatic impairment: There is limited clinical experience in patients with moderate hepatic impairment (Child Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Caution is therefore recommended in these patients. B-type natriuretic peptide (BNP): BNP is not a suitable biomarker of heart failure in patients treated with sacubitril/valsartan because it is a neprilysin substrate. Psychiatric disorders: Psychiatric events such as hallucinations, paranoia and sleep disorders, in context of psychotic events, have been associated with sacubitril/valsartan use. If a patient experiences such events, discontinuation of sacubitril/valsartan treatment should be considered.

Interactions: Contraindicated with ACE inhibitors, 36 hours washout is required. Use with aliskiren contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m²). Should not be coadministered with another ARB. Use with caution when co-administering sacubitril/valsartan with statins or PDE5 inhibitors. No clinically relevant interaction was observed when simvastatin and sacubitril/valsartan were co-administered. Monitoring serum potassium is recommended if sacubitril/valsartan is co-administered with potassium-sparing diuretics or substances containing potassium (such as heparin). Monitoring renal function is recommended when initiating or modifying treatment in patients on sacubitril/valsartan who are taking NSAIDs concomitantly. Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists including sacubitril/valsartan. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. Co-administration of sacubitril/valsartan and furosemide reduced C_{max} and AUC of furosemide by 50% and 28%, respectively, with reduced urinary excretion of sodium. Co-administration of nitroglycerin and sacubitril/valsartan was associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitroglycerine alone, no dose adjustment is required. Co administration of sacubitril/valsartan with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) may increase the systemic exposure of LBQ657 or valsartan. Appropriate care should be exercised. Co-administration of sacubitril/valsartan with metformin reduced both C_{max} and AUC of metformin by 23%. When initiating therapy with sacubitril/valsartan in patients receiving metformin, the clinical status of the patient should be evaluated.

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Undesirable effects: *Very common (≥1/10)*: Hyperkalaemia, hypotension, renal impairment. *Common (≥1/100 to <1/10)*: Anaemia, hypokalaemia, hypoglycaemia, dizziness, headache, syncope, vertigo, orthostatic hypotension, cough, diarrhoea, nausea, gastritis, renal failure, acute renal failure, fatigue, asthenia. *Uncommon (≥1/1,000 to <1/100)*: Hypersensitivity, postural dizziness, pruritis, rash, angioedema.

Packs sizes: Entresto 24 mg/26 mg – x28 tablets; Entresto 49 mg/51 mg – x28 tablets; Entresto 97 mg/103 mg - x28 & x56 tablets.

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Marketing Authorisation Holder: Novartis Europharm Ltd, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland.

Marketing Authorisation Numbers: Entresto 24 mg/26 mg film coated tablets EU/1/15/1058/001; Entresto 49 mg/51 mg film coated tablets EU/1/15/1058/002-004; Entresto 97 mg/103 mg film coated tablets EU/1/15/1058/005-007.

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

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Issue Guide

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Front photo:
Project double exposure,
Martin Agius

The award winning image by Martin Agius, sets the mood for the prevailing situation in many aspects of life including Covid and the natural evolution of any phase of life that comes to an end as part of natural evolution.

In 2012 he obtained an Associateship with the Malta Institute of the Professional Photography (MIPP) and subsequently abroad with the Societies' Photographic Society in the UK (SWPP). Martin was awarded the Societies prestigious UK Press & News Photographer of the Year.

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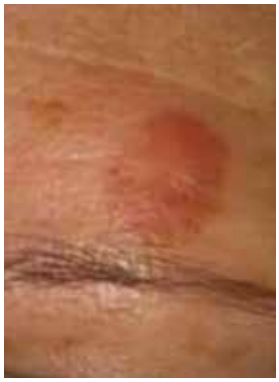

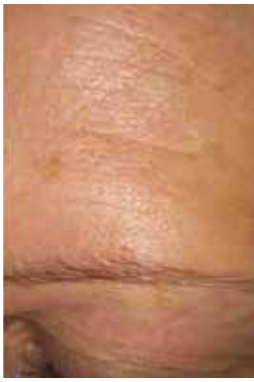

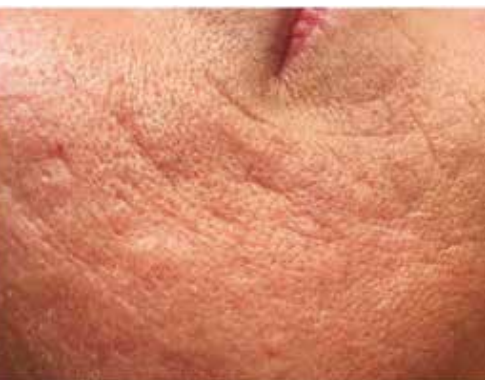

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DR CLIFTON GRIMA
Minister for Education,
Sports, Youth, Research and Innovation

Shaping the Future through R&I

Research and Development (R&D) is defined as innovative work undertaken on a systematic basis to increase the stock of knowledge, including knowledge of mankind, the environment and society, and the use of this stock of knowledge to devise new applications and services, by way of potential solutions to societal challenges.

The Maltese Government is cognisant of the fact that research and innovation (R&I) plays a crucial role in supporting economic growth, and this administration, through its electoral manifesto, has reiterated its commitment to putting R&I at the heart of Malta's future growth and prosperity.

Through the Malta Council for Science and Technology (MCST), we are currently in the process of finalising the draft R&I Strategic Plan, with a view to launch for public consultation in the coming weeks. The draft R&I Strategic Plan sets out the priorities over the coming years, most notably that of strengthening the governance of R&I in our country. This forward-looking Strategic Plan draws on current context as well as performance and progress on the goals set in the previous Strategy.

Strengthening R&I governance makes sense on many levels. It sends the right signals to the researcher community, whether in the public or private sphere. It signals that research is important for Malta's future prosperity. It underscores that research is not only a vibrant economic sector in itself, but it can also act as an enabler for further economic growth and social wellbeing across all economic sectors – from agriculture to transport to tourism and health. It signals that we need to change the narrative and challenge the common mentality surrounding R&I locally.

For us, research and innovation will act as central plank for further diversifying Malta's economy and thus enhancing our resilience as we transition into a new post-COVID reality. For this reason, I believe that we have an urgent need to use R&I effectively to increase the resilience of our economy, public services, business and society. This is in turn dependent on the championing of R&I at the highest levels in Government and Parliament. The mentioned draft plan gives priority to putting in place effective structures and a robust policy design, addressing five main overarching goals: governance and priority-setting, enhanced directionality, local ecosystem development for enhanced performance in the private sector, mainstreaming R&I in public policy, and strengthening implementation structures.

We also need to ensure that the targets for increasing public and private sector R&I investments are met, with an emphasis on the green and digital transitions. For this purpose, we need to further empower both the public and private sector, with the necessary capacities to better undertake research performing endeavours in the coming years. Such a vision can be achieved through a "whole-of-government" approach to research and innovation.

In order to upgrade and modernize Malta's national Research and Innovation (R&I) framework, this Government has adopted a new Smart Specialization Strategy, which will also facilitate access to EU funding for R&I in selected economic sectors. The priority areas covered by the Smart Specialisation Strategy are health and wellbeing, smart manufacturing, marine and maritime technologies, sustainable use of resources and aviation and aerospace. The Strategy will ensure access to the required R&I funding support to strengthen research in the six thematic areas identified and guarantee the continuity of the necessary investments throughout the lifecycle of the strategy.

This Strategy provides, amongst others, a particular focus on fostering business R&I, strengthening public-private cooperation, inter-agency collaboration, raising awareness of R&I funding, and simplification of related procedures. The anticipated benefits of this Strategy are expected to be the better targeting of holistic efforts, increased transformation of research findings into marketable solutions as well as building competitive advantage in the selected niches.

The massive increase in the budget of Horizon Europe, administered locally by MCST, undoubtedly the most ambitious EU funding program for research and innovation ever and the largest transnational programme of its kind worldwide, which now totals the amount of €95.5 billion, gives a clear political message at a European level that Research and Innovation are the key factors to drive our future. Our ambition locally is equally ambitious. Through our reinvigorated R&I policy framework, we shall strive to ensure that Malta can sustain and further develop a vibrant and internationally attractive R&I eco-system.

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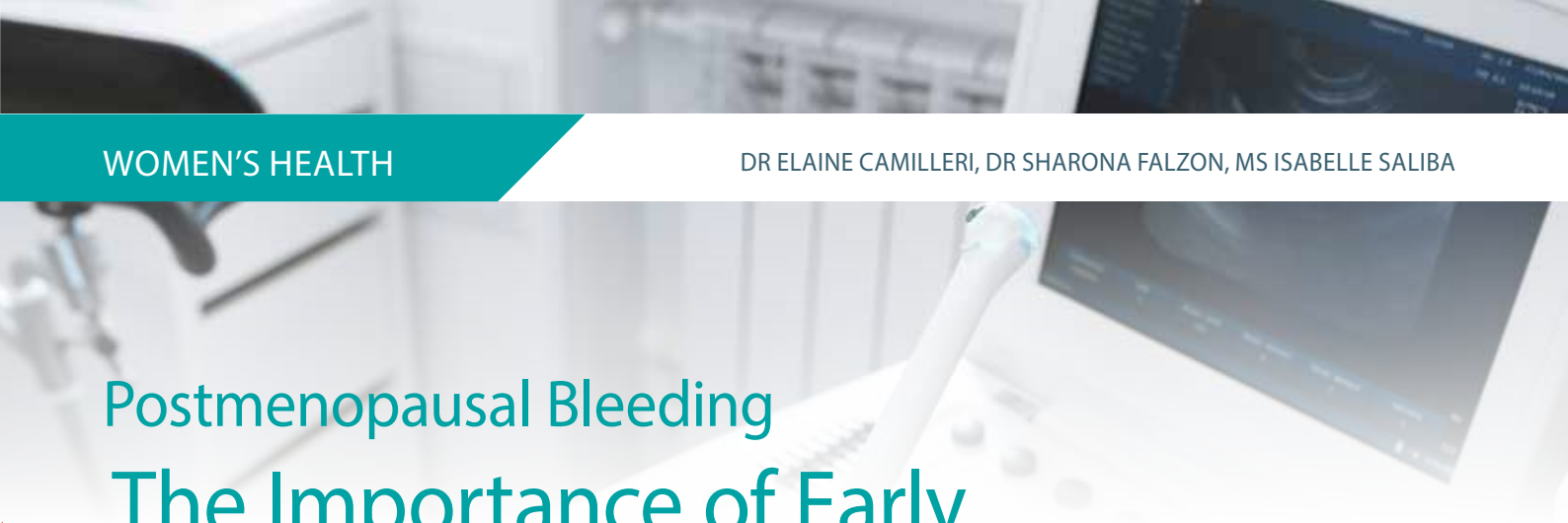

Postmenopausal Bleeding

The Importance of Early Diagnosis in Improving Prognosis

ABSTRACT

Postmeopausal bleeding (PMB) is defined as vaginal bleeding that occurs at least twelve months after a woman's last period. It is a common complaint with a broad differential diagnosis but endometrial cancer must be excluded. About 10% of women over 55 years who present with PMB are at risk of gynaecological cancer and should be investigated promptly. This article highlights the importance of timely diagnosis by healthcare professionals to improve the prognosis of patients with malignant aetiologies. Mater Dei Hospital has a specific fast track clinic for patients with PMB which ensures that patients are seen in a timely manner.

KEYWORDS

Postmenopausal bleeding (PMB), endometrial cancer, endometrial hyperplasia, transvaginal ultrasound.

INTRODUCTION

Menopause is the time in a woman's life when fertility naturally wanes. The average age is around 51 years when the oestrogen levels decline leading to cessation of menstrual periods. It is a retrospective diagnosis, as it can only be confirmed after 12 months of amenorrhoea from the last menstrual period. PMB is defined as bleeding after this time period and it should be investigated. It is a common complaint and its differential diagnosis includes physiological changes of the reproductive tract, benign conditions, as well as malignant conditions. Endometrial cancer is the most common gynaecological malignancy.

This often presents at an early stage when it is possibly curative. Hence, early diagnosis is crucial for a good prognosis.

AETIOLOGY

PMB can be caused by both benign or malignant, gynaecological or non-gnyaecological aetiologies, The most common cause of PMB or spotting is endometrial or vaginal atrophy (also referred to as non-infective endometritis or vaginitis). This is part of the physiological changes that happen in the reproductive tract as the oestrogen levels decline during menopause.

Causes of PMB include the following:

- Polyps which can occur in the endometrium or cervix. They bleed secondary to venous stasis and apical necrosis caused by stromal congestion.
- Endometrial hyperplasia.
- Malignancy: Bleeding secondary to vascular fragility or invasion of the cancer into nearby vessels. In this case PMB is usually attributed to an intrauterine malignancy but any cancer along the genital tract can give rise to PMB: cervical, endometrial, fallopian tube, ovarian, vaginal and vulvar carcinomas.
- Infection along the genital tract cause inflammation and irritation that leads to bleeding.
- Medications such as tamoxifen, and hormone replacement therapy (HRT), as well as herbal supplements (phytoestrogens) may stimulate proliferation of the endometrial lining and subsequently result in bleeding. Antithrombotic therapy may increase the bleeding risk as well.
- Insertion of foreign bodies such as pessaries may cause abrasions resulting in bleeding.

The etiology of bleeding may also be non-gynaecologic i.e. disease in adjacent structures may be mistaken for vaginal bleeding. Bleeding from the urethra (caruncle, diverticulum, urethritis), from bladder (cystitis, malignancy or renal disease leading to hematuria) as well as from bowel (fissures, polyps, colitis, haemorrhoids and malignancy).[1]

EPIDEMIOLOGY

About 4-11% of postmenopausal women report vaginal bleeding.[1] Of these, around 5% present to their gynaecologist and only 10% of those that present to their gynaecologist have endometrial cancer.[1]

91% of cases of endometrial cancer occur in postmenopausal women. Most cases of endometrial carcinoma are adenocarcinomas in origin and are

associated with exposure of oestrogen unopposed by progesterone. It is the most common gynaecological malignancy in women. Risk factors include nulliparity, anovulatory cycles such as polycystic ovarian syndrome, obesity, type 2 diabetes mellitus and hypertension, genetic syndromes such as Lynch syndrome and exogenous unopposed oestrogens.

DIAGNOSIS

A comprehensive history is key to understanding PMB, and menopausal status should be established first. Risk factors for adenocarcinoma should be explored in the medical history. Clinical examination allows a thorough evaluation of the internal and external anatomy of the genital tract. A bleeding site may be identified such as lacerations or lesions on the anus, urethra, external genitalia or cervix. A smear test is recommended even if older than 65 years of age.

In addition to clinical evaluation, a transvaginal ultrasound (TVUS) is the initial investigation of choice.[2] Endometrial thickness (ET) measures the anterior-posterior length of maximal endometrial echo thickness in the long axis view of the uterus. TVUS can also identify adnexal pathology and leiomyomas. An ET equal to or less than 4 mm on scan has a negative predictive value approximately 96-99%. Hence, endometrial sampling is not required below this cut-off value, unless symptoms are recurrent.[3]

Endometrial sampling is necessary if the TVUS shows (in symptomatic women):

1. An ET >4 mm.
2. Increased echogenicity or heterogeneity on scan (both diffuse or locally).
3. Endometrium is not visualised properly.
4. Patients with persistent PMB even if ET <4 mm.

The American College of Obstetricians and Gynaecologists also suggests that in patients with a higher pretest probability for malignancy, endometrial sampling can be used first rather than ultrasound. This is because the 4 mm ET threshold may miss endometrial cancer in 1 in 339 patients.[2,3]

ACCURACY OF ENDOMETRIAL SAMPLING

The accuracy of endometrial sampling correlates with the amount of tissue obtained. Several methods have been used but dilation and curettage is the one which has been most widely used. It is around 90% sensitive.[4] However, less invasive outpatients methods include hysteroscopic biopsies using the Pipelle device or Vabra aspirator. These are very sensitive, with detection rates of 99.6% and 97.1%, respectively.[4,5]

Women with an insufficient sample on biopsy can be reassured and discharged only if there is hysteroscopic evidence of endometrial atrophy and a negative scan (ET less than or equal to 4 mm). Re-investigation is necessary if symptoms recur (for example there may be failure of detection of a small polyp in an atrophic endometrium due to the low cell yield in the sample) (Figure 1).

On the other hand all women with an insufficient sample which have hysteroscopic or ultrasonographic evidence of endometrial thickening or had a recurrent PMB should have an inpatient hysteroscopy and endometrial sampling (Figure 1).[3]

Hysteroscopy allows direct macroscopic visualisation of abnormal endometrium and samples are obtained directly from the lesion.

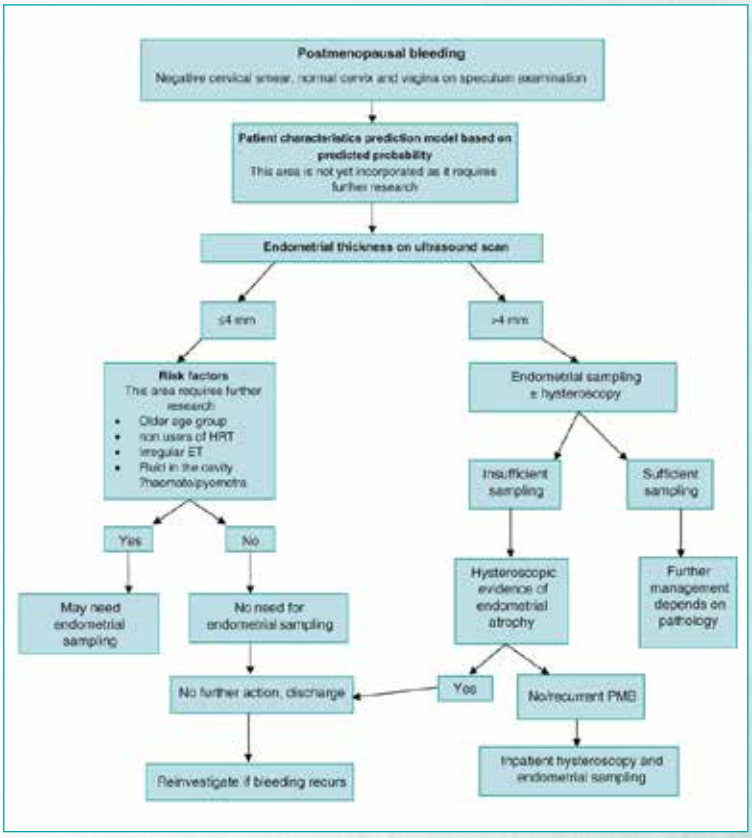

Figure 1: Scheme summarizing the immediate and long-term effect of estrogen decline during menopause.[2]

Decisions about further investigations should be taken on a case by case basis and risk factors for endometrial cancer should be considered. Indeed, current literature states that asymptomatic ET between 8 to 11 mm in postmenopausal women is not abnormal in the first year after the last menstrual period since the endometrium may be thicker secondary to some residual hormonal activity.[6]

Other positive findings on TVUS in asymptomatic women (i.e do not present with PMB) that should be referred for further investigations include inhomogeneous endometrium, ET >11 mm, particulate fluid and increased vascularity.[1]

An effective method for investigating asymptomatic postmenopausal women with an ET of >6 mm is hysteroscopy as the commonest pathology in these cases is endometrial polyps.[5]

MANAGEMENT

The aetiology of PMB dictates the management.

Vaginal atrophy is usually self-limiting but may be treated with vaginal oestrogen or lubricants.

Polyps should be removed hysteroscopically. Polyps are often benign but in 5% cases hyperplasia or malignancy may be found.

Endometrial hyperplasia is classified as hyperplasia with or without atypia. In hyperplasia without atypia the risk of progressing to malignancy is less than 5% over 20 years and most cases regress spontaneously. Observation alone with regular biopsies for follow-up is advised, especially if reversible factors are identified, such as obesity and HRT. However, progesterone treatment (oral or intrauterine for at least 6 months) is indicated in women who, despite observation and follow-ups, failed to regress or are symptomatic with abnormal bleeding. On the other hand, in hyperplasia with atypia, hysterectomy with bilateral salpingo-oophorectomy is the best treatment option. If women are not fit for surgery or they want to preserve fertility, a pretreatment evaluation should be performed to rule out invasive cancer or pre-existing ovarian pathology. First line is intrauterine levonorgestrel, and oral progestogens are the second best option. Once fertility preservation is not an issue then hysterectomy should be offered.[7]

In endometrial carcinoma hysterectomy with bilateral salpingo-oophorectomy followed by staging is recommended. In some circumstances, omentectomy is required. Conservative medical management is the same as above. In advanced cases, palliation of symptoms using high-dose progesterone and external beam radiotherapy to control bleeding should be used.

Fast track PMB clinic in Mater Dei Hospital

Mater Dei Hospital Gynaecology outpatients offers a Fast-track clinic service. The aim of this PMB clinic is to provide the highest quality, evidence-based service for all women presenting with PMB. Referrals to this clinic have to be vetted within 2 weeks. The healthcare professionals in this clinic will perform history taking, preliminary diagnostic investigations (including a TVUS and if the ET is more than 4 mm, endometrial biopsies are performed using a pipelle), counselling and continuing management. An outpatient follow-up appointment is then arranged for the histology result. Our patients benefit from early diagnosis and reduced number of appointments and clinic visits.

Competing interests and funding statements

There are no competing interests to declare. No funding has been received.

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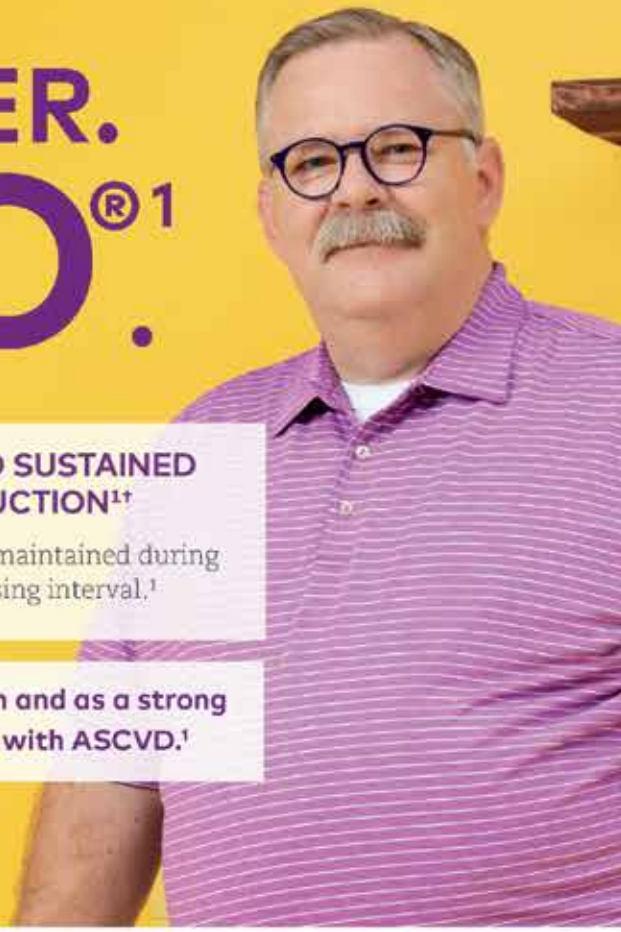

TWO DOSES A YEAR[1*]

*LEQVIO is dosed initially, again at 3 months, and then once every 6 months.[1]

EFFECTIVE AND SUSTAINED LDL-C REDUCTION[1†]

†LDL-C reduction was maintained during each 6-month dosing interval.[1]

Choose LEQVIO first for effective and sustained LDL-C reduction and as a strong complement to a maximally tolerated statin for your patients with ASCVD.[1]

LEQVIO®

PRESENTATION: Leqvio 284 mg solution for injection in prefilled syringe. Each pre-filled syringe contains inclisiran sodium equivalent to 284 mg inclisiran in 1.5 ml solution. Each ml contains inclisiran sodium equivalent to 189 mg inclisiran.

INDICATION: Leqvio is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet: in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

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

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

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

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

PREGNANCY, LACTATION AND FERTILITY: ♦There are no or limited amount of data from the use of inclisiran in pregnant women. As a precautionary measure, it is preferable to avoid the use of inclisiran during pregnancy. ♦It is unknown whether inclisiran is excreted in human milk. A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from inclisiran therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman. ♦ No data on the effect of inclisiran on human fertility are available.

ADVERSE REACTIONS: *Common*: Adverse reactions at the injection site.

LEGAL CATEGORY: POM PACK SIZES: Pre-filled syringe: x1 pre-filled syringe. Pre-filled syringe with needle guard: x1 prefilled syringe with needle guard.

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

MARKETING AUTHORISATION NUMBER: EU/1/20/1494/001-2

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.

2022-MT-LEQ-24-MAR-2022

References: 1. Novartis Europharm Ltd. Leqvio Summary of Product Characteristics.

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LEQVIO® inclisiran

DR PATRICK CHOUEIRY

Role of Hop Extract in Menopause

THE BURDEN OF MENOPAUSE

Hot flashes and vasomotor symptoms occur in approximately 75% of women during perimenopause and in most women these last for one to two years after menopause, however they can continue up to 10 years or more.[1] Additionally, long-term consequences of the lack of estrogenic stimulation are increased risk of atherosclerosis, decrease in bone density, and progressive development of osteoporosis.[2]

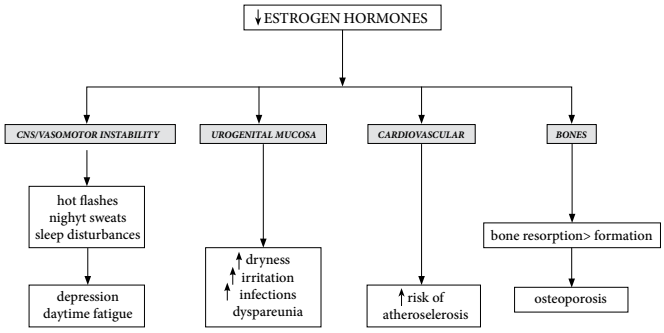


Figure 1: Scheme summarizing the immediate and long-term effect of estrogen decline during menopause.[2]

Clearly, the symptoms resulting from estrogen deficiency during menopause can exert a detrimental effect on women's health and their quality of life and thus require appropriate management. It is generally recognized that postmenopausal hormone therapy (HT - previously and commonly known as hormone replacement therapy or HRT) is the most efficient way for the relief of climacteric discomforts and symptoms.[3]

However, downsides to this form of hormonal therapy include serious adverse events. Indeed, the heart and estrogen/progestin replacement study (HERS) demonstrated an increase of cardiovascular (CVD) events in post-menopausal women in the first year.[4] Similarly, results from the highly publicized women's health initiative study (WHI) showed that HRT can increase the risk of various health issues such as breast cancer, endometrial and ovarian cancer, thromboembolism disorders, stroke and coronary heart disease in this population of women. Despite the many sub-analysis of data from this large study showing a positive benefit-risk ratio from HRT in the majority of patients, the widespread publicity of the WHI study led many women to discontinue the use of HRT and look for other alternatives to overcome their menopausal condition.[5]

PHYTOESTROGENS AS ALTERNATIVE TO HRT

Indeed, during the past 15 years, growing attention has been paid to the use of herbal medicines and food supplements for the management of menopausal symptoms.[6] Plant extracts with potential estrogenic activities include soy, red clover, kudzu, licorice, rhubarb, yam, chasteberry and hops.[7] The extracts with estrogenic properties found in these plants are called phytoestrogens.

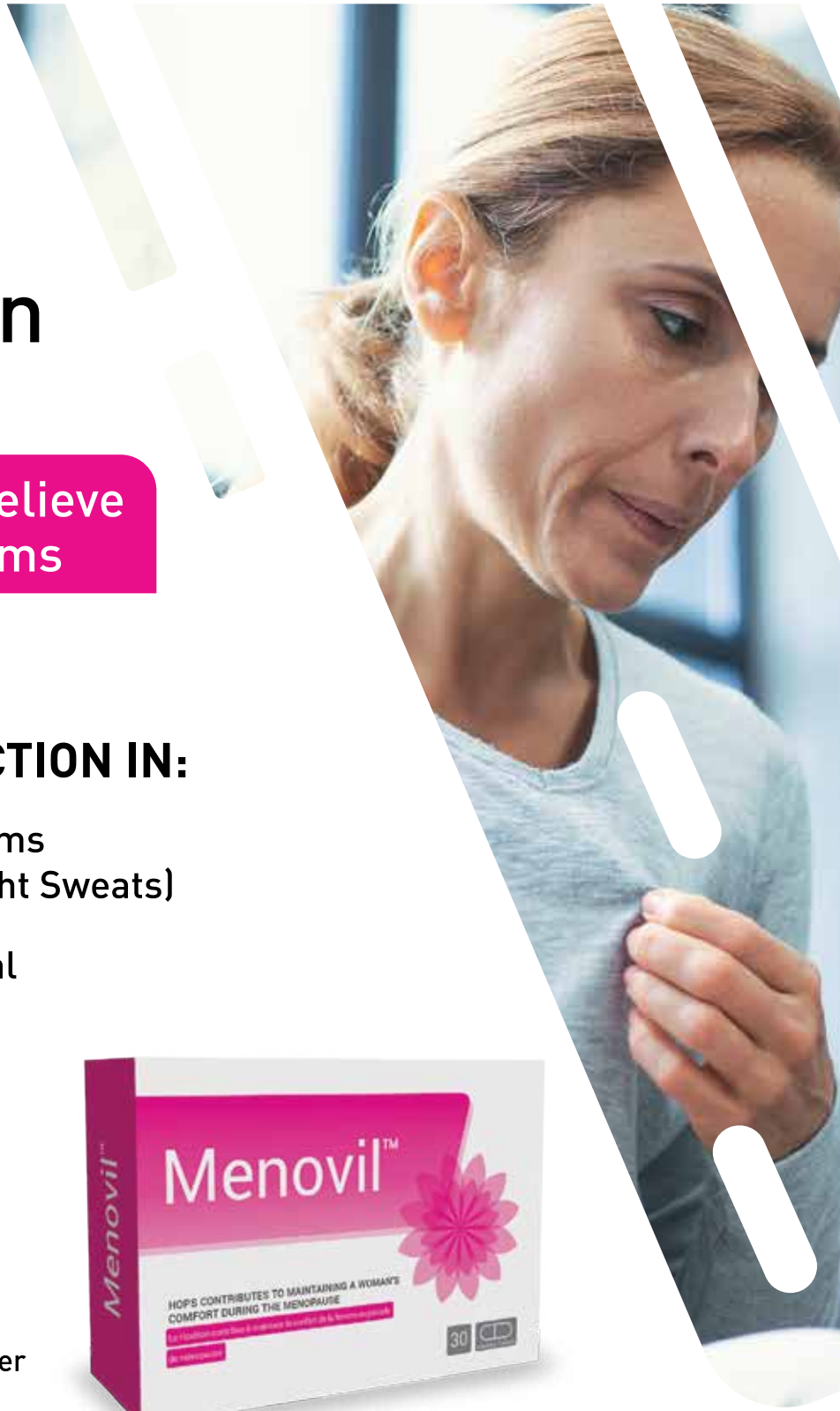
Hop (Humulus lupulus L.) is a key ingredient for beer brewing.[8] It is also a source of many biologically active molecules including 8-prenylnaringenin (8-PN), 6-prenylanaringenin (6-PN), 6,8-diprenylnaringenin (6,8-DPN) and 8-geranylnaringenin (8-GN). These biologically active compounds are fundamental for the potent estrogen activity of hops. However, the remarkable compound 8-PN, which structurally belongs to the group of prenylated flavonoids, is the strongest known phytoestrogen.[2]

8-PN has a higher affinity for estrogen receptors alpha, ERβ, where it is 70 times weaker than estradiol. However, it was reported that 8-PN is 20,000 times weaker than estradiol for the binding affinity to estrogen receptor beta, ERβ.[8] The majority of known phytoestrogens have a higher affinity for the ERβ receptor while 8-PN binds mainly to ERβ, the receptor responsible for decreasing vasomotor symptoms when activated. 8-PN has approximately 20 to 300 times higher affinity to ERβ compared to the isoflavones genistein and daidzein,[8,9] two commonly used phytoestrogens in the management of menopause and found in red clover.

CLINICAL EFFICACY OF HOP IN RELIEVING VASOMOTOR SYMPTOMS

How does this in vitro potency translate into clinical efficacy? The first prospective clinical study assessing the effectiveness of a hop extract against climacteric complaints included 67 women between 45 and 60 years of age who were treated for 12 weeks with capsules containing either placebo or the hop extract (100µg of 8-PN).[10] The responses were determined by means of a modified Kupperman index (KI) and a patients' questionnaire. The KI is a scale indicating the severity of the most common menopausal symptoms. The decrease in hot flushes score (isolated from the KI) was found significant for the hop treatment group after 6 weeks ($P<0.01$) compared to placebo.

Menovil™



THE RIGHT Combination Matters

Efficiently helps to relieve Menopausal symptoms

SIGNIFICANT REDUCTION IN:

- Vasomotor symptoms (Hot Flashes & Night Sweats)
- Physical and Mental fatigue
- Vaginal dryness

Recommended Dosage:
1 capsule a day with a glass of water

References:
1. M. Origoni, C. et al. Hyaluronic acid improves VVA symptoms. European Review for Medical and Pharmacological Sciences. 2016; 20: 4190-4195. 2. Stute P. Is vaginal hyaluronic acid as effective as vaginal estriol for vaginal dryness relief? Arch Gynecol Obstet. 2013 Dec;288(6):1199-201. 3. Marie-Anne Milesi et al. Effect of an oral supplementation with a proprietary melon juice concentrate (Extramel®) on stress and fatigue in healthy people: a pilot, double-blind, placebo-controlled clinical trial. Nutrition Journal 2009, 8:40. 4. Aghamiri V et al. The effect of Hop (Humulus lupulus L.) on early menopausal symptoms and hot flashes: A randomized placebo-controlled trial. Complement Ther Clin Pract. 2016 May;23:130-5. 5. Heyerick et al. A first prospective, randomized, double-blind, placebo-controlled study on the use of a standardized hop extract to alleviate menopausal discomforts. Maturitas. 2006;54(2):164-75. 6. Erkkola.R et al, A randomized, double-blind, placebo-controlled, cross-over pilot study on the use of a standardized hop extract to alleviate menopausal discomforts.Phytomedicine. 2010 May;17(6):389-96. 7. S. Bommer et.al, First Time Proof of Sage's Tolerability and Efficacy in Menopausal Women with Hot Flushes Adv Ther (2011) 28(6):490-500. 8. L.P. Madhubhani P et al. Hops (Humulus lupulus) Inhibits Oxidative Estrogen Metabolism and Estrogen-Induced Malignant Transformation in Human Mammary Epithelial cells (MCF-10A). Cancer Prev Res 2011; 5(1); 73–81. 9. Assessment report on Humulus lupulus L., flos EMA/HMPC/418902/2005. 10. Keiler AM et al. Hop Extracts and Hop Substances in Treatment of Menopausal Complaints, Planta Med 2013; 79: 576–579. 11. L. R. Chadwick, G. F. Pauli, and N. R. Farnsworth. The pharmacognosy of Humulus lupulus L. (hops) with an emphasis on estrogenic properties. Phytomedicine. 2006 Jan; 13(1-2): 119–131.

SURVEAL

The same group of investigators repeated the efficacy study of hop extracts on another number of menopausal women four years later, using a crossover prospective randomized placebo-controlled study model.[11] Capsules containing standardized hop extract (100μg 8-PN) was administered to a group of 36 menopausal women for a period of 8 weeks. For a further 8 weeks, the treatment method was switched from active treatment to placebo, and vice versa. Efficacy and severity of symptoms were assessed using the KI, the Menopause Rating Scale (MRS) and a multifactorial Visual Analogue Scale (VAS). After 16 weeks, only the hop active treatment, after placebo, reduced all outcome measures, whereas placebo after active treatment did not result in a reduction in symptoms. Time-specific estimates of treatment efficacy indicate significant reductions for KI ($p = 0.02$) and VAS ($p = 0.03$), however the symptoms assessed by MRS showed a marginally significant reduction ($p=0.06$)

In 2016, another randomized placebo-controlled trial was carried on 120 peri- and post-menopausal women aged 40-60 years where the assessment of symptoms improvement was carried out using the changes in total Greene Climacteric Scale score over a period of 12 months.[12]. The patients were randomly allocated into two groups, receiving the hop or placebo tablets for 12 weeks. Some of the women experienced premenopausal hot flashes with less than 12 menstrual bleedings within the past 12 months, and the selection parameter for post-menopausal women was a minimum of one year and maximum of 5 years after the last menstruation. At the end of the study the mean Greene score was significantly lower in the hop group than the placebo group at the end of weeks 4 and 12 and the number of hot flashes was significantly lower in the hop group than the control group during the weeks 4 and 12. Hop also decreased significantly all the variables at weeks 4, 8 and 12 such as the psychiatric symptoms for anxiety, the psychiatric symptoms for depression, physical and vasomotor symptoms as well as the loss of interest in sex ($p<0.001$). No adverse effects related to the treatment were identified during the study period.

In many women who suffer from menopause, somatic signs like fatigue, myalgia, arthralgia, paresthesia, palpitations and vaginal dryness are part of climacteric symptoms. These were assessed in a clinical trial using a combination of soy and hop extracts in 78 menopausal women over a duration of 12 weeks.[13] At the end of the study these somatic symptoms decreased significantly compared to the group who did not receive the combination ($p<0.05$). Moreover, measurements of urine N-telopeptide – a biomarker that measures the rate of bone turnover - in participants over 50 years in the treatment group showed a reduced increase of the biomarker possibly indicating an early antiresorptive efficacy on postmenopausal women's bones.

HOP EXTRACTS AND OSTEOPOROSIS

Osteoporosis is another unfavorable condition associated with menopause and is also the target of women seeking phytotherapy or food supplements to prevent its occurrence. In contrast to most other phytoestrogens that have been investigated for the treatment of menopause-related osteoporosis with disappointing results, 8-PN from hop showed more favorable outcomes due to its preferential binding to ERβ, which is predominant in bone tissue.[8] Although the potential of 8-PN to prevent osteoporosis has been assessed using in vitro and in vivo models, unfortunately, no clinical trials in humans have yet been conducted.

In vivo studies have evaluated the ability of 8-PN to promote differentiation of osteoblasts.

8-PN showed a stronger capability to induce the expression of osteoprotegerin (OPG) - an osteoclastogenesis inhibitor - and to increase levels of osteoblast differentiation markers in cultured rat osteoblasts when compared to naringenin, which is another flavanone.[14] Moreover, in rabbit bone marrow cells, 8-PN inhibited the formation and induced apoptosis of osteoclasts to a greater extent than naringenin, confirming the essential role of the prenyl group of 8-PN in bone protective activities. As with vasomotor symptoms, the effects of 8-PN on bone metabolism were shown to be mediated by the ERβ signaling pathway, but the intensities of responses in osteoblast and osteoclast cell lines were weaker in comparison with the effect of 17β-estradiol, but stronger than in the case of genistein and daidzein.[15]

Moreover, in an animal in vivo study using mice osteoblastic cell line MC3T3-E1, 8-PN inhibited the expression of receptor activator of nuclear factor-κB ligand (RANKL), and led to increased expression of OPG. This effect was also facilitated by ERα and was stronger than genistein and daidzein but again weaker than estradiol.[16]

The experimental in vitro and in vivo studies results indicate that hop and 8-PN could play a positive role in the prevention or treatment of osteoporosis and improve mineral bone density, provided more trials are performed in humans.

CONCLUSION

In conclusion, the use of alternative and complementary therapies during menopause has somewhat expanded despite the many re-appraisals of the benefit-risk ratio of large outcome HRT studies, like the WHI or HERS, showing better safety than originally thought and even positive effect of HRT use in younger women or in early postmenopause on the cardiovascular system and all-cause mortality. Nonetheless, the public opinion on HRT has not changed yet, leading to important negative consequences for women's health and quality of life and a shift towards alternative medicine to overcome this issue.[17] The available clinical data on hop extract use for the alleviation of menopausal symptoms show that these products help improve the many climacteric symptoms of early menopause and indicate an absence of side-effects in women using those extracts during the assessment period of time. Yet, more clinical trials are needed to evaluate the long-term impact of phytoestrogens and hop extracts on women's health despite the long safety history of beer consumption.

References can be accessed on **www.thesynapse.net**

PROF. ALBERT CILIA-VINCENTI

Cervical Cyto/Histological Nomenclature

Making Practical Sense of Past and Recent Changes

Before the early 1980s the cytology and histopathology categories of precancerous cervical changes were termed mild, moderate and severe dysplasia (or dyskaryosis) and carcinoma in-situ. Furthermore, a distinctive cytoplasmic clearing in squamous cells was termed koilocytosis, without knowing what exactly caused it.

In the early 1980s electron microscopy determined that koilocytosis was due to HPV infection, later confirmed by the emerging DNA technologies (which also confirmed that cervical cancers contain HPV DNA). So koilocytosis and HPV cytological changes are synonymous. At the same time the histological HPV changes were described as flat condyloma and distinguished from premalignant neoplastic dysplasia.

Also at the same time it was accepted that the distinction between severe dysplasia and carcinoma in-situ didn't exist; the new nomenclature of cervical intraepithelial neoplasia (CIN 1, 2 & 3) was introduced and the label "carcinoma in-situ" dropped.

As the study of evolution of HPV infection and CIN progressed it became obvious that most HPV infections regressed spontaneously (in the immuno-competent – may take up to 2 years), that progression of CIN occurred in stages, that progression to invasive cancer does not happen in every case and, when it does, usually takes several years to do so.

Way back in the 1960s a New Zealand gynaecologist, a certain Mr Green, began a clinical trial (would now be deemed unethical) of following up cases of reported cervical dysplasia, with no ablative treatment whatsoever, to try and prove his theory that reported "dysplasia" had nothing to do with invasive cervical cancer. One needs to remember that in the 1960s the concept of neoplasia as a multi-step/multi-mutation gradual process (pre-malignancy) was a novel and controversial concept. In 1972 he presented his ongoing findings at the histopathology department of the Royal Marsden Hospital in London (I was SHO there that year) – he claimed that most reported dysplasia regressed spontaneously, some reported dysplasia persisted but none progressed to cervical cancer. In the 1960s and 70s the existence and role of HPV was unknown and the observed regression of many "dysplasias" was probably due to regressed HPV changes and not high grade CIN.[1]

The Americans then suggested a simpler CIN grading of low (CIN 1) and high grade (CIN 2/3). This correlated with management recommendations – cytological and histological CIN 1 could safely be followed-up while CIN 2 & 3 needed ablation. Cytological HPV changes (koilocytosis) and histological HPV changes (flat condyloma) could also be safely followed-up, rather than ablated by cone biopsy and risking damaging cervical competence in young women.

More recently the US Bethesda system[2,3] introduced new nomenclature aimed at standardising laboratory reporting but which may create more confusion. What was called "borderline changes" becomes "atypical squamous cells of undetermined significance" (ASCUS). "Borderline" is usually used when the microscopist is unsure whether the slight cellular changes are within normal limits or whether these could represent HPV or CIN 1 changes. What we diagnosed as "HPV changes", or "HPV/?CIN 1" on a smear, Bethesda now recommends "low grade squamous intraepithelial lesion" (LGSIL or LSIL). "CIN 2/3" is Bethesda "high grade squamous intraepithelial lesion" (HGSIL or HSIL). Bethesda does however stick to the old recommendation for follow-up of reported HPV and CIN 1 changes, and for colposcopy and ablation of CIN 2/3 lesions.

Management confusion may accompany "ASCUS" cytology reports, when they are followed immediately by colposcopy and by ablation of some histological "CIN 1" lesions

Distinguishing CIN 1 from reactive/inflammatory/reparative non-neoplastic atypia is very subjective and, therefore, over-investigation and too aggressive treatment in young women is possible. The same could be said for "inflammatory" smears being followed-up by immediate colposcopic biopsy rather than cytology. It is important to keep in mind that invasive cervical cancer doesn't develop overnight but takes several years to do so and one practically always sees it in women (not young girls) who have never (or rarely) had screening cytology.

HPV DNA technology has helped diagnosis particularly when oncogenic (high risk) HPV is present, but ablative therapy can only be justified on a histological report of CIN 2/3 and not on an HPV PCR report. The HPV PCR test has replaced screening cytology in some centres where smear reporting was deemed too slow or diagnostically unreliable – the usual routine here is HPV testing every 5 years and colposcopy if oncogenic HPV is reported.

What about the "inflammatory smear"? Different cytology screening staff have different criteria for diagnosing "non-specific inflammation". Some of them ignore neutrophils in smears and report inflammation only when a non-specific perinuclear vacuolation is present. I do not agree with this interpretation because too many neutrophils may signal a clinically important sexually-transmitted bacterial infection.

Reporting "inflammation" is therefore very subjective. I report it only when there is a significant excess of neutrophils. Relatively small numbers of neutrophils may be regarded as within normal physiological limits (including frequent sexual activity). Judging between relatively small and significant excess of neutrophils is not always easy. It is then entirely up to the clinician's judgement as to whether reported "inflammation" needs any further action.

References can be accessed on **www.thesynapse.net**

Prevenar 13®

2011

A NEXT-GENERATION PNEUMOCOCCAL CONJUGATE VACCINE IS COMING

2022

APEXXNAR®
Pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed)

APEXXNAR IS A 20-VALENT PNEUMOCOCCAL CONJUGATE VACCINE FOR ADULTS.[1]

Built on the foundation of Prevenar 13, APEXXNAR contains the broadest serotype coverage from a pneumococcal conjugate vaccine to help protect against pneumococcal pneumonia and invasive pneumococcal disease.[1-3]

Pfizer

Apexxnar is to be administered as a single dose to individuals 18 years of age and older. The need for revaccination with a subsequent dose of Apexxnar has not been established.[1]

For intramuscular use only. One dose (0.5 mL) of Apexxnar should be administered intramuscularly, preferably in the deltoid muscle, with care to avoid injection into or near nerves and blood vessels.[1]

Please refer to Apexxnar Summary of Product Characteristics for full prescribing details, full dosage and administration details.

References: 1. APEXXNAR. Summary of Product Characteristics. February 2022. **2.** PREVENAR 13. Summary of Product Characteristics. October 2021. 3. VAXNEUVANCE. Summary of Product Characteristics. December 2021.

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

APEXXNAR
Apexxnar suspension for injection in pre-filled syringe
Pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed)

QUALITATIVE AND QUANTITATIVE COMPOSITION One dose (0.5 mL) contains:Pneumococcal polysaccharide serotype 1[1,2] 2.2 µg, Pneumococcal polysaccharide serotype 3[1,2] 2.2 µg, Pneumococcal polysaccharide serotype 4[1,2] 2.2 µg, Pneumococcal polysaccharide serotype 5[1,2] 2.2 µg, Pneumococcal polysaccharide serotype 6A[1,2] 2.2 µg, Pneumococcal polysaccharide serotype 6B[1,2] 4.4 µg, Pneumococcal polysaccharide serotype 7F[1,2] 2.2 µg, Pneumococcal polysaccharide serotype 8[1,2] 2.2 µg, Pneumococcal polysaccharide serotype 9V[1,2] 2.2 µg, Pneumococcal polysaccharide serotype 10A[1,2] 2.2 µg, Pneumococcal polysaccharide serotype 11A[1,2] 2.2 µg, Pneumococcal polysaccharide serotype 12F[1,2] 2.2 µg, Pneumococcal polysaccharide serotype 14[1,2] 2.2 µg, Pneumococcal polysaccharide serotype 15B[1,2] 2.2 µg, Pneumococcal polysaccharide serotype 18C[1,2] 2.2 µg, Pneumococcal polysaccharide serotype 19A[1,2] 2.2 µg, Pneumococcal polysaccharide serotype 19F[1,2] 2.2 µg, Pneumococcal polysaccharide serotype 22F[1,2] 2.2 µg, Pneumococcal polysaccharide serotype 23F[1,2] 2.2 µg, Pneumococcal polysaccharide serotype 33F[1,2] 2.2 µg. [1]Conjugated to CRM197 carrier protein (approximately 51 µg per dose). [2]Adsorbed on aluminium phosphate (0.125 mg aluminium per dose) PHARMACEUTICAL FORM Suspension for injection. The vaccine is a homogeneous white suspension. THERAPEUTIC INDICATIONS Active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in individuals 18 years of age and older. See section *Special warnings and precautions for use* for information on protection against specific pneumococcal serotypes. Apexxnar should be used in accordance with official recommendations. POSOLOGY AND METHOD OF ADMINISTRATION Posology *Individuals 18 years of age and older* Apexxnar is to be administered as a single dose to individuals 18 years of age and older. The need for revaccination with a subsequent dose of Apexxnar has not been established. No data on sequential vaccination with other pneumococcal vaccines or a booster dose are available for Apexxnar. Based on the clinical experience with Prevenar 13 (a pneumococcal conjugate vaccine consisting of 13 polysaccharide conjugates that are also in Apexxnar), if the use of 23-valent pneumococcal polysaccharide vaccine (Pneumovax 23 [PPSV23]) is considered appropriate, Apexxnar should be given first. *Paediatric population* The safety and efficacy of Apexxnar in children and adolescents younger than 18 years of age have not been established. No data are available. *Special populations* There are no data with Apexxnar in special populations. Limited experience from clinical studies with Prevenar 13 (a pneumococcal conjugate vaccine consisting of 13 polysaccharide conjugates that are also in Apexxnar) are available in adults at higher risk of pneumococcal infection either immunocompromised individuals or following bone marrow transplantation (see section Special warnings and precautions for use). Based on these data the following posology was recommended for Prevenar 13: Individuals at higher risk of pneumococcal infection (e.g., individuals with sickle cell disease or HIV infection), including those previously vaccinated with 1 or more doses of PPSV23, were recommended to receive at least 1 dose of Prevenar 13. In individuals with a hematopoietic stem cell transplant (HSCT), the recommended immunisation series with Prevenar 13 consisted of 4 doses of 0.5 mL each. The primary series consisted of 3 doses, with the first dose given 3 to 6 months after HSCT and with an interval of at least 1 month between doses. A booster dose was recommended 6 months after the third dose. Please also refer to section *Special warnings and precautions for use*. Method of administration: For intramuscular use only. One dose (0.5 mL) of Apexxnar should be administered intramuscularly, preferably in the deltoid muscle, with care to avoid injection into or near nerves and blood vessels. CONTRAINDICATIONS Hypersensitivity to the active substances, to any of the excipients or to diphtheria toxoid. SPECIAL WARNINGS AND PRECAUTIONS FOR USE Do not inject Apexxnar intravascularly. Traceability In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. Hypersensitivity As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in case of a rare anaphylactic reaction following the administration of the vaccine. Concurrent illness Vaccination should be postponed in individuals suffering from acute severe febrile illness. However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination. Thrombocytopenia and coagulation disorders The vaccine must be administered with caution to individuals with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration. The risk of bleeding in patients with coagulation disorders needs to be carefully evaluated before intramuscular administration of any vaccine, and subcutaneous administration should be considered if the potential benefit clearly outweighs the risks. Protection against pneumococcal disease Apexxnar will only protect against *Streptococcus pneumoniae* serotypes included in the vaccine and will not protect against other microorganisms that cause invasive disease or pneumonia. As with any vaccine, Apexxnar may not protect all individuals receiving the vaccine from pneumococcal invasive disease or pneumonia. For the most recent epidemiological information in your country, you should consult with the relevant national organisation. Immunocompromised individuals Safety and immunogenicity data on Apexxnar are not available for individuals in immunocompromised groups. Vaccination should be considered on an individual basis. Based on experience with pneumococcal vaccines, some individuals with altered immunocompetence may have reduced immune responses to Apexxnar. Individuals with impaired immune response, whether due to the use of immunosuppressive therapy, a genetic defect, HIV infection, or other causes, may have reduced antibody response to active immunization. The clinical relevance of this is unknown. Safety and immunogenicity data with Prevenar 13 (a pneumococcal conjugate vaccine consisting of 13 polysaccharide conjugates that are also in Apexxnar) are available for a limited number of individuals with HIV infection, or with a HSCT (see section *Undesirable effects*). In adults across all studied age groups, formal non-inferiority criteria were met although numerically lower geometric mean titres were observed with Apexxnar for most of the serotypes compared to Prevenar 13, however the clinical relevance of this observation for immunocompromised individuals is unknown. Excipient This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium free'. UNDESIRABLE EFFECTS Summary of the safety profile *Participants 18 years of age and older* The safety of Apexxnar was evaluated in 4,552 participants 18 years of age and older in six clinical trials (two Phase 1, one Phase 2, and three Phase 3), and 2,496 participants in the control groups. In the Phase 3 trials, 4,263 participants received Apexxnar. This included 1,798 participants 18 through 49 years of age, 334 participants 50 through 59 years of age, and 2,131 participants 60 years of age and older (1,138 were 65 years of age and older). Of the participants who received Apexxnar in the Phase 3 trials, 3,639 were naïve to pneumococcal vaccines, 253 had previously received Pneumovax 23 (pneumococcal polysaccharide vaccine [23 valent]; PPSV23) (≥ 1 to ≤ 5 years prior to enrollment), 246 had previously received Prevenar 13 only (≥ 6 months prior to enrollment), and 125 had previously received Prevenar 13 followed by PPSV23 (the dose of PPSV23 ≥ 1 year prior to enrollment). Participants in the Phase 3 trial B7471007 (Pivotal Study 1007) were evaluated for adverse events for 1 month after vaccination, and serious adverse events through 6 months after vaccination. This study included 447 participants 18 to 49 years of age, 445 participants 50 to 59 years of age, 1,985 participants 60 to 64 years of age, 624 participants 65 to 69 years of age, 319 participants 70 to 79 years of age, and 69 participants ≥ 80 years of age. In participants 18 to 49 years of age in Studies 1007 and a Phase 3 trial B7471008 (Lot Consistency Study 1008), the most frequently reported adverse reactions were pain at injection site (79.2%), muscle pain (62.9%), fatigue (46.7%), headache (36.7%), and joint pain (16.2%). In participants 50 to 59 years of age in Study 1007, the most frequently reported adverse reactions were pain at injection site (72.5%), muscle pain (49.8%), fatigue (39.3%), headache (32.3%), and joint pain (15.4%). In participants ≥ 60 years of age in Study 1007, the most frequently reported adverse reactions were pain at injection site (55.4%), muscle pain (39.1%), fatigue (30.2%), headache (21.5%), and joint pain (12.6%). These were usually mild or moderate in intensity and resolved within a few days after vaccination. Phase 3 Study B7471006 (Study 1006) evaluated Apexxnar in participants ≥ 65 years of age with varying prior pneumococcal status (prior PPSV23, prior Prevenar 13 or prior Prevenar 13 followed by PPSV23). In this study, the most frequently reported adverse reactions for participants were similar in frequency to those described for participants ≥ 60 years of age in Study 1007, with slightly higher injection site pain (61.2%) in participants with prior Prevenar 13, and joint pain (16.8%) in participants with prior Prevenar 13 followed by PPSV23. The adverse reactions from the Phase 3 clinical trials and postmarketing experience are presented below. *Adverse reactions from clinical trials* As Apexxnar contains the same 13 serotype-specific capsular polysaccharide conjugates and the same vaccine excipients as Prevenar 13, the adverse reactions already identified for Prevenar 13 have been adopted for Apexxnar. Below presented adverse reactions reported in Phase 3 trials of Apexxnar, based on the highest frequency among adverse reactions, local reactions, or systemic events after vaccination in any Apexxnar group. In clinical trials, the safety profile of Apexxnar was similar to that of Prevenar 13. No new adverse reactions were identified as compared to Prevenar 13. Adverse reactions are listed in decreasing order of frequency and seriousness. The frequency is defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from available data). **Very Common:** Headache, Joint pain, Muscle pain, Vaccination site pain/tenderness, Fatigue. **Common:** Vaccination-site induration/swelling[a], Vaccination-site erythema[a], Pyrexia. **Uncommon:** Hypersensitivity reaction, including face oedema, dyspnoea, bronchospasm, Diarrhoea[a], Nausea, Vomiting[a], Rash[a], Angioedema, Vaccination-site pruritus, Lymphadenopathy, Vaccination-site urticaria, Chills[a]. **Frequency Not Known:** Decreased appetite[a], Limitation of arm movement[a]. a. Event reported in clinical trials with Prevenar 13 with very common frequency (≥ 1/10). Decreased appetite and limitation of arm movement were not reported in the adult Phase 3 trials of Apexxnar; therefore, the frequency is not known. *Adverse reactions from postmarketing experience* Below presented adverse experiences have been spontaneously reported during the postmarketing use of Prevenar 13, which may also occur with Apexxnar. The postmarketing safety experience with Prevenar 13 is relevant to Apexxnar, as Apexxnar contains all components (polysaccharide conjugates and excipients) of Prevenar 13. These events were reported voluntarily from a population of uncertain size. Therefore, it is not possible to reliably estimate their frequency or to establish, for all events, a causal relationship to vaccine exposure. **Frequency Not Known:** Anaphylactic/anaphylactoid reaction, including shock, Erythema multiforme, Vaccination-site dermatitis. Events reported spontaneously in Prevenar 13 postmarketing experience; therefore, the frequencies could not be estimated from the available data and are considered as not known. Additional information in special populations in studies with Prevenar 13 Participants ≥ 18 years of age with HIV infection have similar frequencies of adverse reactions in Table 1, except for pyrexia (5% to 18%) and vomiting (8% to 12%) which were very common and nausea (< 1% to 3%) which was common. Participants ≥ 18 years of age with an HSCT have similar frequencies of adverse reactions in Table 1, except for pyrexia (4% to 15%), vomiting (6% to 21%), and diarrhoea (25% to 36%) which were very common. Reporting of suspected adverse reactions **Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal** SUPPLY CLASSIFICATION POM. MARKETING AUTHORISATION HOLDER Pfizer Europe MA EEIG, Boulevard de la Plaine 17, 1050 Bruxelles, Belgium. LOCAL REPRESENTATIVE OF THE MARKETING AUTHORISATION HOLDER Vivian Corporation Ltd, 29, Sanitas Building Tower Street, Msida MSD1824, Malta Tel: + 35621 344610 MARKETING AUTHORISATION NUMBER(S) EU/1/21/1612/001-006 DATE OF REVISION OF THE TEXT 02/2022 For additional information please refer to the Summary of Products Characteristics.

IMPORTANT SAFETY INFORMATION

- Apexxnar is indicated for active immunisation for the prevention of invasive disease and pneumonia caused by Streptococcus pneumoniae in individuals 18 years of age and older.[1]
- Apexxnar should be used in accordance with official recommendations.[1]
- The safety and efficacy of Apexxnar in children and adolescents younger than 18 years of age have not been established. No data are available.[1]
- Apexxnar will only protect against Streptococcus pneumoniae serotypes included in the vaccine and will not protect against other microorganisms that cause invasive disease or pneumonia. As with any vaccine, Apexxnar may not protect all individuals receiving the vaccine from pneumococcal invasive disease or pneumonia.[1]
- Hypersensitivity to the active substances, to any of the excipients, or to diphtheria toxoid is a contraindication to the use of Apexxnar.[1]
- As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in case of a rare anaphylactic reaction following the administration of the vaccine.[1]
- Vaccination should be postponed in individuals suffering from acute severe febrile illness. However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination.[1]
- The vaccine must be administered with caution to individuals with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration. The risk of bleeding in patients with coagulation disorders needs to be carefully evaluated before intramuscular administration of any vaccine, and subcutaneous administration should be considered if the potential benefit clearly outweighs the risks.[1]
- Safety and immunogenicity data on Apexxnar are not available for individuals in immunocompromised groups. Vaccination should be considered on an individual basis. Based on experience with pneumococcal vaccines, some individuals with altered immunocompetence may have reduced immune responses to Apexxnar.[1]
- Individuals with impaired immune response, whether due to the use of immunosuppressive therapy, a genetic defect, HIV infection, or other causes, may have reduced antibody response to active immunization. The clinical relevance of this is unknown.[1]
- The most commonly reported adverse reactions in clinical trials with Apexxnar in adults ≥18 years old were (≥10%) vaccination-site pain/tenderness, headache, joint pain, muscle pain, fatigue and (≥1/100 to <1/10) vaccination-site induration/swelling, vaccination-site erythema, pyrexia. In clinical trials, the safety profile of Apexxnar was similar to that of Prevenar 13. No new adverse reactions were identified as compared to Prevenar 13.[1]
- In the clinical trials of Apexxnar, participants who were healthy, or with stable non-immunocompromising chronic medical conditions, in all the age groups analysed had a lower immune response with Apexxnar compared with Prevenar 13 in spite of meeting the predefined non-inferiority margins. The clinical relevance of this observation is unknown.[1]
- In a randomised, active-controlled, double-blind, non-inferiority clinical trial (Pivotal Study 1007) of Apexxnar in the United States and Sweden, in participants 60 years of age and older the response to serotype 8 missed the pre-specified statistical non-inferiority criterion when compared to the response induced by PPSV23 (the lower bound of the 2-sided 95% CI for the GMT ratio is 0.49 instead of >0.50). The clinical relevance of this observation is unknown. Supportive analyses for other serotype 8 endpoints in the Apexxnar group showed favourable outcomes.[1]
- In the clinical trials of Apexxnar, across all the age groups studied, in general, a numerically lower immune response was observed in participants with risk factors compared to participants without risk factors. The clinical relevance of this observation is unknown.[1]
- No efficacy studies have been performed with Apexxnar.[1]

1. APEXXNAR. Summary of Product Characteristics. February 2022.

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Healthcare professionals are asked to report any suspected adverse reactions via:
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Non-Coding RNA-Based Therapy

ABSTRACT

In recent years, some of the physiological and pathophysiological roles of non-coding RNAs (ncRNAs) have been discovered. These discoveries have been pivotal in providing insight on the basis of various diseases where ncRNAs are aberrantly expressed. Moreover, they are being studied in translational research to use these mechanisms for 'non-coding RNA based therapy'. The main players being investigated in non-coding RNA-based therapies include antisense oligonucleotides, locked nucleic acid anti-miRs, miRNA sponges, miRNA mimics, siRNAs and ribozymes.

INTRODUCTION

Only approximately 1.5% of the human genome encodes protein sequence,[1] the rest was once labelled as 'dark matter'. Now we know that a major part of this once proverbial genomic 'dark matter' is represented by non-coding RNAs (ncRNAs), which increase in number with increasing complexity of an organism. Based on their size, ncRNAs are roughly grouped into two major classes, namely, small ncRNA and long ncRNA (lncRNA). MicroRNAs (miRNAs, mi-R, approximately 22 nucleotides long) and transcription initiation RNAs (tiRNAs, 18 nucleotides long) are two examples of the first class. In contrast, lncRNAs, which resemble mRNA transcripts, range from 200 nucleotides to approximately 100 kilobases.[2]

Of the small ncRNAs, microRNAs are the most studied. Indeed, more than 2,000 microRNAs have been described. Their sequence is evolutionary conserved between species, and can be intergenic, intronic or polycistronic. MicroRNA target messenger RNA (mRNA) and inhibit their expression, specifically by either causing repression of their translation or bring about their degradation. So the function of a microRNA is to post-transcriptionally regulate gene expression by the above two mechanisms. Their binding to the targeted mRNA is partially complementary, specifically and usually by a 7 nucleotide sequence called the 'seed sequence'. However, usually there might be more complementary nucleotides but this is not often necessary as long as the seed sequence binds. One microRNA can have more than 100 target genes.

In contrast lncRNAs show poor evolutionary conservation between species but this does not mean that the function is not, because if they fold in the same manner and if the 3-dimensional configuration of the RNA is the same, they can still possibly bind to the same proteins or perform the same function. More than 30,000 lncRNAs have been described. Their expression can be highly tissue specific. Many lncRNAs are localized in the nucleus, but not always. Like miRNA, lncRNA can be anywhere in the genome. They have been described to be intergenic, intronic, bidirectional, sense and anti-sense.

LncRNAs control various cellular functions. For example one function is acting like an 'RNA decoy', binding to transcription factors (TF) (that usually would bind to double-stranded DNA) and thus preventing the TF from binding to the DNA. Other lncRNAs act as 'microRNA sponges', binding to microRNAs and thus prevent the latter from binding to their target mRNA. They can also act as a 'scaffold' to bring proteins together ensuring their interaction. Interestingly, some lncRNAs interact directly with DNA and then recruit chromatin modifiers which then result in genes being turned on or off. In the cytoplasm, lncRNAs can bind to mRNA and so prevent their translation or splicing, or bring about mRNA degradation. The name 'non-coding' is misleading as it implicates that these non-coding RNAs do not code proteins. Van Heesch et al.[3] have discovered that some lncRNAs, which have already been described to have well-defined noncoding functions, also code for functional microproteins. And to make things more complex, Khan et al.[4] found that protein coding genes code for a type of non-coding RNA, called circular RNA by a process called 'backsplicing'.

Research on these noncoding RNAs is showing that they play pivotal roles in cellular homeostasis, cellular growth and development, cellular differentiation, metabolism, apoptosis, aging, and immune regulation. Their exploration has revealed that they are important for health when they function physiologically but cause disease when aberrantly expressed or dysregulated. This has further spurred translational research of these bio-molecules for their clinical utility as disease biomarkers and molecular targets or 'bullets' in medical therapies. This essay deals with the latter, specifically therapy, aimed at or based on, non-coding RNA.

Some of the main players being investigated in non-coding RNA-based therapies include antisense oligonucleotides (ASOs), locked nucleic acid anti-miRs, micro-RNA sponges, micro-RNA mimics, small interfering RNAs (siRNAs) and ribozymes.

ANTISENSE OLIGONUCLEOTIDES (ASOs)

ASOs are short, synthetic, single-stranded oligodeoxynucleotides that interfere with RNA targets e.g. binding to mRNA preventing its translation into protein.

FDA has approved inostersen (Tegsedi®) and golodirsen (Vyondys 53™)as ASO-based therapeutics. Inotersen is indicated for the treatment of hereditary transthyretin amyloidosis (hATTR).[5] It binds to transthyretin (TTR) mRNA, and so inhibits the synthesis of TTR protein in the liver, thus reducing amyloid deposition. Vyondys 53™ is indicated for patients with Duchenne Muscular Dystrophy (DMD) with a mutation of the DMD gene that can have its exon 53 skipped.[6] Specifically, golodirsen binds to exon 53 of the dystrophin pre-mRNA which causes exclusion of exon 53 during mRNA processing. This exon 53 skipping produces a truncated dystrophin protein which still localizes to the sacrolemma in muscle fibres.

Research with ASOs in the field of cardiology is also ongoing. Patients with chronic ischaemic heart failure have increased levels of the cardiac microRNA-132-3p (miR-132). Clinical trial NCT04045405 tested CDR132L, a miR-132 inhibitor, specifically an antisense oligonucleotide. The results show that the miR-132 ASO decreases and reverses heart failure and is safe.[7]

LOCKED NUCLEIC ACID (LNA) ANTI-MIR

A 'locked nucleic acid anti-miR' is a synthetic oligonucleotide that targets specific miRs to cause antisense-based gene silencing.

In a study on mice, Boon et al.[8] used a LNA antisense oligonucleotide to silence miR-29. They showed that increased expression of miR-29 in aortas of old mice is associated with underexpression of many extracellular matrix (ECM) proteins (e.g. elastin, collagens, fibrillins), leading to formation of aortic aneurysms. By using the LNA antisense oligonucleotide they silenced the miR29, allowing ECM proteins to be expressed and thus avoiding aortic aneurysm formation.

MRG-110 is a synthetic LNA antisense oligonucleotide that targets and inhibits miR-92a. miR-92a is an anti-angiogenic miRNA and thus when inhibited increases angiogenesis in multiple organ systems. Corrie et al.[9] showed that MRG-110 speeds up healing of acute and chronic wounds of the skin in mice and pigs. The authors also proposed MRG-110 for a phase one clinical trial, which recruited 42 participants, and was completed in 2019 (ClinicalTrials.gov Identifier: NCT03603431). The trial showed that MRG-110 is safe and well tolerated, supporting the conduct of additional clinical studies.

Dysregulation of several miRNAs has been shown to be involved in the pathogenesis and progression of many malignancies. For example, in colocrectal adenocarcinoma, miR-21 is elevated,[10] and in hepatocellular carcinoma (HCC), miR-23b is high.[11] Studies using LAN anti-miR on malignant cell lines of these cancers suppressed the high levels of the culprit miR and controlled cell proliferation and cell invasion. Such studies have prompted the start of clinical trials.

Indeed, in a phase one clinical trial (ClinicalTrials.gov Identifier: NCT00466583),[12] a LNA antisense oligonucleotide against the hypoxia-inducible factor-1α was tested in patients with solid tumours or lymphoma refractory to treatment. However, the trial was terminated when the sponsor stopped the development of this agent.

LNA anti-miRs are also being studied for their potential use in treatment of parasitic infections where the parasite, like Leishmania[13] and Toxoplasma gondii,[14] uses complex strategies to evade the immune response. It was found that in these infections a specific microRNA is over-expressed, and when these detrimental microRNas are targeted by LNA anti-miR, apoptosis of the host macrophages occurs killing the parasite inside.

Lindholm et al.[15] used LNA anti-sense oligonucleotide to target and degrade the messenger RNA (mRNA) that codes the 'proprotein convertase subtilisin/kexin type 9' (PCSK9) protein in monkeys. PCSK9 causes the degradation of the LDL receptor and thus increases LDL-C level. Given that there were no toxicological side-effects, the authors proposed that LNA antisense oligonucleotides against PCSK9 can be a potential treatment for elevated high LDL-C.

This led to a first-in-human randomized, placebo-controlled trial (ClinicalTrials.gov Identifier: NCT01350960) of a LNA antisense inhibitor of PCSK9 (which in the trial was labelled SPC5001). But the trial was terminated because SPC5001 caused injection site reactions and renal toxicological side-effects.[16] The authors thus concluded that further research was needed to figure exactly the mechanisms involved in the development of the adverse reactions.

miR-155 is mechanistically involved in the formation of blood and lymphoid cells. miR-155 is elevated in specific lymphomas and leukemias, and is believed to promote the growth and survival of the cancerous cells. Clinical trials with identifiers NCT02580552 and NCT03713320 tested cobomarsen (MRG-106), a LAN that targets miR-155 with the aim to treat these blood diseases. The clinical trials showed safety and efficacy even though clinical trial NCT03713320 was terminated early because of financial reasons. In 2020, the FDA granted an 'orphan drug designation' to cobomarsen for patients suffering with T-cell lymphoma.

miRNA SPONGES

miRNA sponges are noncoding RNA molecules that bind miRNAs and thus prevent the latter from binding to their target mRNAs. Together with miRNAs, these endogenous miRNA sponges (also known as competing endogenous RNAs, ceRNAs) are involved in the regulation of gene expression and hence in cellular protein output.[17] They are called sponges as an analogy because they 'soak up' miRNAs. Two major types of endogenous sponges are circular RNAs and long non-coding RNAs.

As a proof-of-principle study for the potential clinical use of circular RNAs as microRNA sponges, Jost et al.[18] engineered circRNA sponges in vitro to soak up microRNA-122 in hepatocyte cell cultures infected with Hepatitis C Virus (HCV), which is a single-stranded RNA virus. The virus uses miRNA-122 by binding its RNA to it and this protects its

degradation and so helps to complete its life-cycle in the infected liver cells. By sponging these protective miRNA-122, the engineered circRNA inhibited the viral replication.

The research on circRNA-based therapeutics is still in its infancy but it is promising.[19] The latter is based on the fact that thousands of circRNAs have been reported to be expressed, that are highly cell-type specific, and they are resistant to exonucleolytic decay.

MICRO-RNA MIMICS

MicroRNA mimics are synthetic miRNAs that are used to restore endogenous miRNAs that are down-regulated. Thus, they have clinical therapeutic potential in various diseases like inflammation, cardiovascular diseases, neurological disorders, cancer and fibrotic conditions, where miRNAs are down-regulated.[20]

There are various studies on miR-29, which is under-expressed in fibrotic conditions like systemic sclerosis,[21] idiopathic pulmonary fibrosis,[22] and scar formation. Montogomery et al.[23] showed that a miR-29 mimic protected and even reversed pulmonary fibrosis in a mouse model of the latter condition. In a phase two clinical trial (ClinicalTrials.gov Identifier: NCT03601052),remlarsen (MRG-201), a miR-29 mimic, was studied for its efficacy and safety profile in human volunteers with a tendency towards keloids. The trial was conducted to investigate whether the miR-29 mimic, given intradermally, could reduce fibrous scar tissue formation. The results demonstrated that Remlarsen was effective.[24]

Another showcase of the potential of mi-R mimics is the clinical trial investigating TargomiRs (ClinicalTrials.gov Identifier: NCT02369198). TargomiRs are targeted mini-cells (nonliving bacterial minicells) containing a mi-R mimic. Specifically an miR-16 mimic was used. miR-16 is under-expressed in various cancers, and when its level is restored it has tumour suppressive activity. In the clinical trial the targets were malignant pleural mesothelioma and non-small lung cancer that over-expressed EGFR (epidermal growth factor receptor). The TargomiRs were injected intravenously and they found their way to the cancer cells because they had an anti-EGFR bispecific antibody that docked to the EGFR-expressing cancer cells and then 'unloaded' their miR-16 mimic cargo. This method is being refined further.[25]

siRNAs

A small interfering RNA (siRNA) is a double-stranded small RNA that targets a specific mRNA for degradation. In the past they have been used to knockdown genes in mammalian cells to understand gene function but nowadays siRNAs are also being utilized in siRNA therapeutics. Indeed, two siRNA, patisiran and givosiran, have been approved by FDA for medical use.

In 2018, FDA approved patisiran to treat adults with polyneuropathy of transthyretin-mediated amyloidosis, a rare, autosomal dominant disease. The approval was based on the significant improvements of the patients in the Phase III APOLLO clinical trial (ClinicalTrials.gov Identifier: NCT03997383).

In 2019, the FDA approved givosiran for adults with acute hepatic porphyria (AHP) after its evaluation in the clinical trial ENVISION (ClinicalTrials.gov Identifier: NCT03338816). Givosiran targets and causes the degradation of the mRNA that codes for aminolevulinate synthase 1 (ALAS1) in hepatocytes. This results in reduced levels of circulating aminolevulinic acid (ALA) and porphobilinogen (PBG), that are the neurotoxic intermediates which are responsible for the disease.

siRNAs are also showing promising results in Age-related Macular Degeneration (AMD) and glaucoma.[26] Bevasiranib is a siRNA that targets the mRNA for VEGF (Vascular Endothelial Growth Factor), the protein that promotes the growth of blood vessels. Thus, the aim here is to slow the growth and leakage from the abnormal blood vessels in the wet type of macular degeneration.

RIBOZYMES

A ribozyme is an RNA molecule that is catalytically active. The definition can be broadened to include RNA-protein complexes where the RNA fraction is the only part that is catalytic.

Zhong et al.[27] demonstrated how such ribozymes can be used in gene therapy, making the latter more safe and efficient. They engineered a type of ribozyme to act as an RNA on-switch of the therapeutic transgene.

In the phase two clinical trial (ClinicalTrials.gov Identifier: NCT00074997) an anti-HIV ribozyme (OZ1) was transduced in autologous CD34+ hematopoietic progenitor cells which were then re-administered to participants with chronic Human Immunodeficiency Virus Type 1 (HIV-1) infection. The OZ1 group had a higher CD4+ lymphocyte counts than the placebo arm and the procedure was shown to be safe.[28]

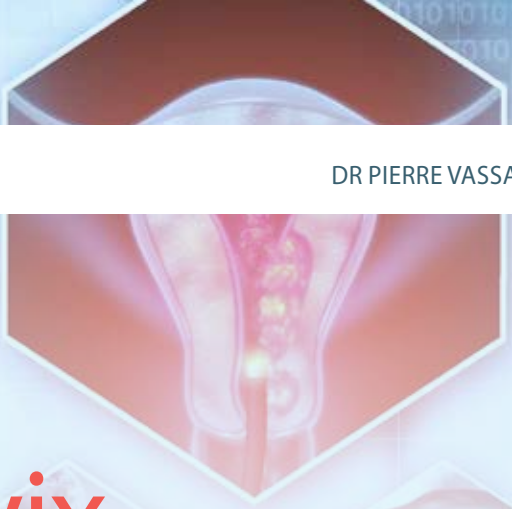
CONCLUSION

Non-coding RNA-based therapy is still in its infancy but is showing great therapeutic promise. Indeed, several RNA-targeted therapeutic projects are in the pipeline and various biotech and pharmaceutical companies are involved. - The two main challenges that must be finely addressed to bring these projects from the bench to the bedside, are stability and delivery. Most RNA molecules are relatively unstable and this is being addressed by their chemical modification. The correct delivery of the RNA to the target organ/s is also being established through the use of nanoparticles, liposome-like particles, or by joining the RNA or the particle to a specific molecule that will bind to a specific receptor on the targeted cells.

Presently many proteins cannot be targeted using small molecule based therapy. Nonetheless, non-coding RNA-based therapy has the potential to create a new class of drugs which will then modulate a multitude of targets. Thus, over the next several years, with further development and progress, noncoding RNA-based therapeutics will definitely be a transformative strategy in therapy as we know it.

References can be accessed on **www.thesynapse.net**

DR PIERRE VASSALLO



Staging Cancer of the Uterine Cervix

Cancer of the uterine cervix (cervical cancer) is the fourth most common cancer in women worldwide.[1] It is staged using the International Federation of Gynaecology and Obstetrics (FIGO) staging system that is based primarily on findings detected on Magnetic Resonance Imaging (MRI) as well as Positron Emission Tomography/Computed Tomography (PET/CT). The FIGO staging system helps guide treatment decisions, which may include fertility-sparing or non-fertility sparing surgery for early disease and chemoradiotherapy for more advanced tumours. It also serves to monitor the efficacy of treatment.

FIGO STAGING OF CERVICAL CANCER

FIGO Stage	Description
0	**Tumor confined to the surface layer** (the cell lining) of the cervix; also called carcinoma in situ
I	**Extension deeper into the cervix** with no spread beyond (extension to the corpus is disregarded)
IA	**Invasive carcinoma ≤5mm**
IA1	Stromal invasion ≤3.0 mm deep
IA2	Stromal invasion between 3.0 mm and 5.0 mm
IB	**Invasion deeper than 5mm**
IB1	Invasion >5mm and ≤2.0cm
IB2	Invasion >2.0cm but ≤4.0cm
IB3	Invasion >4.0 cm
II	**Disease extends beyond the uterus but not to the pelvic wall or the lower one-third of the vagina**
IIA	**No parametrial invasion but involves upper two-thirds of vagina**
IIA1	Clinically visible lesion ≤4.0 cm in greatest dimension
IIA2	Clinically visible lesion >4.0 cm in greatest dimension
IIB	**With parametrial invasion**
III	**Extension to the pelvic wall, involvement of lower one-third of the vagina, or hydronephrosis or non-functioning kidney**
IIIA	Involvement of lower one-third of the vagina with no extension to the pelvic wall
IIIB	Extension to the pelvic wall, hydronephrosis, or non-functioning kidney
IIIC	Extension to pelvic (1) or para-aortic lymph node (2) (based on MRI or PET/CT)
IV	**Involvement of the bladder or rectal mucosa or extension beyond the true pelvis** (biopsy proved); bullous oedema does not convey stage IV disease
IVA	Spread to adjacent organs (bladder and/or rectum)
IVB	Spread to distant organs

Table 1. FIGO Staging of Cervical Cancer.

Table 1 lists the different stages of cervical cancer. It is based on the extent of tumour spread; in **Stage 0** cancer is limited to the cell surface layer; in **Stage I**, there is cervical stomal invasion ≤4cm; in **Stage IIA**, invasion >4cm but not involving the parametrium; in **Stage IIB** parametrial invasion is present; in **Stage III**, there is spread to lower 1/3 of vagina, pelvic sidewall, or lymph nodes; in **Stage IV** there is involvement of rectum and/or bladder or distant organs.

IMAGING FINDINGS BASED ON FIGO STAGE

Stages 0 and IA1 disease are not detectible on MRI and can only be confirmed on histo-pathologic analysis. However, it may be valid to review a stage IA1 cancer with MRI to exclude the possibility underestimated disease, skip metastases and (although unlikely) lymph node involvement.

Stages IA2 disease and higher are detectible on MRI.[2] Stages up to IB1 are eligible to fertility-sparing surgery known as trachelectomy (Fig 1). Stage IB1 disease has also been shown to have a significantly better prognosis than stage IB2 disease.[3]

Stage IB2 (stromal invasion >2cm but ≤4cm) cervical cancers or higher stages are not eligible for fertility-sparing surgery (Figs 2 and 3).

Stage IIA cancers involve the upper two-thirds of the vagina, with stage IIA1 cancers measuring ≤4cm and Stage IIA2 measuring >4cm in diameter (Fig 4). The distinction between tumours measuring up to 4cm and >4cm has prognostic significance in that those measuring >4cm have a higher risk for recurrence and for lymph node metastases.

Stage IIB cancers extend into the tissues between the cervix and the pelvic sidewall; this tissue plane is known as the parametrium. In Stage IIB, there is no involvement of the pelvic sidewall, ureters or bladder (Fig 5).

Stage IIIA and IIIB cancers extend to the pelvic sidewall and involve the lower third of the vagina and the ureter respectively (Fig 6). Stage IIIC cancers involve the pelvic (IIIC1) (Fig 7) or para-aortic (IIIC2) lymph nodes. Lymph node involvement has been shown to be associated with increased recurrence rate and a reduction in overall 5-year survival.[4-6]

It is important to note that lymph node involvement results in frequent upstaging of patients with small primary tumours; however the 5-year survival of a patient with a small primary tumour and lymph node involvement is better than that of a patient with a large primary tumour and lymph node involvement.[4] In addition, patients with para-aortic lymph node involvement (stage IIIC2) have a better prognosis than those with distant metastases (stage IVB).[7]

Stage IV cervical cancer involves other pelvic (bladder and/or rectum) or extrapelvic (supraclavicular, lung, bone, other viscera) organs. Stage IVA cancer involves the bladder and/or rectal mucosa with loss of the intervening fat plane between the cervix and bladder or rectum on MRI (Fig 8). Stage IVB is best assessed with CT or FDG (fluorine-18 fluorodeoxyglucose) PET/CT due to their ease of coverage of the neck, chest, abdomen, and pelvis in one rapid scan (Fig 9).

MRI is the modality of choice for evaluating the primary tumour and local spread (i.e. up to Stage IIIA). CT is more valuable for assessing extra-pelvic spread (Stage IIIB-IVB). FDG PET/CT has the advantage of showing increased metabolic activity in viable tumour tissue. However, poor or no radiotracer uptake in necrotic tumour may lead to underestimating the extent of tumour spread.

CONCLUSION

Treatment options depend on tumour stage that is based on the imaging findings described above. Up to stage IB1, fertility-sparing surgery may be considered if required. If not, a radical hysterectomy and pelvic lymphadenectomy are advised.

For Stages IB2 and IIA1, radical hysterectomy and lymphadenectomy are recommended. In patients who are not fit for surgery, external beam radiation, brachytherapy with or without concurrent chemotherapy are the options. For Stages IB3, IIA2 and higher, non-surgical management with chemoradiotherapy is recommended since the disease is considered locally advanced. The radiotherapy field is extended based on the extent of lymph node involvement that is established on CT or PET/CT.

Finally, there are different types of trachelectomy and hysterectomy procedures that may be employed based on extent of disease and also, on tumour histologic type. This article has concentrated mainly on the staging process of cervical cancer and how it influences treatment.

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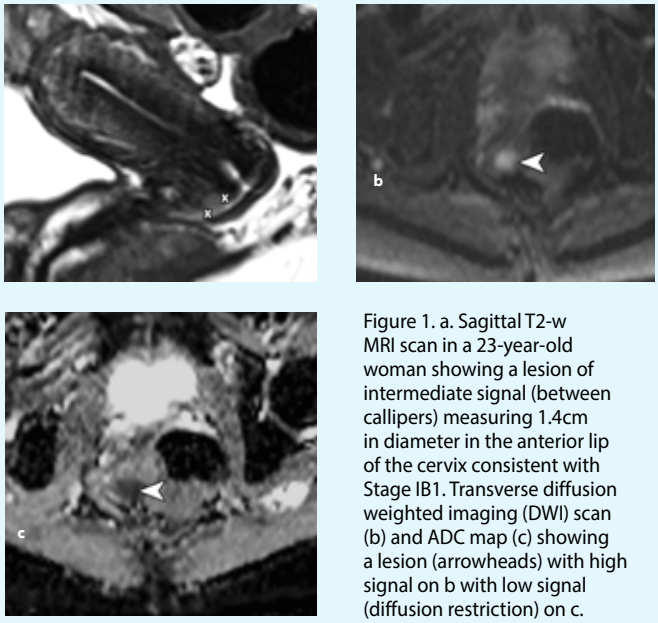

Figure 1. a. Sagittal T2-w MRI scan in a 23-year-old woman showing a lesion of intermediate signal (between callipers) measuring 1.4cm in diameter in the anterior lip of the cervix consistent with Stage IB1. Transverse diffusion weighted imaging (DWI) scan (b) and ADC map (c) showing a lesion (arrowheads) with high signal on b with low signal (diffusion restriction) on c.

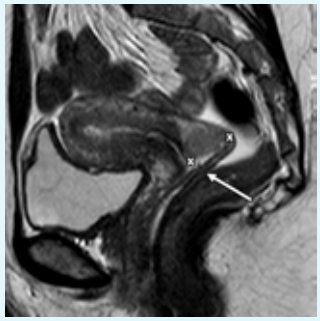

Figure 2. Sagittal T2-w MRI scan in a 34-year-old woman showing a 3cm tumour (between callipers) abutting the posterior vaginal fornix (arrow) consistent with Stage IB2 disease.

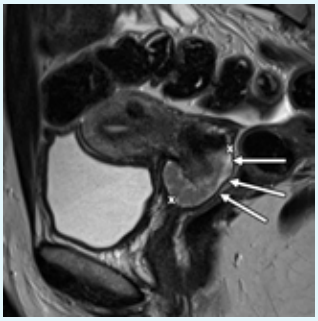

Figure 3. Sagittal T2-w MRI scan in a 46-year-old woman showing a 4.3cm cervical cancer (between callipers) protruding into the upper vagina (arrows); this is consistent with Stage IB3 disease.

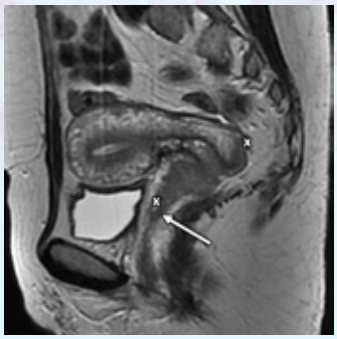

Figure 4. Sagittal T2-w MRI scan in a 50-year-old woman showing a 6.1cm lesion involving the cervix and anterior vaginal wall (between callipers) consistent with a stage IIA2 cancer.

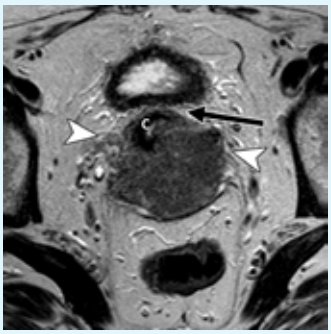

Figure 5. Axial T2-w MRI scan in a 54-year-old woman showing a large tumor of intermediate signal (arrowheads) originating from the posterior aspect of the cervix (C) extending into the parametrium; the posterior upper vaginal wall was also involved. The fat plane between the cervix and posterior bladder wall (arrow) is maintained. This is consistent with a stage IIB tumour.

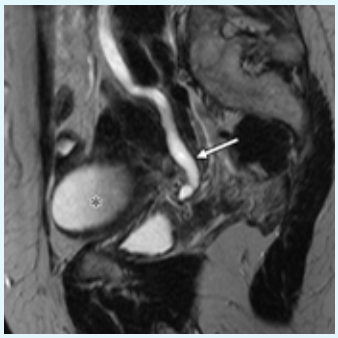

Figure 6. Sagittal T2-w MRI scan in a 50-year-old woman showing a right hydroureter (arrow) due to infiltration by cervical cancer; this is consistent with a stage IIIb cancer. Haematometra (*) is present due to cervical stenosis.

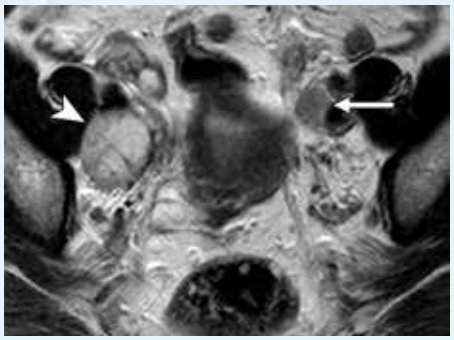

Figure 7. Axial T2-w MRI scan showing enlarged right obturator (arrowhead) and left external iliac lymph nodes (arrow). This is consistent with a stage IIIC1 cancer.

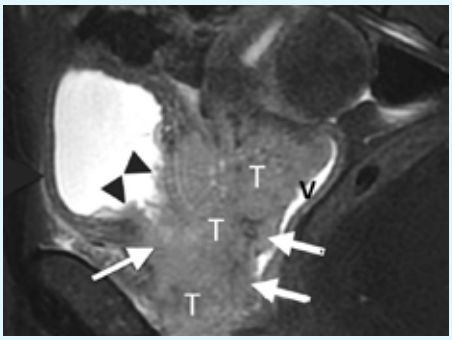

Figure 8: Sagittal T2-w MRI scan in a 56-year-old woman showing a cervical cancer (T) extending into the lower uterine body, the lower two-thirds of the vagina (arrows) and the posterior and anterior bladder walls with mucosal involvement (arrowheads). This is consistent with a stage IVA cancer. V – vagina.

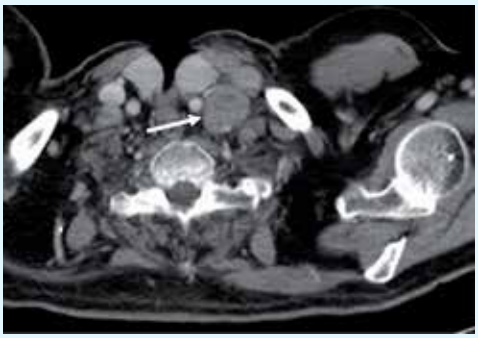

Figure 9. Axial CT Scan slice just above the sternal notch shows a left supraclavicular enlarged lymph node (arrow). This was biopsy proven metastatic cervical cancer. This is consistent with a stage IVB cancer.

DIGIMED

Malta's First Truly Comprehensive and Secure Telemedicine Platform

Thanks to an increasingly tech-savvy world where people are trying to find more and more ways to do things from the comfort of their own homes, international healthcare trends show a clear shift by patients and doctors towards using telemedicine consultations.

In our efforts to embrace the future while using the past as a solid foundation, we are proud to announce that we will soon launch DIGIMED - Malta's first truly comprehensive and secure telemedicine platform.

DIGIMED not only lays down the framework for a telemedicine consultation to be carried out using a comprehensive, multifunctional, and trustworthy platform, but it also makes it possible for a patient to have immediate access to a variety of medical practitioners at the touch of a button. With DIGIMED, spending time in traffic, parking, queuing at the doctor's clinic, and queuing once again to pay will be things of the past.

During the height of the COVID-19 pandemic in Malta, over 200,000 telemedicine consultations took place. This statistic alone shows that the timing was right to introduce an online, state-of-the-art healthcare solution that the Maltese people can benefit from. DIGIMED will not only focus on bridging the communication gap between patients and healthcare service providers, but it will empower patients by giving them control of their health data for the first time. To create greater accessibility and inclusion, the platform will also allow registered patients to book consultations and manage records for children, the elderly, or persons with a disability once their relationship has been verified. We are not reinventing the healthcare system, but we are creating better access for everyone: patients, doctors, and pharmacies.

Doctors can choose from the three types of consultations on offer or use the 'Patient Management System' to record information from in-clinic consultations. The three modes of consultation that doctors can choose from are 'Dr on Demand', 'Scheduled', and 'Home Visit'. The 'Dr on Demand' option is a brand-new concept in Malta, allowing patients to speak to their doctor of choice without any notice or a pre-booked appointment. All the doctors must do is press a button on the system to mark themselves online/available to receive new requests. The 'Scheduled' and 'Home Visit' options are already well-known and utilised in the medical field; however, 'Dr on Demand' can offer instant medical care 24/7.

Key functions of the platform are an advanced patient management system, e-health records, e-prescriptions, referrals and sick notes, and automated insurance claim forms. The patient management system will ensure doctors have a reliable and efficient platform to store and update their patient records accordingly, irrespective of whether they have seen patients online or in their clinic. Patients, too, will have access to their records within their 'Electronic Health Record' database or 'Health Wallet'. Doctors can view the entire history of their patients, even EHRs created by other doctors - this will help save time.

DIGIMED will guide users through a simple Electronic Health Record form for each consultation recorded on the system. Electronic Health Records may be added to an existing diagnosis (case) on the patient's file, or a new case may be opened. Cases may also be marked as chronic. The Electronic Health Record forms include multiple templates designed to help doctors streamline their workflow depending on the treated medical condition.

When it comes to prescriptions, DIGIMED has an integrated e-prescription system allowing doctors to prescribe single or ongoing prescriptions. The platform will provide a secure facility for medical practitioners to issue electronic medical prescriptions to their clients. To provide a safe environment, local pharmacies will be able to connect to a portal on the platform to verify the authenticity of the prescription.

With the platform, it will also be easy to create referrals and sick notes. Through DIGIMED, referral forms may be completed as part of your post-consultation workflow in a streamlined process. Sick notes may also be easily created, signed digitally, and exported to the patient.

DIGIMED also offers an automated insurance claim form process as a bonus. Patients may export their existing records as a structured claim form – this means that doctors no longer need to complete endless insurance claim forms.

Ultimately, we aim to help offer greater accessibility and a more straightforward, faster, more convenient, secure service for every patient and all healthcare professionals. We look forward to revolutionising and modernising healthcare in Malta and giving everyone a better, healthier, and more efficient tomorrow.

The DIGIMED app can be downloaded via a mobile application from the App Store and Play Store. Desktop users can access the web application via the web which will be available soon.

For more information on this innovative healthcare solution, please feel free to get in touch on: info@digimed.health