WHAT'S NEW IN THERAPEUTICS ?

SADECK VAWDA

MEDICAL UPDATE GROUP

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CONTENTS

1. HEPATITIS C:

LATEST ADVANCES IN THERAPY

HEPATITIS C

- GLOBAL HEALTH PROBLEM WITH AN ESTIMATED 185 MILLION PEOPLE INFECTED WORLDWIDE
- 3 TO 4 MILLIONS NEW INFECTIONS EVERY YEAR
- 6 MAJOR GENOTYPES OF THE VIRUS, KNOWN AS HEPATITIS C GENOTYPES 1 TO 6
- RECENT YEARS HAVE SEEN AN EVOLUTION IN THE TREATMENT OF HEPATITIS C INFECTION WITH NEW ANTIVIRALS EMERGING AT REMARKABLE SPEED THAT PROMISE CURE RATES NEVER THOUGHT PREVIOUSLY POSSIBLE
- THERE ARE NO VACCINES FOR HEPATITIS C AT THE MOMENT

HEPATITIS C

GENOTYPES

- **1 to 6**
- **GENOTYPE 1 IS MORE PREVALENT COMPRISING MORE THAN 46% OF ALL CASES.**

- **GENOTYPE 3 COMPRISES 30% OF ALL CASES, WHILE GENOTYPES 2,4 AND 6 ACCOUNT FOR AROUND 23% OF ALL CASES. GENOTYPE 5 ACCOUNTS FOR THE REMAINING 1%.**

HEPATITIS C

TRANSMISSION

THERE ARE SEVERAL ROUTES FOR HEPATITIS C VIRUS TRANSMISSION:

1. **PEOPLE WHO INJECT DRUGS (PWID) ARE AT RISK DUE TO SHARING UNSTERILIZED INJECTING PARAPHERNALIA. AROUND 50% OF PWID IN THE UK ARE CHRONICALLY INFECTED WITH HEPATITIS C VIRUS.**

2. **VERTICAL TRANSMISSION FROM MOTHER TO CHILD OCCURS IN AROUND 2% OF MOTHERS WITH HEPATITIS C. CAN BE AS HIGH AS 20% IN MOTHERS COINFECTED WITH HIV.**

HEPATITIS C

TRANSMISSION

3. **SEXUAL EXPOSURE IS A RARE CAUSE OF TRANSMISSION AND IS ESTIMATED TO ACCOUNT FOR LESS THAN 1% OF CASES. RISK INCREASES IN THOSE WHO ENGAGE IN SEXUAL PRACTICES IN WHICH RISK OF BLOOD CONTACT IS INCREASED.**
4. **TRANSFUSION IS NOW A RARE CAUSE OF TRANSMISSION FOLLOWING IMPROVED DONOR SCREENING AND VIRAL INACTIVATION OF PLASMA PRODUCTS. BEFORE THESE DEVELOPMENTS, PATIENTS WHO RECEIVED INFECTED BLOOD PRODUCTS (e.g. haemophiliacs) WERE AT THE HIGHEST RISK.**
5. **OCCUPATIONAL EXPOSURE IS A POSSIBLE RISK e.g (needle stick injuries) WHICH CAN BE MINIMISED BY SAFE WORKING PRACTICES.**
6. **OTHER POSSIBLE CAUSES INCLUDE TATTOOING, ACUPUNCTURE, DENTAL WORK AND PIERCING. THESE RISKS CAN BE MINIMIZED IF GOOD INFECTION CONTROL PRACTICES ARE FOLLOWED.**

HEPATITIS C

PROGNOSIS

- **HEPATITIS C IS TERMED A SILENT KILLER**
- **IT CAUSES SLOW BUT PROGRESSIVE LIVER DAMAGE**
- **AFTER INITIAL INFECTION WITH THE HEPATITIS C VIRUS, AROUND 75-85% OF PATIENTS WILL FAIL TO CLEAR THE VIRUS AND WILL BECOME CHRONICALLY INFECTED**
- **THESE PATIENTS WILL OFTEN BE ASSYMPTOMATIC UNTIL THEY PRESENT WITH SIGNS OF END-STAGE LIVER DISEASES (e.g ascites, hepatic encephalopathy, etc)**

HEPATITIS C

PROGNOSIS

- THE REMAINING 15-25 % GO ON TO CLEAR THE INFECTION AND DEVELOP ANTIBODIES. IT IS IMPORTANT THAT PATIENTS ARE INFORMED THAT SPONTANEOUS CLEARANCE OF HEPATITIS C DOES NOT MEAN THEY ARE IMMUNE, AND RE-INFECTION CAN OCCUR.
- IT IS ESTIMATED THAT AROUND 30% OF CHRONICALLY INFECTED PATIENTS WILL DEVELOP CIRRHOSIS WITHIN 20 YEARS AND 5% WILL DEVELOP HEPATOCELLULAR CARCINOMA.
- ONLY AROUND 3% OF CHRONICALLY INFECTED HEPATITIS C PATIENTS ARE BEING TREATED EACH YEAR (UK FIGURES).
- RISK FACTORS FOR ACCELERATED PROGRESSION INCLUDE MALE GENDER, OLDER AGE, OBESITY, INFECTION WITH HIV, DIABETES AND A SIGNIFICANT ALCOHOL HISTORY.

HEPATITIS C

LABORATORY DIAGNOSIS

- **ANTI HEPATITIS C ANTIBODIES ARE USUALLY PRESENT THREE TO SIX MONTHS AFTER INFECTION. DIAGNOSIS IS MADE THROUGH A HEPATITIS C ANTIBODY TEST AND A CONFIRMATORY CRNA TEST TO ASSESS FOR ACTIVE INFECTION.**

- **ORAL FLUID TESTING IS POSSIBLE BUT IS OF LOWER SENSITIVITY AND SPECIFICITY.**

HEPATITIS C

LIFE CYCLE

- **HCV IS A BLOOD BORNE SINGLE STRANDED RNA VIRUS.**
- **RNA VIRUSES MUTATE TO A GREATER EXTENT THAN DNA VIRUSES, RESULTING IN DIFFICULTY FOR THE BODY'S IMMUNE SYSTEM TO LOCATE AND DESTROY THEM**

- **STEPS IN THE LIFE CYCLE**
  - **ENTRY IN THE HOST CELL (HEPATOCYTE)**
  - **UNCOATING OF THE VIRAL GENOME**
  - **TRANSLATION OF VIRAL PROTEINS**
  - **VIRAL GENOME REPLICATION**
  - **ASSEMBLY AND RELEASE**

TARGETS FOR NEW DRUGS

- NON STRUCTURAL PROTEINS ARE ESSENTIAL FOR THE VIRAL LIFE CYCLE PROCESSES AND ARE THE PRIMARY TAGETS FOR THE NEW ANTIVIRAL MEDICINES

- IN PARTICULAR THE VIRAL ENZYME NS3/4 PROTEASE (IMPORTANT IN VIRAL PROTEIN PRODUCTION) AND NON STRUCTURAL PROTEINS NS5A AND NS5B (WHICH PLAY A ROLE IN HCV REPLICATION) ARE TARGETS

TREATMENT

- THE PRIMARY AIM OF THE TREATMENT IS TO ACHIEVE VIRAL ERADICATION OR SUSTAINED VIRAL RESPONSE (SVR)

- TRADITIONAL TIME POINT TO ASSESS IF SVR ACHIEVED IS AT 24 WEEKS POST TREATMENT THOUGH 12 WEEKS POST TREATMENT IS NOW WIDELY RECOGNISED

- SECONDARY AIMS:
  - PREVENTING TRANSMISSION
  - PREVENTING PROGRESSION OF LIVER DAMAGE
  - IMPROVING PATIENTS QUALITY OF LIFE

TREATMENT

- RESPONSE RATES TO TREATMENT ARE DICTATED BY GENOTYPE, TREATMENT HISTORY AND PATIENT SPECIFICS (AGE,GENDER,OTHER INFECTIONS PRESENT, ETC)

- THE STAGE OF LIVER DISEASE IS ALSO AN IMPORTANT PREDICTOR OF VIRAL RESPONSE. THOSE WITH ADVANCED FIBROSIS OR CIRRHOSIS ACHIEVED LOWER TREATMENT RESPONSE RATES

CURRENT TREATMENT

PEGINTERFERON AND RIBAVIRIN

PEGINTERFERON

- **PEGINTERFERON AND RIBAVIRIN COMBINATION THERAPY IS AN ESTABLISHED TREATMENT FOR HEPATITIS C INFECTION**
- **PEGINTERFERON AVAILABLE AS ALFA 2A AND ALPHA 2B. THEY ARE ADMINISTERED BY SUBCUTANEOUS INJECTION ONCE WEEKLY.**
- **DOSE MAY BE ADJUSTED DEPENDING ON CLINICAL FACTORS SUCH AS PRESENCE OF THROMBOCYTOPENIA AND LOW MOOD.**

RIBAVIRIN

- **ORAL TABLET ADMINISTERED TWICE DAILY WITH FOOD. DOSE OF RIBAVIRIN IS OFTEN ADJUSTED TO ACCOUNT FOR THE PRESENCE OR ABSENCE OF ANAEMIA.**

CURRENT TREATMENT

PEGINTERFERON AND RIBAVIRIN

- **TREATMENT DURATION RANGES FROM 24 TO 72 WEEKS WITH SVR 24 RATES OF AROUND 40-50% IN PATIENTS WITH HEPATITIS C GENOTYPE 1 AND 40-80% IN PATIENTS WITH GENOTYPES 2 TO 6.**

- **THE PEGINTERFERON/RIBAVIRIN REGIMEN HAS AN EXTENSIVE SIDE EFFECT PROFILE INCLUDING CYTOPENIA AND MOOD DISTURBANCES.**

CURRENT TREATMENT

PEGINTERFERON AND RIBAVIRIN

- **THESE LIMIT THEIR USE IN SOME PATIENTS AND IT IS ESTIMATED THAT AROUND 27% OF PATIENTS PRESCRIBED A PEGINTERFERON STOP TREATMENT DUE TO ADVERSE EFFECTS.**

- **SIDE EFFECTS OF RIBAVIRIN INCLUDE DERMATOLOGICAL SIDE EFFECTS (DERMATITIS, PRURITUS, URTICARIA, ETC) AND HAEMOTOLOGICAL ABNORMALITIES (e.g anaemia)**

SITE OF ACTION OF NEW DRUGS

NS ¾ PROTEASE INHIBITORS	NS 5A INHIBITORS	NS 5B INHIBITORS
TELAPREVIR	DACLATASVIR	SOFOSBUVIR
BOCEPREVIR	LEDIPASVIR	DASABUVIR
SIMEPREVIR	OMBITASVIR	

SOFOSBUVIR

- THE FIRST NON INTERFERON TREATMENT FOR HEPATITIS C
- NEW TREATMENT OPTION FOR CHRONIC HEPATITIS C WHICH OFFERS HOPE OF A CURE
- HAILED AS A MAJOR BREAKTHROUGH AND GAME CHANGER IN THE MANAGEMENT OF HEPATITIS C

SOFOSBUVIR

KEY FACTS

- **NS5B NUCLEOTIDE INHIBITOR. THE NS5B RNA DEPENDENT POLYMERASE IS RESPONSIBLE FOR REPLICATION OF HEPATITIS CRNA**
- **EMEA/FDA APPROVAL IN LATE 2013/BEGINNING 2014 (MARKETED AS SOLVADI)**
- **ORAL ADMINISTRATION AS A 400MG TABLET ONCE DAILY**
- **EFFECTIVE ACROSS ALL GENOTYPES**
- **LIMITED DRUG/DRUG INTERACTIONS (AS NOT METABOLISED BY CYTOCHROME P450)**

SOFOSBUVIR

- MUST BE USED IN COMBINATION WITH RIBAVIRIN
- CAN BE USED WITH OR WITHOUT PEGINTERFERON
- THE COMBINATION THERAPY WITH SOFOSBUVIR MEANS A SHORTER DURATION OF TREATMENT FROM 24 TO 12 WEEKS
- THE CLINICAL EFFICACY HAS BEEN EXAMINED IN A NUMBER OF PHASE III CLINICAL TRIALS WHICH INCLUDED A PROPORTION OF DIFFICULT TO TREAT POPULATIONS, SUCH AS PATIENTS WITH CIRRHOSIS
- RESPONSE RATE CAN RANGE FROM 56-97% DEPENDING ON GENOTYPES AND PROTOCOL REGIMENS

SOFOSBUVIR

- WOMEN OF CHILD BEARING POTENTIAL RECEIVING TREATMENT AND MEN WITH FEMALE PARTNERS SHOULD USE EFFECTIVE CONTRACEPTION TO PREVENT PREGNANCY.

- NO SIDE EFFECTS HAVE BEEN IDENTIFIED THAT ARE SPECIFIC TO SOFOSBUVIR AND DURING COMBINATION TREATMENT THE SIDE EFFECTS WERE CONSISTENT WITH THOSE EXPECTED FOR RIBAVIRIN/PEGINTERFERON.

SOFOSBUVIR

Regimen without Interferon-Alfa 24w vs., 12w vs. Placebo	Regimen with Interferon-Alfa SOF/PEG/RBV vs. Placebo
Fatigue 30% (38%) [24%]	Fatigue 30% [55%]
Headache 30% (24%) [20%]	Headache 36% [44%]
Nausea 13% (22%) [18%]	Nausea 34% [29%]
Insomnia 16% (15%) [4%]	Insomnia 25% [29%]
Pruritus 27% (11%) [8%]	Pruritus 17% [17%]
Anaemia 6% (10%) [0%]	Anaemia 21% [12%]
Asthenia 21% (6%)[3%]	Asthenia 5% [3%]
Chills 2% (2%) [1%]	Chills 17% [18%]
Influenza-like illness 6% (3%) [3%]	Influenza-like illness 16% [18%]

DOSE

- **DOSING ONE TABLET (400mg Daily) WITH CONCOMITTANT RIBAVIRIN WITH OR WITHOUT PEGINTERFERON**

- **HIGH COST DRUG. MAURITIUS WILL BENEFIT FROM AN ACCESS PRICE**

MONITORING PARAMETERS

- ***EFFICACY MONITORING:***
  - **HCV-RNA AT BASELINE, DURING TREATMENT, AT THE END OF TREATMENT AND DURING FOLLOW-UP WHEN CLINICALLY INDICATED**

- ***TOXICITY MONITORING:***
  - **BILIRUBIN, LIVER ENZYMES AND SERUM CREATININE AT BASELINE AND PERIODICALLY WHEN CLINICALLY INDICATED**
  - **PRETREATMENT AND MONTHLY PREGNANCY TEST UP TO 6 MONTHS FOLLOWING THERAPY**

Summary of preliminary recommendations

Population	Treatment History	Interferon Eligibility	Recommendation
Sofosbuvir in combination with peginterferon alfa and ribavirin			
Adults with genotype 1 HCV	treatment naive	interferon eligible	recommended
	treatment experienced	interferon eligible	recommended
Adults with genotype 3 HCV	treatment naive	interferon eligible	not recommended in people without cirrhosis recommended in people with cirrhosis
	treatment experienced	interferon eligible	recommended
Adults with genotype 4, 5, and 6 HCV	treatment naive	interferon eligible	not recommended
	treatment experienced	interferon eligible	not recommended
Sofosbuvir in combination with ribavirin			
Adults with genotype 1 HCV	treatment naive	interferon unsuitable	not recommended
	treatment experienced	interferon unsuitable	not recommended
Adults with genotype 2 HCV	treatment naive	interferon eligible	not recommended
	treatment naive	interferon unsuitable	recommended
	treatment experienced	interferon eligible	recommended
	treatment experienced	interferon unsuitable	recommended
Adults with genotype 3 HCV	treatment naive	interferon unsuitable	not recommended in people without cirrhosis recommended in people with cirrhosis
	treatment experienced	interferon unsuitable	not recommended in people without cirrhosis recommended in people with cirrhosis
Adults with genotype 4, 5, and 6 HCV	treatment naive	interferon unsuitable	not recommended
	treatment experienced	interferon unsuitable	not recommended

HCV – hepatitis C virus;

treatment naïve – people who have not had prior treatment for chronic hepatitis C;

treatment experienced – people who have had prior treatment with interferon based therapy for chronic hepatitis C which did not have an adequate response to that treatment

interferon unsuitable – includes people who are intolerant to and ineligible for interferon.

SOFOSBUVIR + LEDIPASVIR COMBINATION

- A FIXED DOSE COMBINATION OF SOFOSBUVIR 400mg + LEDIPASVIR 90mg IN A SINGLE TABLET FOR ONCE DAILY ADMINISTRATION (MARKETED AS HARVONI)
- EMEA APPROVAL IN NOVEMBER 2014/ US FDA APPROVAL
- INDICATED FOR GENOTYPE 1,3,4 INCLUDING CO-INFECTION WITH HIV
- RECOMMENDED DOSE IS ONCE DAILY FOR 8, 12 OR 24 WEEKS DEPENDING WHETHER THE PATIENT HAS CIRRHOSIS OR HAS RECEIVED TREATMENT PREVIOUSLY.

SOFOSBUVIR + LEDIPASVIR COMBINATION

- **PEGINTERFERON IS NOT USED WITH THIS TREATMENT AND RIBAVIRIN IS ONLY USED IN PATIENTS WITH CIRHOSIS.**

- **OVERALL THE STUDIES FOR HARVONI SHOW A WELL TOLERATED REGIMEN.**

2. PCSK9 INHIBITORS

A NEW ERA FOR LIPID TARGETED THERAPIES

STATINS HAVE BEEN A MAINSTAY OF HEART ATTACK AND STROKE PREVENTION FOR THE PAST 20 YEARS, BUT THE COMPETITION IS ON WITH NEW DRUGS ENTERING THE MARKET THAT TARGET AN ENZYME CALLED PCSK9

HISTORY

- IN 2003, FRENCH RESEARCHERS IDENTIFIED HIGH LEVELS OF PROTEIN IN A FAMILY WITH FAMILIAL HYPERCHOLESTEROLEMIA, AN INHERITED DISEASE THAT LEADS TO DANGEROUSLY HIGH BLOOD CHOLESTEROL AND CONSEQUENTLY INCREASED RISK OF CARDIOVASCULAR DISEASE.

- THE PROTEIN CALLED PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 (PCSK9) HAS BEEN DISCOVERED EARLIER THAT YEAR BY CANADIAN RESEARCHERS.

- A SERIES OF EXPERIMENTS FROM DIFFERENT LABORATORIES SUBSEQUENTLY SHOWED THAT HIGH LEVELS OF PCSK9 STOPPED THE LOW DENSITY LIPOPROTEIN (LDL) RECEPTORS FROM FUNCTIONING.

HISTORY

- 3 YEARS LATER RESULTS FROM A LARGE COMMUNITY STUDY MAPPING LDL CHOLESTEROL LEVELS AND INCIDENCE OF CORONARY HEART DISEASE AGAINST MUTATIONS IN THE PCSK9 GENE WERE RELEASED. THOSE WITH GENETIC VARIATIONS LINKED TO REDUCED PCSK9 FUNCTION WERE FOUND TO HAVE A SIGNIFICANT LOWER LDL LEVELS AND LOWER RISK OF CHD.

- THE HYPOTHESIS THAT INHIBITING PCSK9 ACTIVITY COULD REDUCE CHOLESTEROL LEVEL BECAME AN IMPORTANT RESEARCH TOPIC.

CURRENT TREATMENT - HYPERCHOLESTEROLEMIA

- STATINS WHICH HAVE BEEN ON THE MARKET FOR NEARLY 30 YEARS ARE THE PRIMARY THERAPY TO REDUCE CARDIOVASCULAR EVENTS.
- THEY LOWER LDL-LEVELS BY INHIBITING THE ENZYME HMG-CoA REDUCTASE WHICH HAS A VITAL ROLE IN THE PRODUCTION OF CHOLESTEROL IN THE LIVER.
- THEY CAN REDUCE LDL-C LEVELS BY 30-40 % (DEPENDING ON DOSE AND STATIN)
- HAVE BEEN HUGELY SUCCESSFUL IN TERMS OF SALES. ATORVASTATIN IS THE BEST SELLING DRUGS OF ALL TIMES.
- IN SOME PATIENTS STATINS ARE INEFFECTIVE OR SIDE EFFECTS INTOLERABLE. FURTHERMORE IT IS DIFFICULT TO ACHIEVE VERY LOW LEVELS OF LDL-C.

PCSK9 INHIBITORS

MODE OF ACTION

- HOPE TO ADDRESS THIS UNMET NEED.
- PCSK9 PROTEIN INTERFERES WITH THE CLEARANCE OF LDL-C FROM BLOOD
- LDL RECEPTORS ON LIVER CELLS REMOVE LDL-C FROM BLOOD BY BINDING IT AND THEN MOVING IT INTO THE CELL FOR ELIMINATION.
- WHEN PCSK9 PROTEIN BINDS TO THE LDL RECEPTOR, THE RECEPTOR CANNOT REMOVE LDL-C FROM THE BLOOD, WHICH THEN REMAINS IN BLOOD CAUSING AN INCREASE OF LDL .

PCSK9 INHIBITORS

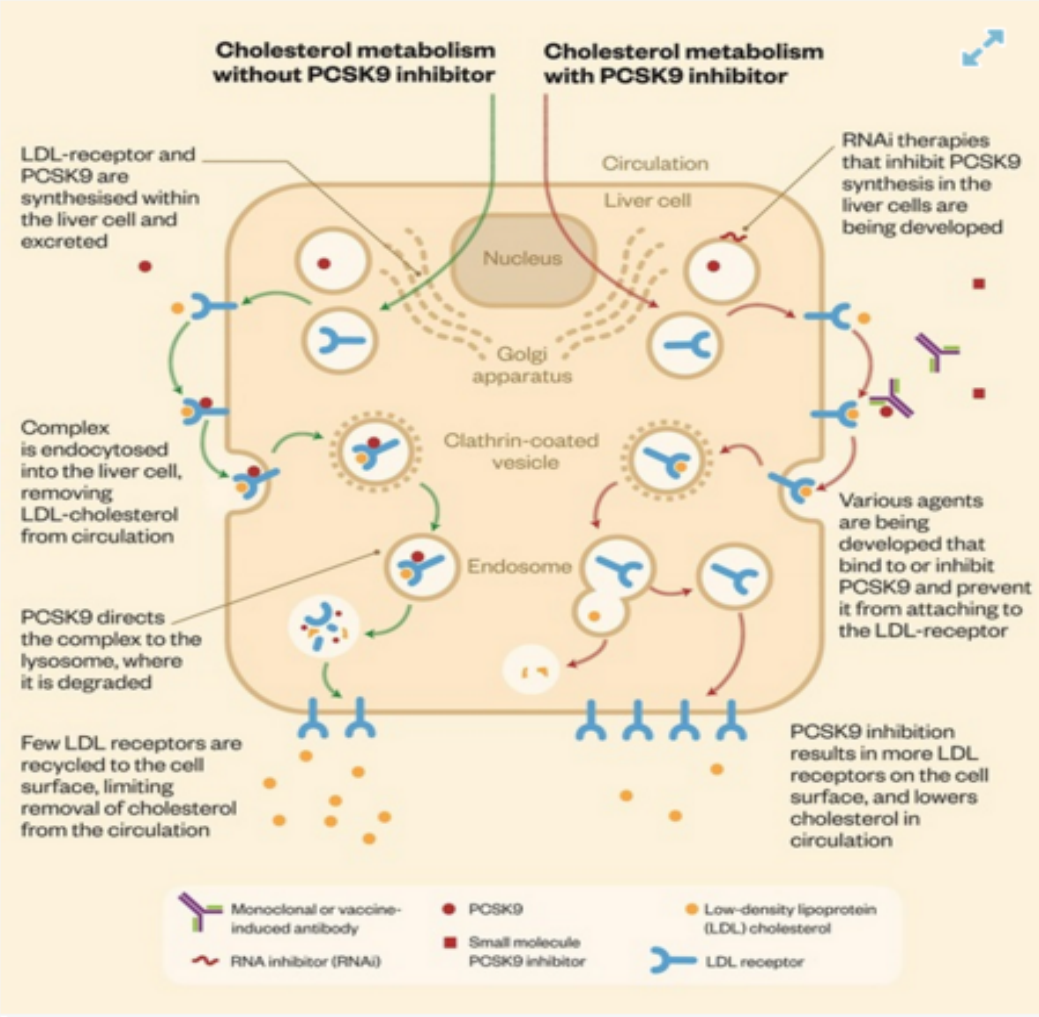
MODE OF ACTION

- PCSK9 INHIBITORS INHIBITS PCSK9 PROTEINS, ENABLING MORE LDL RECEPTORS TO REMOVE LDL FROM BLOOD CIRCULATION

- OVERALL REDUCTION IN CHOLESTEROL LEVELS IN BLOOD

Cholesterol metabolism and PCSK9 inhibitors

The PCSK9 protein interferes with clearance of cholesterol from the blood. Several PCSK9 inhibitors are being developed, which improve the liver's ability to recycle low-density lipoprotein (LDL) receptors, enabling more cholesterol to be removed from the circulation.



From Pharmaceutical Journal 15 April 2015

PCSK9 INHIBITORS

NEW DRUGS

- **THERE ARE AROUND 20 PCSK9 INHIBITORS UNDER DEVELOPMENT**

- **TWO PRODUCTS HAVE BEEN LAUNCHED RECENTLY:**
  - **EVOLOCUMAB (REPATHA) – AMGEN**
  - **ALIROCUMAB (PRALUENT) – SANOFI**

- **BOTH DRUGS ARE INJECTABLE MONOCLONAL ANTIBODIES THAT APPEAR TO BE HIGHLY EFFECTIVE AT REDUCING LDL-C LEVELS, ACHIEVING AN ADDITIONAL 60-75% REDUCTION IN PATIENTS TAKING STATINS**

PCSK9 INHIBITORS

- SO FAR NO SERIOUS ADVERSE EVENTS REPORTED IN PHASE III TRIALS
- COMMON SIDE EFFECTS INCLUDE INJECTION SITE REACTIONS AND COLD/FLU LIKE SYMPTOMS
- BOTH AMGEN AND SANOFI ARE ASSESSING POTENTIAL NEUROCOGNITIVE SIDE EFFECTS, SUCH AS MEMORY LOSS AND CONFUSION
- PCKS9 INHIBITORS ARE EXPECTED TO WORK SYNERGISTICALLY WITH STATINS
- MOST OF THE BENEFITS OF STATIN TREATMENT COMES FROM A NORMAL DOSE. DOUBLING THE DOSE INCREASES LDL-REDUCTION BY ONLY 6%. ADDING PCSK9 INHIBITORS TO STATINS SHOULD RESULT IN A MUCH GREATER REDUCTION IN LDL-C
- THE PROFILE OF PCKS9 INHIBITORS LOOK GOOD IN TERMS OF EFFICACY AND SAFETY

PCSK9 INHIBITORS

- EVOLOCUMAB (REPATHA) – LAUNCHED IN MAY/JUNE 2015
- ALIROCUMAB (PRALUENT) – LAUNCHED IN JULY 2015
- EVOLOCUMAB IS INDICATED FOR THE TREATMENT OF PATIENTS WITH FAMILIAL HYPOCHOLESTEROLEMIA OR WITH PRIMARY HYPERCHOLESTEROLEMIA WHO ARE UNABLE TO CONTROL THEIR CHOLESTEROL WITH CURRENT THERAPIES
- IT IS GIVEN FORTNIGHTLY AS A SC INJECTION AND CAN BE USED IN ADDITION TO STATINS OR ALONE IN PATIENTS INTOLERANT OF STATINS
- COST OF REPATHA IN THE UK (AROUND GBP 340/MONTH)
- ONCE MONTHLY FORMULATION IN THE PIPELINE
- THE RESEARCH BEHIND THESE NEW BIOLOGICS MAY LEAD TO POTENTIAL NEW APPROACHES TO TREATING HYPERCHOLESTEROLEMIA

PCSK9 INHIBITORS

- THE CLINICAL COMMUNITY WILL BE INCLINED TO WAIT FOR THE CULMINATION OF MAJOR OUTCOME STUDIES (WHICH ARE ONGOING) BEFORE PRESCRIBING PCSK9 INHIBITORS FOR MANY PATIENTS.
- RESULTS FROM ALIROCUMAB ODYSSEY OUTCOME TRIALS ARE EXPECTED IN JANUARY 2018 AND FOR EVOLOCUMAB'S FOURIER IN DECEMBER 2017.
- IF OUTCOMES BASED STUDIES CONFIRM PRELIMINARY DATA SUGGESTING A REDUCED RATE OF CARDIOVASCULAR EVENTS AND NO ADDITIONAL NEW TOXICITY EMERGES, THEN PCSK9 INHIBITORS WILL CLEARLY BE A MAJOR ADVANCE IN LIPID LOWERING THERAPY.
- COST AND INJECTABLE ROUTE ARE LIMITING FACTORS.
- PCSK9 INHIBITOR GENERATES NEW HOPE FOR ALL PATIENTS CURRENTLY NOT REACHING LDL-C LEVEL BECAUSE OF SEVERE HYPERCHOLESTEROLEMIA OR INTOLERANCE TO CURRENT THERAPIES.

3. SACUBITRIL/VALSARTAN (ENTRESTO)

THE NEXT BLOCKBUSTER FOR HEART FAILURE TREATMENT?

ENTRESTO

- ORAL TABLETS CONTAINING SACUBITRIL (A NEPRILYSIN INHIBITOR) AND VALSARTAN (AN ANGIOTENSIN RECEPTOR II BLOCKER)

- FIRST IN A NEW CLASS OF NEPRILYSIN INHIBITORS

ENTRESTO

HOW IT WORKS?

- **SACUBUTRIL INHIBITS NEPRILYSIN WHICH INCREASES LEVEL OF PEPTIDES THAT ARE NORMALLY DEGRADED BY NEPRILYSIN.**

- **MORE OF THESE PEPTIDES (NATRIURETIC PEPTIDES, BRADYKININ, ADRENOMEDULLIN) MEANS MORE VASODILATION AND SODIUM LOSS PLUS LESS CARDIAC AND VASCULAR HYPERTROPHY AND REMODELLING.**

- **THIS HELPS TO IMPROVE MANY OF THE PATHOPHYSIOLOGICAL ABNORMALITIES OF HEART FAILURE.**

ENTRESTO

HOW IT WORKS?

- **IN PATIENTS WITH HEART FAILURE, NEPRILYSIN MAY ACTUALLY HAVE INCREASED ACTIVITY, SO BLOCKING IT WITH ENTRESTO MAY PROVIDE EVEN MORE FAVOURABLE RESULTS TO THESE PATIENTS**

- **VALSARTAN BLOCKS ANGIOTENSIN II RECEPTOR AND INHIBIT THE RELEASE OF ANGIOTNESIN II DEPENDENT ALDOSTERONE. THIS ACTION IS NEEDED IN ADDITION TO SACUBITRIL BECAUSE INHIBITING NEPRISYLIN IS ACCOMPANIED BY THE ACTIVATION OF RENIN-ANGIOTENSIN SYSTEM, POSSIBLY BECAUSE ANGIOTENSIN ITSELF MAY BE A SUBSTRATE FOR NEPRILYSIN, HENCE SACUBITRIL SHOULD NOT BE USED ALONE.**

- **THIS COMBINATION OF VALSARTAN AND SACUBITRIL IS DESCRIBED AS AN ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITOR (ARNI).**

ENTRESTO

INDICATIONS

INDICATED TO REDUCE THE RISK OF CARDIOVASCULAR DEATH AND HOSPITALISATION FOR HEART FAILURE PATIENTS WITH NYHA CLASS II TO IV CHRONIC HEART FAILURE AND REDUCED EJECTION FRACTION (≤ 40%)

WHEN USED, THIS DRUG WILL BE ADMINISTERED WITH OTHER HEART FAILURE THERAPIES, IN PLACE OF AN ACEI OR ARB.

ENTRESTO

- WAS FASTRACKED FOR APPROVAL BY FDA/EMEA ON THE BACK OF RESULTS OF A RANDOMISED CLINICAL TRIAL INVOLVING MORE THAN 8000 PATIENTS WHO HAD HEART FAILURE WITH REDUCED EJECTION FRACTION

- THE PATIENTS WERE FOLLOWED UP FOR A MEDIAN OF 27 MONTHS AND THE TRIAL STOPPED EARLY WHEN THE RESULTS SHOWED THAT ENTRESTO WAS MORE EFFECTIVE THAN ENALAPRIL (PARADIGM-HF TRIAL)

ENTRESTO

- RESEARCHERS FOUND THAT 13.3% PATIENTS DIED FROM CARDIOVASCULAR DEATH WHEN USING THE COMBINATION DRUG COMPARED TO 16.5% WITH ENALAPRIL.

- THE TRIAL ALSO FOUND THAT ENTRESTO REDUCED THE NUMBER OF PATIENTS WHO HAD TO BE HOSPITALISED FOR HEART FAILURE.

ENTRESTO DOSE

- AVAILABLE IN SACUBITRIL/VALSARTAN TABLET COMBINATIONS OF 24/26mg (50mg), 49/51mg (100mg) and 97/103mg (200mg)
- STARTING DOSE IS 49/51mg TWICE DAILY
- DOSE SHOULD BE INCREASED EVERY 2-4 WEEKS AS TOLERATED TO A TARGET DOSE OF 97/103mg TWICE DAILY AS MAINTENANCE
- A REDUCED STARTING DOSE OF 24/26mg TWICE DAILY SHOULD BE GIVEN TO PATIENTS IF THEY HAVE NOT HAD PREVIOUS ACE I OR ARB, BEEN ON ONLY LOW DOSE ACE I OR ARB, HAVE SEVERE RENAL IMPAIRMENT (eGFR < 30ml/min/1.73m^2) OR HAVE MODERATE HEPATIC IMPAIRMENT

ENTRESTO

- IF A PATIENT IS SWITCHING FROM AN ACE I TO ENTRESTO, HE SHOULD WAIT FOR 36 HOURS FROM THE LAST DOSE BEFORE TAKING FIRST DOSE OF ENTRESTO

- OVERLAPPING THESE TWO MEDICATIONS CAN INCREASE RISK OF ANGIOEDEMA

- IT IS IMPORTANT TO NOTE (FOR EXAMPLE) THAT THE 103mg OF VALSARTAN IN ENTRESTO'S DOSE IS EQUIVALENT TO 160mg OF VALSARTAN IN TAREG DUE TO THE FACT THAT THEY ARE DIFFERENT SALTS

ENTRESTO

ADVERSE EVENTS

THE MOST COMMON ARE (>5%)

1. **HYPOTENSION**
2. **HYPERKALEMIA**
3. **COUGH**
4. **DIZZINESS**
5. **KIDNEY IMPAIRMENT**

EMEA HAS DECIDED TO MONITOR THE SAFETY BECAUSE OF THE RISK OF ANGIOEDEMA.

ENTRESTO

DRUG INTERACTIONS

- **TO AVOID DUPLICATION OF ACTIVITY ON THE RENIN ANGIOTENSIN SYSTEM, ENTRESTO SHOULD BE NOT GIVEN WITH ACE I, ALISKIREN OR ANOTHER ARB**

- **USING ENTRESTO WITH POTASSIUM SPARING DIURETICS, POTASSIUM SUPPLEMENTS OR SALT SUBSTITUTES CAN INCREASE SERUM POTASSIUM LEVELS**

- **COMBINING ENTRESTO WITH NSAIDS MAY INCREASE RISK OF RENAL IMPAIRMENT**

ENTRESTO

CONTRAINDICATIONS

- **CONTRAINDICATED IN PATIENTS WITH HISTORY OF ANGIOEDEMA WITH A PREVIOUS ACE I OR ARB**
- **CONCOMITTANT USE OF AN ACE I**
- **CONCOMITTANT USE WITH ALISKIREN IN PATIENTS WITH DIABETES**

ENTRESTO

PRECAUTIONS

- **PATIENTS SHOULD BE CLOSELY MONITORED FOR SIGNS AND SYMPTOMS OF ANGIOEDEMA AND HYPOTENSION.**
- **RENAL FUNCTION AND SERUM POTASSIUM LEVELS SHOULD BE MONITORED REGULARLY.**
- **IT IS NOT RECOMMENDED IN PATIENTS WITH SEVERE HEPATIC IMPAIRMENT.**
- **CAN CAUSE FETAL HARM IN PREGNANCY AND SHOULD NOT BE USED. NOT RECOMMENDED FOR LACTATING WOMEN.**

ENTRESTO IN HEART FAILURE

FOR MOST PATIENTS WITH HEART FAILURE THE STANDARD TREATMENT REGIMEN INCLUDES A BETA BLOCKER, ACE I OR ARB AND AN ALDOSTERONE ANTAGONIST. A DIURETIC CAN BE ADDED IF THE PATIENT IS VOLUME OVERLOADED. THIS STANDARD THERAPY HAS BEEN SHOWN TO IMPROVE SURVIVAL AND QUALITY OF LIFE FOR PATIENTS WITH HEART FAILURE.

ENTRESTO IN HEART FAILURE

- THE PARADIGM-HF TRIAL ALLOWED ENTRESTO TO BE COMPARED TO THE ENALAPRIL DOSE THAT HAS BEEN PROVEN TO REDUCE MORTALITY IN HEART PATIENTS

- IN ORDER TO LOWER THE COST, THE MANUFACTURER IS DISCUSSING NOVEL PRICING MODELS. FOR EXAMPLE PAYMENT FOR THE MEDICATION MAY BE BASED ON CLINICAL OUTCOMES WITH AN INITIAL DISCOUNTED PRICE AND FURTHER PAYMENTS IF OUTCOMES, SUCH AS AVOIDANCE OF HOSPITAL ADMISSIONS ARE MET.

ENTRESTO IN HEART FAILURE

- WHEN USED, THIS DRUG REPLACES THE ACE I OR ARB IN A TREATMENT REGIMEN THAT COSTS AS LITTLE AS $10 A MONTH.
- STANDARD HEART FAILURE THERAPY WITH OPTIMAL DOSES SHOULD AS AT DATE STILL BE RECOMMENDED AS FIRST LINE TREATMENT IN MOST PATIENTS WITH HEART FAILURE.
- IF THERE ARE PERSISTENT SYMPTOMS, WITH RECENT EXACERBATIONS OR HOSPITALISATIONS, WHILE ON THE OPTIMIZED TREATMENT, CONSIDER CHANGING THE ACE I OR ARB TO ENTRESTO.
- THE DRUG HAS THE POTENTIAN TO EXTEND THE LIVES OF MANY PATIENTS AS WELL AS PREVENT HOSPITAL ADMISSIONS
- THE NEXT BLOCKBUSTER DRUG?

ENTRESTO IN HEART FAILURE

THE FUTURE

- **OF NOTE, THIS DRUG IS NOT INDICATED FOR PATIENTS WITH PRESERVED EJECTION FRACTION.**

- **THERE IS AN ONGOING STUDY (PARAGON-HF) TO ASSESS THE EFFICACY OF ENTRESTO IN THIS GROUP SCHEDULED TO RUN FROM 2013 TO 2019.**

4. OBESITY: EMERGING DRUG TREATMENTS

OBESITY

- THE PREVALENCE OF OBESITY HAS DOUBLED WORLDWIDE SINCE 1980.
- A RANGE OF NEW TREATMENTS ARE BEING INTRODUCED TO HELP PATIENTS LOSE WEIGHT.

EPIDEMIOLOGY

- IN 2014, MORE THAN 1.9 BILLION ADULTS (39% OF ALL PEOPLE AGED 18 YEARS OR OLDER) WERE OVERWEIGHT, OF WHOM MORE THAN 600 MILLIONS WERE OBESE (13 % OF ALL ADULTS).

- AROUND 42 MILLIONS CHILDREN UNDER THE AGE OF FIVE YEARS WORLDWIDE WERE OVERWEIGHT OR OBESE IN 2013.

- IN UK, AROUND 6% OF ALL DEATHS ARE ATTRIBUTED TO OBESITY COMPARED TO 10% FOR SMOKING AND 1% TO ROAD TRAFFIC ACCIDENTS.

OBESITY

CO-MORBIDITIES

- **POSSIBLE COMORBIDITIES ASSOCIATED WITH OBESITY INCLUDE TYPE 2 DIABETES AND THERE IS EVIDENCE LINKING ABDOMINAL OBESITY TO INSULIN RESISTANCE AND SERIOUS CO-MORBID DISEASE.**
- **THE INTERHEART STUDY DEMONSTRATED THE IMPORTANCE OF ABDOMINAL OBESITY IN THE PATHOGENESIS OF ACUTE MYOCARDIAL INFARCTION (MI) CONTRIBUTING TO AROUND 34% OF RISK OF MI.**
- **RISK OF HYPERTENSION IS FIVE FOLD GREATER IN OBESE PEOPLE COMPARED TO THOSE WITH NORMAL WEIGHT.**
- **LIPID PROFILE IS ADVERSELY AFFECTED LEADING TO A PROFILE OF SMALL, DENSE, LDL PARTICLES, LOW HIGH DENSITY LIPOPROTEIN (HDL) AND RAISED TRIGLYCERUDES CONTRIBUTING TO CORONARY ARTERY DISEASE.**
- **OTHER CONDITIONS LINKED TO OBESITY INCLUDE POLYCYSTIC OVARY SYNDROME, OBSTRUCTIVE SLEEP APNOEA, MENTAL HEALTH PROBLEMS, INFERTILITY AND A VARIETY OF CANCERS.**

PHARMACOTHERAPY

- DRUG THERAPY MAY BE A SUITABLE OPTION FOR PEOPLE WHO HAVE BEEN UNSUCCESSFUL IN LOSING WEIGHT WITH LIFE STYLE CHANGES.

- PATIENTS SHOULD USE MEDICINES IN ADDITION TO APPROPRIATE DIET, PHYSICAL ACTIVITY AND BEHAVIOURAL INTERVENTIONS.

CURRENT THERAPY

ORLISTAT

- PANCREATIC LIPASE INHIBITOR
- CAUSES 30% OF DIETARY FAT TO BE EXCRETED UNABSORBED IN FAECES.
- WEIGHT LOST IS MODEST
- GENERALLY SAFE FOR LONG TERM USE
- SIDE EFFECTS ARE COMMON: INCLUDING OILY STOOLS, CRAMPS, AND OCCASIONAL FECAL INCONTINENCE.
- NICE SUPPORTS USE OF ORLISTAT IN PATIENTS WITH BMI>30 OR BMI>28 WITH COMORBIDITIES.
- TREATMENT SHOULD ONLY BE CONTINUED BEYOND 3 MONTHS IF THE PERSON HAS LOST AT LEAST 5% OF INITIAL BODY WEIGHT SINCE STARTING TREATMENT.
- THE DECISION TO USE LONGER THAN 12 MONTHS, USUALLY FOR WEIGHT MAINTENANCE SHOULD BE MADE AFTER DISCUSSING POTENTIAL BENEFITS AND LIMITATIONS WITH THE PATIENTS.

OBESITY

WITHDRAWN WEIGHT MANAGEMENT DRUGS

MANY OBESITY DRUGS HAVE BEEN WITHDRAWN OVER RECENT YEARS DUE TO SIDE EFFECTS, AMONG WHICH:

1. RIMONABANT - ENDOCANNABINOID RECEPTOR
- LINKS TO DEPRESSIVE MOOD CHANGES AND PERSISTENT LINKS WITH SUICIDALITY

2. SIBUTRAMINE - SATIETY ENHANCER
- INCREASE IN NON-FATAL CARDIOVASCULAR EVENTS

OBESITY

NEW TREATMENTS

1. **LIRAGLUTIDE (SAXENDA)**
   - **GLP-1 RECEPTOR AGONIST (INCRETIN MIMETIC)**
   - **MARKETED AS VICTOZA IN THE MANAGEMENT OF DIABETES**
   - **GIVEN ONCE DAILY AS A SUBCUTANEOUS INJECTION**
   - **AUTHORISED BY USFDA AS AN ANTIOBESITY AGENT. POSITIVE OPINION BY EMEA.**
   - **MECHANISM OF ACTION NOT FULLY UNDERSTOOD BUT APPEARS TO REGULATE APETITE BY INDUCING A FEELING OF FULLNESS AND REDUCING HUNGER PAINS**

OBESITY

NEW TREATMENTS

1. **LIRAGLUTIDE (SAXENDA)**

   - **EMA RECOMMENDS THAT IT SHOULD ONLY BE OFFERED TO ADULTS WITH BMI>30, OR 27 IF THEY HAVE A WEIGHT RELATED CONDITION SUCH AS TYPE 2 DIABETES**

   - **PATIENTS RECEIVE A 3mg DAILY DOSE (COMPARED TO 1.2/1.8mg FOR DIABETES) WITH TREATMENT STOPPED IF BODY WEIGHT HAS NOT BEEN REDUCED BY AT LEAST 5% AFTER 12 WEEKS.**

OBESITY

NEW TREATMENTS

2. LORCASERIN (BELVIQ)

- SEROTONIN 2 C RECEPTOR AGONIST WHICH INCREASES SATIETY
- IT HAS BEEN SHOWN TO RESULT IN A PLACEBO ADJUSTED WEIGHT LOSS OF 3-4 kg AT ONE YEAR, ALONGSIDE IMPROVEMENTS IN FBS, INSULIN SENSITIVITY, BLOOD PRESSURE, TOTAL AND LDL CHOLESTEROL AND C-REACTIVE PROTEIN LEVELS
- USUAL DOSE IS 1 TABLET TWICE DAILY
- APPROVED BY FDA

3. BUPROPRION/NALTREXONE COMBINATION (MYSIMBA/CONTRAVE TABLETS)

- COMBINES AN OPIOD ANTAGONIST (NALTREXONE) WITH DOPAMINE REUPTAKE INHIBITOR (BUPROPRION)
- APPROVED BY US FDA IN 2014 AND EMEA IN 2015
- BUPROPRION PLAYS A ROLE IN THE REGULATION OF APETITE WHILE NALTREXONE PROLONGS THE EFFECT OF BUPOPRION
- RESULTS SHOWED A PLACEBO ADJUSTED WEIGHT LOSS OF AROUND 6% AT ONE YEAR

OBESITY

NEW TREATMENTS

4. TOPIRAMATE AND PHENTERMINE (QSYMIA)

- **PHENTERMINE (A SYMPATHOMIMETIC AMINE)**

  - ANORECTIC (APPETITE SUPPRESSANT) AND TOPIRAMATE (AN ANTIEPILEPTIC DRUG)
- **INDUCED A PLACEBO ADJUSTED WEIGHT LOSS OF UP TO 10% OF BODY WEIGHT (8-9 kg at one year) ALONGSIDE RISK FACTORS IMPROVEMENT**
- **APPROVED BY US FDA**
- **ONCE DAILY ORAL EXTENDED RELEASE FORMULATION**

OBESITY

NEW TREATMENTS

- **MORE STUDIES ARE AWAITED ON THE SAFETY OF THESE PRODUCTS AND CLINICAL OUTCOMES BEFORE THEY ARE USED ROUTINELY IN CLINICAL PRACTICE**

- **WE HAVE TO BEAR IN MIND THAT THE HISTORY OF WEIGHT LOSS DRUGS IS A LITANY OF DISAPPOINTMENTS**

OBESITY

OTHER DRUGS THAT CAN AFFECT WEIGHT

GLUCOSE LOWERING DRUGS:

- SGLT2 INHIBITORS CAN CAUSE SIGNIFICANT WEIGHT REDUCTION
- ORAL DPP4 INHIBITORS AND METFORMIN ARE CONSIDERED TO BE WEIGHT NEUTRAL
- OTHER GLUCOSE LOWERING DRUGS INDUCE WEIGHT GAIN: INSULIN, SULPHONYLUREAS AND PIOGLITAZONE.

DRUGS CAUSING WEIGHT GAIN: CORTICOSTEROIDS, ATYPICAL ANTIPSYCHOTICS, COMBINE ORAL CONTRACEPTIVES AND BETA BLOCKERS

OTHER NEW DRUGS INTRODUCED IN 2014/2015 CONSIDERED AS MAJOR ADVANCES:

- **LUMACAFTOR/IVACAFTOR COMBINATION IN CYSTIC FIBROSIS (ORKAMBI)**
- **FLIBANSERIN TO TREAT HYPOACTIVE SEXUAL DESIRE DISORDER IN WOMEN (ADDYI) CALLED 'THE FEMALE VIAGRA'**
- **RIFAMIXIN (AN ANTIBIOTIC) AND ELUXADOLINE (ACTING ON OPIOD RECEPTORS) FOR IBS**
- **BEDAQUILINE IN MULTI DRUG RESISTANT TB (FIRST NEW MEDICINE IN 40 YEARS)**
- **ZYTIGA (ABIRATERONE) ORAL TREATMENT FOR METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (IN COMBINATION WITH PREDNISOLONE FOR PROSTATE CANCER RESISTANT TO MEDICAL (HORMONAL) TREATMENT OR SURGICAL TREATMENT THAT LOWER TESTOSTERONE)**
- **METHYLNATREXONE FOR OPIOD INDUCED CONSTIPATION**
- **APREMILAST-FIRST IN CLASS ORAL TREATMENT FOR CHRONIC PLAQUE PSORIASIS AND PSORIATIC ARTHRITIS IN PATIENTS WHO HAVE FAILED FIRST LINE SYSTEMIC THERAPIES.**

THANK YOU