HELIOS Kliniken
Jeder Moment ist Medizin

Treatment of Chronic HCV Infection in Children and Adolescents

Guidance for Clinical Trials

Background Information

- Low prevalence in industrialized countries; vertical infection almost exclusive mode of transmission; estimated number of infected children in Europe: 500 – 600 with declining trend
- Spontaneous viral elimination up to 4 years of age approximately 10 – 25%, depending on genotype and route of infection
- Low disease progression, histologically mild inflammatory activity and fibrosis, but steatosis may be a prognostic factor

PEG-IFN-α2b (PegIntron®) und Ribavirin (Rebetol®) (15 mg/kg x Tag)
PEG-IFN-a2a (Pegasys®) und Ribavirin (Rebetol®) (15 mg/kg x Tag)
SVR

* Wirth S et al, J Hepatol 2010, ** Sokal E et al, J Hepatol 2010, #Schwarz et al, Gastroenterology 2011

	Wirth 2005	**Jara 2008**	Wirth 2010* (SPRI)	**Total**	**Schwarz# 2011**	**Sokal 2010****
Dosage	1,5 µg/kgxWo	1,0 µg/kgxWo	60 µg/m²xWo		180 µg/1,73 m²/week	100 µg/m²
Total	36/61 (59%)	15/30 (50%)	70/107 (65,4%)	121/198 (61,1%)	29/55 (53%)	43/65 (66,1%)
Genotype						
1	22/46 (48%)	12/26 (46%)	38/72 (53%)	**72/144 (50%)**	21/45 (47%)	27/47 (59%)
2/3	13/13 (100%)	3/3 (100%)	28/30 (93%)	**44/46 (96%)**	8/10 (80%)	16/17 (94%)
4	1/2	0/1	4/5 (80%)	5/8 (62%)		Included in G1
ALT-levels						
Elevated	12/25 (48%)		27/44 (61%)			19/33 (58%)
Normal	24/36 (67%)		42/63 (67%)			24/30 (80%)
Mode of infection						
Parenteral	19/27 (70%)	7/9 (78%)	5/5 (100%)	31/41(76%)		
Genotype 1	13/21 (62%)		1/1			
Vertical	12/25 (48%)	8/21 (38%)	46/75 (61%)	66/121 (55%)		
Genotype 1	7/20 (35%)		26/52 (50%)	**33/72 (46%)**		
Break through	9,8%				6/41 (15%)	
Relaps	7,7%		8%		6/35 (17%)	

Improved Treatment ist needed

In conclusion:

„Despite considerable progress in the treatment of children with chronic hepatitis C, 40-50% of the patients with genotype 1, which represents the majority of infected individuals, treatment remains unsuccessful“

Aims and Criteria for Treating Children with Chronic Hepatitis C

- Treatment in early childhood is feasible and very well tolerated.
- Primary endpoint is SVR and clinical cure.
- Relieve psychological burden of disease for the patient and families, eliminate the social aspects of having a blood borne disease.
- The aim is not the treatment of a severe ongoing liver disease, but the prevention of a future one.

Guidance for Clinical Trials for Children and Adolescents With Chronic Hepatitis C, JPGN 2011; 52:233-7

Inclusion Criteria for Treating Children with Chronic Hepatitis C

Guidance for Clinical Trials for Children and Adolescents With Chronic Hepatitis C, JPGN 2011; 52:233-7

- All children with chronic HCV infection with a measurable HCV-RNA level should be considered
- Treatment is not indicated before the age of three years
- Stratification according genotypes is necessary
- Two age groups are recommended for documentation and analyses (3 - 10, 10 - 18 years)
- Treatment during rapid growth spurt or puberty should be avoided, if possible (but is no contraindication!)
- Children with previous treatment failure could be included 2 years after the end of treatment
- A baseline liver biopsy is recommended but not mandatory

Study Drugs

- The drug to be tested should have demonstrated noninferiority to present SOC
- No need for a placebo arm
- Test drug could be used in triple combination with peg-IFN and riba or as monotherapy
- Oral treatment would be desirable (proper formulation needed)
- Primarily focus on patients infected with genotype 1 (naive and non-responders)
- Improved efficacy: increased viral clearance rate, or the same SVR with a shorter treatment duration or less side effects

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Recommended baseline investigations before HCV treatment

Clinical examination

- Physical and neuropsychiatric examination,
  Tanner pubertal stage
- Evaluation of growth parameters, z-scores for height and weight, BMI, waist circumference, if possible: growth velocity before starting treatment
- Description of co-morbidities

Morphologic investigations

- Liver Ultrasound
- Liver histology – assessed by Ishak or Metavir scores
- Bone age (> 7 years of age)

Laboratory tests

- Complete red and white blood count, reticulocytes, ALT, AST, gammaGT, AP, bilirubin, albumin, coagulation, Alpha-feto protein, BUN, creatinine, Immunoglobulins, autoantibodies (ANA; LKM1), Ferritin, TSH, thyroid-antibodies, HOMA index, Pregnancy test, anti-HCV, quantitative HCV RNA, genotype

Recommended investigations during/after HCV treatment

Parameter	**Repeat frequency**
Physical and neuropsychiatric examination	Every visit
Tanner pubertal stage	Every 3 months
Evaluation of growth parameters, z-score for height and weight, BMI, waist circumference	Every 3 months
Growth velocity	Every 6 months
Bone age	End of trial
Laboratory tests	
Complete red and white blood count, Alb, ALT, AST, gammaGT, AP, bilirubin, coagulation	Every month during the first 3 months, then every 3 months
Reticulocytes, , albumin, BUN, creatinine, immunoglobulins, autoantibodies (ANA; LKM1), ferritin, TSH, thyroid-antibodies	Every 3 - 6 months
Quantitative HCV RNA,	4, 8, 12 weeks, then every 3 months
HOMA index	End of treatment

Five year follow-up after treatment