Mometasone Furoate Nasal Spray for the Treatment of Nasal Polyposis

Nasal polyposis is a chronic inflammatory disease of the nasal and paranasal sinus mucosa that occurs in up to 4% of the general population and a much higher proportion of patients with conditions such as aspirin intolerance, asthma or cystic fibrosis. The exact cause and underlying mechanisms of nasal polyposis are not well understood, but chronic inflammation is a major factor, as indicated by the increased presence of inflammatory cells, such as eosinophils, in the nasal polyps. The symptoms of nasal polyposis, especially congestion/obstruction and loss of sense of smell, can have a substantial impact on the quality of life (QoL) of patients. Currently, intranasal corticosteroids, including mometasone furoate, are the recommended first-line treatment for mild to moderate nasal polyposis. The benefit of mometasone furoate nasal spray (MFNS) in polyposis has been verified by three large phase III studies, which included almost 1,000 patients. Improvements were seen in all parameters in relation to the disease.

Aetiological Factors and Epidemiology
Nasal polyposis is often associated with chronic rhinosinusitis (CRS). In the recent European Position Paper on Rhinosinusitis and Nasal Polyps, nasal polyposis is considered to be a subgroup of CRS. The aetiology of nasal polyposis remains unclear; however, there is a clear association with systemic diseases such as asthma and cystic fibrosis, as well as with intolerance to aspirin. The reported prevalence of nasal polyposis ranges from 2.1 to 4.3% of the general population in European countries. Nasal polyposis usually develops in adulthood and its incidence increases with age; it also occurs more frequently in males than in females. Nasal polyposis is rare in children unless associated with cystic fibrosis, which is a disease dominated by neutrophil infiltration.

Treatment of Nasal Polyposis
The objectives of the management of nasal polyposis are anti-inflammatory – i.e. to reduce or eliminate polyps – open the nasal airway, improve or restore the sense of smell, prevent polyp recurrence and improve patient QoL. Regular treatment with intranasal corticosteroids is traditionally considered the medical therapy of choice in mild or moderate nasal polyposis, with surgery reserved for more severe cases. The cell infiltration with eosinophils, neutrophils and T cells indicates the necessity of anti-inflammatory treatment of changes in the adjacent nasal mucosa in combination with surgery.

Guidelines on the management of nasal polyposis recommend that surgery to remove nasal polyps should be undertaken only in patients with very large polyps or in those who have failed to respond to corticosteroid therapy. However, the evidence for this is minute and studies with early surgical intervention are lacking. The addition of endoscopic nasal surgery to a combination of oral and nasal corticosteroid treatment has a clear-cut effect on nasal polyp size, but a limited effect on perceived nasal obstruction and other symptoms. Moreover, polyp recurrence rates after endoscopic sinus surgery can be as high as 60%, especially in asthmatic patients or those with aspirin intolerance. Therefore, it may be more appropriate to consider surgery as an anti-inflammatory treatment in these cases.

Mometasone Furoate Nasal Spray
Currently, no definite cure for nasal polyposis is available, but local corticosteroids are recommended as a basic symptomatic treatment. By reducing inflammation they may reduce polyp size, prevent new polyp formation and delay – or potentially prevent – the need for surgery, although most patients with nasal polyposis may eventually require surgery. Mometasone furoate nasal spray (MFNS) (Nasonex®; Schering-Plough Corporation) is a potent intranasal synthetic corticosteroid that is approved for the treatment of nasal polyps in 15 European countries and in the US. It is indicated for treatment in patients aged 18 years and older. The usual recommended starting dose of MFNS for nasal polyposis in many countries is a once-daily dose (QD) of 200µg that may be increased to twice-daily (BID) if symptoms are inadequately controlled after five to six weeks.

Other indications include prophylaxis and treatment of allergic rhinitis, treatment of non-allergic rhinitis and acute rhinosinusitis in adults.

Clinical Studies with Mometasone Furoate Nasal Spray
The efficacy and safety of MFNS for the treatment of nasal polyps in subjects aged 18 years and older have been demonstrated in phase III clinical studies of four months’ duration. A total of 962 patients with bilateral nasal polyps and clinically significant congestion/obstruction were included for treatment in three studies. Two of the studies were similar large-scale, multicentre, randomised, double-blind, placebo-controlled studies involving a total of 664 adults. Subjects were randomly assigned in a 1:1:1 ratio to treatment with MFNS 200µg QD, MFNS 200µg BID or placebo. The third trial, conducted at 12 centres in four Nordic countries (Denmark, Finland, Norway, Sweden), included 298 subjects randomly assigned to receive either MFNS 200µg or placebo.
Effect on Polyp Size

Manifestation of disease may range from no visible polyps to complete airway blockage in the most severe cases. The size and extent of the polyps in each nostril were graded from 0 (no polyps) to 3 (large polyps), a total score of 0–6 points. MFNS is effective in reducing nasal-polyp size and extent. After four months, the reduction in bilateral-polyp grade was significantly greater with MFNS compared with placebo (p<0.05). This change represents a clinical reduction of approximately 30% relative to the baseline score. Given that reducing nasal-polyp size is generally thought to be a slow process, this degree of improvement in four months is notable.

In the Nordic study, a statistically significantly greater proportion of subjects receiving MFNS 200µg QD than those receiving placebo experienced an improvement (reduction of ≥1 point) from baseline to end-point in polyp size: 41.4 versus 26.6%, respectively (p=0.003).

Effect on Congestion/Obstruction

MFNS is effective at reducing congestion/obstruction in patients with nasal polyposis. Congestion/obstruction was scored on a scale of 0 (none) to 3 (severe). Subjects taking part in these studies had to have clinically significant congestion/obstruction (score ≥2) at baseline. It was found that the level of congestion/obstruction was significantly reduced during the first month of treatment with MFNS 200µg QD or BID compared with placebo and that the congestion/obstruction score continued to decrease over the four-month treatment period.

The Nordic study showed that a significantly greater proportion of MFNS subjects (74.3%) than placebo subjects (46.8%; p<0.001) had an improvement in investigator-assessed congestion score (reduction of ≥1 point) from baseline to end-point.

Effect on Other Symptoms

MFNS treatment in subjects with nasal polyposis resulted in significant improvements in secondary end-points, including the loss of sense of smell, anterior rhinorrhea and post-nasal drip. Subjects taking part in these studies had to have clinically significant congestion/obstruction (score ≥2) at baseline. It was found that MFNS produced significantly greater improvements in subject-assessed symptom scores for these three symptom variables compared with placebo over the first month. Moreover, these benefits were sustained over the four-month treatment period, except for one study where the improvement of loss of smell was not significant after the first month of treatment.

Investigator-assessed scores for sense of smell and rhinorrhea in the Nordic study were improved in significantly more MFNS-treated subjects than in placebo subjects.

Impairment or loss of smell (anosmia), occurring in more than 75% of subjects, is one of the most prominent symptoms and is a key factor in the differential diagnosis of nasal polyposis. An earlier study comparing medical (combined systemic and intranasal corticosteroids) and surgical treatment found that surgery had little additional effect on sense of smell over a follow-up period of 12 months after pre-treatment with a combination of oral and local steroids. This underlines the importance of the findings that MFNS can relieve symptoms of nasal polyposis, especially sense of smell, which is a major symptom that affects patients’ wellbeing.

Effect on Peak Nasal Inspiratory Flow

Improvements in subjective symptom scores with MFNS therapy in subjects with nasal polyposis were accompanied by increased nasal air flow as measured objectively using a peak nasal inspiratory flow (PNIF) meter. The increase in PNIF was significantly greater in comparison with placebo after one month of MFNS treatment and all subsequent time intervals. The effect of MFNS on PNIF may be dose-related, as subjects receiving MFNS 200µg BID had significantly greater improvements in PNIF than subjects receiving MFNS 200µg QD.

The exact cause and underlying mechanisms of nasal polyposis are not well understood, but chronic inflammation is a major factor.

These findings support previous studies showing significant increases in PNIF in patients with nasal polyposis during treatment with intranasal corticosteroids.

Effect on Quality of Life

Studies have shown that nasal polyposis causes greater impairment of QoL than perennial allergic rhinitis (p<0.05), which may be a consequence of the greater nasal obstruction and anosmia caused by nasal polyposis. Sleep impairment may contribute to the reduced QoL reported by individuals with nasal polyposis. In a recent study conducted in France, the risk of sleep disturbance more than doubled in patients with nasal polyposis compared with a control group without nasal polyposis.

QoL has been evaluated in the Nordic study. The results showed that significantly more MFNS-treated subjects than placebo recipients had improvements (defined as a change of ≥1 point in score) in breathing (p=0.001), sleep disturbances (p=0.001) and daily activities (p=0.003). Further research of the effects of MFNS on QoL in subjects with nasal polyposis, using validated generic and disease-specific QoL instruments, is needed.

Safety of Mometasone Furoate Nasal Spray

MFNS has been shown to be well tolerated and to have no effects on the hypothalamic-pituitary-adrenal axis in either children or adults. The clinical impact of systemic exposure to corticosteroids with inhaled agents is a concern, especially the potential negative effect on growth in children. Agents with low systemic bioavailability show a low correlation with a negative impact on growth. Studies have established that mometasone furoate has a very low systemic bioavailability, even when a high-dose regimen is used, and thus is not likely to produce adverse systemic effects.

Clinical data show MFNS to be safe and well tolerated in subjects with nasal polyposis. The overall incidence of adverse events with MFNS was comparable to that seen in subjects receiving placebo and similar to the incidence observed in studies of MFNS in subjects with allergic rhinitis. The most common treatment-related adverse events seen in the studies of MFNS in subjects with nasal polyposis were epistaxis and...
headache, where epistaxis was defined to include a wide range of bleeding episodes from frank bleeding to bloody nasal discharge to flecks of blood in the mucus.16–18 A higher incidence of epistaxis was seen in the MFNS 200µg BID group (12 and 15%).16,17

Costs
Intranasal corticosteroids such as MFNS effectively reduce polyp size and alleviate symptoms and, therefore, can be used to reduce the substantial costs associated with surgical treatment of polyposis.

Effective management of nasal polyposis may reduce the burden of the disease.

Important cost drivers in polyposis therapy include diagnostic procedures such as computed tomography scans, surgical procedures, biopsy of polyps, facility costs (for surgical procedures) and pharmacotherapy. A recent study estimated that the cost burden of CRS (including nasal polyposis) was US$1,539 per patient per year.30 Nasal polyposis may account for a large element of these costs due to high healthcare utilisation and disease recurrence. Moreover, surgical procedures account for a far higher percentage of the costs of treating nasal polyposis than pharmacotherapy.31 Importantly, the use of nasal corticosteroids may postpone or delay the need for surgery,3,7,16 although this needs to be further examined in long-term studies.

A retrospective cohort study of a database with 2,652 patients found that those who had surgery (n=999) incurred significantly greater nasal-polyposis-related treatment costs (including procedures and pharmaceuticals) than patients who were treated with pharmaceuticals only (n=1,653). Total treatment costs were US$7,779 for the surgery group and US$1,069 for the non-surgery group (p<0.0001).31

Conclusion
The symptoms of nasal polyposis – especially congestion/obstruction and loss of sense of smell – can have a considerable impact on the wellbeing of patients by reducing their QoL. Effective management of nasal polyposis may reduce the burden of the disease both in terms of its impact on patients and the economic costs associated with its diagnosis and treatment.

Intranasal corticosteroids are the recommended first-line treatment for mild to moderate nasal polyposis. MFNS is the only QD corticosteroid nasal spray approved for the treatment of nasal polyposis in the EU. Clinical studies have demonstrated the efficacy and safety of MFNS for the treatment of nasal polyposis in adults aged 18 years or older. MFNS treatment results in a significant reduction in polyp size and extent, in addition to a significant and sustained reduction in congestion/obstruction, with improvements seen during the first month of treatment. The effect was also good in all parameters, including sense of smell. The present experience shows that treatment with MFNS reduces the overall burden of nasal polyposis for the patient with a favourable safety profile. ■

Acknowledgements
This article was supported by TFS Trial Form Support, Sweden and Schering-Plough AB, Sweden.

33. Krouse J, Nackerl R, Friedman HS, Patterns of care and associated costs for treating patients with nasal polyps, poster presented at European Academy of Allergology and Clinical Immunology, Vienna, Austria, 10-16 June 2006.