

The Need for a Pediatric Statin

A WHITE PAPER

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INTRODUCTION

There are no pediatric dosages available for most medications allowing for the prescription of the right medicine, for the right patient and in the correct amount. Only about a quarter of all the drugs available for prescription contain labeling information for children, and more than two-thirds of the drugs that are prescribed to children have not been studied and labeled for pediatric use. As a result, off-label prescribing has become an accepted practice among physicians, leading to the prescription of extemporaneous formulations with untested bioavailability and stability in children.

One area of clear and immediate need is in the development of a statin product which can help children with genetic risks of developing early-onset heart disease. About one in 500 children have heterozygous familial hypercholesterolemia (HeFH), a condition resulting in severely elevated levels of plasma low-density lipoprotein (LDL-C). Left untreated, this condition has been clearly linked to early atherosclerotic lesions (fibrous plaques) and premature atherosclerosis and cardiovascular disease (CVD).

Development of a safe and effective cholesterol-lowering statin drug formulated specifically for children will allow early intervention. According to the American Academy of Pediatrics, this may make it possible to regress lesions to a degree that is not possible in later adulthood, significantly mitigating the risk of atherosclerosis.

PEDIATRIC DRUG DEVELOPMENT BACKGROUND

In recognition of the need for pediatric labeling instructions, Congress included incentives for conducting needed pediatric studies in the Food and Drug Administration Modernization Act of 1997 (FDAMA). When this failed to have significant impact, Congress passed the Best Pharmaceuticals for Children Act in January 2002, which provided the innovator a six-month extension to exclusivity if prescribed studies were performed. Later, in 2003, Congress passed the Pediatric Research Equity Act

which provided FDA with the authority to use bridging data from adult studies for the approval of pediatric medicines. Although the three acts are designed to encourage the development of pediatric drugs, to date, relatively few drugs are labeled for children.

While it is clear that some drugs are not applicable to children, it is often the case that the adult dose is too high for children. Children have different metabolisms and the pharmacokinetics or pharmacodynamics may differ significantly from adults.

In addition, many of the drugs frequently used in infants and young children are not available in suitable dosage forms. Most of the medications are available either as tablets, capsules or solutions for injection; however, young children frequently have difficulty swallowing the usual solid dosage form and these solid dosage forms are not easily titratable to a customized dose appropriate for a child whose size and metabolism at varying ages can greatly affect the efficacy of any given dose. Of greatest value in pediatric prescription is a liquid formulation that has been studied in children and can be easily titrated to the appropriate dose.

ABOUT HYPERLIPIDEMIA IN CHILDREN

In children, hyperlipidemia may be secondarily associated to conditions such as obesity, but extreme LDL elevations are usually associated with genetic factors. Of these, heterozygous familial hypercholesterolemia (HeFH) is one of the most common and the most clearly documented to have important cardiovascular consequences beginning in childhood.

HeFH has a prevalence of about one in 500 in Caucasian children and is characterized by defective LDL-C receptors, leading to severely elevated levels of LDL-C in the blood. Children as young as 8 with HeFH typically have total cholesterol levels in the range of 270 to 500 mg/dL. In studying children with HeFH, researchers have documented functional and morphological changes of the heart vessel wall, indicating that the atherosclerotic process has already begun. Children with HeFH are characterized by impaired function of the endothelium, the thin layer of cells that line the interior surface of blood vessels and the heart, and the thickening of arterial walls.

On the basis of this knowledge, on July 1, 2008, the American Academy of Pediatrics (AAP) released its



new policy statement on cholesterol in childhood. The new policy has taken on urgency given the current epidemic of childhood obesity with the subsequent increasing risk of type 2 diabetes mellitus, hypertension and cardiovascular disease in older children and adults.

Based on new data and extensive review, it is increasingly clear that cholesterol concentrations can be elevated during childhood and adolescence, and that increased concentrations in childhood are associated with increased risk of atherosclerosis and CVD in adulthood.

The AAP has released its new guidelines relating to the concentrations of LDL at which pharmacologic intervention is recommended for children 8 years and older and adolescents. They also recommend that pharmacologic intervention in children younger than 8 years only be implemented if they have the dramatic elevation of LDL concentration (>500 mg/dL) as seen with the homozygous form of familial hypercholesterolemia. The following table summarizes the new guidelines:

PATIENT CHARACTERISTICS	RECOMMENDED TREATMENT POINTS
No other risk factors for CVD	LDL concentration is persistently >190 mg/dL despite diet therapy
Other risk factors present, including obesity, hypertension, or cigarette smoking or positive family history of premature CVD	LDL concentration is persistently >160 mg/dL despite diet therapy
Children with diabetes mellitus	Pharmacologic treatment should be considered when LDL concentration is \geq 130 mg/dL

CURRENT DEVELOPMENT STATUS

When a decision is made to begin drug treatment, initial therapy with a statin is recommended because bileacid binding resins and cholesterol absorption inhibitors (not yet studied in children) are usually inadequate alone to achieve sufficient LDL reduction. Four statins have been approved by the FDA for the treatment of children with HeFH who are at risk of pre-mature coronary artery disease, all in solid dosage forms. Several recent clinical trials have established both efficacy and safety of statin therapy in children with HeFH, aged 8 to 18 years. Reductions of LDL-C in the studies were quite similar to that for adults and showed no adverse impact on sexual or physical maturation.

Although the benefits are evident and these drugs are approved by the FDA, no statin is currently available in a suitable liquid dosage form for children. The practice of pill splitting to “adjust” doses is a common practice in adults, but pediatric physicians are hesitant to use this practice due to inaccurate splits leading to inappropriate doses.

CONCLUSION

Lifestyle modification is the cornerstone of cardiovascular prevention in childhood and should remain so, but with one-third of U.S. children overweight and about 17% obese, the risk of early-onset CVD is unacceptable. Additionally, genetic factors such as HeFH mean we should be testing all children for high cholesterol levels and treating them both aggressively and as early as possible.

A statin product specifically formulated for children will be a powerful tool in preventing heart attacks when these children have reached their 40s and 50s. We are confident pediatricians everywhere will be eager to use this more appropriate statin formulation.

MADEIRA THERAPEUTICS – CHOLESTEROL-LOWERING STATIN

Madeira Therapeutics in Leawood, KS, has a pediatric statin formulation in liquid form under development. For children it is recommended that stepped titration up to the maximum recommended dose is performed until target LDL levels are achieved or there is evidence of toxicity. Having a statin in oral formulation provides flexibility to customize the dose and individualize therapy according to the child’s specific needs. Approval is anticipated in 2011.