MEDICAL UPDATE GROUP MEETING

WHAT'S NEW IN THERAPEUTICS ?

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SADECK VAWDA

WHAT'S NEW IN THERAPEUTICS ?

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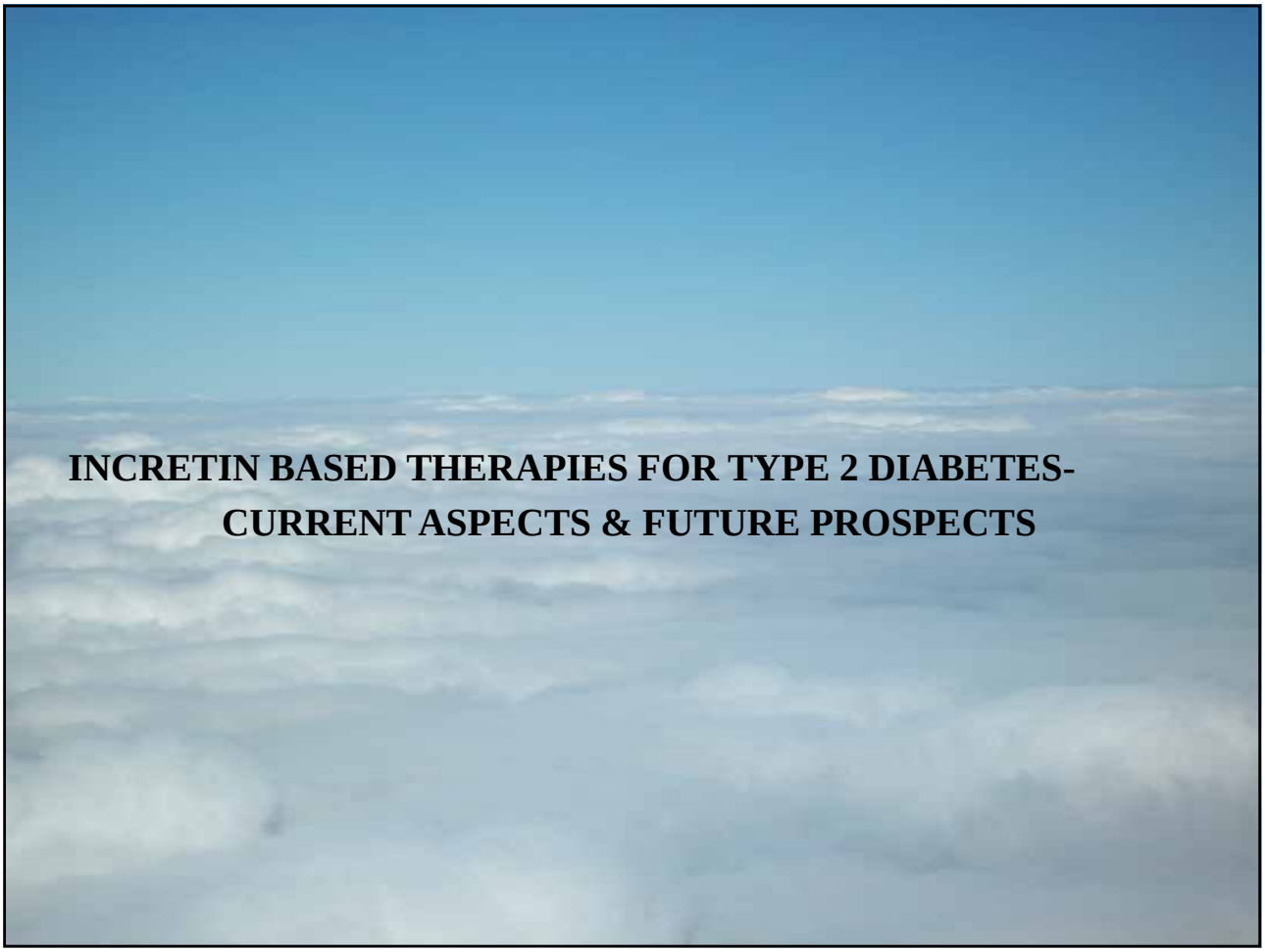

INCRETIN BASED THERAPIES FOR TYPE 2 DIABETES-
CURRENT ASPECTS & FUTURE PROSPECTS

THE INCRETIN SYSTEM

- Incretins are a type of gastro intestinal hormone that cause an increase in the amount of insulin released from the beta cells of Islets of Langerhans
- They also inhibit release of glucagon from the pancreas → Liver reduces its production of glucose
- Example GLP (glucagon like peptide)
  GIP (glucose dependent insulinotropic peptide)
- Inactivated by enzyme DPP4 (dipeptidyl peptidase)
- Patients with type 2 diabetes have a significant reduction of the incretin effect implying that patients have decreased concentration of incretin or resistance to its effect.

INCRETIN BASED THERAPIES

INCRETIN MIMETICS
(GLP analogues / agonists)

EXENATIDE (BYETTA)
LIRAGLUTIDE (VICTOZA)

MIMICKS ENDOGENOUS GLP

INSULIN RELEASE

INCRETIN ENHANCERS
(ORAL DPP4 INHIBITORS)

VILDAGLIPTIN (GALVUS)
SITAGLIPTIN (JANUVIA)
SAXAGLIPTIN (ONGLYZA)

INHIBIT ENZYME DPP4

PREVENT BREAKDOWN OF INCRETINS

PROLONG & ENHANCE THE INCRETIN EFFECT

INSULIN RELEASE

ORAL DPP4 INHIBITORS
(VILDAGLIPTIN, SITAGLIPTIN & SAXAGLIPTIN)

- Inhibits the enzyme (DPP4) – Selective DPP4 inhibitor
- DPP4 inhibitors enhance the incretin effect.
- When blood sugar is high, incretin works in two ways to help the body regulate blood sugar level : It triggers the pancreas to release insulin / signals the liver to reduce production of glucose.
- Incretins also slow the rate of absorption of nutrients in the blood stream by reducing gastric emptying and may indirectly reduce food intake.
- DPP4 inhibitors therefore enhance the body's own ability to control blood sugar by increasing active levels of incretin.

ORAL DPP4 INHIBITORS

- Risk of hypoglycaemia is low as they work only in the presence of glucose. Postprandial, when glucose levels are high, incretins are released and DPP4 inhibitors prevent its breakdown to lower blood sugar levels.
- Weight neutral
- Once daily dosing – With or Without food
- Main side effects : Nausea/Vomiting/Sore throat/Runny nose

ORAL DPP4 INHIBITORS

- Place in therapy :
  - Can be used as monotherapy.
  - Indicated as a second line to improve glycaemic control in combination with diet and metformin when metformin alone does not provide adequate control.
  - As an alternative to sulphonylureas where hypoglycaemia / weight gain is a problem.
  - Useful addition in the range of existing treatment for type 2 diabetes, taking into cosideration recent problems with glitazones
    . Should not be used in type 1 as ineffective.
- Approved for use in 42 countries.
- Recent cases of acute pancreatitis.

INCRETIN MIMETICS
(GLP1 analogues / agonists)

- **EXENATIDE**
- **LIRAGLUTIDE**

INCRETIN MIMETICS

Exenatide – An incretin mimetic

- Exenatide mimicks incretin (mimicks GLP1)
- Injectable form (S/C) – pen device
- Synthetic version of exendin 4, a hormone found in the saliva of the glia monster, a poisonous lizard in the Amazonian southwest.
- Scientists have noticed that glia monster go for long period of time without eating. While fasting the pancreas is literally switched off. When they do eat, exendin 4 is secreted which flips the switch on, hence the meal is digested.

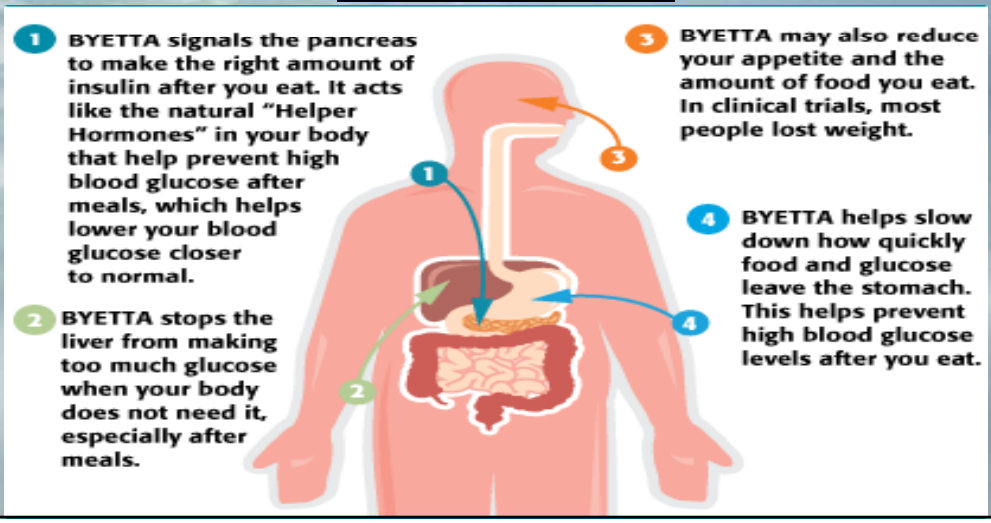
INCRETIN MIMETICS

GLIA MONSTER LIZARD

INCRETIN MIMETICS

Exenatide can be used with metformin, a sulfonylurea, or a glitazone to help keep blood glucose (blood sugar) under control in at least four ways:

HOW IT WORKS



EXENATIDE – An incretin mimetic

- Important reduction in HbA1c
- Main side effects are nausea / vomiting – worst during the first two weeks, gets better with time.
- Twice daily dosing SC (within an hour of eating breakfast / dinner)
- Risk of hypoglycaemia is low on its own. Hypoglycaemia may occur when it is first added to oral medication.
- Causes weight loss. Useful in overweight / obese patients with type 2 diabetes.
- Post Marketing Reports : Few cases of acute pancreatitis.
- Easy to use as patients never have to adjust the dose based on the size of the meal or how much exercise done.

EXENATIDE – An incretin mimetic

- Place in therapy
  - Monotherapy or in combination with oral medications in type 2 diabetes.
  - Cannot be used in type 1 diabetes.
  - Main disadvantage is injectable form.
  - Approved for use in USA and in many countries.
- Future : Exenatide LAR (Once weekly injection)

LIRAGLUTIDE (An incretin mimetic) - VICTOZA

- A long acting GLP1 analogue (incretin mimetic) partly resistant to DPP4.
- Half life of 10-14 hours
- S/C use
- Once daily injection
- Reduces fasting and post prandial glucose and Hb1AC levels by up to 1.75%.
- Induces significant weight loss.
- Studies show that once daily Liraglutide shows better glycaemic control than twice daily exenatide.
- Incidence of hypoglycaemia is low.
- European approval in July 09.

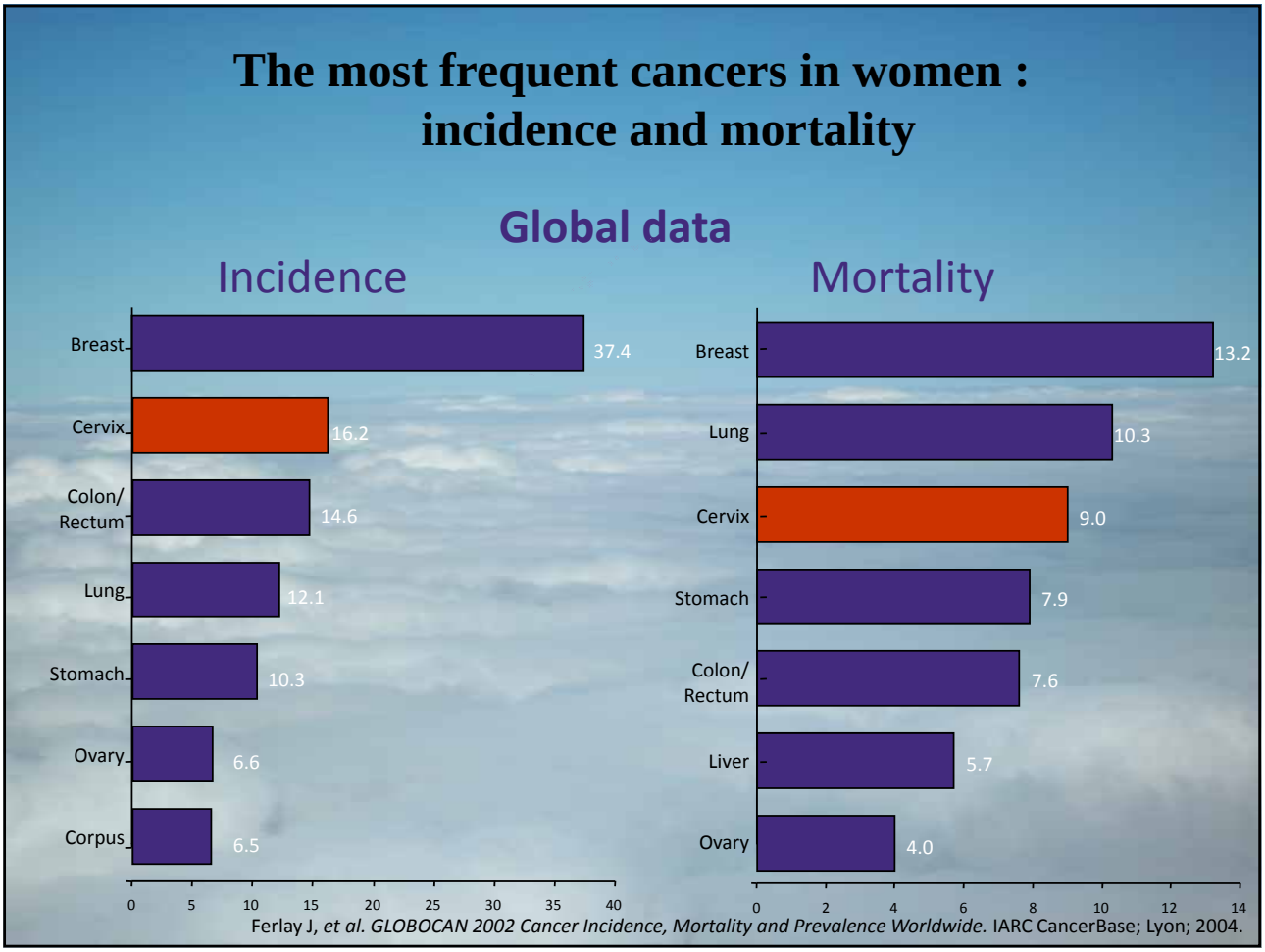
Future developments

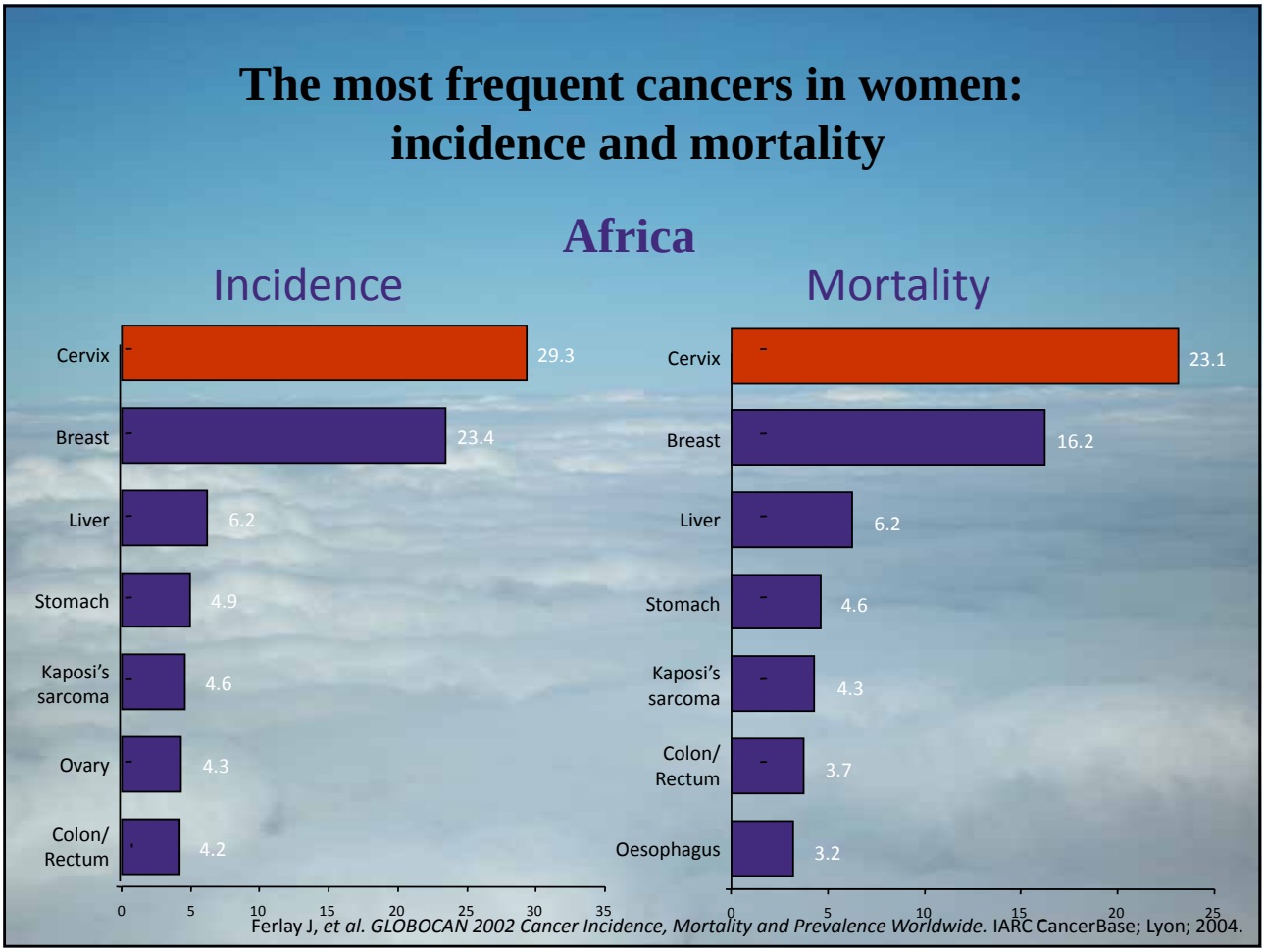
- Animal studies and in vitro studies have shown that GLP1 analogues/ agonists and to a lesser extent oral DPP4 inhibitors prevent beta cell apoptosis and induces beta cells regeneration. An important finding which if confirmed by more clinical research would revolutionize the treatment for type 2 diabetes.
- Improvement of Pharmacokinetic parameters of GLP1 analogues
  - Minimize peak levels to reduce nausea
  - Long acting- for better control and to improve compliance
- Long term mortality / morbidity studies awaited to situate their exact places in the therapy of Type 2 diabetes.


AN UPDATE ON THE CERVICAL CANCER VACCINE

Cervical cancer

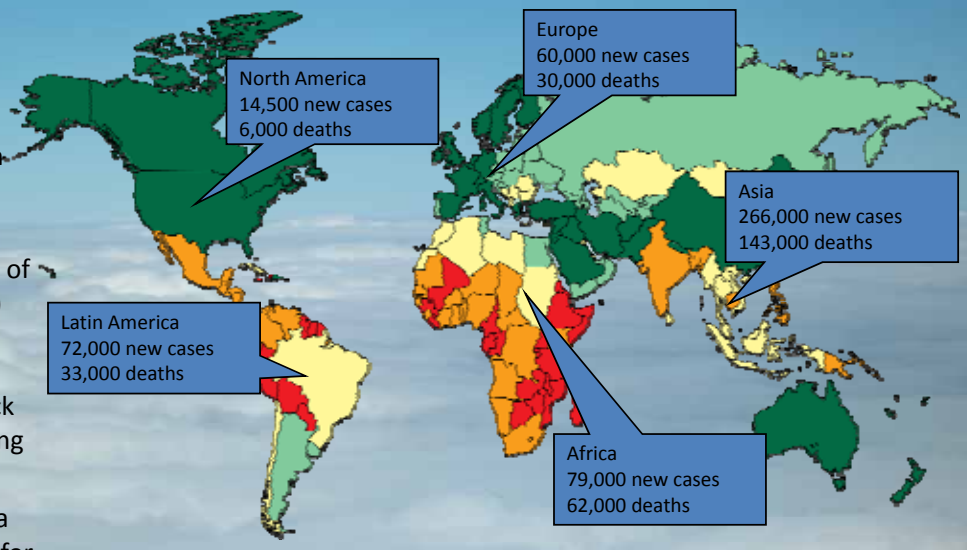
The most common cancer in women in incidence and mortality in Africa , 2nd in the world after breast cancer.


The most frequent cancers in women : incidence and mortality
Global data
Incidence
Breast 37.4
Cervix 16.2
Colon/ Rectum 14.6
Lung 12.1
Stomach 10.3
Ovary 6.6
Corpus 6.5
0 5 10 15 20 25 30 35 40
Mortality
Breast 13.2
Lung 10.3
Cervix 9.0
Stomach 7.9
Colon/ Rectum 7.6
Liver 5.7
Ovary 4.0
0 2 4 6 8 10 12 14
Ferlay J, et al. GLOBOCAN 2002 Cancer Incidence, Mortality and Prevalence Worldwide. IARC CancerBase; Lyon; 2004.


The most frequent cancers in women: incidence and mortality
Africa
Incidence
Cervix
29.3
Breast
23.4
Liver
6.2
Stomach
4.9
Kaposi's sarcoma
4.6
Ovary
4.3
Colon/ Rectum
4.2
0
5
10
15
20
25
30
35
Mortality
Cervix
23.1
Breast
16.2
Liver
6.2
Stomach
4.6
Kaposi's sarcoma
4.3
Colon/ Rectum
3.7
Oesophagus
3.2
0
5
10
15
20
25
Ferlay J, et al. GLOBOCAN 2002 Cancer Incidence, Mortality and Prevalence Worldwide. IARC CancerBase; Lyon; 2004.

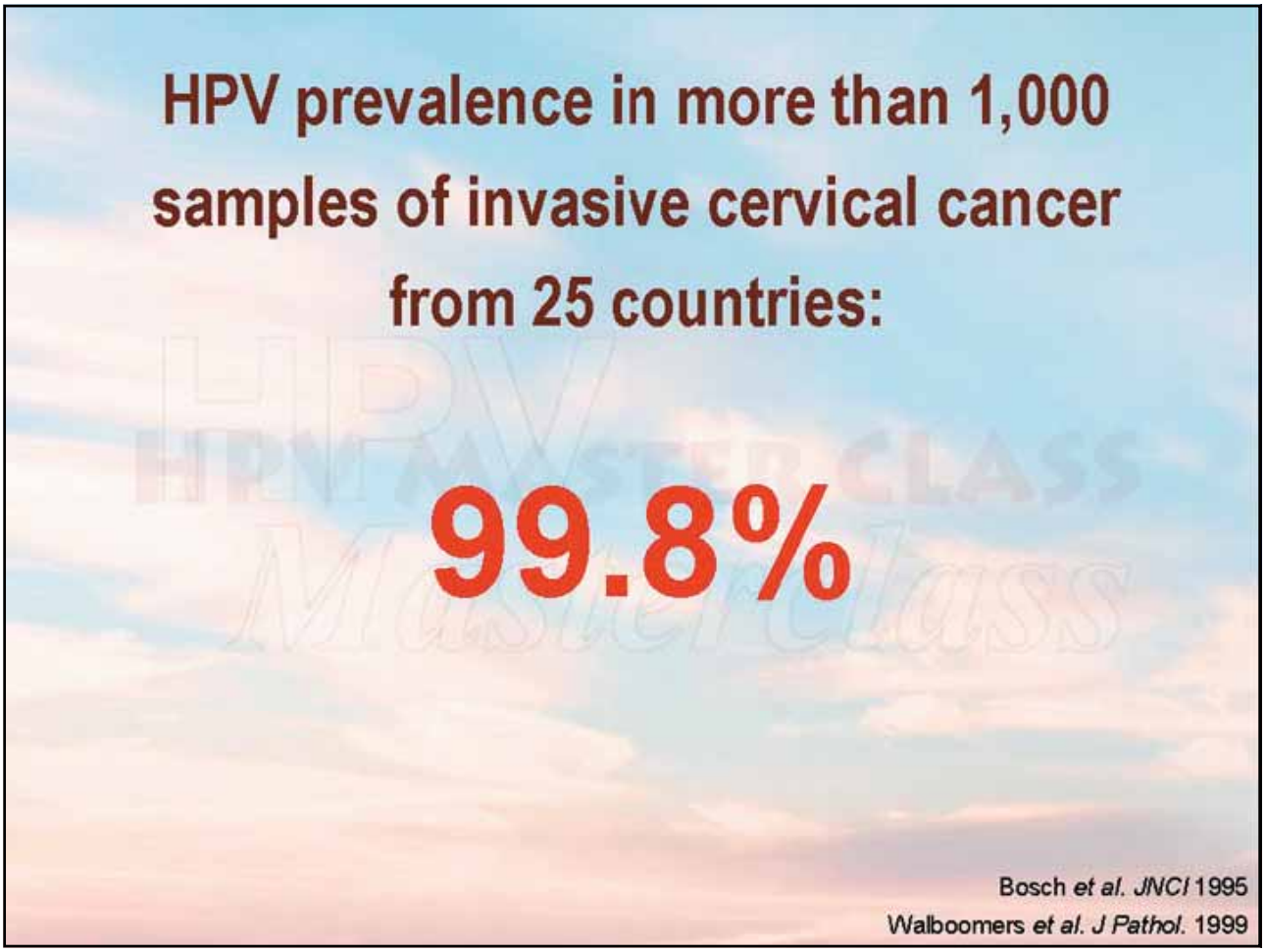
Global mortality per annum

- Worldwide, every 2 minutes a woman dies of cervical cancer[1]
- The highest burden of disease (up to 80%) occurs in less developed regions[1] where there is a lack of effective screening programmes
- This demonstrates a clear medical need for new cervical cancer interventions



Cervical cancer mortality rates worldwide
Cases per 100,000 women per year

1. Ferlay J, *et al. GLOBOCAN 2002 Cancer Incidence, Mortality and Prevalence Worldwide.* IARC CancerBase; Lyon, 2004.


HPV prevalence in more than 1,000 samples of invasive cervical cancer from 25 countries:
99.8%
Bosch et al. JNCI 1995
Walboomers et al. J Pathol. 1999

HUMAN PAPILLOMA VIRUS

- Group of viruses that include more than 100 types
- More than 30 can be passed through sexual contact (anogenital)
- For most women , the body's own defence system will clear the virus
- Some types cause cervical cancer or abnormal cells in the lining of the cervix that can sometimes progress to cancer
- Other types are a major cause of genital warts
- HPV is the most common STD (50% of young adult females aquire it within 3 years of sexual debut)
  - Peak at 20, declines at 30
- HPV 16/18 account for the majority of worldwide cervical cancer
- HPV 6/11 are most often associated with anogenital warts.

HUMAN PAPILLOMA VIRUS

- Antibody response to natural HPV infections is poor, hence

  - Natural infection does not necessarily confer protection
  - Women remain at risk of persistent HPV infection throughout their lives
  - Persistent HPV infections is the cause of cervical cancer

HPV VACCINES

Two vaccines are registered :

- Cervarix → Type 16, 18 (Cervical cancer)
- Gardasil → Type 6,11,16 &18(Cervical cancer and genital warts)

HPV vaccines are subunit vaccines made up of virus like particle

Both vaccines are effective against HPV types 16 and 18 which cause approximately 70% of cervical cancer cases

Virus Like Particle (VLP)

L1 protein pentamer

VLP Looks exactly like the virus but contains no viral DNA

Thus elicits strong immune response without any risk of infection

CERVICAL CANCER VACCINES

How is it administered ?

- Given as three injections over a six month period

Initial dose —(2 months)→ 2nd dose —(4 months)→ 3rd dose

IM (thigh / upper arm)

WHO AND WHEN

- Before sexual debut ?9-13 "screen yourselves-vaccinate your daughters"

BUT

- 20 years to see any impact
- 30-40 years to see benefit on Ca Cx

THEREFORE

- May consider "catch up" vaccination for all sexually active women
  - We know its effective and safe in older women (10-55)
  - We know very few carry both 16 and 18
  - We know most HPV infections are transient

SUGGESTS SIGNIFICANT BENEFIT FOR ALL SEXUALLY ACTIVE WOMEN

WHO AND WHEN

•In other words, vaccinating all sexually active women will probably :

- •Reduce Ca Cx
- •Reduce repeat visits and smears
- •Reduce colposcopies
- •Reduce destructive cervical procedures and the obstetric complications associated with them
- •Reduce hysterectomies for pre-invasive cervical lesions

And consequently reduce the -

- •Psychological
- •Physical
- •Financial

- Morbidity and mortality associated with them

WHO AND WHEN

•? Males	- Controversial
•? Prev abn PAP	- Vaccinate
•? Current abn PAP	- Vaccinate
•? Pre vaccination HPV test	- Not necessary
•? Pregnancy	- Postpone
•? Lactation	- Benefit vs Risk
•? With other vaccines	-Fine
•? Boosters	- Not needed to 5.5 years trials ongoing but look promising for long term

CERVICAL CANCER VACCINES

- Since no vaccination is 100% effective and patient may have been infected prior to vaccination , routine PAP screening remains important.
- How effective ?

  Preliminary results show that it was nearly 100% effective in women who had not been infected prior to vaccination in preventing precancerous cervical lesions caused by HPV type against which the vaccine is directed
- "HAILED as one of the major medical advances of the 21st century"
- Marketed in US / EU countries (Available in Mauritius)
- Mild local side effects (pain, tenderness at the site of injection)
- Routine vaccination in UK as from September 2008

Key Take home messages

- Cervical Cancer is a major cause of cancer deaths world wide
- Persistent HPV infection causes cervical cancer
- Available HPV vaccines are extremely effective in preventing both infection and consequent CIN lesions
- Available HPV vaccines are well tolerated and safe
- The novel AS04 adjuvant in the bivalent vaccine appears to be responsible for stronger and more sustained immune responses
- Vaccinating pre adolescent girls before sexual debut has the maximal potential to prevent Ca Cx
- Women remain at risk for HPV infection throughout their lives and vaccination should be offered to all women

ULIPRISTAL
A NEW OPTION FOR EMERGENCY CONTRACEPTION

- Emergency Contraception (misnomer “morning after pill”) is a safe and effective type of birth control method after unprotected sex or when another contraceptive method may have failed.

- Type of emergency contraception

  - Hormonal pills
  - Intrauterine device

History of emergency contraception (EC)

< 1970 – High dose oestrogens
(diethylstilboestrol/ethinyloestradiol)

1970's – 1990's - YUPZE METHOD
(combination of an oestrogen + progestogen)
- within 3 days of intercourse

2000 – 2009 - Progesterone only pill (levonorgestrel) Norlevo-
within 3 days of intercourse

2010 - ULIPRISTAL (ELLA)- new drug
within 5 days of intercourse

IUD - has to be used up to 5 days after unprotected intercourse to prevent pregnancy

Progesterone only pill (levonorgestrel – Norlevo)

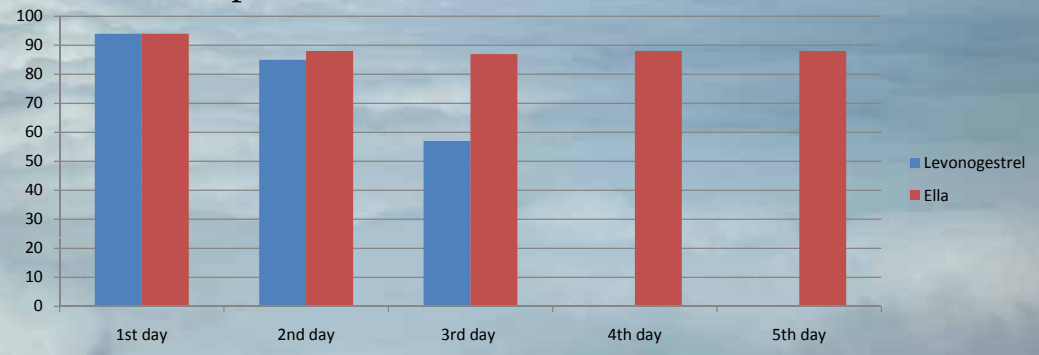
- Mechanism of action
  - Prevents ovulation
  - Prevents implantation of fertilized egg in the uterine lining
- Single dose within 72 hours of unprotected intercourse.
- The sooner the better in terms of efficacy. Highest within 12 hours, decline over time

ULIPRISTAL (ELLA)
A novel emergency contraception

- Effective alternative to levonorgestrel based pills as published in the Lancet (29/1/2010)
- Single dose tablet of 30mg
- Lincensed for emergency contraception for up to 5 days (120 hours)
- Prescription only drug as more data awaited before switching to OTC.
- Pharmacology : Selective progesterone receptor modulator (with antagonist / partial agonist activity). High affinity for progesterone receptors
- Mechanism of action :
  - Inhibits ovulation
  - Alterations to the endometrium
- Most common side effects : nausea/vomiting/ abdominal pain
- Approved for use in European Union, FDA has issued a favorable opinion.

ULIPRISTAL (ELLA)
Advantages over levonorgestrel based emergency contraception

- Higher rates of efficacy (1.8% pregnancy rate to 2.6% in levonorgestrel)
- Efficacy rates nearly stable over 5 days unlike levonorgestrel which declines over 3 days
- Same side effect profile



Based on Phase 2 : "Progesterone Receptor Modulator for Emergency Contraception, Creinin et al, Obstetrics & Gynecology, Vol.108 N5, Nov 2006"

DAPOXETINE

The first drug licensed for premature ejaculation

DAPOXETINE

SEXUAL DYSFUNCTION IS CHARACTERIZED BY DISTURBANCE IN THE PROCESSES THAT CHARACTERIZE THE SEXUAL RESPONSE CYCLE WHICH CAN BE BROKEN DOWN IN 4 PHASES

- DESIRE
- EXCITEMENT
- ORGASM
- RESOLUTION

PREMATURE EJACULATION (PE) IS A PROBLEM ASSOCIATED WITH THE ORGASM PHASE

DAPOXETINE

- PREMATURE EJACULATION is the most common form of sexual dysfunction in men affecting 21% of men aged 18 to 59 years
- PE is defined as persistent or recurrent ejaculation with minimal sexual stimulation before, on ,or shortly after penetration and before the person wishes it
- The diagnostic criteria also include the emotional and interpersonal impact of PE.

DAPOXETINE

Current PE management include :

- OFF Label use of the SSRIs and TCAs group of anti depressants such as fluoxetine , paroxetine , clomipramine etc
- Local anaesthetic creams (ex. STUD, EROS etc)

Dapoxetine is the first drug specifically approved for PE

DAPOXETINE
A novel drug in PE

- Dapoxetine is a selective serotonin reuptake inhibitor.
- Appears to be effective in PE due to the critical role of serotonin in the pathophysiology of the disease.
- Ejaculation is a reflex comprising different sensory pathways, motor centres and nerve pathways.
- The ejaculatory reflex has been shown to be controlled primarily by both serotonin and dopamine
- In PE , there is a reduction in the serotonergic transmission.
- Blocking of serotonin reuptake by dapoxetine increases level of serotonin, hence delays ejaculation.

DAPOXETINE
A novel drug in PE (Priligy)

- A fast acting serotonin reuptake inhibitor (compared to other SSRIs / TCAs)
- Short half life
- Peak plasma concentration attained between 1.4 – 2 hours
- Dosage & administration :

  30-60 mg tablet – 1 to 3 hours before intercourse
- Main adverse effect : nausea,diarrhoea,dizziness and headache

DAPOXETINE
A novel drug in PE (Priligy)

- Approved for use in Germany, Austria, Italy, Spain and Sweden. Recently introduced in the UK. Awaiting US FDA approval.
- Has the potential to as much for men's sexual health as sildenafil. It will give sufferers the chance to improve the quality of their relationships and general well being.
- More studies awaited before defining its exact role and efficacy

NEW ORAL ANTICOAGULANTS FOR MANAGEMENT / PREVENTION OF VTE

History of oral anticoagulation

- Warfarin was of one over 100 coumarin derivatives investigated following the synthesis in 1940 of dicoumarol – the anticoagulant in mouldy clover hay that had been causing fatal haemorrhage in North American cattle since 1920.
- Initially developed for rodent control
- In 1951 – a suicide attempt by a US army recruit drew attention to its effects in humans which led a couple of years later to its clinical use
- In 1955 – given to President Eisenhower after a heart attack
- Before warfarin, for thromboembolic complications there were only aspirin and heparin available and it was not practical to give daily injections of heparin
- Warfarin was thus hailed as a “major breakthrough”

History of oral anticoagulation

- Warfarin is a vitamin K antagonist thus blocking vitamin K which is important in the synthesis of clotting factors II, VII, IX, X and anticoagulation protein C and S. All are required in the coagulation cascade for the formation of thrombin and ultimately fibrin, the fibrous protein that combines with platelets to form blood clots.
- **Rivaroxaban** (**Xarelto** – once daily dosing)

  &

  Dabigatran (**Pradaxa** – twice daily dosing)

  are two new oral anticoagulants recently introduced.

WARFARIN – A highly effective drug but with huge drawbacks

Indications of Warfarin

- Prevention and treatment of VTE and pulmonary embolism
- Post operative prophylaxis in patients undergoing joint surgery or insertion of artificial heart valves.
- Following larger MI especially of the anterior wall or with left ventricular aneurysm.
- Potentially the greatest use is stroke prevention in patients with AF → Patient selection and adherence problems + careful dose titration / regular monitoring mean that only a small proportion benefit from this therapy

Drawbacks of Warfarin therapy

- Slow onset of action (5 days to achieve a stable antithrombotic effect)
- Risk of haemorrhage
- Careful dose titration – It takes a lot of time and disciplined patient to get dosing right.
- Regular Monitoring → Anticoagulant clinics
- Narrow therapeutic index
- Various drug interactions of clinical importance
  - potentiation or reduction of anticoagulant effect with all risk involved
- Interpatient variability

Management of VTE (DVT / PE)

- Anticoagulation remains the cornerstone of VTE
- It is divided into 2 stages

  - Rapid anticoagulation given to minimize the risk of thrombus extension and fatal PE
  - Extended anticoagulation to prevent recurrent VTE

Rapid anticoagulation : Heparins, LMWH and fondaparinux.

LMWH and Fondaparinux – once daily SC dosing

Extended anticoagulation : Warfarin

(Warfarin has a slow onset of action and cannot be used for rapid anticoagulation)

Management of VTE (DVT / PE)

- The majority of patients on LMWH / Fondaparinux are now treated as outpatients. Injectable route is a major drawback which prompted research into longer acting injectable and new oral anticoagulants
- Longer acting injectable : Under development is idraparinux – Once weekly injection.
- New oral anticoagulants are rivaroxaban and dabigatran which are already marketed in the European Union

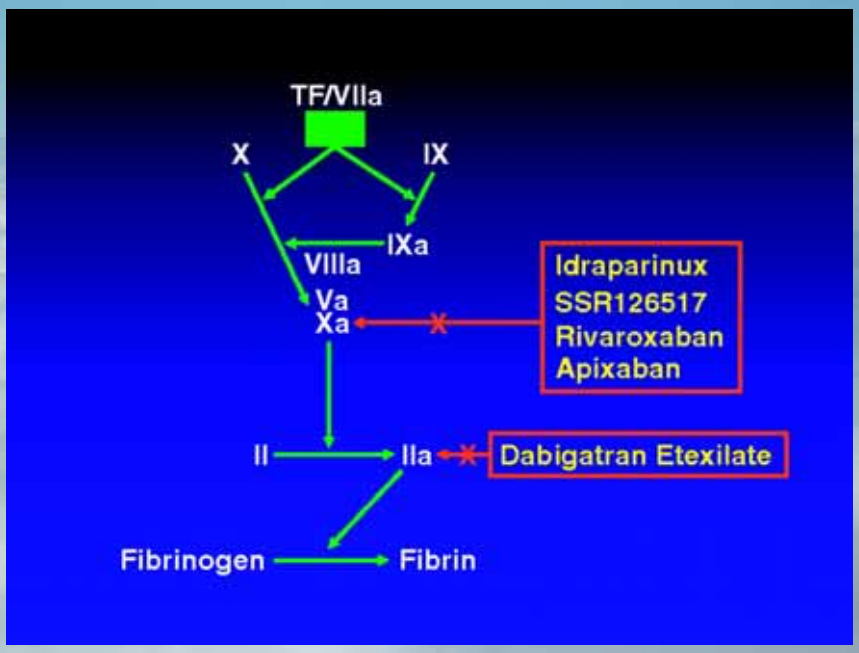
Novel Drugs

Idraparinux – as heparin, LMWH and fondaparinux,injectable
- Factor Xa inhibitor

Rivaroxaban - The first orally acting factor Xa inhibitor

Dabigatran - Orally acting direct thrombin inhibitor
(The first in this class was ximelagatran which was removed from the market due to liver toxicity)

Targets of new anticoagulants for treatment of venous thromboembolism



Opportunities for new anticoagulants in VTE treatments

- Introduction of LMWH was a major advance in the management of VTE as there was no need for coagulation management and patients shifted to outpatient setting
- The new anticoagulants have the potential to further streamline care and may offer safety advantages over existing treatment
- The new oral anticoagulants:
  - Rapid onset of action → peak plasma concentration within 2-4 hours → candidates for rapid anticoagulation

Opportunities for new anticoagulants in VTE treatments

- The new oral anticoagulants

  - Eliminate the need for injectable drug for rapid anticoagulation
  - can be used for extended anticoagulation
  - Fixed dosing
  - No need for anticoagulation monitoring
  - Will prove more convienient than warfarin
  - If risk of bleeding is less than warfarin, it will further expand the frontiers of VTE management

Major drawbacks of new oral anticoagulants

- No specific antidote yet to reverse anticoagulant effects
- Dialysis is likely to clear but more studies needed
- Side effects ? Ximelagatran ?
- More studies needed on risk of bleeding ? Monitoring ?
- In the absence of routine monitoring , compliance is difficult to assess.
- High cost
- These issues will need to be addressed for the exact place in therapy of these new oral anticoagulants be defined

New oral anticoagulants

- Present indication is only in prevention of VTE and not in treatment
- Present indication is thromboprophylaxis after major orthopedic surgery
- Both drugs have shown in several trials a non inferior efficacy to enoxaparin with a similar safety profile
- Both are approved in this indication by NICE

  Ex. Rivaroxaban in once daily dose with the initial dose taken 6-10 hours after surgery. Duration depends on individual risk of VTE

New oral anticoagulants

- More studies awaited on
  1. Efficacy in VTE treatment
  2. Side effect profile
  3. Comparison with LMWH / Warfarin
  4. Use in AF for stroke prevention

Does this mean the end for anticoagulation clinics ?


BIOPHARMACEUTICALS / BIOSIMILARS
- Challenges ahead

BIOPHARMACEUTICALS / BIOSIMILARS
- Challenges ahead

- Few biopharmaceuticals have been around for a while
  - erythropoietin
  - beta interferons
  - recombinant insulin
  - interleukins
  - somatostatin
  - granulocyte colony stimulating factors
  - monoclonal antibodies
  - low molecular weight heparins
  - thrombolytic agents (alteplase)
- But as technology progresses, numbers will increase
- Similarly as patent expires, “biosimilars” are set to become available

History of evolution of drugs

- Beginning of the 20th century – Medicine market was dominated by preparations derived from natural sources of plants , animals or mineral origin.
- Later on the evolution led to the development of synthetic molecules discovered in the laboratory and manufactured in large scale chemical plants. Advantage was that they were consistent in their molecular structure and could easily be purified and characterised.
- By varying the molecules in a homologous series, they could be made more potent with less side effects.
- By the end of the 20th century , the synthetic molecules reaching the market decrease considerably.
- Recombinant DNA technology became available as a manufacturing tool and the age of biopharmaceuticals ushered in the 21st century

WHAT ARE BIOPHARMACEUTICALS ?

- Biopharmaceuticals are complex , high molecular weight proteins and peptides that are produced in living systems.
- Encoding of gene and insertion in DNA of host cells results in a master cell batch suitable for the production process
- Master cell batch split in several aliquots which are stored in deep freeze to preserve their integrity.
- Each aliquot is used in cell culture to produce larger volumes.
- The culture produces a unique product that consists of several different variations on the original molecule (ex. Amino acid chains/ sugar residue can vary)
- Biopharmaceuticals produced by different manufacturing units / processes can never be identical, only similar.

WHAT ARE BIOPHARMACEUTICALS ?

- The term “generics” should not be used for biopharmaceuticals but “biosimilars”
- Production of a biopharmaceutical is a much longer process than chemical manufacturing, hence high cost
- Culture medium includes hamster ovary cells (which secrete product in medium), yeast, or E.coli(needs to be lysed to release product)

WHAT ARE BIOPHARMACEUTICALS ?

- Modification of biopharmaceuticals by glycosylation / pegylation

  e.g. glycosylation of erythropoietin (given 3 times a week)

  → darbepoetin alfa → prolongs duration → given once weekly or every two weeks

  pegylation → e.g. pegylated interferons
- Peptides, hence can only be given by injectable route (S/C / IV)

BIOPHARMACEUTICALS

- Carry a warning that it should not be shaken vigorously
  → to prevent aggregation. Aggregates are known to produce an immune response and to alter pharmacokinetic profile.
- Most should be stored between 2-8 degree Celsius
- As product purification and formulation has improved, some (insulin in pens) can be stored at room temperature
- Although biopharmaceuticals closely resemble the endogenous proteins, it can elicit an immune response : can vary from no perceptible effect to significant clinical effects.
- Product related factors that can influence immunogenicity are amino acid sequence variation / glycosylation / host cell / contaminants / formulation / handling and storage.

BIOSIMILARS

- The worldwide biopharmaceuticals market is worth more than 45 billion Euros annually.
- Copies of these products have been made worldwide in non regulated markets and in regulated markets where patents have expired, other companies other than the originators have been quick to enter this market

  e.g. – Biosimilar Insulin

  - Omnitrope is a biosimilar brand of genotropin, using it as a reference
- Advantages :

  As more suppliers enter the market this will lead to fall in prices with more funds released for the treatment of more patients.

BIOSIMILARS

- Disadvantages :

- cannot make exact copy of originator, hence no true generics
- produced all over the world but to different qualities and standards
- Gel electrophoresis is starting point to compare profile → products showing similar patterns are likely to have similar activity and half life

BIOSIMILARS

- To get into regulated market, biosimilars have to provide a full evaluation comparing them to a reference compound
- European medicine agency (EMA) has produced specific guidelines on biosimilars
- Unlike generics which need to show only bioequivalence, biosimilars need to undergo phase I / phase III clinical trials to show similarity to reference compound.

  e.g. epoietin alpha , epoietin beta & epoietin zeta produced by different manufacuring processes.

BIOSIMILARS

Substitution or clinical interchange

- As more and more biosimilars are inevitable, can they be safely interchanged ?
  - for clinical reasons
  - for cost reasons
- Insulin provides a good analogy
  - switching require clinical monitoring
- Some biopharmaceuticals can be interchanged but prescriber must be involved and patient must be transferred under monitored conditions
- Simple substitution at dispensing level is not acceptable
- BNF recommends to use brand names when prescribing biopharmaceuticals

BIOSIMILARS

The Future

- Several hundred biopharmaceuticals in pipeline, outnumbering new chemical entities
- Moving now into the concept of “biobetters”
  e.g. increase in half life , improved efficacy with less side effects
- Use in gene therapy – 70 % of trials are in cancer
- At present many of the products in use are administered in hospitals / clinics but just like insulin they shall find their way increasingly into common practice.

Miscellaneous breakthroughs

- Cardiovascular
  - Prasugrel – a new antiplatelet agent (3rd generation) Related to clopidogrel
  - Aliskiren - the first direct renin inhibitor for hypertension
- CNS
  - Agomelatine – the first melatonergic agonist for the treatment of major depression
    - effect on melatonin → improve onset and quality of sleep
- GI
  - Methylnatrexone – an opiod antagonist for opiod induced constipation without affecting analgesia

Miscellaneous breakthroughs

- Malignancy
  - Evrolimus – a protein kinase inhibitor for advanced kidney disease
  - Azacitidine – an epigenetic therapy altering gene expression for use in certain forms of leukaemia
- Respiratory
  - Roflumilast as add on COPD treatment
  - Phosphodiesterase 4 inhibitor


THANK YOU