Technology Update

Recent Advances in Approach to Treatment of Genetic Disorders: Clinician's Perspective

Neerja Gupta
Madhulika Kabra

There is no cure for most of the genetic disorders. The only option in most situations is prevention by counseling and prenatal diagnosis. However, over a decade, with the completion of the human genome project and other advances there is better understanding of pathogenesis, improvement in diagnostic strategies and various treatment avenues are opening up for these disorders. The aim of this article is to make the pediatricians aware of the approaches to treatment of common genetic disorders and recent available therapeutic interventions.

Key words: *Enzyme replacement therapy, Genetic disorders, Stem cell.*

Evaluating therapy for genetic diseases is a difficult problem. Three general questions must be asked - (1) Does the treatment improve patient's condition? (2) Does it restore full physiological normality? (3) Does it cure the disease? In the present era if one talks of cure for a genetic disease the options are bone marrow transplantation (done very early in the course of disease), stem cell therapy and gene therapy. All other treatment modalities are largely at the phenotypic, metabolite or enzyme level and have to be life long in most situations(1,2). In the present communication we are reviewing some recent advances and will discuss therapeutic modalities available for the treating clinicians. *Table I* summarizes the available therapeutic options for certain genetic disorders.

From the Genetics Unit, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi 110 029, India.

Correspondence: Dr. Madhulika Kabra, Additional Professor, Genetics Unit, Deptt of Pediatrics, All India Institute of Medical Sciences, New Delhi 110 029, India. E-mail: mkabra_aiims@yahoo.co.in madhulikakabra@hotmail.com

(*A*) *Enzyme replacement therapy* (*ERT*)(3-9)

In the last decade enzyme replacement therapy for lysosomal storage disorders has reached the state of direct delivery to the patient. This has been possible due to the better understanding of complexities of pathogenesis. The most successfully treated disorder with ERT is Gaucher's disease. Over 12 years more than 3500 patients have been treated worldwide with regular, intravenous infusions of purified human acid β-glucocerebrosidase, with a maximum follow up of 11 years. This approach to therapy has proven both safe and highly efficacious and has advanced the care of nonneuronopathic Gaucher's disease throughout the world. The treatment is also found to be effective in Fabry's disease, Mucopolysaccharidosis (I,VI) and glycogen storage disorder (GSD) type II. Exogenous enzyme is modified to expose the mannose residues at oligosaccharide side chain level, in order to ensure binding to the mannose receptor present on the macrophage plasma membrane(3).

Gaucher's disease was the first lysosomal storage disorder to be treated with macrophage targeted enzyme replacement therapy. A recent report has summarized, the results of enzyme replacement on 1028 patients with type I Gaucher's disease enrolled in international registry(4). Assessment of response included serial measurements of hemoglobin, platelet count, liver and spleen volumes and occurrence of bone pain and crises. Patients generally respond well to ERT, irrespective of severity of disease. In anemic patients hemoglobin increased to normal within 6-12 months. In thrombocytopenic patients without splenectomy most rapid response was seen in the first two years. In splenectomized patients, platelet counts returned to normal within 6-12 months. Hepatomegaly and splenomegaly decreased by 30% to 40% and 50-60% respectively after 6 months of therapy. Bone pains disappeared in 52%

TABLE I–*Some Examples of Proven and Experimental Treatments for Genetic Disorders*

Treatment	Disorder
At the level of clinical phenotype	
Avoidance of	
Certain drugs .	Pharmacogenetic disorders
Sun exposure	Albinism, Xeroderma pigmentosa
Trauma	Osteogenesis imperfecta
Pharmacological	
Blood transfusion	Thalassemia
β-adrenergic blockers	Marfan syndrome
Anticonvulsants	Neurodegenerative disorders
Surgical	Cleft lip/palate, Congenital heart disease
Orthopedic reconstruction	Chondrodystrophies
Colectomy	Familial polyposis coli
At the level of metabolite	
Substrate restriction	
Phenylalanine	Phenylketonuria
Branched-chain amino acids	Maple syrup urine disease
Galactose	Galactosemia and galactokinase deficiency
Alternative pathway	
Benzoate and phenyl acetate/ Phenylbutyrate	Urea cycle disorders
Glycine	Isovaleric acidemia
Carnitine	Organic acidemia
Cysteamine	Cystinosis
Penicillamine	Wilson disease
Metabolic inhibition	
Allopurinol	Gout
Mevinolin	Familial hypercholesterolemia (heterozygotes)
NTBC	Hepatorenal tyrosinemia
Replacement of deficient product	
Glucose polymers (Cornstarch)	Glycogen storage disease, types I and III
Uridine	Hereditary orotic aciduria
Corticosteroids	Adrenogenital syndromes
Thyroxine	Familial goiter
Biotin	Biotinidase deficiency
Avoidance	
Antimalarial drugs	G6PD deficiency
Barbiturates	Acute intermittent porphyria
Depletion	
LDL apheresis	Familial hypercholesterolemia (homozygotes)
At the level of dysfunctional protein	
Enhancement of mutant protein function	
Pyridoxine (Vitamin B_6)	Homocystinuria

Treatment	Disorder
Thiamine	Maple syrup urine disease
Protein replacement	
Replacement of extra cellular protein	
Factor VIII	Classic hemophilia
α_1-Antitrypsin	α_1-Antitrypsin deficiency
Growth hormone	Growth hormone deficiency
Extra cellular replacement of an intracellular protein	
Polyethylene glycol-adenosine deaminase	Adenosine deaminase deficiency
Replacement of intracellular protein	Gaucher disease, MPS I, Pompe Disease, Fabry's
(Enzyme replacement)	disease
At the level of mutant RNA	
IV gentamicin	Duchenne muscular dystrophy(point mutations)
At the level of mutant gene	
Pharmacologic modulation of Ilene expression	
Butyrates, hydroxyurea, Decitabine	Sickle cell disease and thalassemia intermedia
Modification of somatic genotype	
Organ transplantation	
As a source for a specific protein	
Allogenic bone marrow	Lysosomal storage diseases, β-thalassemia
Liver	Glycogen storage disease type I, Familial hypercholesterolemia, Ornithine transcarbamoylase deficiency
As a protein source & replacement of a damaged organ	
Liver	α_1-Antitrypsin deficiency, Hepatorenal tyrosinemia
Kidney	Cystinosis
By gene transfer	Hemophilia, SCID, DMD,ADA deficiency
Stem cell transplantation (HSCT)	Lysosomal storage disorders

of patients. Osteopenia or osteoporosis in children partially resolves within 2 years. Presently, there is controversy about using enzyme replacement therapy in Type 2 and type 3 Gaucher's disease, as the enzyme does not cross the blood brain barrier effectively.

The dose recommended for treatment is 30-60 units/kg intravenously once every two weeks and has to be continued life long(5). The primary limiting factor for using this therapy is the cost involved. The approximate cost of enzyme replacement (Cerezyme 200 units/vial and 400 units/vial, manufactured by Genzyme company) for a 10 kg child is one lakh rupees per month (only the cost of the enzyme).

Lower dose treatment regimens (5 IU/Kg 2-3 times weekly or 15 units/kg once every 2 weeks) have also been tried and have shown to improve hematological parameters and organomegaly(7).

Another strategy for treatment of Gaucher's disease is substrate depletion by using OGT9l8/ miglustat that reduces the glycosphingolipids storage by limiting the amount of the precursor synthesized to a level that can be cleared by the affected enzyme with residual hydrolytic activity(7,8); however, the experience with this therapy is limited.

Hurler syndrome (mucopolysaccharidosis type l-MPS I) is another genetic disorder that requires long term ERT with laronidase (Aldurazyme - 500

units/5mL/vial, manufactured by Genzyme Company) to treat the non neurological manifestations of disease. Recommended dosage is 100 units/kg/week as an intravenous infusion in 5-65 years of age. There is significant reduction in liver and spleen size and 70% reduction in urinary GAG levels. It has shown improvement in the range of joint movements, sleep apnoea and global functioning scores as well(9). Cost of therapy is approximately Rs 2.5 lakh per month for a 10 Kg child.

ERT has also been cleared for use by FDA in Maroteux lamy disease (Type VI MPS). Cost is $1450 US per vial (5 mg/5 mL/vial, Naglazyme-Biomarine Company). Dosage of recombinant Aryl sulphatase B at 1 mg/kg results in clinical and biochemical improvements without side effects(10).

Fabry disease is another lysosomal disorder for which effective ERT with agalsidase beta (Fabrazyme 35mg /vial by Genzyme Company) and agalsidase alpha (Replagal; Transkaryotic therapies, Cambridge, Mass) is available. The recommended dose is 1 mg/kg body weight and 0.2 mg/kg respectively. It is given once every 2 weeks as an intravenous infusion in 16-65 years of age group. It results in decrease in pain, reverses abnormal cerebrovascular responses and depletes storage of globotriaosylceramide in major organs of pathology in Fabry disease. Carriers with substantial disease manifestations also should be treated with ERT(11).

Recently, the FDA has granted marketing approval (April 28, 2006) for Myozyme (Genzyme Corp. of Cambridge, Mass) an enzyme replacement product, for the treatment of patients with Pompe disease, a progressive and debilitating disorder. Various clinical trials have shown to decrease cardiomegaly, improve cardiac and skeletal muscle function, and prolong survival. The response to therapy is substantial(12).

The biggest hurdle for enzyme replacement therapy presently is the prohibitive cost in a country like ours and most patients are unable to afford therapy. The other target diseases presently being worked on are Hunter syndrome (MPSII), Niemann Pick disease.

(*B*) *Enzyme enhancement therapy* means enhancing the residual activity of misfolded or unstable enzymes by using small molecule ligands known as chaperons. It offers the possibility of treating lysosomal disorders affecting brain, because low molecular weight chaperons can cross the blood brain barrier. It has been used in the cardiac variant of Fabry's disease and Gaucher's disease(8).

(*C*) *Transplantation*

This modality includes bone marrow transplantation, organ transplantation and stem cell transplantation.

Hemopoietic stem cell transplantation(13-17): Transplantation is the single most useful entity for management of genetic disorders. The transplant can be a source of the missing protein or replace a damaged organ. When a transplant is used as a source of a deficient protein it is important that the protein reaches target tissue. Transplant therapy can be effective for selected metabolic diseases like storage disorders (MPS I, VI, VII, metachromatic leukodystrophy, globoid cell leukodystrophy, X linked adrenoleukodystrophy, fucosidosis, mannosidosis, Gauchers disease, Niemann Pick disease type B, malignant infantile osteopetrosis).

There is no experience of bone marrow transplantation for genetic disorders other than β–thalassemia in our country and encouraging results are well known(17). Results of allogenic bone marrow transplantation at Vellore are comparable to those achieved for patients in transplant units in Western world and cost a mean of US $ 15,000. There is no reason that it will not be successful for other disorders. Evidence from bone marrow transplants (or hemopoietic stem cell transplantation) in MPS patients has been encouraging. It is not clear that if the transplant derived cells/enzymes will cross the blood brain barrier. There are more than 300 patients with Hurler's disease treated by bone marrow transplantation throughout the world(13). In successfully engrafted patients the abnormal facial features have ameliorated, pulmonary, hepatic and splenic abnormalities disappear. The damage to the brain that has occurred prior to the transplant does not reverse but further psychomotor degeneration is probably prevented.

Liver transplantation is useful in tyrosinemia, glycogen storage disease, α_1 antitrypsin deficiency, OTC deficiency and familial hypercholesterolemia.

Treatment is most effective if the transplant is done early. The transplantations procedure will seldom result in improvement of already existing skeletal and neurologic symptoms.

Cord blood transplantation: Cell therapy that involves placement of characterized mature cells embryonic stem cells or umbilical cord blood cells can also be used as an alternative approach with many advantages like increased tolerance to histo-incompatible donor blood cells, decreased risk of graft vs host disease, and wide availability of placental blood. It has been used in more than 2000 patients with malignant or non-malignant disorders. Collection and storage of cord blood has raised ethical considerations.

Embryonic stem cell transplantation(16)*:* Stem cell research has brought an evolutionary change in genetics. Stem cells are self-renewing cells that can proliferate to make differentiated cell types of a tissue in vivo and continue to self renew for lifetime. Embryonic stem cells can give rise to the whole organism (Reproductive cloning) where as non reproductive cloning or therapeutic cloning is likely to provide stem cells for research and therapy. Embryonic stem cell therapy offers a valuable means of obtaining autologous cells for a variety of diseases. Embryonic stem cells are genetically identical to the patient's cells, so the risk of immune rejection and need for immuno-suppression is eliminated. Therapy can be repeated whenever needed. There are inherent ethical issues in the use of embryonic stem cell transplantation and is prohibited in most countries.

Pluripotent embryonic stem cells or multi potent adult stem cells have also been used for therapeutic cloning with ethical and practical limitations. Therapeutic potential of adult stem cells is much lower than embryonic stem cells. Stem cell and progenitor cells of the bone marrow and peripheral blood have been used for repair of cardiac tissue after acute myocardial infarction, neuro-degenerative diseases, amyotrophic lateral sclerosis, periodontal diseases *etc*.

(*D*) *Gene Therapy*(2)

The general view of both the significance of the role for somatic gene therapy and mechanisms for its implementation have evolved dramatically in the past few years. The field of candidates has expanded from just single-gene disorders to include cancer, AIDS, and atherosclerosis. Another area of challenge is the expansion of the delivery systems, which began with retroviral vectors but now includes vectors based on adenovirus, adeno-associated virus (AAV), herpes virus, vaccinia, and other agents. Nonviral systems such as liposomes, DNA-protein conjugates, and DNA-protein-defective virus conjugates are also promising.

Gene therapy has so far been reported to be useful in two genetic disorders, ADA deficiency and hypercholesterolemia due to defect in the LDL receptor protein. Trials have been approved for hemophilia, many malignancies, AIDS, cystic fibrosis, Gaucher's disease, Duchenne Muscular Dystrophy etc. In the present scenario it seems that this form of therapy is far from routine bed side application.

(*E*) *Drugs and Hormonal therapy in Genetic disorders*

1. *Bisphosphonates in Osteogenesis Imperfecta* (18-24)

Osteogenesis Imperfecta (OI) is an autosomal dominant disorder of the connective tissue characterized by combinations of blue sclera, dental abnormalities, repeated fractures and progressive limb and vertebral deformities. The demonstration of increased bone resorption in OI prompted the use of antiresorptive agents for the treatment of the disorder. Pamidronate, an analog of pyrophosphate and a potent inhibitor of osteoclast activity, has been shown to increase BMD, decrease fracture rate and improve functional status in OI. Intravenous (i.v.) Pamidronate is given cyclically in the dose of 1 mg/kg/d for 3 days per cycle four monthly. It results in mean annual increase in bone mineral density and improvement in Z scores, the size of the vertebral bodies, decreased fracture incidence of/ and improved mobility and ambulation. A recent Indian study on efficacy of i.v. pamidronate on

20 patients with OI has shown a significant improvement in BMD Z scores and decrease in fracture rate(23). Recently, therapy with oral bisphosphonates (Alendronate) at a daily dose of 1 mg/kg/d (max 20 mg) has also been reported with equal efficacy. The oral route is highly acceptable in children and has practical advantages over the intravenous route(24). Oral route of therapy is only recommended for older children as all the preparations available are in tablet form and is required to be swallowed with a large amount of water. The patient has to be kept upright for about half an hour after taking the medicine. All these precautions are to take care of the gastric side effects of the drug. The cost of intravenous pamidronate for a 30 mg injection ranges from Rs. 1200-1600 per 30 mg vial. Hence, the minimum cost of i.v. pamidronate therapy for a 10 kg child is Rs. 3600 per year. The cost of oral Alendronate is around Rs. 5/- per 10 mg tab.

2. *NTBC* (2-2*nitro-4-trifluoromethyl-benzoyl*)-1, 3 *cyclo-hexanedione) in Tyrosinemia type I* (25-29)

Type I tyrosinemia is a fatal liver disease and may present in acute or chronic forms. This is caused by accumulation of toxic metabolites due to the deficiency of fumarylacetoacetate, which is the last enzyme in the tyrosine catabolic pathway. NTBC is potent inhibitor of 4-hydroxyphenyl pyruvate deoxygenase and prevents tyrosine degradation. Since the first trial of NTBC in 1991 over 220 patients have been treated and the disease course has changed dramatically. Only 10% of patients did not respond. There is a decreased incidence of development of hepatocellular carcinoma. In about 101 patients the treatment was started before 2 years of age. Recently, there has been some concern about development of corneal opacities in children on long term NTBC therapy probably resulting from elevated serum and ocular levels of tyrosine and poor dietary compliance. Though a recent study has not reported any ocular side effects. The cost of the drug is presently prohibitive.

3. *Growth Hormone* (*GH*) *therapy*

GH therapy has been found to be useful in certain genetic disorders like Turner syndrome and Prader Willi syndrome. It has also been tried for Hypochondroplasia, Noonan syndrome, Achondroplasia, Seckel syndrome and Russel Silver syndrome.

In Turner syndrome the height gain may be up to 8-10 cm. The treatment should ideally be started at about 4 years of age and the doses need to be higher than conventional (1 unit/kg per week). A prospective open trial of GH therapy on 16 Indian Turner syndrome patients in a dose of 1 IU (0.3 mg)/Kg/wk for one year showed a significant improvement in height velocity(30). The minimum cost of GH therapy for a 20 kg child is approximately 2.2 lakh rupees per year.

A recent study on GH treatment in 25 prepubertal Noonan syndrome patients showed improvement in final height with a mean gain of 1.7 SDS (equivalent to 10.4 cm) over a period of 2 years. These children achieved a height close to their mid parental height(31).

Short term recombinant GH therapy treatment in hypochondroplasia is effective to increase growth rate and height SDS but the effect on final height remains unknown(32).

A recent study on 35 children with achondroplasia after 4 years of GH therapy has shown improvement in height without adverse effect on trunk leg disproportion and the effect is comparable to Turner syndrome and Noonan syndrome(33).

4. *Lorenzo's oil in X linked adrenoleuko-dystrophy*(34)

Lorenzo's oil was initially thought to be useful for treatment of adrenoleukodystrophy as it normalized the levels of very long chain fatty acids in blood. Later on it was realized that though the levels normalized, symptoms did not improve as the oil does not cross the blood brain barrier. Lorenzo's oil therapy is now recommended in asymptomatic boys with X-linked adrenoleukodystophy who have normal brain magnetic resonance image (MRI) results.

5. *Reactivation of fetal hemoglobin* (*HbF*) expression is an important therapeutic option in

Key Messages

- Treatment of genetic disorders requires accurate diagnosis, early intervention and knowledge of pathogenesis.
- Treatment modalities like enzyme replacement, stem cell transplantation, bisphosphonates in osteogenesis imperfecta and growth hormone therapy in Turner syndrome are promising.
- Management is relatively expensive and challenging and requires pre and post treatment counseling.

patients with hemolytic anemia especially thalassemia intermedia. In sickle cell disease (SCD), an increase in HbF interferes with the polymerization of sickle hemoglobin while in beta-thalassemia, an increase in gammaglobin chain synthesis would decrease non-alpha:alpha chain imbalance. Hydroxyurea, an inducer of HbF, is the only currently approved agent for the treatment of patients with moderate and/or severe SCD and thalassemia intermedia. However, about one third of patients with SCD do not respond to HU, and in beta thalassemia major, the clinical response is unimpressive(35). Hydroxyurea is being used at a dose of 10-15 mg/kg/d with monitoring of hematological, renal and liver profile. Duration of therapy varies from 18months to 3 years. A recent Indian study on 37 patients with thalassemia intermedia treated with hydroxyurea showed response in 70.2% of patients of which 45.9% became transfusion independent or showed a hemoglobin rise of more than 20 g/L(36). Response was evident within 1 month of starting HU therapy in the majority of responders.

Conclusions

Despite the galloping advances in the understanding of basic cause and pathophysiology of various genetic disorders and the completion of human genome project, the advances in therapeutics have been less exciting. Though few new definite and effective therapeutic modalities for genetic disorders have emerged and it is important for the clinicians to know about these advances. The available therapies have a major cost constraint. Another important issue is that these treatment modalities are new and emerging and should always be monitored and instituted at centers with sufficient experience and expertise. In the absence of definite treatment modalities it is imperative that all clinicians must be familiar with counseling and preventive strategies.

Competing interests: None stated.

Funding: None.

REFERENCES

1. Treacy PE, Valle D, Scriver RC. Treatment of genetic disease. *In:* Scriver RC, Beaudet LA, Sly SW, Valle D, Childs B, Kinzler WK, Vogelstein B, eds. The metabolic and molecular basis of inherited disease. 8th edn. USA: Mc Graw Hill 2001. p. 175-192.
2. Beaudet AL, Scriver RC, Sly SW, Valle D. Genetics, Biochemistry and molecular basis of variant human phenotypes. *In:* Scriver RC, Beaudet LA, Sly SW, Valle D, Childs B, Kinzler WK, Vogelstein B, eds. The metabolic and molecular bases of inherited disease. 8th edn. USA: Mc Graw Hill 2001; p. 3-45.
3. Grabowski GA, Hopkin RJ. Enzyme therapy for lysosomal storage disease: principles, practice and prospects. Ann Rev Genomics Hum Genet 2003; 4: 403-436.
4. Weinreb NJ, Charrow J, Andersson HC, Kaplan P, Kolodny EH, Mistry P, *et al.* Effectiveness of enzyme replacement therapy in 1028 patients with Type I Gaucher's disease after 2 to 5 years of treatment: A report from the Gaucher registry. Am J Med 2002: 113; 112-119.
5. Grabowski GA. Gaucher disease: lessons from a decade of therapy. J Pediatr 2004: S-19.
6. Charrow J, Andersson HC, Kaplan P, Kolodny EH, Mistry P, Pastores G, *et al.* Enzyme replacement therapy and monitoring for children with Type I Gaucher's disease: Consensus recommendations. J Pediatr 2004; 112-120.
7. Germin DP. Gaucher's disease: A paradigm for interventional genetics. Clin Genet 2004; 65: 77- 86.
8. Desnick RJ, Schuchman. Enzyme replacement and enhancement therapies: lessons from lysosomal disorders. Nature reviews 2002; 3: 954-966.

9. Kakkis ED, Muenzer J, Tiller GE, Waber L, Belmont J, Passage M, *et al.* Enzyme-replacement therapy in mucopolysaccharidosis I. N Engl Med 2001; 344: 182-188.

10. Harmatz P, Whitley CB, Waber L, Pais R, Steiner R, Plecko B, *et al.* Enzyme replacement therapy in Mucopolysaccharidosis VI. J Pediatr 2004; 574-580.

11. Desnick RJ, Brady RO. Fabry disease in childhood. J Pediatr 2004: S 20-26.

12. Winkel LP, Kamphoven JH, Van Den Hout JH, Severijnen LA, Van Doorn PA, Reuser AJ, *et al.* Morphological changes in muscle tissue of patients with infantile Pompe's disease receiving enzyme replacement therapy. Muscle Nerve 2003; 27: 743-751.

13. Peters C, Balthazor M, Shapiro EG, King RJ, Kollman C, Hegland JD, *et al.* Outcome of unrelated donor bone marrow transplantation in 40 children with Hurler syndrome. Blood 1996; 87: 4894.

14. Peters C, Shapiro EG, Anderson J, Henslee-Downey PJ, Klemperer MR, Cowan MJ, *et al.* Hurler syndrome: II. Outcome of HLA-genotypically identical sibling and HLA-haplo identical related donor BMT in 54 children. Blood 1998; 91: 2601.

15. Peters C, Steward CG. Hemopoietic cell transplantation for inherited metabolic disease: An overview of outcomes and practice guidelines. Bone Marrow Transplantation 2003; 31: 229-239.

16. Hochedlinger K, Jaenisch R. Nuclear transplantation, embryonic stem cells and potential for cell therapy. NEJM 2003; 349: 275-286.

17. Chandy M, Srivastava A, Dennison D, Mathews V, George B. Allogenic bone marrow transplantation in the developing world: experience from a center in India. Bone Marrow Transplant. 2001; 27: 785-790.

18. Marini JC. Osteogenesis Imperfecta - Managing Brittle Bones. NEJM 1998; 339: 986-987.

19. Glorieux FH, Bishop NJ, Plotkin H, Chabot G, Lanoue G, Travers R. Cyclic administration of pamidronate in children with severe Osteogenesis Imperfecta. NEJM 1998; 339: 947-952.

20. Astrom E, Soderhall S. Beneficial effect of long-term intravenous bisphosphonate treatment of Osteogenesis Imperfecta. Arch Dis Child 2002; 86: 356-364.

21. Falk MJ, Heeger S, Lynch KA, DeCaro KR, Bohach D, Gibson KS, *et al.* Intravenous bisphosphonate therapy in children with Osteogenesis Imperfecta. Pediatric 2003; 3: 573-578.

22. Dimeglio LA, Ford L, McClintock C, Peacock M. A comparison of oral and intravenous bisphosphonate therapy for children with osteogenesis imperfecta. J Pediatr Endocrinol Metab. 2005; 18: 43-53.

23. Bajpai A, Kabra M , Gupta N, Sharda S, Ghosh M. Intravenous Pamidronate Therapy in Osteogenesis Imperfecta: Response to Treatment and Factors Influencing Outcome. J Pediat Ortho 2007 (In press).

24. DiMeglio LA, Peacock M. Two-year clinical trial of oral alendronate versus intravenous pamidronate in children with osteogenesis imperfecta. J Bone Miner Res. 2006; 21: 132-140.

25. Holme E, Lindstedt S. Tyrosinaemia type I and NTBC (2-(2-nitro-4-trifluoromethylbenzoyl 1,3-cyclohexanedione). J Inherit MetabDis 1998; 21: 507-517.

26. Barkaoui E, Debray D, Bahes D, Ogier H, Bernard O. Favorable outcome of treatment with NTBC of acute liver insufficiency disclosing hereditary tyrosinemia type I. Arch Pediar 1999; 6: 540-544.

27. Grompe M. The pathophysiology and treatment of hereditary tyrosinemia type I. Semin Liver Dis 2001; 21: 563-571.

28. Ahmad S, Teckman JH, Lueder GT. Corneal opacities associated with NTBC treatment. Am J Ophthalmol 2002; 134: 266-268.

29. Gissen P, Preece MA, Willshaw HA, McKiernan PJ. Ophthalmic follow-up of patients with tyrosinaemia type Ion NTBC. J Inherit Metab Dis 2003; 26: 13-16.

30. Khadilkar VV, Khadilkar AV, Nandy M, Maskati GB. Growth hormone in turner syndrome. Indian Pediatrics 2006; 43: 236-240.

31. Osio D, Dahlgren J, Wikland KA, Westphal O. Improved final height with long term growth hormone treatment in Noonan Syndrome. Acta Pediatr 2005; 94: 1232-1237.

32. Tanaka N, Katsumata N, Horikawa R, Tanaka T. The comparison of the effects of short term growth hormone treatment in patents with achondroplasia and with hyochondroplaia. Endocr J 2003; 50: 69-75.

33. Hertel NT, Eklof O, Ivarsson S, Aronson S, Westphal O, Sipila I, *et al.* Growth hormone treatment in 35 prepubertal children with achondroplasia: a five year dose response trial. Acta Pediatr 2005; 94: 1402-1410.

34. Moser HW, Raymond GV, Lu SE, Muenz LR, Moser AB, Xu J, *et al*. Follow-up of 89 asymptomatic patients with adrenoleukodystrophy treated with Lorenzo's oil. Arch Neurol 2005; 62: 1073-1080.

35. Atweh GF, Loukopoulos D. Pharmacological induction of fetal hemoglobin in sickle cell disease and beta thalassemia. Seminar Hematol 2001; 38: 367-373.

36. Dixit A, Chatterjee TC, Mishra P, Choudhry DR, Mahapatra M, Tyagi S, Kabra M, Saxena R, Choudhry VP. Hydroxyurea in thalassemia intermedia: A promising therapy. Ann Hematol 2005; 84: 441-446.