5th Challenges in Viral Hepatitis Lausanne, January 10, 2013

Management of HBV Infection: Current Status and Challenges

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Tracing Hepatitis B Virus to the 16th Century in a Korean Mummy

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> Full-length HBV genome cloned from laparoscopic liver biopsy specimen
> HBV genotype C2, originating most likely from China or Japan

> > Kahila Bar-Gal G et al. Hepatology 2012;56:1671-1680.

The Inconvenient Truth about Hepatitis B

- HBV is one of the most common chronic infections worldwide.
- The natural history is very complex.
- Treatment indications and endpoints are evolving.
- HBV is probably never completely eliminated.
- High replication rate and low fidelity of viral rt provide the basis for antiviral resistance.
- Pipeline of new antiviral drugs is limited.



Outline

- Diagnosis of HBV infection
- Natural history and classification of HBV infection
- Current and evolving treatment options
- Special situations
- Conclusions and perspectives

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Diagnosis of Hepatitis B <mark>Genotype</mark>

- Ten genotypes identified (A-J)
- HBeAg-negative CHB rarely develops in European strains of gt A (precore C1858)
- Natural history (HBe seroconversion, disease activity, fibrosis progression rate, HCC)?
- Response to PEG-IFN-α: A > B > C > D
- Does not influence response to NA
- Currently not recommended in clinical practice
 - Based on Lok ASF and McMahon BJ. Hepatology 2009;50:1-36 and EASL Clinical Practice Guideline. J Hepatol 2012;57:167-185.





Diagnosis of Hepatitis B The Evolving Use of qHBsAg

- Reflects the transcriptional activity of cccDNA
- Abbott Architect QT (0.05-250 IU/ml) and Roche Elecsys HBsAg II Quant (0.05-52,000 IU/ml)
- Identification of inactive HBsAg carriers
- Prediction of response to PEG-IFN-α
 (→ stopping rules)
- Prediction of durability of response to NA

Chan HL *et al.* J Hepatol 2011;55:1121-1131. Janssen HLA *et al.* Gut 2012;61:641-645. Locarnini S and Bowden S. Hepatology 2012;56:411-414.



Janssen HLA et al. Gut 2012;61:641-645. Locarnini S and Bowden S. Hepatology 2012;56:411-414. IEASL Clinical Practice Guideline. J Hepatol 2012;57:167-185.











Classifica	tion of	HBV	Infection	
	HBsAg	HBeAg	HBV DNA ¹⁾	ALT
HBeAg-pos. CHB	+	+	10⁵-10 ⁹	1
HBeAg-neg. CHB	+	-	10 ³ -10 ⁷	1
Inactive carrier	+	-	< 2 x 10 ³	=
"Immune tolerant"	+	+	10 ⁷ -10 ¹⁰	=
Resolved hepatitis	B- (anti-HBs)	-	-	=
Consider tx Fo	Ollow (Al loofnagle JH F and McMah cal Practice C	LT ± AFI et al. Hepate non BJ. Hep Guideline. J	P/US) At ology 2007;45:105 atology 2009;50:1- Hepatol 2012;57:10	tn IS 6-1075, 36 and 67-185.

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	Chroi Th	nic Hepatiti erapy 2013	s B
		5	Status CH 01/2013
PEG-IFN-α2a		Pegasys®	licensed 1st line
Lamivudine	LAM	Zeffix®	licensed 1 st line
Adefovir	ADV	Hepsera®	licensed 2 nd line
Telbivudine	LdT	Sebivo [®]	licensed 1 st line
Entecavir	ETV	Baraclude®	licensed 1st line
Tenofovir	TDF	Viread®	licensed 1 st line
Emtricitabine	FTC	+ TDF = Truvada®	licensed for HIV







- Detect resistance early (→ HBV DNA q 3-6 mo)
- Manage resistance adequately

Doerig C et al. Rev Med Suisse 2009;5:203-208





The HBV 'Anti-Virogram'

	LAM	LdT	ETV	ADV	TDF
Wild-type	s	s	s	s	S
M204!/V (± L180M)	R	R	I	s	S
A181T/V	I	I	s	R	S
N236T	s	s	s	R	I.
L180M+M204V/I ± I169 ± T184 ± S202 ± M250	R	R	R	s	S

Adapted from Zoulim F and Locarnini S. J Hepatol 2012;56 Suppl 1:S112-S122 and EASL Clinical Practice Guideline. J Hepatol 2012;57:167-185.

Management of Antiviral Resistance in Chronic Hepatitis B

- LAM or LdT resistance → switch to or add-on TDF
- ADV resistance
 - → switch to TDF and - add LAM, LdT, FTC¹ or ETV if rtN236T
 - add ETV if rtA181T/V
 - → switch to ETV if no prior LAM use
- Incomplete response to ADV (without genotypic resistance) → switch to TDF

¹TDF + FTC = Truvada[®]

Based on EASL Clinical Practice Guideline. J Hepatol 2009;50:227-242, EASL Clinical Practice Guideline. J Hepatol 2012;57:167-185 and Zoulim F and Locarnini S. J Hepatol 2012; 2012;56 Suppl 1:S112-S122.

Can Nucleos(t)ide Analog Therapy of CHB Ever be Stopped?

- Safe to stop: after HBsAg seroconversion
- Worth a try:
 - <u>HBeAg-positive</u> CHB 12 months after HBe seroconversion (if HBV DNA negative and no cirrhosis)
 - HBeAg-negative CHB 12 months after HBsAg clearance

Based on Lok ASF and McMahon BJ. Hepatology 2009;50:1-36, Cornberg M et al. Z Gastroenterol 2011;49:871-930, EASL Clinical Practice Guideline. J Hepatol 2012;57:167-185 and Marcellin P et al. Lancet 2013, in press (epub Dec 7, 2012).

Toward Finite NA Therapy of CHB

CLINICAL—LIVER

Restored Function of HBV-Specific T Cells After Long-term Effective Therapy With Nucleos(t)ide Analogues

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Boni C et al. Gastroenterology 2012;143:963-973.



Toward Finite NA Therapy of CHB

- The OSST Study
- n = 197 pts with HBeAg-positive CHB
- Maintained HBV DNA < 200 IU/ml after 9-36 months on ETV
 → PEG-IFN-α2a 180 µg per week for 48 wks vs. continued ETV
- HBe seroconversion 16 vs. 6% (p=0.03) HBsAg loss 9 vs. 0% (p=0.001) HBs seroconversion 4 vs. 0% (p=0.06)

Ning Q et al. AASLD Meeting 2012 - Hepatology 2012;56 Suppl:300A.

Therapy of Chronic Hepatitis B Current Developments

- Combination therapies (concomitant, sequential, nested)
- New nucleos(t)ide analogs
- New immunomodulators
- Novel therapeutic principles

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HBV and Immune Suppression Screen for HBsAg and anti-HBc before immunosuppressive therapy Vaccinate seronegative patients HBsAg or HBV DNA positive

- → start NA before immune suppression
 → consider NA d/c 12 mo after cessation of IS
- Anti-HBc (± anti-HBs) → HBV DNA
 if HBV DNA pos → see above
 if HBV DNA neg → monitor or start NA

Based on Lalazar G et al. Br J Haematol 2007;136:699-712, AASLD - Lok ASF and McMahon BJ. Hepatology 2009;50:136, EASL Clinical Practice Guideline. J Hepatol 2012;57:167-185 and Lok ASF et al. Ann Int Med 2012;156:743-745.

HBV Infection and Pregnancy

- HBsAg screening during pregnancy
- Active and passive immunoprophylaxis of the newborn: HBV vaccine + HBIG within 12 h
- Breastfeeding allowed
- Consider NA during 3rd trimester in highly viremic (HBV DNA > 2 x 10⁷ IU/ml?) mothers
- Class B: LdT, TDF; class C: LAM, ADV, ETV
- IFN-α contraindicated in pregnancy
- Monitor for exacerbation of CHB after delivery

Based on Dusheiko G. Lancet 2012;379:2019-2021, Brown RS Jr et al. J Hepatol 2012;57:953-959 and EASL Clinical Practice Guideline. J Hepatol 2012;57:167-185.

