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WELCOME Happy New Year 2019

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Hepatology Today and the Future

Hepatology Today and the Future

We have to look at the Past to optimize Today the management of patients and to imagine the Future

The Model of Hepatitis C: The Past

We can celebrate today the 30th Anniversary of the discovery of HCV



From non-A, non-B hepatitis to HCV

The Model of Hepatitis C: The Past

Award PHC 2009 We celebrated the 20th Anniversary of the discovery of HCV







Michael Houghton

Leonard Seeff

Harvey Alter

The Model of Hepatitis C: The Past

Hepatitis C is a model. In twenty years, we moved from a misunderstood and untreatable disease to a well described disease with more than 50% cure. Soon, 70% with triple therapy with protease inhibitors. And why not, almost 100% within the next 10 years. Rendez-vous at the Paris Hepatitis Conference in 2019 !

Introduction of the PHC 2009

The Model of Hepatitis C: Today

- Almost 100% cure
- Cure means:
 - viral eradication
 - regression of fibrosis/cirrhosis
 - improved quality of life
 - improved outcome

Marcellin, Liver 1994 Marcellin, Annals 1999. Maylin, Gastroenterology 2013 Marcellin, Gastroenterology 2009 Kutala, AAC 2015

Cure with DAAs is associated with improved survival

DAAs improve survival (French Hepather cohort)



Backus et al. Hepatology 2018

Hepatitis C: The Future

- Cure does not mean elimination
- Barriers to elimination
 - Awareness
 - Information
 - Education
 - Screening
 - Access to therapy

The WHO Programme Elimination of HCV by 2030



WHO Global Health Sector strategy on viral hepatitis 2016–2021. www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/

Chronic Liver Diseases (CLDs) a major Public Health problem

CLDs compared with other major chronic diseases



Marcellin et Kutala. Liver Inter 2018. Sarwar, Lancet 2010 Ward, Prev Chronic Dis. 2014 GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Lancet 2017

Global epidemiology of CLDs

- Prevalence of CLDs: 18,5%
- Number with CLD: 0.84-1.13 billion
- Prevalence of cirrhosis: 4.5% to 9.5%
- Incidence of HCC: 5.6%/year

Estimated increase within the next decade

CLDs today



Marcellin and Kutala. Liver Int. 2018

CLDs in the Future (5 years) A Changing Pattern



Marcellin and Kutala. Liver Int. 2018

HBV The next Challenge

- Therapeutic vaccines
- cccDNA Inhibitors
- SiRNAs
- Entry inhibitors
- Capside inhibitors
- HBsAg inhibitors
- Immune system activators

Compounds in Development for Chronic Hepatitis B

	Silencing RNA's (siRNAs): Interferes and destroys viral RNA			
ARB-1467	RNAi gene silencer (1.0)	Arbutus Biopharma, USA	Phase II		
RG6004	RNAi gene silencer	Roche, Switzerland	Phase I/II		
ARO-HBV	RNAi gene silencer	Arrowhead Pharma, USA	Phase I/II		
AB-729	RNAi gene silencer	Arbutus Biopharma, USA	Phase I		
	Entry Inhibitors: Interfe	res with HBV getting into liver cells			
Myrcludex B	Entry inhibitor	Hepatera, Russia with MYR GmbH, Germany	Phase II		
Capsid Inhibitors: Interferes with the viral DNA protein shield					
Morphothiadin (GLS4)	Capsid inhibitor	HEC Pharma, PR China	Phase II		
JNJ 56136379	Capsid inhibitor	Janssen, Scotland	Phase II		
ABI-H0731	Capsid inhibitor	Assembly Biosciences, USA	Phase II		
AB-506	Capsid inhibitor	Arbutus Biopharma, USA	Phase I		
ABI-H2158	Capsid inhibitor	Assembly Biosciences, USA	Phase I		
	A g Inhibitang, Intanfanag mi	D-1- C-it-1-1	D_{1}		
HB	sAg Innibitors: Interferes wi	in production of HBV surface antigen ((SAG)		
REP 2139 / REP 2165	sAg inhibitor	Replicor, Canada	Phase II		
Antisense	Molecules: Binds to the viral	mRNA to prevent it from turning into	viral protein		
IONIS-HBVRx (GSK3228836)	Viral protein inhibitor	Ionis Pharma, USA with GSK	Phase II		
IONIS-HBVLRx (GSK33389404)	Viral protein inhibitor	Ionis Pharma with GSK	Phase II		

New Treatments on the Horizon for Hepatitis Delta

Hepatitis Delta Drug Watch

DRUG	MECHANISM	COMPANY	STATUS
Lambda (Pegylated Interferon)	Immune Response Stimulator	Eiger BioPharma, USA	FDA Orphan Drug Designation Phase III (Projected 2018)
Myrcludex B	Entry Inhibitor	MYR-GmbH, Germany	EMA PRIME Eligibility Phase II
Lonafarnib	Prenylation Inhibitor	Eiger BioPharma, USA	FDA Fast Track Designation Phase II
Ezetimibe	NTCP Inhibitor	Ziauddin University Hospital, Pakistan	Phase II
REP 2139 REP 2165	HBsAg Inhibitor	Replicor, Canada	Phase II
GI-18000	Immune Response Stimulator	GlobeImmune, USA	Pre-clinical
ALN-HDV	RNAi Gene Silencer	Alnylam, USA	Pre-clinical

NAFLD A silent epidemic



Browning, Hepatology 2004 Lazo, Semin Liver Dis 2008 Pharm Des 2013 Preiss, Clin Sci. 2008 Argo, Clin Liver Dis 2009 Bhala,

NASH A huge burden

Estimation in the US



NASH

An increasing indication for liver transplantation

UNOS Registry 2004-2013



Wong et al. Gastroenterology 2015

Drugs and Development Status in NASH

Class	Drug	Phase
FXR agonist	Obeticholic acid	Ш
Anti-LOXL2 monoclonal antibody	Simtuzumab	llb
Fatty acid/bile acid modifier	Aramchol	llb
Dual inhibitor of CCR2 and CCR5	Cenicriviroc	llb
Dual PPAR alpha/delta agonist	Elafibranor	
Galectin-3-inhibitor	GR-MD-02	lb
ASK1-Inhibitor	Selonsertib	

Abbreviations: FXR, Farnesoid X receptor; LOXL2, Lysyl oxidase-like 2: CCR2, C-C chemokine receptor types 2 ; CCR5, C-C chemokine receptor types 5 ; PPAR, peroxisome proliferator-activated receptor.

HCC The major Public Health issue

- Incidence: 800 000/year
- 750 000 deaths/year
- 20 Million disability-adjusted life-years
- 1.7 million new cases of HCC due to NAFLD over the next few decades
- Total cost \$850 billion

Bertuccio et al. J Hepatol 2017 Sherman M et al. Annals of Hepatology 2017Forner et al. Lancet 2012Ferlay et al. Int J Cancer 2015

Future promising therapies for HCC

Drug	Key action	Country			
Oncolytic virus therapy					
JX-594 (pexastimogene devacirepvec)	Vaccinia virus	USA and Europe			
Reolysin (pelareorep)	Reovirus	USA and Europe			
CC0070 (Adenovirus)	Adenovirus	USA			
T - Vec (talimogene laherparepvec)	HSV - 1	USA			
G47Δ	HSV - 1	Japan			
Immunotherapy					
Ipilimubmab	Targeting T cells	USA /Europe			
Durvalumab		USA			
Nivolumab		USA			
Tremelimumab		USA			
BMS-986016		USA/Europe			

Coffin et al Immunotheray 2016 Harrington et al Expert Rev Anticancer Ther 2015

New technologies for the Future Hepatology

- Genomic
- Proteomic
- Big data
- Artificial intelligence

New tools for more accurate markers, imaging and logarithms for an optimal personalized diagnosis, prognosis and therapy

Conclusion Today and the Future

- HCV: good job!
 Objective: elimination
- HBV: the next challenge!
 Combination available within 5 years?
 Antiviral + anti-protein + immune stimulator?
 - NASH: understand!

know the epidemiology, learn the natural history, understand the mechanisms, develop effective drugs > change of lifestyle

Alcohol: not forget!

The Future

The new technologies thanks to translational research will accelerate the progress to reach Personalized Hepatology

Wish you a good PHC

Characteristics patients with CLD in the future

Work-up in patients with CLD : a multiorgan approach



NAFLD – Center stage of the metabolic syndrome ?



The future seen from the inside



CLDs: The Future A Changing Pattern



The future oh hepatology starts somewhere

" If one wishes to contemplate the future of hepatology, one may want to climb several mountains to survey the entire panorama which may be distorted by the view from a particular peak."

From Popper Hans, Hepatology. 1984 Jan-Feb;4(1):152-5.



The new technology in the future hepatology



Article | OPEN | Published: 24 April 2018

Epigenetic landscape influences the liver cancer genome architecture



Research Paper

Genomic analysis of liver cancer unveils novel driver genes and distinct prognostic features

Xiangchun Li^{1,6#}, Weiqi Xu^{1#}, Wei Kang³, Sunny H. Wong¹, Mengyao Wang⁴, Yong Zhou⁴, X



Number of patients with CLD (million)



Alcoohol: the Neglected Problem

- 3.3 million deaths (6% of all global deaths). WHO source
- 88,000 deaths/year (US)
- 229 billion \$/year. Increasing
- Effective alcohol policy measures have been shown to reduce alcohol mortality, including ALD-related mortality
- Cost effective measures include increase in taxes on sales of alcohol drinks, minimum sale price for alcohol, raising the legal age for buying alcohol, low level interventions from clinicians

NASH

Primary care setting UK Asymptomatic, low risk CLD N=1118



Tertiary care setting France Increased ALT, histology N=274



Armstrong et al., J Hepatol 2013

De Ledinghen et al. J Hepatol 2006

Inflammation The key of CLD progression



Future Hepatology needs a solid foundation of progress in basic and translational research on inflammation ans fibrosis.

UNIVERSAL SCREENING FOR CLD

- The primary tests for diagnosing *liver disease* include *liver* function tests to test the enzymes
- Measures of inflammation: Liver cell enzymes (GGT, ALT, CDT)
- Liver ultrasound to see any damage....
- Many *liver screening* tests routinely check for *liver* function since many of the symptoms do not show until damage to the liver has already happened.

Criteria WHO for HCV screening test

- Focused testing in most-affected populations regardless of whether delivered through facility- or community-based testing
- General population testing in region with a ≥2% or ≥5% HCV antibody seroprevalence
- Birth cohort testing for older persons with higher risk of infection and morbidity within populations that have an overall lower general prevalence.
- Because of historical exposure to unscreened or inadequately screened blood products and/or poor injection safety.
- Routine testing of pregnant women for HCV infection is currently not recommended.

Transaminases meet all criteria (WHO) for validation of a universal screening test for all CLDs

- ✓ The test must be simple, reliable, fast and inexpensive
- The test must have good sensitivity, specificity, positive and negative predictive values
- ✓ The test must have a sensitivity of at least 75%, a falsepositive rate of < 10% and a rate of invalid results < 5%</p>

Different roles and level to acheive the awareness

- Information to the public
- The role of medical profession
- The health authorities with their policy
- Available and effective health care system

Thanks

"The future hepatology, the art of solving the same problems with a little more ability until the last hepatotoxic agent or the spirit of metabolic syndrom will be died" Said Patrick Marcellin



HCC

The landscape of treatment will change

Radiofrequency ablation (RFA) Trans-arterial chemoembolization (TACE) Highly-focused ultrasound (HIFU), Microwave ablation (MWA) Irreversible electroporation (IRE) Selective internal radiation therapy (SIRT) Oncolytic virus therapy Immunotherapy

> Fukuhara et al. Cancer Sci. 2016 Han et al. Cancer 2017