WHAT'S NEW IN THERAPEUTICS ?

SADECK VAWDA

MEDICAL UPDATE GROUP

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CONTENTS

DRUG REPROFILING

“TEACHING OLD DRUGS NEW TRICKS”

DRUG REPROFILING

- ALSO KNOWN AS DRUG REPURPOSING, DRUG RE-TASKING OR THERAPEUTIC SWITCHING IS THE APPLICATION OF KNOWN DRUGS AND COMPOUNDS TO NEW INDICATIONS AND NEW DISEASES.
- HAS BEEN GROWING IN IMPORTANCE IN THE LAST FEW YEARS AS AN INCREASING NUMBER OF DRUG DEVELOPMENT AND PHARMACEUTICAL COMPANIES HAVE SEEN THEIR DRUG PIPELINES DRYING UP.
- THE DELIVERY OF BLOCKBUSTER DRUGS BY PHARMACEUTICAL COMPANIES TO SUSTAIN THEIR GROWTH OFFERS ENORMOUS CHALLENGES, YET IS REQUIRED TO NOURISH THE COLOSSAL BUDGETS ASSOCIATED WITH THE VERY RISKY BUSINESS OF PHARMACEUTICAL R&D. HENCE REPROFILING LOOKS AN INTERESTING ALTERNATIVE.

DRUG REPROFILING

MAIN ADVANTAGES

- A SIGNIFICANT ADVANTAGE OF DRUG RE-PROFILING OVER TRADITIONAL DRUG DEVELOPMENT IS THAT THE REPROFILED DRUG HAS ALREADY PASSED A SIGNIFICANT NUMBER OF TOXICITY AND OTHER TESTS, SO SAFETY IS KNOWN.THE PHARMACOKINETIC PROFILE IS ALSO KNOWN
- THE RISK OF FAILURE FOR REASONS OF ADVERSE TOXICOLOGY ARE REDUCED. MORE THAN 90% OF DRUGS FAIL DURING DRUG DEVELOPMENT.
- REDUCED COST FOR PHARMACEUTICAL COMPANIES. REPROFILED DRUGS CAN BYPASS MUCH OF THE EARLY COST AND TIME NEEDED TO BRING A DRUG TO THE MARKET AND THERE IS MUCH LESS RISK OF FAILURE, THEREFORE REDUCING SIGNIFICANTLY THE HIGH COSTS OF PHARMACEUTICAL R&D.

DRUG REPROFILING

CHALLENGES

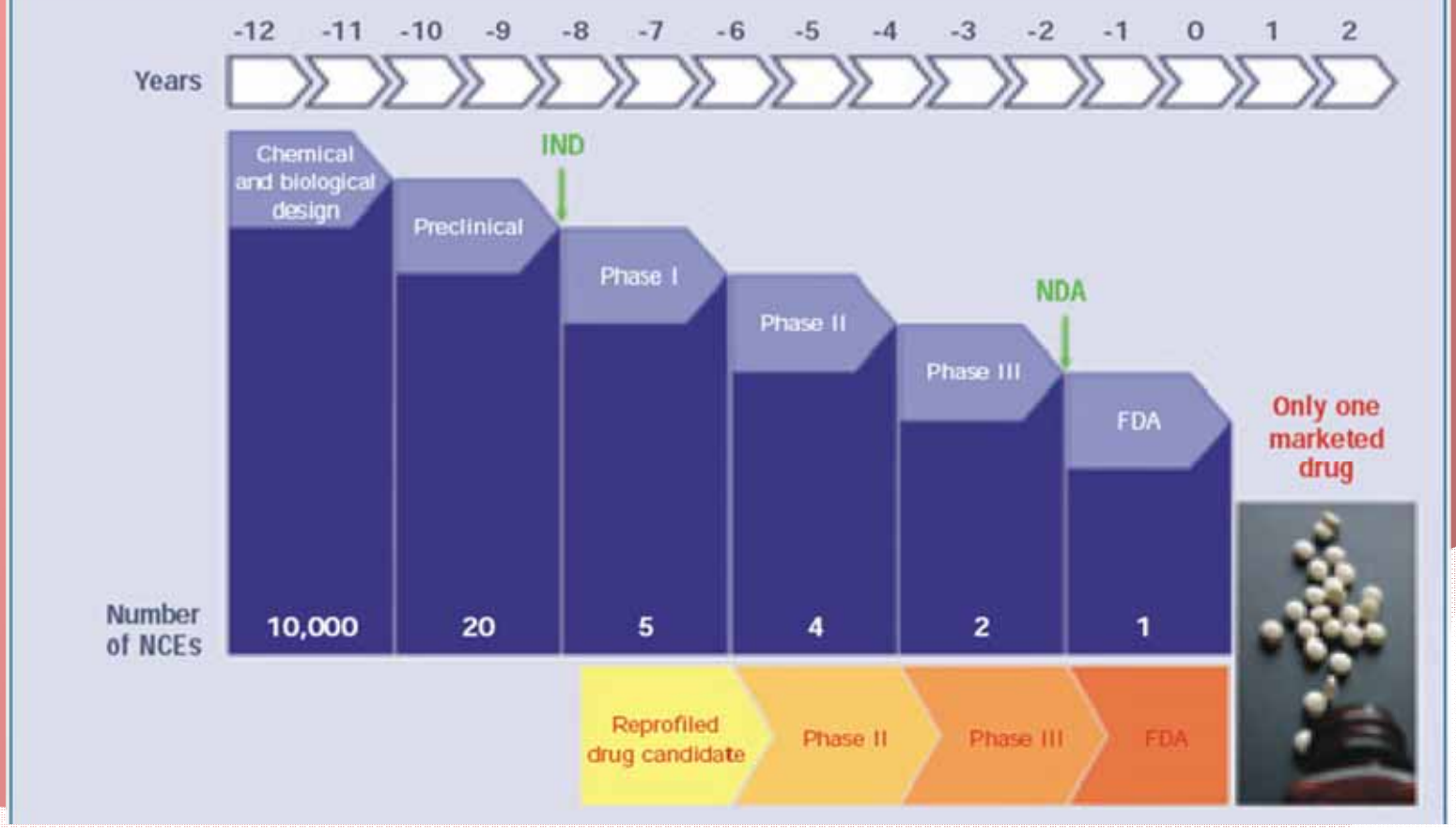
- DRUG REPROFILING FACES SOME CHALLENGES ITSELF SINCE THE INTELLECTUAL PROPERTY ISSUES SURROUNDING THE ORIGINAL DRUG MAY BE COMPLEX AND FROM A COMMERCIAL POINT OF VIEW, IT MAY NOT ALWAYS MAKE SENSE TO TAKE SUCH A DRUG TO MARKET

- MAY NOT FIT LINES OF EXPERTISE/THERAPEUTIC SEGMENTS OF PHARMACEUTICAL COMPANY MARKETING THE DRUG.

CLASSICAL DRUG DEVELOPMENT

Figure 1: Classical drug development versus the reprofiling process

Comparison of the drug development pathway for a novel chemical entity (NCE) and a reprofiled drug. Typically development of a NCE can take over 12 years with less than 1:10,000 reaching the market. Reprofiling 'safe' drugs bypasses the biggest risks to successful drug development and provides a cost and time-efficient delivery of drug candidates for clinical trial. Investigational new drug (IND) (status granted by regulatory authorities); new drug application (NDA) (to an appropriate regulatory authority, such as the Food and Drug Administration (FDA))



CLASSICAL DRUG DEVELOPMENT

SOME FACTS:

- PHARMACEUTICAL RESEARCH IS ASSOCIATED WITH HIGH COSTS, BOTH IN TERMS OF TIME AND MONEY
- A NEW CHEMICAL ENTITY TAKES ON AVERAGE 12 YEARS TO REACH THE MARKET, PROVIDED EFFICACY AND RELATIVE LACK OF TOXICITY ARE SHOWN
- LAST YEAR DRUGS WITH A VALUE OF OVER $20 BILLION DOLLARS HAVE COME OFF PATIENT AND BEEN GENERICIZED.
- MANY PHARMA GIANTS FACE A CRISIS IN THEIR LATE-STAGE PRODUCTS PIPELINE
- A FAILURE FOR A LATE STAGE PRODUCT TO MAKE IT TO THE MARKET DUE LO LACK OF EFFICACY OR EVIDENCE OF TOXICITY REPRESENTS A SIGNIFICANT LOSS FOR A PHARMACEUTICAL COMPANY
- REPROFILING IS INTERESTING AS IT ENCOURAGES MAXIMAL EXPLOITATION OF DRUGS ALREADY PROVEN SAFE, THUS REDUCING COST

AN EXAMPLE OF A NOTABLE FAILURE

- PFIZER'S ANTI-HYPERCHLOLESTEROLEMIA DRUG (↑HDL) TORCETRAPIB WAS IN LATER STAGES OF CLINICAL DEVELOPMENT
- IT'S DEVELOPMENT WAS TERMINATED BECAUSE OF ADVERSE EFFECTS
- BY WHICH TIME AROUND 800 MILLIONS DOLLARS HAD BEEN SPENT ON THE PROJECT WITH LITTLE OR NO CHANCE OF RETURN

THE FAMOUS NOBEL-PRIZE WINNING PHARMACOLOGIST

SIR JAMES BLACK SAID:

“THE MOST FRUITFUL BASIS FOR THE DISCOVERY OF A NEW DRUG IS TO START WITH AN OLD DRUG”

THE PHARMACEUTICAL INDUSTRY IS USING FIVE AVENUES TO EXTEND THE LIFE CYCLE OF THEIR DRUGS

- **IDENTIFYING AN ADVANTAGEOUS REFORMULATION**
- **CHIRALITY**
- **BROADENING THE PATIENT POPULATION (INCLUSION OF CHILDREN FOR EXAMPLE)**
- **EXTENDING THE DRUG USE TO A RELATED INDICATION(FOR EXAMPLE,FURTHER SUB TYPES OF DEPRESSION)**
- **INDENTIFY A NEW INDICATION FOR THE DRUG (REPROFILING)**

EXAMPLES OF REPROFILED DRUGS

	DRUG	ORIGINAL INDICATION	REPROFILED INDICATION
1	APOMORPHINE	PARKINSON'S DISEASE	ERECTILE DYSFUNCTION
2	BUPOPRION	DEPRESSION	SMOKING CESSATION
3	DULOXETINE	DEPRESSION	STRESS URINARY INCONTINENCE
4	ROPIRINOLE	PARKINSON'S DISEASE	RESTLESS LEG SYNDROME
5	SIDENAFIL	HYPERTENSION	ERECTILE DYSFUNCTION

EXAMPLES OF REPROFILED DRUGS

	DRUG	ORIGINAL INDICATION	REPROFILED INDICATION
6	FINASTERIDE	PROSTATE HYPERPLASIA	MALE PATTERN BALDNESS
7	THALIDOMIDE	EMESIS	ERYTHEMA NODOSUM LEPROSUM
8	MYCOPHENOLATE MOFETIL	TRANSPLANTED ORGAN REJECTION	LUPUS NEPHRITIS
9	BUPRENORPHINE	CONTROL OF PAIN	INTERRUPTION AND MAINTENANCE OF HEROIN AND OTHER OPIOID ADDICTIONS
10	PREGABALIN	EPILEPSY	NEUROPATHIC PAIN, GENERALISED ANXIETY DISORDERS

DRUG REPROFILING

FUTURE PROSPECTS

- WITH THE SHRINKING DEVELOPMENT PIPELINES OF MANY PHARMACEUTICAL COMPANIES, A CENTRAL TASK IS THE INVESTIGATION OF ALTERNATIVE APPROACHES TO DRUG DEVELOPMENT

- DRUG REPROFILING IS OF GREAT BENEFIT SINCE IT ALLOWS QUICK AND UNBIASED SCREENING FOR UNKNOWN DRUG TARGETS AT REDUCED COST

- A RAPID EXPANSION OF THIS APPROACH IS FORECASTED IN THE DECADES TO COME

ORAL ANTITHROMBOTICS

- **ORAL ANTICOAGULANTS**
- **ORAL ANTIPLATELET AGENTS**

ORAL ANTITHROMBOTICS

- DESPITE SIGNIFICANT IMPROVEMENTS OVER THE PAST DECADE IN CARDIOVASCULAR RELATED MORTALITY, THE PREVALENCE OF CARDIOVASCULAR DISEASE HAS INCREASED, PARTLY DUE TO AN AGEING POPULATION AND INCREASING RATES OF OBESITY AND DIABETES
- CARDIOVASCULAR DISEASE CONTINUE TO BE A BIG KILLER ATTRIBUTED TO CIRCULATORY DISEASE, WHICH INCLUDES ATHERO AND VENOUS THROMBOTIC CONDITIONS
- RECENT ADVANCES IN ANTIPLATELET AND ANTICOAGULANT THERAPY HAVE RESULTED IN AN INCREASE IN ANTITHROMBOTIC AGENTS ON THE MARKET FOR THESE CONDITIONS, PROVIDING MORE CHOICE TO PHYSICIANS AND PATIENTS BUT POTENTIALLY MAKING TREATMENT DECISIONS MORE COMPLEX

HAEMOSTASIS

- HAEMOSTASIS IS TRIGERRED BY VASCULAR INJURY AND INVOLVES THE TRANSITION OF BLOOD FROM LIQUID TO SOLID STATE. THE PROCESS COMPRISES THREE KEY STAGES AT THE SITE OF VASCULAR INJURY.
- VASOCONSTRICTION – A DAMAGED BLOOD VESSEL CONSTRICTS TO REDUCE BLOOD FLOW
- PLATELET PLUG FORMATION – PATELETS ADHERE TO THE SITE
- BLOOD CLOTTING – COAGULATION THROUGH ACTIVATION OF CLOTTING FACTORS. COAGULATION CASCADE PRODUCES FIBRIN, WHICH TRAPS RED BLOOD CELLS AT THE SITE OF INJURY AND REINFORCES THE PLATELET PLUG. THE RESULT IS A HARD CLOT (THROMBUS) THAT SEALS OFF THE DAMAGED VESSELS, REDUCING BLOOD LOSS

THROMBOSIS

- PATHOLOGICALLY THE PROCESS OF HAEMOSTASIS CAN BE TRIGERRED BY FISSURES OR RUPTURES TO ATHEROSCLEROTIC PLAQUES WITHIN CORONARY OR PERIPHERAL VESSELS.
- IN ADDITION, HAEMOSTATIS MAY BE INITIATED IN RESPONSE TO EXTENDED PERIODS OF IMMOBILITY, PROTHROMBIC STATES (e.g. PREGNANCY, MALIGNANCY) OR FOLLOWING SURGERY PARTICULARLY WHERE PROSTHESIS IS INVOLVED (e.g. HIP, KNEE AND HEART VALVE REPLACEMENTS).
- WHEN THE HAEMOSTATIC PROCESS IS UNCONTROLLED, THE RESULT IS OFTEN THROMBUS FORMATION.
- THE THROMBUS MAY CAUSE OCCLUSION AT ITS SITE OF ORIGIN, OR PART OR ALL OF THE THROMBUS MAY BE DISLODGED AND OCCLUDE ANOTHER SITE (EMBOLISM) LEADING TO EITHER TRANSIENT OR PERMANENT ISCHAEMIA OR NECROSIS

THROMBOSIS

- DIFFERENCES IN BLOOD FLOW AND PRESSURE BETWEEN THE VENOUS AND ARTERIAL SYSTEMS RESULT IN VARIATION IN THE COMPOSITION OF THE THROMBI.
- ARTERIAL THROMBI TEND TO BE RICH IN PLATELET COUNT
- VENOUS THROMBI TEND TO BE FIBRIN RICH
- HENCE THE PRIMARY ANTITHROMBOTIC STRATEGY FOR ARTERIAL THROMBOSIS IS ANTIPLATELET THERAPY AND FOR VENOUS THROMBOSIS IS ANTICOAGULANT THERAPY
- THESE STRATEGIES MAY BE COMBINED IN COMPLEX CASES

ANTIPLATELET AGENTS

ORAL

-ASPIRIN

-DIPYRIMADOLE

-TICLOPIDINE

-CLOPIDOGREL

-PRASUGREL

-TICAGRELOR

} NEW ANTIPLATELET AGENTS

INJECTABLE

-TIROFIBAN (AGGRASTAT)

-EPTIFIBATIDE (INTEGRILLIN)

-ABCIXIMAB (REOPRO)

ANTIPLATELET AGENTS WORK BY DISRUPTING KEY STEPS IN PLATELET ACTIVATION VIA A NUMBER OF MECHANISMS, INCLUDING INHIBITION OF PLATELET AGONISTS AND PLATELET ADHESION OR AGGREGATION.

MODE OF ACTION OF ORAL ANTIPLATELET AGENTS

1. ASPIRIN ⟶ COX 1 INHIBATOR ⟶ BLOCKS FORMATION OF THROMBOXANE (A PLATELET AGONIST) .ALTHOUGH ASPIRIN HAS A SHORT HALF LIFE (20 MINS), BECAUSE INHIBITION IS IRREVERSIBLE, THE EFFECT LASTS FOR THE LIFESPAN OF THE PLATELET (USUALLY 8-10 DAYS)

2. DIPYRIDAMOLE WORKS BY INCREASING THE CONCENTRATION OF THE PLATELET AGGREGATION INHIBITOR CYCLIC AMP BY INHIBITING ITS ENZYMATIC DEGRADATION

MODE OF ACTION OF ORAL ANTIPLATELET AGENTS

3. THE THIENOPYRIDINES TICLOPIDINE, CLOPIDOGREL AND PRASUGREL REDUCE PLATELET ACTIVATION BY NON-COMPETITIVELY AND IRREVERSIBLY BLOCKING THE BINDING OF ADP TO P_2Y_{12} RECEPTORS ON THE PLATELET MEMBRANE. ADP INDUCED PLATELET AGGREGATION IS INHIBITED.
4. TICAGRELOR IS A DIRECT REVERSIBLE P_2Y_{12} RECEPTOR ANTAGONIST BLOCKING THE BINDING OF ADP

MODE OF ACTION OF INJECTABLE ANTIPLATELET AGENTS

TIROFIBAN, EPTIFIBATIDE AND ABCIXIMAB $\longrightarrow$ ARE GLYCOPROTEIN IIb/IIIa INHIBITORS.

GLYCOPROTEIN IIb/IIIa RECEPTORS ARE SITUATED ON THE PLATELET MEMBRANE AND ARE INVOLVED IN PLATELET AGGREGATION .INHIBITION PREVENTS PLATELET AGGREGATION.

USES FOR ORAL ANTIPLATELETS

- **MYOCARDIAL INFARCTION OR UNSTABLE ANGINA** DUAL ANTIPLATELET THERAPY (LONG-TERM ASPIRIN 75mg od AND A P2Y12 BLOCKER). THIS DUAL THERAPY IS ADVOCATED FOR 12 MONTHS, THEN CONTINUE WITH ASPIRN MONOTHERAPY.
- **ELECTIVE PERCUTANEOUS CORONARY INTERVENTION** WITH BARE METAL STENTS, DUAL ANTIPLATELET THERAPY (ASPIRIN 75mg od AND CLOPIDOGREL) FOR AT LEAST 28 DAYS, THEN LONG-TERM ASPIRIN MONOTHERAPY. FOR INTERVENTION WITH DRUG-ELUTING STENTS, DUAL ANTIPLATELET THERAPY (AS ABOVE) FOR AT LEAST 12 MONTHS, THEN LONG-TERM ASPIRIN MONOTHERAPY.
- **STABLE ANGINA OR DOCUMENTED CORONARY ARTERY DISEASE** LONG TERM ASPIRIN (75mg od).
- **ISCHAEMIC STROKE (EXCLUDING ATRIAL FIBRILLATION RELATED)** LONG-TERM CLOPIDOGREL (75mg od). IF CLOPIDOGREL (PLUS PROTON PUMP INHIBATOR) IS NOT TOLERATED, DIPYRIDAMOLE MODIFIED RELEASE(200mg bd) PLUS ASPIRIN (75mg od) IS AN ALTERNATIVE. WHERE BOTH CLOPIDOGREL AND DIPYRIDAMOLE ARE NOT TOLERATED OR CONTRAINDICATED, ASPIRIN (75mg od). AND WHERE CLOPIDOGREL AND ASPIRIN ARE NOT TOLERATED OR CONTRAINDICATED, DIPYRIDAMOLE MODIFIED RELEASE (200mg bd).
- **PERIPHERAL ARTERIAL DISEASE** LONG-TERM CLOPIDOGREL (75mg od).
- **MULTIVASCULAR DISEASE** LONG-TERM CLOPIDOGREL (75mg od).
- **TRANSIENT ISCHAEMIC ATTACK** LONG-TERM DIPYRIDAMOLE MODIFIED RELEASE(200mg bd) PLUS ASPIRIN (75mg od). IF ASPIRIN IS NOT TOLERATED OR CONTRAINDICATED, DIPYRIDAMOLE MODIFIED RELEASE (200mg bd).

NEW ORAL ANTIPLATELET AGENTS

PRASUGREL

- POTENT INHIBITOR OF ADP AT P_2Y_{12} RECEPTOR
- MORE POTENT THAN CLOPIDOGREL
- CLOPIDOGREL AND PRASUGREL ARE PRO DRUGS AND ARE METABOLICALLY TRANSFORMED IN THE LIVER BY CYTOCHROME P_{450} ENZYMES INTO THEIR PLATELET INHIBITING METABOLITES.
- VARIABLE METABOLIC ACTIVITY OF CYTOCHROME P_{450} ENZYMES CONTRIBUTES TO THE OBSERVED INTER INDIVIDUAL VARIABILITY IN CLOPIDOGREL'S INHIBITORY EFFECT.
- PRASUGREL IS LESS AFFECTED THAN CLOPIDOGREL BY VARIATIONS IN THE P_{450} ENZYMES.

NEW ORAL ANTIPLATELET AGENTS

TICAGRELOR

- ORAL ADENOSINE DI PHOSPHATE (ADP) ANTAGONIST
- BLOCKS ADP INDUCED PLATELET AGGREGATION
- IS A REVERSIBLE P2Y12 RECEPTOR ANTAGONIST UNLIKE CLOPIDOGREL/PRASUGREL WHICH BIND IRREVERSIBILY
- REPRESENTS AN ADVANTAGE IF PATIENT HAS TO UNDERGO CABG OR OTHER SURGERY AS THERE IS A FASTER RECOVERY OF PLATELET FUNCTION HENCE A DECREASED IN RISK OF BLEEDING
- DOES NOT REQUIRE METABOLIC ACTIVATION HENCE HAS A MORE RAPID ONSET OF ACTION COMPARED TO CLOPIDOGREL/PRASUGREL
- METABOLISED BY CYP3A4 ENZYME AND HENCE WILL BE AFFECTED BY DRUGS THAT INDUCE OR INHIBIT THIS ENZYME.
- PLASMA HALF LIFE IS 6-13 HRS SO TWICE DAILY DOSING IS NEEDED

NEW ORAL ANTIPLATELET AGENTS

1) COMPARED TO CLOPIDOGREL, TICAGRELOR DECREASES THE RATE OF ALL CAUSE MORTALITY, VASCULAR MORTALITY OR MI WITHOUT AN INCREASE IN RATE OF MAJOR BLEEDING
2) COMPARED TO CLOPIDOGREL, PRASUGREL DECREASES THE RATE OF ISCHEMIC EVENTS INCLUDING STENT THROMBOSIS BUT INCREASES THE RISK OF MAJOR AND FATAL BLEEDING IN PATIENTS UNDERGOING PCI WITHOUT CHANGES IN OVERALL MORTALITY
3) PRASUGREL AND TICAGRELOR HAVE COMPARABLE EFFICACY AND SAFETY EXCEPT PRASUGREL IS MORE PROTECTIVE FOR STENT THROMBOSIS BUT WITH AN INCREASED RISK OF MAJOR BLEEDING

NEW ORAL ANTIPLATELET AGENTS

PLACE IN THERAPY OF ACS

- CLOPIDOGREL REMAINS THE MAINSTAY OF TREATMENT FOR THE MOMENT AND IS RECOMMENDED FIRST LINE IN PATIENTS WITH HYPERSENSITIVITY TO ASPIRIN OR IN DUAL ANTIPLATELET THERAPY WITH ASPIRIN.
- THE REVERSIBILITY OF TICAGRELOR MAY BE ATTRACTIVE, IN THAT IT ALLOWS FASTER RECOVERY OF PLATELET FUNCTION AND THEREFORE GREATER THERAPEUTIC FLEXIBILITY, PARTICULARLY IN SURGICAL PATIENTS.
- REDUCTION IN NON FATAL MI/STENT THROMBOSIS FOR PRASUGREL AND BENEFIT IN MI/VASCULAR AND TOTAL MORTALITY FOR TICAGRELOR SEEM PROMISING.
- MORE DATA NEEDED TO SITUATE THEIR EXACT PLACE IN THERAPY OF ACS AS THE INCREASE OF EFFICACY COMPARED TO CLOPIDOGREL HAS GENERALLY BEEN AT THE EXPENSE OF INCREASED BLEEDING.
- DESPITE ASPIRIN AND CLOPIDOGREL DUAL THERAPY, A GOOD PROPORTION OF PATIENTS CONTINUE TO EXPERIENCE RECURRENT ATHEROTHROMBOTIC EVENTS, SO THE ADVENT OF THESE NEW DRUGS COULD REPRESENT A HOPE FOR SUCH PATIENTS.

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)
- APIXABAN (ELIQUIS – TWICE 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

PROS AND CONS OF WARFARIN THERAPY

PROS

- EVIDENCE BASE SHOWS CLEAR BENEFITS
- ONCE DAILY ADMINISTRATION (LONG HALF-LIFE)
- AVAILABILITY OF A SPECIFIC ANTIDOTE TO REVERSE ANTICOAGULATION
- LOW COST
- REGULAR MONITORING SUPPORTS PATIENT ADHERENCE

CONS

- 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 / FOOD INTERACTIONS OF CLINICAL IMPORTANCE
  - POTENTIATION OR REDUCTION OF ANTICOAGULANT EFFECT WITH ALL RISKS INVOLVED
- INTERPATIENT / INTRAPATIENT VARIABILITY IN PHARMACOKINETICS AND RESPONSE (GENETIC POLYMORPHISMS, AGE, HEALTH STATUS, DIET, ALCOHOL CONSUMPTION)

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

- NEW ORAL ANTICOAGULANTS ARE RIVAROXABAN, APIXABAN AND DABIGATRAN WHICH ARE ALREADY MARKETED IN THE EUROPEAN UNION

NOVEL DRUGS

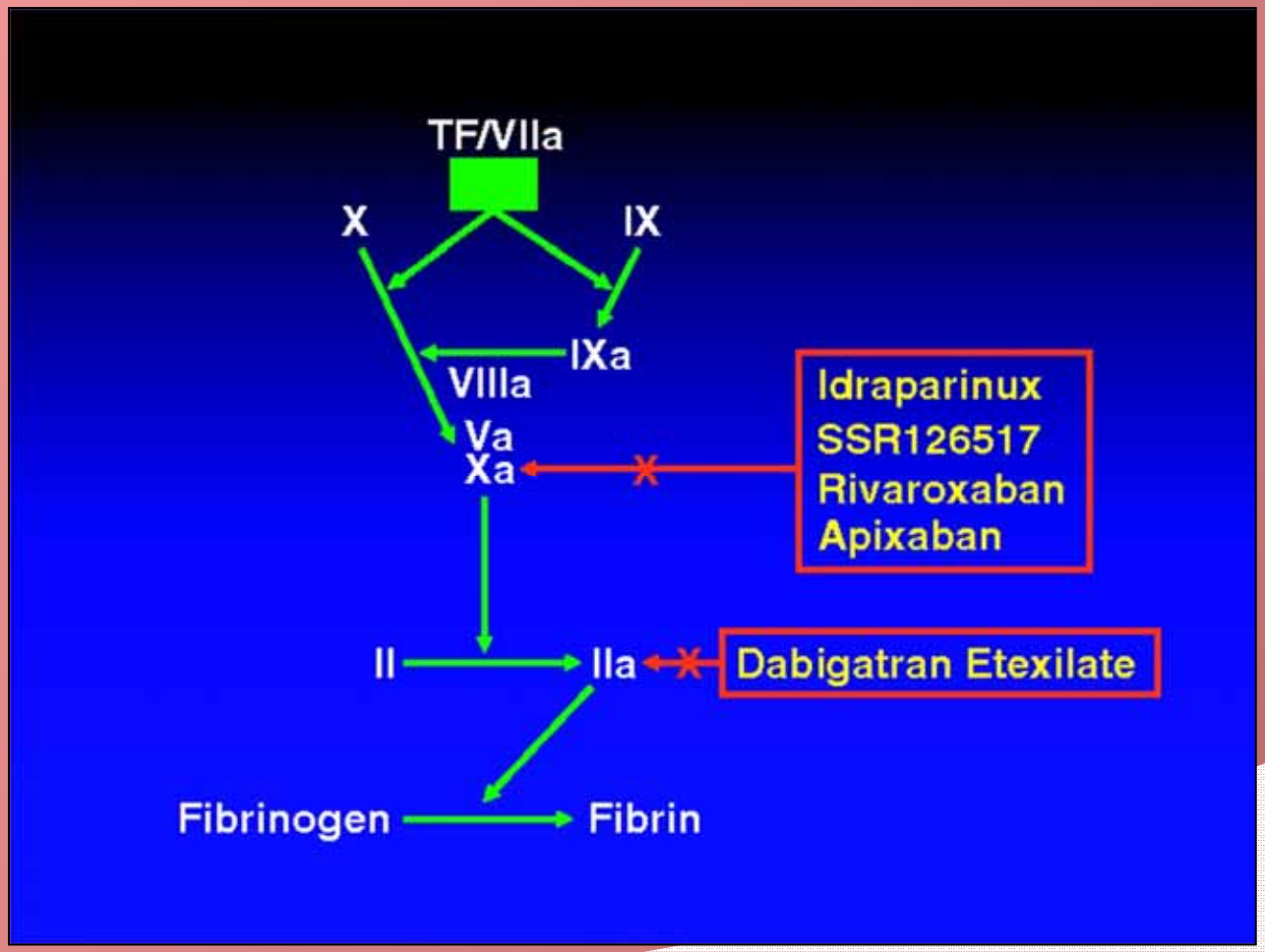
RIVAROXABAN - THE FIRST ORALLY ACTING FACTOR XA INHIBITOR

DABIGATRAN - ORALLY ACTING DIRECT THROMBIN INHIBITOR

(THE FIRST IN THIS CLASS WAS XIMELAGATRAN WHICH WAS REMOVED FROM THE MARKET DUE TO LIVER TOXICITY)

APIXABAN – A NEW ORALLY ACTING FACTOR XA INHIBITOR RECENTLY INTRODUCED

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 CONVENIENT 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

USES OF NEW ANTICOAGULANTS

	DABIGATRAN	RIVAROXABAN	APIXABAN
VTE PREVENTION POST HIP OR KNEE REPLACEMENT	LICENSED*	LICENSED*	LICENSED*
ACUTE DVT TREATMENT, SECONDARY VTE PREVENTION	LICENCE SUBMISSION UNDER EVALUTATION	LICENSED‡	LICENCE EXPECTED
ACUTE PULMONARY, EMBOLISM TREATMENT, SECONDARY VTE PREVENTION	LICENCE SUBMISSION UNDER EVALUTATION	LICENCE EXPECTED₸	LICENCE EXPECTED
STROKE PREVENTION IN NON-VALVULAR ATRIAL FIBRILLATION	LICENSED*	LICENSED‡	LICENCE EXPECTED§
ACUTE CORONARY SYNDROME		LICENCE EXPECTED	

NEW ORAL ANTICOAGULANTS

- IN THROMBOPROPHYLAXIS AFTER MAJOR ORTHOPEDIC SURGERY
- DABIGATRAN HAS SHOWN IN SEVERAL TRIALS A NON INFERIOR EFFICACY TO ENOXAPARIN WITH A SIMILAR SAFETY PROFILE AND RIVAROXABAN HAS SHOWN A SUPERIOR EFFICACY
- 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

PLACE IN THERAPY

- REPRESENTS CERTAIN ADVANTAGES OVER WARFAIN IN TERMS OF MONITORING, DOSING AND RAPID AND EXTENDED COAGULATION.
- EXTENDED INDICATIONS: MANAGEMENT OF VTE,PRIMARY VTE PREVENTION, SECONDARY VTE PREVENTION, STROKE PREVENTION IN NON-VALVULAR ATRIAL FIBRILLATION SEEM ATTRACTIVE.
- LIMITATIONS: RISK OF BLEEDING? NEW DATA EMERGING
- DOES THIS MEAN THE END OF THE ANTICOAGULANT CLINIC?

FUTURE INDICATIONS

ACS – MI/ANGINA? FOR RIVAROXABAN. IN THE ATLAS ACS2 TIMI SI TRIAL, WHEN LOW DOSE RIVAROXABAN WAS ADDED TO CLOPIDOGREL AND ASPIRIN, THERE WAS A REDUCTION IN ALL CAUSE MORTALITY AND CARDIOVASCULAR MORTALITY.

HOWEVER THE RISK OF MAJOR BLEEDING AND INTRACRANIAL HAEMORRHAGE (BUT NOT FATAL BLEEDING) WAS INCREASED.

MANAGEMENT OF

AGE RELATED MACULAR DEGENERATION (AMD)

AMD

THE DISEASE GENERALLY AFFECTS CENTRAL VISION SO PATIENTS HAVE DIFFICULTY READING OR RECOGNISING FACES BUT BECAUSE THEY RETAIN PERIPHERAL VISION THEY ARE USUALLY ABLE TO NAVIGATE AND MAINTAIN THEIR MOBILITY.

WHAT IS AMD?

- AMD IS A TERM APPLIED TO CHANGES IN THE EYE, CHARACTERISED BY EXTENSIVE DRUSEN AND PIGMENTARY ABNORMALITIES, IN PEOPLE OVER 50 YEARS.
- DRUSENS ARE ACCUMULATIONS OF LIPID MATERIAL BELOW THE RETINAL PIGMENT EPITHELIUM AND WITHIN THE BRUCH'S MEMBRANE, APPEARING AS YELLOW SPOT ON THE RETINA.
- PIGMENTARY ABNORMALITIES CAN BE HYPOPIGMENTATION OR HYPERPIGMENTATION.
- THESE CHANGES DO NOT AUTOMATICALLY LEAD TO CENTRAL VISION LOSS BUT A NUMBER OF PEOPLE WITH THESE SIGNS WILL GO ON TO DEVELOP SEVERE CENTRAL VISION LOSS.

WHAT IS AMD?

- **LOSS OF VISION OCCURS AS A RESULT OF "GEOGRAPHIC ATROPY" *(A DEMARCATED AREA OF PARTIAL OR COMPLETE DEPIGMENTATION CAUSED BY ATROPHY OF RETINAL PIGMENT EPITHELIUM)* A FEATURE OF DRY AMD OR THE GROWTH OF BLOOD VESSELS INTO SUBRETINAL PLACE (NEOVASCULARISATION), A FEATURE OF WET AMD.**
- **NOT ALL PATIENTS WITH EARLY SIGNS OF AMD PROGRESS TO ADVANCED DISEASE.**
- **MOST PATIENTS (80%) WITH AMD HAVE DRY TYPE.**
- **SEVERE SIGHT LOSS ASSOCIATED WITH WET TYPE.**
- **HOWEVER DRY AMD CAN EASILY CONVERT TO WET AMD AND THE DISTINCTION IS NOT ALWAYS CLEAR.**

WHAT IS AMD?

- IN NEOVASCULAR DISEASE (WET TYPE), THE FORMATION OF NEW VESSELS IS THOUGHT TO BE UNDER THE CONTROL OF VEGF-A (VASCULAR ENDOTHELIAL GROWTH FACTOR A), A PRO-ANGIOGENIC GROWTH FACTOR WHICH INCREASES VASCULAR PERMEABILITY

- LEAKAGE OF BLOOD CONSTITUENTS RESULT IN A SEPARATION OF BRUCH'S MEMBRANE, RETINAL PIGMENT EPITHELIUM AND RETINA AND A THICKENING OF RETINA DUE TO FLUID ACCUMULATION.

- THIS EVENTUALLY LEADS TO DEGENERATIVE CHANGES IN PHOTORECEPTORS AND FIBROSIS.

SYMPTOMS

SYMPTOMS ARE PURELY VISUAL AND DEPEND ON TYPE OF AMD

- DIFFICULTY IN READING
- WAVY LINES AND A DARK SPOT
- VISUAL HALLUCINATIONS (e.g. REPEARED PATTERNS OR FLASHES OF LIGHT, ODD SHAPES)

RISK FACTORS

- EXACT CAUSE IS UNKNOWN BUT IT IS PROPOSED THAT MACULAR DEGENERATION RESULTS FROM CUMULATIVE EFFECTS OF OXIDATIVE STRESS.
- THE RETINA AND RETINAL PIGMENT EPITHELIUM HAVE A HIGH EXPOSURE TO LIGHT AND OXYGEN, BOTH OF WHICH CAN POTENTIATE THE FORMATION OF FREE RADICALS.
- SMOKING IS A MAJOR RISK FACTOR. SMOKERS HAVE A 2-3 FOLD INCREASE RISK OF DEVELOPING AMD
- GENETICS IS A MAJOR RISK FACTOR. RACE HAS A BEARING ON INCIDENCE. INCIDENCE IS HIGHER IN WHITE THAN IN BLACK PEOPLE.
- WEARING SUN GLASSES WITH 100% PROTECTION AGAINST UVA/UVB IN BRIGHT SUNLIGHT WOULD SEEM PRUDENT.

DIETARY FACTORS AND ADVICE

- MACULAR PIGMENT IS COMPOSED OF TWO CAROTENOIDS, LUTEIN AND ZEAXANTHIN FOUND IN GREEN LEAFY VEGETABLES AND EGGS AND SOME TRIALS SUGGEST A HIGHER DIETARY INTAKE OF THESE NUTRIENTS DECREASE INCIDENCE OF AMD.
- OTHER STUDIES HAVE SHOWN THAT OMEGA 3 FATTY ACIDS-DHA AND EPA MAY ALSO BE PROTECTIVE.
- AREDS 2 IS A 4,000 PARTICIPANTS FIVE YEAR CONTROLLED TRIAL (2008-13) INVESTIGATING THE PROTECTIVE EFFECT OF LUTEIN, ZEANXATHIN AND OMEGA 3 FATTY ACIDS. REDUCTION IN INCIDENCE WAS STATISTICALLY SIGNIFICANT IN CERTAIN CATEGORIES OF PATIENTS.
- SUPPLEMENTS MARKETED FOR AMD SHOULD CONTAIN THE FORMULATION MARKETED IN AREDS TRIAL.

MANAGEMENT

- THERE ARE NO SPECIFIC TREATMENT FOR DRY AMD. PATIENTS SHOULD BE ENCOURAGED TO STOP SMOKING AND EAT A DIET RICH IN GREEN LEAFY VEGETABLES, EGGS AND A PORTION OF OILY FISH ONCE A WEAK AND SEEK AN URGENT APPOINTMENT IF ANY DETERIORATION IN VISION LOSS.

- WET AMD CAN BE TREATED

TREATMENT OPTIONS

- LASER THERAPY (TO DESTROY ABNORMAL BLOOD VESSELS): SUITABLE FOR FEW PATIENTS AND HAS LIMITATIONS – IT CAUSES SCARRING AND DISEASE TENDS TO RECUR.
- PHOTODYNAMIC THERAPY : VERTEPORFIN IS A PORPHYRIN SENSITISER, PREFERENTIALLY TAKEN BY RAPIDLY PROLIFERATING ENDOTHELIAL CELLS.
- IT IS GIVEN INTRAVENOUSLY BY INFUSION OVER 10 MINUTES. IT IS ACTIVATED BY LASER LIGHT DIRECTED TO THE CHOROIDAL NEOVASCULAR LESION AT A SINGLE SPOT. THROMBOTIC OCCLUSION OF THE BLOODVESSELS WITHIN THE LESION OCCURS.
- PATIENTS NEEDS TO BE CHECKED EVERY 3 MONTHS AND RETREATMENT IS GIVEN IN CASE OF RECURRENCE (LICENSED TO UP TO FOUR TREATMENTS/YEAR).
- ITS USE HAS FALLEN WITH THE ADVENT OF VEGF INHIBITORS. IT IS RESERVED FOR PATIENTS IN WHICH INTRAVITREAL INJECTIONS ARE CONTRAINDICATED OR UNACCEPTABLE.

TREATMENT OPTIONS

ANTI VEGF AGENTS

- TWO LICENSED TREATMENTS AND ONE OFF-LICENCE TREATMENT AT THE MOMENT:

  - LICENCED TREATMENT (RANIBIZUMAB/PEGAPTANIB) AND

  - OFF LICENCE TREATMENT (BEVACIZUMAB)

- ALL HAVE TO BE GIVEN BY INTRAVITREAL INJECTIONS.
- THESE INJECTIONS RUN THE RISK OF CAUSING ENDOPHTHALMITIS (SIGHT THREATING INFECTION), RETINAL DETACHMENT, UVEITIS AND TRAUMATIC LENS INJURY). THEY CAN ALSO INCREASE INCIDENCE OF CATARACT FORMATION.
- PEGAPTANIB (MACUGEN) – USE EVERY 6 WEEKS. NICE DO NOT RECOMMEND PEGAPTANIB FOR AMD AS IT SEEMS TO BE LESS EFFICACIOUS THAN RANBIZUMAB.

TREATMENT OPTIONS

ANTI VEGF AGENTS

- **RANBIZUMAB (LUCENTIS)**

  - MONOCLONAL ANTIBODY BINDS TO VEGF-A THUS PREVENTING ITS BINDING TO THE RECEPTOR.

  - RECOMMENDED BY NICE

  - LICENSEDN FOR 3 INITIAL MONTHLY INJECTIONS AND PATIENTS ARE THEN REVIEWED EVERY MONTH AND THEY RECEIVE FURTHER DOSES IF THERE ARE ANY SIGNS OF DISEASE PROGRESSION.

- **BEVACIZUMAB (AVASTIN)**

  - LICENSED FOR VARIOUS CANCERS BUT USED OFF LICENSE FOR INTRAVITREAL USE IN AMD

  - WIDELY USED IN THE US AS IT COSTS LESS

  - EQUALLY EFFECTIVE AND SIMILAR SAFETY PROFILES TO RANIBIZUMAB

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	- YUZPE METHOD (COMBINATION OF AN OESTROGEN + PROGESTOGEN) - WITHIN 3 DAYS OF INTERCOURSE
2000 – 2009	- PROGESTERONE ONLY PILL (LEVONORGESTREL-NORLEVO)-WITHIN 3 DAYS OF INTERCOURSE
2011	- ULIPRISTAL (ELLA ONE)-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)

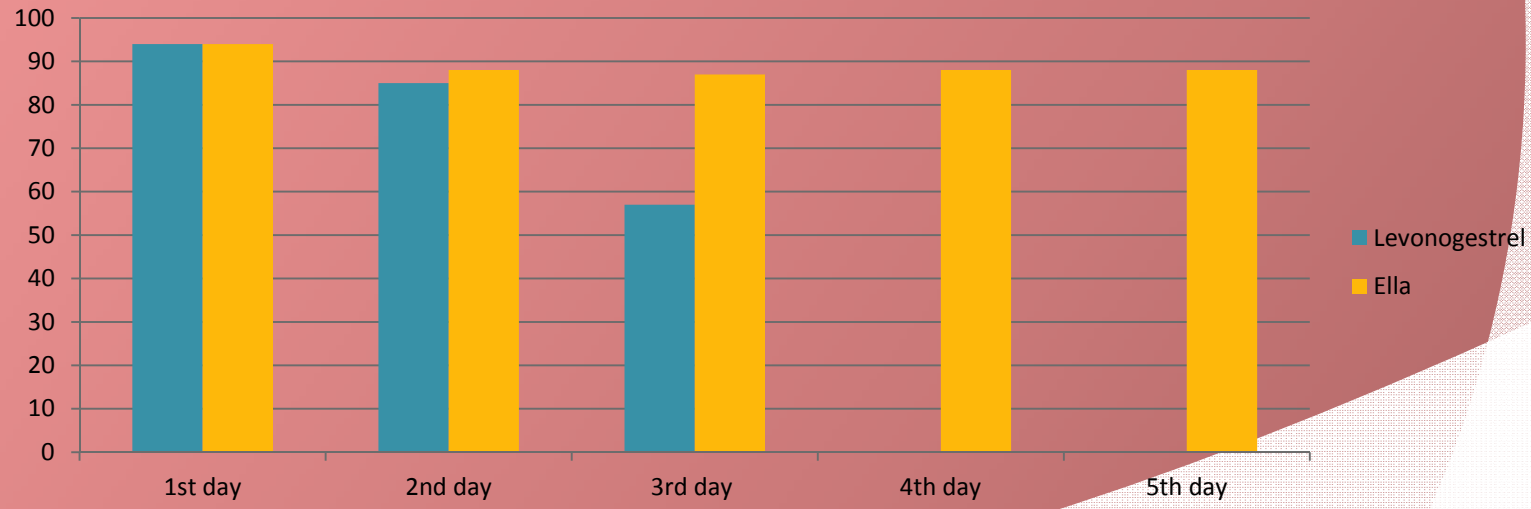
- MECHANISM OF ACTION
  - PREVENTS OVULATION
  - PREVENTS IMPLANTATION OF FERTILIZED EGG IN THE UTERINE LINING
- SINGLE DOSE WITHIN 72 HOURS OF UNPROTECTED INTERCOURSE.
- THE SOONER THE BETTER IN TERMS OF EFFICACY. HIGHEST WITHIN 12 HOURS, DECLINE OVER TIME

ULIPRISTAL (ELLA ONE)
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/RETARDS OVULATION
  - ALTERATIONS TO THE ENDOMETRIUM
- MOST COMMON SIDE EFFECTS : NAUSEA/VOMITING/ ABDOMINAL PAIN
- APPROVED FOR USE IN EUROPEAN UNION, US FDA APPROVAL OBTAINED

ULIPRISTAL (ELLA ONE)
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”

RIFAXIMIN – A NEW TREATMENT FOR TRAVELLER'S DIRRHOEA

TRAVELLER'S DIRRHOEA

- TRAVELLER'S DIRRHOEA AFFECTS UP TO 60% OF THE 800 MILLION PLUS TRAVELLERS EACH YEAR.
- IN MOST CASES THE DIRRHOEA OCCURS IN PEOPLE WHO TRAVEL TO AREAS OF POOR HYGIENE.
- SYMPTOMS USUALLY OCCUR AROUND SEVEN DAYS IN AN OVERSEAS TRIP AND USUALLY RESOLVE SPOTANEOUSLY WITHIN 3-4 DAYS.
- HOWEVER UP TO ¼ OF AFFECTED TRAVELLERS FIND THEIR HOLIDAY OR BUSINESS ACTIVITIES AFFECTED.

TRAVELLER'S DIRRHOEA

- MILD TO MODERATE TRAVELLER'S DIRRHOEA (ONE OR TWO STOOLS IN 24 HOURS WITH OR WITHOUT ANOTHER ENTERIC SYMPTOM) SHOULD BE TREATED WITH REHYDRATION AND WHERE NEEDED, SYMPTOMATIC THERAPY.
- MODERATE TO SEVERE CASES (AT LEAST THREE STOOLS IN 24 HOURS PLUS OTHER ENTERIC SYMPTOMS: ABDOMINAL CRAMPS, FEVER, NAUSEA, VOMITTING OR BLOOD IN STOOLS) OR DIRRHOEA THAT HAS NOT RESPONDED TO SYMPTOMATIC TREATMENT SHOULD BE TREATED WITH ANTIBIOTICS.
- THE CAUSES OF TRAVELLER'S DIRRHOEA DEPEND ON THE SEASON, SETTING AND DESTINATION.
- HALF TO THREE QUARTERS ARE CAUSED BY BACTERIA SUCH AS E COLI, CAMPYLOBACTER, SALMONELLA AND SHIGELLA SPECIES WITH ENTEROTOXIGENIC AND ENTERO AGGREGATIVE ECOLI BEING IMPLICATED IN SOME PATIENTS.
- THE REMAINING PORTION OF CASES ARE CAUSED BY VIRUSES, PARASITES AND FOOD POISONING TOXINS.
- TRAVEL TO AFRICA, CENTRAL AND SOUTH AMERICA AND MOST OF ASIA PRESENT THE HIGHEST RISKS OF TRAVELLER'S DIRRHOEA.

RIFAXIMIN

- RIFAXIMIN IS A NEW ALTERNATIVE TO CIPROFLOXACIN FOR TREATING TRAVELLER'S DIRRHOEA.
- IT IS A SEMI-SYNTHETIC ANALOGUE OF RIFAMPICIN.
- IT IS NOT ABSORBED IN THE GASTROINTESTINAL TRACT.
- INHIBITS BACTERIAL RNA SYNTHESIS.
- INDICATED FOR TREATING TRAVELLER'S DIRRHOEA ASSOCIATED WITH NON-INVASIVE STRAINS OF E COLI.

RIFAXIMIN

ADMINISTRATION

- IT IS TAKEN ORALLY AS A 200MG TABLET EVERY 8 HOURS FOR 3 DAYS.
- IT MUST NOT TO BE USED FOR MORE THAN 3 DAYS.
- IT SYMPTOMS CONTINUE OR RECUR, A SECOND COURSE SHOULD NOT BE TAKEN.
- DOSE ADJUSTMENT IN HEPATIC OR RENAL INSUFFICIENCY IS NOT NECESSARY.
- DUE TO ITS LOW GASTROINTESTINAL ABSORPTION (LESS THAN 1%), THE POTENTIAL FOR SYSTEMIC DRUG INTERACTIONS IS LOW.
- SIDE EFFECTS ARE MILD AND MAY INCLUDE GASTROINTESTINAL EFFECTS, DIZZINESS AND HEADACHE.
- STUDIES HAVE SHOWN THAT IT CAN REDUCE THE DURATION OF DIRRHOEA BY 27-36 HOURS.

PLACE IN THERAPY

- CURRENT FIRST LINE EMPIRICAL ANTIBIOTIC THERAPY IS CIPROFLOXACIN 500mg PO BD FOR 3 DAYS, WITH AZITHROMYCIN 500mg O D FOR 3 DAYS RESERVED FOR PATIENTS WHO HAVE TRAVELLED TO SOUTH EAST ASIA (WHERE CAMPYLOBACTER RESISTANCE TO CIPROFLOXACIN IS PREVALENT) OR WHO CANNOT TOLERATE QUINOLONES.

- RIFAXIMIN HAS NOT DEMONSTRATED SUPERIOR EFFICACY TO RECOMMENDED FIRST LINE THERAPIES AND IS NOT LICENSED FOR USE IN PATIENTS UNDER 18 YEARS, HENCE IS UNLIKELY TO BE USED AS A FIRST LINE TREATMENT.

- IT COULD BE RESERVED FOR PATIENTS WHERE A DRUG WITH LOW SYSTEMIC ABSORPTION COULD REPRESENT AN ADVANTAGE OR WHERE THE FIRST LINE AGENTS ARE CONTRAINDICATED.

FIDAXOMICIN

A NEW ANTIBIOTIC TO TACKLE CLOSTRIDIUM DIFFICILE

CLOSTRIDIUM DIFFICILE INFECTION (CDI)

- CLOSTRIDIUM DIFFICILE IS A GRAM POSITIVE, SPORE FORMING, ANAEROBIC BACTERIUM THAT CAN CAUSE INFECTION IN SUSCEPTIBLE PATIENTS DURING OR AFTER EXPOSURE TO BROAD SPECTRUM ANTIBIOTICS DUE TO OVERGROWTH OF NORMAL GUT FLORA.
- SYMPTOMS OF INFECTION CAN RANGE FROM MILD, SELF LIMITING DIRRHOEA TO LIFE THREATENING ILLNESS INVOLVING PARTIAL OR COMPLETE ILEUS OR TOXIC MEGACOLON AND SEPSIS.
- CDI IS THE MOST IMPORTANT FORM OF HOSPITAL ACQUIRED DIRRHOEA.
- CLOSTRIDIUM DIFFICILE SPORES ARE ABLE TO SURVIVE OUTSIDE THE BODY FOR SEVERAL HOURS SO STRICT INFECTION CONTROL IS IMPORTANT TO PREVENT DISEASE SPREAD.
- CURRENT CONVENTIONAL TREATMENT INCLUDE SHORT COURSES OF ORAL METRONIDAZOLE OR VANCOMYCIN OR A COMBINATION OF BOTH IN SEVERE INFECTIONS.

FIDAXOMICIN

HOW IT WORKS?

- FIRST IN CLASS, NARROW SPECTRUM, MACROCYCLIC ANTIBIOTIC THAT HAS BACTERICIDAL ACTIVITY AGAINST CLOSTRIDIUM DIFFICILE.
- IT WORKS BY INTERFERING WITH RNA SYSTHESIS, INHIBITING REPLICATION.
- IN ADDITION TO ITS ACTIVITY, FIDAXOMICIN HAS ALSO SHOWN TO INHIBIT CL. DIFFICILE TOXIN SYNTHESIS AND SPORE PRODUCTION IN VITRO AND THIS MAY EXPLAIN THE DECREASE IN RECURRENCE RATES COMPARED TO CONVENTIONAL TREATMENT IN CLINICAL TRIALS.
- FIDAXOMICIN IS NOT ABSORBED SYSTEMICALLY AFTER ORAL ADMINISTRATION.

FIDAXOMICIN

RESEARCH

- TWO LARGE DOUBLE BLIND STUDIES COMPARING 10 DAYS TREATMENT (200mg bd) WITH 10 DAYS' TREATMENT OF ORAL VANCOMYCIN (125mg qds) IN PATIENTS WHO HAD TOXIN POSITIVE CDI HAVE SHOWN A NON-INFERIOR CURE RATE OF FIDAXOMICIN COMPARED TO VANCOMYCIN.
- RECURRENCE RATES WERE SIGNIFICANTLY BETTER WITH FIDAXOMICIN (15.4% COMPARED TO 25.3% FOR VANCOMYCIN IN THE 1ST STUDY AND 12.7% COMPARED TO 26.9% IN THE 2ND STUDY).

ADMINISTRATION

FIDAXOMICIN IS TAKEN ORALLY TWICE DAILY WITH OR WITHOUT FOOD FOR 10 DAYS.AVAILABLE AS A 200mg TABLET.

FIDAXOMICIN

- APPEARS TO BE WELL TOLERATED
- ADVERSE EFFECTS PRIMARILY GASTROINTESTINAL (NAUSEA/VOMITTING/CONSTIPATION)
- INCREASED (OF ≥ 7.9) PH WAS FOUND TO DECREASE ACTIVITY OF FIDAXOMICIN SO DRUGS SUCH AS PROTON PUMP INHIBITORS/H2 ANTAGONISTS COULD REDUCE ITS EFFICACY.
- INDICATED IN ADULTS ABOVE 18 YEARS, AS SAFETY HAS NOT BEEN YET ESTABLISHED IN CHILDREN.

FIDAXOMICIN

PLACE IN THERAPY

- BEARING IN MIND THE DECREASE IN RECURRENCE RATES (AROUND 12-15%) COMPARED WITH CONVENTIONAL TREATMENT (20-30%), A NEW TREATMENT LIKE FIDAXOMICIN IS WELCOMED.
- SIMILAR CURE RATES AND DECREASED RECURRENT RATES COMPARED TO AVAILABLE TREATMENT IS LIKELY TO LEAD TO AN INCREASE OF ITS USE IN CLINICAL PRACTICE.
- AS A NOVEL TREATMENT, FIDAXOMICIN IS YET TO FIND ITSELF EMBEDDED IN NATIONAL GUIDELINES. IT WILL PROBABLY FIND ITS NICHE IN THE TREATMENT OF RESISTANT OR RECURRENT INFECTIONS THAT HAVE FAILED CONVENTIONAL THERAPY.
- ITS HIGH COST LIMITS ITS USE.

THANK YOU