Azelastine: a treatment for allergic rhinitis.

**Background:**
Allergies are a response of the immune system to innocuous substances resulting in a wide spectrum of symptoms that can range in severity anywhere from mild discomfort to life threatening anaphylactic shock. One of the key components in the inflammatory response that characterize allergies is the histamine response; one of the four receptor types that mediates this response is the H-1 receptor. This g-protein coupled receptor is located on the surface of smooth muscle cells, and cells in the heart, vascular endothelial cells and the central nervous system. Most current antihistamines are antagonists of the H-1 receptor.

Azelastine is a selective histamine H1 antagonist but has additional anti-inflammatory effects, preventing release of histamine from mast cells and inhibiting leukotriene synthesis. Leukotrienes are a key mediator of allergic inflammation that lead it to be originally considered as a treatment for asthma, because of its effect on the leukotriene signaling pathway (another key mediator of allergic inflammation). There is evidence to support the hypothesis that this effect is due to the inhibitory effects on 5-lipoxygenase, which plays a role in the synthesis of leukotrienes. This triple action (histamine receptor antagonism, histamine release and leukotriene inhibition) makes azelastine a particularly interesting molecule to study for the treatment of many types of hyperactive immune diseases.

In addition, azelastine has also been implicated as a potential inhibitor of tumor necrosis factor alpha (TNF) release --a cytokine, which is involved in a number of inflammatory responses. The roles of these processes in allergic and inflammatory response is summarized in figure 1.
We focus on the most recent FDA approved use for azelastine, as a treatment for allergic rhinitis (based entirely on the H1 inhibitory effects of this molecule). This treatment is delivered as a nasal spray in 0.15% solutions (see astelin.com)—a novel treatment for allergic rhinitis as most intranasal treatments for allergic rhinitis are corticosteroids, which multiple studies have shown to have significantly greater efficacy than orally dosed antihistamines. Azelastine, however, is able to achieve similar efficacy to the leading corticosteroid Flonase while having a significantly faster onset of action.

Synthesis:

A summary of the hydrazine/sodium hydroxide route of synthesis is shown below.

![Synthesis of Azelastine](image)

Chemical Properties / Pharmacokinetics:
Azelastine is administered through an intranasal route as a spray. This is essentially a topical delivery route, and allows for fast uptake of the drug and a localization targeting the nasal mast cells that are responsible for initiation of much of the allergic response. Bioavailability is 40% through this route, with a 2-3 hour time to achieve maximum plasma concentrations, and a 22h half-life. The drug is oxidatively metabolized by the cytochrome P450 family into an active metabolite desmethylazelastine and 2 inactive carboxylic acid metabolites.

Azelastine has a significant competitive binding effect on the histamine H1 receptor (pKi 10.1), which is higher than the very effective first generation H1 antagonist diphenhydramine (pKi 8.22). This is largely a result of the slow dissociation kinetics (especially compared with other H1 antagonists like diphenhydramine), which also results in a significantly longer time to equilibrium.

Summary of Experimental and Clinical Evidence

Beginning in the early 2000’s Meda Pharmaceuticals began to direct efforts involving Azelastine toward the treatment of seasonal allergic rhinitis (SAR). Despite being a well saturated field they felt there could still be a market for Azelstine, especially given its well documented safety profile and history. At the time (and still) the king of the allergy treatment hill was Allegra (Fexofenadine), another second generation antihistamine with a similar structure. In 2003 a study was conducted to determine the efficacy of Azelastine nasal spray in SAR patients who remained symptomatic following treatment with Fexofenadine. Enrolled patients had a minimum two-year history of SAR in addition to a positive skin test within the past year. The study began with a one-week open-label lead in period during which all patients received 60mg tablets of Fexofenadine twice per day. During this period the patients kept a diary of their symptoms that was used to evaluate their total nasal symptom score (TNSS: a measure of the severity of runny nose, sneezing, nasal congestion, etc.). Those patients who either experienced a worsening of the symptoms or an improvement of less than 33% by the end of the week were invited to continue in the study. Of the initial 443 patients, 344 satisfied the criteria for continuation, with 324 completing the entire 2 week trial. They were randomized into three blinded treatment groups:

1) Azelastine, 2 sprays per nostril, per day + placebo pills twice per day.
2) Azelastine, 2 sprays per nostril, per day + plus Fexofenadine, 60mg tablet twice per day.
3) Placebo spray (saline solution) 2 sprays per nostril, per day + placebo pills twice per day.

As with the lead-in period patients kept a diary of their symptoms, with baseline scores being subtracted from the daily TNSS score to evaluate the change from baseline.
The Azelastine mono therapy demonstrated equal effectiveness as the combined Azelastine/Fexofenadine treatment and a statistically significant improvement over the placebo group. From this the authors concluded that there was no additional benefit to be gained from coadministration of an oral antihistamine with Azelastine. One potential draw back of this study is that after the base-line establishment, there was no comparison against Fexofenadine alone. The most common adverse event (by percentage) was a bitter taste followed by nasal passage irritation.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Azelastine, 112</th>
<th>Azelastine plus Fexofenadine, 112</th>
<th>Placebo, 111</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bitter taste</td>
<td>10.7</td>
<td>9.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Nasal passage irritation</td>
<td>4.5</td>
<td>3.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Sneezing</td>
<td>1.8</td>
<td>1.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Headache</td>
<td>0.0</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>0.9</td>
<td>1.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0.9</td>
<td>0.9</td>
<td>0.0</td>
</tr>
</tbody>
</table>

It is interesting to note that while the placebo group received a nasal saline spray 2X daily, their reported incidence of nasal passage irritation was four to five fold lower than the groups receiving Azelastine. The study’s authors did not address this and no patients dropped out due nasal irritation.

A follow up study conducted in 2004 was designed to test the effectiveness of Azelastine in what the authors referred to as “real world conditions.” This comprised a 2-week open label trial with 4364 patients using Azelastine as their only rhinitis medication. The results are show below, with the percentage of patients reporting varying degrees of improvement of each symptom.
As with the earlier studies, result data was based on patient diaries of their symptoms. A large drawback to this methodology is the lack of hard quantifiable evidence (such as actually measuring the amount of mucus produced, allergen exposure, etc.) combined with the open label aspect making the results extremely susceptible to a placebo effect.

Two more rigorous double-blind studies were conducted in 2006 with a total patient population of 554. Both studies were run using the same methodology, assessing patients who were still symptomatic after a 1-week lead in period of placebo treatment. Following this lead in period, patients were randomized for two weeks of double blind treatment with either Azelastine nasal spray or a placebo nasal spray. Prior to this using the same TNSS system as the prior study, the measured variable used to determine efficacy was improvement from the baseline score established during the lead-in period. Symptoms are measured on a scale of 0-3, with 0 = no symptoms, and 3 = severe symptoms. In study 1, the percentage improvement in TNSS was 14.1% from baseline with Azelastine and 4.5% with placebo. Study 2 had a greater degree of improvement results with Azelastine treatment, 22.1% over baseline, but also saw better improvement in the placebo group at 12.0%.

Figure 4: Monotherapy results of Azelastine. All results are self reported from an open label study.
Again, the most common adverse event was a bitter taste reported by 8.3% of the participants. Some patients and physicians reported this could be ameliorated by lowering the force of spray.20

A 2008 meta-analysis of prior trials combined with a study comparing the efficacy of 0.15% to 0.10% Azelastine formulations was enough for FDA to approve marketing Azelastine at 0.15% for the treatment of SAR. As with the earlier studies, the patients endured a week long lead-in period during which they received placebo nasal sprays twice daily. From this lead in period their baseline TNSS scores were established. Following the lead-in period, the patients were randomized in a 1-1-1 ratio: 0.15% Azelastine, 0.10% Azelastine, Placebo. These groups were tracked and their TNSS scores measured as an improvement from Baseline. While there was improvement in the placebo group, it was outperformed by both Azelastine cohorts. There was no increase in adverse events with the increased concentration to 0.15%.21

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Figure 6: Double blind study results comparing placebo, 0.10% Azelastine, and 0.15% Azelastine. Baseline was established by having all cohorts take placebo for one week prior to beginning. TNSS scores are based upon patient symptom diaries. 21
Contraindications & Safety Concerns:

Azelastine is a fairly remarkable drug given its wide range of targets/effects while having very few safety concerns or contraindications. The single largest contraindication is for patients not to take it if they have a known “sensitivity to Azelastine.” In every study examined, bitter taste was the single greatest complaint with 4-16% incidence. Somnolence, a more serious side effect, was reported as well but only in the range of 0.0-1.0%\textsuperscript{16,20,21}.

Using post marketing surveillance data the FDA recently (January 2012) added nasal sores to the list of adverse reactions.\textsuperscript{22} There is no data available for acceptable use in pregnant women and safety trials in children aged 12 and younger are currently in progress.

REFERENCES:

11. The organic chemistry of drug synthesis


