SASLT
الجمعية السعودية لأمراض وزراعة الكبد
Saudi Society for the Study of Liver Disease and Transplantion

الجمعية تحت إشراف
الهيئة السعودية للتخصصات الصحية
Saudi Commission for Health Specialties

SASLT NEWSLETTER

9TH ISSUE JULY 2024

Tabel Of Content

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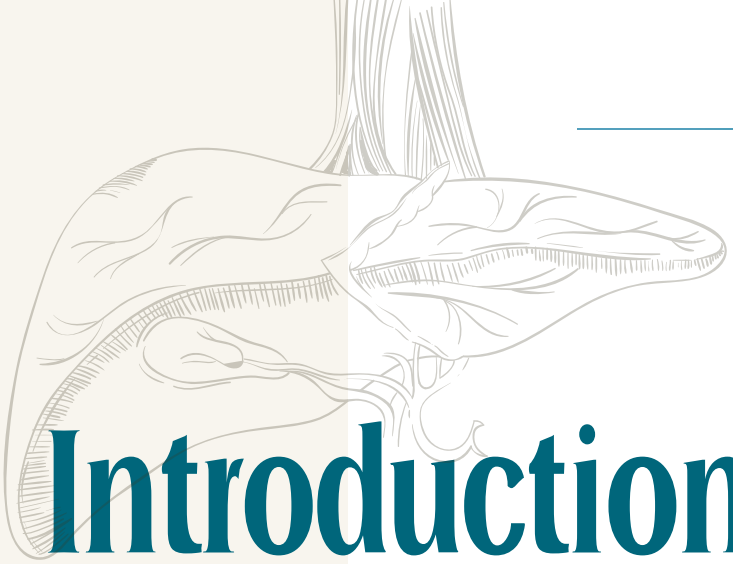
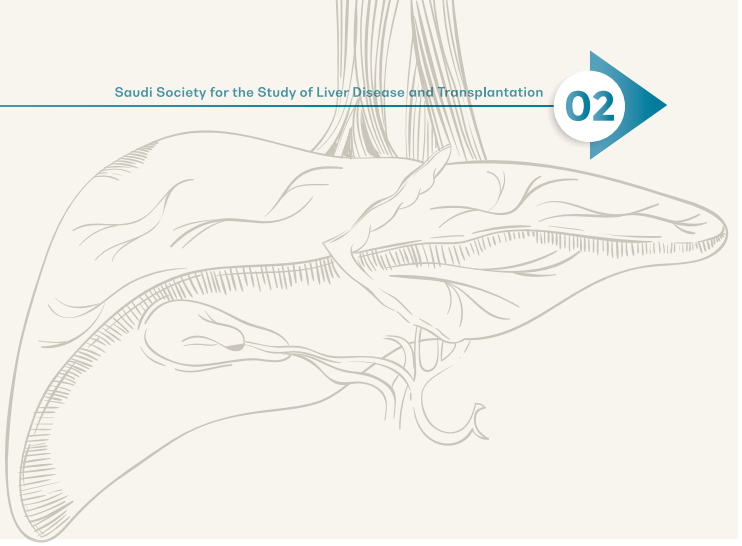


Introduction

AS WE COMMENCE WITH OUR 2024 ISSUE OF THE SASLT NEWSLETTER, WE ARE DELIGHTED TO SHARE OUR INTENTION OF INCREASING THE FREQUENCY OF PUBLICATION THIS YEAR. THIS IS MAINLY DUE TO THE OVERWHELMINGLY POSITIVE RESPONSE WE RECEIVED TO OUR 2023 ISSUE, AND WE WERE THRILLED TO HAVE AN INFLUX OF INTERNATIONAL CONTRIBUTORS FROM EUROPE AND NORTH AMERICA JOIN OUR EFFORTS. WE ARE DEEPLY GRATEFUL FOR THE CONTINUED SUPPORT FROM THE BOARD OF DIRECTORS AND PRESIDENT OF SASLT, DR. FAISAL ABULKHALIL, AS WELL AS THE INVALUABLE ASSISTANCE OF MY COLLEAGUE, DR. SAAD AL-GHAMDI.

FOR THIS YEAR'S THEMES, WE WILL BE SHIFTING OUR FOCUS TO THE BASIC SCIENCES AND GENETICS IN LIVER DISEASE, AS THIS CUTTING-EDGE FIELD IS RAPIDLY ADVANCING OUR UNDERSTANDING OF BOTH PEDIATRIC AND ADULT LIVER CONDITIONS, PARTICULARLY IN THE AREAS OF CHOLESTASIS AND GENETIC FACTORS.

WE ARE OPTIMISTIC THAT YOU WILL FIND GREAT VALUE IN THE CONTENT WE HAVE CURATED FOR THIS NEWSLETTER. PLEASE FEEL FREE TO CONTACT ME OR DR. SAAD WITH ANY SUGGESTIONS FOR ARTICLES OR AUTHORS YOU WOULD LIKE TO SEE FEATURED, AS WE ARE DEDICATED TO CONTINUOUSLY IMPROVING THIS PUBLICATION TO BEST SERVE OUR MEDICAL COMMUNITY.



Sateesh Maddirevula, PhD

Biography

SATEESH IS WORKING AS A SCIENTIST IN CENTER FOR GENOMIC MEDICINE (CGM), KING FAISAL HOSPITAL RESEARCH CENTER, RIYADH, SAUDI ARABIA. HE IS A TRAINED MOLECULAR GENETICIST (BY DR.FOWZAN ALKURYA) WITH EXTENSIVE EXPERIENCE IN DECODING MENDELIAN FORM FOR RARE DISEASES. HE POSSESSES NINE YEARS' EXPERIENCE IN NGS BASED DATA ANALYSIS (PANELS, EXOME, GENOME AND RNASEQ) AND OPTICAL GENOME MAPPING (OGM) (BIONANO'S SAPHYR® SYSTEM FOR STRUCTURAL VARIATION DETECTION). HE PUBLISHED MORE THAN 70 PEER REVIEWED ARTICLES AND DISCOVERED MORE THAN 100 CANDIDATE GENES FOR RARE DISEASE INCLUDING INTELLECTUAL DISABILITY, BRAIN MALFORMATIONS, CILIOPATHIES, INFERTILITY, LIVER DISEASE ETC. 80% OF THE PROPOSED CANDIDATE GENES GOT ADDITIONAL CONFORMATIONS AND ESTABLISHED ON OMIM. FEW OF THE GENES ARE CONSIDERED FOR SAUDI ARABIA PREMARITAL SCREENING PROGRAM. HE IDENTIFIED 100S OF FOUNDER VARIANTS IN THE LOCAL POPULATION. HE IS WORKING AS A HEAD OF THE GENOTYPING UNIT AND RUNNING ARRAY BASED CLINICAL TEST LIKE WHOLE GENOME SNP ARRAY AND PHARMACOGENOMICS (PGX).

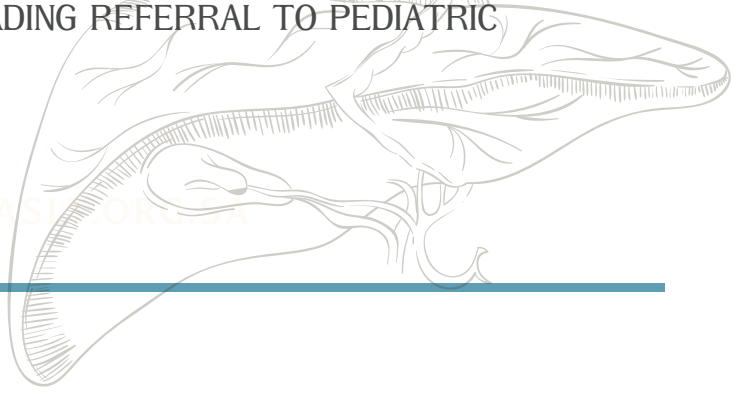
HE DISCOVERED VARIOUS NOVEL GENES (KIF12, PPM1F, USP53, LSR, WDR83OS, ZNF808) AND HUNDREDS OF NOVEL AND FOUNDER VARIANTS IN KNOWN GENES FOR LIVER DISEASE. A LARGE STUDY OF PEDIATIC CHOLESTASIS IS UNDER REVIEW WITH AROUND 60% DIAGNOSTIC YIELD FROM LOCAL POPULATION. ALL THESE CHICLVEMENTS MADE HIM AS A MEMBERS OF GENCC CONSORTIUM AND NATURAL COURSE AND PROGNOSIS OF PFIC AND EFFECT OF BILIARY DIVERSION (NAPPED) CONSORTIUM (NAPPED CREATED A GLOBAL NETWORK FOCUSED ON RARE GENETIC LIVER DISEASES IN THE PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS (PFIC) SPECTRUM). HE IS INTERESTED IN RARE DISEASE RESEARCH, POSITIONAL MAPPING, HAPLOTYPES, NGS BASED PIPELINES, LONG READ SEQUENCING, PHARMACOGENOMICS, DRUGGABLE GENOME AND MOLECULAR DIAGNOSTIC KITS

Genetics of Pediatrics liver disease in Saudi Arabia KFSHRC *experience*

MENDELIAN DISEASES SPAN ALL BODY SYSTEMS AND DEVELOPMENTAL STAGES. THOUSANDS OF GENES HAVE ALREADY BEEN LINKED TO THESE DISEASES AND THOUSANDS MORE WILL LIKELY BE LINKED IN THE FUTURE. UNTIL RECENTLY, MOLECULAR DIAGNOSIS OF MENDELIAN DISEASES RELIED ON THEIR SUCCESSFUL CLINICAL DELINEATION SUCH THAT ONE OR A FEW RELEVANT GENES ARE SEQUENCED CLINICALLY. HOWEVER, NEXT GENERATION SEQUENCING MADE IT POSSIBLE TO OVERCOME THIS LIMITATION BY ENABLING THE SEQUENCING OF THE ENTIRE GENOME OR RELEVANT PARTS THEREOF. THE CLINICAL UTILITY OF CAUSAL VARIANT IDENTIFICATION IN MENDELIAN DISEASES ENTAILS THE PROVISION OF A PRECISE DIAGNOSTIC LABEL, INFORMING MANAGEMENT DECISIONS, AND EMPOWERING INDIVIDUALS (PATIENTS AND UNAFFECTED CARRIERS) TO MAKE REPRODUCTIVE CHOICES AS WELL AS TO UNDERSTAND DISEASE RISK IN FAMILY MEMBERS AND FUTURE GENERATIONS.

BILE IS A CONCENTRATED MIXTURE OF CHOLESTEROL-DERIVED BILE ACIDS AND CONJUGATED BILIRUBIN THAT FACILITATES, AMONG OTHER PHYSIOLOGICAL ROLES, THE EMULSIFICATION AND ABSORPTION OF LIPIDS IN THE INTESTINE.1 HEPATOCYTES AND CHOLANGIOCYTES ARE THE EPITHELIAL CELLS IN THE LIVER, AND THEY BOTH PARTICIPATE IN THE PRODUCTION OF BILE. BILE SECRETION DEPENDS ON THE FUNCTION OF MEMBRANE TRANSPORT SYSTEMS IN HEPATOCYTES AND CHOLANGIOCYTES AND ON THE STRUCTURAL INTEGRITY OF THE BILIARY TREE. CANALICULAR BILE IS PRODUCED BY POLARIZED HEPATOCYTES THAT POSSESS DISTINCT TRANSPORTERS IN THEIR BASOLATERAL (SINUSOIDAL) AND APICAL (CANALICULAR) PLASMA MEMBRANE. THESE TRANSPORTERS ARE TRAFFICKED ACCORDINGLY FROM THEIR SITES OF SYNTHESIS AND STORAGE, AND UNDERGO DISTINCT POSTTRANSLATIONAL MODIFICATIONS.

DEFECTS IN ANY OF THE ABOVE DEVELOPMENTAL, STRUCTURAL, OR FUNCTIONAL CHARACTERISTICS MAY IMPAIR BILE HOMEOSTASIS AND RESULT IN CHOLESTATIC JAUNDICE, A DISEASE THAT AFFECTS APPROXIMATELY 1:2500 TERM INFANTS. APART FROM THE DETRIMENTAL EFFECTS IMPAIRED BILE CIRCULATION CAN HAVE ON NUTRITION, DETOXIFICATION, AND CHOLESTEROL HOMEOSTASIS, SERIOUS LIVER INJURY IS A COMMON COMPLICATION OF LONGSTANDING CHOLESTASIS OWING TO THE TOXIC (DETERGENT) NATURE OF BILE ACIDS. IN FACT, SEVERE CHOLESTATIC LIVER DISEASE IS A LEADING REFERRAL TO PEDIATRIC LIVER TRANSPLANT CENTERS.



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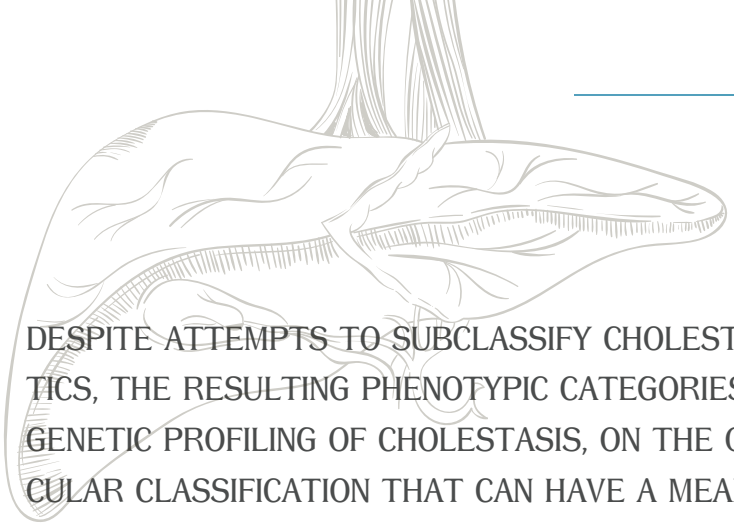

DESPITE ATTEMPTS TO SUBCLASSIFY CHOLESTASIS BASED ON CLINICAL CHARACTERISTICS, THE RESULTING PHENOTYPIC CATEGORIES REMAIN BROAD AND HETEROGENEOUS. GENETIC PROFILING OF CHOLESTASIS, ON THE OTHER HAND, OFFERS A PRECISE MOLECULAR CLASSIFICATION THAT CAN HAVE A MEANINGFUL IMPACT ON MANAGEMENT AND CERTAINLY ON PREVENTION. IT IS CURRENTLY UNKNOWN WHAT PERCENTAGE OF PEDIATRIC CHOLESTASIS IS GENETIC IN ETIOLOGY, WITH ESTIMATES RANGING FROM 25% TO 50% . IN A RECENT STUDY, WE DEMONSTRATED THE UTILITY OF A COMPREHENSIVE GENE PANEL THAT COVERS KNOWN CHOLESTASIS-RELATED GENES IN PATIENTS WITH ADVANCED CHOLESTATIC LIVER DISEASE. A LIKELY CAUSAL PATHOGENIC VARIANT WAS IDENTIFIED IN THE MAJORITY (N-=-60, 61%) WITH PATHOGENIC VARIANTS IN ABCB11, ABCB4, AND TJP2 BEING THE MOST COMMON. OTHER GENETIC DIAGNOSES MADE INCLUDE PFIC1 (PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS CAUSED BY ATP8B1 PATHOGENIC VARIANTS), ALAGILLE SYNDROME, BILE ACID SYNTHESIS DEFECT, TYROSINEMIA, WILSON DISEASE, G6PC-RELATED GLYCOGEN STORAGE DISEASE, SLC10A2-RELATED BILE ACID MALABSORPTION, MYO5B-RELATED MICROVILLUS INCLUSION DISEASE AND VIPAS39-RELATED CHOLESTASIS, RENAL IMPAIRMENT, AND ARTHROGRYPOSIS (ARC) SYNDROME.

IN ANOTHER RECENT STUDY IN WHICH WE AIMED TO CHARACTERIZE THE LANDSCAPE OF MENDELIAN PATHOGENIC VARIANTS IN 1000 SAUDI FAMILIES WITH VARIOUS PHENOTYPES, WE IDENTIFIED A POTENTIAL GENETIC CAUSE IN 53% (10/19) OF PATIENTS WITH SEVERE CHOLESTATIC LIVER DISEASE. THIS CONSISTENT DIAGNOSTIC YIELD OF SCREENING KNOWN DISEASE GENES IN CHILDREN WITH ADVANCED CHOLESTATIC LIVER DISEASE MAY BE INTERPRETED AS THE LIMIT OF MONOGENIC CONTRIBUTION TO THE ETIOLOGY. HOWEVER, SEVERAL OF THE NEGATIVE CASES HAVE A STRONG FAMILY HISTORY COMPATIBLE WITH AN AUTOSOMAL RECESSIVE ETIOLOGY, WHICH SUGGESTS THE POSSIBILITY OF NOVEL GENETIC CAUSES AS THE ALTERNATIVE EXPLANATION. INDEED, NEW GENETIC ETIOLOGIES CONTINUE TO BE DESCRIBED IN THE LITERATURE, E.G., A NOVEL UNC54A-RELATED SYNDROME OF CHOLESTASIS WITH DIARRHEA, DEAFNESS, AND IMPAIRED BONE STRENGTH WAS VERY RECENTLY PUBLISHED.

WE EXPLOITED THE SPECIAL CHARACTERISTICS OF OUR POPULATION (CONSANGUINITY AND LARGE FAMILY SIZE) TO SEARCH FOR SIMILARLY NOVEL DISEASE GENETIC FACTORS IN PEDIATRIC CHOLESTASIS BY EMPLOYING GENOME SEQUENCING AND POSITIONAL MAPPING. WITH THIS APPROACH ALLOWED TO UNLOCK NOVEL GENES (TABLE 1), NOVEL VARIANTS IN DISEASE CAUSING GENES , FOUNDER VARIANTS AND GENE WITH PHENOTYPIC EXPANSION,

Table 1 CANDIDATE GENES AND PHENOTYPIC EXPANSION IDENTIFIED IN LOCAL POPULATION FROM LARGE LIVER DISEASE COHORTS.

Gene	Phenotype	Reference
USP53	Cholestasis, progressive familial intrahepatic, 7, with or without hearing loss	PMID: 30250217, 3275999
KIF12	Cholestasis, progressive familial intrahepatic, 8	PMID:33456446, 30250217
TTC26	Biliary, renal, neurologic, and skeletal syndrome	PMID: 31595528
LSR	Intractable itching, normal GGT cholestasis, Growth failure/speech delay and short stature	PMID: 30250217 , 32303357
WDR83OS	Intractable itching, hypercholanemia, Intellectual disability	PMID: 30250217
PPM1F	High GGT cholestasis, Tongue pigmentation, short stature	PMID: 30250217
SCYL1	Acute liver failure and encephalopathy	PMID: 37344829
IGFBP7	Liver cirrhosis	PMID: 31130284

THE GENETIC ETIOLOGY OF PEDIATRIC CHOLESTASIS IS NOT FULLY UNDERSTOOD, WITH ESTIMATES RANGING FROM 25% TO 50%. RECENT STUDIES HAVE IDENTIFIED CAUSAL PATHOGENIC VARIANTS IN KNOWN CHOLESTASIS-RELATED GENES, WITH SOME CASES REVEALING NOVEL GENETIC CAUSES. OUR AIM IS TO UTILIZE THE UNIQUE POPULATION CHARACTERISTICS, SUCH AS CONSANGUINITY AND LARGE FAMILY SIZE, TO DISCOVER NOVEL GENETIC FACTORS CONTRIBUTING TO PEDIATRIC LIVER DISEASE THROUGH GENOME SEQUENCING AND POSITIONAL MAPPING. CURRENTLY, A WORLD'S LARGEST PEDIATRIC CHOLESTASIS IS UNDER REVIEW WITH AROUND 60% DIAGNOSTIC YIELD WITH A BRAND NEW GENE FOR CILIOPATHY, FEW ATYPICAL PHENOTYPES, NOVEL VARIANTS AND FOUNDER VARIANTS.

Reference:

ALABDI L, MADDIREVULA S, SHAMSELDIN HE, ET AL. DIAGNOSTIC IMPLICATIONS OF PITFALLS IN CAUSAL VARIANT IDENTIFICATION BASED ON 4577 MOLECULARLY CHARACTERIZED FAMILIES. NAT COMMUN. 2023;14(1):5269. PUBLISHED 2023 AUG 29. DOI:10.1038/S41467-023-40909-3

Team

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Biography

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Title: Unraveling the Complexities of Fibrocystic Liver Disease: A Comprehensive Overview

Introduction

FIBROCYSTIC LIVER DISEASE, A RARE YET SIGNIFICANT CONDITION, HAS GARNERED ATTENTION IN RECENT YEARS DUE TO ITS INTRICATE CLINICAL PHENOTYPE AND UNDERLYING MOLECULAR GENOTYPE. ORIGINALLY RECOGNIZED AS ADULT POLYCYSTIC LIVER DISEASE (PCLD) AND LATER ELABORATED AS CONGENITAL HEPATIC FIBROSIS (CHF), THIS CONDITION AFFECTS A NOTABLE FRACTION OF THE POPULATION, WITH AN INCIDENCE RATE RANGING FROM 1 IN 10,000 TO 20,000 INDIVIDUALS. THE CORE PATHOLOGY OF THIS DISEASE LIES IN DUCTAL PLATE MALFORMATIONS (DPMS) (PICTURE 1), ALSO KNOWN AS FIBROCYSTIC LIVER DISEASES, WHICH MANIFEST AS CONGENITAL CYSTIC LESIONS AFFECTING BOTH INTRAHEPATIC AND EXTRAHEPATIC BILE DUCTS (PICTURE 2).

Understanding Ciliopathies

CENTRAL TO THE PATHOLOGY OF FIBROCYSTIC LIVER DISEASE ARE CILIOPATHIES, A GROUP OF GENETIC DISORDERS CHARACTERIZED BY DYSFUNCTIONAL CILIA – ORGANELLES PRESENT ON THE SURFACE OF VARIOUS CELL TYPES (PICTURE 3 AND 4). IN THE CONTEXT OF FIBROCYSTIC LIVER DISEASE, CHOLANGIOCYTES, THE EPITHELIAL CELLS LINING INTRAHEPATIC BILE DUCTS, EXHIBIT PRIMARY CILIA ESSENTIAL FOR NORMAL CELLULAR FUNCTIONS. MUTATIONS IN GENES ENCODING CILIARY-ASSOCIATED PROTEINS LEAD TO A SPECTRUM OF DISORDERS COLLECTIVELY TERMED CHOLANGIOCILIOPATHIES, ENCOMPASSING CYSTIC AND/OR FIBROTIC LIVER DISEASES ALONG WITH SYNDROMES SUCH AS AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD), AUTOSOMAL RECESSIVE PKD (ARPKD), AND OTHERS.

Clinical Manifestations and Diagnosis

THE CLINICAL MANIFESTATIONS OF FIBROCYSTIC LIVER DISEASE VARY WIDELY, RANGING FROM ASYMPTOMATIC CASES TO SEVERE COMPLICATIONS SUCH AS PORTAL HYPERTENSION, RECURRENT CHOLANGITIS, AND HEPATOBILIARY MALIGNANCIES. DIAGNOSIS TYPICALLY INVOLVES A COMBINATION OF RADIOLOGICAL IMAGING MODALITIES INCLUDING ULTRASONOGRAPHY (US), COMPUTED TOMOGRAPHY (CT), AND MAGNETIC RESONANCE IMAGING (MRI), COMPLEMENTED BY HISTOPATHOLOGICAL EXAMINATION OF LIVER BIOPSY SAMPLES. THESE DIAGNOSTIC TOOLS ENABLE CLINICIANS TO IDENTIFY CHARACTERISTIC FEATURES SUCH AS DUCTAL PLATE MALFORMATIONS, FIBROUS BANDS IN PORTAL TRACTS, AND CYSTIC DILATATION OF BILE DUCTS, AIDING IN THE ACCURATE ASSESSMENT OF DISEASE SEVERITY AND PROGRESSION

Recent Developments about Ciliopathies

RECENT RESEARCH IN THE FIELD OF CILIOPATHIES HAS FOCUSED ON ELUCIDATING THE MOLECULAR MECHANISMS UNDERLYING CILIA ASSEMBLY, MAINTENANCE, AND FUNCTION, AS WELL AS IDENTIFYING NOVEL GENETIC CAUSES OF CILIOPATHIES. ADVANCES IN GENOMIC TECHNOLOGIES SUCH AS WHOLE-EXOME SEQUENCING (WES) AND GENOME-WIDE ASSOCIATION STUDIES (GWAS) HAVE FACILITATED THE DISCOVERY OF NEW GENES ASSOCIATED WITH CILIOPATHIES, PROVIDING INSIGHTS INTO THE DIVERSE CLINICAL MANIFESTATIONS AND UNDERLYING PATHOPHYSIOLOGY OF THESE DISEASES.

IN 2015, MARKUS SCHUELER AND COLLEAGUES PROVIDED THE FIRST DESCRIPTION OF NEPHRONOPHTHISIS-RELATED CILIOPATHIES (NPHP-RC) AS RECESSIVE DISEASES CHARACTERIZED BY RENAL DYSPLASIA OR DEGENERATION. THEIR STUDY IDENTIFIED MUTATIONS IN DCDC2 AS THE CAUSE OF A RENAL-HEPATIC CILIOPATHY. THEY OBSERVED THAT DCDC2 LOCALIZES TO BOTH THE CILIARY AXONEME AND MITOTIC SPINDLE FIBERS IN A CELL-CYCLE-DEPENDENT MANNER. KNOCKDOWN OF DCDC2 IN IMCD3 CELLS DISRUPTED CILIOGENESIS, A PHENOMENON RESCUED BY WILD-TYPE (WT) HUMAN DCDC2 BUT NOT BY CONSTRUCTS REFLECTING HUMAN MUTATIONS. FURTHERMORE, THE RESEARCHERS DEMONSTRATED THAT DCDC2 INTERACTS WITH DVL AND THAT DCDC2 OVEREXPRESSION INHIBITS B-CATENIN-DEPENDENT WNT SIGNALING, WITH AN EFFECT ADDITIVE TO WNT INHIBITORS.

IN 2021, MAJID ALFADHEL AND COLLEAGUES PUBLISHED ON TTC26, SHEDDING LIGHT ON ITS PIVOTAL ROLE IN SEVERE CILIOPATHIES. THIS STUDY EMPHASIZES THE SIGNIFICANCE OF HOMOZYGOUS VARIANTS WITHIN THE TTC26 GENE IN DRIVING THE PATHOGENESIS OF THESE DISORDERS. SUCH FINDINGS NOT ONLY CONTRIBUTE TO ADVANCING OUR COMPREHENSION OF THE GENETIC UNDERPINNINGS OF CILIOPATHIES BUT ALSO PROVIDE VALUABLE INSIGHTS THAT MAY INFORM THE DEVELOPMENT OF DIAGNOSTIC AND THERAPEUTIC APPROACHES FOR AFFECTED INDIVIDUALS.

IN 2019, WE PRESENTED THE INITIAL CASE OF HEPATOCELLULAR CARCINOMA (HCC) WITHIN THE CONTEXT OF FIBROCYSTIC LIVER DISEASE. OUR REPORT DOCUMENTS A RARE OCCURRENCE OF HCC LINKED TO FIBROCYSTIC LIVER DISEASE. IT HIGHLIGHTS THE IMPORTANCE OF CONSIDERING THE PRESENCE OF HCC WHEN DIAGNOSING FIBROCYSTIC LIVER DISEASE IN INDIVIDUALS WITHOUT KNOWN RISK FACTORS, AND VICE VERSA. NOTABLY, THIS CASE REPRESENTS THE FIRST DOCUMENTED INSTANCE OF HCC ASSOCIATED WITH FIBROCYSTIC LIVER DISEASE IN A 10-YEAR-OLD CHILD, AS FAR AS OUR KNOWLEDGE EXTENDS.

Management Strategies and Complications

CURRENTLY, THERE IS NO CURATIVE TREATMENT FOR FIBROCYSTIC LIVER DISEASE, AND MANAGEMENT PRIMARILY FOCUSES ON ALLEVIATING SYMPTOMS AND PREVENTING COMPLICATIONS. ANTI-FIBROTIC THERAPIES SUCH AS COLCHICINE AND ANGIOTENSIN II INHIBITORS HAVE SHOWN LIMITED EFFICACY IN EXPERIMENTAL MODELS BUT HAVE NOT DEMONSTRATED SIGNIFICANT BENEFITS IN CLINICAL TRIALS. RADIOLOGICAL INTERVENTIONS, INCLUDING TRANSJUGULAR I NTRAHEPATIC PORTOSYSTEMIC SHUNTS, MAY PROVIDE SYMPTOMATIC RELIEF IN SELECT CASES, WHILE LIVER TRANSPLANTATION REMAINS THE ONLY DEFINITIVE TREATMENT OPTION FOR END-STAGE DISEASE. COMPLICATIONS SUCH AS CHOLANGIOCELLULAR CARCINOMA UNDERSCORE THE IMPORTANCE OF TIMELY DIAGNOSIS AND INTERVENTION TO MITIGATE DISEASE PROGRESSION AND IMPROVE PATIENT OUTCOMES.

Conclusion

IN CONCLUSION, FIBROCYSTIC LIVER DISEASE REPRESENTS A COMPLEX AND CHALLENGING CONDITION CHARACTERIZED BY DUCTAL PLATE MALFORMATIONS AND CILIARY DYSFUNCTION. DESPITE ADVANCES IN DIAGNOSTIC IMAGING AND THERAPEUTIC MODALITIES, SIGNIFICANT GAPS REMAIN IN OUR UNDERSTANDING OF DISEASE PATHOGENESIS AND OPTIMAL MANAGEMENT STRATEGIES. FUTURE RESEARCH ENDEAVORS AIMED AT ELUCIDATING THE MOLECULAR MECHANISMS UNDERLYING FIBROCYSTIC LIVER DISEASE AND IDENTIFYING NOVEL THERAPEUTIC TARGETS ARE ESSENTIAL FOR IMPROVING PATIENT CARE AND OUTCOMES IN THIS RARE BUT CLINICALLY SIGNIFICANT DISORDER.

Data from King Faisal Specialist Hospital and Research Centre (KFSH&RC)

BETWEEN JANUARY 2011 AND MAY 31, 2023, REVEALED THAT A TOTAL OF 652 PEDIATRIC LIVER TRANSPLANTS WERE PERFORMED DURING THIS PERIOD. THE MAJORITY OF THESE TRANSPLANTS WERE SOURCED FROM LIVING DONORS, ACCOUNTING FOR 92.9% OF CASES, WHILE THE REMAINING 7.1% WERE FROM DECEASED DONORS.

THE PRIMARY INDICATIONS FOR LIVER TRANSPLANTATION DURING THIS TIMEFRAME INCLUDED BILIARY ATRESIA AND PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS, WITH CILIOPATHIES REPRESENTING 5% OF THE TOTAL CASES. AT THE TIME OF PRESENTATION, 45% OF PATIENTS EXHIBITED HIGH GGT CHOLESTASIS, WHILE 55% PRESENTED WITH PORTAL HYPERTENSION.

REFERRAL DIAGNOSES COMMONLY INCLUDED CONGENITAL HEPATIC FIBROSIS, SCLEROSING CHOLANGITIS, AND CHRONIC LIVER DISEASE. HOWEVER, SUBSEQUENT DIAGNOSIS REVISIONS OCCURRED FOLLOWING WHOLE EXOME SEQUENCING, REVEALING CONDITIONS SUCH AS DCDC2 AND TTC 26 MUTATIONS, AUTOSOMAL POLYCYSTIC KIDNEY DISEASE, AND CONGENITAL HEPATIC FIBROSIS WITH UNKNOWN ETIOLOGY.

THE MEDIAN AGE AT PRESENTATION WAS 4 YEARS OLD.

NOTABLY, TWO PATIENTS WERE DIAGNOSED WITH HEPATOCELLULAR CARCINOMA (HCC) UPON EXAMINATION OF EXPLANTED LIVERS.

Picture 1

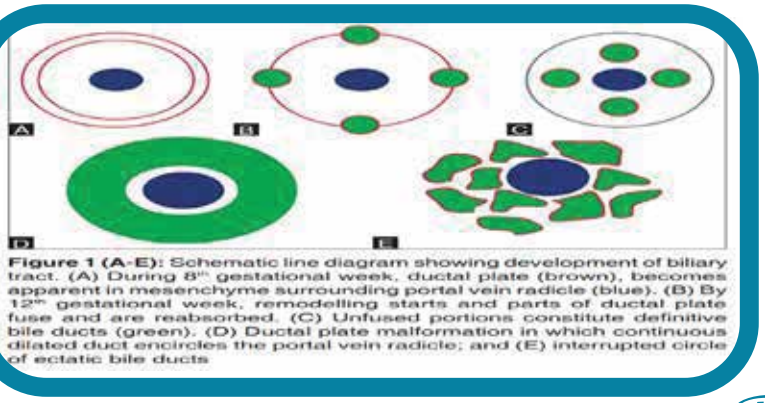
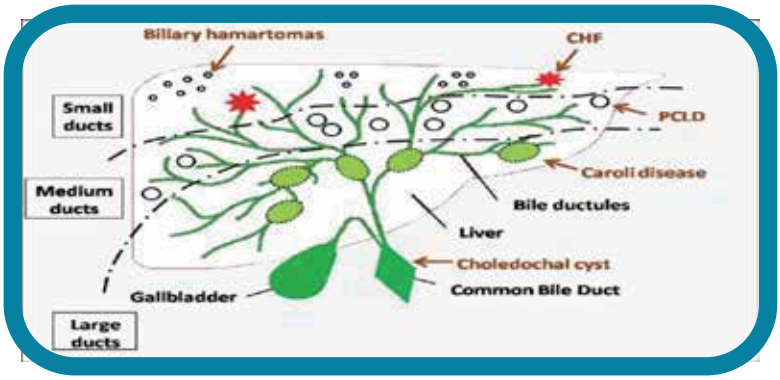
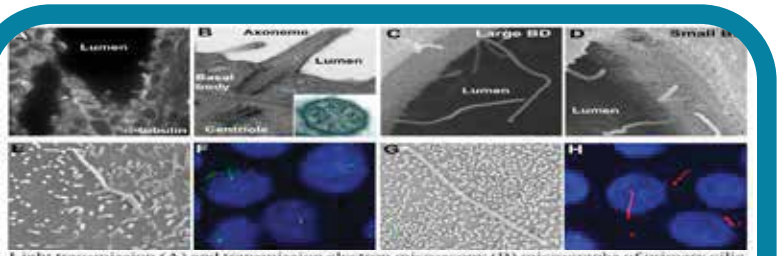


Figure 1 (A-E): Schematic line diagram showing development of biliary tract. (A) During 8th gestational week, ductal plate (brown), becomes apparent in mesenchyme surrounding portal vein radicle (blue). (B) By 12th gestational week, remodelling starts and parts of ductal plate fuse and are reabsorbed. (C) Unfused portions constitute definitive bile ducts (green). (D) Ductal plate malformation in which continuous dilated duct encircles the portal vein radicle; and (E) interrupted circle of ectatic bile ducts

Picture 2

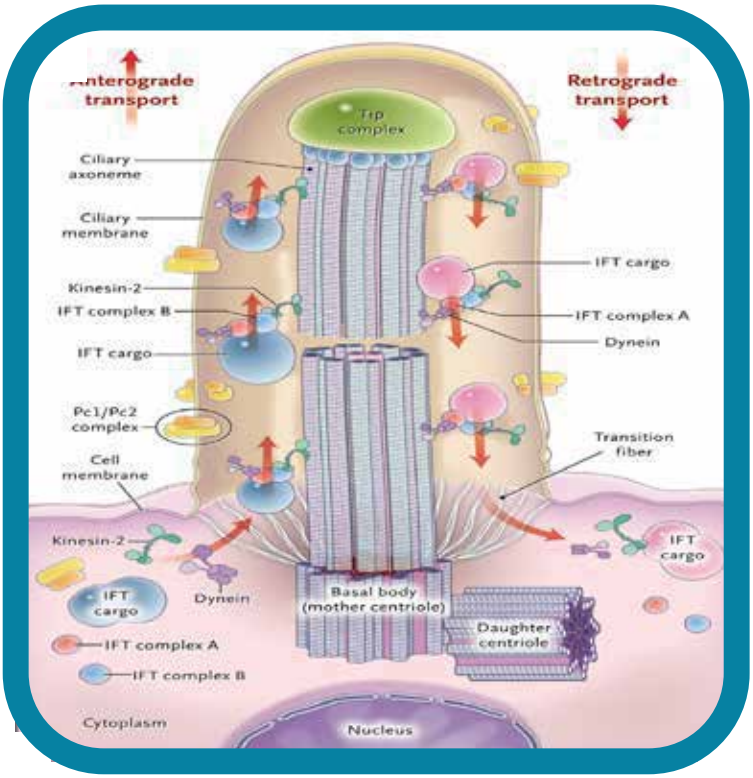


Picture 3



Light transmission (A) and transmission electron microscopy (B) micrographs of primary cilia extending from the cholangiocyte apical plasma membrane into the ductal lumen. The insert in B shows a 9+0 pattern of the ciliary axoneme. In A, cilia were stained with an antibody to the ciliary marker, acetylated α-tubulin. Scanning electron microscopy images of primary cilia in large (C) and small (D) bile ducts in the rat liver. In the large bile ducts (C), cilia are approximately 2 times longer than in the small bile ducts (D). Scanning electron microscopy (E and G) and immuno-fluorescence confocal microscopy (F and H) images of primary cilia in normal mouse (E and F) and rat cholangiocyte cell lines grown on a collagen gel for 10–14 days after confluence. In F and H, cilia were stained with acetylated α-tubulin (green and red, respectively), nuclei were stained with DAPI (blue). Images A–D are reproduced from (Hunag et al., 2006) with permission. Image G is reproduced from (Muff et al., 2006) with permission

Picture 4



Editorial Team

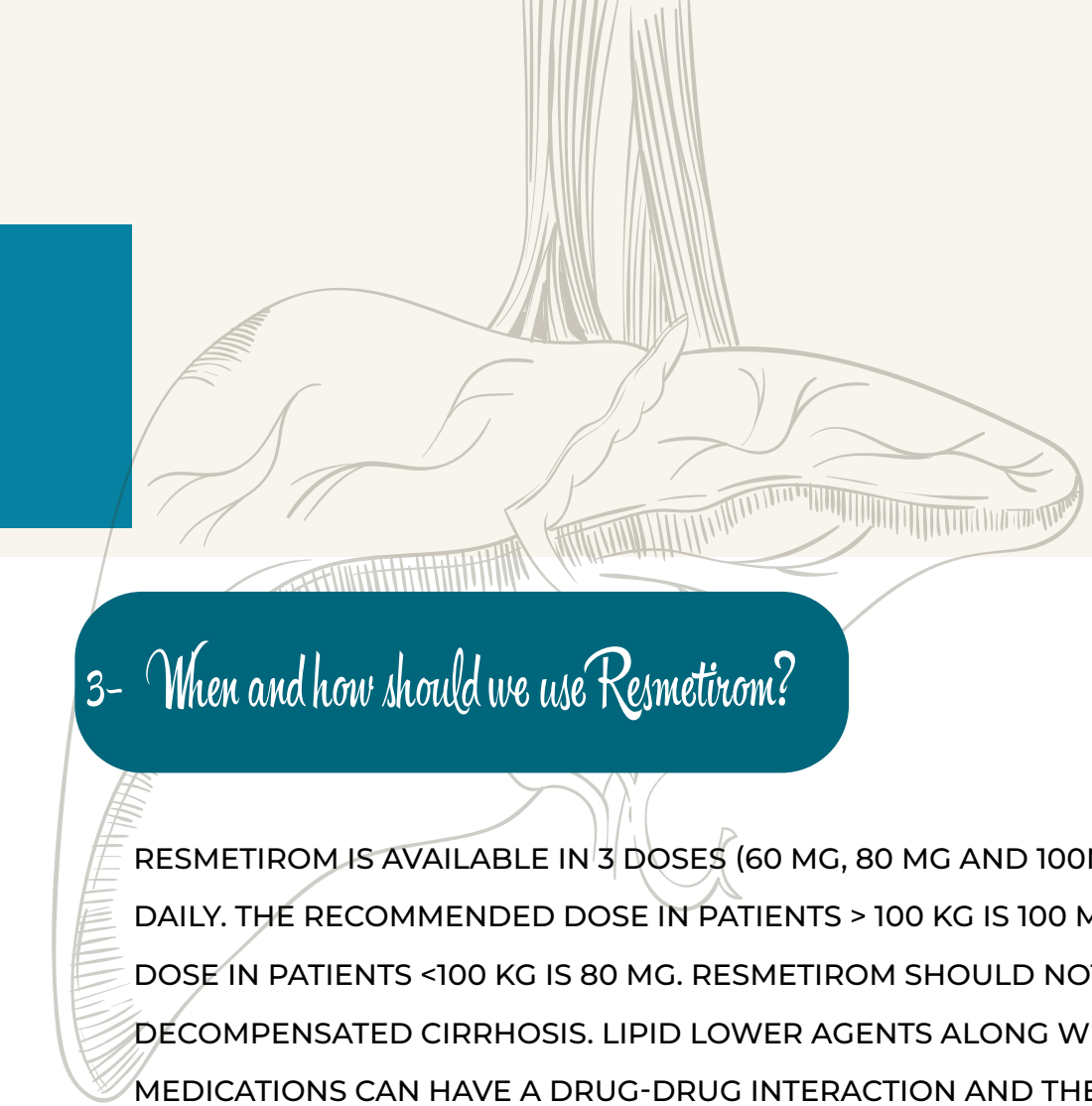
Dr. Bader Alhumayyd
Biography

DR. ALHUMAYYD IS A GASTROENTEROLOGIST/TRANSPLANT HEPATOLOGIST ASSISTANT PROFESSOR . HE RECEIVED HIS MEDICAL DEGREE FROM KING SAUD UNIVERSITY AND COMPLETED A MASTER OF ADVANCED STUDIES IN CLINICAL RESEARCH FROM THE UNIVERSITY OF CALIFORNIA , SAN DIEGO. HE COMPLETED HIS INTERNAL MEDICINE RESIDENCY IN DALHOUSIE UNIVERSITY IN CANADA. HE THEN WENT TO WAHSINGTON UNIVERSITY IN ST. LOUIS WHERE HE COMPLETED HIS GASTROENTEROLOGY AND TRANSPLANT HEPATOLOGY. HE IS CURRENTLY A GASTROENTEROLOGY/HEPATOLOGY ASSISSTANT PROFESSOR AND THE PROGRAM DIRECTOR GASTROENTEROLOGY/HEPA-TOLOGY IN KING KHALID UNIVERSITY HOSPITAL

All you need to know about the first FDA approved medication for Metabolic-dysfunction associated steatohepatitis, Resemitrom

1- What is Resmetirom and how does it work?

RESMETIROM (MARKETED AS “REZDIFFRA”) IS THE FIRST FDA APPROVED MEDICATION FOR METABOLIC-DYSFUNCTION ASSOCIATED STEATOHEPATITIS (MASH). IT WAS APPROVED THROUGH THE FDA ACCELERATED PATHWAY ON MARCH 14/2024. RESMETIROM IS A SELECTIVE THYROID HORMONE RECEPTOR (THR-B) AGONIST DEVELOPED BY MADRIGAL PHARMACEUTICALS FOR TREATING MASH WITH FIBROSIS. THERE HAS BEEN A GROWING INTEREST IN THYROID HORMONES GIVEN THE ASSOCIATION OF THYROID DYSREGULATION AND THE DEVELOPMENT OF METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) 1. THYROID HORMONES EXERT THEIR EFFECT THROUGH TWO RECEPTORS, THR-A AND THR-B. THR-B IS THE DOMINANT ISOFORM IN THE LIVER, WHICH INCREASES B-OXIDATION OF THE LIVER MITOCHONDRIA, DECREASES THE PRODUCTION AND SECRETION OF VERY LOW-DENSITY LIPOPROTEIN AND FREE FATTY ACID AS WELL AS INCREASING THE EXPRESSION OF LDL RECEPTORS, WHICH IN TURN DECREASE CHOLESTEROL AND TRIGLYCERIDES LEVELS2. IN ADDITION, THE SELECTIVE THR-B AGONIST REDUCES FREE T4 LEVELS WITHOUT AFFECTING THE ACTIVE FORM OF THYROID HORMONE, T3. THIS RESULTS IN IMPROVED LIPID METABOLISM3.



3- When and how should we use Resmetirom?

RESMETIROM IS AVAILABLE IN 3 DOSES (60 MG, 80 MG AND 100MG) TAKEN ORALLY ONCE DAILY. THE RECOMMENDED DOSE IN PATIENTS > 100 KG IS 100 MG. THE RECOMMENDED DOSE IN PATIENTS <100 KG IS 80 MG. RESMETIROM SHOULD NOT BE USED IN DECOMPENSATED CIRRHOSIS. LIPID LOWER AGENTS ALONG WITH SELECTIVE MEDICATIONS CAN HAVE A DRUG-DRUG INTERACTION AND THEREFORE, DOSE SHOULD BE REDUCED TO 60 MG 8. ALTHOUGH PATIENT SELECTION IN THE MAESTRO-NASH WAS BASED ON HISTOLOGICAL CRITERIA 6, THERE IS NO PRE-REQUISITE ON THE DRUG LABEL TO DO A LIVER BIOPSY PRIOR TO STARTING THE MEDICATION, THEREFORE, A SUGGESTED APPROACH WOULD BE TO USE THE CLINICAL DIAGNOSTIC CRITERIA FOR MASH ALONG WITH THE COMBINATION USE OF FIBROSCAN-LSM TO DETERMINE WHO WOULD BENEFIT FROM RESMETIROM9. IN REGARD TO RESPONSE TO THERAPY, IT IS STILL UNCLEAR HOW WE DEFINE A TREATMENT RESPONSE AND HOW LONG SHOULD WE CONTINUE RESMETIROM BEFORE YOU CONSIDER THE PATIENT AS A NON-RESPONDER. SOME DATA SUGGESTS AN IMPROVEMENT OF LIVER FAT CONTENT BY ≥30% ON MRI-PDFF IN A 3 MONTH PERIOD OR A REDUCTION IN ALT≥17 MIGHT CORRELATE WITH HISTOLOGICAL RESPONSE10. LONG TERM DATA FROM THE MAESTRO-NASH TRIAL IS NEEDED TO HAVE MORE CLARITY INTO ANSWERING THESE QUESTIONS.

2- What is the clinical efficacy of Resmetirom?

THE PHASE 2 RANDOMIZED DOUBLE-BLINDED CLINICAL TRIAL LASTING 36 WEEKS INCLUDED 125 ADULTS WITH BIOPSY PROVEN MASH WITH FIBROSIS (STAGE 1-3) AND MRI – PROTEIN DENSITY FAT FRACTION (MRI-PDFF) >10%. PATIENTS WERE RANDOMIZED TO EITHER ONCE-DAILY 80 MG RESMETIROM (OR 100 MG IN THE HIGHER EXPOSURE GROUP) OR PLACEBO. AT THE END OF 36 WEEKS, THE PRIMARY ENDPOINT WAS MET WITH REDUCTION IN HEPATIC FAT CONTENT SEEN BY MRI-PDFF BY 22.5% AT WEEK 12 AND 28.8% AT WEEK 36 IN THE RESMETIROM GROUP. THERE WAS ALSO A CHANGE IN THE HISTOLOGICAL DISEASE ACTIVITY DEFINED BY A REDUCTION IN THE NAFLD ACTIVITY SCORE (NAS) BY >2 IN THE HIGHER EXPOSURE GROUP. OTHER ENDPOINTS FOLLOWED THE SAME TREND WITH SIGNIFICANT REDUCTION IN LIVER ENZYMES AND BLOOD-BASED FIBROSIS BIOMARKERS 4. IN AN OPEN LABEL EXTENSION OF THE STUDY, IN 31 PATIENTS WHO HAD PERSISTENT ELEVATED LIVER ENZYMES (14 EXPOSED TO PLACEBO), RESMETIROM SIGNIFICANTLY REDUCED FAT CONTENT MEASURED BY MRI-PDFF AT WEEK 36 ALONG WITH REDUCED LIVER ENZYMES AND BLOOD-BASED FIBROSIS MARKERS 5. THESE RESULTS LED TO THE PHASE 3 TRIALS MAESTRO-NAFLD1 AND MAESTRO-NASH. IN THE MAESTRO-NASH TRIAL, 966 ADULTS WITH BIOPSY PROVEN MASH FIBROSIS (STAGE 1-3) WERE ENROLLED AND RECEIVED EITHER RESMETIROM 80 MG ,100MG OR PLACEBO. BOTH DOSES OF RESMETIROM 80 MG AND 100 MG WERE SUPERIOR TO PLACEBO IN HISTOLOGICAL MASH RESOLUTION (25.9%, 29.9% AND 9.7% RESPECTIVELY), AND IMPROVEMENT OF LIVER FIBROSIS BY AT LEAST 1 STAGE (24.2%, 25.9% AND 14.2 RESPECTIVELY) AT 52 WEEKS. RESMETIROM ALSO WAS SUPERIOR AT BOTH DOSES TO PLACEBO AMONG OTHER ENDPOINTS, INCLUDING REDUCTION OF FAT CONTENT ON MRI-PDFF, LIVER ENZYMES, FIBROSCAN – LIVER STIFFNESS MEASUREMENT (LSM), BLOOD-BASED FIBROSIS MARKERS AND REDUCTION IN TRIGLYCERIDE, LDL, LIPOPROTEIN (A) AT 52 WEEKS 6. IN THE MAESTRO-NAFLD 1 TRIAL, 1143 ADULTS WERE ENROLLED WITH MASLD AND PRESUMED MASH WHO DID NOT MEET THE HISTOLOGICAL CRITERIA TO BE ENROLLED IN THE MAESTRO-NASH TRIAL. THEY RECEIVED RESMETIROM 80MG AND 100 MG FOR 52 WEEKS. SIGNIFICANT IMPROVEMENT IN MRI-PDFF AND FIBROSCAN-LSM WERE FOUND AT 52 WEEKS 7.

4- What is the safety profile of Resmetirom?

THE MEDICATION IS GENERALLY WELL TOLERATED. DATA FORM THE MAESTRO-NASH TRIAL SHOWED THAT 91% OF THE RESMETIROM ARM AND 92.8% OF THE PLACEBO ARM EXPERIENCED AT LEAST 1 ADVERSE EVENT. MOST OF THE ADVERSE EVENT WERE MILD TO MODERATE. THE MOST COMMON ADVERSE EFFECTS WERE GASTROINTESTINAL RELATED (DIARRHEA IN ~30 % IN THE RESMETIROM GROUP COMPARED TO 15% IN THE PLACEBO GROUP AND NAUSEA OCCURRED ~20% IN THE RESMETIROM GROUP COMPARED TO12.5% IN THE PLACEBO ARM). OTHER ADVERSE EVENTS INCLUDED ARTHRALGIA, BACK PAIN, URINARY TRACT INFECTION, FATIGUE, PRURITIS AND VOMITING. NAUSEA AND DIARRHEA OCCURRED AT THE INITIATION OF RESEMTIROM. SERIOUS ADVERSE EVENTS WERE SIMILAR ACROSS ALL GROUPS (10.9% IN 80-MG RESMETIROM, 12.7% IN 100-MG RESMETIROM AND 11.5% IN THE PLACEBO GROUP). SERIOUS EVENT INCLUDED ACUTE GALLSTONE DISORDERS, COVID-19, MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER. CANCER WAS REPORTED IN 1.2 % IN THE 80 MG RESMITROM GROUP, 3.7% IN THE 100 MG RESMITROM GROUP AND 3.7% IN THE PLACEBO GROUP.

5- What are the clinical challenges facing Resmetirom?

THERE ARE SEVERAL CHALLENGES FACING RESMETIROM AS THE MEDICATION HAS BEEN APPROVED THROUGH THE FDA ACCELERATED PATHWAY, NECESSITATING FURTHER LONG-TERM STUDIES TO CONFIRM LONG TERM EFFICACY AND SAFETY. IDENTIFYING WHO WILL BENEFIT FROM EARLY TREATMENT AND PATIENT'S RESPONSE ASSESSMENT REMAINS CHALLENGING AS THE MAESTRO-NASH TRIAL ENROLLED PATIENTS BASED ON HISTOLOGICAL MARKERS. SURROGATE NON-INVASIVE MARKERS NEED TO BE IDENTIFIED TO OBVIATE THE NEED FOR INVASIVE TESTING WITH A LIVER BIOPSY OR THE USE OF IMAGING SUCH AS MRI-PDFF WHICH IS NOT WIDELY AVAILABLE. ANOTHER CHALLENGE IS THE SIDE EFFECT PROFILE. WHILE THE MEDICATION IS GENERALLY TOLERATED, RESMETIROM COMMON SIDE EFFECTS, SUCH AS DIARRHEA AND VOMITING MIGHT IMPACT PATIENT'S COMPLIANCE. VARIABILITY IN RESPONSE IS AN AREA THAT ALSO NEEDS TO BE ADDRESSED. NOT ALL PATIENTS RESPOND EQUALLY. THIS REQUIRES FURTHER RESEARCH LOOKING AT UNDERLYING FACTORS THAT INFLUENCE TREATMENT OUTCOMES. LASTLY, NAVIGATING THE REGULATORY LANDSCAPE AND ACHIEVING MARKET SUCCESS, PARTICULARLY IN REGIONS OUTSIDE THE UNITED STATES, CAN BE COMPLEX. CURRENTLY, RESMETIROM LISTING PRICE AT 47,400$ ANNUALLY. THIS PRICE WAS CHOSEN TO ALIGN WITH THE COST EFFECTIVENESS STUDY DONE BY INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW (ICER)11.

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