Wegener granulomatosis

Lester D.R. Thompson, MD

Wegener granulomatosis (WG) is an idiopathic, nonneoplastic, aseptic, necrotizing disease characterized by vasculitis and destructive properties. In general, affected patients exhibit disease in the sinonasal tract, lungs, and kidney, in some cases metachronously. Patients may present with systemic or localized disease; patients with systemic disease are usually quite sick. Disease progression may be seen when localized disease becomes systemic, but many patients will remain with limited disease.

The ELK classification system is used to define the disease: E indicates ear, nose, and throat involvement; L indicates lung involvement; and K indicates kidney involvement. Localized upper aerodigestive tract WG (WG-E) tends to affect men more often than women, although laryngeal disease is seen predominantly in women. The sinonasal tract is affected more often than the nasopharynx, larynx, or oral cavity. Symptoms are usually nonspecific and can include sinusitis, rhinorrhea, obstruction, pain, epistaxis, and headaches, depending on which anatomic site is affected.

One of the critical elements of the diagnostic evaluation is laboratory testing for antineutrophil cytoplasmic antibody (ANCA) and proteinase 3 (PR3). There is usually an elevation of ANCA and PR3, with a specificity between 85 and 98%. There are two types of ANCA—cytoplasmic (c-ANCA) and perinuclear (p-ANCA). WG is much more frequently associated with c-ANCA (figure 1). PR3-ANCA is highly specific for WG. Laboratory results vary according to the extent of disease and disease activity, and they normalize 6 to 8 weeks after remission.

It is important to note that a negative test does not exclude WG, and positive results can be seen in other vasculitides, including microscopic polyangiitis and allergic granulomatous angiitis. Various treatment regimens can result in a complete remission, although relapses do occur. Renal or pulmonary insufficiency and/or complications from therapy can result in morbidity and death.

WG presents clinically as ulcerative and crusted lesions with tissue destruction. The histologic triad of vasculitis, granulomatous inflammation, and biocollagenolytic necrosis is characteristic, but all three findings are uncommon in a single biopsy. The vasculitis involves destruction of small to medium-sized arteries that contain an inflammatory infiltrate within the vessel wall and subendothelial space, leading to destruction of the elastic lamina (figure 1).

Continued on page 22
INDICATION: ZETONNA® (ciclesonide) Nasal Aerosol is a corticosteroid indicated for the treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older.

IMPORTANT SAFETY INFORMATION: In clinical studies local nasal effects of epistaxis, ulcerations, and nasal septal perforations were observed with ZETONNA® (ciclesonide) Nasal Aerosol. In the short-term and long-term trials combined, nasal septal perforations were reported in 2 patients of 2335 treated with ZETONNA compared with none of 892 treated with placebo. Both perforations occurred in 2-week SAR trials while none occurred in the longer term trials. In clinical trials with another formulation of ciclesonide, the development of localized infections of the nose or pharynx with \textit{Candida albicans} has occurred. Corticosteroids can interfere with wound healing.

Prior to initiating therapy, examine patients for evidence of septal perforation, erosions, ulceration, nasal surgery, and trauma. Avoid spraying ZETONNA directly onto the nasal septum. Avoid use in patients with recent septal perforation, nasal erosion, nasal ulcers, nasal surgery, or nasal trauma. Monitor patients periodically for signs of adverse reactions on the nasal mucosa. Discontinue ZETONNA if erosions, ulcerations or perforations occur.

Nasal and inhaled corticosteroids may result in the development of glaucoma and cataracts. Monitor patients closely with a change in vision or with a history of increased intraocular pressure, glaucoma, or cataracts.

ZETONNA is contraindicated in patients with a known hypersensitivity to ciclesonide or any of the ingredients of ZETONNA. Cases of hypersensitivity reactions following administration of ciclesonide with manifestations such as angioedema, with swelling of the lips, tongue and pharynx have been reported.

Patients using immunosuppressive drugs, like corticosteroids, can cause potential worsening of existing tuberculosis; fungal, bacterial, viral or parasitic infections; or ocular herpes simplex. Chicken pox and measles can have a more serious or even fatal course in susceptible individuals. Use caution in patients with the above because of the potential for worsening of these infections.

When intranasal corticosteroids are used at very high dosages or at the regular dosage in susceptible individuals, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, discontinue ZETONNA slowly.

Corticosteroids may cause a reduction in growth velocity in children. Monitor growth routinely in pediatric patients receiving ZETONNA.

In trials 2-6 weeks in duration, the most common adverse events that occurred with an incidence of at least 2% and more frequently with ZETONNA than with placebo were nasal discomfort, headache and epistaxis.

Please see Brief Summary of Prescribing Information on the following pages.

**5.5 Hypothalamic-Pituitary-Adrenal Axis Effect**

Hypercorticism and Adrenal Suppression: When intranasal corticosteroids are used at higher than recommended dosages or in susceptible individuals at recommended dosages, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, the dosage of ZETONNA Nasal Aerosol should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency. In addition, some patients may experience symptoms of corticosteroid withdrawal, e.g., joint and muscular pain, lassitude, and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, rapid decreases in systemic corticosteroid dosages may cause a severe exacerbation of their symptoms.

**5.6 Effect on Growth**

Corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth routinely (e.g., via stadiometry) in pediatric patients receiving ZETONNA Nasal Aerosol. [see Pediatric Use (8.4)]

**6 ADVERSE REACTIONS**

Systemic and local corticosteroid use may result in the following:

- Epistaxis, ulcerations, nasal septal perforations, *Candida albicans* infection, impaired wound healing [see Warnings and Precautions (5.1)]
- Glaucoma and cataracts [see Warnings and Precautions (5.2)]
- Immunosuppression [see Warnings and Precautions (5.4)]
- Hypothalamic-pituitary-adrenal (HPA) axis effects, including growth reduction [see Warnings and Precautions (5.5, 5.6), Use in Specific Populations (8.4)]

**6.1 Clinical Trials Experience**

The safety data described below for adults and adolescents 12 years of age and older are based on 4 clinical trials evaluating doses of ciclesonide nasal aerosol from 74 to 282 mcg. Three of the clinical trials were 2 to 6 weeks in duration and one trial was 26 weeks in duration with an additional 26-week open-label extension. Data from the first 6 weeks of the 26-week trial were pooled with data from the three 2-week trials. Short-term data (2 to 6 weeks) included 3001 patients with seasonal and perennial allergic rhinitis, of these, 884 received ZETONNA Nasal Aerosol 74 mcg once daily and 892 received placebo. The short-term data included 1098 (36.6%) males, 1903 (63.4%) females, 2587 (86.2%) Caucasians, 320 (10.7%) Blacks, 49 (1.6%) Asians, and 45 (1.5%) patients classified as Other. The 26-week trial was conducted in 1110 patients with perennial allergic rhinitis (394 [35.5%] males and 716 [64.5%] females, ages 12 to 78 years old) treated with ZETONNA Nasal Aerosol 74 mcg, 148 mcg or placebo once daily. Of these patients, 236 were treated with 74 mcg ZETONNA Nasal Aerosol, 505 with 148 mcg, and 307 with placebo. The racial distribution in this trial included 922 (83.1%) Caucasians, 146 (13.2%) Blacks, 18 (1.6%) Asians, and 24 (2.2%) patients classified as Other. The 26-week open-label extension included 824 patients [295 (36.5%) males and 529 (64.2%) females, ages 12 to 78 years old] given ZETONNA Nasal Aerosol 148 mcg once daily. The nasal distribution in the open-label extension included 690 (85.7%) Caucasians, 104 (12.6%) Blacks, 15 (1.8%) Asians, and 15 (1.8%) patients classified as Other. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

**Adults and Adolescents 12 Years of Age and Older in Short-Term (2-6 weeks) Trials**

In three short-term trials and the first 6 weeks of one long-term trial, conducted in the US, 884 patients with a history of seasonal or perennial allergic rhinitis were treated with ZETONNA Nasal Aerosol 74 mcg daily. Adverse reactions did not differ appreciably based on age, gender, or race. The table below displays reactions that occurred with an incidence of at least 2.0% and more frequently with ZETONNA Nasal Aerosol 74 mcg than with placebo in seasonal or perennial allergic rhinitis clinical trials of 2 to 6 weeks duration.
When considering the data from higher doses evaluated in the short-term trials, epistaxis demonstrated a dose response. In addition, two patients treated with ZETONNA Nasal Aerosol 74 mcg experienced nasal septal perforations in the short-term trials compared to no patients treated with placebo. Approximately 1.2% of patients treated with ZETONNA Nasal Aerosol 74 mcg in clinical trials discontinued due to adverse reactions; this rate was similar for patients treated with placebo. Discontinuations due to local adverse reactions were similar in ZETONNA Nasal Aerosol 74 mcg treated patients (0.6%) compared to placebo treated patients (0.6%). Local adverse reactions leading to discontinuation that occurred only in ZETONNA Nasal Aerosol treated patients included ear infection, nasal discomfort, nasal dryness, nasal mucosal/septum disorders, pharyngitis, streptococcal pharyngitis, sinus headache, and tinnitus.

### Pediatric Patients Aged 2 to 11 Years:

Trials of ZETONNA Nasal Aerosol have not been conducted in pediatric patients aged 2 to 11 years. The safety and efficacy of ZETONNA Nasal Aerosol in children aged 2 to 11 years have not been assessed. Therefore, ZETONNA Nasal Aerosol should not be used in children aged 2 to 11 years.

### Long-Term (26-Week Double-Blind and 26-Week Open-Label) Safety Trial:

In one 26-week double-blind, placebo-controlled safety trial that included 1110 adult and adolescent patients with perennial allergic rhinitis, additional adverse reactions, with an incidence of at least 2%, that occurred more frequently with ZETONNA Nasal Aerosol than with placebo were upper respiratory tract infection, urinary tract infection, oropharyngeal pain, nasal mucosal/septum disorders, viral upper respiratory tract infection, cough, influenza, bronchitis, streptococcal pharyngitis, muscle strain, and nausea. Nasal discomfort (5.7%) and epistaxis (11.4%) were also more frequent in the 26-week safety trial compared to clinical trials 2 to 6 weeks in duration. Nasal mucosal/septum disorders and cough demonstrated a dose response. Discontinuations due to adverse reactions were higher in ZETONNA Nasal Aerosol treated patients compared to placebo treated patients and demonstrated a dose response. Local adverse reactions leading to discontinuation were also higher in ZETONNA Nasal Aerosol 74 mcg treated patients (1.7%) compared to placebo treated patients (0.7%). The only local adverse reaction leading to discontinuation that occurred in ZETONNA Nasal Aerosol treated patients and was not observed in the 2- to 6-week trials was upper respiratory tract infection.

A total of 824 patients with perennial allergic rhinitis who completed the 26-week double-blind trial enrolled into an open-label extension and received ZETONNA Nasal Aerosol 148 mcg for 26 weeks. Additional adverse reactions, observed with an incidence of at least 2% were sinusitis, nasopharyngitis, and back pain. A total of 4 nasal septal ulcerations were also reported in the 26-week open-label extension. There were no reports of nasal septal perforations in the long-term safety trial.

### 6.2 Post-marketing Experience

Additional adverse reactions have been identified during worldwide post-marketing use with other formulations of ciclesonide, ALVESCO® Inhalation Aerosol and OMNARIS® Nasal Spray. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

ALVESCO® Inhalation Aerosol: immediate or delayed hypersensitivity reactions such as angioedema with swelling of the lips, tongue, and pharynx. OMNARIS® Nasal Spray: nasal congestion, nasal ulcer, and dizziness. Localized infections of the nose or mouth with Candida albicans have also occurred with OMNARIS® Nasal Spray.

### 7. DRUG INTERACTIONS

In vitro studies and clinical pharmacology studies suggested that des-ciclesonide has no potential for metabolic drug interactions or protein binding-based drug interactions [see Clinical Pharmacology (12.3) in the full prescribing information]. In a drug interaction study, co-administration of orally inhaled ciclesonide and oral ketoconazole, a potent inhibitor of cytochrome P450 3A4, increased the exposure (AUC) of des-ciclesonide by approximately 3.6-fold at steady state, while levels of ciclesonide remained unchanged. Erythromycin, a moderate inhibitor of cytochrome P450 3A4, had no effect on the pharmacokinetics of either des-ciclesonide or erythromycin following oral inhalation of ciclesonide [see Clinical Pharmacology (12.3) in the full prescribing information].

### 8. USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Teratogenic Effects:** Pregnancy Category C.

There are no adequate and well-controlled trials in pregnant women. ZETONNA Nasal Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

Oral administration of ciclesonide in rats at approximately 120 times the maximum recommended human daily intranasal dose (MRHDID) in adults (on a mcg/m² basis at a maternal dose of 900 mcg/kg/day) produced no teratogenicity or other fetal effects. However, subcutaneous administration of ciclesonide in rabbits at similar to MRHDID (on a mcg/m² basis at a maternal dose of 5 mcg/kg/day) produced fetal toxicity. This included fetal loss, reduced fetal weight, cleft palate, skeletal abnormalities including incomplete ossifications, and skin effects. No toxicity was observed at 1/4 of the MRHDID in adults (on a mcg/m² basis at a maternal dose of 225 mcg/kg/day).

**Nonteratogenic Effects:** Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

#### 8.3 Nursing Mothers

It is not known if ciclesonide is excreted in human milk. However, other corticosteroids are excreted in human milk. In a study with lactating rats, minimal but detectable levels of radiolabeled ciclesonide were recovered in milk. Caution should be used when ZETONNA Nasal Aerosol is administered to nursing women.

#### 8.4 Pediatric Use

The safety and effectiveness for seasonal and perennial allergic rhinitis in children 12 years of age and older have been established. The safety and efficacy of ZETONNA Nasal Aerosol for treatment of the symptoms of seasonal and perennial allergic rhinitis in patients 11 years of age and younger have not been established.

Controlled clinical trials have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA)-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for “catch-up” growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including ZETONNA Nasal Aerosol, should be monitored routinely (e.g., via stadiometry). A 52-week, multicenter, double-blind, randomized, placebo-controlled parallel-group trial was conducted to assess the effect of orally inhaled ciclesonide (ALVESCO® Inhalation Aerosol) on growth rate in 609 pediatric patients with mild persistent asthma, aged 5 to 8.5 years. Treatment groups included orally inhaled ciclesonide 40 mcg or 160 mcg or placebo given once daily. Growth was measured by stadiometer height during the base-line, treatment and follow-up periods. The primary comparison was the difference in growth rates between ciclesonide 40 and 160 mcg and placebo groups. Conclusions cannot be drawn from this trial because compliance could not be assured. Ciclesonide blood levels were also not measured during the one-year treatment period. There was no difference in HPA-axis measures between the placebo and the orally inhaled ciclesonide (ALVESCO® Inhalation Aerosol) groups.

### Table 1: Adverse Reactions Occurring with a Frequency of at Least 2.0% and Greater Than Placebo from Controlled Clinical Trials 2 to 6 Weeks in Duration in Patients 12 Years of Age and Older with Seasonal or Perennial Allergic Rhinitis

| Adverse Reaction     | ZETONNA Nasal Aerosol 74 mcg Once Daily | Placebo  
|----------------------|----------------------------------------|--------
| N = 884 (%)          | N = 892 (%)                            |
| **Nasal discomfort** | 28 (3.2)                               | 16 (1.8) |
| **Headache**         | 27 (3.1)                               | 11 (1.2) |
| **Epistaxis**        | 26 (2.9)                               | 24 (2.7) |

* Nasal discomfort includes both nasal discomfort and instillation site discomfort.
The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of safe and effective noncorticosteroid treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, each patient should be titrated to the lowest dose that effectively controls his/her symptoms. The potential for ZETONNA Nasal Aerosol to cause growth suppression in susceptible patients or when given at higher than recommended dosages cannot be ruled out.

8.5 Geriatric Use
Clinical trials of ZETONNA Nasal Aerosol did not include sufficient numbers of patients age 65 and over to determine whether they responded differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSE
Chronic overdosage may result in signs or symptoms of hypercorticism [see Warnings and Precautions (5.5)]. There are no data on the effects of acute or chronic overdosage with ZETONNA Nasal Aerosol.

16 STORAGE
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temp]. For optimal results, canister should be at room temperature when used.

CONTENTS UNDER PRESSURE
Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 49°C (120°F) may cause bursting. Never throw canister into fire or incinerator.

Keep out of reach of children. Avoid spraying in eyes or directly onto the nasal septum.
ZETONNA Nasal Aerosol 37 mcg, 60 metered actuations; net fill weight 6.1 g.
NDC Number 63402-737-60

SUNOVION
Manufactured for:
Sunovion Pharmaceuticals Inc.
Marlborough, MA 01752 USA
Made in the United Kingdom

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PATHOLOGY CLINIC

Continued from page 18

Figure 2. A: Biocollagenolytic necrosis has a dark-blue granular appearance in a geographic arrangement. Note a vessel with sclerosis in the middle of the field. B: The blue granular collagen destruction yields a very characteristic appearance for Wegener granulomatosis.

A smudgy, dirty, basophilic, ischemic or geographic type of biocollagenolytic necrosis, in which the stromal collagen is destroyed, is quite characteristic (figure 2). Surface ulceration is nonspecific. Granulomatous inflammation is often limited and difficult to find. There are often isolated multinucleated giant cells (figure 1) and occasional epithelioid histiocytes, but well-formed granulomas are not seen. The background inflammation is composed of lymphocytes, histiocytes, neutrophils, eosinophils, and plasma cells.

Histologically, the diagnosis of WG is often one of exclusion. The pathologist must ensure that infections (fungal, mycobacterial, bacterial, viral, and parasitic), cocaine abuse, lymphoma, and Churg-Strauss syndrome, among others, have been ruled out by special studies or clinical evaluation.

Suggested reading