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Hydroxychloroquine in Children With Interstitial (diffuse parenchymal) Lung Diseases

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Summary. Hydroxychloroquine (HCQ) is one of the drugs frequently used for the treatment of interstitial lung disease (ILD) in children (chILD). This use is off-label and studies to analyze the effect and safety of HCQ in chILD are lacking. Therefore, a literature research on the usage of chloroquine (CQ) and HCQ in these conditions was done. Eighty-five case reports and small series in the period from 1984 to 2013 were identified in which children with different diagnoses of ILD were treated with CQ or HCQ, sometimes in combination with other medication including steroids. A favorable response to HCQ or CQ was reported in 35 cases, whereas in the other cases the effect was negative or not clear. The dose of HCQ used was between 5 and 10 mg/kg body weight/day (bw/d). No pharmacokinetic studies have been done. The side effect profile in children seemed to be similar to that in adults. Most often gastrointestinal symptoms were reported. Three patients were found developing retinal changes during the treatment with CQ, whereas in none of the patients treated with HCQ retinal changes were reported. Based on retrospective case reports and small series likely to be reported with bias, the use of HCQ in chILD might be classified as safe. As no prospective data on efficacy and safety of HCQ in chILD are available, systematic collection is necessary. This may be achieved by web-based registers like the European Management Platform for Childhood Interstitial Lung Diseases. Prospective and controlled investigations of HCQ in patients with chILD are mandatory. **Pediatr Pulmonol. 2015;50:410–419.**

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INTRODUCTION

In children diffuse parenchymal lung diseases (DPLD), previously also called childhood interstitial lung diseases (chILD), are rather rare conditions. The estimated prevalence is 0.36/100 000,[1] whereas the incidence of DPLD was 1.32 new cases per 1 million of children per year in a German study.[2]

DPLD in children consist of over 200 different entities with different, mostly unknown pathomechanisms, genetics, symptoms, and clinical courses. The prognosis of the diseases varies from only mild respiratory symptoms and spontaneous recovery over time to severe and often lethal outcomes.

Unfortunately, all of these diseases have in common the fact that there are no evidence based treatments and latest guidelines indicate that treatment decisions have to be made on a case-by-case basis.[3] Treatment is also very much dependent on the treating physician's experience. Beside symptomatic therapy with oxygen supplementation, mechanical ventilation if necessary, physiotherapy and adequate nutrition, a small number of drugs have been used and can be considered for empiric treatment of some of the entities of chILD.

The most frequently used drugs in the treatment of DPLD in children are systemic steroids. These can be administered orally or intravenous, in pulses or as continuous long-time treatment.[4] So far in most cases it

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is not possible to predict whether the patient will respond to the treatment with steroids or not. If receiving steroids, the patient should be closely monitored for side effects, including measurement of weight, glucose homeostasis, bone density, growth, and ophthalmologic screening. Additionally, the use of other immunomodulatory drugs (methotrexate, cyclophosphamide, azathioprine, macrolides) may be indicated.

Another drug that is often used for the treatment of DPLD in children is hydroxychloroquine (HCQ). This anti-malarial drug, also used in rheumatic diseases, is supposed to have immunological effects. So far controlled studies are lacking to evaluate which patients benefit from the use of HCQ.

The goal of this review is to collect data on HCQ to allow the rational usage of HCQ in pediatric DPLD and to pledge to assess treatment effects in systematic clinical studies.

METHODS

To get an overview of the experience in the use of HCQ in chILD, we conducted a systematic literature search. For this review, we used a PubMed search to sample as much information published in the English literature as possible concerning the use of HCQ in pediatric DPLD. We used the following word combinations for the search: "hydroxychloroquine interstitial lung disease," "hydroxychloroquine pneumonitis," "hydroxychloroquine surfactant protein b," "hydroxychloroquine surfactant protein c," "hydroxychloroquine ABCA3," "hydroxychloroquine pulmonary alveolar proteinosis." Articles published between 1984 and 2013 were reviewed. Articles dealing with chloroquine (CQ) were also included, as both drugs are equally effective for malaria, however initially CQ was used more frequently. With time it has been replaced by HCQ due to less ophthalmologic side effects.[5] Also in the treatment of systemic lupus erythematosus (SLE) the two substances showed similar mechanisms of action and immunomodulatory effects.[6]

In addition we used different review articles on the topic of pediatric DPLD,[7,8] to find older case reports using HCQ in DPLD in children. The literature available on this topic was reviewed independently by at least two persons.

RESULTS

HCQ Pharmacokinetics

HCQ has a molecular weight of 336 Da and as such is a small molecule; the chemical structures of CQ and HCQ are indicated in Figure S1 (online only). After oral administration HCQ is rapidly and almost completely absorbed from the gastrointestinal tract. There is a relevant variation of distribution and concentrations in different tissues. The maximum blood levels are reached 4–8 hr after application. With a constant daily dose, a constant plasma level is reached after 4–6 weeks.[9] The volume of distribution is large. In whole blood the largest amount of HCQ is ligated to cellular compartments. Approximately, 50% of the proportion found in the plasma is ligated to plasma proteins.

HCQ accumulates in blood cells and cells of other organs. Despite low plasma levels, tissue levels can be much higher. Accumulation takes place in the liver, spleen, kidney, lung, adrenal glands, skin, and especially in the choroid and iris.[10,11] Compared to the plasma concentration, in heart, lungs, kidneys, and liver concentration ratios of more than 10 times, in parenchymal cells of about 100- to 500-fold and in pigmented cells up to 1000 times can be found.

The excretion from the deep compartments is slow. The terminal elimination half-life for HCQ in healthy patients has been calculated to be 50 ± 16 days by Tett et al.[12] The blood clearance has been calculated to be 96 ml/min.

In a study of Carmichael et al.[13] HCQ serum levels of patients were measured, who had been treated with HCQ for at least 6 months. It was shown, that there are pharmacokinetic variations leading to rather different serum levels of HCQ. For malaria prophylaxis plasma levels above 9.6 μg/L (30 nmol/L) up to 32 μg/L are required. For Malaria therapy plasma levels of 96–192 μg/L are required.[14]

HCQ is metabolized in the liver to two active substances. The main metabolite is the desethylhydroxychloroquine. Excretion is mainly via the stool and only to a small part through the kidneys. Sixty percent of the excreted material in the urine consists of unchanged drug substance.[14]

Pharmacodynamics

HCQ is part of the group 4-aminoquinolines and suitable for malaria prevention and treatment. In the treatment of malaria, HCQ interferes with digestive vacuole function within sensitive malarial parasites by increasing the pH and interfering with lysosomal degradation of hemoglobin.[15]

Besides the effect against malaria HCQ is used as a long-term treatment for rheumatoid arthritis. It may modify the disease course to a remission. Further, there are positive effects in the treatment of connective tissue disease, that is, systemic lupus erythematosus, with HCQ.[16] The exact mechanism of action for the antirheumatic and immunomodulatory effect so far is unknown.

Ben-Zvi et al.[17] described various immunomodulatory mechanisms of action of HCQ. These include among others the interference with lysosomal acidification and

inhibition of proteolysis, chemotaxis, phagocytosis, and antigen presentation,[18] decreasing macrophage-mediated cytokine production, especially IL(interleukin)-1 and IL-6,[19] inhibition of phospholipase A_2,[20] and the inhibition of T and B-cell receptors calcium signaling,[21] matrix metalloproteinases,[22] toll-like receptors signaling[23] and of IL-17 and IL-22 production.[24]

Use of HCQ in Different Indications

Use in Malaria

CQ and HCQ are used for prophylaxis and treatment of malaria in adults and children. Depending on the region and malaria-subtype chloroquine-resistance is frequent.[25,26]

Use in Systemic Autoimmune Diseases

Beside the usage of HCQ as an anti-malarial drug it is used to treat SLE as well as rheumatoid arthritis and juvenile idiopathic arthritis (JIA). Usage in SLE has been recently reviewed considering publications from 1982 till 2007. A total of 95 articles on randomized controlled trials (RCT) and observational studies of children and adults were included in the review. The authors conclude that the use of HCQ is also suitable for use over the entire course of the disease as well as during pregnancy, due to its favorable spectrum of activity and safety profile.[27]

The joint recommendations of the European League against Rheumatism (EULAR) and the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) for the management of adult and pediatric lupus nephritis include the statement that HCQ is recommended for all patients with lupus nephritis to improve the outcome, including pregnant women and children.28,[1616]

Dosage

HCQ is available in two forms, as hydroxychloroquine sulfate and base. Two hundred milligram hydroxychloroquine sulfate is equivalent to 155 mg base. The most common used form is hydroxychloroquine sulfate (for example Quensyl®, Plaquenil®, Sanofi-Aventis Germany and Canada).[29] The dosage of HCQ for adults is mainly depending on the indication of treatment. If used as malaria prophylaxis the dose is low, about 400 mg once per week, whereas the dosage in malaria treatment is much higher, that is, 2000 mg apportioned over 3–4 days.[26] The recommended dose for the long-term use in rheumatoid arthritis or SLE is 200–400 mg/day.[28] Dosage recommendations for the use of HCQ in children can be found in the literature for rheumatic diseases in children. The therapeutic effect and the side effects are directly correlated with the serum concentration, which correlates with the daily dose.[30,31] Maximum serum concentrations for HCQ are considered safe from 370–470 μg/L (1.4–1.5 μmol/L), which are achieved with doses of 5–7 mg/kg body weight/day (bw/d).[30] From this data the following dose recommendation for rheumatic diseases has been derived[32]: HCQ: 6 mg/kg bw/d for a period of 4–6 weeks, followed by 5 mg/kg bw/d (daily oral dose). The recommendation is based on the ideal (lean) body weight,[33] as HCQ does not accumulate in the adipose tissue.

Safety of HCQ

Side Effects and Recommended Monitoring

At a dose calculation in mg/kg bw, the safety profile in children and adults can be considered comparable.[32,34]

The most important known side effects in adults and children are various and include ophthalmological changes, cardiovascular disorders, hematological disorders, skin lesions, hearing disorders, and central nervous system disorders. The most common side effects include gastrointestinal symptoms, such as nausea, vomiting, diarrhea, loss of appetite, and, rarely, elevated liver enzymes, as well as neurological side effects, such as headache and dizziness. In younger children, nausea and vomiting are often described as a sign of stomach irritation.[35] Usually, the side effects are dose-related, such as pruritus, excessive sweating, or headache.

Before starting the treatment with HCQ a baseline ophthalmological examination as well as a blood testing, including full blood counts, liver, and kidney function tests, is recommended.[29]

The ophthalmological side effects can be divided into reversible changes, such as precipitations in the corneal epithelium, and sometimes irreversible changes which can be the case in retinal toxicity.

Recommendations for ophthalmological screening for HCQ toxicity are not consistent. The American Academy of Ophthalmology recommends performing a baseline examination within the first year of starting HCQ treatment to document any complicating ocular conditions and to document the baseline status. If there are no special risk factors, for adult patients annual screenings at the ophthalmologist should be performed after 5 years of HCQ treatment.[36]

The product monographs recommend much shorter screening intervals for all patients up to every three months.[14,29] The American College of Rheumatology recommends annual ophthalmological screening from the beginning of the treatment in children, although the evaluation of color vision can be difficult in young children.[37] The British Society for Paediatric and Adolescent Rheumatology recommends to consult an ophthalmologist at baseline for assessment of baseline visual assessment including:

- Visual acuity and reading acuity.
- Central visual field, using an Amsler Chart (preferably red on black) or automated perimetry (e.g., Humphrey 10–2 protocol).

- Slit lamp examination of the cornea.
- Stereoscopic slit lamp examination of the retina (e.g., with a 90 D or 78 biconvex lens).

Evaluation may need to be extended according to signs and symptoms to include retinal photography, ocular coherence tomography (OCT), fundus autofluorescence (FAF) imaging and visual electrophysiological tests. Subsequent examinations should be at the discretion of the ophthalmologist, but indefinite follow up is not likely to be required for most patients. For patients who have received continuous treatment for more than 5 years, an individual arrangement should be agreed with the local ophthalmologist.[38]

During the treatment with HCQ cases of cardiomyopathy have been reported, which can lead to heart failure. Life-threatening or fatal side effects have been reported as a result of overdoses and affect the cardiac excitability such as depressed excitability and conductibility of cardiac muscle.[39,40] Therefore, cardiological monitoring for symptoms of cardiomyopathy, for example cardiac conduction disorders or biventricular hypertrophy, is recommended.[29] We suggest annual ECG and echocardiography.

The product monograph recommends blood count at baseline and every 2 months during treatment due to a possible bone marrow depression,[14,29] which in clinical practice this is not done so frequently. A regular monitoring of skeletal muscle function and tendon reflexes is recommended, as HCQ can lead to myopathies of the skeletal muscles, neuropathies, reduced tendon reflexes, and disturbed nerve conduction.

If there are any changes in blood testing, ophthalmological examination, musculoskeletal function or signs of cardiomyopathy treatment with HCQ is recommended to be discontinued.

The following table modified from the review article by Lee et al. 2011[16] shows the frequencies of side effects associated with the use of HCQ and CQ, as they occurred in various studies (see Table S1, online only).

Contradictions

Absolute contradictions for the use of HCQ are (1) severe renal impairment; (2) pre-existing maculopathy; and (3) known hypersensitivity to 4-aminoquinoline compounds.

Relative contradictions includes: (1) mild to moderate renal impairment; (2) neurological disorders, especially epilepsy and myasthenia gravis; (3) liver disease; (4) severe gastrointestinal disorders; (5) metabolic disorders including porphyria, glucose-6-phosphate-dehydrogenase deficiency and quinine sensitivity; and (6) psoriasis.[29,38]

Drug Interactions

Combination of HCQ with other drugs may increase or decrease plasma levels. This does not only affect the therapeutic activity of HCQ but also its rate of side effects. These data are summarized in Table S2 (online only). Very relevant to pediatric patients with chILD are the frequently concomitantly used systemic corticosteroids; such a combination may increase the risk of myopathy or cardiomyopathy, possibly leading to fatal cardiac failure. HCQ should not be used in combination with arrhythmogenic drugs as for example amiodarone or moxifloxacine, as there is an increased risk for ventricular arrhythmias. Combined use of aminoglycosides may lead to increased neuromuscular blockade and HCQ by itself can lower the convulsive threshold.

Overdosage and Urgency Treatment

Especially in children even small doses like 1–2 g of HCQ can lead to intoxications with fatal outcome.[14,41] Symptoms of an overdose with HCQ are headache, drowsiness, visual changes, tinnitus, reduced auditory acuity, seizures, hypokalemia, cardiac arrhythmias (inclusive prolongation of QRS and QT-interval, Torsade de pointes, ventricular tachycardia, ventricular fibrillation), and cardiovascular failure. This can occur suddenly and can lead to death. As these symptoms can occur shortly after the overdose, an immediate medical treatment is necessary. In case of ingestion of a larger or unknown amount of HCQ, the patient should be referred to an emergency department for observation and cardiac monitoring. There is no specific antidote existing. Depending on the ingested dose and time point of ingestion, a gastric lavage and administration of charcoal can reduce further absorption. Parenterally administered diazepam may reduce chloroquine-associated cardiotoxicity. Symptomatic support in an intensive care unit is recommended.[41,42]

Use of HCQ in Special Patient Groups

Treatment With HCQ in Pregnant Women

HCQ crosses the placenta, in cord blood almost the same concentrations of HCQ are measured as in the maternal blood.[43] Several studies demonstrated that neither pregnancy outcome, nor number or type of malformations differed from that of unexposed pregnancies.[44,45]

In a review article, all published data on ocular toxicity in neonates after HCQ exposure in utero were analyzed.[46] A total of nine studies involving 246 children in whom an ophthalmological finding existed were included in the review. None of the children showed clinical retinal changes. In four children subclinical ocular toxicity was suspected. From these data the authors did not conclude any significant risk of retinal toxicity after exposure to HCQ in utero.[46,47] Based on these and other data the EULAR/ERA-EDTA recommendations state that HCQ should be continued during pregnancy or instituted if immunosuppressive agents need to be stopped.[28] The Centers for Disease Control and Prevention (CDC)

statement on malaria therapy (http://www.cdc.gov/malaria/resources/pdf/clinicalguidance.pdf) explicitly recommends the treatment with CQ/HCQ during pregnancy.[48]

Treatment With HCQ in Children

Antimalarial drugs are used in various indications in children. In addition to parasitic diseases, such as malaria, they are mainly used in rheumatic diseases (JIA), immune disorders (SLE and discoid lupus erythematosus) or in the treatment of various juvenile dermatoses.[32,49]

Based on their body weight children often have a higher clearance of foreign substances than adults. The clearance correlates better with the body surface than in adults. However, this is not the fact in newborn and premature babies. There are significant differences in the time to full maturity of the enzymes of the cytochrome P-450 system and various isoforms of the Uridine 5′-diphosphoglucuronosyltransferase, so that the enzyme activity is very difficult to calculate in neonates and infants.[50]

The pharmacokinetics of CQ and HCQ are not significantly different in children and adults.[51] In a dose-finding study of HCQ and CQ in children with JIA measuring serum concentrations Laaksonen et al. describe hair loss, fatigue, ECG changes, disturbances in accommodation, and dizziness.[30] Keratopathy is mentioned as the most serious side effect. Keratopathy is seen in combination with high serum concentrations of HCQ as a sign of toxicity. The authors recommend as a safe dose for HCQ 4 mg/kg bw/d. Corresponding serum concentrations for HCQ were 370–470 μg/L (1.4–1.5 μmol/L).

In children HCQ and CQ are mainly used in the treatment of JIA, but also in other autoimmune diseases such as dermatomyositis,[52] porphyria cutanea tarda,[10] skin manifestations of systemic diseases such as lupus erythematosus panniculitis[53] or DLE.[54] Studies usually include small numbers of patients, the dosage recommendations in the publications are based on the recommendations for the treatment of juvenile rheumatoid diseases.[10,32,34,54]

In a summary of several studies involving almost 240 children that were diagnosed with JIA, Grondin et al.[55] found that 15–75% of the children that were treated with HCQ and CQ had an improvement of their disease and 45% had a remission of the JIA. Rare side effects affect the gastrointestinal tract with vomiting, nausea and loss of appetite; as a severe side effect an irreversible retinal damage is described, however, it occurs only very rarely with a dose of <7 mg/kg bw/d and only after many years of use. Regular eye checkups with review of color vision are necessary.[56]

Further studies for the use of HCQ in children with JIA, also from the 1980s, compared the treatment with HCQ with other medications such as gold and D-Penicillamin. The dosages used for HCQ were 5–6 mg/kg bw/d. The average age of the children was 10 years.[31,57]

Use of HCQ in Lung Disease

Treatment With HCQ in Adult DPLD

In the spectrum of adult DPLD, HCQ is mainly used for the treatment of sarcoidosis. For this, both CQ and HCQ have been widely used for over 40 years, especially in cutaneous sarcoidosis.[58] Baltzan et al.[59] conducted a study with 23 patients with pulmonary sarcoidosis who were randomized after initial therapy with CQ over 6 months to prolonged maintenance treatment with CQ or observation. A small advantage of the maintenance treatment with CQ was shown.

In other DPLD, such as idiopathic pulmonary fibrosis (IPF), vasculitis, or amyloidosis, HCQ plays no major role for routine drug treatment.

Treatment With HCQ in Pediatric DPLD (chILD)

The term "chronic interstitial lung diseases in children" (chILD) summarizes a group of over 200 different diseases, each of which usually is rare to ultra-rare. Parenchymal lung tissue is diffusely and mostly chronically involved. The natural course of many of these diseases is associated with a high morbidity and mortality. Often these children require long-term oxygen therapy or sometimes artificial ventilation.[2]

Nowadays treatment with HCQ is performed off-label in all the patient groups and diseases listed in Table 1. In simple terms, these patients are children mostly older than about 3 weeks and suffer from an interstitial lung disease (ILD) that is genetically, histologically or clinically diagnosed.

Cases Reported in the Literature Between 1984 and 2013

In reflection of this predicament in the literature on pharmacological therapy for chILD only case reports and very small case series can be found. So far, there are no controlled studies on the treatment with HCQ in pediatric ILD.

In our literature search, we identified 85 case reports or small series of children with ILD who were treated with HCQ or CQ, which had been published during the time period from 1984 to 2013.[60–91] All individual cases and their relevant clinical data were extracted and summarized in Table S3 (online only).[61–90]

Of these patients, 16 children were treated exclusively with HCQ or CQ, whereas the other children also received additional drugs, such as systemic steroids, azathioprine, cyclophosphamide, or some macrolide antibiotics. The disease course under the treatment with HCQ or CQ was very different from case to case. There are reports of cases in which patients who did not respond to steroids,

TABLE 1— Children (Older Than 3 Weeks of Age) With Diffuse Parenchymal Lung Diseases (chronic interstitial lung diseases, chILD) Currently Treated With Off-Label HCQ at the Discretion of the Pediatric Pneumology Expert

a) chILD genetically diagnosed
Surfactant dysfunction disorders including patients with disease causing mutations in SFTPC, SFTPB, ABCA3, TTF-1 (Nkx2-1) and further extremely rare entities
b) chILD histologically diagnosed
Chronic pneumonitis of infancy
Desquamative interstitial pneumonitis (DIP)
Lipoid pneumonitis or cholesterol pneumonia
Nonspecific interstitial pneumonitis (NSIP)
PAP after the exclusion of mutations in GMCSF-Ra/b and GMCSF autoantibodies
DPLD due to microvasculopathy, cryptogenic organizing pneumonia (bronchiolitis obliterans organizing pneumonia), diffuse alveolar damage and acute interstitial pneumonia, acute fibrinous and organizing pneumonia
Usual interstitial pneumonitis (UIP)
Sarcoidosis
Follicular bronchitis/bronchiolitis/Lymphocytic interstitial pneumonia (LIP) unless associated with immunodeficiency
Giant cell interstitial pneumonia (GIP)
Storage disease with primary pulmonary involvement (e.g., Niemann Pick)
Pulmonary interstitial glycogenosis (cellular interstitial pneumonitis, histiocytoid pneumonia)
Neuroendocrine cell hyperplasia (NEHI)
Hermansky–Pudlak Syndrome
c) chILD clinically diagnosed
Unclear respiratory distress syndrome in the mature neonate and the non-neonate, after the exclusion, as far as possible, of infectious, lung structural, vascular and all other known causes of chILD and the presence of radiological evidence of chILD; and the presence of either tachypnea, dyspnea or oxygen requirement, or need for mechanical ventilation
Idiopathic pulmonary hemorrhage

ABCA3 = human ATP-binding cassette transporter, sub-family A, member 3; GMCSF = granulocyte macrophage colony-stimulating factor; GMCSF-Ra/b = granulocyte macrophage colony-stimulating factor receptor; PAP = pulmonary alveolar proteinosis; SFTPB = surfactant protein B; SFTPC = surfactant protein C; TTF- 1 = thyroid transcription factor-1.

benefited from HCQ or CQ. However, there are also case reports in which the therapy with HCQ or CQ resulted in no improvement of symptoms. This may be associated with the fact that no systematic outcome parameters, no response criteria and no systematic monitoring were performed. Observations were retrospective. Lastly, there is a strong reporting bias, as more likely positive and successful cases will be reported. Thus, it has to be kept in mind that the quality level of the data is very low.

Overall, in 35 of the 85 patients reported, the symptoms improved during treatment with HCQ or CQ. Of the 16 patients who were treated exclusively with HCQ or CQ, the symptoms improved in 14 cases. In the 54 patients who received HCQ or CQ in combination with steroids in 38 cases, a response was observed to therapy.

In most of the reported cases the time to a response to the treatment with HCQ or CQ is not well documented. In 15 cases the time to the first observation of an effect of the treatment is sufficiently described and ranges from 2 days to 24 weeks. The medium duration to response was about 4 weeks.

The spectrum of diseases that had been treated with HCQ or CQ in the case reports is wide. It includes the following conditions:

Histological Diagnosis

Chronic interstitial pneumonitis, cellular interstitial pneumonitis, desquamative interstitial pneumonitis (DIP), early interstitial pneumonitis, fibrosing alveolitis, IPF, idiopathic pulmonary hemosiderosis (IPH), lymphocytic interstitial pneumonia, non-specific interstitial pneumonitis, pulmonary alveolar proteinosis, usual interstitial pneumonitis.

Genetic Diagnosis

Surfactant protein C deficiency, Human ATP-binding cassette transporter, sub-family A, member 3 (ABCA3) deficiency.

Eighteen cases showed the histological diagnosis of DIP and/or fibrosing alveolitis. In these cases the number of patients that benefited from the treatment with HCQ or CQ was equal to those who had no positive effect of the treatment.

The reported cases of histologically diagnosed lymphocytic interstitial pneumonia, usual interstitial pneumonitis, IPH, IPF, or cellular interstitial pneumonitis showed a positive effect of treatment with HCQ or CQ in most cases. Among the other conditions the effect was mostly negative or not clear.

In 21 patients with genetically proven surfactant protein C deficiency nine patients improved during the treatment with HCQ while in 12 patients there was no clear effect noticed.

Among three patients with mutations in the ABCA3 region in two patients a benefit from the treatment with HCQ was noticed whereas in one patient the effect was unclear.

In summary, it can be concluded that it is currently not possible to predict which patient will benefit from the treatment with HCQ, and in which period of time, and which will not.

Dose

In those case reports in which the dosage of HCQ given was mentioned, it ranged between 3.5 and 10 mg/kg bw/d. A maximum of 600 mg/d was given in one case (case number 80) when the patient already had reached adulthood. In almost all case reports it remains not clear, whether the drug hydroxychloroquine sulfate or base was dosed. More common in current practice is the use of hydroxychloroquine sulfate (for e.g., Quensyl® or Plaquenil®, Sanofi-Aventis Germany and Canada).[29] In the cases reviewed, the most common practice (in about 69% of the cases) in dosing patients with chILD was up to 10 mg/kg bw/d HCQ independent of the patient's age. We recommend starting HCQ treatment with 10 mg/kg bw/d for 1 week, followed by 6.5 mg/kg bw/d. If possible, all new treatments should be introduced one after the other, in order to have a chance to judge on the clinical effect. In case of severe respiratory distress a multidrug approach is sometimes done. Under these conditions interactions (see above, in particular with steroids), need to be taken into account. Discontinuation of HCQ treatment should be considered when clinical condition is stable. Both, starting and stopping HCQ in chILD should preferably be done in the framework of randomized trials (see below), as not sufficient information on dose, indication, side effects and outcome is available.

Ophthalmological and Other Side Effects

Regarding the side effect profile, in 3 of 28 cases (case numbers 2, 11, 31) in which the children had received CQ, retinal changes have been reported. In these three patients, the duration of treatment with CQ varied between 20 months and 9 years at a dose ranging from 1.5 to 10 mg/kg bw/d.

In the first patient (case number 2) with DIP treatment with CQ was started at the age of 5 months and macular pigmentation was noticed after about 20 months of treatment with a dose from 6 mg/kg bw every second day. Thereafter, the CQ dose was reduced to 3 mg/kg bw every second day, but later increased to 5 mg/kg bw/d because of a relapse of the pulmonary disease. With this treatment no further retinal change was noticed.

The second case (case number 11) is a patient with IPH, who was started on chloroquine sulfate 400 mg/d at the age of 17 years. Three years later CQ was discontinued and restarted after 6 months on a dose of 200 mg/d due to a relapse of the disease. Retinal changes were detected during a routine ophthalmological control and CQ was discontinued.

In the third case (case number 31) in a patient with DIP treatment with CQ was started at the age of 14 months with a dose of 10 mg/kg bw/d. At the age of 3 years with a CQ dose of 7 mg/kg bw/d macular eye changes were noticed. Therefore, the dose was reduced which lead to a relapse of the pulmonary disease, and the patient was restarted on the dose of 7 mg/kg bw/d.

In contrast to CQ ($n = 25$), the application of HCQ ($n = 55$) was not associated with retinal side effects in these cases and small studies in patients with chILD.

Some patients reported abdominal pain during the first week of HCQ administration, which settled thereafter. In one patient a mild intermittent elevation of the ALT was reported (case number 79).

Nevertheless, it should be noted that possibly not all side effects are listed in the case reports due to reporting bias.

Outlook

Taken together, in agreement with the results from rheumatologic patients, the experience in everyday pediatric pneumology practice also shows that HCQ is a well-tolerated drug in most cases with relatively few side effects. Therefore, major obstacles for progress with HCQ treatment in chILD are administrative and practical hurdles that hinder systematical and prospective data collection. Even if empirical treatment of isolated cases is often done in combination with corticosteroids, macrolide antibiotics, immunosuppressive agents, and HCQ during complex clinical situations, we must prospectively assess empiric drug use. A first step would be to report all cases treated with HCQ for chILD to registers ("I have a case" at www.childeu.net) of the European Management Platform for Childhood Interstitial Lung Disease. Usage of this register and bio-bank is open to all interested including subjects and following the terms of use. A randomized controlled clinical trial is going to be conducted by this consortium. Amongst others, this clinical trial aims to evaluate the efficacy and safety of HCQ against placebo in chILD. Participation in the study is welcome and technically prepared for interested large centers, provided investigator driven approval by relevant competent authorities and ethics boards. All this will help to collect high quality information over time in such patients and to allow objective judgment on risk benefit ratios for all types of ILD in children.

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