**LEADING ARTICLE**

# Emerging Treatments for Childhood Interstitial Lung Disease

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## Abstract

Childhood interstitial lung disease (chILD) is a large and heterogeneous group of disorders characterized by diffuse lung parenchymal markings on chest imaging and clinical signs such as dyspnea and hypoxemia from functional impairment. While some children already present in the neonatal period with interstitial lung disease (ILD), others develop ILD during their childhood and adolescence. A timely and accurate diagnosis is essential to gauge treatment and improve prognosis. Supportive care can reduce symptoms and positively influence patients' quality of life; however, there is no cure for many of the chILDs. Current therapeutic options include anti-inflammatory or immunosuppressive drugs. Due to the rarity of the conditions and paucity of research in this field, most treatments are empirical and based on case series, and less than a handful of small, randomized trials have been conducted thus far. A trial on hydroxychloroquine yielded good safety but a much smaller effect size than anticipated. A trial in fibrotic disease with the multitargeted tyrosine kinase inhibitor nintedanib showed similar pharmacokinetics and safety as in adults. The unmet need for the treatment of chILDs remains high. This article summarizes current treatments and explores potential therapeutic options for patients suffering from chILD.

### Key Points

No specific therapy is approved yet for childhood interstitial lung disease (chILD).

Improved understanding of disease pathogenesis is instrumental to the development of novel therapies.

The disease course is highly heterogeneous, and when treatment is required, immunosuppressive and anti-inflammatory drugs are often the first-line therapies.

Multi-stakeholder collaboration is key to develop novel drugs and move the field of chILD forward.

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## 1 Introduction

The term childhood interstitial lung disease (chILD) was coined to collect a large and heterogeneous group of rare and ultra-rare entities manifesting during childhood. Despite being uncommon, the burden of chILD is high for both caregivers and the health system [1, 2]. Indeed, chILD has a high morbidity and mortality rate, and a global prevalence of 1.6–46 per million [3–6]. Interstitial lung disease (ILD) in children is approximately ten times rarer and, at the same time, 100 times less studied and published than adult ILD [7]. The diagnosis of chILD should be suspected if at least three of the following four elements are present for more than 4 weeks in the absence of a respiratory tract infection: (1) symptoms like exercise intolerance, tachypnea, (dry) cough; (2) respiratory signs including dyspnea, crackles on lung auscultation, failure to thrive; (3) respiratory insufficiency with hypoxia/low oxygen saturation; and (4) diffuse parenchymal lung abnormalities on chest computed tomography (CT) scan or chest X-ray [8].

When chILD is suspected, a detailed anamnesis and family history (with emphasis on siblings/relatives with a history of ILD or early death from lung disease), clinical examination searching for potential rheumatological, immunological, or dermatological manifestations, and a chest X-ray should be performed, before referring the patient to an expert center. Additional clinical signs may include wall

deformity or pectus excavatum (for example, in patients with surfactant disorders), or digital clubbing.

As with adult ILD, the diagnostic algorithm includes non-invasive (i.e., pulmonary function tests, assessment of ventilation and oxygenation, and chest imaging) and invasive procedures (i.e., bronchoscopy, and lung biopsy). Moreover, genetic testing has been implemented in most expert centers, thus improving diagnostic accuracy and reducing the need for invasive diagnostic modalities. Despite considerable progress in recent years, disease pathogenesis remains unknown in many of the chILDs, making the development of efficacious treatments challenging [9, 10]. Moreover, the rarity of each condition and the fact that patients are often living in geographically dispersed areas represent additional important hurdles when planning clinical trials among many other obstacles [11]. In this regard, the importance of collaboration among expert centers with the aim of establishing patient registries and databases cannot be overemphasized [12]. In this review, we explore the landscape of pharmacological treatment of chILD.

## 2 ChILD Classification

Although the term chILD has the advantage of allowing easy communication and is popular, it has several disadvantages, including lumping together many conditions with completely different presentations, treatments, and outcomes, even including conditions involving the lung interstitium only indirectly or very mildly, like in patients with persistent tachypnea of infancy [13]. Thus, the need for a simple classification system emerged over the years. In 2004, a task force conducted by the European Respiratory Society, which included respiratory physicians and basic scientists, reviewed 185 cases of chILD and classified them with a system similar to that used for adult disease [14]. A few years later, a new classification scheme based on lung histology was proposed for ILD in children < 2 years of age [15, 16]. This classification system was later extended to all pediatric age groups [17]. Recently, an etiological classification system combining pediatric and adult lung ILD in a single system was proposed [18]. The system differentiates four main categories, i.e., lung-only (native parenchymal) disorders, systemic disease-related disorders, exposure-related disorders, and vascular disorders. Of particular importance are those conditions closely linked to lung development and thus representing the majority of "typical" chILD, such as those in children not surviving into adulthood, those infrequently diagnosed at adult age, and those that transition into adulthood, as is now being seen more and more [19]. They include "Diffuse developmental disorders (A1)," usually resulting in death within the neonatal period; "Growth abnormalities with deficient alveolarization (A2)," such as

lung hypoplasia, chronic lung disease of prematurity (bronchopulmonary dysplasia [BPD]), and others with a somewhat better prognosis; and "Infant conditions of undefined etiology (A3)," comprising the overall most frequent diagnoses in these children, i.e., neuroendocrine cell hyperplasia of infancy (NEHI) (or more correctly labeled as persistent tachypnoea of infancy [PTI]) [13, 20, 21]. Lastly, "ILD related to the alveolar surfactant region (A4)" includes surfactant dysfunction disorders [22] and pulmonary alveolar proteinosis (PAP) [23]. Patients with the latter diagnosis now often reach adulthood or are diagnosed at adult age [24–26]. Many other conditions, in particular "ILD related systemic disease processes (B1)," with examples like sarcoidosis [27] and connective tissue diseases [28], are ILDs with increasing frequency in adulthood.

Recently, the Children's Interstitial and Diffuse Lung Disease Research Network (chILDRN) published data regarding a prospective registry including 683 individuals enrolled from different centers in the United States. NEHI was the most frequent diagnosis (23%), the second being ILD associated with connective tissue or immune-mediated disorders (16.5%). Notably, 11% of cases of chILD remained "unclassified" (Table 1) [29].

## 3 Genetic Background

Despite intrinsic peculiarities, chILDs often share similar clinical and radiological manifestations and may be difficult to differentiate from one another. Genetic testing can identify disease-causing mutations, thus reducing the need for invasive diagnostic procedures (Table 2) [30]. The number of genetic etiologies identified as causes of ILD in children continues to grow and includes genes involved in surfactant production (*SFTPB, SFTPC*, *ABCA3*, and *NKX2-1*) [31–35] and catabolism (*CSF2RA* and *CSF2RB*) [36, 37], immune regulation (*COPA*) [38, 39], and lung development (*FLNA* and *TBX4*, among others) [40, 41]. Some chILDs are associated with high mortality, whereas others have a favorable outcome. For instance, surfactant protein B (SP-B) deficiency has the worst prognosis, whereas variants within *SFTPC* may lead to a range of phenotypes and prognoses (Fig. 1) [42]. On the contrary, most but not all children with PTI/NEHI tend to experience a favorable prognosis; therefore, a limited follow-up to 10 or 15 years of age needs to be considered [43].

## 4 Current Therapeutic Options for ChILD

Corticosteroids, hydroxychloroquine, and azithromycin are the most common pharmacological treatments for patients with chILD [44]. Less frequently used medications include

**Table 1** Distribution of chILD diagnoses and subgroups [29]

| Diagnosis/categories | Percentage of patients |
|---|---|
| NEHI | 23% |
| Connective tissue disease-related/immunomediated<br> Systemic juvenile idiopathic arthritis<br> Systemic sclerosis<br> Systemic lupus erythematosus<br> Other | 16.5% |
| Surfactant dysfunction | 12% |
| Bronchiolitis obliterans | 11% |
| Alveolar hemorrhage | 9.2% |
| Alveolar growth disorders | 4.8% |
| Others (including PAP, environmental/toxic/drug-related, pulmonary interstitial glycogenosis) | 13% |
| Unclassifiable ILD | 11% |

*ChILD* childhood interstitial lung disease, *ILD* interstitial lung disease, *NEHI* neuroendocrine cell hyperplasia of infancy, *PAP* pulmonary alveolar proteinosis

azathioprine, cyclophosphamide, and colchicine [45]. Acute exacerbations in chILD were treated with β-lactam antibiotics (54%), systemic glucocorticosteroids (25%), inhaled bronchodilators (24%), or macrolides (19%) [46].

Intravenous pulse methylprednisolone (10–30 mg/kg) is used in critical patients or those needing ventilation [47]. Chronic treatments with oral glucocorticosteroids in children are done rarely, and the frequency and (potential) severity of side effects of corticosteroids must always be considered [48]. Consequently, close clinical monitoring is mandatory, including bone density, periodic complete blood count, and growth measurements [49].

Hydroxychloroquine is an antimalarial drug used in several autoimmune diseases, including arthritis [50]; historically, it has been used also in some chILDs, although its role in this disease remains controversial. Between 1984 and 2013, 85 case reports and small case series reported on children with different forms of ILD who were treated with chloroquine or hydroxychloroquine. In 35 cases, the effect was beneficial, while in the remaining, the results were

**Table 2** Overview of genes involved in chILD

| Gene | | Position | Inheritance | Clinical presentation | Treatment |
|---|---|---|---|---|---|
| **Surfactant protein disorders** | | | | | |
| *SFTPB* | Surfactant protein B | 2p11.2 | AR | Neonatal respiratory distress, poor prognosis | Symptomatic; lung transplantation |
| *SFTPC* | Surfactant protein C | 8p21.3 | AD | Variable presentation | Corticosteroids and hydroxychloroquine; lung transplantation |
| *ABCA3* | ATP-binding cassette-family A member 3 | 16p13.3 | AR | Neonatal and poor prognosis or late presentation with good prognosis | Hydroxychloroquine; azithromycin; lung transplantation |
| **Pulmonary alveolar proteinosis** | | | | | |
| *CSF2RA* | Colony stimulating factor 2 receptor alpha | Xp22.32 | X-linked | Infancy or adult presentation | Whole lung lavage |
| *CSF2RB* | Colony stimulating factor 2 receptor beta | 22q12.3 | AR | Infancy or adult presentation | Whole lung lavage |
| *MARS* | Methionyl–transfer RNA synthetase | 12q13.3 | AR | ILD, anemia, hypothyroidism | Symptomatic; whole lung lavage |
| **General disorders** | | | | | |
| *COPA* | Coatomer associate protein subunit alpha | 1q23.2 | AD | ILD or hemorrhage, inflammatory arthritis | Janus kinase inhibitors; lung transplantation |
| *NKX2-1* | NK2 homeobox 1 | 14q13.3 | AD | Congenital hypothyroidism, chorea and lung disease | Symptomatic; lung transplantation |
| *FLNA* | Filamin A | Xq28 | X-linked recessive | Severe manifestations and respiratory failure | Symptomatic; lung transplantation |
| *TBX4* | T-box transcription factor4 | 17q23.2 | AD | Acinar dysplasia and pulmonary hypertension | Lung transplantation |

*AD* autosomal dominant, *AR* autosomal recessive, *ATP* adenosine triphosphate, *chILD* childhood interstitial lung disease, *ILD* interstitial lung disease, *NK* natural killer

**Fig. 1** Seventeen-year-old girl with SP-C deficiency and interstitial lung disease. CT scans show extensive ground glass opacity and traction bronchiectasis throughout both lungs. *CT* computed tomography, *SP-C* surfactant protein C
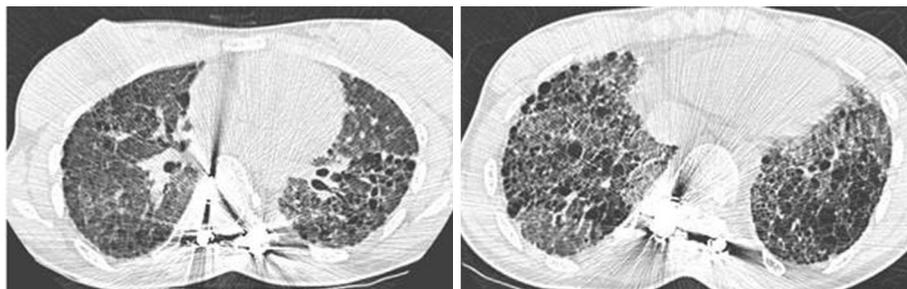


unsatisfactory or inconclusive [51]. Hydroxychloroquine is generally safe, but its chronic use may be associated with visual loss, making regular visual assessment mandatory [52]. The effect of hydroxychloroquine in patients with chILD has been recently evaluated in a phase 2a, randomized, double-blind, placebo-controlled, multinational study [53, 54]. The primary endpoint of presence or absence of response to treatment as assessed by oxygenation (calculated from a change in transcutaneous $O_2$ saturation of $\geq 5\%$, respiratory rate $\geq 20\%$, or level of respiratory support) did not differ between hydroxychloroquine and placebo. Acknowledging major limitations such as the small study population ($n = 26$), the heterogeneity of included patients, the treatment duration (12 weeks followed by an open observation period of 12 weeks), and the lack of lung function data below the age of 6 years, the authors warned that prescription of hydroxychloroquine in daily practice needs to be reassessed. It is very likely that the beneficial effect of hydroxychloroquine is mutation specific, particularly in *ABCA3* deficiency [55].

Azithromycin is an anti-inflammatory and immunomodulatory antibiotic that is used in a range of respiratory diseases; however, the evidence favoring its utility in chILD is limited to less than a handful of case reports [56]. Although widely used, no clinical trial of azithromycin has been conducted in chILD, and its role remains marginal and empirical; the potential risk of microbial resistance to azithromycin should also be considered [57]. Although prospective data are needed, several case reports have reported improvements of adult ILD associated with *ABCA3* deficiency following azithromycin treatment, suggesting a possible benefit to be evaluated in selected chILDs [24, 58].

Whole lung lavage (WLL) is the standard treatment in PAP, but this procedure is available only in specialized centers. Indeed, special techniques are necessary in infants, due to the small airway dimensions [59–61]. In addition, although safe and efficacious, WLL is invasive and time-consuming [62].

Specific therapies with a mechanistically plausible role exist, but they are applicable only in a minority of conditions (biologics [i.e., rituximab], immunomodulatory therapies in connective tissue disorders, or stem cell transplant in alveolar proteinosis) [63, 64].

## 5 Non-pharmacological Treatments

Supportive care is similarly important for children with ILD. As with adult disease, chILD patients with gas exchange impairment may benefit from supplemental oxygen, whereas children with severe respiratory failure may benefit from invasive or non-invasive ventilation [65]. Patients with chILD may display poor somatic growth, thus needing specific nutritional support. Lessons learned from BPD and cystic fibrosis (CF) suggest that growth should be closely monitored also in patients with chILD.

Similar to adult ILD patients, preventing further damage to the lung is critically important. Pneumonia and other infections impart an important morbidity and mortality burden on children with ILD. Therefore, vaccination (pneumococcal and annual influenza), avoidance of harmful environmental exposures (such as second-hand smoke), and appropriate personal hygiene (both for children and caregivers) are strongly recommended [16].

Gastroesophageal reflux disease (GERD), a common comorbidity in adult ILD patients, has been investigated also in chILD. In a study by Dziekiewicz and colleagues, the prevalence of GERD among children with ILD ($n = 18$) aged 0.2–11.6 years was 50% [66].

Lung transplantation is rarely indicated but has been successfully performed in cases of SP-B and SP-C deficiency, in patients carrying variants within *ABCA3* and *NKX2-1*, and in children with chronic pneumonitis of infancy. In comparison with adolescents, children are more often transplanted for ILD and precapillary pulmonary hypertension than for respiratory diseases, but with a similar in-hospital mortality [67]. A single-lobe lung transplantation has been successfully performed from a living donor to a patient with *ABCA3* disorder [68].

# 6 Treatment of Specific Conditions

To date, there is no therapy specifically approved for chILD. However, in 2015, the chILD-EU collaboration created standard operating procedures and protocols for a staged investigation of chILD. In addition, participating centers across Europe developed a Delphi consensus process with the aim of harmonizing treatment protocols such as the use of intravenous and oral corticosteroids, and add-on therapies such as hydroxychloroquine and azithromycin [17]. Thus, the development of efficacious and well-tolerated drugs is a particularly urgent need [69]. Because of the rarity of these diseases, many barriers exist to drug development for chILD, including the low economic benefits for the pharma industry and limited funding for researchers. Yet, the burden of chILD on the healthcare system is very high [1]. At present, the management of patients with chILD largely relies on case series investigating the effect of anti-inflammatory and immunomodulatory drugs to prevent the development of lung fibrosis. In this regard, most of the drugs used for chILD derive from the treatment of adult disease [70].

## 6.1 Fibrosing ILD

Two drugs with pleiotropic antifibrotic effects (pirfenidone and nintedanib) can reduce the rate of functional decline—as assessed by forced vital capacity (FVC)—and disease progression in adult patients with idiopathic pulmonary fibrosis (IPF) [71, 72] and ILD that progress despite appropriate treatment (nintedanib) [73]. The similarities between childhood and adult diseases provided the rationale for assessing the efficacy of antifibrotic drugs approved for adult diseases also in chILD. In a recent phase 2, double-blind, randomized, placebo-controlled trial (NCT04093024—InPedILD trial) [74], 39 patients aged 6–17 years with fibrosing ILD on chest CT and clinically significant disease were randomized 2:1 to receive nintedanib ($n = 26$) or placebo ($n = 13$) for 24 weeks. Co-primary endpoints were the area under the plasma concentration–time curve at steady state at weeks 2 and 26 and the proportion of patients with treatment-emergent adverse events at week 24. Two patients (7.7%) discontinued nintedanib because of adverse events. As with adult patients, diarrhea was the most frequent adverse event associated with nintedanib, being reported in 38.5% of cases (compared to 15.4% in the placebo group). Mean change in FVC % predicted at week 24 was 0.3% in the nintedanib group versus −0.9% in the placebo group. A stabilization of peripheral oxygen saturation ($SpO_2$) at rest over 24 weeks in the nintedanib group was also observed; both results were not statistically significant, although the study was not powered to assess efficacy. Overall, in children and adolescent with fibrosing ILD, a weight-based regimen resulted in exposure to nintedanib similar to adult patients, with an acceptable safety and tolerability profile. An open-label extension to assess long-term safety and tolerability of nintedanib in children and adolescents with ILD is currently recruiting (NCT05285982) [75].

## 6.2 Telomere-Related Diseases

Similar to adult disease, short telomeres and variations in telomere-related genes can manifest as ILD also in children [76, 77]. A phase 1/2 study has shown that danazol, a synthetic sex hormone with androgenic properties, leads to telomere elongation in patients with telomere diseases (NCT01441037) [78]. A multicenter, phase 2, double-blind, placebo-control trial that is currently ongoing will assess the safety and efficacy of danazol (in combination with standard of care) in adults and pediatric patients with pulmonary fibrosis associated with short telomeres. With regard to the pediatric population (age < 16 years), enrollment in the trial is limited to patients with a diagnosis of dyskeratosis congenita who will receive danazol 2 mg/kg/day, while adult patients will receive a dosage of 4 mg/kg/day (TELO-SCOPE—NCT04638517) [79]. The primary endpoint is the annual change in absolute telomere length from baseline. The efficacy of danazol is also investigated in the French ANDROTELO study (NCT03710356). The results should be available soon, but without the chILD population.

## 6.3 Disorders of Surfactant Dysfunction

Ivacaftor and genistein, two drugs approved for CF, have been evaluated as potential treatments in patients carrying *ABCA3* variants, the rationale being that the *ABCA3* gene has some degree of homology with *CFTR*, with the cystic fibrosis transmembrane conductance regulator (CFTR) also being an ABC transporter (Fig. 2). In CF, both ivacaftor and genistein increase CFTR channel opening, which translates to several beneficial effects, including lung function, surfactant function, weight gain, and fertility. Disorders related to *ABCA3* dysfunction lead to respiratory distress syndrome, early death, and chronic ILD in children and adults [24]. Kinting and colleagues have shown that disease-causing misfolding *ABCA3* variants can be rescued in vitro by the bithiazole correctors C13 and C17 as well as by the chemical chaperone trimethylamine *N*-oxide and low temperature [80]. Moreover, in A549 cells expressing *ABCA3* variants, the same authors demonstrated that ivacaftor and genistein can rescue variants N568D, F629L, and G667R [81]. These observations make CFTR potentiators a potential therapeutic option for patients suffering from surfactant deficiency caused by *ABCA3* variants. Other genes involved in surfactant production include *SFTPA*, *SFTPB*, and *SFTPC*, with

**Fig. 2** Seven-year-old boy
*ABCA3*-related interstitial lung
disease. CT scans show bilateral
ground glass opacity. *CT* com-
puted tomography
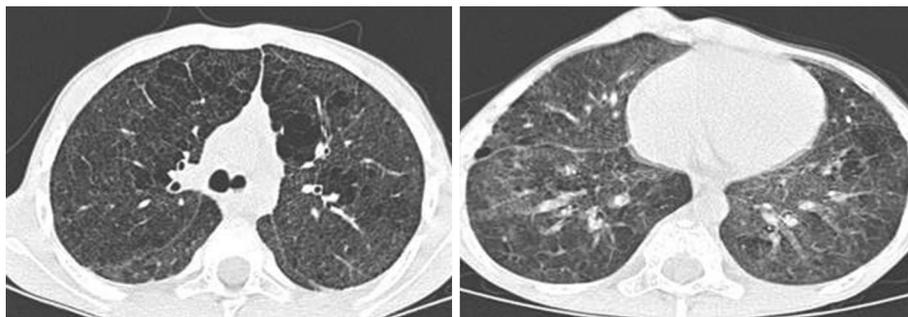


variants within these genes leading to abnormal surfactant production and clearance [82]. Cyclosporine A (CsA), a calcineurin inhibitor, has recently been suggested as a new potential candidate for ABCA3-specific molecular correction using high-content screening [83] and was used in association with pirfenidone in a child suffering from systemic lupus erythematosus ILD. An improvement in symptoms, pulmonary function, and chest CT images was observed after 2 years of treatment [84]. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a cytokine with a key role in surfactant physiology, and GM-CSF$^{-/-}$ mice display defective clearance of surfactant by alveolar macrophages, leading to PAP [85]. The safety and efficacy of inhaled sargramostim, a recombinant human GM-CSF, were assessed in children with hereditary PAP caused by bi-allelic variants in *CSF2RA* or *CSF2RB* (NCT01511068). However, the study was prematurely discontinued because of slow recruitment. The effect of inhaled sargramostim in patients with PAP was also assessed in a phase 2, multicenter, randomized, double-blind, placebo-controlled trial conducted in Japan (NCT02835742). The study enrolled 64 patients, including patients aged 16–18 years [86]. The frequency and severity of the adverse events did not differ significantly between the sargramostim and placebo groups. The mean change in the alveolar–arterial oxygen gradient between baseline and week 25, the primary endpoint, was significantly better in the GM-CSF group than in the placebo group ($-4.50 \pm 9.03$ mmHg vs. $0.17 \pm 10.50$ mmHg; $p = 0.02$). However, inhaled GM-CSF provided no clinical benefits. On the other hand, in a more recent double-blind, placebo-controlled trial in adult patients with autoimmune PAP, molgramostim (an *Escherichia coli*-produced recombinant GM-CSF formulated as a nebulizer solution) resulted in greater improvements in pulmonary gas transfer and functional health status than placebo, with similar rates of adverse events [87]. Inhaled GM-CSF has also been used in pediatric patients with autoimmune PAP, among other treatments [88].

Following anecdotal case reports [89, 90], methionine has recently been evaluated in patients with PAP carrying pathogenic variants within *MARS* (NCT03887169) [91].

*MARS* encodes the methionyl–transfer RNA synthetase (MetRS), and the addition of methionine to the culture medium restores MetRS function in mutated yeast [92]. The study enrolled four children who were evaluated for respiratory, hepatic, and inflammation-related outcomes. For all patients, methionine supplementation was associated with respiratory improvement, reduced liver dysfunction, and reduced need for WLL. While encouraging, these data need to be validated in prospectively enrolled, larger populations of patients.

### 6.4 SAVI and COPA Disorders

STING-associated vasculopathy with onset in infancy (SAVI) is a genetic autoinflammatory disease secondary to perpetual STING (STimulator of INterferon Genes) activation. The disease, which is characterized by small vessel inflammation, generally has a neonatal or infantile-onset [93]. Recently, a phase 2/3 multicenter, open-label study (NCT04517253) [94] investigated the role of baricitinib, a Janus kinase (JAK)-1/2 inhibitor, in adult and pediatric Japanese patients with SAVI and other diseases, such as Nakajo–Nishimura syndrome (NNS) and Aicardi-Goutières syndrome (AGS). Nine patients were enrolled, including three with SAVI. At the end of the maintenance period (52 weeks), all patients experienced an improvement in their symptoms, and one patient reported a serious drug-related adverse event. COPA syndrome is a rare, genetic autoimmune disorder that is caused by dysfunctional coatomer associate protein subunit alpha (COPα), a protein that functions in the retrograde transport from the Golgi to the endoplasmic reticulum [39]. COPA syndrome can affect multiple organs, especially the lungs, joints, and kidneys [39]. Recent data have linked *COPA* mutations to STING-dependent interferon signaling. The JAK inhibitors baricitinib and ruxolitinib have recently been suggested as promising therapeutic options for patients with COPA syndrome, but additional data are needed to corroborate these preliminary findings [95–97].

## 7 Emerging Therapies

### 7.1 Gene Transfer Therapies

Gene transfer may allow the application of recent advances in molecular biology to clinical practice [98]. Synthetic gene transfer vectors have been tested in experimental models both in vitro and in vivo in patients with chILDs, including those related to dysfunctional *SFTPC*, *SFTPB*, and *ABCA3*. Viral vectors (i.e., retroviral vectors, lentiviral vectors, adeno-associated viral [AAV] vectors, or adenoviral [Ad]-based vectors) have shown great potential in gene modulation, particularly for SP-B deficiency [99–101]. Nuclease-encoding, chemically modified mRNA is able to deliver site-specific nucleases in a mouse model of SP-B deficiency and improve survival of the animals. Kang and co-workers have recently shown that an AAV vector can restore surfactant activity and improve survival in SP-B knockout mice [102]. However, the development of a delivery vector requires knowledge of the precise disease target(s), transgene expression, and vector design. For instance, Ad-based vectors provide robust expression and a relatively large carrying capacity (~ 10 kb). Conversely, lentiviral vectors have a packaging capacity of at least 7.5 kb. Moreover, Ad-based vectors transduce both dividing and non-dividing cells with good tissue tropism and flexibility. Viral vectors have been evaluated in a range of diseases, including hereditary PAP with *CSF2RA* mutations. Hetzel and colleagues have shown that a lentiviral vector was able to induce Csf2ra complementary DNA (cDNA) expression in Csf2ra$^{-/-}$ macrophages, leading to restoration of GM-CSF signaling in hereditary PAP macrophages. The lentiviral vector had no adverse effects in the intended target cells, supporting testing lentivirus-mediated gene transfer therapy in hereditary PAP in humans [103].

### 7.2 Mesenchymal Stromal Cells

Cell therapy has fueled significant interest as a treatment for a range of respiratory diseases. Due to their low immunogenicity, easy isolation, and fleet differentiation in multiple lineages, mesenchymal stem cells (MSCs) are attractive therapeutic strategies also for chILD [104]. MSCs can be easily obtained from various fonts, including amniotic fluid, bone marrow, skeletal muscle, spleen, and lung. Previous studies in vitro and in vivo have explored the ability of MSCs to differentiate into alveolar epithelial cells, with the aim of assessing their potential utility in human lung disease [105]. Ahn and colleagues [106] conducted a phase 2, double-blind, placebo-controlled trial to assess the efficacy of intratracheal transplantation of human umbilical cord blood-derived MSCs (hUC-MSCs) (NCT01828957) in patients with BPD, a chronic lung disease limited to infants, typically caused by prolonged ventilation [107]. The study enrolled 66 premature infants aged between 23 and 28 gestational weeks. After 1 week, hUCB-MSC therapy significantly reduced the levels of several pro-inflammatory cytokines (i.e., interleukin [IL]-1, IL-6, IL-8, tumor necrosis factor [TNF]α, and matrix metallopeptidase [MMP]-9) in the tracheal aspirate fluid compared to placebo. However, the primary outcomes of survival and disease progression were not significantly improved by MSC transplantation. Based on a subgroup analysis suggesting that the secondary outcome of severe BPD was significantly improved in the 23–24 gestational week group, a larger phase 2 study is underway, focusing on infants in this age range (NCT03392467 – PNEUMOSTEM). Several clinical trials are currently evaluating the safety and efficacy of MSCs in BPD (ClinicalTrials.gov). MSCs are administered either intratracheally or intravenously. Induced pluripotent stem cells have been used in a mouse model of PAP induced by *CSF2RB* deficiency [108]. In addition, Wu and colleagues have shown that hUC-MSCs combined with low-dose pirfenidone reduce bleomycin-induced pulmonary fibrosis in mice more than the two therapies individually [109]. As with other therapeutic approaches, the safety and efficacy of MSCs in chILD need to be validated in larger studies.

### 7.3 Future Perspectives

In the past few years, genetic testing and whole genome sequencing (WGS) have increased both our ability to diagnose chILD and our understanding of disease pathobiology [110]. New insights have also emerged regarding disease-associated biomarkers. For example, unique protein signatures are shown in the bronchoalveolar lavage fluid (BALF) of NEHI patients and in other surfactant disorders [111]. Moreover, a number of blood biomarkers deeply investigated in adult ILD, including mucin-5B (MUC-5B) and Krebs von den Lungen-6 (KL-6), could also be useful in chILD to predict the risk of disease development and progression [112, 113]. However, research focused on gene-to-protein translation is also needed. Because of the limited availability of human lung tissue (especially in children) and with animal models of lung fibrosis recapitulating only partially the complexity of human disease, lung "organoids" of varying cellular components have recently emerged as novel strategies to model, among other organs, the lung and airway [114]. Organoids are promising tools for studying complex cellular interactions, thus mimicking disease environments; indeed, they arise from colonies generated by single cells and maintain the genomic profile of the parent tissue. However, current organoid models cannot reproduce *in toto* the physiological repertoire of their respective organs [114].

# 8 Conclusion

The interest in childhood ILD has increased substantially in recent years, fueled mainly by genetic discoveries and the development of large national and international registries collecting rare and ultra-rare cases (Europe: chILD-EU; France: Respirare; USA: children; Australia: chILDRN). These consortia have also disseminated new knowledge on the management of these diseases and have improved the care for these children. Controlled studies of accepted but unproven treatments and novel treatments are urgently needed. To this end, participation of children in adult drug evaluation programs, the obligate implementation of pediatric investigational plans for all drugs introduced in adults, and the set-up of trials for conditions mainly prevalent in pediatrics must be realized. Continuing the build-up of international collaborations between expert centers and large databases of phenotypically well-defined patients is instrumental to any progress in these rare conditions.

## Declarations

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