Clinical Policy Bulletin: Interferons

Number: 0404

Policy

Subject to the qualification described below regarding length of treatment and response to treatment, Aetna considers interferon alpha, pegylated interferon, interferon beta, and interferon gamma medically necessary for persons who meet the criteria for each drug specified below.

Interferon alpha 2a and 2b

Aetna considers interferon alpha 2a and 2b medically necessary for the following indications:

1. AIDS-associated Kaposi's sarcoma;
2. Carcinoid syndrome;
3. Chronic myelogenous leukemia;
4. Condylomata acuminata (genital warts) (intralesional only);
5. Cutaneous T-cell lymphoma (including mycosis fungoides);
6. Desmoid tumors (fibromatosis)
7. Essential thrombocythemia;
8. Giant cell tumor of bone;
9. Hairy cell leukemia, relapsed or refractory;
10. Hepatitis C (non-A, non-B hepatitis). Continued treatment with interferon alpha is considered not medically necessary for persons with HCV genotypes 1 and 4 through 6 who have failed to attain an early virologic response after 12 weeks of treatment (where early virologic response is indicated by achievement of at least a 100-fold (2 log10) decrease in serum HCV from pretreatment baseline). Up to a maximum of 24 weeks of interferon alpha is considered medically necessary for persons with HCV genotypes 2, 3, and 7 through 10; and up to a maximum of 48 weeks of interferon alpha is considered medically necessary for persons with HCV genotypes 1 and 4 through 6. A course of standard interferon alpha in persons with hepatitis C who have failed to respond or relapsed after an adequate course of pegylated interferon alpha or consensus interferon is considered experimental and investigational because of a lack of evidence on the effectiveness of standard interferon in these persons. Note: Upon medical review, extended treatment with interferon alpha beyond these limits may be considered medically necessary for persons with cryoglobulinemia and for liver transplant recipients with recurrent hepatitis C infection;
11. Hyper-eosinophilic syndrome that is not adequately responsive to glucocorticoids;
12. Kasabach-Merritt syndrome;
13. Leptomeningeal metastases of CNS tumors, intracerebrospinal fluid treatment;
14. Life-threatening hemangiomma of infancy (intralesional) when member is intolerant of, or the hemangiomma is resistant to, corticosteroid therapy;
15. Malignant melanoma;
16. Meningioma, recurrent, surgically inaccesible;
17. Multiple myeloma, solitary plasmacytoma, or systemic light chain amyloidosis;
18. Neuroendocrine tumors of the GI tract, lung and thymus;
19. Non-Hodgkin's lymphoma (including adult T-cell leukemia/lymphoma (chronic, smoldering or acute), mycosis fungoides/Sezary syndrome) and primary cutaneous anaplastic large cell lymphoma (ALCL) with multifocal lesions);
20. Ocular herpes simplex (interferon alpha eye drops);
21. Persons with chronic hepatitis B who meet all of the following criteria:
   a. Member has compensated liver disease (Child-Pugh score less than or equal to 6 [class A]);
      and
   b. Serum aminotransferase (AST) greater than double the upper limit of normal range (AST normal range 0 to 35 u/l).

A course of standard interferon alpha in persons with hepatitis B who have failed an adequate course of pegylated interferon alpha is considered experimental and investigational because of a lack of evidence on the effectiveness of standard interferon in these persons.

(The use of interferon alpha is considered contraindicated in the following persons with hepatitis B: those who are HIV positive; hepatitis B surface antigen (HBs Ag) positive persons undergoing liver transplantation; and those with a history of or currently active autoimmune hepatitis);

22. Persons with polycythemia vera who meet all of the following criteria:
   a. Oral therapy with hydroxyurea or other myelosuppressive agent is not effective, not tolerated, or is contraindicated; and
   b. Phlebotomy is not effective, not tolerated, or contraindicated.

Note: Failure of phlebotomy and/or myelosuppressive agents may be defined as any of the following:

   - Lack of hematological control (e.g., hematocrit greater than 45 or platelet count greater than 600 x 10^9/L);
   - Occurrence of intractable symptoms (e.g., headaches, pruritis);
   - Occurrence of symptoms related to hepatosplenomegaly;
   - Occurrence of thrombotic or hemorrhagic complications; or
   - Phlebotomy required more often than once every 2 months

23. Renal cell carcinoma;
24. Respiratory papillomatosis; or
25. Vulvar vestibulitis

Aetna considers interferon alpha 2a and 2b experimental and investigational for all other indications because it has not been shown to be effective for them:

1. Acute hepatitis B;
2. Age-related macular degeneration;
3. AIDS-related complex;
4. AIDS in combination with AZT;
5. Basal cell carcinoma;
6. Behçet's uveitis;
7. Breast cancer;
8. Cervical cancer;
9. Chickenpox;
10. Cholangiocarcinoma;
11. Chronic delta hepatitis;
12. Colorectal cancer;
13. Cutaneous warts;
14. Cytomegalovirus (CMV);
15. Familial Mediterranean fever;
16. Gardner syndrome;
17. Hepatocellular carcinoma;
18. Hepatitis D;
19. Hereditary hemorrhagic telangiectasia;
20. Herpes keratoconjunctivitis;
21. Islet cell tumors;
22. Keloids;
23. Mesothelioma;
24. Multiple sclerosis;
25. Osteosarcoma;  
26. Ovarian cancer;  
27. Pancreatic cancer;  
28. Peyronie's disease;  
29. Plexiform neurofibroma;  
30. Primitive neuroectodermal tumor (PNET);  
31. Prostate cancer;  
32. Rhinoviruses;  
33. Sjogren's syndrome-associated dry eye;  
34. Sudden hearing loss;  
35. Vaccinia;  
36. Varicella zoster virus (VZV); and  
37. Waldenstrom's macroglobulinemia.

Pegylated interferon alpha

I. Hepatitis C

Note: REQUIRES PRECERTIFICATION*

*Note: Precertification of oral drugs for hepatitis C (protease inhibitors (e.g., simeprevir (Olysio)), polymerase inhibitors (e.g., sofosbuvir (Sovaldi)) and NS5A inhibitor combinations (e.g., ledipasvir (Harvoni)) is required of all Aetna participating providers and members in applicable plan designs. For precertification of oral hepatitis C drugs, call (866) 503-0857, or fax (888) 267-3277. See Pharmacy CPB on Hepatitis C for coverage criteria for oral hepatitis C regimens.

A. Aetna considers the following pegylated interferon alpha (pegylated interferon alfa-2a (Pegasys), pegylated interferon alpha-2b (PegIntron)) regimens for hepatitis C medically necessary for the following indications:

1. Aetna considers pegylated interferon alpha, either as monotherapy or in combination with ribavirin (Rebetol) and (for persons with genotype 1) the protease inhibitors boceprevir (Victrelis), telaprevir (Incivek), or simeprevir (Olysio), medically necessary for the treatment of chronic hepatitis C in persons who are interferon naive or who have relapsed or failed to respond to prior non-pegylated interferon alpha therapy. (Note: Simeprevir (Olysio) is considered experimental and investigational for person with HCV genotype 1a containing the Q80K polymorphism because it has been shown to have substantially reduced effectiveness for persons with this polymorphism.)

2. Continued treatment with pegylated interferon alpha is considered not medically necessary for persons with HCV genotypes 1 and 4 through 6 who have failed to attain an early virologic response after 12 weeks of therapy. Early virologic response is indicated by achievement of at least a 100-fold (2 log10) decrease in serum HCV RNA from pretreatment baseline.

3. For persons infected with HCV genotype 1 and genotypes 4 through 6 who have attained an early virologic response by 12 weeks of therapy, up to 48 weeks of treatment with pegylated interferon alpha is considered medically necessary.

4. Up to 72 weeks of treatment with pegylated interferon alpha is considered medically necessary for persons with HCV genotype 1 infection who have delayed virus clearance. Delayed virus clearance is indicated by an HCV RNA test becoming negative between weeks 12 and 24.

5. For persons with other HCV genotypes (i.e., genotypes 2 and 3, and genotypes 7 through 10) up to 24 weeks of treatment with pegylated interferon alpha is considered medically necessary.

6. A course of therapy with pegylated interferon alpha plus telaprevir, boceprevir or simeprevir is considered medically necessary for persons with genotype 1 hepatitis C who have failed to respond to a prior course of treatment with standard or pegylated interferon alpha without telaprevir, boceprevir, sofosbuvir or simeprevir. The medically necessary duration of treatments with pegylated interferon alpha and ribavirin and protease inhibitors is the same as for treatment of interferon naive persons described above.

7. Repeat treatment with pegylated interferon alpha without telaprevir, boceprevir, sofosbuvir, or simeprevir is considered experimental and investigational for persons...
who have completed or failed to respond to a therapeutic course of pegylated interferon alpha.

8. Repeat treatment with pegylated interferon alpha and telaprevir, boceprevir, or simeprevir is considered experimental and investigational for persons who have completed or failed to respond to a therapeutic course of pegylated interferon alpha and telaprevir, boceprevir, or simeprevir.

9. Chronic maintenance treatment with pegylated interferon alpha and telaprevir, boceprevir, or simeprevir is considered experimental and investigational.

10. Simultaneous treatment with pegylated interferon alpha and two protease inhibitors or simultaneous treatment with pegylated interferon alpha, a protease inhibitor and sofosbuvir is considered experimental and investigational for HCV.

11. Up to 48 weeks of pegylated interferon alpha is considered medically necessary for persons coinfectcd with HIV and HCV, regardless of HCV genotype, are on stable antiretroviral therapy, and (for HCV genotypes 1 and 4 through 6 only) have achieved an early virologic response after 12 weeks of therapy.

12. Notes: See appendix for dosing of the protease inhibitors telaprevir, boceprevir and simeprevir. For protease inhibitor regimens for hepatitis C that do not include pegylated interferon alpha, see Pharmacy CPB on Hepatitis C.

B. Upon medical review, extended treatment with pegylated interferon alpha beyond these limits may be considered medically necessary for persons with cryoglobulinemia and for liver transplant recipients with recurrent hepatitis C infections.

II. Aetna considers pegylated interferon alpha and sofosbuvir (Sovaldi) combination regimens medically necessary for the following indications:

A. Aetna considers up to 12 weeks of sofosbuvir (Solvadi) plus up to 12 weeks of pegylated interferon alpha plus ribavirin medically necessary for the treatment of interferon naïve persons with chronic hepatitis C genotypes 1, 3, 4, 5 and 6, including persons who are coinfectcd with HIV.

B. Aetna considers up to 12-weeks of sofosbuvir plus up to 24 weeks of pegylated interferon alpha plus ribavirin medically necessary for treatment of persons with genotype 1 hepatitis C, including persons coinfectcd with HIV, who are liver transplant recipients or who have relapsed or failed to respond to a course of treatment with standard or pegylated interferon alpha with or without ribavirin and telaprevir, boceprevir, or simeprevir.

C. Aetna considers up to 12-weeks of sofosbuvir plus up to 12 weeks of pegylated interferon alpha plus ribavirin medically necessary for persons with genotypes 2, 3, 4, 5, and 6 hepatitis C, including persons coinfectcd with HIV, who have relapsed or failed to respond to a course of treatment with standard or pegylated interferon alpha with or without ribavirin and telaprevir, boceprevir, or simeprevir.

D. Aetna considers combination treatment with sofosbuvir, protease inhibitors and pegylated interferon alpha experimental and investigational.

E. Aetna considers repeat or chronic maintenance treatment with pegylated interferon alpha and sofosbuvir experimental and investigational.

F. Aetna considers combination treatment with sofosbuvir and pegylated interferon alpha experimental and investigational for all other indications.

G. Notes: See appendix for dosing of sofosbuvir. For sofosbuvir regimens for hepatitis C that do not include pegylated interferon alpha, see Pharmacy CPB on Hepatitis C.

III. See also Aetna Pharmacy CPB on Hepatitis C.

Hepatitis B

Peginterferon alfa-2a (Pegasys) is considered medically necessary for the treatment of adult persons with HBeAg positive or HBeAg negative chronic hepatitis B who have compensated liver disease (Child-Pugh score less than or equal to 6 [Class A]) and evidence of viral replication (HBV greater than 500,000 copies per ml for HBeAg positive and HBV greater than 100,000 copies per ml for HBeAg negative) and liver inflammation (serum aminotransferase (AST) greater than the upper limit of normal range (AST normal range 0 to 35 u/l)), and who are interferon naïve or who have relapsed or failed to respond to prior non-pegylated interferon therapy.
Treatment of chronic hepatitis B with peginterferon alfa-2a for more than 48 weeks is considered experimental and investigational. Repeat or chronic maintenance treatment with peginterferon alfa-2a is considered experimental and investigational for persons who have completed a therapeutic course of pegylated interferon and ribavirin. Note: Upon medical review, extended treatment with peginterferon alfa-2a beyond these limits may be considered medically necessary for liver transplant recipients with recurrent hepatitis B infections.

Chronic myelogenous leukemia

For follow-up therapy for patients who are unable to tolerate imatinib, dasatinib, nilotinib, bosutinib, or ponatinib; or Post-transplant follow-up treatment in patients with molecular relapse, cytogenic relapse or those who are not in cytogenic remission.

Melanoma, adjuvant treatment

Giant cell tumor of the bone

Persons with polycythemia vera who meet all of the following criteria:

- Oral therapy with hydroxyurea or other myelosuppressive agent is not effective, not tolerated, or is contraindicated; and

- Phlebotomy is not effective, not tolerated, or contraindicated.

Note: Failure of phlebotomy and/or myelosuppressive agents may be defined as any of the following:

- Lack of hematological control (e.g., hematocrit greater than 45 or platelet count greater than 600 x 10^9/L);
- Occurrence of intractable symptoms (e.g., headaches, pruritis);
- Occurrence of symptoms related to hepatosplenomegaly;
- Occurrence of thrombotic or hemorrhagic complications; or

- Phlebotomy required more often than once every 2 months

Aetna considers pegylated interferon alpha experimental and investigational for desmoid tumor, eosinophilia/hyper-eosinophilic syndrome, human papilloma virus, osteosarcoma, plexiform neurofibroma, progressive multi-focal leukoencephalopathy, warts, and all other indications.

Note: Pegylated interferons are self-administered subcutaneously once-weekly.

Consensus Interferon (Interferon alfacon-1)*

* Note: Infergen (interferon alfacon-1) was discontinued in September 2013.

1. Consensus interferon (Infergen interferon alfacon-1) is considered medically necessary for initial treatment of persons with chronic hepatitis C.

2. Consensus interferon is considered medically necessary for retreatment of chronic hepatitis C who have failed to respond to a complete therapeutic course of pegylated interferon, defined as less than a 2 log decline in viral load after undergoing at least 12 weeks of previous pegylated interferon plus ribavirin therapy with greater than 80% adherence, or a detectable viral load at end-of-treatment after completing at least 24 weeks of therapy. Up to 48 weeks of treatment with consensus interferon is considered medically necessary for retreatment. Continued treatment with consensus interferon is considered not medically necessary for persons with a poor response to re-treatment at week 12 (defined as less than 2 log10 reduction in viral load from baseline) or persons who have detectable virus at week 24.

3. Use of consensus interferon for persons with hepatitis C who have failed to respond or relapsed after an adequate course of standard alpha interferon is considered experimental and investigational. Although there is limited evidence regarding the use of consensus interferon in persons with hepatitis C...
C who have relapsed or failed to respond to standard alpha interferon therapy, current guidelines indicate pegylated interferons as the treatment of choice for persons with hepatitis C, including those who relapsed or failed to respond to standard alpha interferon therapy. There is insufficient evidence in the peer-reviewed published medical literature comparing consensus interferon to pegylated interferons in persons with hepatitis C who have failed standard interferon therapy.

4. Repeat or chronic (more than 48 weeks) maintenance treatment with consensus interferon is considered experimental and investigational because there is insufficient evidence to show that repeat or prolonged therapy has a clinically significant impact on long term outcomes.

5. Consensus interferon is considered experimental and investigational for all other indications.

**Interferon beta**

Aetna considers Rebif (interferon beta-1a) monotherapy medically necessary for the treatment of relapsing/remitting multiple sclerosis (MS) in members who meet all of the conditions described below.

Aetna considers Avonex (interferon beta-1a), Plegridy (peginterferon beta-1a), Betaseron or Extavia (interferon beta-1b) monotherapy medically necessary for the treatment of relapsing/remitting MS in members who meet all of the conditions described below, and who have a contraindication, allergy, intolerance, or failure of a 1-month trial of Copaxone plus a contraindication, allergy, intolerance or failure of a 1-month trial of Rebif.

Member meets either of the following criteria for clinically definite or laboratory supported definite MS:

1. Clinically definite MS is defined as either:
   - Two attacks and clinical evidence of 2 separate lesions; or
   - Two attacks; clinical evidence of 1 lesion and para-clinical evidence of another, separate lesion

2. Laboratory-supported definite MS consists of demonstration of any of the following:
   - Two attacks; either clinical or para-clinical evidence of 1 lesion; and cerebro-spinal fluid (CSF) OB/IgG*; or
   - One attack; clinical evidence of 2 separate lesions; and CSF OB/IgG*; or
   - One attack; clinical evidence of 1 lesion and para-clinical evidence of another separate lesion; and CSF OB/IgG*

*CSF OB/IgG is defined as either:
   - IgG oligoclonal band (OB) in the CSF; or
   - Increased CNS synthesis of IgG (IgG is higher in CSF than in serum, and is increased in the CSF in the presence of a normal concentration of total protein).

Limits: Oligoclonal bands must not be present in the member's serum and the serum IgG level must be normal.

Aetna considers interferon beta medically necessary for treatment of persons with clinically isolated syndromes who are at high-risk of developing MS.

Aetna considers use of interferon beta in combination with other disease modifying treatments (Tysabri, Copaxone, Gilenya, Aubagio, or Tecfidera) experimental and investigational because there is a lack of reliable evidence that interferon beta in combination with other disease modifying treatment is more effective than interferon beta alone.

Aetna considers interferon beta experimental and investigational for all other indications (e.g., chronic inflammatory demyelinating polyradiculoneuropathy, Guillain Barre syndrome, pancreatic cancer; not an all-inclusive list) because its effectiveness for indications other than the ones listed above has not been established.

Aetna considers testing for neutralizing antibodies to interferon beta experimental and investigational (see CPB 0264 - Multiple Sclerosis).

**Notes:** Interferon beta and glatiramir acetate (Copaxone) are first-line treatments for multiple sclerosis. There are several brands of interferon beta on the market. There is a lack of reliable evidence that any one brand
of interferon beta is superior to other brands for relapsing-remitting multiple sclerosis. Rebif (interferon beta-1a) brand of interferon beta ("least cost brand of interferon beta") is less costly to Aetna. Consequently, because other brands (Avonex (interferon beta-1a), Plegridy (peginterferon beta-1a), Betaseron (interferon beta-1b), and Extavia (interferon beta-1b)) are more costly than the least cost brand of interferon beta, and the least cost brand of interferon beta is at least as likely to produce equivalent therapeutic results, no other brands of interferon beta will be considered medically necessary unless the member has a contraindication, allergy, intolerance or failure of an adequate trial of the least cost brand of interferon beta plus an adequate trial of Copaxone. For purpose of this policy, failure of an adequate trial of multiple sclerosis treatment is defined as follows:

- The member has increasing relapses (defined as two or more relapses in a year, or one severe relapse associated with either poor recovery or MRI lesion progression); or
- The member has lesion progression by MRI (increased number or volume of gadolinium-enhancing lesions, T2 hyperintense lesions or T1 hypointense lesions); or
- The member has worsening disability (sustained worsening of Expanded Disability Status Scale (EDSS) score or neurological examination findings).

Intolerance is defined as intolerable side effects despite optimized management strategies.

Because interferon beta is administered subcutaneously or intramuscularly, it is appropriate for administration by the member in the home setting.

The Biojector 2000 (Bioject, Inc.) is a needle-free injection system that uses CO2 as the power source and disposable needle-free syringes to deliver medication in a fraction of a second through a tiny orifice. Biojector 2000 is considered a medically necessary acceptable alternative to conventional needle and syringes for members with exacerbating-remitting MS who cannot safely use needles for self-injection due to tremors and decreased coordination.

See also CPB 0264 - Multiple Sclerosis.

**Interferon alpha-N3 (Alferon)**

Aetna considers interferon alpha-N3 (Alferon N) medically necessary for intralesional treatment of refractory or recurring external condylomata acuminata (venereal/genital warts). Aetna considers interferon alpha-N3 experimental and investigational for all other indications.

**Interferon gamma**

Aetna considers interferon gamma medically necessary for the following indications:

1. Chronic granulomatous disease, to reduce the frequency and severity of infections; or
2. Chronic recalcitrant atopic dermatitis; or
3. Mycosis fungoides and Sezary syndrome; or
4. Severe, malignant osteopetrosis, to delay time to disease progression.

Aetna considers interferon gamma experimental and investigational for the treatment of brain tumors, idiopathic pulmonary fibrosis, malignant neoplasm of peritoneum, pancreatic cancer, pulmonary tuberculosis, Waldenstrom's macroglobulinemia, and all other indications because its effectiveness for indications other than the ones listed above has not been established.

**Background**

Interferons are biological response modifiers that are indicated in the treatment of numerous malignant and infectious disease conditions.

Interferon alpha products (Roferon; Intron-A; Alferon; Infergen) have been granted orphan-drug status by the Food and Drug Administration (FDA) for several types of malignancies and viral infections and have unlabeled uses for several others. Although the efficacy of all alpha interferons (e.g., interferon alpha 2a, alpha 2b, alpha-n3, and alfacon-1) for various indications appear to be similar, differences in relative efficacy for a particular indication may exist. Interferon alpha should be used with caution in patients with pre-existing psychiatric conditions or a history of severe psychiatric disorders. According to the product labeling, depression, confusion, and other alterations of mental status have been observed in some patients and suicidal ideation and attempted suicide have been observed rarely.
A Cochrane evidence review of treatments for herpes simplex eye disease (Wilhelmus, 2007) found that the combination of interferon-alpha eye drops and either trifluridine or acyclovir resulted in faster healing of dendritic keratitis than treatment with trifluridine or acyclovir alone; 90 % of eyes healed within 1 week with combined interferon-antiviral therapy.

In an interventional, comparative case series, Lane and colleagues (2009) examined if interferon (IFN)-alpha-2a treatment after radiation or enucleation reduces death rates in patients with uveal melanoma. Patients were identified through the oculer oncology clinic of the Massachusetts Eye and Ear Infirmary. Subjects eligible for the study were at increased risk of metastasis because of the presence of at least 1 of the following characteristics: (i) age greater than or equal to 65 years, (ii) largest tumor diameter (LTD) greater than or equal to 15 mm, (iii) ciliary body involvement of the tumor, or (iv) extra-scleral tumor extension. A total of 121 patients with choroidal or ciliary body melanoma began a 2-year course of therapy (3 million international units [MIU] IFN-alfa-2a subcutaneously 3 times per week), initiated within 3 years of primary therapy. All patients underwent regular monitoring for drug toxicity. To evaluate IFN-alfa-2a efficacy, these researchers selected a series of historical controls frequency-matched (2:1) to IFN-alfa-2a-treated patients on age (+/- 5 years), LTD (+/- 3 mm), gender, and survival time between primary therapy and initiation of IFN therapy. Survival status was ascertained for all patients. Main outcome measures were melanoma-related mortality, metastasis, IFN-related toxicities. A total of 55 patients (45 %) completed therapy; the median dose for IFN-alfa-2a-treated patients was 792 MIU (85 % of the theoretic dose). The median follow-up time in the IFN-alfa-2a-treated group was approximately 9 years. Treatment and control groups were similar with respect to age (p = 0.78), LTD (p = 0.38), and gender (p = 1.0). Of 363 patients, 108 developed metastasis under observation; 42 of these were IFN-alfa-2a-treated patients. Cumulative 5-year melanoma-related death rates were 17 % in the radiation or enucleation-only group, 15 % in those who completed the entire IFN-alfa-2a course, and 35 % in those who discontinued IFN-alfa-2a therapy. In multivariate Cox regression, IFN-alfa-2a had no significant influence on melanoma-related mortality (rate ratio = 1.02, 95 % confidence interval [CI]: 0.68 to 1.5, p = 0.91) or all-cause mortality (rate ratio = 0.84, 95 % CI: 0.58 to 1.2, p = 0.34). The authors concluded that interferon-alfa-2a has no material influence on survival in patients with choroidal melanoma.

PegIntron, peginterferon alfa-2b powder for injection, either alone or in combination with ribavirin (Rebetol), is an alternative to standard interferon alfa plus ribavirin for treatment of chronic hepatitis C. PegIntron is a covalent conjugate of recombinant alfa interferon with monomethoxy polyethylene glycol (PEG). It offers an alternative to patients in whom combination therapy may be a contraindication or who are intolerant of that therapy. The drug is self-administered subcutaneously once-weekly by patients and, therefore, is more convenient to use than the standard interferon alfa, which is injected 3 times weekly. Recently, studies of combination therapy with weekly PegIntron and daily ribavirin (Rebetol) reported that this combination was somewhat more effective than alpha interferon (Intron A) with Rebetol. Twenty-four weeks after treatment ended, 52 % of patients who received the PegIntron combination had undetectable HCV virus levels in the blood compared to 46 % for the Intron A combination. In patients with genotype 1 virus (a particularly difficult to treat variant of the HCV virus), the difference in sustained responses was 41 % compared to 33 %. PegIntron from Schering-Plough is the first pegylated interferon to have FDA approval in the United States.

Roche Pharmaceutical's Pegasys (pegylated interferon alfa-2a) has also been approved by the FDA for the treatment of adults with chronic hepatitis C who have compensated liver disease and have not previously been treated with interferon alpha. Patients in whom efficacy was demonstrated included patients with compensated cirrhosis. Pegasys was granted approval based on the results of 3 phase III clinical trials that demonstrated it is an effective treatment for patients with chronic hepatitis C, including cirrhotic patients with compensated liver disease, versus treatment with Roferon-A (interferon alfa-2a). The sustained virological response rate in the patients treated with pegylated interferon alfa-2a was as high as 38 % in the overall population versus 19 % in the interferon alfa-2a group. The sustained virological response in patients with cirrhosis treated with pegylated interferon alfa-2a was as high as 30 % versus 8 % in the interferon alfa-2a group. Higher sustained virological response results were also found in patients with genotype 1, on pegylated interferon alfa-2a treatment (23 %) versus interferon alfa-2a (6 %), the most common type in the U.S. and most difficult to treat. Sustained virological response was defined as undetectable serum hepatitis C RNA levels post-treatment (on or after study week 68). Pegylated interferon alfa-2a is dosed at 180 µg as a subcutaneous injection once-weekly for a recommended duration of 48 weeks.

Clinical trials of pegylated interferon alfa-2a have shown that patients with HCV genotypes 1 and 4 can determine at 12 weeks if they are unlikely to attain an early virological response with pegylated interferon alfa-2a. According to an NIH Consensus Statement on Hepatitis C (1997; 2002), 12 weeks after beginning an initial course of therapy, patients who are unlikely to respond to that dosage and frequency can be
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RNA remained detectable (Pearlman et al, 2007), and the other was a post-hoc analysis of a study in which homogeneous, differing in their baseline characteristics and the regimens utilized were different. Tapias et al, 2006). One study randomized subjects to either 48 or 72 weeks of treatment at week 12 if HCV randomization of treatment duration occurred at baseline (Berg et al, 2006). The study populations were not pegylated interferon is more similar to that for genotypes 2 and 3 than for genotypes 1 and 4. The infection with hepatitis C virus (HCV) genotype 6 compared to genotype 1. Forty-two patients chronically infected with HCV were treated with pegylated interferon combined with oral ribavirin for 48 weeks. The genotype 6 than in those infected with genotype 1. This suggests that the response of HCV genotype 6 to investigators stated that further studies are required to determine whether lower dosages and 24 weeks of reduction) should continue treatment until 48 weeks. For people in whom viral load at 12 weeks exceeds 1 % of its level at the start of treatment, treatment should be discontinued. These guidelines note that people infected with more than one genotype that includes one or more of genotypes 1, 4, 5, or 6 should be treated as for genotype 1 (NICE, 2004; see also Hadziyannis et al, 2004; NIH, 2002). These guidelines are based upon the observation that the SVRs for patients infected with HCV genotype 1 are much lower than those for genotypes 2 and 3, whereas SVRs for genotypes 4, 5 and 6 appear to be between those of the more prevalent genotypes.

Guidelines from the American Association for the Study of Liver Diseases (Ghany et al, 2009) state that “for patients with genotype 1 infection who have delayed virus clearance (HCV RNA test becomes negative between weeks 12 and 24), consideration should be given to extending therapy to 72 weeks (Class IIa, Level B).” The strategy of extending therapy in naive subjects with delayed virological responses, defined as clearance of HCV RNA between weeks 12 and 24, was evaluated in two studies (Berg et al, 2006; Sanchez-Tapias et al, 2006). One study randomized subjects to either 48 or 72 weeks of treatment at week 12 if HCV RNA remained detectable (Pearlman et al, 2007), and the other was a post-hoc analysis of a study in which randomization of treatment duration occurred at baseline (Berg et al, 2006). The study populations were not homogeneous, differing in their baseline characteristics and the regimens utilized were different. Nevertheless, the results showed a trend toward a higher SVR rate by extending therapy from 48 to 72 weeks. The SVR rate increased from 18 % for 48 weeks treatment to 38 % for 72 weeks of treatment in one study (Pearlman et al, 2007) and 17 % to 29 % in the other study (Berg et al, 2006). The increased SVR was primarily due a lower relapse rate in the patients treated for 72 weeks. An additional study demonstrated that patients who failed to achieve an RVR (HCV RNA detectable at treatment week 4) also seemed to benefit from extending therapy from 48 to 72 weeks (Sanchez-Tapias et al, 2006). The SVR rates were significantly higher in patients who received treatment for 72 (45 %) compared to those treated for 48 weeks (32 %). It is clear that not all patients will benefit from extended therapy judging from the results of the trial in which randomization to 48 or 72 weeks of therapy occurred at baseline (Berg et al, 2006). No difference in SVR rates was observed between those treated for 48 compared to 72 weeks (53 % versus 54 %, respectively). Thus, prolonging therapy can be considered in patients who are slow to respond (clearance of HCV RNA between weeks 12 and 24) (Ghany et al, 2009). Further studies are needed to determine whether extended therapy would be beneficial to patients who fail to clear virus between weeks 4 and 12.

For persons with other HCV genotypes (i.e., genotypes 2 and 3, and 7 through 11), there is no proven benefit to extending therapy beyond 24 weeks (Hadziyannis et al, 2004; NIH, 2002; NICE, 2004).

Infection with hepatitis C virus (HCV) genotype 6 is common in patients from parts of China and Southeast Asia. There is limited evidence regarding the appropriate duration of therapy for persons with genotype 6. Fung et al (2008) evaluated the effectiveness of pegylated interferon plus ribavirin for the treatment of chronic infection with hepatitis C virus (HCV) genotype 6 compared to genotype 1. Forty-two patients chronically infected with HCV were treated with pegylated interferon combined with oral ribavirin for 48 weeks. The investigators found no difference between genotypes 1 and 6 in the rates of early virological response (76 % versus 81 %) and end-of-treatment response (71 % versus 81 %). Patients infected with genotype 6 had a higher SVR than did patients infected with genotype 1 (86 % versus 52 %). The overall adverse-effects profile was similar in both genotype groups. The investigators concluded that treatment with pegylated interferon and ribavirin for 48 weeks resulted in a significantly higher rate of SVR in patients infected with genotype 6 than in those infected with genotype 1. This suggests that the response of HCV genotype 6 to pegylated interferon is more similar to that for genotypes 2 and 3 than for genotypes 1 and 4. The investigators stated that further studies are required to determine whether lower dosages and 24 weeks of therapy may be sufficient for the treatment of genotype 6 infection. The findings of a higher SVR with interferon treatment in persons infected with genotype 6 versus genotype 1 was also found in an earlier study of standard interferon plus ribavirin (Yuen and Lai, 2006).

Nguyen et al (2004) reported on a retrospective study of 190 consecutive Asian-American patients who were diagnosed with HCV genotype 6 at a gastroenterology clinic in northern California between 2001 and 2004,
66 of whom were treatment-naïve and subsequently completed 24 weeks of interferon plus ribavirin or pegylated interferon plus ribavirin, or 48 weeks of pegylated interferon plus ribavirin therapy. These investigators found no statistical difference in SVR of 31 patients treated with 24 weeks of interferon plus ribavirin and in 23 patients treated with 24 weeks of pegylated interferon plus ribavirin (51.6 % versus 39 %, p = 0.363). The SVR in 12 patients treated with 48 weeks of pegylated interferon plus ribavirin was significantly higher than that in those treated for only 24 weeks (75 % versus 39 %, p = 0.044). The investigators concluded that treatment-eligible patients with HCV genotype 6 should be treated with a full course of 48 weeks as tolerated. The investigators noted that larger prospective studies of patients with HCV genotype 6 are needed to confirm the optimal treatment duration with pegylated interferon plus ribavirin.

Data are scarce on patients infected with hepatitis C virus of genotype 5, due to the low prevalence of this genotype around the world. Antaki et al (2008) reported on a retrospective study of treatment outcomes of 26 HCV genotype 5 patients who had completed a course of therapy and a 6-month follow-up. Treatment consisted of ribavirin plus standard or pegylated interferon. Patients were treated for 24 or 48 weeks. The investigators reported that an SVR was achieved in 54 % (47 % with standard interferon and 67 % with pegylated interferon, p = 0.43). A trend towards better results was observed for younger patients, low viremia and mild fibrosis. The investigators reported that SVR was similar for treatment course of 24 or 48 weeks. The investigators concluded that treatment of HCV genotype 5 with combination therapy resulted in SVR in 54 % of patients. The investigators stated that 24 weeks of treatment might be adequate, and that further research should evaluate the ideal duration of treatment.

Peginterferon alpha-2a (Pegasys) has also been approved by the FDA for treatment of hepatitis C in HIV coinfected persons, whose HIV disease is clinically stable (e.g., anti-retroviral therapy not required or receiving stable antiretroviral therapy). In studies submitted to the FDA, 868 HCV/HIV coinfected patients were randomized to receive peginterferon alpha-2a plus placebo, peginterferon alpha-2a plus ribavirin, or interferon alpha-2a plus ribavirin (Roche, 2005). All subjects received 48 weeks of therapy, and sustained virologic response was assessed at 24-weeks of treatment free follow-up. All subjects included in the study had compensated liver disease, a CD4+ cell count greater than or equal to 200 cells/µL or CD4+ cell count greater than or equal to 100 cells/µL but less than 200 cells/µL and HIV-1 RNA less than 5,000 copies/ml, and stable status of HIV. Approximately 15 % of patients in the study had cirrhosis. Sustained virologic response was noted in 40 % of subjects treated with peginterferon alpha-2a plus ribavirin, 20 % of patients treated with peginterferon alpha-2a plus placebo (p < 0.0001), and 11 % of subjects treated with interferon alpha-2a plus ribavirin (p < 0.0001). Of patients who did not demonstrate either either undetectable HCV RNA or at least a 2 log 10 reduction from baseline in HCV RNA titer by 12 weeks of peginterferon alpha-2a and ribavirin combination therapy, 2 % achieved a sustained virologic response.

There is inadequate evidence for the effectiveness of use of pegylated interferons as maintenance therapy. According to the FDA-approved labeling for pegylated interferons, there are no safety and efficacy data on treatment with pegylated interferons for more than one year.

The NIH Consensus Conference on Hepatitis C (2002) stated: "Failure to respond to optimal therapy with pegylated interferon and ribavirin presents a significant problem, particularly in the presence of advanced fibrosis or cirrhosis. Currently, several large-scale, multi-center U.S. trials are evaluating the role of maintenance therapy with pegylated interferon alone in preventing further progression of cirrhosis, clinical decompensation, or development of HCC. Until the results of these studies are available, the role of long-term, continuous therapy with pegylated interferon (or ribavirin or both) for non-responders should be considered experimental."

Patients without initial responses to peginterferon and ribavirin did not benefit from long-term low-dose peginterferon therapy in the HALT-C trial.

The HALT-C trial found that patients without initial responses to peginterferon and ribavirin did not benefit from long-term low-dose peginterferon therapy (Di Bisceglie et al, 2008). In this multi-center study, 1,050 patients with chronic hepatitis C and advanced fibrosis who had not responded to previous treatment were randomized to receive maintenance therapy with weekly peginterferon alfa-2a or no therapy for 3.5 years. Patients were seen every 3 months and underwent liver biopsies at baseline and 1.5 and 3.5 years after randomization. The criteria for the primary outcome -- progression of liver disease -- varied according to whether patients had cirrhosis or noncirrhotic fibrosis at baseline. Maintenance therapy was associated with significant decreases in aminotransferase and hepatitis C virus RNA levels, but it did not influence the likelihood of disease progression, which was about 34 % in each group (hazard ratio, 1.01). Serious adverse events occurred in 39 % of peginterferon recipients versus 32 % of untreated patients (p = 0.07). Commenting on this study, Baddour (2008) said that long-term low-dose peginterferon does not reduce the
The impact of interferon (IFN) treatment on the occurrence of complications related to HCV-related cirrhosis is controversial since the majority of studies are retrospective. In a randomized controlled trial, Fartoux et al (2007) compared the effectiveness of prolonged IFN alpha-2a treatment versus non-treatment on complication-free survival in patients with compensated HCV cirrhosis. A total of 102 patients (mean age of 60.5 +/- 9.5 years; male/female ratio, 0.82) with biopsy examination-proven HCV cirrhosis, Child-Pugh score A, who were hepatocellular carcinoma (HCC) free, and had at least 1 risk factor of complications, were randomized to receive IFN or no therapy for 24 months. During the follow-up evaluation, the complication rate was 24.5%: HCC occurred in 12 and decompensation unrelated to HCC occurred in 13 patients. The number of HCC patients was similar in both groups. The probability of complication-free survival was not significantly different between treated and untreated patients (98% and 72.3% versus 90% and 70.7% at 12 and 24 months, respectively, p = 0.59). The median time until complication occurrence was 17.1 months in the treated group versus 13.6 months in the untreated group (p = 0.2). The authors concluded that this randomized controlled trial showed that a 2-year course of IFN has little or no impact on complication-free survival in patients with high-risk compensated HCV cirrhosis.

A technology assessment of ribavirin and pegylated interferon in hepatitis C for the Wessex Institute for Health Research and Development (Shepherd et al, 2004) noted that cryoglobulinemia and vasculitis occurs in a minority of patients with hepatitis C, and these conditions are not likely to be the subject of clinical trials because of the relatively small number of patients affected. The report noted, however, that clinicians point out that in some patients with vasculitis due to viral/antibody complexes the vasculitis can resolve after long-term treatment. The report stated that appropriate treatment of such patients needs to be addressed.

HCV-related liver cirrhosis is the most common indication for liver transplantation in most transplant centers. However, recurrence of hepatitis C-infection after liver transplant in HCV positive patients is almost universal (Neumann and Neuhaus, 2004). Severity of graft hepatitis increases during the long term follow-up and up to 30% of patients develop severe graft hepatitis and cirrhosis. This led to decreased patient and graft survival in HCV positive patients. Prophylactic or therapeutic regimes which alter the course of disease in HCV positive patients are not established yet. Anti-viral treatment with ribavirin in combination with pegylated interferon is being investigated to reduce the complications of HCV recurrence in the future (Triantos et al, 2005). Treatment of recurrent hepatitis C virus after liver transplantation with either interferon or interferon and ribavirin has yielded only limited success (Shiffman et al, 2003; Triantos et al, 2005). Regardless of this, treatment is instituted. Pegylated interferon is more effective than standard interferon for treatment of chronic hepatitis C virus infection in the non-transplantation setting when used either alone or with ribavirin. The effectiveness of peginterferon, both with and without ribavirin in the posttransplantation setting, is currently being explored.

Triantos et al (2005) reported on the results of a systematic evidence review of anti-viral therapy for HCV in liver transplant recipients. The authors concluded that anti-viral therapy for recurrent HCV infection and disease after liver transplantation has only been evaluated in 16 randomized studies (534 patients) and thus robust data to evaluate efficacy is scanty. However it is clear from both randomized and the 74 non-randomized (2,061 patients) that treatment is far less effective and with more side effects than for chronic HCV hepatitis pre-transplant. Moreover, the data concerning combinations of either interferon or pegylated interferon with ribavirin mainly reflect on treatment virologic response (OTVR) (maximum 36%) or end of treatment virologic response (ETVR) (maximum 32%) with very little data on sustained virologic response (SVR). Thus, the authors concluded, currently there is no easily applicable, nor reasonably effective, anti-viral therapy for HCV recurrence after liver transplantation, considering the frequency of side effects and need to reduce doses or to discontinue therapy. The most applicable strategy is to treat established disease with pegylated interferon and ribavirin but only future results of ongoing randomized studies will define the cost-effectiveness and applicability of this regimen. The authors noted that the number of patients who have already failed antiviral therapy pretransplant may well further limit the likelihood of sustained viral clearance. Most importantly data on stopping the progression of fibrosis or slowing it down significantly, are not available and unfortunately initial results are not promising.

Consensus guidelines from the from the International Liver Transplantation Society Expert Panel on Liver Transplantation and HCV (Wiesner et al, 2003) state that “[a]lthough no firm recommendations can be made based on data, there are enough anecdotal and single center reports that suggest that a patient with recurrent HCV disease who has grade II fibrosis or higher should be given a trial of combination therapy with interferon.” Regarding maintenance therapy in liver transplant recipients with recurrent HCV diseases, the Expert panel agreed that there were no data to recommend maintenance therapy as an approach.
Regarding the role of preemptive therapy in liver transplant recipients prior to HCV recurrence, the Expert panel stated that preemptive therapy should be considered in patients who undergo retransplantation for rapidly progressive recurrent hepatitis C and HCV-negative transplant recipients who receive organs from HCV-positive donors because of great clinical need. The Expert panel noted, however, that “demonstration of efficacy is lacking at this time.”

The safety and effectiveness of peginterferon alpha-2a (Pegasys) for the treatment of chronic hepatitis B was assessed in 2 phase III controlled clinical trials in HBeAg positive and HBeAg negative patients with hepatitis B. In each study, patients were randomized to peginterferon alpha-2a 180 µg subcutaneously once-weekly, lamivudine 100 mg once-daily, or both peginterferon alpha-2a plus lamivudine. All patients received 48 weeks of their assigned therapy followed by 24 weeks of treatment-free follow-up. These 2 clinical trials demonstrated that 24 weeks after a defined 48 week period of therapy, more patients achieved a sustained response with peginterferon alpha-2a than with lamivudine (Epivir). These studies demonstrated that the addition of lamivudine to peginterferon alpha-2a did not improve response rates over peginterferon alpha-2a alone.

All patients included in these studies of peginterferon alpha-2a for chronic hepatitis B virus (HBV) infection were adults with compensated liver disease and evidence of HBV replication (serum HBV greater than 500,000 copies/ml for the study of HBeAg positive patients and serum HBV greater than 100,000 copies/ml for the study of HBeAg negative patients). All patients had serum alanine aminotransferase (ALT) between 1 and 10 times the upper limit of normal and liver biopsy findings compatible with the diagnosis of chronic hepatitis.

In a study of HBeAg positive patients with chronic HBV infection, 32 % of 271 patients treated with peginterferon alpha-2a seroconverted by the end of follow-up versus 19 %sero-conversion among 272 patients treated with lamivudine. Subjects treated with peginterferon alpha-2a had a higher rate of DNA response (defined as less than 100,000 copies per ml) (32 %) by the end of follow-up than subjects treated with lamivudine (22 %). In a study of HBeAg negative patients with chronic HBV infection, 43 % of 177 patients treated with peginterferon alpha-2a exhibited a HBV DNA response (defined as less than 20,000 copies per ml) by the end of follow-up versus 29 % of 181 patients treated with lamivudine. Subjects treated with peginterferon alpha-2a had a higher rate of ALT normalization (59 %) by the end of follow-up than subjects treated with lamivudine (44 %). Conclusions regarding comparative efficacy of peginterferon alpha-2a and lamivudine treatment based upon the end of follow-up results are limited by the different mechanisms of action of the two compounds. Most treatment effects of lamivudine are unlikely to persist 24 weeks after therapy is withdrawn.

The effectiveness of repeat or maintenance pegylated interferon treatment of chronic HBV infection is unknown. According to guidelines from the American Gastroenterological Association (Dienstag and McHutchison, 2006), re-treatment is indicated for persons who have relapsed (with relapse defined as where HCV RNA is undetectable during and at the end of therapy but re-appears after completion of therapy) after having completed a course of less-effective therapy. For example, it may be appropriate to re-treat a person with pegylated interferon plus ribavirin who have relapsed after a course of standard interferon plus ribavirin. However, relapers are likely to experience a response only to subsequently relapse again with a subsequent course of the same therapy (e.g., re-treatment of a person with pegylated interferon plus ribavirin who had relapsed following previous treatment with this same regimen).

The American Academy of Neurology (AAN) has concluded that, on the basis of several consistent Class I studies, interferon-beta has been demonstrated to reduce the attack rate (whether measured clinically or by MRI) in patients with multiple sclerosis (MS) or with clinically isolated syndromes who are at high-risk for developing MS (Type A recommendation). The AAN has stated that treatment of MS with interferon beta produces a beneficial effect on MRI measures of disease severity such as T2 disease burden and probably also slows sustained disability progression (Type B recommendation).

There currently are two types of interferon beta (recombinant) commercially available in the United States, interferon beta-1a and interferon beta-1b. Important differences in beneficial effects (clinical, MRI measures of response) between these different types of interferon beta in the management of multiple sclerosis have not been reported and the existence of such differences is as yet unknown (Luzzio, 2013). Clinical interpretation of head-to-head comparative studies involving various interferon beta preparations is limited by methodologic problems (e.g., short duration, open-label studies, nonstandardized dosages and/or routes of administration). In addition, the comparative efficacy of interferon beta preparations and other disease-modifying agents (e.g., glatiramer acetate, mitoxantrone) has not been evaluated in well-designed, controlled studies (Luzzio, 2013).
The efficacy of interferon beta-1a (Avonex, Rebif) and interferon beta-1b (Betaseron, Extavia) appear similar for reducing the frequency and severity of exacerbations in relapsing, remitting MS. A randomized clinical study comparing Avonex to Rebif in 677 patients with primary relapsing/remitting MS found a statistically significant difference in favor of Rebif in the proportion of patients who were relapse free at 24 weeks. The investigators found that 75% of patients treated with Rebif were relapse-free, compared to 63% of patients treated with Avonex. However, the design of the study did not support any conclusion regarding effects on accumulation of disability.

However, the effectiveness of interferon beta in slowing disease progression and lessening accumulation of disability in secondary progressive MS is still being studied. Furthermore, the FDA has not approved interferon beta for the additional indication of chronic progressive MS.

The Therapeutics and Technology Assessment Subcommittee of the AAN (Goodin et al, 2007) evaluated the clinical and radiological impact of developing neutralizing antibodies (NAbs) to interferon beta (IFN-beta) while on this therapy for MS. On the basis of Class II and III evidence, it is concluded that treatment of patients with MS with IFN-beta is associated with the production of NAbs (Level A). NAbs in the serum are probably associated with a reduction in the radiological and clinical effectiveness of IFN-beta treatment (Level B). In addition, the rate of NAb production is probably less with IFN-beta-1a treatment than with IFN-beta-1b treatment, although the magnitude and persistence of this difference is difficult to determine (Level B). Finally, it is probable that there is a difference in sero-prevalence due to variability in the dose of IFN-beta injected or in the frequency or route of its administration (Level B). Regardless of the explanation, it seems clear that IFN-beta-1a (as it is currently formulated for IM injection) is less immunogenic than the current IFN-beta preparations (either IFN-beta-1a or IFN-beta-1b) given multiple times per week subcutaneously (Level A).

However, because NAbs disappear in some patients even with continued IFN-beta treatment (especially in patients with low titers), the persistence of this difference is difficult to determine (Level B). Although the finding of sustained high-titer NAbs (greater than 100 to 200 NU/ml) is associated with a reduction in the therapeutic effects of IFN-beta on radiographical and clinical measures of MS disease activity, there is insufficient information on the utilization of NAb testing to provide specific recommendations regarding when to test, which test to use, how many tests are necessary, or which cutoff titer to apply.

Hughes et al (2010) carried out a dose-ranging efficacy study of IFN-beta-1a in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Adults with intravenous immunoglobulin (IVIG)-dependent CIDP (n = 67) were enrolled in this 32-week double-blind trial and randomized to intramuscular (IM) IFN-beta-1a. Patients received 30 microg once-weekly plus placebo (n = 12), IM IFN-beta-1a 60 microg once-weekly plus placebo (n = 11), IM IFN-beta-1a 30 microg twice-weekly (n = 11), IM IFN-beta-1a 60 microg twice-weekly (n = 11), or placebo twice-weekly (n = 22). Participants were maintained on IVIG through week 16, when IVIG was discontinued. Patients who worsened were re-started on IVIG. The primary outcome was total IVIG dose (g/kg) administered from week 16 to 32. There was no difference in total IVIG dose administered after week 16 for patients treated with IFN-beta-1a (1.20 g/kg) compared with placebo (1.34 g/kg; p = 0.75). However, exploratory analyses suggested IFN-beta-1a significantly reduced total dose of IVIG compared with placebo for participants who required either high-dose IVIG (greater than 0.95 g/kg per month) or had greater weakness at baseline (Medical Research Council sum score less than 51). Adverse events included flu-like symptoms, headache, and fatigue in the IFN-beta-1a groups. The authors concluded that IFN-beta-1a therapy did not provide significant benefit over IVIG therapy alone for patients with CIDP. However, IFN-beta-1a might be beneficial for patients with more severe disability or those needing high doses of IVIG. This study was designed to provide Class I evidence for the safety and efficacy of IM IFN-beta-1a in the treatment of CIDP but has been subsequently classified as Class II due to a greater than 20% patient drop-out rate. Thus, this randomized controlled trial (RCT) provided Class II evidence of no effect on primary and secondary endpoints of 4 dosage regimens of IM IFN-beta-1a added to IVIG in persons with CIDP.

Currently, the only FDA-approved indications for interferon gamma (Actimmune) is for treatment of chronic granulomatous disease, and for delaying time to disease progression in patients with severe, malignant osteopetrosis. Interferon gamma has also been shown to be effective for the treatment of atopic dermatitis and Waldenstrom's macroglobulinemia.

Idiopathic pulmonary fibrosis (IPF) is a condition that has a poor prognosis, with a median survival of 4 to 5 years. Preliminary data from a phase III trial of interferon (IFN) gamma-1b injection for the treatment of IPF failed to show a significant difference between IFN gamma-1b-treated patients and control group patients in progression free survival time, the primary endpoint of the study. The double-blind, placebo-controlled trial at 58 U.S. and European centers randomized 300 patients to receive either placebo or 200 mcg of IFN gamma-1b injected subcutaneously 3 times a week. However, there was non-significant 10% difference in
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IPF were eligible for the study if they had histologically proven IPF, or, in the absence of surgical biopsy, poor. Prednisone has been the mainstay of therapy since its release for clinical use in 1948. Recently, a number of other drug combinations have been tried with prednisone (e.g., methotrexate, colchicine, penicillamine, or cyclosporine) but have failed or are not well-tolerated by the patient. Few high quality, prospective, controlled clinical trials have been performed. Thus, there is no good evidence to support the routine use of any specific therapy in the management of IPF. Additional large clinical trials are needed to confirm the potential usefulness of the newer agents (e.g., IFN gamma-1b, pirfenidone, N-acetylcysteine, coumadin, bosentan, or etanercept).

It should be noted that in March 2007, InterMune abandoned efforts to develop Actimmune (IFN gamma-1b) as a treatment for IPF because results from a late-stage clinical trial showed the drug did not prolong lives. The phase 3 INSPIRE clinical trial evaluating Actimmune (IFN gamma-1b) in IPF patients with mild-to-moderate impairment in lung function was discontinued based upon the recommendation of the study’s independent data monitoring committee (DMC). In a planned interim analysis that included a total of 115 deaths, the DMC found the overall survival result crossed a pre-defined stopping boundary for lack of benefit of Actimmune relative to placebo. Among the 826 randomized patients, there was not a statistically significant difference between treatment groups in overall mortality (14.5 % in the Actimmune group as compared to 12.7 % in the placebo group). Based on a preliminary review of the interim safety data, the adverse events associated with Actimmune appear generally consistent with prior clinical experience, including constitutional symptoms, neutropenia and possibly pneumonia.

In a multi-center, randomized, placebo-controlled study, King et al (2009) evaluated if treatment with IFN gamma-1b improved survival compared with placebo in patients with IPF and mild-to-moderate impairment of pulmonary function. A total of 826 patients with IPF were enrolled from 81 centers in 7 European countries, the USA, and Canada. Patients were randomly assigned (double-blind) in a 2:1 ratio to receive 200 microg IFN gamma-1b (n = 551) or equivalent placebo (n = 275) subcutaneously, 3 times per week. Eligible patients were aged 40 to 79 years, had been diagnosed in the past 48 months, had a forced vital capacity of 55 to 90 % of the predicted value, and a hemoglobin-corrected carbon monoxide diffusing capacity of 35 to 90 % of the predicted value. The primary endpoint was overall survival time from randomization measured at the second interim analysis, when the proportion of deaths had reached 75 % of those expected by the study conclusion. At the second interim analysis, the hazard ratio for mortality in patients on IFN gamma-1b showed absence of minimum benefit compared with placebo (1.15, 95 % CI: 0.77 to 1.71, p = 0.497), and indicated that the study should be stopped. After a median duration of 64 weeks (IQR 41 to 84) on treatment, 80 (15 %) patients on IFN gamma-1b and 35 (13 %) on placebo had died.
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Almost all patients reported at least 1 adverse event, and more patients on IFN gamma-1b group had constitutional signs and symptoms (influenza-like illness, fatigue, fever, and chills) than did those on placebo. Occurrence of serious adverse events (e.g., pneumonia, respiratory failure) was similar for both treatment groups. Treatment adherence was good and few patients discontinued treatment prematurely in either group. The authors concluded that they can not recommend treatment with IFN gamma-1b since the drug did not improve survival for patients with IPF, which refutes previous findings from subgroup analyses of survival in studies of patients with mild-to-moderate physiological impairment of pulmonary function.

Guidelines from the National Comprehensive Cancer Network (NCCN, 2008) recommend the use of interferon gamma-1b in selected persons with mycosis fungoides (MF) and Sezary syndrome (SS). NCCN guidelines recommend use of IFN gamma-1b as primary treatment as systemic biologic therapy in patients with stage IA to IIA MF and SS with blood involvement, and stage IIB to IV MF and SS. NCCN guidelines recommend use of IFN gamma-1b a single agent or in combination therapy as indicated below:

- Single agent for stage IA to IIA and stage III MF with blood involvement
- Single agent or in combination with radiation therapy for stage IIB MF limited-extent tumor disease
- Single agent or in combination with systemic retinoids, phototherapy, or photopheresis (with or without systemic retinoids) stage IA to IIB with large cell transformed MF, stage IIB MF (generalized tumor disease or limited-extent tumor disease with blood involvement) or SS
- Single agent or in combination with skin-directed therapies (corticosteroids, carmustine, mechloretamine hydrochloride, phototherapy, or total skin electron beam therapy) for stage III MF with no blood involvement.

According to NCCN (2008) guidelines, interferon gamma-1B may be used as adjuvant systemic biologic therapy after total skin electron beam therapy for stage IIB MF generalized tumor disease or limited tumor disease with blood involvement or large cell transformation or after chemotherapy for stage IV MF with bulky lymph nodes or visceral disease. NCCN guidelines also indicate interferon gamma-1B as systemic biologic therapy for patients with refractory or progressive MF, as a single agent or in combination with systemic retinoids, phototherapy, or photopheresis (with or without systemic retinoids).

There is a lack of published evidence of the effectiveness of interferon gamma for Waldenstrom's macroglobulinemia. National Comprehensive Cancer Network guidelines on Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma did not include a recommendation for use of interferon gamma (NCCN, 2012).

Consensus interferon (interferon alfacon-1; Infergen) is a non-naturally occurring recombinant type 1 alpha interferon. It has been approved by the FDA for use in the treatment of chronic hepatitis C in person 18 years of age or older with compensated liver disease who have anti-hepatitic C virus serum antibodies and/or the presence of hepatitis C virus RNA. Although there are studies comparing standard alpha interferon to consensus interferon, and limited evidence regarding the use of consensus interferon in persons with hepatitis C who fail to respond to standard alpha interferon therapy, current guidelines indicate pegylated interferons as the treatment of choice for persons with hepatitis C, including those who fail to respond to standard alpha interferon therapy. There are insufficient published studies comparing consensus interferon to pegylated interferons in persons with hepatitis C who have failed standard interferon therapy.

An open-label multicenter controlled clinical trial evaluated the effectiveness of consensus interferon plus ribavirin in persons with hepatitis C who were non-responsive to previous pegylated interferon and ribavirin. This study, the DIRECT (Daily-Dose Consensus Interferon and Ribavirin: Efficacy of Combined Therapy) trial compared the effectiveness of ribavirin plus 2 different doses of consensus interferon versus no treatment in subjects with hepatitis C who were nonresponsive to pegylated interferon and ribavirin therapy (Bacon et al, 2006; Bacon et al, 2009; Three Rivers Pharmaceuticals, 2010). This study compared 2 doses of consensus interferon (9 mcg or 15 mcg) administered daily plus ribavirin (1,000 mg or 1,200 mg weight-based dosed) administered daily for 48 weeks to subjects who were non-responders to previous pegylated interferon plus ribavirin therapy. Prior non-response was defined as a less than 2 log decline in viral load while undergoing at least 12 weeks of previous pegylated interferon/ribavirin therapy with greater than or equal to 80 % adherence or a detectable viral load at end-of-treatment after completing at least 24 weeks of therapy. Ninety-five percent of study subjects were infected with genotype 1. Approximately 80 % of subjects were null responders (less than 2 log drop in viral load during their previous pegylated interferon/ribavirin therapy). In study IRHC-001, 515 subjects were randomized to consensus interferon 9 mcg plus ribavirin, consensus interferon 15 mcg plus ribavirin, or no treatment. In study IRHC-002, 144 subjects in the no treatment arm of IRHC-001 were re-randomized to either consensus interferon 9 mcg plus ribavirin or consensus interferon 15 mcg plus ribavirin. Subjects were treated for up to 48 weeks. The primary endpoint was sustained virologic response, defined as undetectable HCV RNA 24 weeks after the
end of treatment. None of the subjects in the no-treatment arm of IRHC-001 achieved a sustained virologic response. The overall rate of sustained virologic response in subjects treated with consensus interferon 9 mcg plus ribavirin was 5 %, and 9 % for subjects treated with consensus interferon 15 mcg plus ribavirin. Persons with genotype 1 had less benefit from retreatment. The sustained virologic response rates for persons infected with genotype 1 was 4 % for persons assigned to consensus interferon 9 mcg and 6 % for persons assigned to consensus interferon 15 mcg. The sustained virologic response rates for other genotypes was 21 % for consensus interferon 9 mcg and 67 % for consensus interferon 15 mcg. Persons with high viral load were less likely to benefit from re-treatment. The sustained virologic response rate for persons with HCV RNA less than 850,000 IU/ml was 13 % and 14 % for persons assigned to 9 mcg and 15 mcg of consensus interferon, respectively. The sustained virologic response rate for persons with HCV RNA greater than or equal to 850,000 IU/ml was 2 % and 6 % for persons assigned to 9 mcg and 15 mcg of consensus interferon, respectively.

The recommended dose of consensus interferon for monotherapy is 9 mcg 3 times weekly for 24 weeks (as initial treatment) or 15 mcg 3 times weekly for up to 48 weeks (as retreatment). The recommended dose of combination treatment is 15 mcg consensus interferon daily with 1,000 mg or 1,200 mg ribavirin (for body weight less than 75 kg and greater than or equal to 75 kg) daily for up to 48 weeks (as re-treatment). According to the product labeling, persons who fail to achieve at least a 2 log drop at 12 weeks or undetectable HCV-RNA at week 24 are highly unlikely to achieve a sustained virologic response and discontinuation of therapy should be considered.

Recurrence is common following hepatic resection for HCC. Interferon possesses anti-angiogenic, anti-proliferative, anti-viral, and immunomodulatory effects; and may be an effective form of adjuvant therapy. Small randomized controlled clinical trials suggest a benefit from prolonged interferon therapy following resection of hepatocellular carcinoma in persons with hepatitis C (Shiratori et al, 2003; Nishiguchi et al, 2005; Mazzaferrro et al, 2006).

Chen et al (2012) examined the clinical efficacy of adjuvant interferon alfa-2b (IFNα-2b) therapy on recurrence-free survival (RFS) of patients with post-operative viral hepatitis-related hepatocellular carcinoma (HCC). Patients with curative resection of viral hepatitis-related HCC were eligible, and were stratified by underlying viral etiology and randomly allocated to receive either 53 weeks of adjuvant IFNα-2b treatment or observation alone. The primary endpoint of this study was RFS. A total of 268 patients were enrolled with 133 in the IFNα-2b arm and 135 in the control arm. Eighty percent of them were hepatitis B surface antigen sero-positive. At a median follow-up of 63.8 months, 154 (57.5 %) patients had tumor recurrence and 84 (31.3 %) were deceased. The cumulative 5-year recurrence-free and overall survival rates of intent-to-treat analysis showed that adjuvant interferon had no survival benefit for pTNM stage I/II tumor (5-year survival 90 % in both groups; p = 0.828, log-rank test). Adjuvant IFNα-2b treatment was associated with a significantly higher incidence of leucopenia and thrombocytopenia. Thirty-four (24.8 %) of treated patients required dose reduction, and 5 (3.8 %) of these patients subsequently withdrew from therapy because of excessive toxicity. Adjuvant IFNα-2b only temporarily suppressed viral replication during treatment period. The authors concluded that in this study, adjuvant IFNα-2b did not reduce the post-operative recurrence of viral hepatitis-related HCC. They stated that more potent anti-viral therapy deserves to be explored for this patient population.


Interferon is also being evaluated for use following resection of hepatocellular carcinoma in persons with hepatitis B. Lo et al (2007) performed a randomized controlled trial of adjuvant interferon therapy in patients with predominantly hepatitis B-related HCC to examine if the prognosis after hepatic resection could be improved. Patients with no residual disease after hepatic resection for HCC were randomly assigned with stratification by pathologic tumour-node-metastasis (pTNM) stage to receive no treatment (control group), interferon alpha-2b 10 MIU/m (IFN-I group) or 30 MIU/m (IFN-II group) three-weekly for 16 weeks. Enrollment to the IFN-II group was terminated because adverse effects resulted in treatment discontinuation in the first 6 patients. A total of 40 patients each had been enrolled into the control group and IFN-I group. The baseline clinical, laboratory, and tumor characteristics of both groups were comparable. The 1- and 5-year survival rates were 85 % and 61 %, respectively, for the control group and 97 % and 79 %, respectively, for the IFN-I group (p = 0.137). After adjusting for the confounding prognostic factors in a Cox model, the relative risk of death for interferon treatment was 0.42 (95 % CI: 0.17 to 1.05; p = 0.063). Exploratory subset analysis showed that adjuvant interferon had no survival benefit for pTNM stage I/II tumor (5-year survival 90 % in both groups; p = 0.917) but prevented early recurrence and improved the 5-year survival of patients with stage III/IVA tumor from 24 % to 68 % (p = 0.038). The authors concluded that in a group of patients with predominantly hepatitis B-related HCC, adjuvant interferon therapy showed a trend for survival benefit,
Interferons

primarily in those with pTNM stage III/IVA tumors. They stated that further larger RCTs stratified for stage are needed. An editorial that accompanied the afore-mentioned article stated that any new strategy to prevent HCC recurrence following resection must still be tested in randomized controlled studies, including a control group without treatment (Clavien, 2007).

Guidelines from the NCCN (2008) recommend use of interferon alpha in desmoid tumors, as a low-dose single agent for gross residual disease following surgery or for unresectable disease either as an initial treatment or for recurrence. NCCN guidelines cite for support the results of a non-randomized, retrospective study of 13 patients with extra-abdominal desmoid tumors, which found encouraging response rates with interferon alpha treatment. Seven of the patients included in the study also received tretinoin. After a mean of 27 months of treatment, local control was seen in 11 of 13 patients (85%). Seven patients had no evidence of disease at a mean disease-free interval of 22 months; in 2 patients progressive disease occurred after only 7 and 9 months, respectively, of observation. In another 4 patients, progression of the desmoid tumor was stabilized. The investigators concluded that these data suggest that treatment with interferon may be effective in prolonging the disease-free interval of patients with desmoid tumors after intralesional or marginal surgery.

Hypereosinophilic syndromes (HES) constitute a rare and heterogeneous group of disorders, defined as persistent and marked blood eosinophilia (greater than 1.5 x 10⁹/L for more than 6 consecutive months) associated with evidence of eosinophil-induced organ damage, where other causes of hypereosinophilia such as allergic, parasitic, and malignant disorders have been excluded (Roufosse et al, 2007). Target-organ damage mediated by eosinophils is highly variable among patients, with involvement of skin, heart, lungs, and central and peripheral nervous systems in more than 50 % of cases. Other frequently observed complications include hepato- and/or splenomegaly, eosinophilic gastroenteritis, and coagulation disorders. Diagnosis of HES relies on observation of persistent and marked hypereosinophilia responsible for target-organ damage, and exclusion of underlying causes of hypereosinophilia, including allergic and parasitic disorders, solid and hematological malignancies, Churg-Strauss disease, and HTLV infection (Roufosse et al, 2007). Therapeutic management should be adjusted to disease severity and eventual detection of pathogenic variants. For patients with the FIP1L1-PDGFRα fusion gene (F/P+) variant, imatinib is first line therapy. For others, corticosteroids are generally administered initially. Interferon alpha is the drug of choice for patients with hypereosinophilic syndromes who do not respond to corticosteroids, or as a corticosteroid-sparing agent in those who require higher doses of corticosteroids (Roufosse et al, 2008). Other second line options for corticosteroid-resistant cases include hydroxycarbamide and imatinib (Roufosse et al, 2007).

In a double-blind, placebo-controlled trial, Tunca et al (2004) examined the effect of INF-alpha on acute attacks of familial Mediterranean fever (FMF). These investigators treated 34 acute abdominal attacks with IFN-alpha 5 MIU or placebo subcutaneously in the early phase of the attack. Leucocytes, thrombocytes, the erythrocyte sedimentation rate, fibrinogen, C-reactive protein (CRP), serum amyloid A protein (SAA), haptoglobin, transferrin, IL-1beta and TNF-alpha were measured at hours 0, 6, 12, 24 and 48. The median time to recovery in those treated with IFN-alpha and placebo was not significantly different, while the leucocytosis and high levels of fibrinogen were significantly more prolonged in placebo-treated patients; CRP and SAA were extremely elevated and peaked at 24 hours, remaining less marked in the patients treated with IFN-alpha, but the difference was not statistically significant. Observations regarding the other parameters were unremarkable. The authors concluded that although there were some clues indicating a depressed inflammatory response with IFN-alpha, they could not demonstrate a definitive effect of this agent in this double-blind trial. The drug may suppress the acute inflammation of FMF only if administered at the earliest phase.

Schmidt and associates (2007) stated that data from a phase II clinical trial combining chemoradiotherapy with IFN-alpha (CapRI scheme) for adjuvant treatment of pancreatic carcinoma are very encouraging. Thus, a phase III trial comparing chemotherapy with the chemoradiotherapy with IFN-alpha scheme has been initiated in August 2004. Translational research with a focus on immunomodulation is performed in parallel to the study. Blood and serum samples were taken at various time points. Patients in arm A (chemoradioimmunotherapy) receive a single low-dose interferon injection before therapy to investigate the direct effect of IFN-alpha. So far, samples from 44 patients have been investigated for surface molecule expression, cytokine levels, natural killer cell cytotoxicity, and antigen-specific Granzyme B release. Patients in arm A showed 1 day after IFN-alpha injection a significant increase in spontaneous cytotoxicity; this effect was fading after repeated injections. Furthermore, cells releasing Granzyme B after stimulation with CA 19.9 and MUC-1 protein increased under therapy. Five days after the first IFN-alpha injection, interleukin-12 and tumor necrosis factor-alpha serum levels peak. These researchers observed significant increases of monocytes, peripheral dendritic cells, CD40 cells, central and effector memory T cells, and CD8 cells, CD4
Interferons combined chemo-radioimmunotherapy lead to controlled disease in 5 of 7 patients. The overall toxicity was well-managed. The authors concluded that these findings strengthened the hypothesis of concomitant chemo-radioimmunotherapy with 5-FU, IFN-alpha and cisplatin as a possible new treatment of pancreatic cancer in resected patients.

In a feasibility study, Nitsche and colleagues (2008) noted that recent studies give rise to the hypothesis, that adjuvant chemoradioimmunotherapy with 5-fluorouracil (5-FU), cisplatin and IFN-alpha might be a possible new treatment of pancreatic cancer in resected patients. These researchers reported the up-to-now experience at their institution. A total of 11 patients with histological diagnosis of localized carcinoma of the pancreas (n = 7) or peri-ampullary (n = 4) were prospectively analyzed. Four patients were deemed unresectable because of local invasion of adjacent organs (neoadjuvant setting) and 7 patients underwent curative resection (adjuvant setting). Eight patients were classified as T3 carcinomas and 3 T4 carcinomas. Six of the 11 (55 %) patients presented with positive lymph node involvement. One histological grade I, 6 grade II and 3 grade III were detected. External conformal irradiation to a total dose of 50.4 Gy with 1.8 Gy per day was delivered. All patients received a concomitant chemotherapy with continuous 5-FU 200 mg/m2 per day on 28 treatment days and intravenous bolus cisplatin 30 mg/m2 per week (day 2, 9, 16, 23, 30). A recombinant r-IFN-alpha was administered on 3 days weekly during week 1 to 5 of the radiotherapy course as subcutaneous injections with 3*3 Mio. I.U. weekly. The 4-year overall survival rate for all patients was 55 %.

In the neoadjuvant group, 3 of 4 patients died due to progressive disease; in the adjuvant group, combined chemo-radioimmunotherapy lead to controlled disease in 5 of 7 patients. The overall toxicity was well-managed. The authors concluded that these findings strengthened the hypothesis of concomitant chemo-radioimmunotherapy with 5-FU, IFN-alpha and cisplatin as a possible new treatment of pancreatic cancer in resected patients.

Furthermore, the NCCN guidelines include no recommendation for the use of IFN-alpha in the treatment of patients with pancreatic adenocarcinoma.

In an open, non-randomized, uncontrolled, interventional, prospective study, Sobaci et al (2010) evaluated the intermediate-term safety and effectiveness of interferon alpha-2a (IFN-alpha2a) in patients with Behcet's uveitis (BU) refractory to corticosteroids and immunosuppressive agents. A total of 53 patients (106 eyes) with active, vision-threatening BU who failed to respond to conventional treatments were included in this study. In 53 patients, acute inflammation was suppressed with effective prednisolone dosage (1 to 2 mg/kg/day, tapered to 10 mg within 4 to 6 weeks). The patients were treated with IFN-alpha2a 4.5 MIU 3 times per week for the first 3 months followed by IFN-alpha2a 3 MIU 3 times per week for the next 3 months. Observation or other treatment methods were performed according to the decision tree developed for this study. Primary outcome measures were remission and complete response; secondary outcome measures were frequency of uveitis attacks, visual acuity (VA), and adverse effects. During 2 years of follow-up (median of 65 months, range of 12 to 130 months), compliance with the therapy was excellent. At the end of 1-year follow-up, treatment response was obtained in 45 of 53 patients (84.9 %). The mean attack rate of 3.6 +/- 1.1 per year (range of 2 to 8) decreased to 0.56 +/- 0.75 (range of 0 to 4) per year (p = 0.001). Visual acuity improved (greater than or equal to 0.2 logarithm of the minimum angle of resolution units from initial VA) in 30 eyes (28.3 %) and worsened in 12 eyes (11.3 %). Five patients (9.4 %) did not respond to the initial treatment, and 3 patients (5.6 %) developed severe adverse effects, including psoriasis, epileptic seizure, and extreme tiredness. Fifteen patients (28.3 %) were off treatment for all the medications and disease free for 28 +/- 13.1 months (range of 12 to 50 months). The authors concluded that these findings suggested that IFN-alpha2a may be a valuable treatment option in BU that is refractory to corticosteroids and conventional immunosuppressive agents. The possible role of IFN-alpha2a as a first-line agent in BU should be validated in RCTs against newly described biologic agents.

In a phase I clinical trial, Jakacki et al (2011) evaluated preliminary effectiveness and determined the recommended phase II dose (RP2D) for pegylated interferon-α-2b (PI) in patients with unresectable progressive or symptomatic plexiform neurofibromas (PN). Pegylated interferon-α-2b was administered weekly in cohorts of 3 to 6 patients during the dose-finding phase and continued for up to 2 years. A total of 12 patients were treated at the RP2D to further evaluate toxicity and activity. Thirty patients (median age of 9.3 years, range of 1.9 to 34.7 years) were enrolled in this study. No dose-limiting toxicity (DLT) was seen in patients treated at the 3 μg/kg dose level (DL) during the first 4 weeks. All 5 patients treated at the 4.5 μg/kg DL came off study or required dose reductions for behavioral toxicity or fatigue. Similar DLT on the 3 μg/kg DL became apparent over time. There was 1 DLT (myoclonus) in 12 patients enrolled at the 1.0 μg/kg DL. Eleven of 16 patients with pain showed improvement and 13 of 14 patients with a palpable mass had a decrease in size. Five of 17 patients (29 %) who underwent volumetric analysis had a 15 % to 22 % decrease in volume. Three of 4 patients with documented radiographical progression before enrollment...
showed stabilization or shrinkage. The authors concluded that the RP2D of PI for pediatric patients with PN is 1 μg/kg/wk. Clinical and radiographical improvement and cessation of growth can occur. The authors acknowledged the limitations of using subjective assessments to determine clinical response and more stringent, validated criteria have been incorporated into an ongoing phase II clinical study.

In a Cochrane review, Hughes et al (2011) reviewed systematically the evidence from RCTs for pharmacological agents other than plasma exchange, intravenous immunoglobulin and corticosteroids for the treatment of Guillain Barré syndrome. Only very low quality evidence was found for 4 different interventions. One RCT with 13 participants showed no significant difference in any outcome between IFN beta-1a and placebo. Another with 10 participants showed no significant difference in any outcome between brain-derived neurotrophic factor and placebo. A third with 37 participants showed no significant difference in any outcome between cerebrospinal fluid filtration and plasma exchange. In a fourth with 20 subjects, the risk ratio of improving by 1 or more disability grades after 8 weeks was significantly greater with the Chinese herbal medicine tripterygium polyglycoside than with corticosteroids (risk ratio 1.47; 95 % CI: 1.02 to 2.11). The authors concluded that the quality of the evidence was very low. Three small RCTs, of IFN beta-1a, brain-derived neurotrophic factor and cerebrospinal fluid filtration, showed no significant benefit or harm. A fourth small trial showed that the Chinese herbal medicine tripterygium polyglycoside hastened recovery significantly more than corticosteroids but this result needs confirmation. It was not possible to draw useful conclusions from the few observational studies.

Boceprevir capsules (Victrelis, Merck) is a protease inhibitor that has been FDA approved to treat adults with chronic hepatitis C genotype 1 with compensated liver disease, and who either have not been previously treated with interferon therapy for their hepatitis C or who have failed such treatment. Boceprevir is approved for use in combination with peginterferon alfa and ribavirin. The safety and effectiveness of boceprevir was evaluated in 2 phase 3 clinical trials with 1,500 adult patients. In both trials, 2/3 of patients receiving boceprevir in combination with pegylated interferon and ribavirin experienced a significantly increased sustained virologic response (i.e., the hepatitis C virus was no longer detected in the blood 24 weeks after stopping treatment), compared to pegylated interferon and ribavirin alone. Boceprevir is taken 3 times a day with food. The most commonly reported side effects in patients receiving boceprevir in combination with pegylated interferon and ribavirin include fatigue, anemia, nausea, headache and dysgeusia. According to the FDA-approved labeling, 800 mg of boceprevir is administered orally 3 times daily in combination with peginterferon alfa and ribavirin. Duration of therapy is determined by Response-Guided Therapy (RGT) guidelines based upon the patient’s HCV-RNA levels at treatment weeks 8, 12 and 24.

Telaprevir tablets (Incivek, Vertex) are protease inhibitors that have received FDA approval to treat chronic hepatitis C genotype 1 infection in adults who have either not received interferon-based drug therapy for their infection or who have not responded adequately to prior therapies. Telaprevir is approved for use with peginterferon alfa and ribavirin. The safety and effectiveness of telaprevir was evaluated in 3 phase 3 clinical trials with about 2,250 adult patients who were previously untreated, or who had received prior therapy. In all studies patients also received the drug with standard of care. In previously untreated patients, 79 % of those receiving telaprevir experienced a sustained virologic response. The sustained virologic response for patients treated with telaprevir across all studies, and across all patient groups, was between 20 and 45 % higher than current standard of care. Studies indicate that treatment with telaprevir can be shortened from 48 weeks to 24 weeks in most patients; 60 % of previously untreated patients achieved an early response and received only 24 weeks of treatment (compared to the standard of care of 48 weeks). The sustained virologic response for these patients was 90 %. According to the FDA-approved labeling, 750 mg of telaprevir is taken 3 times a day (7 to 9 hours apart) with food (not low fat). The labeling states that telaprevir must be administered with both peginterferon alfa and ribavirin for all patients for 12 weeks, followed by a response-guided regimen of either 12 or 36 additional weeks of peginterferon alfa and ribavirin depending on viral response and prior response status. The most commonly reported side effects in patients receiving telaprevir in combination with peginterferon alfa and ribavirin include rash, low red blood cell count, nausea, fatigue, headache, diarrhea, pruritus, and anal or rectal irritation and pain. Rash can be serious and can require stopping telaprevir or all 3 drugs in the treatment regimen.

Commenting on the data from randomized trials of protease inhibitors in genotype 1 hepatitis C, Rosen (2011) stated that a reasonable initial regimen would be telaprevir with peginterferon and ribavirin for 12 weeks. If tests for HCV RNA were negative at weeks 4 through 12 (indicating an extended rapid virologic response), only 12 additional weeks of peginterferon and ribavirin would be recommended, whereas if an extended rapid virologic response were not achieved, peginterferon and ribavirin would be continued for an additional 36 weeks. If boceprevir were used, according to FDA guidelines, a 4-week lead-in phase of peginterferon and ribavirin would be followed by peginterferon and ribavirin and boceprevir for 24 weeks (a
total of 28 weeks) if tests for HCV RNA were negative at weeks 8 through 24 of treatment. If the tests were positive between weeks 8 and 24 but negative at week 24, peginterferon and ribavirin and boceprevir would be continued for an additional 8 weeks, followed by an additional 12 weeks of peginterferon-ribavirin (a total of 48 weeks).

Primitive neuroectodermal tumor (PNET) is a neural crest tumor. It is a rare tumor, usually occurring in children and young adults under 25 years of age. After successful chemotherapy or radiotherapy, the 5-year survival rate is only 8%. Primitive neuroectodermal tumor belongs to the Ewing family of tumors; ependymoblastoma is a synonym for PNET. Based on location in the body, PNET is classified into 2 types: (i) peripheral PNET and (ii) central nervous system (CNS) PNET. It is also possible to add a third category, involving tumors of the autonomic nervous system, such as neuroblastoma. The peripheral PNET (pPNET) is now thought to be virtually identical to Ewing sarcoma. Primitive neuroectodermal tumor of the CNS are grossly divided into supra-tentorial PNET and infra-tentorial PNET, the latter being more common. An example of infra-tentorial PNET includes medulloblastoma, which occurs in the cerebellum. An example of supra-tentorial PNET includes pinealoblastoma, which occurs in the pineal region. National Comprehensive Cancer Network’s guidelines on Ewing sarcoma make no recommendation for use of interferon alpha. Furthermore, NCCN guidelines on CNS cancers only recommend interferon alpha for meningiomas, making no recommendation for use of interferon alpha for medulloblastoma or supratentorial PNET.

Akpek et al (2011) reviewed treatment options for patients with dry eye secondary to Sjogren’s syndrome (SS). A search strategy was developed to identify prospective, interventional studies of treatments for SS-associated dry eye from electronic databases. Eligible references were restricted to English-language articles published after 1975. These sources were augmented by hand searches of reference lists from accessed articles. Study selection, data extraction, and grading of evidence were completed independently by 4 or more review authors. The searches identified 3,559 references as of August 10, 2010. After duplicate review of the titles and abstracts, 245 full-text papers were assessed, 62 of which were relevant for inclusion in the review. The authors concluded that in the current literature on SS-associated dry eye, there is a paucity of rigorous clinical trials to support therapy recommendations. Nonetheless, the recommended treatments include topical lubricants, topical anti-inflammatory therapy, and tear-conserving strategies. The efficacy of oral secretagogues seems greater in the treatment of oral dryness than ocular dryness. Although oral hydroxychloroquine is commonly prescribed to patients with SS to alleviate fatigue and arthralgias, the literature lacks strong evidence for the efficacy of this treatment for dry eye. Intrferon-alpha was discussed in this review; but it was not recommended as a therapeutic option.

Gao et al (2011) evaluated the safety and effectiveness of adjunctive therapy using interferon-gamma (IFN-\(\gamma\)) for the treatment of pulmonary tuberculosis (TB). These investigators conducted a systematic review of controlled clinical trials that compared anti-TB drugs in combination with IFN-\(\gamma\) with the same anti-TB drugs alone for the treatment of pulmonary TB. A total of 9 trials were identified, with IFN-\(\gamma\) being aerosolized or administered subcutaneously in 1 trial, aerosolized only in 5 trials, and administered intramuscularly in 3 trials. The methodology quality of all trials was rated “C”. Meta-analysis of the trials with aerosolized IFN-\(\gamma\) showed statistical benefits on sputum negative conversion and chest radiograph: the pooled relative risk (RR) for conversion was 1.97 (95% CI: 1.20 to 3.24, p = 0.008) after 1 month of treatment, 1.74 (95% CI: 1.30 to 2.34, p = 0.0002) after 2 months of treatment, 1.53 (95% CI: 1.16 to 2.01, p = 0.003) after 3 months of treatment, 1.57 (95% CI: 1.20 to 2.06, p = 0.001) after 6 months of treatment, and 1.55 (95% CI: 1.17 to 2.05, p = 0.002) at the end of treatment; the pooled RR for the chest radiograph was 1.38 (95% CI: 1.10 to 1.71, p = 0.006) at the end of treatment. For intramuscularly administered IFN-\(\gamma\), meta-analysis of 3 trials showed its significant improvement on sputum negative conversion after 2 months of treatment. A RCT with aerosolized and subcutaneously administered IFN-\(\gamma\) reported significant reductions in the symptoms of fever, wheeze, and night sweats in the IFN-\(\gamma\)-treated groups compared with the control group after 1 month of treatment. No patients discontinued treatment because of adverse effects caused by IFN-\(\gamma\). The authors concluded that adjuvant therapy using IFN-\(\gamma\), especially by aerosol, might be beneficial to TB patients, but large RCTs are needed for further evaluation of its safety and effectiveness considering the quality of the trials analyzed.

Kanemaru et al (1997) employed IFN-alpha in the treatment of severe idiopathic sudden sensorineural hearing loss (ISSHL). A total of 42 patients were studied and had an average hearing ability of greater than or equal to 70 dB before treatment. These researchers also examined 2’-5’ oligoadenylate synthetase (2,5A-S) activity, one of the parameters indicating anti-viral activity of IFN, to investigate the relationship between the suppression of viral proliferation and prognosis and explain the pathogenesis of ISSHL. Complete recovery was found in 27 patients (64.3%) after IFN therapy. Increased 2,5A-S activity was observed on the 3rd day of IFN therapy in 24 of the 27 patients who completely recovered. No severe adverse events
were reported after IFN therapy. The authors concluded that these findings suggested that IFN therapy may be effective and safe in the treatment of ISSHL and calls for further investigation.

The American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF)'s clinical practice guideline on "Sudden hearing loss" (Stachler et al, 2012) noted that "[t]he panel made a recommendation against clinicians routinely prescribing anti-virals, thrombolytics, vasodilators, vasoactive substances, or anti-oxidants to patients with ISSNHL .... In addition to the therapies discussed above, a host of other therapies have been used to treat SSNHL (i.e., vitamins, minerals, interferon, nitroglycerin, and other complementary and alternative medications). The evidence base for these therapies was insufficient to review in this guideline and no comment is made on their use".

In a Cochrane review, Nava et al (2014) evaluated the benefit and harms of available treatments for neuro-Behcet's syndrome (NBS), including biologics, colchicine, corticosteroids, immunosuppressants and IFN-alpha. The authors concluded that there is no evidence to support or refute the benefit of biologics, colchicine, corticosteroids, immunosuppressants and IFN-alpha for the treatment of patients with NBS. They stated that well-designed multi-center RCTs are needed in order to inform and guide clinical practice.

Booy et al (2014) stated that pancreatic cancer is a highly aggressive malignancy with limited treatment options. To improve survival for patients with pancreatic cancer, research has focused on other treatment modalities like adding biological modulators such as type-I interferons (IFNs). Type I IFNs (i.e., IFN-α/IFN-β) have anti-proliferative, anti-viral as well as immunoregulatory activities. Furthermore, they are able to induce apoptosis, exert cell cycle blocking, and sensitize tumor cells for chemo- and radiotherapy. A few years ago, in-vitro, in-vivo, and several clinical trials have been described regarding adjuvant IFN-α therapy in the treatment of pancreatic cancer. Some studies reported a remarkable increase in the 2- and 5-year survival. Unfortunately, the only RCT did not show a significant increase in overall survival, although the increased median survival implicated that some patients in the experimental group benefitted from the adjuvant IFN-α therapy. Furthermore, encouraging in-vitro and in-vivo data pointed to a possible role for adjuvant IFN therapy. However, up till now, the use of IFNs in the treatment of pancreatic cancer remains controversial.

An UpToDate review on “Adjuvant therapy for resected exocrine pancreatic cancer” (Ryan and Mamon, 2015) does not mention interferon as a therapeutic option.

National Comprehensive Cancer Network’s Drugs & Biologics Compendium (2015) does not list pancreatic cancer as a recommended indication of interferon gamma-1B.

Appendix

Table 1: Child-Pugh Score

<table>
<thead>
<tr>
<th>Measure</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
<th>units</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bilirubin (total)</strong></td>
<td>&lt; 34 (&lt;2)</td>
<td>34-50 (2-3)</td>
<td>&gt; 50 (&gt;3)</td>
<td>µmol/l (mg/dl)</td>
</tr>
<tr>
<td><strong>Serum albumin</strong></td>
<td>&gt; 3.5</td>
<td>2.8-3.5</td>
<td>&lt; 2.8</td>
<td>g/dl</td>
</tr>
<tr>
<td><strong>INR</strong></td>
<td>&lt; 1.7</td>
<td>1.71-2.20</td>
<td>&gt; 2.20</td>
<td>no unit</td>
</tr>
<tr>
<td><strong>Ascites</strong></td>
<td>None</td>
<td>Mild</td>
<td>Severe</td>
<td>no unit</td>
</tr>
<tr>
<td><strong>Hepatic encephalopathy</strong></td>
<td>None</td>
<td>Grade 1-2 (or suppressed with medication)</td>
<td>Grade 3-4 (or refractory)</td>
<td>no unit</td>
</tr>
</tbody>
</table>

Child-Pugh Grade: Class A (5 to 6 points); Class B (7 to 9 points); Class C (10 to 15 points).

Table 2: West Haven Criteria for Grading Hepatic Encephalopathy:

- **Grade 1** - Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
- **Grade 2** - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior
- **Grade 3** - Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation
- **Grade 4** - Coma (unresponsive to verbal or noxious stimuli)
### Table 3: Duration of Boceprevir Therapy for Persons Without Cirrhosis† Using Response-Guided Therapy (RGT) Guidelines

<table>
<thead>
<tr>
<th></th>
<th>HCV-RNA Results at Treatment Week 8</th>
<th>HCV-RNA Results at Treatment Week 24</th>
<th>Recommendation*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Previously Untreated Patients</strong></td>
<td>Undetectable</td>
<td>Undetectable</td>
<td>Complete 3-medicine regimen at treatment week 28</td>
</tr>
<tr>
<td><strong>Previously Untreated Patients</strong></td>
<td>Detectable</td>
<td>Undetectable</td>
<td>1. Continue all 3 medicines and finish through treatment week 36; and then 2. Administer peginterferon alpha and ribavirin and finish through treatment week 48</td>
</tr>
<tr>
<td><strong>Previous Partial Responders or Relapsers</strong></td>
<td>Undetectable</td>
<td>Undetectable</td>
<td>Complete 3-medicine regimen at treatment week 36</td>
</tr>
<tr>
<td><strong>Previous Partial Responders or Relapsers</strong></td>
<td>Detectable</td>
<td>Undetectable</td>
<td>1. Continue all 3 medicines and finish through treatment week 36; and then 2. Administer peginterferon alpha and ribavirin and finish through treatment week 48</td>
</tr>
</tbody>
</table>

*Treatment Futility: If the patient has HCV-RNA results greater than or equal to 100 IU/ml at treatment week 12, then discontinue 3-medicine regimen. If the patient has confirmed, detectable HCV-RNA at treatment week 24, then discontinue 3-medicine regimen.

† Duration of Boceprevir Therapy for Persons with Cirrhosis: All persons with compensated cirrhosis should receive 4 weeks peginterferon alfa and ribavirin followed by 44 weeks boceprevir in combination with peginterferon alfa and ribavirin.

Source: Victrelis Prescribing Information, 2011.

### Table 4: Duration of Telepravir Therapy Using Response-Guided Therapy (RGT) Guidelines

<table>
<thead>
<tr>
<th></th>
<th>HCV-RNA results at treatment week 4</th>
<th>HCV-RNA results at treatment week 12</th>
<th>Recommendation*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Previously untreated and prior relapse patients</strong></td>
<td>Undetectable</td>
<td>Undetectable</td>
<td>1. Continue all 3 medicines and finish through treatment week 12; and then 2. Administer peginterferon alpha and ribavirin and finish through treatment week 24 (or through treatment week 48 for previously untreated patients with cirrhosis)</td>
</tr>
</tbody>
</table>
Previously untreated and prior relapse patients

<table>
<thead>
<tr>
<th>Detectable (1000 IU/ml or less)</th>
<th>Detectable (1000 IU/ml or less)</th>
<th>1. Continue all 3 medicines and finish through treatment week 12; and then 2. Administer peginterferon alpha and ribavirin and finish through treatment week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously untreated and prior relapse patients</td>
<td>Detectable (1000 IU/ml or less)</td>
<td>Detectable (1000 IU/ml or less)</td>
</tr>
</tbody>
</table>

Prior partial and null responder patients

<table>
<thead>
<tr>
<th>All patients</th>
<th>All patients</th>
<th>1. Continue all 3 medicines and finish through treatment week 12; and then 2. Administer peginterferon alpha and ribavirin and finish through treatment week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior partial and null responder patients</td>
<td>All patients</td>
<td>All patients</td>
</tr>
</tbody>
</table>

* Treatment Futility Rules for All Patients: (i) if HCV-RNA is greater than 1,000 IU/ml at treatment week 4 or treatment week 12, telaprevir and peginterferon alpha and ribavirin should be discontinued at treatment week 12; (ii) if HCV-RNA is detectable at treatment week 24, discontinue peginterferon alpha and ribavirin.

Source: Incivek Prescribing Information, 2011.

Table 5: Duration of Treatment for Olysio, Peginterferon Alpha, and Ribavirin

<table>
<thead>
<tr>
<th>Treatment with Olysio, Peginterferon alpha, and Ribavirin*</th>
<th>Treatment with Peginterferon alpha and Ribavirin*</th>
<th>Total Treatment Duration*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naive and prior relapser patients†, including those with cirrhosis</td>
<td>First 12 weeks</td>
<td>Additional 12 weeks</td>
</tr>
<tr>
<td>Prior nonresponder patients‡ (including partial and null responders) including those with cirrhosis</td>
<td>First 12 weeks</td>
<td>Additional 36 weeks</td>
</tr>
</tbody>
</table>

* Recommended duration of treatment if patient does not meet stopping rule
† Prior relapser: undetectable HCV RNA at the end of prior interferon-based therapy and detectable HCV RNA during follow-up
‡ Prior partial responder: prior on-treatment ≥ 2 log10 IU/ml reduction in HCV RNA from baseline at Week 12 and detectable HCV RNA at end of prior interferon-based therapy. Prior null responder: prior on-treatment < 2 log10 reduction in HCV RNA from baseline at Week 12 during prior interferon-based therapy

Treatment Stopping Rules in Any Patient with Inadequate On-treatment Virologic Response:

<table>
<thead>
<tr>
<th>HCV RNA</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment week 4: greater than or equal to 25 IU/ml</td>
<td>Discontinue Olysio, peginterferon alpha and ribavirin</td>
</tr>
<tr>
<td>Treatment week 12: greater than or equal to 25 IU/ml</td>
<td>Discontinue peginterferon alpha and ribavirin (treatment with Olysio is completed at week 12)</td>
</tr>
<tr>
<td>Treatment week 24: greater than or equal to 25 IU/ml</td>
<td>Discontinue peginterferon alpha and ribavirin</td>
</tr>
</tbody>
</table>
Table 6: Recommended Regimens and Treatment Duration for Sovaldi Combination Therapy in HCV Mono-infected and HCV/HIV-1 Coinfected Patients

<table>
<thead>
<tr>
<th>Patients with genotype</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or 4 CHC</td>
<td>Sovaldi plus peginterferon alpha plus ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>2 CHC</td>
<td>Sovaldi plus ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>3 CHC</td>
<td>Sovaldi plus ribavirin</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

Sovaldi in combination with ribavirin for 24 weeks can be considered as a therapeutic option for CHC patients with genotype 1 infection who are ineligible to receive an interferon-based regimen.

For patients with hepatocellular carcinoma awaiting liver transplantation, Sovaldi in combination with ribavirin is recommended for up to 48 weeks or until the time of liver transplantation, whichever occurs first, to prevent post-transplant HCV reinfection.

Table 7: Quantity Limits for Protease Inhibitors and Nucleotide Analog Polymerase Inhibitors for Hepatitis C:

According to the manufacturer, Incivek, Olysio, Sovaldi and Victrelis can be dosed up to a maximum daily dose at the interval(s) as indicated in the table below. A quantity of these drugs will be considered medically necessary as indicated in the table below:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Maximum Daily Dose/ Dosing Interval</th>
<th>Dosage Strength</th>
<th>Quantity Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incivek</td>
<td>2,250 mg/3 times a day</td>
<td>375 mg</td>
<td>Up to 180 tablets in 30 days</td>
</tr>
<tr>
<td>Olysio</td>
<td>150 mg/1 times a day</td>
<td>150 mg</td>
<td>Up to 30 tablets in 30 days</td>
</tr>
<tr>
<td>Sovaldi</td>
<td>400 mg/1 times a day</td>
<td>400 mg</td>
<td>Up to 30 tablets in 30 days</td>
</tr>
<tr>
<td>Victrelis</td>
<td>2,400 mg/3 times a day</td>
<td>200 mg</td>
<td>Up to 360 tablets in 30 days</td>
</tr>
</tbody>
</table>

Source: Incivek, Olysio, Sovaldi and Victrelis Prescribing Information.

Table 8: Expanded Disability Status Scale (EDSS)

The EDSS scale ranges from 0 to 10 in 0.5 unit increments that represent higher levels of disability. Scoring is based on an examination by a neurologist.

<table>
<thead>
<tr>
<th>EDSS</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>No disability, minimal signs in one FS</td>
</tr>
<tr>
<td>1.5</td>
<td>No disability, minimal signs in more than one FS</td>
</tr>
<tr>
<td>2.0</td>
<td>Minimal disability in one FS</td>
</tr>
<tr>
<td>2.5</td>
<td>Mild disability in one FS or minimal disability in two FS</td>
</tr>
<tr>
<td>3.0</td>
<td>Moderate disability in one FS, or mild disability in three or four FS. No impairment to walking</td>
</tr>
<tr>
<td>3.5</td>
<td>Moderate disability in one FS and more than minimal disability in several others. No impairment to walking</td>
</tr>
<tr>
<td>4.0</td>
<td>Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m</td>
</tr>
<tr>
<td>4.5</td>
<td>Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>------</td>
<td>-------------</td>
</tr>
<tr>
<td>5.0</td>
<td>Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m</td>
</tr>
<tr>
<td>5.5</td>
<td>Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100m</td>
</tr>
<tr>
<td>6.0</td>
<td>Requires a walking aid - cane, crutch, etc - to walk about 100m with or without resting</td>
</tr>
<tr>
<td>6.5</td>
<td>Requires two walking aids - pair of canes, crutches, etc - to walk about 20m without resting</td>
</tr>
<tr>
<td>7.0</td>
<td>Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair, though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day</td>
</tr>
<tr>
<td>7.5</td>
<td>Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorised wheelchair</td>
</tr>
<tr>
<td>8.0</td>
<td>Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms</td>
</tr>
<tr>
<td>8.5</td>
<td>Essentially restricted to bed much of day. Has some effective use of arms, retains some self-care functions</td>
</tr>
<tr>
<td>9.0</td>
<td>Confined to bed. Can still communicate and eat</td>
</tr>
<tr>
<td>9.5</td>
<td>Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow</td>
</tr>
<tr>
<td>10.0</td>
<td>Death due to MS</td>
</tr>
</tbody>
</table>

CPT Codes / HCPCS Codes / ICD-9 Codes

*Interferon Alpha:*

Other CPT codes related to the CPB:

- 11900 Injection, intralesional; up to and including 7 lesions
- 11901 more than 7 lesions
- 87520 - 87522 Infectious agent detection by nucleic acid (DNA or RNA); hepatitis C reverse transcription and direct probe technique, amplified probe technique, or quantification

**HCPCS codes covered if selection criteria are met:**

- J9212 Injection, interferon alfacon-1, recombinant, 1 mcg
- J9213 Injection, interferon, alfa-2A, recombinant, 3 million units
- J9214 Injection, interferon, alfa-2B, recombinant, 1 million units
- J9215 Injection, interferon, alfa-N3, (human leukocyte derived), 250,000 IU

Other HCPCS codes related to the CPB:

- S9559 Home injectable therapy; interferon, including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drug and nursing visits coded separately), per diem

**ICD-9 codes covered if selection criteria are met:**
070.22 Viral hepatitis B with hepatic coma, chronic, without mention of hepatitis delta [see criteria]
070.23 Viral hepatitis, B with hepatic coma, chronic, with hepatitis delta [see criteria]
070.32 Viral hepatitis B without mention of hepatic coma, chronic, without mention of hepatitis delta [see criteria]
070.33 Viral hepatitis B without mention of hepatic coma, chronic, with hepatitis delta [see criteria]
070.41 Acute hepatitis C with hepatic coma [see criteria]
070.44 Chronic hepatitis C with hepatic coma [see criteria]
070.51 Acute hepatitis C without mention of hepatic coma [see criteria]
070.54 Chronic hepatitis C without mention of hepatic coma [see criteria]
070.70 - 070.71 Unspecified viral hepatitis C [see criteria]
078.11 Condyloma acuminatum [genital warts (intralesional only)]
153.0 - 154.8 Malignant neoplasm of colon, rectum, rectosigmoid junction, and anus
172.0 - 172.9 Malignant melanoma of skin
176.0 - 176.9 Kaposi's sarcoma [AIDS-associated]
188.0 - 188.9 Malignant neoplasm of bladder
189.0 - 189.1 Malignant neoplasm of kidney [renal cell carcinoma]
198.0 Secondary malignant neoplasm of kidney
198.4 Secondary malignant neoplasm of other parts of nervous system [leptomeningeal metastases of central nervous system tumors] [code is being added to be consistent with NCCN guidelines]
200.00 - 200.88 Lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue
202.00 - 202.98 Other malignant neoplasms of lymphoid and histiocytic tissue
203.00 - 203.02 Multiple myeloma
204.10 - 204.12 Lymphoid leukemia, chronic [chronic myelogenous leukemia (not in accelerated phase)]
205.10 - 205.12 Myeloid leukemia, chronic
212.1 Benign neoplasm of larynx [respiratory papillomatosis]
225.2 Benign neoplasm of cerebral meninges [recurrent, surgically inaccessible meningioma]
228.00 - 228.09 Hemangioma, any site [intralesional] [life-threatening hemangioma of infancy when member is intolerant/resistant to corticosteroids]
230.3 Carcinoma in situ of colon
232.0 - 232.9 Carcinoma of skin in situ
233.1 Carcinoma in situ of cervix uteri
233.7 Carcinoma in situ of bladder
238.0 Neoplasm of uncertain behavior of bone and articular cartilage [giant cell tumor] [code is being added to be consistent with NCCN guidelines]
238.4 Polycythemia vera [see criteria]
238.71 Essential thrombocythemia
259.2 Carcinoid syndrome
273.3 Macroglobulinemia [Waldenstrom's]
287.30 - 287.39 Primary thrombocytopenia
288.3 Eosinophilia [Hypereosinophilic syndrome]
289.0 Polycythemia, secondary
625.71 Vulvar vestibulitis
776.4 Polycythemia neonatorum
V02.61 Hepatitis B carrier

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

042 Human immunodeficiency virus [HIV] disease [AIDS-related complex] [AIDS in combination with AZT]
051.02 Vaccinia not from vaccination
052.0 - 052.9 Chicken pox
053.21 Herpes zoster keratoconjunctivitis
054.40 - 054.9 Herpes simplex
070.20 Viral hepatitis B with hepatic coma, acute or unspecified, without mention of hepatitis delta [see criteria]
070.21 Viral hepatitis B with hepatic coma, acute or unspecified, with hepatitis delta [see criteria]
070.30 Viral hepatitis B without mention of hepatic coma, acute or unspecified, without mention of hepatitis delta [see criteria]
070.31 Viral hepatitis B without mention of hepatic coma, acute or unspecified, with hepatitis delta [see criteria]
070.42 Hepatitis delta without mention of active hepatitis B disease with hepatic coma [see criteria]
070.52 Hepatitis delta without mention of active hepatitis B disease or hepatic coma [see criteria]
078.10 Viral warts, unspecified [cutaneous]
078.5 Cytomegaloviral disease [CMV]
079.3 Rhinovirus
136.1 Behcet's syndrome
155.0 - 155.1 Malignant neoplasm of liver, primary and intrahepatic bile ducts [cholangiocarcinoma] [hepatocellular carcinoma]
157.0 - 157.3 Malignant neoplasm of pancreas [except pancreatic islet cell carcinoma]
157.8 - 157.9
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>157.4</td>
<td>Malignant neoplasm of Islets of Langerhans</td>
</tr>
<tr>
<td>163.0 - 163.9</td>
<td>Malignant neoplasm of pleura [mesothelioma]</td>
</tr>
<tr>
<td>170.0 - 170.9</td>
<td>Malignant neoplasm of bone and articular cartilage (osteosarcoma)</td>
</tr>
<tr>
<td>173.00 - 173.99</td>
<td>Other malignant neoplasm of skin [basal cell carcinoma - see criteria]</td>
</tr>
<tr>
<td>174.0 - 175.9</td>
<td>Malignant neoplasm of breast</td>
</tr>
<tr>
<td>180.0 - 180.9</td>
<td>Malignant neoplasm of cervix uteri</td>
</tr>
<tr>
<td>183.0 - 183.9</td>
<td>Malignant neoplasm of ovary and other uterine adnexa</td>
</tr>
<tr>
<td>185</td>
<td>Malignant neoplasm of prostate</td>
</tr>
<tr>
<td>191.0 - 191.9</td>
<td>Malignant neoplasm of brain [for primitive neuroectodermal tumor (PNET)]</td>
</tr>
<tr>
<td>192.0 - 192.9</td>
<td>Malignant neoplasm of other and unspecified parts of nervous system [for primitive neuroectodermal tumor (PNET)]</td>
</tr>
<tr>
<td>197.5</td>
<td>Secondary malignant neoplasm of large intestine and rectum</td>
</tr>
<tr>
<td>198.81</td>
<td>Secondary malignant neoplasm of breast</td>
</tr>
<tr>
<td>211.3</td>
<td>Benign neoplasm of colon [Gardner's syndrome]</td>
</tr>
<tr>
<td>211.7</td>
<td>Secondary malignant neoplasm of large intestine and rectum</td>
</tr>
<tr>
<td>215.0 - 215.9</td>
<td>Other benign neoplasm of connective and other soft tissue [plexiform neurofibroma]</td>
</tr>
<tr>
<td>233.0</td>
<td>Carcinoma in situ of breast</td>
</tr>
<tr>
<td>277.31</td>
<td>Familial Mediterranean fever</td>
</tr>
<tr>
<td>340</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>362.50 - 362.52</td>
<td>Macular degeneration [age-related]</td>
</tr>
<tr>
<td>388.2</td>
<td>Unspecified sudden hearing loss</td>
</tr>
<tr>
<td>448.0</td>
<td>Hereditary hemorrhagic telangiectasia</td>
</tr>
<tr>
<td>571.40 - 571.49</td>
<td>Chronic hepatitis</td>
</tr>
<tr>
<td>607.85</td>
<td>Peyronie's disease</td>
</tr>
<tr>
<td>701.4</td>
<td>Keloid scar</td>
</tr>
<tr>
<td>710.2</td>
<td>Sicca syndrome</td>
</tr>
<tr>
<td>789.51 - 789.59</td>
<td>Ascites</td>
</tr>
<tr>
<td>999.0</td>
<td>Generalized vaccinia</td>
</tr>
</tbody>
</table>

**Other ICD-9 codes related to the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>238.1</td>
<td>Neoplasm of uncertain behavior of connective and other soft tissue [desmoid tumors, for unresectable disease or gross residual disease following surgery]</td>
</tr>
<tr>
<td>273.2</td>
<td>Other paraproteinemias</td>
</tr>
<tr>
<td>279.00 - 279.9</td>
<td>Disorders involving the immune mechanism</td>
</tr>
<tr>
<td>571.0 - 573.9</td>
<td>Chronic liver disease, liver abscess and sequelae of chronic liver disease, and other disorders of liver</td>
</tr>
<tr>
<td>V42.0 - V42.9</td>
<td>Organ or tissue replace by transplant</td>
</tr>
<tr>
<td>V58.11 - V58.12</td>
<td>Encounter for antineoplastic chemotherapy and immunotherapy</td>
</tr>
</tbody>
</table>


**Pegylated Interferon Alpha:**

**Other CPT codes related to the CPB:**

87520 - 87522 Infectious agent detection by nucleic acid (DNA or RNA); hepatitis C, direct probe technique, amplified probe technique, or quantification

**HCPCS codes covered if selection criteria are met:**

S0145 Injection, pegylated interferon alfa-2a, 180 mcg per ml
S0148 Injection, pegylated interferon alfa-2b, 10 mcg

**Other HCPCS codes related to the CPB:**

S9559 Home injectable therapy; interferon, including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drug and nursing visits coded separately), per diem

**ICD-9 codes covered if selection criteria are met:**

070.32 Viral hepatitis B without mention of hepatic coma, chronic, without mention of hepatitis delta [see criteria]
070.33 Viral hepatitis B without mention of hepatic coma, chronic, with hepatitis delta [see criteria]
070.44 Chronic hepatitis C with hepatic coma [see criteria]
070.54 Chronic hepatitis C without mention of hepatic coma [see criteria]
172.0 - 172.9 Malignant melanoma of skin
205.10 - 205.12 Chronic myeloid leukemia
238.0 Neoplasm of uncertain behavior bone and articular cartilage [giant cell tumor]
238.4 Polycythemia vera

**ICD-9 codes not covered for indications listed in the CPB (not all inclusive):**

046.3 Progressive multifocal leukoencephalopathy
078.10 - 078.19 Viral warts
079.4 Human papillomavirus
170.0 - 170.9 Malignant neoplasm of bone and articular cartilage [osteosarcoma]
215.0 - 215.9 Other benign neoplasm of connective and other soft tissue [plexiform neurofibroma]
238.1 Neoplasm of uncertain behavior of connective and other soft tissue [desmoid tumor and plexiform neurofibroma]
238.4 Polycythemia vera
288.3 Eosinophilia [eosinophilia/hyper-eosinophilic syndrome]
795.05 Cervical high risk human papillomavirus (HPV) DNA test positive
795.09 Other abnormal Papanicolaou smear of cervix and cervical HPV
795.15 Vaginal high risk human papillomavirus (HPV) DNA test positive
795.19 Other abnormal Papanicolaou smear of vagina and vaginal HPV
796.75 Anal high risk human papillomavirus (HPV) DNA test positive
796.79 Other abnormal Papanicolaou smear of anus and anal HPV
Other ICD-9 codes related to the CPB:

273.2 Other paraproteinemias
279.00 - 279.9 Disorders involving the immune mechanism
571.0 - 573.9 Chronic liver disease, liver abscess and sequelae of chronic liver disease, and other disorders of liver
V42.0 - V42.9 Organ or tissue replace by transplant

**Interferon beta:**

**HCPCS codes covered if selection criteria are met:**

J1826 Injection, interferon beta-1a, 30 mcg
J1830 Injection interferon beta-1b, 0.25 mg (code may be used for Medicare when drug administered under direct supervision of a physician, not for use when drug is self-administered) [covered for relapsing, remitting multiple sclerosis in persons with a contraindication, allergy, intolerance or failure of a one-month trial of Copaxone plus have a contraindication, allergy, intolerance or failure of a 1-month trial of Avonex, or Rebif]
Q3027 Injection, interferon beta-1a, 1 mcg for intramuscular use

**Other HCPCS codes related to the CPB:**

S9559 Home injectable therapy; interferon, including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drug and nursing visits coded separately), per diem

**ICD-9 codes covered if selection criteria are met:**

340 Multiple sclerosis [relapsing/remitting] [see criteria]

**ICD-9 codes not covered for indications listed in the CPB:**

357.0 Acute infective polyneuritis [Guillain Barre syndrome]
357.81 Chronic inflammatory demyelinating polyneuritis

**Other ICD-9 codes related to the CPB:**

995.27 Other drug allergy
995.29 Unspecified adverse effect of other drug medicinal and biological substance. [intolerance of one-month trial of Avonex, Copaxone, or Rebif]

**Interferon gamma:**

**HCPCS codes covered if selection criteria are met:**

J9216 Injection, interferon, gamma-1B, 3 million units

**ICD-9 codes covered if selection criteria are met:**

202.10 - 202.18 Mycosis fungoides
202.20 - 202.28 Sezary's disease
288.1 Functional disorders of polymorphonuclear neutrophils [chronic granulomatous disease, to reduce frequency and severity of infections]
691.8 Other atopic dermatitis and related conditions [chronic recalcitrant]
756.52 Osteopetrosis
ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

011.0 - 011.96 Tuberculosis of lung, infiltrative
158.0 - 158.9 Malignant neoplasm of retroperitoneum and peritoneum
191.0 - 191.9 Malignant neoplasm of brain
197.6 Secondary malignant neoplasm of retroperitoneum and peritoneum
225.0 Benign neoplasm of brain
273.3 Macroglobulinemia [Waldenstrom’s]
516.31 Idiopathic pulmonary fibrosis

Other ICD-9 codes related to the CPB:
V58.11 - V58.12 Encounter for antineoplastic chemotherapy and immunotherapy

Sofosbuvir in combination with Pegylated Interferon Alpha:

Other CPT codes related to the CPB:
87520 - 87522 Infectious agent detection by nucleic acid (DNA or RNA); hepatitis C, direct probe technique, amplified probe technique, or quantification

HCPCS codes covered if selection criteria are met:

Sofosbuvir:
No specific code
S0145 Injection, pegylated interferon alfa-2a, 180 mcg per ml
S0148 Injection, pegylated interferon alfa-2b, 10 mcg

Other HCPCS codes related to the CPB:
S9559 Home injectable therapy; interferon, including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drug and nursing visits coded separately), per diem

ICD-9 codes covered if selection criteria are met:
070.44 Chronic hepatitis C with hepatic coma
070.54 Chronic hepatitis C without mention of hepatic coma

Other ICD-9 codes related to the CPB:
042 Human immunodeficiency virus [HIV] disease
V42.7 Liver replaced by transplant

The above policy is based on the following references:


191. Yuen MF, Lai CL. Response to combined interferon and ribavirin is better in patients infected with hepatitis C virus genotype 6 than genotype 1 in Hong Kong. Intervirology. 2006;49(1-2):96-98.


