

Interferons and Their Use in Persistent Viral Infections

Stéphane Chevaliez and Jean-Michel Pawlotsky

Contents

1	Interferons	205
1.1	Type I IFNs	205
1.2	Type II IFNs	205
1.3	Type III IFNs	207
2	IFN Production during Viral Infections	207
2.1	Viral Triggering of IFN Production	207
2.2	IFN Gene Induction	209
3	Responses to IFN	210
3.1	IFN-Induced Signaling Pathways	210
3.2	IFN Antiviral Effectors	211
3.3	Immunomodulatory Properties of IFNs	211
4	Therapeutic Forms of IFN	212
4.1	Standard IFN- α	212
4.2	Pegylated IFN- α	212
4.3	Other IFNs	213
5	IFN-Based Treatment of Hepatitis C Virus Infection	214
5.1	Treatment of Chronic HCV Infection with IFN- α	214
5.2	Treatment of Acute HCV Infection with IFN- α	217
5.3	Future Perspectives of IFN-Based HCV Therapy	217
6	IFN-Based Treatment of Hepatitis B Virus Infection	220
6.1	Treatment of Chronic HBV Infection with IFN- α	221
6.2	Treatment of Chronic HBV Infection with Other Type I IFNs	225
6.3	Treatment of Chronic HBV Infection with Type II IFN	226
7	IFN-Based Treatment of Hepatitis D/Delta Virus Infection	226
7.1	Standard IFN- α Monotherapy	226
7.2	Pegylated IFN- α Monotherapy	227
7.3	IFN- α Combination with Nucleoside/Nucleotide Analogues	227
8	Treatment of HIV Infection with IFN- α	228
8.1	Standard IFN- α	228
8.2	Pegylated IFN- α	229

J.-M. Pawlotsky (✉)

Department of Virology, Hôpital Henri Mondor, 51 avenue du Maréchal de Lattre de Tassigny,
94010 Créteil, France
jean-michel.pawlotsky@hmn.aphp.fr

H.-G. Kräusslich, R. Bartenschlager (eds.), *Antiviral Strategies*, Handbook of Experimental
Pharmacology 189,
© Springer-Verlag Berlin Heidelberg 2009

9	Treatment of Other Viral Infections with Type I IFN in Humans	229
10	Conclusion	230
	References	230

Abstract In 2007, the world celebrated the 50th anniversary of the discovery of interferon (IFN) by Isaacs and Lindenmann. Subsequently, the IFN- α gene was cloned, fully sequenced and IFN- α was produced in recombinant form. Recombinant IFN- α is now used as the basis for treatment of chronic hepatitis C virus infection and can also be used to treat certain forms of chronic hepatitis B virus infections. IFNs have also been used in other viral infections, although with less success. The antiviral mechanisms of IFNs are reviewed in this chapter as well as the utility of IFNs in the treatment of persistent viral infections.

Abbreviations

<i>CARD</i>	Caspase recruitment domains
<i>ds</i>	Double-stranded
<i>ERK 1/2</i>	Extracellular signal-regulated kinase 1/2
<i>GAF</i>	γ -IFN activation factor
<i>GAS</i>	γ -IFN activation site
<i>HAART</i>	Highly active antiretroviral therapy
<i>HBV</i>	Hepatitis B virus
<i>HCV</i>	Hepatitis C virus
<i>HDV</i>	Hepatitis D/delta virus
<i>IFN</i>	Interferon
<i>ISRE</i>	IFN-stimulated response element
<i>LRR</i>	Leucine-rich repeats
<i>MDA-5</i>	Melanoma differentiation-associated gene 5
<i>MEK 1/2</i>	Mitogen-activated/extracellular signal-regulated kinase 1/2
<i>NK</i>	Natural killer cells
<i>PKR</i>	RNA activated protein kinase
<i>PRR</i>	Pattern-recognition receptors
<i>RIG-1</i>	Retinoic acid-inducible gene 1
<i>RLR</i>	Retinoic acid-inducible gene 1 (RIG-1)-like helicase receptors
<i>TIR</i>	Toll/IL-1R/resistance
<i>TLR</i>	Toll-like receptors
<i>TNF</i>	Tumor necrosis factor
<i>TRAM</i>	TRIF-related adaptor molecule
<i>TRIF</i>	TIR domain-containing adaptor inducing IFN- β
<i>TRIM</i>	Tripartite motif protein

In 2007, the world celebrated the 50th anniversary of the discovery of interferon (IFN) by Isaacs and Lindenmann (Isaacs and Lindenmann 1957). Human IFN- α was the first cytokine to be purified to homogeneity. Subsequently, the IFN- α gene

was cloned, fully sequenced and IFN- α was produced in recombinant form in *E. coli* (Nagata et al. 1980). Recombinant IFN- α is now used as the basis for treatment of chronic hepatitis C virus (HCV) infection and can also be used to treat certain forms of chronic hepatitis B virus (HBV) infections. IFNs have also been used in other viral infections, although with less success.

1 Interferons

IFNs are natural glycoproteins produced by the cells of most vertebrates in response to the challenge by foreign agents, such as infectious organisms (viruses, bacteria, fungi, and parasites), and by tumor cells. IFNs can be produced by cells of the innate and adaptive immune systems and by non-immune cells such as fibroblasts and epithelial cells.

1.1 Type I IFNs

Type I IFNs form a superfamily of innate cytokines that comprise IFN- α (alpha), with 13 human subtypes, IFN- β (beta), IFN- ω (omega), IFN- τ (tau), IFN- κ (kappa), IFN- ϵ (epsilon), IFN- λ (lambda), and IFN- ζ (zeta) (Pestka et al. 2004). Only IFN- α , IFN- β , IFN- ω , IFN- κ , and IFN- ϵ are expressed in humans. All IFN- α subtypes are secreted by leukocytes, whereas IFN- β is also produced by fibroblasts. IFN- τ is exclusively expressed in ruminants at a specific stage of pregnancy (Martal et al. 1998), whereas IFN- κ is expressed by human keratinocytes (LaFleur et al. 2001).

There are 17 human type I IFN genes, all clustering on chromosome 9. They are intronless and encode secretory signal peptide sequences that are proteolytically cleaved prior to secretion from the cell. Type I IFNs are genetically and structurally closely related. They range in length from 161 to 208 amino acids and have apparent molecular weights of 15–24 kDa (Table 1) (Chen et al. 2004). The different subtypes of human IFN- α have approximately 50% amino acid sequence identity, whereas IFN- α shares approximately 22% amino acid identity with human IFN- β and 37% with human IFN- ω (Chen et al. 2004).

1.2 Type II IFNs

There is only one known type II IFN, IFN- γ , discovered in 1965 (Wheelock and Sibley 1965). IFN- γ is exclusively produced by immune cells, such as activated thymus-derived T cells and natural killer (NK) cells, after stimulation by foreign antigens or mitogens in the early stages of the innate immune response (Boehm et al. 1997). The human IFN- γ gene maps to chromosome 12. IFN- γ is a noncovalent

Table 1 Characteristics of the principal human IFN genes

	Type I IFNs			Type II IFN	Type III IFNs	
	IFN- α	IFN- β	IFN- ω	IFN- γ	IFN- λ 1 (IL-29)	IFN- λ 2/3 (IL-28A/B)
Gene	<i>IFNA</i>	<i>IFNB</i>	<i>IFNW</i>	<i>IFNG</i>	<i>IFNL</i>	<i>IFNL</i>
Chromosomal localization	Chromosome 9	Chromosome 9	Chromosome 9	Chromosome 12	Chromosome 19	Chromosome 19
Number of amino acids	165 or 166	166	172	143	181	175
Number of structural genes	13	1	1	1	5	6
Number of introns	None	None	None	3	5	6
Receptor	IFNAR-1/2	IFNAR-1/2	IFNAR-1/2	IFNGR-1/2	IFNLR-1/IL10R2	IFNLR-1/IL10R2
Producing cells	Hematopoietic cells, mainly leukocytes	Fibroblasts and some epithelial cell types	Hematopoietic cells, mainly leukocytes	Immune cells, mainly T cells and NK cells	Hematopoietic cells, mainly monocytes	Hematopoietic cells, mainly monocytes

homodimer composed of two identical 17-kDa polypeptide chains 166 residues long (Ealick et al. 1991). The 23-residue hydrophobic signal sequence is removed by proteolytic cleavage prior to secretion from the cell (Table 1) (Boehm et al. 1997).

1.3 Type III IFNs

Recently, a novel class of type I-like human IFNs, named IFN- λ 1 or IL-29, IFN- λ 2 (IL-28A) and IFN- λ 3 (IL-28B), was identified (Dumoutier et al. 2003; Sheppard et al. 2003). The three IFN- λ genes cluster on human chromosome 19 and comprise 5 exons for IFN- λ 1 and 6 for IFN- λ 2 and IFN- λ 3, and several introns (Table 1). They encode 20- to 22-kDa secreted monomeric proteins of 196 to 200 amino acids. Type III IFNs have also been identified in other species such as mice, birds, and fish.

2 IFN Production during Viral Infections

Production of types I and III IFNs is an essential component of the innate immune response, the first line of defense against an invading pathogen (Gale and Foy 2005). IFNs exert auto- and paracrine actions within a few hours in response to a viral infection. Their protective function is dual: they induce an antiviral cellular state and facilitate the clearance of infected cells by activating apoptosis, in synergy with other proapoptotic agents such as tumor necrosis factor (TNF) family members, depending on the intracellular level of double-stranded (ds) RNAs (Clemens 2003).

2.1 Viral Triggering of IFN Production

Most cell types recognize incoming RNA or DNA viruses, owing to the presence of intracellular RNAs with a 5' triphosphate end (i.e. lacking a 5' cap structure) or dsRNA structures generated during viral RNA replication. Indeed, dsRNA replication intermediates are essential for the synthesis of new RNA genomes, whereas DNA viruses often have overlapping open reading frames lying in opposite orientations, and these generate mRNA transcripts that can base-pair to form dsRNA stretches. The conserved molecular patterns of dsRNAs are recognized by pattern-recognition receptors (PRR), of which the best known are Toll-like receptors (TLR) and retinoic acid-inducible gene 1 (RIG-1)-like helicase receptors (RLR) (Yoneyama et al. 2004). TLRs are present at the cell surface and in endosomes and recognize various microbial structures, whereas RLRs are expressed ubiquitously in the cytoplasm and recognize only viral structures. Their activation leads to the production of both type I and III IFNs, and this production appears to be regulated by

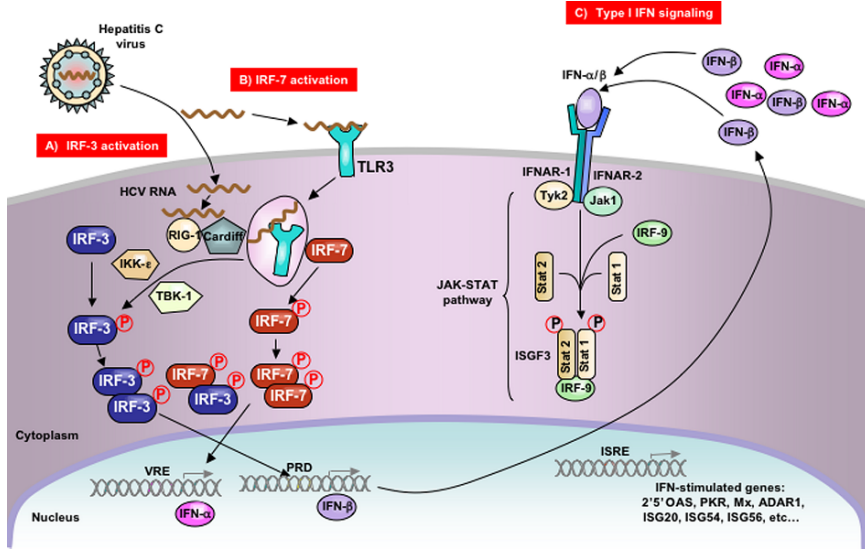


Fig. 1 Type I IFN production and signaling pathways. (a) Interferon regulatory factor 3 (IRF-3) activation. HCV RNA binding to retinoic acid-inducible gene 1 (RIG-1) or Toll-like receptor 3 (TLR-3) results in the phosphorylation and activation of IRF-3 by the tumor necrosis factor receptor-associated factor-associated nuclear factor κ B (NF- κ B) activator binding kinase 1 (TBK-1) or inhibitory κ B kinase ϵ (IKK- ϵ) protein kinases. The dimer of phosphorylated IRF-3 translocates to the cell nucleus, interacts with its transcription partners, and binds to the cognate-DNA positive regulatory domain (PRD) in the promoter region of IRF-3 target genes, including IFN- β , resulting in IFN- β production and secretion. (b) IRF-7 activation. IRF-7 is a transcription factor and an IFN-stimulated gene (ISG). It is activated after expression by viral components through signaling pathways that overlap with the pathways of IRF-3 activation. IRF-7 phosphorylation, dimerization, and heterodimerization with IRF-3 allow it to bind its cognate virus-responsive element (VRE) in the promoter region of IFN- α genes, resulting in the production of various IFN- α subtypes that further signal ISG expression. (c) Type I IFN signaling. Type I IFN binding to the receptor signals the activation of the associated Tyk2 and Jak1 protein kinases to direct the phosphorylation and assembly of a Stat1–Stat2 heterodimer and trimeric IFN-stimulated gene factor 3 (ISGF3) complex containing IRF-9. The ISGF3 complex locates to the cell nucleus, where it binds to the IFN-stimulated response element (ISRE) on target genes to direct ISG expression. Adapted from Gale and Foy (Gale and Foy 2005) and Stephen J. Polyak, presentation at the Post-Graduate Course of the 41st Annual Meeting of the European Association for the Study of the Liver, Vienna (Austria), April 26–27, 2006, with permission

a common mechanism (Ank et al. 2006; Onoguchi et al. 2007; Uze and Monneron 2007). Type I IFN production is described in Fig. 1.

2.1.1 TLR Pathways

At least 12 different TLRs have so far been identified in mammals (Uematsu and Akira 2007). TLRs are type I transmembrane PRRs that possess an extracellular domain containing leucine-rich repeats (LRR), a transmembrane domain, and an

intracellular signaling domain known as the Toll/IL-1R/resistance (TIR) domain. The difference in the amino acid number and the molecular weight of different TLRs is principally related to differences in the number of LRRs in their extracellular domain, which allow them to recognize different ligands. The TIR domain can interact with various adaptor molecules, such as myeloid differentiation primary response protein 88 (MyD88), TIR domain-containing adaptor inducing IFN- β (TRIF), and TRIF-related adaptor molecule (TRAM), thereby activating intracellular signaling pathways.

2.1.2 RLR Pathways

In cell types other than dendritic cells, RLRs such as RIG-1 and melanoma differentiation-associated gene 5 (MDA-5) appear to play a key role in the response to viral infections (Kato et al. 2005). RIG-1 contains two tandem caspase recruitment domains (CARD), which are needed to activate NF- κ B and IRF-3. Double-stranded RNA binding to the RNA helicase domain of RIG-1 induces a conformational change that exposes the CARD domains to downstream signaling proteins. MDA-5 also contains two CARD domains that can activate the IFN- β promoter (Creagh and O'Neill 2006; Seth et al. 2006). A recent study has shown that the tripartite motif protein 25 (TRIM25), a ubiquitin ligase, catalyzes RIG-1 ubiquitination, a crucial step in the cytosolic pathway by which RIG-1 elicits host antiviral responses (Gack et al. 2007).

2.2 IFN Gene Induction

The induction of type I and III IFN gene transcription is principally controlled by transcription factors NF- κ B, IRF-3, and IRF-7 (Fig. 1). In its inactive state, NF- κ B is held in the cytosol by members of the inhibitory κ B (I κ B) family. In the presence of incoming viruses, the I κ B kinase (IKK) is activated and phosphorylates I κ B, which is subsequently ubiquitinated and degraded by the proteasome. Free NF- κ B translocates into the nucleus, where it increases the transcription of target genes. Like NF- κ B, the inactive form of IRF-3 is cytosolic. In response to a viral infection, IRF-3 is phosphorylated by two IKK-like kinases: TNF receptor-associated factor (TRAF)-associated NF- κ B activator (TANK) binding kinase 1 (TBK-1) and IKK ϵ . IRF-3 phosphorylation leads to its dimerization and translocation into the nucleus (Hayden et al. 2006; Seth et al. 2006). IRF-7 is expressed at low levels in most cells. It is also activated through phosphorylation by TBK-1 and IKK ϵ (Honda et al. 2005). NF- κ B, IRF-3, IRF-7, and nuclear architecture proteins assemble into a complex in the nucleus that remodels the chromatin in IFN gene promoters, resulting in an increase in transcriptional initiation.

3 Responses to IFN

3.1 *IFN-Induced Signaling Pathways*

On binding to its receptor, the IFN molecule is sandwiched between the two chains of the receptor, thus forming a ternary complex that activates the canonical Jak/Stat pathway through activation of the transduction elements located in the intracytoplasmic tail of each receptor subunit (Fig. 1).

3.1.1 Type I and III IFNs

The similarity of the transcriptional responses induced by type I and type III IFNs has been confirmed by microarray analysis of Jak/Stat pathway gene expression in various cell lines (Doyle et al. 2006; Dumoutier et al. 2004). Figure 1 shows type I IFN signaling through the Jak-Stat pathway. Type I and III IFN binding to their specific receptor triggers the activation of Jak1 and Tyk2 through tyrosine transphosphorylation. The activated kinases induce the formation of the IFN-stimulated gene factor-3 (ISGF3), itself composed of two elements, ISGF3 α and ISGF3 γ . ISGF3 α is formed of two cytoplasmic peptides, Stat1 (p91) and Stat2 (p113), which share 42% nucleotide identity. ISGF3 γ is a member of the IRF family, which has been renamed IRF-9. The IRF-9 protein is a single polypeptide with an apparent molecular weight of 48 kDa. It comprises two domains: a conserved amino-terminal DNA-binding domain and a carboxy-terminal Stat-binding domain. IRF-9 is mostly cytoplasmic and inactive in untreated cells. It migrates to the nucleus after IFN treatment.

The phosphotyrosyl residues of activated Jak proteins serve as docking sites for Stat1 and Stat2, both of which are phosphorylated on a single tyrosine residue by activated Jak proteins. Stat1 and Stat2 phosphorylation induces their release from the IFNARs and their dimerization through their SH2 domain. Stat1–Stat2 heterodimers then move to the nucleus to form the ISGF3 complex, together with IRF-9 (Fig. 1). ISGF3 then interacts directly with the IFN-stimulated response element (ISRE), a DNA sequence that characterizes ISGs. These may contain one or several ISRE sequences in their promoter sequence. Other Stat proteins have been shown to be activated by type I and III IFNs, but their involvement in IFN responses may be restricted to certain cell types (Takaoka and Yanai 2006).

3.1.2 Type II IFN

IFN- γ receptor subunits IFNGR1 and IFNGR2 trigger the activation of Jak1 and Jak2 through tyrosine phosphorylation. Jak1 and Jak2 activation leads to the formation of a multimeric complex, γ -IFN activation factor (GAF), that transduces the signal to the target DNA sequence in ISGs, known as the γ -IFN activation site (GAS). GAF is a homodimer of tyrosine-phosphorylated Stat1 proteins. GAF exists in latent form in the cell cytoplasm. It can be rapidly activated following IFN- γ

binding to its receptor by phosphorylation at Stat1 tyrosine residue 701. Once activated, GAF translocates into the nucleus and binds GAS sequences to induce ISG transcription. It was recently shown that Stat1–Stat2 heterodimers can also activate GAS elements (Takaoka and Yanai 2006). In addition, a novel *c-Jun*-dependent signal transduction pathway induced by type II IFN has been identified. This pathway involves protein kinases other than Jaks, including extracellular signal-regulated kinase 1/2 (ERK1/2) and mitogen-activated/extracellular signal-regulated kinase 1/2 (MEK1/2). This pathway appears to operate in parallel with the canonical Jak/Stat signaling pathway (Gough et al. 2007).

3.2 IFN Antiviral Effectors

The antiviral state induced by different types of IFNs is mediated by various IFN-induced proteins. The best-known antiviral effectors produced as a result of IFN cascade induction are shown in Table 2. They include 2′–5′ oligoadenylate synthetase (2′–5′OAS), double-stranded RNA activated protein kinase (PKR), and myxovirus (Mx) proteins. Additional effectors include RNA-specific adenosine deaminase 1 (ADAR1), the 20-kDa ISG product (ISG20), ISG54 and ISG56, and IFN-stimulated micro RNAs (Pedersen et al. 2007).

3.3 Immunomodulatory Properties of IFNs

In addition to their direct antiviral properties described earlier, IFNs exhibit potent immunomodulatory properties that contribute to their antiviral effects by activating

Table 2 Interferon-induced antiviral effectors

Short name	Name	Function(s)
2′-5′ OAS	2′-5′ oligoadenylate synthetase	Activate a latent endoribonuclease, RNase L, which degrades viral and cellular mRNAs and rRNAs
PKR	Double-stranded RNA-activated protein kinase	A serine threonine kinase that phosphorylates eIF2 α on serine residue 51 when activated
MxA and MxB	Mixovirus proteins A and B	IFN-induced GTPases that block intracellular transport of viral components
ADAR1	Adenosine deaminase acting on RNA 1	Involved in RNA editing
ISG20	IFN-stimulated gene product of 20 kDa	A member of the DEDD exonuclease superfamily with RNase and DNase activity
ISG54 and ISG56	IFN-stimulated gene products of 54 and 56 kDa	Inhibit translation
miRNA	IFN-induced micro RNAs	Specifically target viral transcripts

cells other than those that are infected (Pestka et al. 1987). IFNs can stimulate the effector function of NK cells, cytotoxic T lymphocytes, and macrophages, upregulate the expression of major histocompatibility complex (MHC) class I and class II molecules, induce immunoglobulin synthesis by B cells, and stimulate the proliferation of memory T cells. This offers various modes to control viral replication, by modulating the innate and adaptive immune responses (Guidotti and Chisari 2001). Type I IFNs act through activation and maturation of dendritic cells, leading to MHC upregulation. They can also upregulate various chemokines, chemokine receptors, and costimulatory molecules, which, in turn, stimulate CD4-positive and CD8-positive T cell responses and modulate T lymphocyte responses through the promotion of Th1 differentiation (Solis et al. 2006).

IFN- γ is a major immunoregulatory cytokine involved in the regulation of nearly all phases of immune and inflammatory responses, including activation and differentiation of T cells, B cells, NK cells, and macrophages. The expression of class II MHC molecules on immune cells is principally regulated by IFN- γ , especially on monocytes and macrophages. IFN- γ also increases the transcription of the β_2 -microglobulin light chain of MHC class I molecules. In addition, IFN- γ regulates T cell functions and modulates neutrophil functions by modulating the surface expression of various molecules, including integrins and chemokine receptors (Gattoni et al. 2006a, b).

4 Therapeutic Forms of IFN

4.1 Standard IFN- α

Different forms of IFN- α have been available for the treatment of chronic hepatitis B and C, including IFN- α 2a and IFN- α 2b. The administered dose was 3–5 mega-units three times a week subcutaneously.

4.2 Pegylated IFN- α

Polyethylene glycol (PEG) consists of repeating units of ethylene glycol forming linear or branched polymers with different molecular masses. Pegylation is the process by which PEG chains are covalently attached to IFN molecules. Pegylation confers a number of properties on IFN- α molecules, such as sustained blood levels that enhance antiviral effectiveness and reduce adverse reactions, as well as a longer half-life and improved patient compliance (Kozlowski et al. 2001).

Two forms of pegylated IFN- α have been approved by the Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) for the

Table 3 Pharmacological parameters of pegylated IFN- α molecules approved for the treatment of chronic hepatitis C

	Pegylated IFN- α 2a	Pegylated IFN- α 2b
Chemical parameters		
Molecular weight (kDa)	60	31
PEG structure	Branched	Linear
Production	Recombinant (<i>E. coli</i>)	
Pharmacokinetic parameters		
C_{\max}	Dose-related	Dose-related
T_{\max} (h)	72–96	15–44
Half-life (h)	80 ^a	40 ^a
Apparent volume of distribution (l)	6–14	69
Clearance	Principally renal	Not fully elucidated ^c
Posology and administration		
Approved dose	180 μ g qw	1.5 μ g/kg qw
Route of administration	Subcutaneous	Subcutaneous

^aAfter subcutaneous injection

treatment of chronic hepatitis C in adults, namely pegylated IFN- α 2a and pegylated IFN- α 2b, in which the IFN- α molecules are linked to PEG molecules of different sizes (Table 3).

4.3 Other IFNs

Other IFNs that can be used in the treatment of viral infections include IFN- β , IFN- ω , a molecule that is more potent than its nonglycosylated form, which itself has activity comparable to that of IFN- α (Buckwold et al. 2007), and that will be delivered continuously by an implantable device, IFN- γ and IFN- λ 1, a pegylated form of which will soon be available.

New IFN- α molecules are also being developed. They include albumin-IFN- α 2b (Alb-IFN- α 2b, Human Genome Sciences, Rockville, Maryland, and Novartis, Basel, Switzerland), a novel 87.5-kDa recombinant protein consisting of an IFN- α 2b molecule attached to a human albumin moiety. Alb-IFN- α 2b has a half-life of up to 159 h, allowing dosing at intervals of 2–4 weeks (Balan et al. 2006). Pharmacokinetic studies in monkeys showed approximately 140-fold slower clearance and an 18-fold longer half-life than IFN- α after a single subcutaneous injection (Osborn et al. 2002).

Novel IFN- α variants have been created experimentally by means of DNA shuffling (“gene-shuffled” IFN- α). In this technique, natural IFN- α genes are fragmented and then reassembled through recombination, a process that mimics evolution. Gene-shuffled IFN variants may have increased antiviral and antiproliferative activity (Chang et al. 1999). A library of clones has been generated (Maxygen,

Redwood City, California, and Roche) and two clones have been selected for their improved *in vitro* activity relative to human IFN- α . One of them has been pegylated but its development has been halted because of strong immune reaction.

IFN alphacon-1 (Infergen, Amgen, Thousand Oaks, California) is a synthetic recombinant “consensus” IFN- α molecule created by scanning the sequences of several natural IFNs and assigning to the recombinant molecule the most frequently observed amino acid at each position (Keeffe and Hollinger 1997). The intrinsic antiviral activity of this IFN appears to be 10- to 100-fold higher than that of standard IFNs (Blatt et al. 1996; Ozes et al. 1992). The future of consensus IFN- α will depend on the development of a pegylated or otherwise pharmacologically modified form. Multiferon (Viragen, Plantation, Florida) is a highly purified, multi-subtype natural human IFN- α derived from human leukocytes. Medusa[®] (Flamel Technologies, Lyon, France) is a self-assembled poly-aminoacid nanoparticle system that can be used as a protein carrier for novel long-acting native protein drugs. Medusa IFN- α 2a and Medusa IFN- β are currently in early clinical development. Various types of orally administered IFN- α are also being developed.

5 IFN-Based Treatment of Hepatitis C Virus Infection

5.1 Treatment of Chronic HCV Infection with IFN- α

Chronic HCV infection is curable, and cure is the goal of antiviral therapy. Successful treatment is characterized by a sustained virological response (SVR), defined by undetectable HCV RNA in a sensitive assay (detection limit ≤ 50 international units (IU)/ml) 6 months after the end of therapy. Recent large-scale follow-up studies have shown no relapse or recurrence after 4–6 years in more than 99% of patients who have an SVR (McHutchison et al. 2006; Swain et al. 2007).

The choice of IFN- α as a potential treatment for chronic hepatitis C in 1986 was empirical (Hoofnagle et al. 1986). At this time, the causative agent of chronic “non-A, non-B” hepatitis had not yet been identified, and there was no way of evaluating HCV replication or, thus, the antiviral activity of a drug. In the first cohort of 10 patients with chronic non-A, non-B hepatitis treated with IFN- α , a significant decline in alanine aminotransferase (ALT) levels was observed in 8 patients, and liver histology had improved at the end of therapy in the three patients who were biopsied (Hoofnagle et al. 1986). Ten years later, 5 of the 10 patients were free of infection (Lau et al. 1998).

5.1.1 Standard IFN- α and Pegylated IFN- α Monotherapy

The first National Institutes of Health (NIH) Consensus Development Conference on Management of Hepatitis C, held in 1997 (1997), recommended that standard

IFN- α be used at the same dose for 48 weeks for the treatment of chronic hepatitis C. However, the SVR rates were still only 12–20% with this treatment schedule (Di Bisceglie and Hoofnagle 2002; Lindsay et al. 2001). The development of pegylated IFN- α was found to ensure sustained drug exposure. Pegylated IFN- α 2a is administered at a fixed dose of 180 μ g/week, whereas pegylated IFN- α 2b is administered at a weight-adjusted dose of 1.5 μ g/kg/week. Both pegylated IFNs have been reported to yield a twofold higher SVR rate than the corresponding standard IFN- α when administered alone for 48 weeks

5.1.2 IFN- α -Ribavirin Combination Therapy

Ribavirin is a guanosine analogue with a broad spectrum of activity against DNA and RNA viruses (Sidwell et al. 1972). Ribavirin modestly and transiently inhibits HCV replication in vivo (Pawlotsky et al. 2004), but it efficiently prevents relapses during IFN-ribavirin combination therapy (Bronowicki et al. 2006). The underlying mechanisms are unknown. In the first trial of standard IFN- α and ribavirin combination therapy, HCV was eradicated in 40% of patients who received the combination, but in none of those on IFN- α monotherapy (Brillanti et al. 1994). Further randomized controlled trials (McHutchison et al. 1998; Poynard et al. 1998) led to the approval of the standard IFN- α -ribavirin combination as the standard treatment for chronic hepatitis C, before the development of pegylated IFNs (1999).

Ribavirin is administered at a dose of 0.8–1.2 g/day, depending on body weight and the HCV genotype (2002). Higher doses may be necessary for heavy patients. The addition of ribavirin increased the SVR rate to 41% and 43%, respectively, compared to 16% and 19% with standard IFN- α 2a and IFN- α 2b monotherapy (McHutchison et al. 1998; Poynard et al. 1998). In the three main registration trials (randomized controlled studies involving patients without cirrhosis), pegylated IFN- α plus ribavirin gave global SVR rates of 54–56%, compared to 18–39% with pegylated IFN- α monotherapy (Fried et al. 2002; Hadziyannis et al. 2004; Manns et al. 2001). The SVR rates ranged from 76% to 84% in patients with HCV genotype 2 or 3 infection and from 42% to 52% in patients with HCV genotype 1 infection. Little information is available on patients with other genotypes, but the SVR rates in patients with HCV genotype 4 infection appear to be close to those in patients with genotype 1 infection. Pretreatment variables that correlated with sustained viral eradication included HCV genotypes 2 and 3, lower baseline viral load, lower body weight, younger age, and milder hepatic fibrosis (Fried et al. 2002; Hadziyannis et al. 2004; Manns et al. 2001). In pivotal trials approximately 10% of patients discontinued therapy because of adverse events, and dose reductions were required in about 30% of cases (Fried et al. 2002; Hadziyannis et al. 2004; Manns et al. 2001). Neutropenia and thrombocytopenia were frequently associated with IFN- α administration, and hemolytic anemia was the most frequent adverse effect of ribavirin administration (Fried et al. 2002; Hadziyannis et al. 2004; Manns et al. 2001). Ribavirin-associated anemia can be severe and demand discontinuation or dose reduction.

5.1.3 Optimized Pegylated IFN- α -Ribavirin Combination Therapy

Pegylated IFN- α -ribavirin combination therapy can be improved by increasing the dose of pegylated IFN- α and/or ribavirin in selected patients and by tailoring the length of treatment to the virological response.

Elevated Doses

The optimal dose of ribavirin is still uncertain. The approved dose is 0.8 g/day for patients infected with HCV genotypes 2 and 3, and 1.0–1.2 g/day in patients (weighting less and more than 75 kg, respectively) infected with HCV genotypes 1, 4, 5, and 6. However, several studies have suggested that higher serum ribavirin concentrations are associated with higher SVR rates (Jen et al. 2000, 2002; Lindahl et al. 2005). In patients infected with HCV genotype 1, the probability of an SVR increases with the AUC of ribavirin concentrations (Snoeck et al. 2006). In addition, the proportion of patients achieving an SVR is higher with a standard weight-based dose of ribavirin than with a low dose (Jensen et al. 2006). Although adverse effects are more frequent and more serious, the use of high ribavirin doses (average 2.5 g/day) to treat patients with high-viral-load HCV genotype 1 infection is feasible and leads to an SVR in 9 out of 10 patients (Lindahl et al. 2005). The use of higher ribavirin doses is offset by the potential increase in drug-related toxicity (principally hemolytic anemia), especially at doses above 15 mg/kg. Epoetin (or darbepoetin, an epoetin prodrug) can be used to reduce the incidence and severity of anemia. However, neither the FDA nor the EMEA has approved the use of these drugs in the treatment of chronic hepatitis C, and the cost-effectiveness of this approach has been questioned (McHutchison et al. 2007b). In patients with HCV genotype 2 or 3 infection, the SVR rate is not strongly influenced by the dose of ribavirin, and 0.8 g/day is probably sufficient to maximize the chances of achieving an SVR (Fried et al. 2002; Hadziyannis et al. 2004; Manns et al. 2001). Whether lower doses of ribavirin could be sufficient to achieve the same SVR rates is currently under investigation.

In a so-called difficult-to-treat patient population (HCV RNA > 800,000 IU/ml and body weight > 85 kg), raising the doses of both pegylated IFN- α and ribavirin significantly increased the SVR rate (Fried et al. 2006). In another study, weight-based ribavirin administration up to 1.4 g/day was more effective than a fixed dose of 0.8 g/day in patients infected with HCV genotype 1 (Jacobson et al. 2005). In a small number of cirrhotic patients infected with HCV genotype 1 who had not responded to a previous course of pegylated IFN- α and ribavirin, 180 μ g of pegylated IFN- α 2a every 5 days, combined with ribavirin, induced an SVR in several cases (Hézode et al. 2006). Ongoing trials are assessing more frequent administration and higher weekly doses of pegylated IFN- α , and higher doses of ribavirin, in nonresponder and difficult-to-treat patients. Patients receiving such reinforced therapy must be carefully monitored for toxicity, and the merits and drawbacks of growth factor administration should be considered.

Tailoring the Treatment Duration to the Virological Response

Current guidelines state that the length of treatment should be tailored to the HCV genotype (Pawlotsky 2006). Patients infected with HCV genotypes 1, 4, 5, and 6 should be treated for 48 weeks (with 1.0–1.2 g/day ribavirin), whereas patients infected with HCV genotypes 2 and 3 should be treated for 24 weeks only (with 0.8 g/day ribavirin) (2002; Hadziyannis et al. 2004). Treatment must be stopped at week 12 in genotype 1-infected patients who do not have a 2-log drop in their HCV RNA level. Rapid virologic responses (RVR) are defined by an HCV RNA level below 50 IU/ml at week 4 of therapy. Several recent reports suggest that patients with an RVR could qualify for shorter treatment, which would improve adherence and reduce the cost of therapy. Conversely, extending treatment duration beyond 48 weeks may achieve an SVR in patients infected with HCV genotype 1 who have a slow virologic response, defined as an HCV RNA decline of more than 2 log IU/ml but a value above 50 IU/ml at week 12. For more detailed information, see the chapter by Zeuzem, this volume.

5.2 Treatment of Acute HCV Infection with IFN- α

HCV infection is rarely diagnosed in the acute phase, as most acutely infected individuals are asymptomatic. Between 50% and 90% of patients develop chronic infection, however, and this warrants early therapy. After occupational exposure with a known date, treatment should not be started before the acute episode characterized by alanine aminotransferase elevation, but it should always be started within 24 weeks after the onset of symptoms. The optimal treatment schedule for acute hepatitis C is controversial. Pegylated IFN- α monotherapy at the standard dose for 24 weeks yielded SVR rates close to 100% in symptomatic patients referred to tertiary care centers (De Rosa et al. 2006; Jaeckel et al. 2001; Santantonio et al. 2005; Wiegand et al. 2006). Shorter therapy may be envisaged (Calleri et al. 2007). Combination with ribavirin is recommended if a first course of pegylated IFN- α monotherapy fails to eradicate the infection. Viral elimination appears to be independent of the HCV genotype and the HCV RNA level (Calleri et al. 2007; De Rosa et al. 2006; Jaeckel et al. 2001).

5.3 Future Perspectives of IFN-Based HCV Therapy

5.3.1 Other IFNs

Several studies have tested IFN- β for chronic hepatitis C, achieving response rates similar to those obtained with IFN- α and with similar or fewer adverse effects (Barbaro et al. 1999; Castro et al. 1997; Habersetzer et al. 2000; Montalto et al.

1998; Villa et al. 1996). Recent reports from Japan suggest that daily IFN- β administration is highly effective in patients with low or moderate HCV RNA levels (Horiike and Onji 2003; Shiratori et al. 2000). Twice-daily administration of IFN- β as induction therapy has also been reported to be effective (Kim et al. 2005; Nakajima et al. 2003). It is unlikely, however, that IFN- β will be used in routine clinical practice unless it is pegylated or otherwise modified, and until specific clinical trials are done.

IFN- ω (Intarcia Therapeutics, Emeryville, California) has been reported to be well tolerated and safe, in patients infected with various HCV genotypes, at doses of 15–120 μg three times weekly for 12 weeks, with dose-dependent virological and biochemical responses (Plauth et al. 2002). At a dose of 25 μg daily, IFN- ω induced a 2-log HCV RNA decline at week 12 in two-thirds of 74 patients infected with HCV genotype 1 (Gorbakov et al. 2005). In a recent trial, SVR was achieved in 6% and 36% of patients receiving the same dose of IFN- ω without and with ribavirin, respectively (Novozhenov et al. 2007). A new trial of IFN- ω , delivered continuously by an implantable device, will start soon.

IFN- γ has potent activity against HCV in the subgenomic replicon system (Dash et al. 2005; Frese et al. 2002; Lanford et al. 2003). Synergistic immunomodulatory effects of IFN- γ 1b and IFN- α have been reported (Wang et al. 2006). However, a pilot study of IFN- γ at a dose of 100–400 μg three times per week showed no antiviral efficacy in patients infected with HCV genotype 1 who had not responded to standard therapy or who had relapsed (Soza et al. 2005).

IFN- λ 1 exhibits dose- and time-dependent inhibition of HCV replication in various models, independently of type I and II IFN receptors and induced pathways (Marcello et al. 2006). A pegylated form of IFN- λ will soon enter clinical evaluation.

5.3.2 New IFN- α Molecules

Alb-IFN- α 2b has been reported to induce a dose-dependent antiviral response in previously untreated patients and in nonresponders to the pegylated IFN- α and ribavirin combination (Bain et al. 2006; Balan et al. 2006). The results of a phase II trial in untreated genotype 1-infected patients were recently reported: the SVR rates were not significantly different among four groups of patients receiving either the standard pegylated IFN- α 2a and ribavirin combination or alb-IFN- α 2b at doses of 900 μg every two weeks, 1,200 μg every 2 weeks and 1,200 μg every 4 weeks (Zeuzem et al. 2007). End-of-treatment responses to alb-IFN- α 2b administered every 2 or 4 weeks in combination with ribavirin are similarly frequent in patients infected with HCV genotypes 2 and 3 (Bain et al. 2007). Higher doses of alb-IFN- α 2b given every 4 weeks are currently under investigation, and the product will soon enter phase III clinical evaluation.

Consensus IFN- α has been used in various populations of HCV-infected patients but the published results are variable. Consensus IFN- α gave a higher response rate than the combination of standard IFN- α and ribavirin in patients who relapsed

after standard IFN- α monotherapy (Miglioresi et al. 2003). In patients in whom the standard IFN- α -ribavirin combination failed, an SVR rate of approximately 30% was obtained with consensus IFN- α (Bocher et al. 2006). In contrast, an SVR was achieved in only 8% of patients who did not respond to standard IFN- α 2b plus ribavirin (Moskovitz et al. 2003). Recently, a direct comparison of consensus IFN- α -ribavirin and pegylated IFN- α -ribavirin showed similar SVR rates of 37% and 41%, respectively, in previously untreated patients infected with HCV genotype 1 (Sjogren et al. 2007). Nevertheless, there is no clear evidence that consensus IFN- α is superior to other IFNs when given at equivalent doses. The future of consensus IFN- α will depend on the development of a pegylated or otherwise pharmacologically modified form.

5.3.3 Enhanced IFN- α -Based Therapy

The results of IFN- α -based therapy can theoretically be improved by using better-tolerated drugs that mimic the action of ribavirin and/or by using HCV inhibitors that, when combined, substantially reduce HCV replication. Since the mechanism of action of ribavirin is still unknown, no credible alternative approach is currently available. In contrast, many specific inhibitors of the HCV replication cycle are in preclinical development and several have reached clinical development (Pawlotsky et al. 2007). A number of them are being tested in combination with pegylated IFN- α , with or without ribavirin.

The NS3/4A serine proteinase inhibitors telaprevir (VX-950, Vertex Pharmaceuticals, Cambridge, Massachusetts) and boceprevir (SCH 503034, Schering-Plough Corporation, Kenilworth, New Jersey) have now advanced to phase II clinical trials. In a recent trial, HCV RNA became undetectable (below 10 IU/ml) in all 12 patients receiving the triple combination of pegylated IFN- α 2a, ribavirin, and telaprevir for 28 days (Rodriguez-Torres et al. 2006). Preliminary results of the PROVE 1 phase II trial showed that, after 12 weeks of treatment with telaprevir plus both pegylated IFN- α and ribavirin, HCV RNA was undetectable (<10 IU/ml) in significantly more genotype 1-infected treatment-naïve patients than in the arm receiving only the dual combination of pegylated IFN- α and ribavirin, without telaprevir (70% and 39%, respectively). Telaprevir administration was associated with more frequent dermatological (especially rash and pruritus) and gastrointestinal side effects (McHutchison et al. 2007a). Telaprevir was withdrawn after 12 weeks in all the groups, and the patients will continue on pegylated IFN- α and ribavirin for various times. Other trials of the triple combination given for 12 or 24 weeks and a dual combination of pegylated IFN- α and telaprevir (without ribavirin) are undergoing in treatment-naïve and nonresponder patients (PROVE 2 and PROVE 3).

In nonresponders to IFN- α -ribavirin, the antiviral effect of boceprevir appeared to be strictly additive to that of pegylated IFN- α 2b (Sarrazin et al. 2007). In an ongoing phase II clinical trial, higher doses of boceprevir are being administered to treatment-naïve patients, in combination with pegylated IFN- α and ribavirin.

Resistance is a problem when these drugs are administered alone and will need to be carefully monitored when they are used in combination with IFN- α and ribavirin.

Inhibitors of the RNA-dependent RNA polymerase belong to two categories: nucleoside/nucleotide inhibitors target the catalytic site of the enzyme, and non-nucleoside inhibitors target allosteric sites of the RdRp (Pawlotsky et al. 2007). Three RdRp inhibitors have been tested in clinical trials, including two nucleoside inhibitors, valopicitabine (NM283, Idenix Pharmaceuticals, Cambridge, Massachusetts, and Novartis) and R1626 (Roche), and a non-nucleoside inhibitor, HCV-796 (ViroPharma, Exton, Pennsylvania, and Wyeth Pharmaceuticals, Madison, New Jersey) (Pawlotsky et al. 2007).

In a phase IIb trial involving 190 HCV genotype-1-infected treatment-refractory patients, valopicitabine had a dose-dependent additive effect to that of pegylated IFN- α 2a (Afdhal et al. 2006). Frequent gastrointestinal side-effects have been reported and the development of valopicitabine has been halted. In a phase II trial in which HCV genotype 1- and non-1-infected patients received the combination of pegylated IFN- α 2b and HCV-796 for 14 days, the HCV RNA level fell more than with pegylated IFN alone (3.3–3.5 log IU/ml in the combination groups and 1.6 log IU/ml in the pegylated IFN- α group), and no viral breakthroughs due to resistance selection occurred during the 14 days of administration (Villano et al. 2007). R1626, combined with pegylated IFN alpha and ribavirin, has recently progressed to phase II clinical development. Further studies are needed to establish the potential benefits and drawbacks of adding HCV replication cycle inhibitors to the pegylated IFN- α -ribavirin combination, the current standard of care.

6 IFN-Based Treatment of Hepatitis B Virus Infection

HBV-infected patients can be subdivided into two groups according to the presence or absence of circulating hepatitis B e (HBe) antigen (Ag). HBeAg-negative patients do not produce HBeAg because the infecting virus harbors precore and/or core promoter nucleotide substitutions (Carman et al. 1989). They generally have lower, fluctuating HBV DNA levels and a more severe course of disease. Chronic HBV infection currently is not curable, because covalently closed circular DNA (cccDNA) persists in the hepatocyte nucleus. Antiviral treatment of chronic hepatitis B has a triple aim: (1) to slow the progression of fibrosis to cirrhosis; (2) to prevent hepatic failure; and (3) to prevent hepatocellular carcinoma. Profound and sustained inhibition of HBV replication is necessary if these goals are to be achieved. Treatment can consist of short-term therapy, generally with IFN- α , or long-term (possibly life-long) therapy with specific nucleoside/nucleotide analogue inhibitors of HBV replication.

The virological response, which is assessed by measuring HBV DNA levels in serum during and after therapy, is the best predictor of the outcome of antiviral treatment. It has been suggested that HBV viral load should be reduced to less than 2,000 IU/mL (de Franchis et al. 2003; Keeffe et al. 2006; Liaw et al. 2005;

Lok and McMahon 2007), but the ideal outcome is undetectable HBV DNA (< 10–30IU/ml) in highly sensitive real-time PCR-based assays. In HBeAg-positive patients, loss of HBeAg followed by the emergence of anti-HBe antibodies (“e” seroconversion) indicates a sustained response to therapy when it persists after treatment cessation. HBs seroconversion (loss of HBsAg and emergence of anti-HBs antibodies) is the most desirable endpoint, as it indicates a complete response with sustained remission from HBV disease. It is rarely achieved with current therapies.

6.1 Treatment of Chronic HBV Infection with IFN- α

IFN- α was first used empirically in chronic hepatitis B in 1986 (Peters et al. 1986). The effect of human recombinant IFN- α on lymphocyte proliferation and differentiation was studied in 18 patients with chronic hepatitis B. Inhibition of immunoglobulin synthesis was observed, and the authors postulated that the immunomodulatory effect of IFN- α could be important in the therapeutic response of chronic hepatitis B (Peters et al. 1986). The first study to evaluate the antiviral efficacy of IFN- α involved nine patients, who received different doses administered three times a week for two weeks. Two of them entered sustained remission, with undetectable HBV DNA, loss of HBeAg, and ALT normalization (Dooley et al. 1986). Two forms of IFN- α have been used in the treatment of chronic hepatitis B, namely standard and pegylated IFN- α .

6.1.1 Standard IFN- α Monotherapy

Standard IFN- α has been used in chronic HBV infection at a dose of 5 million units (MU) daily or 9–10 MU three times a week (de Franchis et al. 2003). A 4- to 6-month course was initially recommended, but it soon appeared that longer treatment (12 months or more) could result in more frequent and more durable responses (Hui et al. 2006; Lampertico et al. 1997; Lampertico et al. 2003).

HBsAg-Positive Patients

A meta-analysis of 15 randomized controlled trials involving HBeAg-positive patients showed that, after 12–24 weeks of treatment, HBeAg was lost in 33% of cases, with HBe seroconversion in 18% of them, compared to 12% in the control arm (Wong et al. 1993). HBeAg relapsed in 10–30% of patients who received the shortest treatments (Lau et al. 1997; Lok et al. 1993; Niederau et al. 1996; van Zonneveld et al. 2004). Clearance of HBsAg and seroconversion to anti-HBs antibodies were rare and occurred late (5–10% of patients 1 year after treatment in European studies). HBsAg was lost in 11–25% of sustained HBe seroconverters after 5 years (Bortolotti et al. 2000; Fattovich et al. 1998; Niederau et al. 1996).

Standard IFN- α treatment has been shown to reduce the risk of cirrhosis and hepatocellular carcinoma (Lin et al. 2007).

HBeAg-Negative Patients

The use of IFN- α -based therapy is more controversial in HBeAg-negative patients, in whom sustained responses such as HBe seroconversion cannot be expected. Four randomized controlled trials showed a reduction in the HBV DNA level at the end of treatment in 60–70% of patients, compared to 10–20% of untreated controls (Fattovich et al. 2000; Lampertico et al. 1997; Manesis and Hadziyannis 2001; Pastore et al. 1992). However, about half the virological responders relapsed after treatment discontinuation, and relapses continued to occur for up to 5 years post-therapy (Papatheodoridis et al. 2001). Despite the high relapse rates, a sustained virological response (sustained inhibition of viral replication) was achieved in about one-third of patients 5 years after treatment (Kaymakoglu et al. 2007a). Longer IFN treatment periods (12 months or more) are associated with higher rates of sustained virological response (Lampertico et al. 1997, 2003).

Retreatment of nonresponders with standard IFN- α

Two small studies of repeat therapy with standard IFN- α involved both HBeAg-positive and HBeAg-negative patients (Carreno et al. 1999; Manesis and Hadziyannis 2001). Retreatment of nonresponders and responder-relapsers resulted in sustained virological responses in 33% and 35% of cases, respectively. However, the results were difficult to interpret, as the first IFN- α dose regimen and the interval before retreatment were both variable.

6.1.2 Pegylated IFN- α Monotherapy

Pegylated IFN- α 2a, but not pegylated IFN- α 2b, has been approved by the American and European authorities for the treatment of chronic hepatitis B, based on two large pivotal trials involving HBeAg-positive and HBeAg-negative patients (Lau et al. 2005; Marcellin et al. 2004). Pegylated IFN- α 2b has also been tested in HBeAg-positive and HBeAg-negative patients (Flink et al. 2006b; Janssen et al. 2005; Kaymakoglu et al. 2007b; Zhao et al. 2007).

HBeAg-Positive Patients

In a clinical phase II trial, the efficacy of various doses of pegylated IFN- α 2a (90–270 μ g weekly) administered for 24 weeks was studied in treatment-naïve patients, by comparison with standard IFN- α 2a at a dose of 4.5 MU three times a week

(Cooksley et al. 2003). At the end of follow-up, 24 weeks after the end of therapy, HBeAg had been lost by 35% of patients receiving pegylated IFN- α 2a 180 μ g weekly and by 25% of patients receiving standard IFN- α . In addition, an endpoint combining HBeAg loss, HBV DNA $< 5.0 \times 10^6$ (6.7 log₁₀ copies/mL), and ALT normalization was reached by 24% of pegylated IFN- α -treated patients, whatever the dose regimen, compared to 12% of patients receiving standard IFN- α (Cooksley et al. 2003). A larger clinical trial tested pegylated IFN- α 2a monotherapy at a weekly dose of 180 μ g (Lau et al. 2005). At the end of follow-up, HBeAg seroconversion had occurred in 32% of the patients and ALT had normalized in 41% of patients. The approved pegylated IFN- α 2a treatment schedule for HBeAg-positive patients is currently 180 μ g weekly for 48 weeks. It is possible, however, that a lower dose and/or shorter treatment may be sufficient (Zhao et al. 2007), and further studies are therefore needed (Hui et al. 2006). With pegylated IFN- α 2b, 52 weeks of therapy yielded a 29% seroconversion rate 24 weeks after the end of treatment (Janssen et al. 2005).

Several recent studies have suggested that the HBV genotype influences treatment outcome, HBV genotype A or B infection tending to respond better to pegylated IFN- α than HBV genotype C or D infection (Flink et al. 2006b; Janssen et al. 2005; Zhao et al. 2007). However, more data are needed before using the HBV genotype to tailor treatment.

HBeAg-Negative Patients

One large trial evaluated 48 weeks of treatment with pegylated IFN- α 2a in HBeAg-negative patients (Marcellin et al. 2004). After 24 weeks of follow-up, 36% of the patients had normal ALT levels and HBV DNA levels below 20,000 copies/mL. HBeAg was lost in 4% of cases. In a trial of pegylated IFN- α 2b given for 48 weeks, 26% of patients achieved an HBV DNA level below 400 copies/mL (Kaymakoglu et al. 2007b).

Nonresponders to Standard IFN- α and Lamivudine

In two published cohort studies, pegylated IFN- α was effective in approximately one-third of HBeAg-positive patients in whom standard IFN- α or lamivudine had failed (Flink et al. 2006a; Leemans et al. 2006).

6.1.3 Combination Therapy with IFN- α Alpha and Nucleoside/Nucleotide Analogues

A few studies have evaluated standard IFN- α 2a and - α 2b combined with lamivudine, whereas more recent trials tested pegylated IFN- α combined with nucleoside/nucleotide analogues. The aim was to determine whether combination therapy

could increase antiviral efficacy, reduce adverse effects, and hinder the emergence of analogue-resistant viral variants. Simultaneous and sequential protocols were both tested.

Simultaneous Combination Therapy

Several studies have tested lamivudine and standard IFN- α given simultaneously for 16–24 or 48–52 weeks. In one trial, involving HBeAg-positive patients, sustained HBe seroconversion and undetectable HBV DNA (<1.6 pg/mL) were significantly more frequent at the end of follow-up in patients receiving the combination than in patients treated with lamivudine alone (33% and 15%, respectively) (Barbaro et al. 2001). In contrast, lamivudine plus standard IFN- α was not more effective than lamivudine alone in HBeAg-negative patients (Akarca et al. 2004; Yurdaydin et al. 2005). The incidence of lamivudine resistance was nonetheless lower when IFN- α was coadministered (Jang et al. 2004; Santantonio et al. 2002).

Conflicting results have been reported with pegylated IFN- α and lamivudine combination therapy. In a randomized controlled trial involving HBeAg-positive patients, a sustained virological response (HBV DNA $< 500,000$ copies/mL) and HBe seroconversion were more frequent in patients receiving pegylated IFN- $\alpha 2b$ 1.5 μ g/kg/week and lamivudine 100 mg daily than in patients receiving lamivudine monotherapy (Chan et al. 2005a, b). In contrast, there was no difference in the rate of ALT normalization or histological improvement. Lamivudine resistance was more frequent with lamivudine monotherapy than with combination therapy (40% and 21% of patients, respectively). Another trial involving HBeAg-positive patients favored pegylated IFN- $\alpha 2a$ or - $\alpha 2b$ plus lamivudine over lamivudine monotherapy, but not over pegylated IFN- α monotherapy, despite an additive antiviral effect (Lau et al. 2005). In another study involving HBeAg-positive patients, 52 weeks of treatment with pegylated IFN- $\alpha 2b$ yielded an HBe seroconversion rate of 29%, whether IFN- $\alpha 2b$ was given alone or combined with lamivudine (Janssen et al. 2005). The combination did not improve liver histological status (van Zonneveld et al. 2006), but it induced less resistance to lamivudine. In HBeAg-negative patients, lamivudine combination with pegylated IFN- $\alpha 2a$ or - $\alpha 2b$ did not improve the rate of ALT normalization or HBV DNA suppression at the end of follow-up compared to pegylated IFN- α alone. Nevertheless, the decline in viral load was more pronounced and lamivudine resistance was less frequent with the combination (Kaymakoglu et al. 2007b; Marcellin et al. 2004).

One trial assessed the combination of pegylated IFN- $\alpha 2b$ and adefovir dipivoxil given for 48 weeks to both HBeAg-positive and HBeAg-negative patients. There was no control arm. Both liver cccDNA and serum HBsAg levels fell strongly, and 4 (17%) of the 26 patients seroconverted to anti-HBs at the end of follow-up (Wursthorn et al. 2006).

Sequential Combination Therapy

The use of sequential combination therapy is based on the notion that lowering the HBV DNA level with nucleoside/nucleotide analogues, thereby permitting partial immune recovery, might improve the subsequent efficacy of pegylated IFN- α . One trial compared 8 weeks of lamivudine monotherapy followed by 16 weeks of lamivudine/standard IFN- α combination therapy, with 52 weeks of lamivudine monotherapy in HBeAg-positive patients (Sarin et al. 2005). The rate of sustained virological responses, defined by HBe seroconversion and undetectable HBV DNA ($<1.4 \times 10^5$ copies/mL) 24 weeks after the end of treatment, was significantly higher with the combination than with lamivudine monotherapy. A recent study of HBeAg-positive patients conducted by the same group compared 4 weeks of lamivudine monotherapy followed by 24 weeks of pegylated IFN- α therapy with 24 weeks of pegylated IFN- α monotherapy (Sarin et al. 2007). Six months after the end of treatment, HBV DNA was undetectable (below 4,700 copies/mL) in 50% of the patients who received sequential therapy and 15% of patients on pegylated IFN- α monotherapy. HBeAg loss was also more frequent in the sequential therapy group (39% vs. 15%, respectively) (Sarin et al. 2007).

In HBeAg-negative patients, 12 weeks of lamivudine monotherapy followed by 36 months of pegylated IFN- α 2b therapy (including 3 months of concomitant administration) has been compared with 48 weeks of lamivudine monotherapy (Vassiliadis et al. 2007). At the end of follow-up, the rate of ALT normalization was significantly higher with the sequential therapy than with lamivudine alone. No difference in the proportion of patients with undetectable HBV DNA was observed. Similar results were obtained in a Chinese cohort study (Shi et al. 2006).

6.2 Treatment of Chronic HBV Infection with Other Type I IFNs

6.2.1 Standard IFN- β Monotherapy

The antiviral efficacy of IFN- β administered for 24 weeks at a dose of 3 million units daily has been studied in a small series of HBeAg-positive patients. HBe seroconversion was observed in half the patients and ALT normalization in four patients out of five (Kagawa et al. 1993). Sequential therapy with lamivudine and IFN- β has been tested in HBeAg-positive patients (Enomoto et al. 2007). A sustained virological response was achieved in only 7 (29%) of the 24 patients, 24 weeks after the end of therapy. In a pilot study of IFN- β therapy in 29 patients in whom IFN- α therapy had failed, HBV DNA became undetectable in 6 patients (21%) (Munoz et al. 2002).

6.2.2 Standard IFN- λ

The antiviral efficacy of IFN- λ has been evaluated in vitro in human hepatocyte-derived cells. IFN- λ reduced HBV replication but the results suggested that antiviral efficacy in vivo would be limited (Hong et al. 2007).

6.3 Treatment of Chronic HBV Infection with Type II IFN

IFN- γ exhibits antiviral activity against HBV in vitro (Parvez et al. 2006). In addition, IFN- γ was found to reduce hepatic fibrosis by 63% after 9 months, compared to 24% in untreated controls (Weng et al. 2005).

7 IFN-Based Treatment of Hepatitis D/Delta Virus Infection

Worldwide, 15 million HBsAg carriers are also infected with hepatitis D/delta virus (HDV) (Gaeta et al. 2000). This situation represents a major therapeutic challenge, as most of these patients have advanced liver disease, including cirrhosis in 60–70% of cases, and hepatocellular carcinoma (Fattovich et al. 2000; Saracco et al. 1987). No specific HDV inhibitors have been developed, and IFN- α -based treatment is more difficult in HBV–HDV infection than in HBV mono-infection. HDV RNA levels in serum can be used to monitor treatment efficacy. The endpoint of therapy is HDV RNA clearance and ALT normalization, and this is sometimes achieved after the end of treatment. A sustained response can lead to HBsAg clearance from serum.

7.1 Standard IFN- α Monotherapy

To date, standard IFN- α , but not pegylated IFN- α , has been approved by the American and European authorities for the treatment of chronic hepatitis D. Clinical pilot trials conducted in the early 1990s suggested that IFN- α could inhibit HDV replication. The sustainability of this inhibition depended on the dose and duration of IFN- α therapy, and relapse was frequent (Farci et al. 1994; Gaudin et al. 1995; Madejon et al. 1994; Rosina et al. 1991). A complete response, characterized by normalization of ALT levels and undetectable HDV RNA, was observed six months after the end of treatment in 50% of patients receiving a high dose of standard IFN- α , compared to 21% and 0% of patients receiving a low dose of IFN- α and no treatment, respectively (Farci et al. 2004). IFN- α treatment has been shown to provide a clinical benefit, with regression of advanced hepatic fibrosis. No pretreatment characteristics have been shown to predict the response to IFN- α , and the possible influence of the HDV genotype on the response is not known (Niro et al. 2005b).

Several strategies have been developed to improve the efficacy of standard IFN- α treatment; in particular, treatment has been prolonged, for up to 12 years, but tolerability was poor (Lau et al. 1999b).

7.2 Pegylated IFN- α Monotherapy

Three recent studies evaluated the efficacy and safety of pegylated IFN- α monotherapy in patients with HBV–HDV infection (Castelnau et al. 2006; Erhardt et al. 2006; Niro et al. 2006). The first tested was pegylated IFN- α 2b, given for 48 weeks to 14 patients. A virological response, defined by undetectable HDV RNA, was achieved in 43% of patients. ALT normalization was more frequent at the end of follow-up than at the end of therapy (Castelnau et al. 2006). The second study, a randomized controlled trial, evaluated the efficacy of 72 weeks of pegylated IFN- α 2b therapy. A virological response was achieved in 25% of patients (Niro et al. 2006). The last study assessed the efficacy and safety of 48 weeks of pegylated IFN- α 2b administration in 12 patients. A sustained virological response, defined by undetectable HDV RNA and ALT normalization, occurred in only 2 patients (17%) (Erhardt et al. 2006). The different rates of sustained virological response might be explained by different frequencies of cirrhosis in the three study populations.

7.3 IFN- α Combination with Nucleoside/Nucleotide Analogues

Drugs such as ribavirin that may directly reduce HDV replication and specific inhibitors of HBV replication such as lamivudine and adefovir dipivoxil have been tested in combination with IFN- α in patients with chronic hepatitis D.

7.3.1 Standard IFN- α Plus Ribavirin

Ribavirin inhibits HDV replication in hepatocyte cultures (Di Bisceglie 1997). However, ribavirin monotherapy is not effective in patients with chronic hepatitis D. A pilot study evaluated the efficacy of ribavirin, 15 mg/kg, administered for 16 weeks to 9 patients. At the end of follow-up, HDV RNA levels were reduced in only one patient and ALT levels never normalized (Garripoli et al. 1994). The efficacy of standard IFN- α , 9–10 MU three times a week, combined with ribavirin, 1,000–1,200 mg daily, has been evaluated in two studies each lasting 24 months (Gunsar et al. 2005; Kaymakoglu et al. 2005). Ribavirin did not increase the efficacy of IFN- α . Another trial tested the efficacy of a 72-week course of pegylated IFN- α 2b alone vs. 48 weeks of pegylated IFN- α 2b plus ribavirin followed by 24 weeks of pegylated IFN- α 2b alone. A virological response was achieved in 25% and 18% of patients, respectively, while the rates of biochemical response were similar (Niro et al. 2006).

Thus, ribavirin is ineffective in chronic hepatitis D, whether given alone or in combination with IFN- α .

7.3.2 Standard IFN- α Plus Lamivudine

Lamivudine monotherapy has no effect on HDV (Lau et al. 1999a; Niro et al. 2005a), and lamivudine adjunction only slightly improves the efficacy of standard IFN- α (Canbakan et al. 2006; Wolters et al. 2000).

7.3.3 Pegylated IFN- α Plus Adefovir Dipivoxil

A recent randomized multicenter trial compared the efficacy of pegylated IFN- α 2a monotherapy, adefovir monotherapy, and the pegylated IFN- α 2a/adefoviro combination administered for 48 weeks to patients with chronic hepatitis D. Adefovir did not inhibit HDV replication, and the combination had no additional benefit compared with pegylated IFN- α monotherapy in terms of the HDV RNA level (Yurdaydin et al. 2006).

8 Treatment of HIV Infection with IFN- α

IFN- α was one of the first drugs to be tested against human immunodeficiency virus (HIV) in the 1980s. Recombinant human IFN- α inhibits HIV replication in normal peripheral blood mononuclear cells (Ho et al. 1985). However, the ability of IFN- α to inhibit HIV replication in vitro depends largely on the viral isolate, the target cells, the IFN concentration, and the inoculum. IFN- α appears to interfere with the assembly and/or release of newly formed virions (Fernie et al. 1991; Hansen et al. 1992; Poli et al. 1989). In addition, IFN- α may inhibit viral protein synthesis by blocking viral RNA translation (Coccia et al. 1994), and may also prevent cell infection (Gendelman et al. 1990). In vivo, IFN- α has been suggested to block de novo infection rather than virion production, a finding supported by in vitro studies showing that IFN- α is more effective when used before rather than after viral challenge (Neumann et al. 2007). IFN therapy of HIV infection was abandoned because of its adverse effects, its modest inherent antiviral efficacy, and the development of highly active antiretroviral therapy (HAART) (Lane 1994).

8.1 Standard IFN- α

Several trials have evaluated the antiviral efficacy of standard IFN- α in HIV-infected patients also receiving zidovudine, in comparison with zidovudine alone.

The combination was not more effective than zidovudine monotherapy, either in adults (Fernandez-Cruz et al. 1995; Fischl et al. 1997; Krown et al. 1999) or in infants (Giovannini et al. 1992).

8.2 Pegylated IFN- α

In a prospective pilot study involving nine patients coinfecting by HIV and HCV genotype 1, HIV replication showed a slow continuous decline during the first week of pegylated IFN- α administration, and there was no rebound when pegylated IFN- α was withdrawn (Neumann et al. 2007). Pegylated IFN- α was also reported to display antiretroviral activity in two patients with refractory HIV-related Kaposi's sarcoma (van der Ende et al. 2007) and in HIV-infected patients with condylomata acuminata (Brockmeyer et al. 2006). Finally, pegylated IFN- α has been shown to participate in early control of viral replication during primary HIV-1 infection when combined with antiretroviral drugs (Emilie et al. 2001). However, there was no control group in this study, and further investigations are therefore needed.

9 Treatment of Other Viral Infections with Type I IFN in Humans

Table 4 is illustrating the role of type I IFN in other human viral infections (Hodson et al. 2007; Isomura et al. 1982; Kalil et al. 2005; Lewis and Amsden 2007; Phillipotts et al. 1984; Rahal et al. 2004; Sainz et al. 2004; Scagnolari et al. 2004; Solomon et al. 2003).

Table 4 Treatment of viral infections other than chronic viral hepatitis and HIV with type I IFNs

Virus	Protection	References
Avian influenza A virus	No significant protection	Isomura et al. 1982; Phillipotts et al. 1984
Coronavirus	IFN- β more protective than IFN- α	Sainz et al. 2004; Scagnolari et al. 2004
Cytomegalovirus (CMV)	Synergistic effect of IFN- α and IFN- β No significant reduction of the risk of CMV disease Reduced CMV viremia on IFN- α treatment	Hodson et al. 2007
Arthropod-borne virus infections	Under investigation	Kalil et al. 2005; Lewis and Amsden 2007; Rahal et al. 2004; Solomon et al. 2003

10 Conclusion

In conclusion, IFNs have proven to be invaluable tools in the fight against chronic viral hepatitis. In these indications, their antiviral properties play a major role and it remains unclear whether their immunomodulatory properties are also important. Disappointing results obtained with purely immunomodulatory molecules, such as interleukins or Toll-like receptor agonists suggest that, if immunomodulation plays any role, potent inhibition of viral replication is also needed. The role of IFNs in the treatment of viral infections other than hepatitis B and C remains elusive.

References

- (1997) National Institutes of Health Consensus Development Conference Panel statement: management of hepatitis C. *Hepatology* 26:2S–10S
- (1999) EASL International Consensus Conference on hepatitis C. Paris, 26–27 February 1999. Consensus statement. *J Hepatol* 31 Suppl 1:3–8
- (2002) National Institutes of Health Consensus Development Conference statement: management of hepatitis C: 2002-June 10–12, 2002. *Hepatology* 36:S3–S20
- Afdhal NH, O'Brien C, Godofsky E, Rodriguez-Torres M, Pappas SC, Pockros P, Lawitz E, Bzowej N, Rustgi V, Sulkowski M, Sherman KE, Jacobson I, Chao G, Knox S, Pietropaolo K, Brown N (2006) Valopicitabine (NM283), alone or with peg-interferon, compared to peg-interferon/ribavirin (PEGIFN/RBV) retreatment in hepatitis C patients with prior non-response to PEGIFN/RBV: week 24 results. *J Hepatol* 44 Suppl 2:S19
- Akarcu US, Ersoz G, Gunsar F, Karasu Z, Saritas E, Yuce G, Batur Y (2004) Interferon-lamivudine combination is no better than lamivudine alone in anti-HBe-positive chronic hepatitis B. *Antivir Ther* 9:325–334
- Ank N, West H, Bartholdy C, Eriksson K, Thomsen AR, Paludan SR (2006) Lambda interferon (IFN-lambda), a type III IFN, is induced by viruses and IFNs and displays potent antiviral activity against select virus infections in vivo. *J Virol* 80:4501–4509
- Bain VG, Kaita KD, Yoshida EM, Swain MG, Heathcote EJ, Neumann AU, Fiscella M, Yu R, Osborn BL, Cronin PW, Freimuth WW, McHutchison JG, Subramanian GM (2006) A phase 2 study to evaluate the antiviral activity, safety, and pharmacokinetics of recombinant human albumin-interferon alfa fusion protein in genotype 1 chronic hepatitis C patients. *J Hepatol* 44:671–678
- Bain VG, Marotta P, Kaita K, Yoshida E, Swain MG, Bailey R, Neumann AU, Cronin PW, McHutchison JG, Pulkstenis E, Subramanian GM (2007) Comparable antiviral response rates with albumin interferon alpha-2b dosed at Q2W or Q4W intervals in naive subjects with genotype 2 or 3 chronic hepatitis C. *J Hepatol* 46:S7
- Balan V, Nelson DR, Sulkowski MS, Everson GT, Lambiase LR, Wiesner RH, Dickson RC, Post AB, Redfield RR, Davis GL, Neumann AU, Osborn BL, Freimuth WW, Subramanian GM (2006) A Phase I/II study evaluating escalating doses of recombinant human albumin-interferon-alpha fusion protein in chronic hepatitis C patients who have failed previous interferon-alpha-based therapy. *Antivir Ther* 11:35–45
- Barbaro G, Di Lorenzo G, Soldini M, Giancaspro G, Pellicelli A, Grisorio B, Barbarini G (1999) Intravenous recombinant interferon-beta versus interferon-alpha-2b and ribavirin in combination for short-term treatment of chronic hepatitis C patients not responding to interferon-alpha. *Scand J Gastroenterol* 34:928–933
- Barbaro G, Zechini F, Pellicelli AM, Francavilla R, Scotto G, Bacca D, Bruno M, Babudieri S, Annesse M, Matarazzo F, Di Stefano G, Barbarini G (2001) Long-term efficacy of interferon

- alpha-2b and lamivudine in combination compared to lamivudine monotherapy in patients with chronic hepatitis B. An Italian multicenter, randomized trial. *J Hepatol* 35:406–411
- Blatt LM, Davis JM, Klein SB, Taylor MW (1996) The biologic activity and molecular characterization of a novel synthetic interferon-alpha species, consensus interferon. *J Interferon Cytokine Res* 16:489–499
- Bocher WO, Schuchmann M, Link R, Hillenbrand H, Rahman F, Sprinzl M, Mudter J, Lohr HF, Galle PR (2006) Consensus interferon and ribavirin for patients with chronic hepatitis C and failure of previous interferon-alpha therapy. *Liver Int* 26:319–325
- Boehm U, Klamp T, Groot M, Howard JC (1997) Cellular responses to interferon-gamma. *Annu Rev Immunol* 15:749–795
- Bortolotti F, Jara P, Barbera C, Gregorio GV, Vegnente A, Zancan L, Hierro L, Crivellaro C, Vergani GM, Iorio R, Pace M, Con P, Gatta A (2000) Long term effect of alpha interferon in children with chronic hepatitis B. *Gut* 46:715–718
- Brillanti S, Garson J, Foli M, Whitby K, Deaville R, Masci C, Miglioli M, Barbara L (1994) A pilot study of combination therapy with ribavirin plus interferon alfa for interferon alfa-resistant chronic hepatitis C. *Gastroenterology* 107:812–817
- Brockmeyer NH, Poffhoff A, Bader A, Hochdorfer B, Schlottmann R, Rasokat H, Altmeyer P, Kreuter A (2006) Treatment of condylomata acuminata with pegylated interferon alfa-2b in HIV-infected patients. *Eur J Med Res* 11:27–32
- Bronowicki JP, Ouzan D, Asselah T, Desmorat H, Zarski JP, Foucher J, Boulrière M, Renou C, Tran A, Melin P, Hézode C, Chevallier M, Bouvier-Alias M, Chevaliez S, Montestruc F, Lonjon-Domanec I, Pawlowsky JM (2006) Effect of ribavirin in genotype 1 patients with hepatitis C responding to pegylated interferon alpha-2a plus ribavirin combination. *Gastroenterology* 131:1339–1341
- Buckwold VE, Wei J, Huang Z, Huang C, Nalca A, Wells J, Russell J, Collins B, Ptak R, Lang W, Scribner C, Blanchett D, Alessi T, Langecker P (2007) Antiviral activity of CHO-SS cell-derived human omega interferon and other human interferons against HCV RNA replicons and related viruses. *Antiviral Res* 73:118–125
- Calleri G, Cariti G, Gaiottino F, De Rosa FG, Bargiacchi O, Audagnotto S, Quaglia S, De Blasi T, Romano P, Traverso A, Leo G, Carbone R, Del Mastro B, Tinelli M, Caramello P, Di Perri G (2007) A short course of pegylated interferon-alpha in acute HCV hepatitis. *J Viral Hepat* 14:116–121
- Canbakan B, Senturk H, Tabak F, Akdogan M, Tahan V, Mert A, Sut N, Ozaras R, Midilli K, Ozbay G (2006) Efficacy of interferon alpha-2b and lamivudine combination treatment in comparison to interferon alpha-2b alone in chronic delta hepatitis: a randomized trial. *J Gastroenterol Hepatol* 21:657–663
- Carman WF, Jacyna MR, Hadziyannis S, Karayiannis P, McGarvey MJ, Makris A, Thomas HC (1989) Mutation preventing formation of hepatitis B e antigen in patients with chronic hepatitis B infection. *Lancet* 2:588–591
- Carreno V, Marcellin P, Hadziyannis S, Salmeron J, Diago M, Kitis GE, Vafiadis I, Schalm SW, Zahm F, Manzarbeitia F, Jimenez FJ, Quiroga JA (1999) Retreatment of chronic hepatitis B e antigen-positive patients with recombinant interferon alfa-2a. *Hepatology* 30:277–282
- Castelnaud C, Le Gal F, Ripault MP, Gordien E, Martinot-Peignoux M, Boyer N, Pham BN, Maylin S, Bedossa P, Deny P, Marcellin P, Gault E (2006) Efficacy of peginterferon alpha-2b in chronic hepatitis delta: relevance of quantitative RT-PCR for follow-up. *Hepatology* 44:728–735
- Castro A, Suarez D, Inglada L, Carballo E, Dominguez A, Diago M, Such J, Del Olmo JA, Perez-Mota A, Pedreira J, Quiroga JA, Carreno V (1997) Multicenter randomized, controlled study of intramuscular administration of interferon-beta for the treatment of chronic hepatitis C. *J Interferon Cytokine Res* 17:27–30
- Chan HL, Hui AY, Wong VW, Chim AM, Wong ML, Sung JJ (2005a) Long-term follow-up of peginterferon and lamivudine combination treatment in HBeAg-positive chronic hepatitis B. *Hepatology* 41:1357–1364
- Chan HL, Leung NW, Hui AY, Wong VW, Liew CT, Chim AM, Chan FK, Hung LC, Lee YT, Tam JS, Lam CW, Sung JJ (2005b) A randomized, controlled trial of combination therapy for

- chronic hepatitis B: comparing pegylated interferon-alpha2b and lamivudine with lamivudine alone. *Ann Intern Med* 142:240–250
- Chang CC, Chen TT, Cox BW, Dawes GN, Stemmer WP, Punnonen J, Patten PA (1999) Evolution of a cytokine using DNA family shuffling. *Nat Biotechnol* 17:793–797
- Chen J, Baig E, Fish EN (2004) Diversity and relatedness among the type I interferons. *J Interferon Cytokine Res* 24:687–698
- Clemens MJ (2003) Interferons and apoptosis. *J Interferon Cytokine Res* 23:277–292
- Coccia EM, Krust B, Hovanessian AG (1994) Specific inhibition of viral protein synthesis in HIV-infected cells in response to interferon treatment. *J Biol Chem* 269:23087–23094
- Cooksley WG, Piratvisuth T, Lee SD, Mahachai V, Chao YC, Tanwandee T, Chutaputti A, Chang WY, Zahm FE, Pluck N (2003) Peginterferon alpha-2a (40kDa): an advance in the treatment of hepatitis B e antigen-positive chronic hepatitis B. *J Viral Hepat* 10:298–305
- Creagh EM, O'Neill LA (2006) TLRs, NLRs and RLRs: a trinity of pathogen sensors that cooperate in innate immunity. *Trends Immunol* 27:352–357
- Dash S, Prabhu R, Hazari S, Bastian F, Garry R, Zou W, Haque S, Joshi V, Regenstein FG, Thung SN (2005) Interferons alpha, beta, gamma each inhibit hepatitis C virus replication at the level of internal ribosome entry site-mediated translation. *Liver Int* 25:580–594
- de Franchis R, Hadengue A, Lau G, Lavanchy D, Lok A, McIntyre N, Mele A, Paumgartner G, Pietrangelo A, Rodes J, Rosenberg W, Valla D (2003) EASL International Consensus Conference on Hepatitis B. 13–14 September, 2002 Geneva, Switzerland. Consensus statement (long version). *J Hepatol* 39 Suppl 1:S3–S25
- De Rosa FG, Bargiacchi O, Audagnotto S, Garazzino S, Cariti G, Veronese L, Raiteri R, Calleri G, Di Perri G (2006) The early HCV RNA dynamics in patients with acute hepatitis C treated with pegylated interferon-alpha2b. *Antivir Ther* 11:165–171
- Di Bisceglie A (1997) Hepatitis D virus. Marcel Dekker, NY
- Di Bisceglie AM, Hoofnagle JH (2002) Optimal therapy of hepatitis C. *Hepatology* 36:S121–S127
- Dooley JS, Davis GL, Peters M, Waggoner JG, Goodman Z, Hoofnagle JH (1986) Pilot study of recombinant human alpha-interferon for chronic type B hepatitis. *Gastroenterology* 90:150–157
- Doyle SE, Schreckhise H, Khuu-Duong K, Henderson K, Rosler R, Storey H, Yao L, Liu H, Barahmand-pour F, Sivakumar P, Chan C, Birks C, Foster D, Clegg CH, Wietzke-Braun P, Mihm S, Klucher KM (2006) Interleukin-29 uses a type 1 interferon-like program to promote antiviral responses in human hepatocytes. *Hepatology* 44:896–906
- Dumoutier L, Lejeune D, Hor S, Fickenscher H, Renauld JC (2003) Cloning of a new type II cytokine receptor activating signal transducer and activator of transcription (STAT)1, STAT2 and STAT3. *Biochem J* 370:391–396
- Dumoutier L, Tounsi A, Michiels T, Sommereyns C, Kotenko SV, Renauld JC (2004) Role of the interleukin (IL)-28 receptor tyrosine residues for antiviral and antiproliferative activity of IL-29/interferon-lambda 1: similarities with type I interferon signaling. *J Biol Chem* 279:32269–32274
- Ealick SE, Cook WJ, Vijay-Kumar S, Carson M, Nagabhushan TL, Trotta PP, Bugg CE (1991) Three-dimensional structure of recombinant human interferon-gamma. *Science* 252:698–702
- Emilie D, Burgard M, Lascoux-Combe C, Laughlin M, Krzysiek R, Pignon C, Rudent A, Molina JM, Livrozet JM, Souala F, Chene G, Grangeot-Keros L, Galanaud P, Sereni D, Rouzioux C (2001) Early control of HIV replication in primary HIV-1 infection treated with antiretroviral drugs and pegylated IFN alpha: results from the Primoferon A (ANRS 086) Study. *AIDS* 15:1435–1437
- Enomoto M, Tamori A, Kohmoto MT, Hayashi T, Jomura H, Habu D, Sakaguchi H, Takeda T, Kawada N, Seki S, Shiomi S, Koh N, Nishiguchi S (2007) Lamivudine and IFN-beta sequential therapy in HBe antigen-positive patients with chronic hepatitis B virus genotype C infection. *J Interferon Cytokine Res* 27:201–207
- Erhardt A, Gerlich W, Starke C, Wend U, Donner A, Sagir A, Heintges T, Haussinger D (2006) Treatment of chronic hepatitis delta with pegylated interferon-alpha2b. *Liver Int* 26:805–810

- Farci P, Mandas A, Coiana A, Lai ME, Desmet V, Van Eyken P, Gibo Y, Caruso L, Scaccabarozzi S, Criscuolo D et al (1994) Treatment of chronic hepatitis D with interferon alfa-2a. *N Engl J Med* 330:88–94
- Farci P, Roskams T, Chessa L, Peddis G, Mazzoleni AP, Scioscia R, Serra G, Lai ME, Loy M, Caruso L, Desmet V, Purcell RH, Balestrieri A (2004) Long-term benefit of interferon alpha therapy of chronic hepatitis D: regression of advanced hepatic fibrosis. *Gastroenterology* 126:1740–1749
- Fattovich G, Giustina G, Sanchez-Tapias J, Quero C, Mas A, Olivotto PG, Solinas A, Almasio P, Hadziyannis S, Degos F, de Moura MC, Krogsgaard K, Pantalena M, Realdi G, Corrocher R, Schalm SW (1998) Delayed clearance of serum HBsAg in compensated cirrhosis B: relation to interferon alpha therapy and disease prognosis. *Am J Gastroenterol* 93:896–900
- Fattovich G, Giustina G, Christensen E, Pantalena M, Zagni I, Realdi G, Schalm SW (2000) Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B. *Gut* 46:420–426
- Fernandez-Cruz E, Lang JM, Frissen J, Furner V, Chateauvert M, Boucher CA, Dowd P, Stevens J (1995) Zidovudine plus interferon-alpha versus zidovudine alone in HIV-infected symptomatic or asymptomatic persons with CD4+ cell counts > 150 × 10(6)/L: results of the Zidon trial. *AIDS* 9:1025–1035
- Fernie BF, Poli G, Fauci AS (1991) Alpha interferon suppresses virion but not soluble human immunodeficiency virus antigen production in chronically infected T-lymphocytic cells. *J Virol* 65:3968–3971
- Fischl MA, Richman DD, Saag M, Meng TC, Squires KE, Holden-Wiltse J, Meehan PM (1997) Safety and antiviral activity of combination therapy with zidovudine, zalcitabine, and two doses of interferon-alpha2a in patients with HIV. *J Acquir Immune Defic Syndr Hum Retrovirol* 16:247–253
- Flink HJ, Hansen BE, Heathcote EJ, Feinman SV, Simsek H, Karayalcin S, Mach T, Leemans WF, de Man RA, Verhey E, Schalm SW, Janssen HL (2006a) Successful treatment with peginterferon alfa-2b of HBeAg-positive HBV non-responders to standard interferon or lamivudine. *Am J Gastroenterol* 101:2523–2529
- Flink HJ, van Zonneveld M, Hansen BE, de Man RA, Schalm SW, Janssen HL (2006b) Treatment with Peg-interferon alpha-2b for HBeAg-positive chronic hepatitis B: HBsAg loss is associated with HBV genotype. *Am J Gastroenterol* 101:297–303
- Frese M, Schwarzle V, Barth K, Krieger N, Lohmann V, Mihm S, Haller O, Bartenschlager R (2002) Interferon-gamma inhibits replication of subgenomic and genomic hepatitis C virus RNAs. *Hepatology* 35:694–703
- Fried M, Jensen D, Rodriguez-Torres M, Nyberg L, Di Bisceglie A, Morgan T, Pockros PJ, Lin A, Cupelli L, Nelson D (2006) Improved sustained virological response (SVR) rates with higher, fixed doses of peginterferon alfa-2a (40 kD) (Pegasys) plus ribavirin (RBV) (Copegus) in patients with “difficult-to-treat” characteristics. *Hepatology* 44 Suppl 1:314A
- Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncalves FL Jr, Haussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J (2002) Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 347:975–982
- Gack MU, Shin YC, Joo CH, Urano T, Liang C, Sun L, Takeuchi O, Akira S, Chen Z, Inoue S, Jung JU (2007) TRIM25 RING-finger E3 ubiquitin ligase is essential for RIG-I-mediated antiviral activity. *Nature* 446:916–920
- Gaeta GB, Stroffolini T, Chiaramonte M, Ascione T, Stornaiuolo G, Lobello S, Sagnelli E, Brunetto MR, Rizzetto M (2000) Chronic hepatitis D: a vanishing disease? An Italian multicenter study. *Hepatology* 32:824–827
- Gale M Jr, Foy EM (2005) Evasion of intracellular host defence by hepatitis C virus. *Nature* 436:939–945
- Garripoli A, Di Marco V, Cozzolongo R, Costa C, Smedile A, Fabiano A, Bonino F, Rizzetto M, Verme G, Craxi A et al (1994) Ribavirin treatment for chronic hepatitis D: a pilot study. *Liver* 14:154–157

- Gattoni A, Parlato A, Vangieri B, Bresciani M, Derna R (2006a) Interferon-gamma: biologic functions and HCV therapy (type I/II) (1 of 2 parts). *Clin Ter* 157:377–386
- Gattoni A, Parlato A, Vangieri B, Bresciani M, Derna R (2006b) Interferon-gamma: biologic functions and HCV therapy (type I/II) (2 of 2 parts). *Clin Ter* 157:457–468
- Gaudin JL, Faure P, Godinot H, Gerard F, Trepo C (1995) The French experience of treatment of chronic type D hepatitis with a 12-month course of interferon alpha-2B. Results of a randomized controlled trial. *Liver* 15:45–52
- Gendelman HE, Baca LM, Turpin J, Kalter DC, Hansen B, Orenstein JM, Dieffenbach CW, Friedman RM, Meltzer MS (1990) Regulation of HIV replication in infected monocytes by IFN-alpha. Mechanisms for viral restriction. *J Immunol* 145:2669–26676
- Giovannini M, Zuccotti GV, Biasucci G, Locatelli V, Riva E (1992) Combined zidovudine and interferon-alpha 2a therapy in children with acquired immune deficiency syndrome. *J Int Med Res* 20:295–301
- Gorbakov VV, Kim H, Oronsky B, Lang W (2005) HCV RNA results from a Phase II, randomized, open-labeled study of omega interferon (IFN) with or without ribavirin in IFN-naive genotype 1 chronic HCV patients. *Hepatology* 42:705A
- Gough DJ, Sabapathy K, Ko EY, Arthur HA, Schreiber RD, Trapani JA, Clarke CJ, Johnstone RW (2007) A novel c-Jun-dependent signal transduction pathway necessary for the transcriptional activation of interferon gamma response genes. *J Biol Chem* 282:938–946
- Guidotti LG, Chisari FV (2001) Noncytolytic control of viral infections by the innate and adaptive immune response. *Annu Rev Immunol* 19:65–91
- Gunsar F, Akarca US, Ersoz G, Kobak AC, Karasu Z, Yuce G, Ilter T, Batur Y (2005) Two-year interferon therapy with or without ribavirin in chronic delta hepatitis. *Antivir Ther* 10:721–726
- Habersetzer F, Boyer N, Marcellin P, Bailly F, Ahmed SN, Alam J, Benhamou JP, Trepo C (2000) A pilot study of recombinant interferon beta-1a for the treatment of chronic hepatitis C. *Liver* 20:437–441
- Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, Ramadori G, Bodenheimer H Jr, Bernstein D, Rizzetto M, Zeuzem S, Pockros PJ, Lin A, Ackrill AM (2004) Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 140:346–355
- Hansen BD, Nara PL, Maheshwari RK, Sidhu GS, Bernbaum JG, Hoekzema D, Meltzer MS, Gendelman HE (1992) Loss of infectivity by progeny virus from alpha interferon-treated human immunodeficiency virus type 1-infected T cells is associated with defective assembly of envelope gp120. *J Virol* 66:7543–7548
- Hayden MS, West AP, Ghosh S (2006) NF-kappaB and the immune response. *Oncogene* 25:6758–6780
- Hezode C, Bouvier-Alias M, Roudot-Thoraval F, Zafrani S, Dhumeaux D, Mallat A, Pawlotsky JM (2006) Efficacy and safety of peginterferon alpha-2a administered every five days in combination with ribavirin in HCV genotype 1-infected patients with severe fibrosis not responding to weekly administrations of peginterferon in combination with ribavirin. *Hepatology* 44:322A
- Ho DD, Hartshorn KL, Rota TR, Andrews CA, Kaplan JC, Schooley RT, Hirsch MS (1985) Recombinant human interferon alfa-A suppresses HTLV-III replication in vitro. *Lancet* 1:602–604
- Hodson EM, Jones CA, Strippoli GF, Webster AC, Craig JC (2007) Immunoglobulins, vaccines or interferon for preventing cytomegalovirus disease in solid organ transplant recipients. *Cochrane Database Syst Rev* CD005129
- Honda K, Yanai H, Negishi H, Asagiri M, Sato M, Mizutani T, Shimada N, Ohba Y, Takaoka A, Yoshida N, Taniguchi T (2005) IRF-7 is the master regulator of type-I interferon-dependent immune responses. *Nature* 434:772–777
- Hong SH, Cho O, Kim K, Shin HJ, Kotenko SV, Park S (2007) Effect of interferon-lambda on replication of hepatitis B virus in human hepatoma cells. *Virus Res* 126:245–249
- Hoofnagle JH, Mullen KD, Jones DB, Rustgi V, Di Bisceglie A, Peters M, Waggoner JG, Park Y, Jones EA (1986) Treatment of chronic non-A, non-B hepatitis with recombinant human alpha interferon. A preliminary report. *N Engl J Med* 315:1575–1578
- Horiike N, Onji M (2003) Combination therapy with interferon-alpha and ribavirin as immunomodulators in patients with chronic hepatitis C. *J Gastroenterol* 38:302–304

- Hui CK, Lai LS, Lam P, Zhang HY, Fung TT, Lai ST, Wong WM, Lo CM, Fan ST, Leung N, Lau GK (2006) 48 weeks pegylated interferon alpha-2a is superior to 24 weeks of pegylated interferon alpha-2b in achieving hepatitis B e antigen seroconversion in chronic hepatitis B infection. *Aliment Pharmacol Ther* 23:1171–1178
- Isaacs A, Lindenmann J (1957) Virus interference. I. The interferon. *Proc R Soc Lond B Biol Sci* 147:258–267
- Isomura S, Ichikawa T, Miyazu M, Naruse H, Shibata M, Imanishi J, Matsuo A, Kishida T, Karaki T (1982) The preventive effect of human interferon-alpha on influenza infection; modification of clinical manifestations of influenza in children in a closed community. *Biken J* 25:131–137
- Jacobson IM, Brown RS, Freilich B, Afdhal N, Kwo P, Santoro J, Becker S, Wakil A, Pound D, Godofsky E, Staruss R, Bernstein D, Flamm S, Bala N, Araya V, Davis M, Monsour H, Vierling J, Regenstien F, Balan V, Dragutsky M, Epstein M, Herring RW, Rubin R, Galler G, Pauly MP, Griffel LH, Brass CA (2005) Weight-based ribavirin dosing (WBD) increases sustained viral response (SVR) in patients with chronic hepatitis C (CHC): final results of the WIN-R study, a US community-based trial. *Hepatology* 42 Suppl 1:749A
- Jaeckel E, Cornberg M, Wedemeyer H, Santantonio T, Mayer J, Zankel M, Pastore G, Dietrich M, Trautwein C, Manns MP (2001) Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med* 345:1452–1457
- Jang MK, Chung YH, Choi MH, Kim JA, Ryu SH, Shin JW, Kim IS, Park NH, Lee HC, Lee YS, Suh DJ (2004) Combination of alpha-interferon with lamivudine reduces viral breakthrough during long-term therapy. *J Gastroenterol Hepatol* 19:1363–1368
- Janssen HL, van Zonneveld M, Senturk H, Zeuzem S, Akarca US, Cakaloglu Y, Simon C, So TM, Gerken G, de Man RA, Niesters HG, Zondervan P, Hansen B, Schalm SW (2005) Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. *Lancet* 365:123–129
- Jen J, Laughlin M, Chung C, Heft S, Affrime MB, Gupta SK, Glue P, Hajian G (2002) Ribavirin dosing in chronic hepatitis C: application of population pharmacokinetic-pharmacodynamic models. *Clin Pharmacol Ther* 72:349–361
- Jen JF, Glue P, Gupta S, Zambas D, Hajian G (2000) Population pharmacokinetic and pharmacodynamic analysis of ribavirin in patients with chronic hepatitis C. *Ther Drug Monit* 22:555–565
- Jensen DM, Morgan TR, Marcellin P, Pockros PJ, Reddy KR, Hadziyannis SJ, Ferenci P, Ackrill AM, Willems B (2006) Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon alpha-2a (40 kd)/ribavirin therapy. *Hepatology* 43:954–960
- Kagawa T, Morizane T, Saito H, Tsunematsu S, Tada S, Kumagai N, Tsuchimoto K, Sugiura H, Mukai M, Tsuchiya M (1993) A pilot study of long-term weekly interferon-beta administration for chronic hepatitis B. *Am J Gastroenterol* 88:212–216
- Kalil AC, Devetten MP, Singh S, Lesiak B, Poage DP, Bargaquast K, Fayad P, Freifeld AG (2005) Use of interferon-alpha in patients with West Nile encephalitis: report of 2 cases. *Clin Infect Dis* 40:764–766
- Kato H, Sato S, Yoneyama M, Yamamoto M, Uematsu S, Matsui K, Tsujimura T, Takeda K, Fujita T, Takeuchi O, Akira S (2005) Cell type-specific involvement of RIG-I in antiviral response. *Immunity* 23:19–28
- Kaymakoglu S, Karaca C, Demir K, Poturoglu S, Danalioglu A, Badur S, Bozaci M, Besisik F, Cakaloglu Y, Okten A (2005) Alpha interferon and ribavirin combination therapy of chronic hepatitis D. *Antimicrob Agents Chemother* 49:1135–1138
- Kaymakoglu S, Danalioglu A, Demir K, Karaca C, Akyuz F, Onel D, Badur S, Cevikbas U, Besisik F, Cakaloglu Y, Okten A (2007a) Long-term results of interferon alpha monotherapy in patients with HBeAg-negative chronic hepatitis B. *Dig Dis Sci* 52:727–731
- Kaymakoglu S, Oguz D, Gur G, Gurel S, Tankurt E, Ersoz G, Ozenirler S, Kalayci C, Poturoglu S, Cakaloglu Y, Okten A (2007b) Pegylated interferon alfa-2b monotherapy and pegylated interferon alfa-2b plus lamivudine combination therapy for patients with hepatitis B virus E antigen-negative chronic hepatitis B. *Antimicrob Agents Chemother* 51:3020–3022
- Keefe EB, Hollinger FB (1997) Therapy of hepatitis C: consensus interferon trials. *Hepatology* 26:101S–107S

- Keeffe EB, Dieterich DT, Han SH, Jacobson IM, Martin P, Schiff ER, Tobias H, Wright TL (2006) A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: an update. *Clin Gastroenterol Hepatol* 4:936–962
- Kim KI, Sasase N, Taniguchi M, Mita K, Kinoshita K, Togitani T, Shikata M, Kimura N, Izawa S, Ohtani A, Nakao K, Muramoto Y, Kim SR, Nabeshima S, Ishii F, Tanaka K, Hayashi Y (2005) Interferon-beta induction/interferon-alpha2b plus ribavirin therapy in patients with chronic hepatitis C. *Int J Clin Pharmacol Res* 25:71–76
- Kozlowski A, Charles SA, Harris JM (2001) Development of pegylated interferons for the treatment of chronic hepatitis C. *BioDrugs* 15:419–429
- Krown SE, Aeppli D, Balfour HH Jr (1999) Phase II, randomized, open-label, community-based trial to compare the safety and activity of combination therapy with recombinant interferon-alpha2b and zidovudine versus zidovudine alone in patients with asymptomatic to mildly symptomatic HIV infection. *J Acquir Immune Defic Syndr Hum Retrovirol* 20:245–254
- LaFleur DW, Nardelli B, Tsareva T, Mather D, Feng P, Semenuk M, Taylor K, Buergin M, Chinchilla D, Roshke V, Chen G, Ruben SM, Pitha PM, Coleman TA, Moore PA (2001) Interferon-kappa, a novel type I interferon expressed in human keratinocytes. *J Biol Chem* 276:39765–39771
- Lampertico P, Del Ninno E, Manzin A, Donato MF, Rumi MG, Lunghi G, Morabito A, Clementi M, Colombo M (1997) A randomized, controlled trial of a 24-month course of interferon alfa 2b in patients with chronic hepatitis B who had hepatitis B virus DNA without hepatitis B e antigen in serum. *Hepatology* 26:1621–1625
- Lampertico P, Del Ninno E, Vigano M, Romeo R, Donato MF, Sablon E, Morabito A, Colombo M (2003) Long-term suppression of hepatitis B e antigen-negative chronic hepatitis B by 24-month interferon therapy. *Hepatology* 37:756–763
- Lane HC (1994) Interferons in HIV and related diseases. *AIDS* 8 Suppl 3:S19–S23
- Lanford RE, Guerra B, Lee H, Averett DR, Pfeiffer B, Chavez D, Notvall L, Bigger C (2003) Antiviral effect and virus-host interactions in response to alpha interferon, gamma interferon, poly(i)-poly(c), tumor necrosis factor alpha, and ribavirin in hepatitis C virus subgenomic replicons. *J Virol* 77:1092–1104
- Lau DT, Everhart J, Kleiner DE, Park Y, Vergalla J, Schmid P, Hoofnagle JH (1997) Long-term follow-up of patients with chronic hepatitis B treated with interferon alfa. *Gastroenterology* 113:1660–1667
- Lau DT, Kleiner DE, Ghany MG, Park Y, Schmid P, Hoofnagle JH (1998) 10-Year follow-up after interferon-alpha therapy for chronic hepatitis C. *Hepatology* 28:1121–1127
- Lau DT, Doo E, Park Y, Kleiner DE, Schmid P, Kuhns MC, Hoofnagle JH (1999a) Lamivudine for chronic delta hepatitis. *Hepatology* 30:546–549
- Lau DT, Kleiner DE, Park Y, Di Bisceglie AM, Hoofnagle JH (1999b) Resolution of chronic delta hepatitis after 12 years of interferon alfa therapy. *Gastroenterology* 117:1229–1233
- Lau GK, Piratvisuth T, Luo KX, Marcellin P, Thongsawat S, Cooksley G, Gane E, Fried MW, Chow WC, Paik SW, Chang WY, Berg T, Flisiak R, McCloud P, Pluck N (2005) Peginterferon alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med* 352:2682–2695
- Leemans WF, Flink HJ, Janssen HL, Niesters HG, Schalm SW, de Man RA (2006) The effect of pegylated interferon-alpha on the treatment of lamivudine resistant chronic HBeAg positive hepatitis B virus infection. *J Hepatol* 44:507–511
- Lewis M, Amsden JR (2007) Successful treatment of West Nile virus infection after approximately 3 weeks into the disease course. *Pharmacotherapy* 27:455–458
- Liaw YF, Leung N, Guan R, Lau GK, Merican I, McCaughan G, Gane E, Kao JH, Omata M (2005) Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2005 update. *Liver Int* 25:472–489
- Lin SM, Yu ML, Lee CM, Chien RN, Sheen IS, Chu CM, Liaw YF (2007) Interferon therapy in HBeAg positive chronic hepatitis reduces progression to cirrhosis and hepatocellular carcinoma. *J Hepatol* 46:45–52

- Lindahl K, Stahle L, Bruchfeld A, Schvarcz R (2005) High-dose ribavirin in combination with standard dose peginterferon for treatment of patients with chronic hepatitis C. *Hepatology* 41:275–279
- Lindsay KL, Trepo C, Heintges T, Shiffman ML, Gordon SC, Hoefs JC, Schiff ER, Goodman ZD, Laughlin M, Yao R, Albrecht JK (2001) A randomized, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C. *Hepatology* 34:395–403
- Lok AS, McMahon BJ (2007) Chronic hepatitis B. *Hepatology* 45:507–539
- Lok AS, Chung HT, Liu VW, Ma OC (1993) Long-term follow-up of chronic hepatitis B patients treated with interferon alfa. *Gastroenterology* 105:1833–1838
- Madejon A, Cotonat T, Bartolome J, Castillo I, Carreno V (1994) Treatment of chronic hepatitis D virus infection with low and high doses of interferon-alpha 2a: utility of polymerase chain reaction in monitoring antiviral response. *Hepatology* 19:1331–1336
- Manesis EK, Hadziyannis SJ (2001) Interferon alpha treatment and retreatment of hepatitis B e antigen-negative chronic hepatitis B. *Gastroenterology* 121:101–109
- Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK (2001) Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 358:958–965
- Marcellin P, Lau GK, Bonino F, Farci P, Hadziyannis S, Jin R, Lu ZM, Piratvisuth T, Germanidis G, Yurdaydin C, Diago M, Gurel S, Lai MY, Button P, Pluck N (2004) Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 351:1206–1217
- Marcello T, Grakoui A, Barba-Spaeth G, Machlin ES, Kotenko SV, MacDonald MR, Rice CM (2006) Interferons alpha and lambda inhibit hepatitis C virus replication with distinct signal transduction and gene regulation kinetics. *Gastroenterology* 131:1887–1898
- Martal JL, Chene NM, Huynh LP, L'Haridon RM, Reinaud PB, Guillomot MW, Charlier MA, Charpigny SY (1998) IFN-tau: a novel subtype I IFN1. Structural characteristics, non-ubiquitous expression, structure-function relationships, a pregnancy hormonal embryonic signal and cross-species therapeutic potentialities. *Biochimie* 80:755–777
- McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, Goodman ZD, Ling MH, Cort S, Albrecht JK (1998) Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. *N Engl J Med* 339:1485–1492
- McHutchison JG, Shiffman ML, Gordon SC, Lindsay KL, Morgan T, Norkrans G, Esteban-Mur R, Poynard T, Pockros PJ, Albrecht JK, Brass C (2006) Sustained virologic response (SVR) to interferon-alpha-2b +/- ribavirin therapy at 6 months reliably predicts long-term clearance of HCV at 5-year follow-up. *J Hepatol* 44 Suppl 2:S275
- McHutchison JG, Everson GT, Gordon S, Jacobson I, Kauffman R, McNair L, Muir AJ (2007a) Results of an interim analysis of a Phase II study of telaprevir (VX-950) with peginterferon alfa-2a and ribavirin in previously untreated subjects with hepatitis C. *J Hepatol* 46:S296
- McHutchison JG, Manns MP, Brown RS Jr, Reddy KR, Shiffman ML, Wong JB (2007b) Strategies for managing anemia in hepatitis C patients undergoing antiviral therapy. *Am J Gastroenterol* 102:880–889
- Miglioresi L, Bacosi M, Russo F, Patrizi F, Saccetti P, Ursitti A, Angelis AD, Ricci GL (2003) Consensus interferon versus interferon-alpha 2b plus ribavirin in patients with relapsing HCV infection. *Hepatology* 37:253–259
- Montalto G, Tripi S, Cartabellotta A, Fulco M, Soresi M, Di Gaetano G, Carroccio A, Levrero M (1998) Intravenous natural beta-interferon in white patients with chronic hepatitis C who are nonresponders to alpha-interferon. *Am J Gastroenterol* 93:950–953
- Moskovitz DN, Manoharan P, Heathcote EJ (2003) High dose consensus interferon in nonresponders to interferon alpha-2b and ribavirin with chronic hepatitis C. *Can J Gastroenterol* 17:479–482
- Munoz R, Castellano G, Fernandez I, Alvarez MV, Manzano ML, Marcos MS, Cuenca B, Solis-Herruzo JA (2002) A pilot study of beta-interferon for treatment of patients with chronic hepatitis B who failed to respond to alpha-interferon. *J Hepatol* 37:655–659

- Nagata S, Taira H, Hall A, Johnsrud L, Streuli M, Ecsodi J, Boll W, Cantell K, Weissmann C (1980) Synthesis in *E. coli* of a polypeptide with human leukocyte interferon activity. *Nature* 284:316–320
- Nakajima H, Shimomura H, Iwasaki Y, Ikeda F, Umeoka F, Chengyu P, Taniguchi H, Ohnishi Y, Takagi SJ, Fujioka S, Shiratori Y (2003) Anti-viral actions and viral dynamics in the early phase of three different regimens of interferon treatment for chronic hepatitis C: differences between the twice-daily administration of interferon-beta treatment and the combination therapy with interferon-alpha plus ribavirin. *Acta Med Okayama* 57:217–225
- Neumann A, Polis M, Rozenberg L, Jackson J, Reitano K, McLaughlin M, Koratich C, Dewar R, Masur H, Haagmans B, Kottlilil S (2007) Differential antiviral effect of PEG-interferon-alpha-2b on HIV and HCV in the treatment of HIV/HCV co-infected patients. *AIDS* 21:1855–1865
- Niederau C, Heintges T, Lange S, Goldmann G, Niederau CM, Mohr L, Haussinger D (1996) Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. *N Engl J Med* 334:1422–1427
- Niro GA, Ciancio A, Tillman HL, Lagget M, Olivero A, Perri F, Fontana R, Little N, Campbell F, Smedile A, Manns MP, Andriulli A, Rizzetto M (2005a) Lamivudine therapy in chronic delta hepatitis: a multicentre randomized-controlled pilot study. *Aliment Pharmacol Ther* 22:227–232
- Niro GA, Rosina F, Rizzetto M (2005b) Treatment of hepatitis D. *J Viral Hepat* 12:2–9
- Niro GA, Ciancio A, Gaeta GB, Smedile A, Marrone A, Olivero A, Stanzone M, David E, Braccaccio G, Fontana R, Perri F, Andriulli A, Rizzetto M (2006) Pegylated interferon alpha-2b as monotherapy or in combination with ribavirin in chronic hepatitis delta. *Hepatology* 44:713–720
- Novozhenov V, Zakharova N, Vinogradova E, Nikitin I, Gorbakov VV, Yakovlev A, Pak S, Rafalski V, Bogomolov P, Alessi T, Blanchett D, Lang W, Langecker P, McNally J, McHutchison JG (2007) Phase 2 study of omega interferon alone or in combination with ribavirin in subjects with chronic hepatitis C genotype-1 infection. *J Hepatol* 46:S8
- Onoguchi K, Yoneyama M, Takemura A, Akira S, Taniguchi T, Namiki H, Fujita T (2007) Viral infections activate types I and III interferon genes through a common mechanism. *J Biol Chem* 282:7576–7581
- Osborn BL, Olsen HS, Nardelli B, Murray JH, Zhou JX, Garcia A, Moody G, Zaritskaya LS, Sung C (2002) Pharmacokinetic and pharmacodynamic studies of a human serum albumin-interferon-alpha fusion protein in cynomolgus monkeys. *J Pharmacol Exp Ther* 303:540–548
- Ozes ON, Reiter Z, Klein S, Blatt LM, Taylor MW (1992) A comparison of interferon-Con1 with natural recombinant interferons-alpha: antiviral, antiproliferative, and natural killer-inducing activities. *J Interferon Res* 12:55–59
- Papatheodoridis GV, Manesis E, Hadziyannis SJ (2001) The long-term outcome of interferon-alpha treated and untreated patients with HBeAg-negative chronic hepatitis B. *J Hepatol* 34:306–313
- Parvez MK, Sehgal D, Sarin SK, Basir SF, Jameel S (2006) Inhibition of hepatitis B virus DNA replicative intermediate forms by recombinant interferon-gamma. *World J Gastroenterol* 12:3006–3014
- Pastore G, Santantonio T, Milella M, Monno L, Mariano N, Moschetta R, Pollice L (1992) Anti-HBe-positive chronic hepatitis B with HBV-DNA in the serum response to a 6-month course of lymphoblastoid interferon. *J Hepatol* 14:221–225
- Pawlotsky JM (2006) Therapy of hepatitis C: from empiricism to eradication. *Hepatology* 43:S207–S220
- Pawlotsky JM, Chevaliez S, McHutchison JG (2007) The hepatitis C virus life cycle as a target for new antiviral therapies. *Gastroenterology* 132:1979–1998
- Pawlotsky JM, Dahari H, Neumann AU, Hezode C, Germanidis G, Lonjon I, Castera L, Dhumeaux D (2004) Antiviral action of ribavirin in chronic hepatitis C. *Gastroenterology* 126:703–714
- Pedersen IM, Cheng G, Wieland S, Volinia S, Croce CM, Chisari FV, David M (2007) Interferon modulation of cellular microRNAs as an antiviral mechanism. *Nature* 449:919–922
- Pestka S, Langer JA, Zoon KC, Samuel CE (1987) Interferons and their actions. *Annu Rev Biochem* 56:727–777

- Pestka S, Krause CD, Walter MR (2004) Interferons, interferon-like cytokines, and their receptors. *Immunol Rev* 202:8–32
- Peters M, Walling DM, Kelly K, Davis GL, Waggoner JG, Hoofnagle JH (1986) Immunologic effects of interferon-alpha in man: treatment with human recombinant interferon-alpha suppresses in vitro immunoglobulin production in patients with chronic type B hepatitis. *J Immunol* 137:3147–3152
- Phillipotts RJ, Higgins PG, Willman JS, Tyrrell DA, Freestone DS, Shepherd WM (1984) Intranasal lymphoblastoid interferon (“Wellferon”) prophylaxis against rhinovirus and influenza virus in volunteers. *J Interferon Res* 4:535–541
- Plauth MM, Meisel H, Langecker P, Moran M, Lang W, Blanchett D, Jetschmann JU, Brack J, von Wussow P (2002) Open-labeled study of omega interferon in previously untreated HCV-infected patients. In: Proceedings of the 37th annual meeting EASL
- Poli G, Orenstein JM, Kinter A, Folks TM, Fauci AS (1989) Interferon-alpha but not AZT suppresses HIV expression in chronically infected cell lines. *Science* 244:575–577
- Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G, Bain V, Heathcote J, Zeuzem S, Trepo C, Albrecht J (1998) Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. *Lancet* 352:1426–1432
- Rahal JJ, Anderson J, Rosenberg C, Reagan T, Thompson LL (2004) Effect of interferon-alpha2b therapy on St. Louis viral meningoencephalitis: clinical and laboratory results of a pilot study. *J Infect Dis* 190:1084–1087
- Rodriguez-Torres M, Lawitz E, Muir AJ, Keane J, Kieffer TL, McNair L, McHutchison JG (2006) Current status of subjects receiving peginterferon alfa-2a (PEG-IFN) and ribavirin (RBV) follow-on therapy after 28-day treatment with the hepatitis C protease inhibitor telaprevir (VX-950), PEG-IFN and RBV. *Hepatology* 44 Suppl 2:532A
- Rosina F, Pintus C, Meschievitz C, Rizzetto M (1991) A randomized controlled trial of a 12-month course of recombinant human interferon-alpha in chronic delta (type D) hepatitis: a multicenter Italian study. *Hepatology* 13:1052–1056
- Sainz B Jr, Mossel EC, Peters CJ, Garry RF (2004) Interferon-beta and interferon-gamma synergistically inhibit the replication of severe acute respiratory syndrome-associated coronavirus (SARS-CoV). *Virology* 329:11–17
- Santantonio T, Niro GA, Sinisi E, Leandro G, Insalata M, Guastadisegni A, Facciorusso D, Gravinese E, Andriulli A, Pastore G (2002) Lamivudine/interferon combination therapy in anti-HBe positive chronic hepatitis B patients: a controlled pilot study. *J Hepatol* 36:799–804
- Santantonio T, Fasano M, Sinisi E, Guastadisegni A, Casalino C, Mazzola M, Francavilla R, Pastore G (2005) Efficacy of a 24-week course of PEG-interferon alpha-2b monotherapy in patients with acute hepatitis C after failure of spontaneous clearance. *J Hepatol* 42:329–333
- Saracco G, Rosina F, Brunetto MR, Amoroso P, Caredda F, Farci P, Piantino P, Bonino F, Rizzetto M (1987) Rapidly progressive HBsAg-positive hepatitis in Italy. The role of hepatitis delta virus infection. *J Hepatol* 5:274–281
- Sarin SK, Kumar M, Kumar R, Kazim SN, Guptan RC, Sakhuja P, Sharma BC (2005) Higher efficacy of sequential therapy with interferon-alpha and lamivudine combination compared to lamivudine monotherapy in HBeAg positive chronic hepatitis B patients. *Am J Gastroenterol* 100:2463–2471
- Sarin SK, Sood A, Kumar M, Arora A, Amrapurkar D, Sharma BC, Konar A, Chawla YK, Jain RK, Nanda V, Kumar A, Hissar S, Lavate P, Lahoti D (2007) Effect of lowering HBV DNA levels by initial antiviral therapy before adding immunomodulator on treatment of chronic hepatitis B. *Am J Gastroenterol* 102:96–104
- Sarrazin C, Kieffer TL, Bartels D, Hanzelka B, Muh U, Welker M, Wincheringer D, Zhou Y, Chu HM, Lin C, Weegink CJ, Reesink HW, Zeuzem S, Kwong AD (2007) Dynamic HCV genotypic and phenotypic changes in patients treated with the protease inhibitor telaprevir (VX-950). *Gastroenterology* 132:1767–1777

- Scagnolari C, Vicenzi E, Bellomi F, Stillitano MG, Pinna D, Poli G, Clementi M, Dianzani F, Antonelli G (2004) Increased sensitivity of SARS-coronavirus to a combination of human type I and type II interferons. *Antivir Ther* 9:1003–1011
- Seth RB, Sun L, Chen ZJ (2006) Antiviral innate immunity pathways. *Cell Res* 16:141–147
- Sheppard P, Kindsvogel W, Xu W, Henderson K, Schlutsmeyer S, Whitmore TE, Kuestner R, Garrigues U, Birks C, Roraback J, Ostrander C, Dong D, Shin J, Presnell S, Fox B, Haldeman B, Cooper E, Taft D, Gilbert T, Grant FJ, Tackett M, Krivan W, McKnight G, Clegg C, Foster D, Klucher KM (2003) IL-28, IL-29 and their class II cytokine receptor IL-28R. *Nat Immunol* 4:63–68
- Shi M, Wang RS, Zhang H, Zhu YF, Han B, Zhang Y, Jin LJ, Yang ZJ, Xu YP (2006) Sequential treatment with lamivudine and interferon-alpha monotherapies in hepatitis B e antigen-negative Chinese patients and its suppression of lamivudine-resistant mutations. *J Antimicrob Chemother* 58:1031–1035
- Shiratori Y, Nakata R, Shimizu N, Katada H, Hisamitsu S, Yasuda E, Matsumura M, Narita T, Kawada K, Omata M (2000) High viral eradication with a daily 12-week natural interferon-beta treatment regimen in chronic hepatitis C patients with low viral load. *Dig Dis Sci* 45:2414–2421
- Sidwell RW, Huffman JH, Khare GP, Allen LB, Witkowski JT, Robins RK (1972) Broad-spectrum antiviral activity of Virazole: 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide. *Science* 177:705–706
- Sjogren MH, Sjogren R Jr, Lyons MF, Ryan M, Santoro J, Smith C, Reddy KR, Bonkovsky H, Huntley B, Faris-Young S (2007) Antiviral response of HCV genotype 1 to consensus interferon and ribavirin versus pegylated interferon and ribavirin. *Dig Dis Sci* 52:1540–1547
- Snoeck E, Wade JR, Duff F, Lamb M, Jorga K (2006) Predicting sustained virological response and anaemia in chronic hepatitis C patients treated with peginterferon alfa-2a (40KD) plus ribavirin. *Br J Clin Pharmacol* 62:699–709
- Solis M, Goubau D, Romieu-Mourez R, Genin P, Civas A, Hiscott J (2006) Distinct functions of IRF-3 and IRF-7 in IFN-alpha gene regulation and control of anti-tumor activity in primary macrophages. *Biochem Pharmacol* 72:1469–1476
- Solomon T, Dung NM, Wills B, Kneen R, Gainsborough M, Diet TV, Thuy TT, Loan HT, Khanh VC, Vaughn DW, White NJ, Farrar JJ (2003) Interferon alfa-2a in Japanese encephalitis: a randomised double-blind placebo-controlled trial. *Lancet* 361:821–826
- Soza A, Heller T, Ghany M, Lutchman G, Jake Liang T, Germain J, Hsu HH, Park Y, Hoofnagle JH (2005) Pilot study of interferon gamma for chronic hepatitis C. *J Hepatol* 43:67–71
- Swain MG, Lai MY, Shiffman ML, Cooksley WGE, Abergel A, Lin A, Connell E, Diago M (2007) Durable sustained virological response after treatment with peginterferon alfa-2a (Pegasys) alone or in combination with ribavirin (Copegus): 5-year follow-up and the criteria for a cure. *J Hepatol* 46 Suppl 1:S3
- Takaoka A, Yanai H (2006) Interferon signalling network in innate defence. *Cell Microbiol* 8:907–922
- Uematsu S, Akira S (2007) Toll-like receptors and type I interferons. *J Biol Chem* 282:15319–15323
- Uze G, Monneron D (2007) IL-28 and IL-29: newcomers to the interferon family. *Biochimie* 89:729–734
- van der Ende M, Mulder JW, van den Berge M, Blok W, Schutten M (2007) Complete clinical and virological remission of refractory HIV-related Kaposi's sarcoma with pegylated interferon alfa. *AIDS* 21:1661–1662
- van Zonneveld M, Honkoop P, Hansen BE, Niesters HG, Murad SD, de Man RA, Schalm SW, Janssen HL (2004) Long-term follow-up of alpha-interferon treatment of patients with chronic hepatitis B. *Hepatology* 39:804–810
- van Zonneveld M, Zondervan PE, Cakaloglu Y, Simon C, Akarca US, So TM, Flink HJ, de Man RA, Schalm SW, Janssen HL (2006) Peg-interferon improves liver histology in patients with HBeAg-positive chronic hepatitis B: no additional benefit of combination with lamivudine. *Liver Int* 26:399–405

- Vassiliadis T, Tziomalos K, Patsiaoura K, Zagris T, Giouleme O, Soufleris K, Grammatikos N, Theodoropoulos K, Mpoumponaris A, Dona K, Zezos P, Nikolaidis N, Orfanou-Koumerkeridou E, Balaska A, Eugenidis N (2007) Lamivudine/pegylated interferon alpha-2b sequential combination therapy compared with lamivudine monotherapy in HBeAg-negative chronic hepatitis B. *J Gastroenterol Hepatol* 22:1582–1588
- Villa E, Trande P, Grottola A, Buttafoco P, Rebecchi AM, Stroffolini T, Callea F, Merighi A, Camellini L, Zoboli P, Cosenza R, Miglioli L, Loria P, Iori R, Carulli N, Manenti F (1996) Alpha but not beta interferon is useful in chronic active hepatitis due to hepatitis C virus. A prospective, double-blind, randomized study. *Dig Dis Sci* 41:1241–1247
- Villano SA, Raible D, Harper D, Speth J, Chandra P, Shaw P, Bichier G (2007) Antiviral activity of the non-nucleoside polymerase inhibitor, HCV-796, in combination with pagylated interferon alpha-2b in treatment-naive patients with chronic HCV. *J Hepatol* 46:S24
- Wang T, Blatt LM, Seiwert SD (2006) Immunomodulatory activities of IFN-gamma1b in combination with type I IFN: implications for the use of IFN-gamma1b in the treatment of chronic HCV infections. *J Interferon Cytokine Res* 26:473–483
- Weng HL, Wang BE, Jia JD, Wu WF, Xian JZ, Mertens PR, Cai WM, Dooley S (2005) Effect of interferon-gamma on hepatic fibrosis in chronic hepatitis B virus infection: a randomized controlled study. *Clin Gastroenterol Hepatol* 3:819–828
- Wheelock EF, Sibley WA (1965) Circulating virus, interferon and antibody after vaccination with the 17-D strain of yellow-fever virus. *N Engl J Med* 273:194–198
- Wiegand J, Buggisch P, Boecher W, Zeuzem S, Gelbmann CM, Berg T, Kauffmann W, Kallinowski B, Cornberg M, Jaeckel E, Wedemeyer H, Manns MP (2006) Early monotherapy with pegylated interferon alpha-2b for acute hepatitis C infection: the HEP-NET acute-HCV-II study. *Hepatology* 43:250–256
- Wolters LM, van Nunen AB, Honkoop P, Vossen AC, Niesters HG, Zondervan PE, de Man RA (2000) Lamivudine-high dose interferon combination therapy for chronic hepatitis B patients co-infected with the hepatitis D virus. *J Viral Hepat* 7:428–434
- Wong DK, Cheung AM, O'Rourke K, Naylor CD, Detsky AS, Heathcote J (1993) Effect of alpha-interferon treatment in patients with hepatitis B e antigen-positive chronic hepatitis B. A meta-analysis. *Ann Intern Med* 119:312–323
- Wursthorn K, Lutgehetmann M, Dandri M, Volz T, Buggisch P, Zollner B, Longerich T, Schirmacher P, Metzler F, Zankel M, Fischer C, Currie G, Brosgart C, Petersen J (2006) Peginterferon alpha-2b plus adefovir induce strong cccDNA decline and HBsAg reduction in patients with chronic hepatitis B. *Hepatology* 44:675–684
- Yoneyama M, Kikuchi M, Natsukawa T, Shinobu N, Imaizumi T, Miyagishi M, Taira K, Akira S, Fujita T (2004) The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses. *Nat Immunol* 5:730–737
- Yurdaydin C, Bozkaya H, Cetinkaya H, Sahin T, Karaoguz D, Toruner M, Erkan O, Heper AO, Erden E, Bozdayi AM, Uzunalimoglu O (2005) Lamivudine vs lamivudine and interferon combination treatment of HBeAg(-) chronic hepatitis B. *J Viral Hepat* 12:262–268
- Yurdaydin C, Wedemeyer H, Dalekos G, Erhardt A, Cakaloglu Y, Degertekin H, Gurel S, Zeuzem S, Zachou K, Bozkaya H, Dienes HP, Bock T, Manns MP (2006) A multicenter randomized study comparing the efficacy of pegylated interferon-alpha-2a plus adefovir dipivoxil versus pegylated interferon-alpha-2a plus placebo versus adefovir dipivoxil for the treatment of chronic hepatitis delta hepatitis: the HEP-NET/International Delta Hepatitis Intervention Trial (HID-IT). *Hepatology* 44:230A
- Zeuzem S, Benhamou Y, Bain V, Shouval D, Pianko S, Flisiak R, Grigorescu M, Rehak V, Yoshida E, Kaita K, Cronin PW, Pulkstenis E, Subramanian GM, McHutchison JG (2007) Antiviral response at week 12 following completion of treatment with Albinterferon alpha-2b plus ribavirin in genotype 1, IFN-naive, chronic hepatitis patients. *J Hepatol* 46:S293
- Zhao H, Kurbanov F, Wan MB, Yin YK, Niu JQ, Hou JL, Wei L, Wang GQ, Tanaka Y, Mizokami M, Si CW (2007) Genotype B and younger patient age associated with better response to low-dose therapy: a trial with pegylated/nonpegylated interferon-alpha-2b for hepatitis B e antigen-positive patients with chronic hepatitis B in China. *Clin Infect Dis* 44:541–548