



Pro-Con Debate

Over-the-counter intranasal corticosteroids: why the time is now

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On July 31, 2013, with a 10 to 6 vote with 2 abstentions, the US Food and Drug Administration's (FDA's) Nonprescription Drugs Advisory Committee, which included 3 board-certified allergists from the Pulmonary/Allergy FDA Advisory Committee, supported Sanofi Pharmaceutical's new drug application for the switch of triamcinolone acetonide nasal spray (Nasacort AQ) to over-the-counter (OTC) status. The new application is for the same indication and ages as it currently is used as a prescription product. In fact, 2 of 3 of the board-certified allergists voted in favor of a switch to OTC use for triamcinolone acetonide nasal spray. The FDA's final decision on the OTC switch will also be based on data submitted from 13 placebo-controlled efficacy studies and safety information from 43 clinical studies, as well as information from 16 years of post-marketing surveillance data. It is clear that much of the allergy community is not in favor of this move, and both major allergy organizations voiced strong opposition at the advisory committee meeting. I spoke in favor of the switch to OTC use and would like to give my reasons why I think this is an appropriate action by the FDA for the large population with allergic rhinitis.

Would the United States be the first country in the world to switch triamcinolone acetonide nasal spray to OTC status? The answer is no. Triamcinolone acetonide nasal spray is already approved for OTC use in 11 countries, including Australia, New Zealand, Finland, Norway, Sweden, Switzerland, Denmark, Uruguay, Malaysia, and Malta. In fact, it was in 1994 that an intranasal corticosteroid, beclomethasone, was made available without a prescription in the United Kingdom. Australia allowed OTC status in 1999. Currently, every country in the European Union has several different intranasal corticosteroid (INS) brands available without a prescription. So allergy patients in many parts of the world have been using INSs without health care professional supervision for almost 20 years.

In the 1990s, the FDA labeled allergic rhinitis as a disease that can be recognized and treated without a "learned intermediary." In other words, this is a condition that does not require oversight by

a health care professional. Patients are able to self-diagnose and self-select to use products for the treatment of allergic rhinitis.

The FDA has already approved first- and second-generation antihistamines, oral and topical decongestants, and intranasal cromolyn sodium for OTC use. It was in 2002 that the FDA approved the switch of loratadine to OTC status. At that FDA advisory board meeting, the major allergy organizations testified against the switch with concerns of safety and cost for the allergic rhinitis patient. As we have seen, this switch led to easier access and a reduction in costs for loratadine and other second-generation antihistamines for patients, with no evidence of any adverse safety signals.

The Food, Drug, and Cosmetic Act restricts a drug to prescription status if "because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drugs." This has been interpreted to mean that a drug should be restricted to prescription use if intervention of a learned intermediary is required for its proper use (administration and monitoring); otherwise, the drug can be marketed for OTC use. The FDA, therefore, does not question the already approved efficacy when moving an agent to OTC status but whether it is safe to use without supervision, and patients can understand the proper use of the agent. So what do the data tell us about the safety and unsupervised use of triamcinolone acetonide nasal spray and other INSs?

The first INS was approved in the United States in 1981. Since launch, 50 million bottles of triamcinolone acetonide nasal spray have been distributed in the United States. During the last 30 years, volumes of data have accumulated on the safety of INSs. The most common adverse effects seen with INSs are nasal dryness and epistaxis. Nosebleeds can be severe, but in most cases are mild and can be easily managed by the patient. A high percentage of the population has nosebleeds each year,¹ and other agents already approved for OTC use, such as topical decongestants, are associated with this problem. A more serious concern is nasal septal perforation. These are extremely rare complications with all INSs, and in the postmarketing data with triamcinolone acetonide nasal spray, only one case was reported in a patient who had had previous nasal surgery.² As far as topical adverse effects, INSs have an excellent safety profile with rare problems even with long-term use.^{3,4}

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What are the data on systemic adverse effects with INSs? The FDA addressed immunosuppression, ocular effects, hypothalamic-pituitary-adrenal (HPA) axis effects, and reduction in growth velocity in the advisory board hearings. No evidence has been seen of immunosuppression or opportunistic infections with INSs.² There was no evidence of glaucoma or cataracts seen in any of the triamcinolone acetonide nasal spray clinical studies. A recent 2-year study of the treatment of patients with perennial allergic rhinitis did not reveal significant differences between fluticasone furoate nasal spray and placebo in time to occurrence of ocular events for posterior subcapsular cataracts and increased intraocular pressure.⁵ A real-world study⁶ in children with budesonide nasal spray also failed to detect any adverse ocular effects in a 2-year period.

HPA axis suppression is a concern with the use of all corticosteroid products. The data fail to demonstrate that INSs in recommended doses, even for long-term use, lead to adrenal suppression. Three studies of triamcinolone acetonide nasal spray, with one that included children as young as 2 years, evaluated HPA axis suppression, with no effects was seen.² Other INSs, including beclomethasone in children,⁷ also fail to show adrenal suppression.

Another concern is corticosteroid burden. What about patients who are using more than one steroid preparation? The only other corticosteroid preparation available OTC is 1.0% hydrocortisone cream. It is highly unlikely that using an INS and 1.0% hydrocortisone cream together would affect the HPA axis. A bigger concern is the common use of INSs with inhaled corticosteroids in patients with allergic rhinitis and asthma. Of course, all patients with asthma will still be followed up by a health care professional who should monitor for any evidence of corticosteroid adverse effects. We can be reassured from several articles in the literature that failed to find any additional increase in HPA axis suppression when INSs are added to inhaled corticosteroids in asthma treatment.^{8,9}

The safety issue, which I believe is of the most concern for allergists and their patients, is a reduction in growth velocity in prepubertal children. In 2007, the FDA guidance to industry on growth studies in children taking INSs was strengthened. The triamcinolone acetonide nasal spray study fell under those guidelines.¹⁰ A total of 299 children with allergic rhinitis between 3 and 9 years of age participated in a double-blind, placebo-controlled trial receiving either triamcinolone acetonide nasal spray, 110 µg, or placebo daily. Stadiometry was used to measure height beginning 4 months before treatment, during treatment for 1 year, and 2 months after treatment. The primary end point was the rate of growth (centimeters per year). The mean growth rates in the placebo group were 6.09 cm/y, whereas it was 5.65 cm/y in the triamcinolone acetonide nasal spray group. This was statistically significant but was less than 0.25 in. The growth rate difference was most pronounced in the first 2 months of treatment, similar to placebo the remaining year, and at 2-month follow-up appeared increased to placebo. Notably, this study was not of adult height obtained or an evaluation of catch-up growth. It does not represent what one would see in clinical practice in that it is unlikely a child would continuously use triamcinolone acetonide nasal spray every day for 1 year. Also a 0.25-in change is unlikely to be detected in clinical practice and therefore unlikely to lead to any changes in treatment. If the FDA approves triamcinolone acetonide nasal spray for OTC use in children as young as 2 years, the probable drug facts label will mention a possibility of growth velocity reduction and advise parents to inform the child's health care professionals when starting. Of course, the FDA may modify the OTC label to 12 or 18 years and older, which would make this issue moot.

Can patients understand how to use INSs without a health care professional? Before a medication can be switched to an OTC status, the sponsoring company must perform studies to prove that patients understand the drug facts label and how to use the

medication. Studies conducted for Sanofi by Saul Shiffman, PhD, at the University of Pittsburgh found excellent comprehension of the triamcinolone acetonide nasal spray label even in a group of patients with low-literacy and high scores in a human factors test to show ability to use the spray correctly.²

What is the benefit for the patient? By switching INSs to an OTC status, the expanded access provides another choice of a more effective treatment option. As stated in the Practice Parameters, "Intranasal corticosteroids are the most effective medication class for controlling symptoms of allergic rhinitis."¹¹ As a prescription, there are economic and practical barriers to obtaining this class of medicines. As I stated in my testimony before the FDA, patients are concerned about taking time off of work because a visit to the physician can consume 2 to 4 hours. Parents or caregivers are often reluctant to take their child out of school to see a health care professional for nasal allergies, and thus these children are left untreated or undertreated. Some may be concerned that the cost for the patient may increase if INSs gain OTC status. That may be true for some patients with good pharmaceutical benefits when the switch first occurs, but as we have seen with OTC antihistamines, the costs continue to decrease with more and more competition. Currently, to get a prescription of an INS, the patient has to make a copayment for the medication and a copayment to see the clinician and incur the indirect cost of missing work or school for the office visit. Patients without pharmaceutical benefits will see a major reduction in cost from day one.

Another concern is what would happen if the patient uses an INS without physician supervision and does not have allergies. If the patient has a cold, there is no injury with the use of an INS, and the condition will resolve in approximately 10 days. What about acute rhinosinusitis? In fact, studies have found that INSs lead to improvement of symptoms with better efficacy than oral antibiotics.^{12,13} Of course, if the patient is not getting better with the INS, he or she will stop using it and no damage will be done.

So when a product achieves OTC status, it does not mean that physicians are no longer going to be involved in the patient's treatment. How many patients do you see daily in whom OTC antihistamines have failed? Therefore, if patients are not getting better with OTC INSs, they are going to seek medical care, just like the patients who do not respond to OTC oral antihistamines now. We, as allergists, have other modalities, especially allergen immunotherapy, for the patients in whom INSs fail. Patients with comorbidities, such as asthma and chronic sinus disease, will continue to seek our services.

Currently, most prescriptions for INSs are for generic fluticasone propionate due to managed care restrictions. If you want to use a different INS, especially a branded one, how much uncompensated time do you or your office staff spend attempting to get approval from insurance companies? How many times do you get returning call for less expensive INSs, or how many times does the patient just leaves the pharmacy without getting the INS because of cost? If these agents gain OTC status, we can tell the patient to get the exact INS we think is best for their condition.

Since the 2006 position statement on OTC INSs from the American College of Allergy, Asthma, and Immunology and the American Academy of Allergy, Asthma, and Immunology,¹⁴ my opinion has evolved with additional data on safety and reassurance about OTC INS use in most other countries. As allergists, we believe "first the patient, second the patient..." The use of OTC INSs allows better access for the patient to these effective treatments that have a high benefit-to-risk ratio.

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