New Interferons and Immunomodulators

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Interferons

What are they?

Who cares?
The Interferon family

• Type 1: 3 subtypes, all cell types, IFNAR1 and 2
  • IFN-α, 14 species
  • IFN-β, 1 species
  • IFN-ω, 1 species
• Type II: IFN-γ, one species, activated T and NK cells, IFNGR1 and 2
• Type III: IFN-λ, 3 species (λ1, 2 and 3; IL29, IL28A, IL28B), possibly one more (λ4), all cell types; IFNLR1 and IL10RB (limited tissue distribution)
Interferon-λ: Antiviral Response & Hepatitis C
IFN-α vs IFN-λ

- Different receptors
- IFN-λ receptor with limited tissue distribution (not in hematopoietic cells)
- Same signaling pathway
- Different kinetics and profiles of gene inductions

O’Brien TR, Nat Genet 2009
IFN-λ3/IL28B Polymorphisms and HBV Infection

- IL28B SNPs (favorable in HCV) are associated with serologic response (HBeAg loss) to PEG-IFN in HBeAg-positive chronic hepatitis B
- IL28B SNPs are associated with post-IFN HBsAg loss in HBeAg-negative patients (genotype D)
- IL28B SNPs are associated with HBV chronicity?

Sonneveld et al, Gastroenterol 2012; Lampertico et al, Hepatol 2013
Tseng et al, Antivir Ther; de Niet et al, Scan J Gastroenterol 2012; Zhang et al, J Viral Hepatitis 2013
Interferons in Hepatitis B and C Therapy

• IFN-α: mainstay of therapy for HBV and HCV
• IFN-β: similar effect as IFN-α for HBV; used as induction therapy in HCV
• IFN-γ: never tested in HBV, though potent antiviral role in animal models; not effective in HCV
• IFN-λ (Peg-IFN-λ1)
  - HCV: similar efficacy as Peg-IFN-α but better side effect profile
  - HBV?

Ishikawa et al, Hepatol Res 2012; Morikawa et al, Hepatol Res 2013
Guidotti et al, Annu Rev Pathol 2006; Soza et al, Hepatol 2005
Muir et al, Hepatol 2010; Muir et al, AASLD 2012
Peg-Interferon-λ in Hepatitis B Therapy

- Randomized-controlled study in HBeAg+ patients
- Comparing Peg-IFN-α with Peg-IFN-λ
- 48-wk treatment and 24 wk follow-up
- Endpoint: HBeAg loss and anti-HBe seroconversion
- Peg-IFN-λ less effective than Peg-IFN-α

Chan et al, AASLD 2012; BMS website
New Interferons for Hepatitis Therapy

- Albuferon: albumin-conjugated IFN-α2b; halted development
- Locterone: controlled release interferon-α2b, microsphere-based, every 2 weeks, comparable effect as Peg-IFN in hepatitis C
- Omega Duros Interferon: extended release depot for 3-12 months
- Interferon-α XL: controlled release, Medusa hydrogel, weekly dosing
- Oral interferon (Beloferon): single amino acid substitution of IFN-α, oral administration

Dzyublyk et al, J Viral Hepat 2011; Jansen et al EASL 2011
Trepo et al, AASLD 2011; www.Flamel.com
www.Armarbio.com
New Interferons for Viral Hepatitis Therapy

- Improved pharmacokinetics
- Stronger antiviral activities
- Fewer side effects
- Better compliance
- Reduced cost?
- Interferon-intolerant patients and limited access to DAAs in HCV patients
Immunomodulators

Interferon-inducers

Toll-like Receptor Agonists
Toll-like Receptors

- Play a key role in innate and adaptive immunity
- Recognize structurally conserved molecules from microbes as pattern recognition receptors (PRR)
- Induction of type I interferons and other cytokines
- More than 13 different TLRs
- TLR3: viral dsRNA; TLR7/8: viral ssRNA; TLR9: CpG DNA sequences
TLR Agonists in Clinical Development for Viral Hepatitis

• TLR3 agonist
  - Poly ICLC (Hiltonol), anti-cancer drug, preclinical development as antiviral, good safety profile (Oncovir)

• TLR7 agonist: preferred for antiviral therapy
  - Imidazoquinoline: Imiquimo (Aldara), Resiquimod, PF-4878691 (3M/Coley/Pfizer)
  - Nucleoside analog: ANA245 (Isatoribine), 975, 773 (Anadys/Roche); SM-276001 (Sumitomo), GS-9620 (Gilead)
  - Weak antiviral effects (HCV) in clinical trials and substantial side effects

• TLR8 agonist: proinflammatory, cancer therapy
  - VTX-2337 and 1463 (VentiRx)

• TLR9 agonist: weaker interferon inducer
  - CPG10101 (Coley/Pfizer), IMO-2125 (Idera)
  - Weak antiviral (HCV) effects in clinical trials; vaccine adjuvant
Effect of GS-9620 in HBV-Infected Chimpanzees

- Potent interferon-inducer and high selectivity, high hepatic extraction and less systemic exposure
- Three HBV-infected chimpanzees
- GS-9620 at 1-2 mg/kg, oral administration, 3 times weekly for 4 weeks
- Follow viral titers, and levels of IFN-α and interferon-stimulated genes in both serum and liver

\[\text{IFN-α (pg/mL)}\]

\[\begin{align*}
0.3 \text{ mg/kg} & : \quad \text{0} \\
1 \text{ mg/kg (A)} & : \quad \text{1} \\
1 \text{ mg/kg (B)} & : \quad \text{2}
\end{align*}\]

\[\text{Time (hr)}\]

\[\begin{align*}
0 & : \quad \text{0} \\
4 & : \quad \text{1} \\
8 & : \quad \text{2} \\
12 & : \quad \text{3} \\
16 & : \quad \text{4} \\
20 & : \quad \text{5} \\
24 & : \quad \text{6}
\end{align*}\]

\[\text{Serum HBV DNA}\]

\[\begin{align*}
1 \text{ mg/kg} & : \quad 10^6 \\
2 \text{ mg/kg} & : \quad 10^7 \\
38 & : \quad 10^8 \\
58 & : \quad 10^9 \\
78 & : \quad 10^{10}
\end{align*}\]

\[\text{Day}\]

\[\begin{align*}
-28 & : \quad 10^1 \\
18 & : \quad 10^2 \\
38 & : \quad 10^3 \\
58 & : \quad 10^4 \\
78 & : \quad 10^5 \\
98 & : \quad 10^6 \\
118 & : \quad 10^7 \\
138 & : \quad 10^8
\end{align*}\]

Lanford et al, Gastroenterol 2013
TLR Agonists for Viral Hepatitis Therapy

- Oral formulation
- Less systemic exposure
- Side effects the major concern
- Better compliance
- Combination therapy with NA in HBV patients
- Interferon-intolerant patients and limited access to DAAs in HCV patients
New Interferons and Immunomodulators:
Take Home Messages

• Probably no advantage in HCV therapy
• Potentially of value in HBV therapy
• Newer forms of IFNs need to be tested against standard Peg-IFN for various parameters
• TLR agonists in development and have promise
• Need to be used in combination with other anti-HBV drugs
• Potentially curative in HBV