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Paediatric addendum to CHMP note for guidance on clinical investigation of medicinal products in the treatment of lipid disorders

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Executive summary

This is an addendum to the Note for Guidance on Clinical Investigation of Medicinal products in the Treatment of Lipid Disorders (EMEA/CHMP/EWP/3020/03). It is not meant as a guidance document on its own but rather highlights differences from adult patients with lipid disorders and points out paediatric specific issues.

1. Introduction

The atherosclerotic process in children with inherited lipid disorders, so called **primary lipid disorders**, begins in childhood with progression mediated by well identified risk factors.[1,2] These disorders include monogenic dyslipidemia due to homozygous and heterozygous familial hypercholesterolaemia, and familial defective apolipoprotein B. Vascular damage starts from birth and morphological and functional vascular changes have been demonstrated from as early as 8 years.[3] Treatment goals for children are complete reversal of vascular damage at an early age with full compliance and in absence of adverse effects. Early intervention is needed to prevent/delay morbidity and mortality. When possible, primary prevention should be achieved through lifestyle intervention, diet and physical activity. In these genetic disorders this approach is usually insufficient and should be combined with medication, initiated from early onwards.[4] Revised recommendations now propagate to start pharmacological intervention, in particular statins, at 8 years of age or even earlier, depending on actual LDL levels, sex, presence of other risk factors and an important family history of premature vascular disease.[5,6] These disorders have been the primary focus of studies with lipid lowering agents in children so far. Other familial lipid disorders, such as familial combined hyperlipidemia, dysbetalipoproteinemia and familial hypoalphalipoproteinemia, (such as lecithin:cholesterol acyl transferase (LCAT) ABCA1 and apolipoprotein A1 (ApoA1) deficiency), may also be candidates for early pharmacological treatment, but sufficient data are not available to make specific recommendations regarding treatment of other lipid abnormalities than elevated LDL-cholesterol, particularly elevated triglycerides and/or decreased HDL.[5]

Other lipid disorders in children, so called **secondary lipid disorders**, may be an expression of an underlying cause, such as diabetes mellitus type 1 and type 2, transplantation, HIV infection, Kawasaki disease, systemic lupus erythematosus, congenital liver disorders, obesity and metabolic syndrome.[1] These disorders include patients with hypercholesterolemia, but also patients with concurrent or isolated hypertriglyceridemia and/or low HDL-cholesterol. The majority of children with dyslipidemia will have idiopathic dyslipidemias (polygenetic, risk factor-associated or multifactorial).[7] Obesity may be a major contributing factor in these patients. Complications occur in most cases late in life and it still has to be established if and when treatment has to start before the age of 18 years. Emphasis will be on healthy life styles and behaviour modification. However, in certain high risk patient groups cardiovascular events may occur early in life, with recommendations to start medication aimed at correction of lipid abnormalities at an early stage.[1,5,6]

2. Scope

Similar to the adult guideline, this addendum will focus on hypercholesterolemia, in particular children with primary lipid disorders.

3. Legal basis

This addendum to the CHMP Note for Guidance on Clinical Investigation of Medicinal products in the Treatment of Lipid Disorders has to be read in conjunction with the introduction and general principles of the Annex I to Directive 2001/83 as amended. All pertinent elements outlined in current and future EU and ICH guidelines and regulations should also be taken into account especially those on:

- ICH 11 Clinical Investigation of Medicinal Products in the paediatric population (CHMP/ ICH/ 2711/ 99);
- Guideline on clinical trials in small populations (CHMP/ EWP/ 83561/ 2005).

4. Criteria of efficacy

4.1 Morbidity and mortality

The primary goal is to prevent cardiovascular morbidity and mortality associated with lipid disorders. There has not been nor will likely ever be a controlled trial comparing the effect of risk reductions beginning in childhood on the subsequent development of cardiovascular disease.[2] Beneficial effects on cardiovascular outcome therefore have to be extrapolated from studies in adults, if available. However, observational studies after marketing may provide additional information and should be part of the follow-up plan once paediatric use is approved on the basis of surrogate endpoint indicators for lipid levels as well as vascular damage. Annual follow up of study cohorts (2 and 5 years completed and published for pravastatin) will surpass in the next assessment (10 years) deceased peers due to cardiovascular disease and generate evidence for treatment.

4.2 Lipid levels

In young children lowering LDL-cholesterol to ≤ 3.5 mmol/L might be sufficient to reverse vascular damage.[8,9] Whether further lowering of LDL-cholesterol (< 3.1 mmol/L, <2.85 mmol/L or < 3 mmol/L LDL cholesterol (according to European guidelines in adults)) will result in further morbidity and mortality reduction, without compromising cholesterol synthesis and its products in growing and maturing children is currently unknown. Lipid profiles, in particular triglycerides and HDL-cholesterol, may be included as they may predict vascular changes as well.[10] Age/gender specific reference values should be applied where indicated.

4.3 Vascular

Evaluation of vascular damage may be of value as surrogate marker and has been used in clinical trials in children.[5,9] Atherosclerosis progression can be evaluated in young children by carotid intima-media thickness (cIMT).[10] Other possible functional evaluation of endothelial tissue (flow mediated dilation (FMD) or ultrastructure of the vasculature may be useful for short term observations.[11] Newer techniques, such as MRI and PET may provide valuable additional information on effects on vascular damage but this needs to be evaluated further.[12] Below the age of 18 years vascular abnormalities are complete reversible due to unloading of lipid from macrophages in the arterial wall. On the contrary, irreversible damage starts between 18 and 20 years of age, which makes the LDL-C lowering target in adults different from children.[14,15] The relationship between vascular damage and LDL cholesterol levels may be variable to some extent and inclusion of a full lipoprotein profile may provide further information.

4.4 Selection

Criteria for diagnosis and classification of **primary lipid disorders,** in particular homo- and hetero-zygous familial hypercholesterolaemia (HeFH) and familial defective apolipoprotein B (FDB) in children, should be based on LDL-cholesterol levels and family history and, if indicated (e.g. homozygous hypercholesterolemia), supported by genetic analysis (available for >90%) of the disorder in children.[6,7,8] The elevated levels of LDL-cholesterol are related to the genetic variant, ranging from 3.5 to 12.0 mmol/L in conjunction with decreased HDL-cholesterol levels.[6] Benefit of treatment in genetic low HDL-cholesterol disorders should be studied first in adults, before including children as long as proof of concept is lacking. Some genetic variants have elevated triglycerides as well. Cholesterol levels are lower during growth spurt.[13] When conducting studies during adolescence, age, ethnic background and gender differences should be taken into account. Dietary and lifestyle intervention should be initiated prior to a pharmacological intervention study. Children below the age of 10 should be statin-naïve in trials.

Criteria for diagnosis and classification of **secondary lipid disorders** will depend on the type of the dyslipidemia and its associated cardiovascular risk, as discussed under 1. Therapeutic recommendations are less well defined than in primary lipid disorders and should be based on current and future knowledge. These criteria should also take into account underlying cause, concomitant treatment, ethnic background and gender differences. Dietary and lifestyle intervention should be initiated prior to a pharmacological intervention study.

5. Strategy – Design

5.1 Human pharmacology studies

The development of special paediatric formulations is encouraged. Pharmacokinetic data should be provided for the claimed age group, starting from 6 years. Tablet or capsule size is more important than liquid formulations.

5.2 Exploratory therapeutic studies

These studies should determine the appropriate dose for the confirmatory trials. Placebo-controlled studies as suggested in the adult guideline are not always acceptable or feasible in children, for instance in patients with homozygous hypercholesterolemia. This should be discussed by the MAH.

5.3 Confirmatory therapeutic studies

Depending on the indication, these studies will mostly be controlled studies with reference therapy, lasting at least three months up to 2 years with long term follow-up. A limited number of lipid lowering agents, including some statins, fibrates and cholesterol adsorption inhibitors have been tested and are available as reference therapy[5,6,712], but newer treatments such as improved niacin products or CETPi are currently being studied. If no reference therapy is available, in particular in the case of poly drug therapy, placebo controlled trials may need to be carried out. A 3 months duration is acceptable for placebo controlled studies. For cardiovascular measurements, siblings are adequate controls. Apart from effects on lipid levels, the use of other parameters, such as vascular imaging and/or function should be included. Long term controlled outcome studies in children/adolescents over many years are not feasible, but follow-up cohorts after marketing will provide additional information. It is mandatory to assess baseline lipid profiles and vascular measurements to allow long term follow up studies in these cohorts.

6. Safety aspects

To obtain optimal effect of the drug, minimal or absent adverse effects should be present to prevent the negative impact of reduced compliance. Studies should include instructions for down titration of the drug when any adverse event occurs. Long-term issues in relation to growth, cognitive development and sexual maturity are of particular importance, as well as changes in muscular and liver enzyme levels (similar to adults). Follow-up of the consequences of lowering cholesterol synthesis and its products should be made possible, since biochemical tools are currently lacking. A pharmacovigilance model should be developed. HDL-cholesterol raising drugs should be followed for changes in steroid hormone profiles and their biological actions.

Definitions

Refer to section 1.

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