

American Thoracic Society International Conference

PEDIATRIC YEAR IN REVIEW



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Pediatric Year in Review Bibliography

Sunday, May 20

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TOPICS

Pharmacologic Management of Severe Asthma in Children 1

What to Expect When You're Expectorating:
Update on the Pediatric Microbiome and Respiratory Disease 5

Update on Treatment of Neuromuscular Diseases in Children 9

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PHARMACOLOGIC MANAGEMENT OF SEVERE ASTHMA IN CHILDREN

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DISCONTINUING OMALIZUMAB

Ledford D, Busse W, Trzaskoma B, Omachi TA, Rosén K, Chipps BE, Luskin AT, Solari PG. **A randomized multi-center study evaluating Xolair persistence of response after long-term therapy.** *J Allergy Clin Immunol.* 2017 Jul;140(1):162-169.e2. doi:10.1016/j.jaci.2016.08.054.

Summary

Omalizumab, an anti-IgE monoclonal antibody, is the first biologic approved for use in children with asthma. XPORT was a one-year randomized double-blind trial which included patients 17 and over with moderate to severe asthma who had been on long term omalizumab (avg 5 years). 176 patients were randomized to discontinue or continue omalizumab with the primary endpoint being the number of patients experiencing a severe exacerbation. 33% of those on omalizumab versus 52% on placebo had a severe exacerbation (19.3% absolute difference, 95% CI 5-33.6%, OR 0.45, 95% CI 0.24-0.83). Symptom control was also better in the omalizumab group although there was no difference in FEV1. From baseline to week 52, there was an increase in the total IgE and basophil expression of FCεRI in the placebo group compared with the omalizumab group. In the placebo group, those who had an exacerbation had an increased serum eosinophil count at baseline compared with those that didn't have an exacerbation ($p < 0.001$); this was not seen in the omalizumab group. A subset of patients ($n=78$) had FeNO measured and although there was no difference in the FeNO (change from baseline) between the groups, those who had an exacerbation had an increase in their FeNO between baseline and week 12 which was more pronounced in the placebo group compared to the omalizumab group.

Comments

1. This is the first randomized double-blind controlled trial examining outcomes after discontinuation of long-term omalizumab.
2. Half of patients who discontinued omalizumab did not experience a severe exacerbation in the year following discontinuation, which is similar to data from real world observational trials.
3. It is difficult to know how generalizable these data are to patients with severe asthma given that the baseline severity of asthma was in this group was not defined and 15% of patients were not on any ICS at the time of discontinuing omalizumab.

4. Serum eosinophils and FeNO may be useful in determining who is at risk for exacerbation following discontinuation of omalizumab; this mirrors studies that show that those with increased FeNO and serum eosinophils had a greater benefit with omalizumab.
5. Further trials examining the effect of lengthening the duration between omalizumab doses would be useful in the management of patients on omalizumab.
6. This study was not able to determine if there was a persistence in the clinical effects of omalizumab after discontinuation; however, the downregulation of FCεRI which occurs with omalizumab does not persist after the medication is stopped

TINA: TIOTROPIUM IN ASTHMA?

Hamelmann E, Bernstein JA, Vandewalker M, Moroni-Zentgraf P, Verri D, Unseld A, Engel M, Boner AL. **A randomised controlled trial of tiotropium in adolescents with severe symptomatic asthma.** *Eur Respir J.* 2017 Jan 11;49(1). pii: 1601100. doi: 10.1183/13993003.01100-2016.

Szefler SJ, Murphy K, Harper T 3rd, Boner A, Laki I, Engel M, El Azzi G, Moroni-Zentgraf P, Finnigan H, Hamelmann E. **A phase III randomized controlled trial of tiotropium add-on therapy in children with severe symptomatic asthma.** *J Allergy Clin Immunol.* 2017 Nov;140(5):1277-1287. doi: 10.1016/j.jaci.2017.01.014.

Summary

Tiotropium is a long-acting muscarinic antagonist (LAMA) which acts as a bronchodilator and is the only LAMA approved for use in asthma. These two identical phase 3 clinical trials in patients 6-11 (VivaTinA, $n=401$) and 12-17 (PensieTinA, $n=392$) years of age, examined the benefit of once-daily tiotropium add-on in patients not controlled on high-dose ICS + \geq one controller or medium-dose ICS + ≥ 2 controllers (mean ICS dose 770ug/d in 12-17yo, 450ug/d in 6-11yo, budesonide equiv). Patients were randomized to placebo, tiotropium 2.5ug/day, or tiotropium 5ug/day. These 12-week trials had a primary endpoint of peak FEV1 within 3 hours of dosing. In adolescents 2.5ug but not 5ug led to a significant improvement in peak FEV1 (111ml, 95% CI 2-220, $p=0.046$ in the 2.5ug group; 90ml, 95% CI -19 to 198ml, $p=0.104$ in the 5ug group). Exploratory secondary outcomes showed that the number of patients experiencing a worsening of asthma symptoms was lower in the tiotropium groups (11.5% 5ug, 14.2% 2.5ug,

18.5% placebo) but no difference was seen in severe exacerbations which was low in all groups. In children, there was improvement in the peak FEV1 in the 5ug group (139ml 95% CI 75-203, $p < 0.001$) but not the 2.5ug group (35ml 95% CI -28-99, $p = 0.27$). There was improvement in the trough FEV1 for the 5ug but not the 2.5ug group. There was no consistent effect on exacerbations.

Comments

1. These two trials provide data on children with severe asthma, ~80% of whom were on a LABA as well as moderate to high dose ICS, although the average dose of ICS in these trials is lower than in consensus definitions of severe asthma.
2. In contrast to previous studies of tiotropium add-on in children and adolescents with asthma uncontrolled on medium dose ICS, results from these trials did not show a consistent improvement in peak FEV1 with 2.5ug and 5ug of tiotropium, possibly because most patients were already on a long acting bronchodilator.
3. Although adult trials of tiotropium in severe asthma (PRIMOTinA) show an improvement in lung function and exacerbations, there is still a lack of clinical trials in children and adolescents designed to assess clinically relevant endpoints such as exacerbations or asthma control.

PREDICTING RESPONSE TO BIOLOGICS

FitzGerald JM, Bleecker ER, Menzies-Gow A, Zangrilli JG, Hirsch I, Metcalfe P, Newbold P, Goldman M. **Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies.** *Lancet Respir Med.* 2018 Jan;6(1):51-64. doi: 10.1016/S2213-2600(17)30344-2.

Summary

Benralizumab is an anti-IL5 receptor monoclonal antibody that has recently been approved for use in pediatric severe eosinophilic asthma in some countries. This study pooled results from two phase 3 trials of benralizumab (SIROCCO, CALIMA) which included adolescents and adults requiring moderate to high doses of steroids + LABA who had at least 2 severe exacerbations in the previous year. This pooled analysis only included the patients who required high dose ICS + LABA ($n = 2295$, $n = 79$ adolescents). The pooled analysis was done to determine if baseline serum eosinophils (Eo) or exacerbation history was associated with a clinical response to benralizumab. There was a consistent decrease in exacerbations in patients with serum Eo of ≥ 300 cells/ul and improvement in FEV1 in patients with serum Eo of ≥ 450 cells/ul with greater improvements the higher the Eo count. Those with more than 3 exacerbations in the previous year also showed a greater decrease in exacerbation rates. The number of adolescents is too small

to make meaningful conclusions however the subgroup analysis in adolescents shows a trend towards favoring placebo.

Comments

1. This study adds to the body of literature that shows an association between higher serum eosinophil counts and greater benefit from anti-IL5 biologics.
2. Similar to post-hoc and subgroup studies of omalizumab trials, those with more exacerbations prior to enrollment had a greater benefit with benralizumab.
3. Despite approval of benralizumab for use in adolescents in some countries, there is little data for efficacy in this age group.

REVISITING THE ROLE OF AZITHROMYCIN IN ASTHMA

Gibson PG, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, Jenkins C, Peters MJ, Marks GB, Baraket M, Powell H, Taylor SL, Leong LEX, Rogers GB, Simpson JL. **Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial.** *Lancet.* 2017 Aug 12;390(10095):659-668. doi: 10.1016/S0140-6736(17)31281-3.

Summary

This 48 week trial was conducted in adults with symptomatic asthma despite ICS and LABA (85% of participants on high dose ICS + LABA). Patients were phenotyped using sputum eosinophils or if not available serum eosinophils and were randomized to azithromycin 500mg 3x/week or placebo. The azithromycin group had a significant reduction in moderate and severe asthma exacerbations (1.07 exacerbations/person year 95% CI 0.85-1.29 in azithromycin group, 1.86 exacerbations/person year 95% CI 1.54-2.18). This effect was seen in patients with eosinophilic and non-eosinophilic asthma. Azithromycin was associated with an increased incidence of diarrhea compared to placebo (34% vs. 19%). There was no difference in azithromycin-resistant organisms between groups, although in the very small sub-sample that had paired sputum samples the azithromycin group had 3 azithromycin-resistant organisms at baseline and 6 at the end of treatment; whereas, the placebo group had 4 azithromycin-resistant organisms at baseline and end of treatment.

Comments

1. Azithromycin is often considered a treatment specific for neutrophilic asthma.
2. This study in adults uncontrolled on ICS+LABA found that the addition of azithromycin decreased exacerbations irrespective of inflammatory phenotype.
3. Unfortunately a pediatric study (MARS) that was designed to determine if azithromycin increased the time

to loss of asthma control was terminated because of slow enrollment; thus, this question is still unanswered in children.

4. Although azithromycin is readily available and well tolerated, further trials need to be done in children before this treatment is recommended, given the implications of causing widespread macrolide resistance.

MEDICATIONS COMING THROUGH THE PIPELINE

Gonem S, Berair R, Singapuri A, Hartley R, Laurencin MFM, Bacher G, Holzhauser B, Bourne M, Mistry V, Pavord ID, Mansur AH, Wardlaw AJ, Siddiqui SH, Kay RA, Brightling CE. **Fevipirant, a prostaglandin D2 receptor 2 antagonist, in patients with persistent eosinophilic asthma: a single-centre, randomised, double-blind, parallel-group, placebo-controlled trial.** *Lancet Respir Med.* 2016 Sep;4(9):699-707. doi: 10.1016/S2213-2600(16)30179-5.

Summary

Fevipirant (QAW039) is an oral, once a day prostaglandin D2 receptor (PGD2) antagonist. PGD2 is a product of activated mast cells and increases the migration of eosinophils, type 2 lymphocytes, basophils and Type 2 innate lymphoid cells. This paper reports the results of the proof of concept trial in moderate to severe adults with asthma. Patients had to have sputum eosinophils $\geq 2\%$ and have either uncontrolled symptoms or an exacerbation in the previous year. Patients on fevipirant had a decrease in sputum eosinophilia that was 3.5 times greater than that of the placebo group (95% CI 1.7-7, $p=0.0014$), which was the primary outcome. There was no change in serum eosinophils. Exploratory outcomes such as quality of life and post-bronchodilator FEV1 improved but asthma control score and pre-bronchodilator FEV1 showed no difference between groups. A proportion of patients underwent pre and post bronchial biopsies and an improvement in the bronchial submucosal eosinophil numbers and the proportion of denuded epithelium were seen in the treatment group. There was no difference in adverse events between groups and no serious adverse events reported in either group.

Comments

1. It is exciting that a new oral medication for asthma is being developed that has a different mechanism compared to existing therapies.
2. This is the first trial to assess DP2 antagonists in moderate to severe patients and illustrates that this drug decreases sputum eosinophils and has the potential to improve clinical outcomes in patients already on substantial asthma therapy.
3. The result of clinical trials (NCT02555683, NCT02563067) which are powered to assess the ability of fevipirant to decrease exacerbations in adolescents and adults with

GINA 4/5 asthma are needed before determining the role of this medication in our patient population.

4. Although this drug has been shown to improve lung function in a group of mild patients with an undifferentiated inflammatory phenotype, it is not clear if it will be beneficial in severe asthmatics with non-eosinophilic inflammation.
5. Acknowledge the contribution of patients whose willingness to undergo pre and post-therapy bronchial biopsies have provided insights into the relationship between markers of eosinophilic inflammation and epithelial integrity.

Corren J, Parnes JR, Wang L, Mo M, Roseti SL, Griffiths JM, van der Merwe R. **Tezepelumab in Adults with Uncontrolled Asthma.** *N Engl J Med.* 2017 Sep 7;377(10):936-946. doi: 10.1056/NEJMoa1704064.

Summary

Thymic stromal lymphopoietin (TSLP) is a cytokine that regulates Th2 inflammation upstream from IL-4, IL-5 and IL-13. Tezepelumab is a human IgG2 monoclonal antibody that binds to TSLP and prevents it from binding to its receptor. The PATHWAY trial is the first randomized placebo-controlled trial of subcutaneous tezepelumab in adults with moderate to severe asthma. Three doses of tezepelumab (70mg q4w, 210mg q4w, 280 q2w) were compared to placebo in patients not controlled on medium to high doses of ICS + LABA with the primary outcome of exacerbations. All three doses of tezepelumab resulted in decreased annualized rates of exacerbations compared to placebo (exacerbation rates were 61%, 71%, and 66% lower in the low, medium and high dose tezepelumab groups compared to placebo). This improvement was seen regardless of baseline FeNO, serum eosinophils or Th2 status although decreases in FeNO, serum eosinophils and IgE were seen in the tezepelumab treatment groups. There was no difference in adverse events between treatment groups although three serious adverse events (pneumonia, stroke, Guillain Barre syndrome) were felt to be related to study drug.

Comments

1. Tezepelumab is a promising novel biologic that decreases exacerbations in patients with moderate to severe asthma regardless of inflammatory profile in this initial clinical trial.
2. Further studies of how anti-TSLP antibodies improve outcomes in those without markers of Th2 inflammation may provide insights into other pathways of inflammation in severe asthma.

3. Larger patient populations are needed to assess the safety of this drug given the serious adverse events seen in this initial trial.
4. An ongoing trial recruiting adolescents and adults with moderate to severe asthma is scheduled for completion in 2020 and will help to determine the role of this medication in our patient population.

OTHER ARTICLES OF INTEREST

OTHER DRUGS IN THE PIPELINE

Cahill KN, Katz HR, Cui J, Lai J, Kazani S, Crosby-Thompson A, Garofalo D, Castro M, Jarjour N, DiMango E, Erzurum S, Trevor JL, Shenoy K, Chinchilli VM, Wechsler ME, Laidlaw TM, Boyce JA, Israel E. **KIT Inhibition by Imatinib in Patients with Severe Refractory Asthma.** *N Engl J Med.* 2017 May 18;376(20):1911-1920. doi: 10.1056/NEJMoa1613125

MECHANISMS OF EXACERBATIONS IN SEVERE ASTHMA

Deschildre A, Pichavant M, Engelmann I, Langlois C, Drumez E, Pouessel G, oileau S, Romero-Cubero D, Decleyre-Badiu I, Dewilde A, Hober D, Néve V, Thumerelle C, Lejeune S, Mordacq C, Gosset P. **Virus-triggered exacerbation in allergic asthmatic children: neutrophilic airway inflammation and alteration of virus sensors characterize a subgroup of patients.** *Respir Res.* 2017 Nov 14;18(1):191. doi: 10.1186/s12931-017-0672-0. PubMed PMID: 29137638

Esquivel A, Busse WW, Calatroni A, Togias AG, Grindle KG, Bochkov YA, Gruchalla RS, Kattan M, Kercksmar CM, Khurana Hershey G, Kim H, Lebeau P, Liu AH, Szeffler SJ, Teach SJ, West JB, Wildfire J, Pongracic JA, Gern JE. **Effects of Omalizumab on Rhinovirus Infections, Illnesses, and Exacerbations of Asthma.** *Am J Respir Crit Care Med.* 2017 Oct 15;196(8):985-992. doi: 10.1164/rccm.201701-0120OC. PubMed PMID: 28608756

Welsh KG, Rousseau K, Fisher G, Bonser LR, Bradding P, Brightling CE, Thornton DJ, Gaillard EA. **MUC5AC and a Glycosylated Variant of MUC5B Alter Mucin Composition in Children With Acute Asthma.** *Chest.* 2017 Oct;152(4):771-779. doi: 10.1016/j.chest.2017.07.001. Epub 2017 Jul 14. PubMed PMID: 28716644

PHENOTYPES AND ENDOTYPES

Guiddir T, Saint-Pierre P, Purenne-Denis E, Lambert N, Laoudi Y, Couderc R, Gouvis-Echraghi R, Amat F, Just J. **Neutrophilic Steroid-Refractory Recurrent Wheeze and Eosinophilic Steroid-Refractory Asthma in Children.** *J Allergy Clin Immunol Pract.* 2017 Sep - Oct;5(5):1351-1361. e2. doi: 10.1016/j.jaip.2017.02.003. Epub 2017 Mar 28. PubMed PMID: 28363401

Fitzpatrick AM, Stephenson ST, Brown MR, Nguyen K, Douglas S, Brown LAS. **Systemic Corticosteroid Responses in Children with Severe Asthma: Phenotypic and Endotypic Features.** *J Allergy Clin Immunol Pract.* 2017 Mar-Apr;5(2):410-419.e4. doi: 10.1016/j.jaip.2016.08.001. Epub 2016 Sep 21. PubMed PMID: 27665382

COMORBIDITIES IN SEVERE ASTHMA

Radhakrishna N, Tay TR, Hore-Lacy F, Stirling R, Hoy R, Dabscheck E, Hew M. **Validated questionnaires heighten detection of difficult asthma comorbidities.** *J Asthma.* 2017 Apr;54(3):294-299. doi: 10.1080/02770903.2016.1212369. Epub 2016 Oct PubMed PMID: 27715354

APPROACH TO MANAGEMENT OF SEVERE ASTHMA/GUIDELINES

Barsky EE, Giancola LM, Baxi SN, Gaffin JM. **A Practical Approach to Severe Asthma in Children.** *Ann Am Thorac Soc.* 2017 Dec 8. doi: 10.1513/AnnalsATS.201708-637FR. [Epub ahead of print] PubMed PMID: 29220200

FitzGerald JM, Lemiere C, Loughheed D, Ducharme FM, Dell SD, Ramsey C, Yang CL, Cote A, Watson W, Olivenstein R, Van Dam A, Villa-Roell C, Grad R. **Recognition and management of severe asthma: A Canadian Thoracic Society position statement.** *Canadian Journal of Respiratory, Critical Care, and Sleep Medicine* 2017: 199-221. doi.org/10.1080/24745332.2017.1395250

WHAT TO EXPECT WHEN YOU'RE EXPECTORATING: UPDATE ON THE PEDIATRIC MICROBIOME AND RESPIRATORY DISEASE

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RESPIRATORY MICROBIOTA AND CHILDHOOD ASTHMA

Depner M, Ege MJ, Cox MJ, Dwyer S, Walker AW, Birzele LT, Genuneit J, Horak E, Braun-Fahrländer C, Danielewicz H, Maier RM, Moffatt MF, Cookson WO, Heederik D, von Mutius E, Legatzki A. **Bacterial microbiota of the upper respiratory tract and childhood asthma.** *J Allergy Clin Immunol.* 2017 Mar;139(3):826-834.e13.

Summary

There is increasing evidence for a relationship between abnormalities (“dysbiosis”) in the microbiology of the lower respiratory tract and the development (or worsening) of diverse respiratory diseases, including asthma. However, these studies are rarely performed on large and/or vulnerable populations, because sampling the lower respiratory tract can be difficult, invasive, and imprecise. By comparison, upper airway samples are relatively simple, convenient and safe to collect. Therefore, a growing number of studies have examined the relationships between upper airway microbiology and lower respiratory tract disease. Several groups have demonstrated correlations between the development of wheezing during childhood and the presence and/or abundance of specific bacteria in upper respiratory tract samples. In addition, there is evidence that children who live on farms are different in these respects from “nonfarm” children. In this study, the investigators compared the microbiota from two sites in the upper respiratory tract- the oropharynx and the nose- among school-aged rural children who did and did not live on farms. The investigators found an association between presence of asthma and decreased microbial diversity in nasal samples. Asthma was also correlated with the relative abundance of *Moraxella*, but only among nonfarm children.

Comments

1. Despite having a relatively large collection of oropharyngeal (OP) samples, no relationship was found between OP sample microbiota and asthma.
2. The microbial differences between these two upper airway sites agree with others’ findings and underscore how compartmentalized the respiratory tract is with respect to microbiology.
3. The findings of this study support the concept from studies of several mucosal sites that reduced microbial diversity can favor the outgrowth of potentially harmful

bacteria- in this case, *Moraxella*, assuming its relationship with asthma is causal, but only among nonfarm children.

4. The authors suggest that the higher microbial diversity to which farm children are presumably exposed might neutralize the effects that *Moraxella* may have in nonfarm children based on these results.

RESPIRATORY MICROBIOTA AND BRONCHIOLITIS SEVERITY

Stewart CJ, Mansbach JM, Wong MC, Ajami NJ, Petrosino JF, Camargo CA, Hasegawa K. **Associations of Nasopharyngeal Metabolome and Microbiome with Severity among Infants with Bronchiolitis: A Multiomic Analysis.** *American Journal of Respiratory and Critical Care Medicine* 2017; 196(7):882-891.

Summary

Severity of bronchiolitis varies substantially among infants, from mild to fatal. However, little is known about the determinants of severity. Recent evidence suggests that bronchiolitis pathogenesis involves a complex interaction between host immunity and airway microbiomes, including viruses. Here, the authors applied a combination of two “omics” methods—metabolomics followed by sequencing-based microbiome analysis-- to nasopharyngeal washes of infants hospitalized with bronchiolitis, searching for host and airway microbial characteristics correlating with subsequent treatment with positive pressure ventilation (PPV). With metabolomics, the investigators first identified a 25-metabolite panel that provided high sensitivity and specificity for predicting PPV use. This panel also correlated with relative abundance of *Streptococcus pneumoniae*. The investigators also examined metabolic pathways—mechanistically-linked sets of molecules identified by metabolomics—for associations with PPV treatment, identifying a significant correlation with sphingolipid metabolism, for which similar associations have been found previously in studies of other respiratory diseases, such as cystic fibrosis. The abundance of *Streptococcus* correlated with those of the predictive metabolites, and supportive evidence was found from the microbiome analysis. The authors concluded that changes in the metabolites found to correlate with bronchiolitis severity resulted from a combination of microbial and host metabolic activity.

Comments

1. This study was particularly notable for the combined use of multiple “ ‘omics” approaches that supported and complemented each other to provide new hypotheses about the pathophysiology of bronchiolitis.
2. While this study demonstrated the ability to predict disease severity in the study population, external validation in a new population is required.
3. There is evidence for important impacts of both sphingolipid metabolism and *Streptococcus* in diverse lower respiratory tract diseases.
4. Regardless of whether either the reported metabolome or microbiome results ultimately impact clinical care of bronchiolitis, this study demonstrates the power of a “multiomic” approach to generate new hypotheses about respiratory disease pathogenesis and mechanisms of host-microbe interactions.

NATURAL HISTORY OF INFANT NASOPHARYNGEAL MICROBIOTA DEVELOPMENT

Bosch AATM, Piters WAAS, van Houten MA, Chu MLJN, Biesbroek G, Kool J, Pernet P, de Groot PCM, Eijkemans MJC, Keijser BJF, Sanders EAM, Bogaert D. **Maturation of the Infant Respiratory Microbiota, Environmental Drivers, and Health Consequences.** A Prospective Cohort Study. *Am J Respir Crit Care Med.* 2017 Dec 15;196(12):1582-1590.

Summary

Acute respiratory tract infections are among the most common causes of pediatric mortality. There is marked variation among children in terms of susceptibility to respiratory infections, as well as in severity of symptoms. The sources of this clinical variation are not yet clear. However, it has been hypothesized that the respiratory microbiota play a role in modulating susceptibility to acute respiratory tract infections. Soon after birth, the infant upper respiratory tract becomes rapidly colonized with bacteria from a variety of sources, and these microbiota are influenced by a number of perinatal, environmental, dietary, and pharmacological factors. The authors of this study had previously found evidence for a relationship between early nasopharyngeal microbiota and susceptibility to early respiratory tract infections. In this study, the investigators longitudinally analyzed the nasopharyngeal microbiota of 112 infants, demonstrating a close relationship between early microbiota and subsequent development of respiratory tract infection symptoms. Early microbiota constituency appeared to be influenced by mode of delivery, mode of feeding, early antibiotic use, and crowding. The investigators hypothesize based on these results that early-life microbiota development impacts long-term respiratory health.

Comments

1. The identification of “respiratory tract infection” events relied on parental report of symptoms, a limitation acknowledged by the authors.
2. The authors show that overall nasopharyngeal microbiota community instability- change in community constituency over time- correlated with the subsequent development of respiratory tract infections.
3. These results support prior studies that correlated early infancy nasopharyngeal microbiota with subsequent development of otitis media and also more severe course of respiratory syncytial virus infections (as well as article 2).
4. The identification of potential environmental drivers of early nasopharyngeal microbiome development, and the focus on this early developmental pattern and its relationship with outcomes, was new and innovative.

CYSTIC FIBROSIS RESPIRATORY MICROBIOLOGY DURING TREATMENT

Hisert KB, Heltshe SL, Pope C, Jorth P, Wu X, Edwards RM, Radey M, Accurso FJ, Wolter DJ, Cooke G, Adam RJ, Carter S, Grogan B, Launspach JL, Donnelly SC, Gallagher CG, Bruce JE, Stoltz DA, Welsh MJ, Hoffman LR, McKone EF, Singh PK. **Restoring Cystic Fibrosis Transmembrane Conductance Regulator Function Reduces Airway Bacteria and Inflammation in People with Cystic Fibrosis and Chronic Lung Infections.** *Am J Respir Crit Care Med.* 2017 Jun 15;195(12):1617-1628.

Summary

Despite extensive research over many decades, the microbial determinants of CF lung disease are still not entirely clear. Many of the published studies were observational, comparing clinical culture results with clinical outcomes. Recently, molecular methods have identified many abundant microbial taxa in CF respiratory specimens not identified by routine CF clinical laboratory procedures. In general, these studies identified average decreases in sputum microbial diversity with age; this decline in diversity also correlates with average decreases in lung function, increases in antibiotic exposure, and dominance by traditional pathogens. Because these studies have generally been observational, it is difficult to distinguish cause from effect among these covariates. This study begins to address causality by correlating sputum microbiota and clinical improvement among 12 adults with CF and G551D CFTR mutations over 3 years of treatment with ivacaftor. While standard, qualitative clinical sputum cultures demonstrated no significant changes (i.e., eradication) with ivacaftor, both quantitative cultures and microbiome methods demonstrated significant changes, including decreases in sputum abundance of all bacteria

and of traditional pathogens, particularly *P. aeruginosa*, resulting in an average increase in sputum microbial diversity, resembling sputum microbiology from earlier stages of CF lung disease. These microbial changes correlated with improvement in lung function.

Comments

1. The particularly marked change of *P. aeruginosa* in this study supports the well-described strong relationship between CF airway disease and this organism.
2. This study underscores the power of combining microbiome methods with new treatment interventions in untangling difficult questions of causality that arise from observational studies.
3. These results do not establish where each of the microbes came from; it is possible that some were from the oropharynx, the sinuses, or the nasopharynx.
4. Because significant relationships with lung function improvement were found for several sputum microbiological changes with ivacaftor treatment, including decreased *P. aeruginosa* abundance, decreased total bacterial abundance, and increased diversity, the individual effect of *P. aeruginosa* itself, as opposed to diversity or total bacterial abundance, on lung function is still not entirely clear, but in many patients *P. aeruginosa* was the dominant organism.

AIRWAY MICROBIOTA OF INFANTS WITH BRONCHOPULMONARY DYSPLASIA

Wagner BD, Sontag MK, Harris JK, Miller JI, Morrow L, Robertson CE, Stephens M, Poindexter BB, Abman SH, Mourani PM. **Airway Microbial Community Turnover Differs by BPD Severity in Ventilated Preterm Infants.** *PLoS One*. 2017 Jan 27;12(1):e0170120.

Summary

Observational studies have identified some environmental, clinical, and maternal risk factors for the development of BPD. It is also known that dysfunctional lung inflammatory responses to environmental stimuli can modulate risk of BPD. Because mucosal microbiota can modulate these inflammatory responses, and based on some published findings (for example, prior work identified associations with *Ureaplasma* species and BPD), the authors of this work hypothesized that lung microbiota, acquired postnatally, can impact BPD risk. This study included both cross-sectional and longitudinal analyses of tracheal aspirates from mechanically-ventilated preterm neonates to test the hypothesis that specific early respiratory tract microbiome patterns in these infants would be associated with the development and/or severity of subsequent BPD. This analysis identified three promising characteristics of the tracheal aspirate microbiota that correlated with

development of severe BPD in the longitudinal analyses: Increased turnover, or taxonomic change, in the microbiota over time; high initial relative abundance of *Ureaplasma* species; and decreasing relative abundance of *Staphylococcus*. The authors concluded that longitudinal changes in airway microbial communities over time in mechanically ventilated preterm infants may be associated with BPD severity.

Comments

1. The authors wisely note that, as with the above observational studies, causality is not established between these microbiological and clinical findings.
2. The authors also note the potential confounding effects of antibiotic treatment and other characteristics in the study population.
3. The relationship with community “turnover”, or change in community constituency, is novel and intriguing, but could also be due to differences in treatment.

OTHER ARTICLES OF INTEREST

REVIEWS

Hahn A, Warnken S, Pérez-Losada M, Freishtat RJ, Crandall KA. **Microbial diversity within the airway microbiome in chronic pediatric lung diseases.** *Infect Genet Evol*. 2017 Dec 7.

Man WH, de Steenhuijsen Pijters WA, Bogaert D. **The microbiota of the respiratory tract: gatekeeper to respiratory health.** *Nat Rev Microbiol*. 2017 May;15(5):259-270.

MULTI-OMICS STUDIES

Garg N, Wang M, Hyde E, da Silva RR, Melnik AV, Protsyuk I, Bouslimani A, Lim YW, Wong R, Humphrey G, Ackermann G, Spivey T, Brouha SS, Bandeira N, Lin GY, Rohwer F, Conrad DJ, Alexandrov T, Knight R, Dorrestein PC. **Three-Dimensional Microbiome and Metabolome Cartography of a Diseased Human Lung.** *Cell Host Microbe*. 2017 Nov 8;22(5):705-716.

RESPIRATORY TRACT EXPOSURE TO MICROBES AND ASTHMA

Birzele LT, Depner M, Ege MJ, Engel M, Kublik S, Bernau C, Loss GJ, Genuneit J, Horak E, Schloter M, Braun-Fahrlander C, Danielewicz H, Heederik D, von Mutius E, Legatzki A. **Environmental and mucosal microbiota and their role in childhood asthma.** *Allergy*. 2017 Jan;72(1):109-119.

FECAL MICROBIOTA AND ASTHMA

Arrieta MC, Arévalo A, Stiemsma L, Dimitriu P, Chico ME, Loo S, Vaca M, Boutin RCT, Morien E, Jin M, Turvey SE, Walter J, Parfrey LW, Cooper PJ, Finlay B. **Associations between infant fungal and bacterial dysbiosis and child-**

hood atopic wheeze in a nonindustrialized setting. *J Allergy Clin Immunol*. 2017 Nov 30.

CYSTIC FIBROSIS RESPIRATORY MICROBIOTA

Acosta N, Whelan FJ, Somayaji R, Poonja A, Surette MG, Rabin HR, Parkins MD. **The Evolving Cystic Fibrosis Microbiome: A Comparative Cohort Study Spanning 16 Years.** *Ann Am Thorac Soc*. 2017 Aug;14(8):1288-1297.

Zemanick ET, Wagner BD, Robertson CE, Ahrens RC, Chmiel JF, Clancy JP, Gibson RL, Harris WT, Kurland G, Laguna TA, McColley SA, McCoy K, Retsch-Bogart G, Sobush KT, Zeitlin PL, Stevens MJ, Accurso FJ, Sagel SD, Harris JK. **Airway microbiota across age and disease spectrum in cystic fibrosis.** *Eur Respir J*. 2017 Nov 16;50(5).

Pittman JE, Wylie KM, Akers K, Storch GA, Hatch J, Quante J, Frayman KB, Clarke N, Davis M, Stick SM, Hall GL, Montgomery G, Ranganathan S, Davis SD, Ferkol TW; Australian Respiratory Early Surveillance Team for Cystic Fibrosis. **Association of Antibiotics, Airway Microbiome, and Inflammation in Infants with Cystic Fibrosis.** *Ann Am Thorac Soc*. 2017 Oct;14(10):1548-1555.

Frayman KB, Armstrong DS, Carzino R, Ferkol TW, Grimwood K, Storch GA, Teo SM, Wylie KM, Ranganathan SC. **The lower airway microbiota in early cystic fibrosis lung disease: a longitudinal analysis.** *Thorax*. 2017 Dec;72(12):1104-1112.

UPDATE ON TREATMENT OF NEUROMUSCULAR DISEASES IN CHILDREN

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Division of Respiratory Medicine, Department of Pediatrics
Toronto, Ontario, Canada**NUSINERSEN FOR INFANTS WITH SPINAL MUSCULAR ATROPHY TYPE I: THE ENDEAR TRIAL**

Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, Chiriboga CA, Saito K, Servais L, Tizzano E, Topaloglu H, Tulinius M, Montes J, Glanzman AM, Bishop K, Zhong ZJ, Gheuens S, Bennett CF, Schneider E, Farwell W, De Vivo DC for the ENDEAR Study Group. **Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy.** *N Engl J Med* 2017;377; 18: 1723-32

Summary

Spinal Muscular Atrophy (SMA) is an autosomal recessive neuromuscular disorder caused by a mutation in the survivor motor neuron (SMN) 1 gene. A second gene, SMN 2 also encodes SMN protein but usually 90-95% of the translated protein is truncated because of aberrant splicing. Infants with a higher copy number of SMN2 generally have a milder phenotype. Nusinersen is an antisense oligonucleotide drug that promotes increased production of full-length SMN protein by modifying pre-messenger RNA splicing of the SMN2 gene. This could be an effective treatment strategy for SMA. The ENDEAR trial was a 13 month, randomized, double-blind, sham-controlled, phase 3 efficacy and safety trial of intrathecal nusinersen in infants with SMA1. The primary endpoints were motor-milestone response and event-free survival (time to death or the use of permanent assisted ventilation). Secondary endpoints included overall survival and subgroup analyses of event-free survival according to disease duration at screening. 122 infants were randomized (81 were assigned to the nusinersen group and 41 to the control group). In the interim analysis, a higher percentage of infants in the nusinersen group than in the control group had a motor-milestone response [21/51 infants (41%) vs 0/27 (0%), $P < 0.001$]. The likelihood of event-free survival was higher in the nusinersen group than the control group for both death as well as permanent assisted ventilation. The trial was terminated early due to the interim analysis results.

Comments

1. Infants born with SMA type 1 (SMA1) have symptom onset before 6 months of age and a median life expectancy of less than 2 years without respiratory support. After diagnosis, infants continue to lose motor milestones as they become progressively weaker.
2. In the ENDEAR trial, infants with a shorter disease duration at screening were more likely than those with

a longer disease duration to benefit from nusinersen suggesting that early initiation of treatment maximizes efficacy.

3. Study results demonstrate that nusinersen is a treatment not a cure in symptomatic infants; some infants treated with nusinersen died, none achieved normal motor milestones and some needed continued ventilatory and feeding support.
4. Additional studies with longer follow up periods are needed to better understand if treatment with nusinersen results in continued motor-milestone improvement after 13 months.
5. Nusinersen has been approved as the first disease modifying treatment for SMA1 in the USA, European Union, Canada, Japan, Korea, Australia, and Brazil.

NUSINERSEN VERSUS SHAM CONTROL IN LATER-ONSET SPINAL MUSCULAR ATROPHY: THE CHERISH STUDY

Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, Iannaccone ST, Kirschner J, Kuntz NL, Saito K, Shieh PB, Tulinius M, Mazzone ES, Montes J, Bishop KM, Yang Q, Foster R, Gheuens S, Bennett CF, Farwell W, Schneider E, De Vivo DC, Finkel RS, for the CHERISH Study Group. **Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy.** *N Engl J Med* 2018; 378; 625-35

Summary

Nusinersen was shown to be an effective treatment for infants with Spinal Muscular Atrophy Type 1 in the ENDEAR study. The CHERISH trial was a randomized, double-blind, sham-controlled, phase 3 efficacy and safety trial of nusinersen in 126 non-ambulatory children age 2 to 12 years old with later-onset Spinal Muscular Atrophy (SMA). Later onset SMA was defined as symptom onset after 6 months of age. Children with symptomatic SMA were randomized 2:1 (stratified based on screening age <6 versus >6 years) to receive 4 doses of intrathecal nusinersen (12mg) or sham procedure control over 9 months during this 15 month study. Eligibility criteria included confirmed 5q SMA and onset of SMA clinical symptoms at ≥ 6 months of age. The primary endpoint was change from baseline in Hammersmith Functional Motor Scale Expanded (HFMSE) score at Month 15. 84 children received nusinersen therapy and 42 were in the control group. The median age (range) in years at screening was 3.0 (2-7) and 4.0 (2-9) for control

and nusinersen groups, respectively. In the pre-specified interim analysis, there was a significant least-squares mean difference in change of 5.9 points in HFSME score from baseline to month 15 prompting early termination of the trial. Results of the final analysis were consistent with the interim analysis results. There were no treatment discontinuations due to adverse events.

Comments

1. Of note, children with more severe later onset SMA were excluded from the CHERISH trial [exclusion criteria: severe contractures, severe scoliosis (Cobb angle > 40 degrees), ventilation use >6 hrs/ day, or gastrostomy tube]. As a result the enrolled population was younger and milder than the population cared for in clinical practice. Only 16% of trial participants were 6 years of age or older.
2. A change in HFMSE of ≥ 3 points is considered to be the minimum clinically important difference.
3. 57% of children in the nusinersen group versus 26% in the control group had an increase in the HFMSE score of at least 3 points ($p < 0.001$).
4. Notably, the choice of primary endpoint as well as the definition of a clinically meaningful difference relating to change in the HFMSE was different for the ENDEAR and CHERISH trials.
5. Additional studies with longer follow up periods are needed to better understand if treatment with nusinersen results in continued motor-milestone improvement after 15 months and if the results are generalizable to an older and more severe cohort of later onset SMA patients.

GENE THERAPY FOR INFANTS WITH SPINAL MUSCULAR ATROPHY TYPE I

Mendell JR, Al-Zaidy S, Shell R, Arnold WD, Rodino-Klapac LR, Prior TW, Lowes L, Alfano L, Berry K, Church K, Kissel JT, Nagendran S, L'Italien J, Sproule DM, Wells C, Cardenas JA, Heitzer MD, Kaspar A, Corcoran S, Braun L, Likhite S, Miranda C, Meyer K, Foust KD, Burghes AHM, Kaspar BK. **Single-Dose Gene Replacement Therapy for Spinal Muscular Atrophy.** *N Engl J Med* 2017;377; 18: 1713-22

Summary

Infants with Spinal Muscular Atrophy type 1 (SMA1) have a median life expectancy of less than 2 years without respiratory support; there is no cure for SMA. Mendell et al. present their data from a phase I trial of gene replacement therapy for SMA1. Fifteen patients with SMA1 received a single intravenous dose of adeno-associated virus serotype 9 (AAV9) carrying complementary DNA encoding the missing SMN protein. Three infants received low dose and the remaining 12 received high dose. The primary endpoint was safety. The secondary endpoint was time until death or

the need for permanent assisted ventilation. In exploratory analyses, the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scale of motor function (ranging from 0 to 64, higher scores indicate better function) was used to compare the two cohorts. 16 patients were screened but 1 was excluded because of persistently elevated AAV9 antibody titers. The mean age of patients at the time of treatment for low and high dose was 6.3 months (range 5.9-7.2) and 3.4 months (range 0.9-7.9), respectively. All 15 patients were alive as compared to a survival rate of 8% in the historical cohort. At baseline, 3/3 and 2/12 infants required assisted ventilation. At the time of the last pulmonary assessment (cohort 1: median age 30.8 months; cohort 2: median age 25.7 months), 3 additional infants required assisted ventilation.

Comments

1. Gene replacement therapy has been previously studied in a murine model. This approach successfully increased SMN expression in motor neurons and peripheral tissues; the average survival increased in this model from 15 days to 28.5 days with low dose and to more than 250 days with higher doses of the vector.
2. One-time intravenous infusion of high dose adeno-associated viral vector containing DNA coding for SMN in patients with SMA1 resulted in extended survival, improved motor function and increased scores on the CHOP INTEND scale to levels not previously reported for SMA1 in a cohort of 15 infants.
3. By the end of the follow up period, CHOP INTEND scores were as follows: patients in cohort 1 had a mean increase of 7.7 points from a baseline of 16.3 points, and those in cohort 2 had a mean increase of 24.6 points from a mean baseline of 28.2 points.
4. There was a mean decline of 10 points or more between 6 to 12 month follow up in the historical cohort.
5. Further studies are needed to assess the long-term safety and durability of gene-replacement therapy in patients with SMA1.

NUSINERSEN FOR SPINAL MUSCULAR ATROPHY: ETHICAL CONSIDERATIONS

Burgart AM, Magnus D, Tabor HK, Paquette ED, Frader J, Glover JJ, Jackson BM, Harrison CH, Urion DK, Graham RJ, Brandsema JF, Feudtner C. **Ethical Challenges Confronted When Providing Nusinersen Treatment for Spinal Muscular Atrophy.** *JAMA Pediatr* 2018;172(2):188-192. doi:10.1001/jamapediatrics.2017.4409

Summary

Nusinersen has been recently approved as a disease modifying therapy for clinical use for patients with Spinal Muscular Atrophy (SMA) in several countries worldwide.

Burgart et al. summarize six main ethical challenges that lie ahead for clinicians and institutions. 1) Cost: Nusinersen's cost of \$175,000/dose will inevitably result in inequitable access to the medication based on public versus private healthcare system structure as well as variability in insurance coverage. 2) Limitation of Evidence: Based on the current evidence, it is not known if nusinersen's efficacy is generalizable to patients that fall outside the studies' inclusion criteria and/or sustained beyond 13-15 months. Coverage of the medication may become linked to demonstrated patient benefit but this may be problematic if the endpoints chosen are not sensitive enough to detect changes in more severely affected children. 3) Informed Consent: Ongoing conversations discussing risks versus benefits of treatment with patients and families will be needed as new information becomes available. 4) Treatment allocation: A systematic queuing system incorporating utility and fairness while maximizing benefit will need to be developed to meet the demands for treatment. 5) Fair distribution of roles and responsibilities: Regional treatment centers will need to be developed and distributed to maximize access for patients. 6) Transparency and stakeholder engagement: To ensure patients and families are making informed decisions about whether and where to initiate treatment, medical centers will need to publicize their center's process and queuing processes for each center.

Comments

1. Nusinersen's remarkable cost poses a significant barrier to treatment access. Treatment centers will need to develop a systematic approach to the management of patients with partial or no medication coverage. Pressure must be applied to reduce the cost of the medication.
2. Additional studies are needed to further understand the long-term efficacy of nusinersen as well as the treatment effects in patients that fall outside the eligibility criteria of the completed studies.
3. Informed consent discussions for patients and families need to be dynamic and responsive to updated study data.
4. The cohesive development of regional treatment centers with systematic queuing systems for treatment allocation is required across a country to maximize equitable and fair access to treatment while ensuring maximum benefit for patients.
5. The queuing system criteria and clinical workflows must be publicized and accessible to patients and families.

GLUCOCORTICOID TREATMENT FOR DUCHENNE MUSCULAR DYSTROPHY

McDonald CM, Henricson EK, Abresch RT, Duong T, Joyce NC, Hu F, Clemens PR, Hoffman EP, Cnaan A, Gordish-Dressman H; CINRG Investigators. **Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study.** *The Lancet*. 2018 Feb 3;391(10119):451-461. doi: 10.1016/S0140-6736(17)32160-8. Epub 2017 Nov 22.

Summary

There is moderate quality evidence from randomized controlled trials that glucocorticoid treatment for Duchenne Muscular Dystrophy (DMD) improves muscle strength and/or function in the short term up to 2 years. However, it is unknown if long-term treatment will result in decreased disease progression and improved survival. McDonald et al. conducted a prospective, cohort study to examine the long-term effects of glucocorticoids on milestone-related disease progression across the lifespan as well as survival in boys with DMD. 440 males aged 2 to 28 years were enrolled and followed for 10 years. The authors compared no glucocorticoid treatment or cumulative treatment duration of less than 1 month versus treatment of 1 year or longer with regards to progression of nine disease-related mobility and upper limb milestones (Davis Functional Milestones for measuring disease progression). 440 patients were enrolled during two recruitment periods (2006-9 and 2012-16). The mean (SD) age in years at the baseline visit was 10.7 (5.7). Time to all disease progression milestone events was significantly longer in patients treated with glucocorticoids for 1 year or longer than in patients treated for less than 1 month or never treated. Glucocorticoid treatment was associated with reduced risk of death.

Comments

1. In patients with DMD, glucocorticoid treatment was associated with reduced risk of losing clinically meaningful mobility and upper limb disease progression milestones across the lifespan.
2. Kaplan-Meier analyses were used to assess the median time to each milestone with varying stratification based on glucocorticoid use (greater than or equal to 12 months versus <1 month or not treated). This analysis excludes participants who entered the study after the event in question occurred.
3. Deflazacort was associated with increased median age at loss of three milestones by 2.1-2.7 years in comparison with prednisone or prednisolone.
4. Age at loss of ambulation was found to predict future age at progression to absolute FVC less than 1 Liter.
5. This was a pragmatic study and reflects observation of patients managed in routine clinical practice at 20 centers in 9 countries.

ATALUREN TREATMENT FOR DUCHENNE MUSCULAR DYSTROPHY

McDonald CM, Campbell C, Torricelli RE, Finkel RS, Flanigan KM, Goemans N, Heydemann P, Kaminska A, Kirschner J, Muntoni F, Osorio AN, Schara U, Sejersen T, Shieh PB, Sweeney HL, Topaloglu H, Tulinius M, Vilchez JJ, Voit T, Wong B, Elfring G, Kroger H, Luo X, McIntosh J, Ong T, Riebling P, Souza M, Spiegel RJ, Peltz SW, Mercuri E, the Clinical Evaluator Training Group, and the ACT DMD Study Group. **Ataluren in patients with nonsense mutation Duchenne muscular dystrophy (ACT DMD): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial.** *The Lancet* 2017; 390:1489-98

Summary

Duchenne Muscular Dystrophy (DMD) is a progressive, neuromuscular disease due to dystrophin deficiency. Ataluren is a mutation specific strategy for the treatment of DMD aimed at restoring dystrophin protein production via read-through of a nonsense mutation. Ataluren improved dystrophin expression in skeletal muscle of patients with nonsense mutation DMD after 28 days of treatment in a phase 2a trial. A phase 2b trial showed a clinical benefit in the six-minute walk distance (6MWD) for ataluren versus placebo at 48 weeks. McDonald et al. conducted a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial to assess the safety and efficacy of ataluren in ambulatory boys with nonsense mutation DMD. Boys 7-16 years of age with nonsense mutation DMD and baseline 6MWD of 150m or more and 80% or less of the predicted normal value for age and height were randomized to ataluren or placebo. Randomization was stratified by age, duration of previous corticosteroid use and baseline 6MWD (<350m vs ≥350m). The primary endpoint was change in 6MWD from baseline to week 48. 230 patients were randomized to ataluren (n=115) or placebo (n=115). Change in 6MWD did not differ significantly between patients, neither in the intention-to-treat population nor in the pre-specified subgroups with a baseline 6MWD of less than 300m or more than 400m.

Comments

1. In a subgroup of DMD patients with nonsense mutation DMD and a baseline 6MWD >300 meters and <400m, there was a treatment benefit of ataluren over 48 weeks.
2. This finding is most likely due to increased sensitivity of the outcome measure in this subgroup experiencing a transition to ambulatory deterioration.
3. Additional study of ataluren is needed to confirm these findings.
4. The FDA has not yet approved ataluren for clinical use in DMD.

OTHER ARTICLES OF INTEREST

Finkel RS, Chiriboga CA, Vajsar J, Day JW, Montes J, De Vivo DC, Yamashita M, Rigo F, Hung G, Schneider E, Norris DA, Xia S, Bennett CF, Bishop KM. **Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open label, dose escalation study.** *Lancet* 2016; 388:3017-26

Chiriboga CA, Swoboda KJ, Darras BT, Iannaccone ST, Montes J, De Vivo DC, Norris DA, Bennett CF, Bishop KM. **Results from a phase 1 study of nusinersen (ISIS-SMN(Rx)) in children with spinal muscular atrophy.** *Neurology* 2016; 8;86(10): 890-7

Finkel RS, Mercuri E, Meyer OH, Simonds AK, Schroth MK, Graham RJ, Kirschner J, Iannaccone ST, Crawford TO, Woods S, Muntoni F, Wirth B, Montes J, Main M, Mazzone E, Vitale M, Snyder B, Quijano-Roy S, Bertini E, Hurst Davis R, Qian Y, Sejersen T for the SMA Care group. **Diagnosis and Management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; an ethics.** *Neuromuscular Disorders* 2017; published online November 13, 2017.

Matthews E, Brassington R, Kuntzer T, Jichi F, Manzur AY. **Corticosteroids for the treatment of Duchenne muscular dystrophy.** *Cochrane Database Syst Rev* 2016; 5: CD003725.

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