

New Drugs for Children in the Food and Drug Administration Pipeline

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Several drugs in development have the potential to benefit children. New Drug Applications (NDA) and preliminary filings with the Food and Drug Administration (FDA) in the past 4 months include a new antiepileptic, several long-awaited drugs for the treatment of Duchenne muscular dystrophy, a chemotherapeutic agent for neuroblastoma, a CFTR corrector to be used in combination with ivacaftor in patients with cystic fibrosis, and a monoclonal antibody for patients with severe eosinophilic asthma.

Brivaracetam

On January 21, 2015, UCB announced regulatory filings at the FDA and the European Medicines Agency (EMA) for brivaracetam.¹ This drug, structurally similar to levetiracetam, has a more than 30-fold higher affinity for synaptic vesicle protein 2A (SV2A) ligand in the human cerebral cortex. Both oral and intravenous formulations are under investigation. Three phase 3 studies, enrolling over 3,000 adults and children, have been conducted to establish the safety and efficacy of brivaracetam. A recently published phase 3 randomized, double-blind, placebo-controlled trial conducted in 398 adults found that a dose of 100 mg/kg/day reduced baseline-adjusted focal seizures by 11.7% over placebo ($p = 0.004$).² Thirty-six percent of patients receiving brivaracetam achieved a reduction in seizure frequency of 50% or greater.

An open-label pharmacokinetic, safety, and efficacy study of brivaracetam as adjunctive therapy in 101 children (1 month-16 years of age) with epilepsy was completed in 2014.³ In patients younger than 8 years of age, brivaracetam was initiated at a dose of 0.5 mg/kg given twice daily for the first week. The dose was increased to 1 mg/kg twice daily for week 2 and 2 mg/kg twice daily for week 3. Patients were evaluated for the presence of treatment-emergent adverse effects, change in seizure frequency, and treatment adherence at the end of week 3. After assessment, the dose was reduced in the same stepwise manner on weeks 4 and 5. For patients 8 years of age and older, the dose

was initiated at 0.4 mg/kg given twice daily for the first week, followed by 0.8 mg/kg twice daily for week 2 and 1.6 mg/kg twice daily for week 3. Down-titration was done in the same manner for weeks 4 and 5. The results of the study have not yet been published. Several other studies of brivaracetam are currently enrolling patients, including a pediatric follow-up study.⁴

Drugs for Duchenne Muscular Dystrophy

Ataluren

On December 23, 2014, PTC Therapeutics announced that it will begin a rolling NDA submission for ataluren (Translarna[®]), a new therapy for Duchenne muscular dystrophy (DMD).⁵ The rolling submission allows the manufacturer to submit completed portions of the NDA for review by the FDA on an ongoing basis, potentially avoiding delays in the approval process. Ataluren is a protein restoration therapy for patients with genetic diseases caused by a nonsense mutation.^{5,6} It is estimated that 13% of boys with DMD have a nonsense mutation in the dystrophin gene. Ataluren enables a readthrough of the premature stop codon in the mRNA of DMD patients, leading to production of full-length functional dystrophin protein.

In 2013, Finkel and colleagues published the results of a phase 2a open-label dose-ranging study of ataluren in 38 boys with nonsense mutation DMD.⁶ Six patients (the first cohort) received ataluren at 4 mg/kg in the morning, 4 mg/kg at midday, and 8 mg/kg in the evening for 28 days. The second cohort (20 children) received 10, 10, and 20 mg/kg. The third (12 children) received 20, 20, and 40 mg/kg. The primary endpoint for the study was the change in full-length dystrophin protein expression, based on immunostaining of muscle biopsy specimens. Sixty-one percent of the boys demonstrated increases in dystrophin expression. The increase was not associated with age, type of nonsense mutation, or exon location. Target ataluren plasma concentrations (2-10 mcg/mL) were consistently achieved. There were no serious adverse events. Mild adverse effects included nausea, vomiting, diarrhea, and abdominal pain.

A phase 2b randomized, double-blind, placebo-controlled trial of ataluren was published in 2014.⁷ A total of 174 patients were enrolled of one of 37 sites. Patients were randomized to receive placebo, ataluren at a dose of 10, 10, 20 mg/kg (40 mg/kg/day) or 20, 20, 40 mg/kg (80 mg/kg/day). At week 48, the mean decline in predicted 6-minute walk test (6MWT) was 7.6% in the placebo group, compared to 2.7% in the ataluren 40 mg/kg/day group ($p = 0.055$). Mean decline in the 80 mg/kg/day group was 7.7%, similar to placebo, suggesting a bell-shaped exposure-response relationship. Ataluren was well tolerated, with no serious adverse effects.

In the January 2015 issue of *Neuromuscular Disorders*, Haas and colleagues published a review of the ataluren study data submitted to the EMA which led to the granting of a conditional marketing authorization in the European Union on August 5, 2014.⁸ This excellent review provides not only a detailed analysis of the study data, but also a concise review of the drug's mechanism of action and adverse effect profile, as well as a benefit to risk assessment.

Deflazacort

On January 19, 2015, Marathon Pharmaceuticals announced that the FDA had given deflazacort, an oxazoline derivative of prednisolone, a Fast Track designation for the treatment of patients with DMD.⁹ The Fast Track designation was developed to facilitate the approval process by providing earlier and more frequent interaction between the manufacturer and the FDA. The FDA ruling also makes the drug eligible for the Accelerated Approval and Priority Review process. The drug was previously granted Orphan Drug status for the treatment of patients with DMD. The Orphan Drug designation is given by the FDA to drug products used to treat rare diseases, defined as those affecting fewer than 200,000 patients in the U.S. Marathon anticipates filing the completed NDA in 2016.

Although it has never been approved in the U.S., deflazacort is widely prescribed in Canada and a number of European countries. When compared to prednisone, deflazacort has been shown to cause fewer adverse effects and to better preserve bone density with long-term use. In 2012, McAdam and colleagues published a review of the Canadian experience with deflazacort in DMD, using data from Montreal and Toronto to compare patients treated with deflazacort with those not given steroids. Deflazacort was found to slow the time to loss of ambulation in the Montreal data, from 9.6 ± 1.4 years in the controls to 11.5 ± 1.9 years. The percentage of DMD patients who developed scoliosis was lower with treatment, 27% compared to 67% of controls in Montreal and 10% versus 90% of controls in Toronto. Rates of long bone fractures were no different (24-26%), but height was decreased in the deflazacort

groups at both centers, suggesting a possible adverse effect on growth. Cataracts were more also common in the deflazacort groups.

In 2013, Lebel and colleagues at Toronto's Hospital for Sick Children published a long-term follow-up of deflazacort in 54 boys with DMD.¹¹ The decision to initiate deflazacort was made by the patients' families. Patients were evaluated every 4-6 months for up to 15 years. Five boys in the non-treatment group and one in the deflazacort group died during follow-up. Of the survivors, 6 (20%) in the deflazacort group and 22 (92%) of the controls developed scoliosis and underwent spinal surgery. There was no difference in the frequency of long bone fractures. Height, however, was impacted by treatment, with the patients receiving deflazacort measuring a mean of 17 cm less than the controls. The incidence of cataracts was also significantly higher in the treatment group (70% versus zero). The authors concluded that the long-term use of glucocorticoids was associated with a substantial decrease in the need for spinal surgery for scoliosis.

Drisapersen

On October 10, 2014, Prosensa announced that the FDA had given drisapersen, another agent for DMD, a Fast Track designation.¹² The manufacturer has begun a rolling NDA submission and anticipates completion in 2015. Drisapersen is an antisense oligonucleotide which induces skipping of exon 51 of the human dystrophin pre-mRNA, resulting in production of more function dystrophin protein.¹³ More than 300 patients from more than 25 countries have participated in drisapersen trials, with mixed results. While several phase 2 trials gave promising results, an unpublished 48-week placebo-controlled trial failed to show significant benefit in the 6MWT.¹⁴

The results of the DEMAND II trial, a randomized double-blind, placebo-controlled phase 2 study of drisapersen for the treatment of DMD, were published last year by Voit and colleagues.¹⁵ Fifty-three patients (mean age 7 years) were enrolled at 13 centers in nine countries. Patients received either drisapersen 6 mg/kg or placebo subcutaneously either weekly or intermittently (9 doses over 10 weeks). At week 25, the mean 6MWT had increased by 31.5 meters from baseline for weekly drisapersen, with a mean difference in the change from baseline of 35.09 meters (95% CI 7.59, 62.6, $p = 0.014$) versus placebo. There was no significant improvement with intermittent dosing. The most common adverse effects were injection site reactions and subclinical proteinuria. The authors suggest the benefit of drisapersen seen in their study may reflect use in a younger patient population compared to previous studies.

Entrectinib

On December 29, 2014, Ignyta, Incorporated announced that the FDA had granted Orphan Drug status and a Rare Pediatric Disease designation for entrectinib for the treatment of neuroblastoma.¹⁶ Entrectinib is an oral selective tyrosine kinase inhibitor. It inhibits tyrosine kinase receptors (TrkA, TrkB, and TrkC) as well as ROS1 and ALK proteins. It is being studied in both adult and pediatric solid tumors that have activation alterations to these targets. Entrectinib is currently in phase 1 and 2 trials. Preliminary study results have shown no dose-limiting toxicity. Interim results include a complete response in one patient with ROS1-positive non-small cell lung cancer (NSCLC) and partial responses in patients with NSCLC, colorectal cancer, and neuroblastoma.

Lumacaftor

Vertex Pharmaceuticals issued a press release on November 5, 2014 to announce the submission of an NDA to the FDA and a Marketing Authorization Application to the EMA for a combination formulation of lumacaftor and ivacaftor.¹⁶ Approval is being requested for use in adults and children 12 years of age and older with two copies of the phe508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. It is estimated that approximately 22,000 people worldwide have this genetic mutation. The combination of lumacaftor and ivacaftor was given a Breakthrough Therapy designation by the FDA 2012. A similar designation of Accelerated Assessment was granted by the EMU.

Lumacaftor is a CFTR corrector that increases trafficking of phe508del CFTR to the cell surface. Ivacaftor potentiates CFTR, and the two drugs work synergistically to increase the flow of sodium chloride and water across cell membranes. Boyle and colleagues published the results of a phase 2a randomized controlled trial of the combination in 2014. The study was conducted with three adult cohorts enrolled from 24 centers worldwide. Cohort 1 included phe508del CFTR homozygous patients given lumacaftor 200 mg once daily for 14 days followed by the addition of ivacaftor 150 mg or 250 mg every 12 hours for 21 days or placebo. Cohorts 2 and 3 consisted of homozygous and heterozygous patients randomized to either lumacaftor (200, 400, or 600 mg once daily for cohort 2 and 400 mg every 12 hrs for cohort 3) for 28 days with ivacaftor added for the remainder of the study, or placebo, for 56 days. Mean sweat chloride values decreased significantly with combination therapy in the first cohort (9.1 mmol/L, $p < 0.001$), but not in cohorts 2 or 3. Phe508del CFTR homozygous patients also were shown to have significant improvement in FEV₁, but no benefit was seen in the heterozygous patients.

The efficacy and safety of the combination have also been studied in two global phase 3 studies, TRAFFIC and TRANSPORT, conducted in adults and children 12 years of age and older. Vertex has released preliminary information from both studies that show improvement in FEV₁ and a reduction in pulmonary CF exacerbations over 24 weeks.

Mepolizumab

Submission of an NDA for mepolizumab was announced by GSK on November 5, 2014. The drug is a humanized monoclonal antibody specific for interleukin 5 (IL-5) designed as maintenance therapy in adults and children 12 years of age and older with severe eosinophilic asthma. Mepolizumab prevents endogenous IL-5 from binding to eosinophils, preventing eosinophilic inflammation and the need for systemic corticosteroids.

The safety and efficacy of mepolizumab were evaluated in two randomized, double-blind phase 3 studies in *The New England Journal of Medicine*: the Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) study and the Steroid Reduction with Mepolizumab Study (SIRIUS) study. The MENSA study enrolled 76 patients 12 to 82 years of age with severe asthma resulting in at least two exacerbations within the previous year and an elevated eosinophil count. Patients were randomized to receive mepolizumab (75 mg IV or 100 mg subcutaneously) or placebo every 4 weeks for 32 weeks. Exacerbations were reduced by 47% in the IV mepolizumab group compared to placebo (95% CI 29, 61, $p < 0.001$) and by 53% in the subcutaneous mepolizumab group (95% CI 37, 65, $p < 0.001$). The mean increase from baseline FEV₁ was 100 mL greater in the IV group than in the controls ($p = 0.03$) and 98 mL greater in the subcutaneous group than the controls ($p = 0.03$). Reductions in emergency department visits and hospitalizations, improvements in symptom scores, and the 5-item Asthma Control Questionnaire (ACQ-5) were all significantly greater in the treatment groups.

The SIRIUS trial enrolled 135 patients 16 to 74 years of age with severe asthma who had been taking an oral glucocorticoid for at least 6 months. Each patient completed an optimization phase to establish their lowest effective dose and was randomized to mepolizumab 100 mg or placebo given subcutaneously every 4 weeks for 20 weeks. More patients in the mepolizumab group were able to have steroid dose reduced by 90-100% (23% versus 11% of controls) or by at least 70-90% (17% versus 8% of controls). Treatment produced a reduction in the annualized exacerbation rate of 32% (1.44 per year versus 2.12 for controls, $p = 0.04$). Respiratory symptom questionnaire and ACQ-5 scores improved with treatment. Adverse effects with mepolizumab were similar to placebo.

Summary

The last several months have seen a significant number of NDA and other filings at the FDA, including unique therapies that may play a significant role in the management of diseases previously without treatment. Pharmaceutical manufacturers are increasingly taking advantage of the non-traditional programs offered by the FDA to facilitate earlier availability of innovative therapies. The full impact of these programs, on approval time, as well as clinical trial design, is yet to be seen.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their December 2014 and January 2015 meetings:

1. Dasatinib (Sprycel[®]) was added to the formulary for the treatment of patients with Philadelphia chromosome positive (Ph⁺) chronic myeloid leukemia or Ph⁺ acute lymphoblastic leukemia with resistance or intolerance to prior therapy.
2. Degarelix (Firmagon[®]), a GnRH receptor antagonist, was added for the treatment of advanced prostate cancer.
3. The restriction on prescribing of abciximab was amended to include acute thrombosis in peripheral endovascular small vessel interventions.
4. The indications for loperamide were amended to include use in an extemporaneous topical preparation for wound management.
5. Lidocaine/heparin/sodium bicarbonate bladder instillation was added for management of interstitial cystitis.
6. Dexamethasone/ciprofloxacin/clotrimazole/boric acid ototopical powder was added for use by Otolaryngology-Head and Neck Surgery.
7. The restriction on tranexamic acid was amended to include intraoperative and postoperative use for spine surgery.

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