

DNA Technology May Revolutionize Flu Vaccine

BY DOUG BRUNK

The way Dr. Joseph Kim sees it, influenza vaccine development needs an extreme makeover.

“Every year, three flu strains are selected by the flu experts around the world, which determines which strains the vaccine makers should make,” Dr. Kim, president and CEO of San Diego-based Inovio Biomedical Corp.,

said in an interview. “They can guess right, or they can guess wrong, but every year, you have to change the vaccine.” He wants to change that paradigm.

Since 2005, he and his associates at Inovio have been developing DNA-based influenza vaccines capable of providing broad protection against existing as well as newly emerging, unknown seasonal and pandemic influenza strains. To design vaccines, the company developed a

process known as SynCon, a way of targeting consensus proteins from multiple strains of H1N1, H2N2, H3N2, and H5N1, “which have collectively caused greater than 90% of all seasonal and pandemic flu events in people in the last 100-plus years,” Dr. Kim said.

What separates Inovio’s SynCon approach from that of other DNA vaccine manufacturers is that the SynCon vaccines demonstrate potential to protect

against new strains that do not specifically match the vaccine. “So, if the 2009 H1N1 virus mutates, there is no plan B,” Dr. Kim said. “There is no backup option; 2009 swine flu could be a big problem or not.”

Origins of an Alternative

DNA-based influenza vaccines began to draw serious attention about 6 years ago, when infectious diseases experts around the globe expressed concern about a

BRIEF SUMMARY

(See package insert for Full Prescribing Information)

Dysport (abobotulinumtoxinA) for Injection

Rx Only

Distant Spread of Toxin Effect

Postmarketing reports indicate that the effects of *Dysport* and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children and adults, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and at lower doses.

INDICATIONS AND USAGE

Glabellar Lines

Dysport is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients < 65 years of age.

CONTRAINDICATIONS

Dysport is contraindicated in patients with known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation.

This product may contain trace amounts of cow’s milk protein. Patients known to be allergic to cow’s milk protein should not be treated with *Dysport*.

Dysport is contraindicated for use in patients with infection at the proposed injection site(s).

WARNINGS AND PRECAUTIONS

Lack of Interchangeability between Botulinum Toxin Products
The potency Units of *Dysport* are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of *Dysport* cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method.

Spread of Toxin Effect

Postmarketing safety data from *Dysport* and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children and adults, and in approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia.

Facial Anatomy in the Treatment of Glabellar Lines

Caution should be exercised when administering *Dysport* to patients with surgical alterations to the facial anatomy, excessive weakness or atrophy in the target muscle(s), marked facial asymmetry, inflammation at the injection site(s), ptosis, excessive dermatochalasis, deep dermal scarring,

thick sebaceous skin or the inability to substantially lessen glabellar lines by physically spreading them apart.

Do not exceed the recommended dosage and frequency of administration of *Dysport*. In clinical trials, subjects who received a higher dose of *Dysport* had an increased incidence of eyelid ptosis.

Pre-existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of *Dysport*.

Human Albumin

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been reported for albumin.

Intradermal Immune Reaction

The possibility of an immune reaction when injected intradermally is unknown. The safety of *Dysport* for the treatment of hyperhidrosis has not been established.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not be predictive of rates observed in practice.

In placebo-controlled clinical trials of *Dysport*, the most frequently reported adverse events ($\geq 2\%$) following injection of *Dysport* were nasopharyngitis, headache, injection site pain, injection site reaction, upper respiratory tract infection, eyelid edema, eyelid ptosis, sinusitis and nausea.

Table 3 reflects exposure to *Dysport* in 398 subjects aged 19 to 75 who were evaluated in the randomized, placebo-controlled clinical studies that assessed the use of *Dysport* for the temporary improvement in the appearance of glabellar lines. Adverse events of any cause were reported for 48% of the *Dysport*-treated subjects and 33% of the placebo-treated subjects. Treatment-emergent adverse events were generally mild to moderate in severity.

Table 3: Treatment-emergent Adverse Events with > 1% incidence

Adverse Events by Body System	<i>Dysport</i> n=398 (%)*	Placebo n=496 (%)*
Any Treatment-emergent Adverse Event	191 (48)	163 (33)
Eye Disorders		
Eyelid Edema	8 (2)	0
Eyelid Ptosis	6 (2)	1 (<1)
Gastrointestinal Disorders		
Nausea	6 (2)	5 (1)
General Disorders and Administration Site Conditions		
Injection Site Pain	11 (3)	8 (2)
Injection Site Reaction	12 (3)	2 (<1)
Infections and Infestations		
Nasopharyngitis	38 (10)	21 (4)
Upper Respiratory Tract Infection	12 (3)	9 (2)
Sinusitis	8 (2)	6 (1)
Investigations		
Blood Urine Present	6 (2)	1 (<1)
Nervous System Disorders		
Headache	37 (9)	23 (5)

* Subjects who received treatment with placebo and *Dysport* are counted in both treatment columns.

pandemic of H5N1 influenza virus, noted Dr. William Schaffner, chair of the department of preventive medicine at Vanderbilt University, Nashville, Tenn.

“Since that time, the United States government and private capital have gone into research to develop more improved influenza vaccines and to improve the vaccine technology. There has been more research into those areas in the past 5 or 6 years than there has been in the previous 50 years,” said Dr. Schaffner.

The concept of DNA vaccines first emerged in the early 1990s, when academic scientists discovered that immu-

nizing animals with plasmids—a circular string of DNA that encodes for a specific antigen or vaccine target—generates vaccine responses.

“The beauty of this technology is speed,” said Vijay B. Samant, president and CEO of San Diego-based Vical, which develops DNA vaccines. “It’s not cell culture. It’s not egg-based. It’s simple fermentation and two purification steps. It does not require the manufacturer to handle the pathogen. All it needs is a gene sequence; that’s good enough for us to make the vaccine.”

Instead of viruses, “you’re taking a

very simple plasmid . . . and you’re putting in a genetic blueprint designed for a specific target, in this case hemagglutinin,” Dr. Kim explained. Once injected, “it uses our own cellular machinery to manufacture those proteins as antigens, and presents them in a customized way. It’s like mimicking viral infection without the side effects and replication. DNA vaccines can never replicate. They do not infect; they do not cause disease, ever.”

Delivery Poses Challenges

Until recently, Dr. Kim and other researchers in the field faced a barrier to

the advancement of DNA vaccines: inefficient delivery. However, a technology developed in the 1990s known as in vivo electroporation is proving to be an effective way to deliver DNA vaccines.

Electroporation works like this: After a DNA vaccine is injected via syringe into the upper arm or into skin, a short, controlled electrical pulse is delivered directly into that tissue. This “coaxes the cell membranes to open up their pores,” Dr. Kim said. “That brings in the DNA. We remove the electric field and the pores close up. This has been shown in animal species to be effective in up to a 1,000-fold increase in DNA vaccine uptake.”

Not all DNA vaccine manufacturers are using electroporation.

Vical, the first company to produce a vaccine against the pandemic influenza

In the overall safety database, where some subjects received up to twelve treatments with *Dysport*, adverse events were reported for 57% (1425/2491) of subjects. The most frequently reported of these adverse events were headache, nasopharyngitis, injection site pain, sinusitis, URI, injection site bruising, and injection site reaction (numbness, discomfort, erythema, tenderness, tingling, itching, stinging, warmth, irritation, tightness, swelling).

Adverse events that emerged after repeated injections in 2–3% of the population included bronchitis, influenza, pharyngolaryngeal pain, cough, contact dermatitis, injection site swelling, and injection site discomfort.

The incidence of eyelid ptosis did not increase in the long-term safety studies with multiple re-treatments at intervals \geq three months. The majority of eyelid ptosis events were mild to moderate in severity and resolved over several weeks.

Post-marketing Spontaneous Reports

There is extensive post-marketing experience outside the U.S. for the treatment of glabellar lines. Adverse reactions are reported voluntarily from a population of uncertain size; thus, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure. The following adverse reactions have been identified during post-marketing use: vertigo, eyelid ptosis, diplopia, vision blurred, photophobia, dysphagia, nausea, injection site reaction, malaise, influenza-like illness, hypersensitivity, sinusitis, amyotrophy, burning sensation, facial paresis, dizziness, headache, hypoesthesia, erythema, and excessive granulation tissue.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. In addition, the observed incidence of antibody positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies across products in this class may be misleading.

Testing for antibodies to *Dysport* was performed for 1554 subjects who had up to nine cycles of treatment. Two subjects (0.13%) tested positive for binding antibodies at baseline. Three additional subjects tested positive for binding antibodies after receiving *Dysport* treatment. None of the subjects tested positive for neutralizing antibodies.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with *Dysport*.

Patients treated concomitantly with botulinum toxins and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like agents) should be observed closely because the effect of the botulinum toxin may be potentiated. Use of anticholinergic drugs after administration of *Dysport* may potentiate systemic anticholinergic effects such as blurred vision.

The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive weakness may be exacerbated by another administration of botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of *Dysport*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

Dysport produced embryo-fetal toxicity when given to pregnant rats at doses similar to or greater than the maximum recommended human dose (MRHD) of 1000 Units on a body weight (Units/kg) basis.

In an embryo-fetal development study in which pregnant rats received intramuscular injections daily (2.2, 6.6, or 22 Units/kg on gestation days 6 through 17) or intermittently (44 Units/kg on gestation days 6 and 12 only) during organogenesis, increased early embryonic death was observed with both dosing schedules. The no-effect dose for

embryo-fetal developmental toxicity was 2.2 Units/kg (one-tenth the MRHD on a body weight basis). Maternal toxicity was seen at 22 and 44 Units/kg. In a pre- and post-natal development study in which female rats received 6 weekly intramuscular injections (4.4, 11.1, 22.2, or 44 Units/kg) beginning on day 6 of gestation and continuing through parturition to weaning, an increase in stillbirths was observed at the highest dose, which was maternally toxic. The no-effect dose for pre- and post-natal developmental toxicity was 22.2 Units/kg (approximately equal to the MRHD on a body weight basis).

There are no adequate and well-controlled studies in pregnant women. *Dysport* should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether *Dysport* is excreted in human milk.

Pediatric Use

Dysport is not recommended for use in pediatric patients less than 18 years of age.

Geriatric Use

Of the total number of subjects in the placebo-controlled clinical studies of *Dysport*, 8 (1%) were 65 and over. Efficacy was not observed in subjects 65 years and over. For the entire safety database of geriatric subjects, although there was no increase in the incidence of eyelid ptosis, geriatric subjects did have an increase in the number of ocular adverse events compared to younger subjects (11% vs. 5%).

Ethnic Groups

Exploratory analyses in trials for glabellar lines in African-American subjects with Fitzpatrick skin types IV, V, or VI and in Hispanic subjects suggested that response rates at Day 30 were comparable to and no worse than the overall population.

OVERDOSAGE

Excessive doses of *Dysport* may be expected to produce neuromuscular weakness with a variety of symptoms. Respiratory support may be required where excessive doses cause paralysis of respiratory muscles. In the event of overdose, the patient should be medically monitored for symptoms of excessive muscle weakness or muscle paralysis. Symptomatic treatment may be necessary.

Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur, the person should be medically supervised for several weeks for signs and symptoms of excessive muscle weakness or paralysis.

In the event of an overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at (770) 488-7100. More information can be obtained at <http://www.cdc.gov/ncidod/srp/drugs/drug-service.html>.

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Full Prescribing Information for *Dysport* is available at www.DysportUSA.com.



‘DNA vaccines can never replicate. They do not infect; they do not cause disease, ever.’

DR. KIM

A(H1N1) virus after initial reports of outbreaks in Mexico, uses a patented adjuvant known as Vaxfectin, “which does an amazing job of protecting the DNA before it enters the skeletal muscle cells,” Mr. Samant said. “Being a proinflammatory, it attracts the immune system toward the site of the injection to facilitate creation of the right immune response and immune memory.”

Phase I Trials Begin

In October, the U.S. Navy awarded Vical a contract to support a phase I clinical trial of its vaccine against H1N1 influenza. “Our goal is to get that trial done by later this year,” Mr. Samant said.

In a virus challenge and protection study of Inovio’s SynCon H1N1 vaccine, mice were injected with the H1N1 virus that caused the 1918 Spanish flu. Mice that received the H1N1 vaccine were completely protected from the virus, whereas all of the unvaccinated animals died within 1 week.

In 2010, the SynCon H5N1 vaccine will undergo human testing in healthy volunteers, followed by tests in combination with the SynCon H1N1 vaccine.

Potential Pitfall

“If we are correct, we can revolutionize how flu vaccines are made and delivered,” Dr. Kim said. One potential pitfall of the DNA vaccine technology is the impending backlash from vaccine naysayers, cautioned Dr. Schaffner. “We have a hardcore group of vaccine skeptics,” he said. “Any innovation, whether it is the addition of an adjuvant, or a new technology such as this, will come to their attention and draw some of their skepticism and opposition. We have to brace for this.”

Dr. Schaffner has been a consultant for various vaccine manufacturers. He also is a member of a data safety committee for Merck for experimental vaccines. ■