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REVIEW ARTICLE

Novel Treatments for Chronic Rhinosinusitis

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ABSTRACT

As we move into the era of personalized medicine, there has been considerable progress made toward an increasingly sophisticated understanding of chronic rhinosinusitis. Precise understanding of the pathophysiology and natural history of the disease has unlocked a novel range of therapeutic options, both medical and surgical. This literature review aims to appraise some of these developments, including the utility of monoclonal antibodies, office based procedures such as balloon sinuplasty and steroid-eluting stents, and adjuncts to surgery such as image guidance. In reviewing the evidence for these novel interventions we aim to provide an insight to the tools which may become commonplace in the arsenal of the rhinologist of the future.

Keywords: Chronic rhinosinusitis, Monoclonal antibodies, Nasal polyposis, Robotic surgery, Sinus.

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BACKGROUND

Chronic rhinosinusitis (CRS) remains a disease of many contradictions: a common disease, yet one which is frequently underrecognized,[1] which causes considerable morbidity, but thankfully low mortality; a disease where we spend considerable time emphasizing on the importance of compliance with pharmacotherapy to patients and in the next breath counsel them on the benefits of surgery. As we move into the era of personalized medicine, there has been considerable progress made toward resolving some of these contradictions with an increasingly sophisticated understanding of the pathophysiology of the disease and its natural history. This has unlocked a range of therapeutic options, both medical and surgical. This literature review aims to appraise some of these novel interventions, which may form part of the rhinologist's arsenal of the future.

NOVEL MEDICAL TREATMENTS

The publication of the European Position Paper on Rhinosinusitis and Nasal polyps[2] has proven to be a touchstone for guidance of primary and specialist physicians in treatment of CRS, and has been cited by nearly 2,000 authors. By providing a clear clinical definition for CRS with and without nasal polyps (CRS with polyposis, CRSwNP; and without, CRSsNP), it has provided a reference guide both for treatment of individual patients and also a useful definition for research purposes. However, as identified in EPOS, the clinical phenotypes of CRS do not represent the underlying pathophysiological drivers of the development and maintenance of disease. There has been much recent interest in the concept of endotypes that are defined by precise pathophysiological mechanisms,[3] providing not only a more accurate picture of the cause of disease, but also unlocking potential therapeutic targets.

Recent literature reports have seen particular focus on the role of the T-cell in CRS, and, in particular, the differential weighting of a T helper (Th)1- or Th2-type response.[4] Skewing toward a Th2-type response is associated with development of nasal polyposis, characteized by production of cytokines including interleukin (IL)-4 and IL-5, eosinophilic infiltration, and production of immunoglobulin E (IgE).[5] In Caucasians with nasal polyps, Th2-type inflammation occurs independently of allergy[6] and mooted triggers for activation include superantigen production by pathogens, such as *Staphylococcus aureus*,[7] and mast cell activation secondary to defective tight junctions of the nasal epithelium.[8] While further investigations of these potential trigger events are ongoing, novel therapeutic interventions may target downstream products of the Th2-inflammatory cascade to downregulate inflammation. These include monoclonal antibodies that bind to the IL-4 (dupilumab), IL-5 (mepolizumab), and IgE receptors (omalizumab). Proofs of concept trials utilizing these agents have yielded positive results. A recently published trial compared groups randomized to either dupilumab plus mometasone or placebo plus mometasone; the dupilumab group demonstrated superior outcomes in reduction of polyp size, sinonasal outcome test (SNOT)-22 score, and smell as measured by the smell identification test.[9] In addition, patients with asthma treated with dupilumab had a significant improvement in their subjective asthma control and forced expiratory volume in 1 minute. Similarly, patients treated with omalizumab demonstrated significant reductions in polyp size, quality-of-life scores, and asthma control compared with those treated with placebo

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alone.[10] Mepolizumab, additionally, has been shown to be superior to placebo in polyp size reduction, although interestingly there was no significant difference between the groups in subjective perception of symptoms following treatment.[11] Common adverse events noted with monoclonal antibodies include rhinopharyngitis and reaction at the injection site,[9-11] and generalizability of these findings are limited by relatively small study group sizes. Further research is required to investigate head-to-head comparisons of monoclonal agents, long-term outcomes of treatment, and the optimum dose and duration of therapy. At present, widespread clinical use of monoclonal antibodies is limited by the significant associated cost—a 12-month course of omalizumab may cost from £1665 to £26,640 depending on the dosage required,[12] and limited availability of suitable biomarkers to guide patient selection. In future, it is likely that biomarkers will be able to identify those patients likely to have a chronic relapsing course, and allow this selected group to receive the most appropriate monoclonal antibody, tailored to their specific endotype, prior to the patient undergoing repeated surgical interventions.

This pattern of inflammation in CRSwNP has been reasonably well established in the Caucasian population, with 80% of patients expressing a Th2-dominant profile, but it seems that other cell types may predominate in non-Caucasian racial backgrounds. For example, studies of populations from central China reveal a skew toward Th17-dominant response and neutrophilic predominance.[6] Cytokines derived from innate lymphoid cells, such as IL-25 and IL-33 have also been demonstrated to play a significant role in the pathogenesis of CRSwNP in Asian populations and, as such, a potential therapeutic target.[13] Indeed, animal models using anti-IL-25 have demonstrated promising results in reduction of nasal polyp burden[14] with the promise of phase 3 trials reporting in the near future.

The role of immunomodulators in CRS has also been investigated, with recent attention paid to the role of vitamin D3 and its mooted influences upon upregulation of dendritic cells and promotion of fibroblast growth factors.[15] A systematic review of vitamin D3 levels found significantly lower levels in patients with CRSwNP, although interestingly there was no difference between controls and those with CRSsNP.[16] Clinically, there are no studies of vitamin D supplementation specifically directed to the treatment of nasal polyposis. Looking to the field of respiratory medicine, there is some evidence that suggests promise—supplementation has been associated with a reduction in upper respiratory tract infections[17] and in asthma exacerbations[18]—and this may lead the way for similar interventions for CRS. As yet, however, there are no large-scale trials examining the utility of this potential therapeutic intervention.

In contrast to the reasonably well-outlined model of inflammation of CRSwNP, there appears only a modest skew toward Th1-driven inflammation in CRSsNP.[19] A study using flow cytometry to identify T-cell subtypes found a heterogenous population of Th1, Th17, and Th2 in patients with CRSsNP with only limited differences in subtype predominance compared with a control population.[20] These findings have led to the hypothesis that CRSsNP represents a fibrotic process rather than an inflammatory one, typified by the finding of upregulation of transforming growth factor-beta production and stimulation of collagen deposition in the extracellular matrix of the nasal mucosa. As yet, there are no therapeutic agents capable of reversing this remodeling process, and patients with CRSsNP remain reliant upon the more traditional forms of treatment, such as corticosteroids—although, as discussed later, there may be new avenues for treatment by novel delivery methods for these traditional agents.

Novel Office-based Procedures

Globally, there is a trend toward patient and provider preference for health care to be provided in ambulatory settings, utilizing minimally invasive interventions that require little or no inpatient stay. Sinus disease lends itself ideally to this type of care, as virtually the whole of the paranasal sinus complex can be visualized transnasally with an endoscope and topical anesthetic for patient comfort. Several new technologies have been developed to take advantage of this, and the choice of options includes devices that may remove hyperplastic mucosa, dilate natural ostia, or deliver medications in high concentrations to the required regions.

Balloon sinuplasty (BSP) is one such technology that has exploded in popularity over the last decade: One survey of providers in the United States discovered a 3.7% annual increase in total number of sinus procedures between 2000 and 2014—a phenomenon due solely to balloon procedures, which increased by 58% in contrast to a 3.1% decrease in nonballoon procedures.[21] The principle of BSP is a minimally invasive approach to sinus obstruction, dilating the natural ostia without removal of mucosa or bone. This permits BSP to be performed for patients with CRS in the clinic setting under local anesthesia or light sedation. Patient satisfaction is reported to be equitable between BSP and traditional endoscopic sinus surgery (ESS), and short-term clinical outcomes are comparable in reduction of SNOT-22, acute infections, and medication usage[22-24] in a selective cohort of CRS

patients with limited disease. Longer term follow-up data beyond 2 years are somewhat lacking, with one study suggesting an increased revision rate for BSP at 5 years compared with ESS.[24] Certainly, BSP holds appeal for patients and physicians alike, and with reimbursement rates estimated to be ten times higher for BSP than ESS,[21] it certainly seems a treatment modality that will continue to increase in popularity in the future. On a similar theme to balloon dilation, other devices are being developed to enlarge the sinus ostia in an office-based setting. For example, a simple mechanical device can be deployed to dilate the maxillary or frontal sinus ostia in much the same manner as BSP, but utilizing osmotic forces to expand gradually over a period of 1 hour. This has been demonstrated to be well tolerated, suitable for use in the outpatient clinic, and with short-term outcomes comparable with BSP,[25,26] but has seen limited adoption so far compared with BSP procedures.

One obvious limitation to the use of BSP is the patient with polyp disease. The use of powered instruments, such as a microdebrider is almost well established, but largely restricted to the operating theatre. The development of a single-use, disposable, vacuum-powered microdebrider has enabled the technology to be adapted to the outpatient clinic setting for polypectomy under local anesthesia. Feasibility studies have demonstrated that it is a safe, effective technology that is acceptable to both patients and surgeons.[25] Certainly, the device has appeal for patients either unfit or unwilling for polypectomy under a general anesthetic. Further evaluation of the technology with direct comparison of outcomes and cost-effectiveness of office polypectomy with the gold standard of endoscopic surgery with adjuvant polypectomy is required before conclusions about its generalizable appeal can be made.

Stenting of the sinuses is a well-established technique, particularly in the frontal sinuses, but a range of innovative devices have become available, which offer benefits beyond traditional materials. These can be used as an adjunct to ESS or independently. Recent stent designs have been promoted specifically for the delivery of topical corticosteroids, and although primarily designed as an adjunct to ESS may also be used in the office setting. Most often, these stents are designed from bioabsorbable polymers similar to suture material, impregnated with corticosteroids, such as dexamethasone or mometasone furoate, and placed into the ethmoid recess after ESS. Animal models have demonstrated the ability of these stents to deliver slow-release steroids over a 30-day period.[27] Clinical trials have demonstrated that placement of drug-eluting stents is safe, and meta-analysis of outcomes of drug-eluting stent placement after ESS has suggested a beneficial effect in reduction of inflammation, adhesions, and the need for postoperative interventions. In addition, several small case series have investigated the use of drug-eluting stents in patients with recurrence of nasal polyposis after previous ESS. Placement of the drug-eluting stent may be performed under local anesthesia in the outpatient clinic, and a significant reduction in polyp size has been noted at 1 month and sustained at 6 months.[28-30] The cost of drug-eluting stents is approximately $1500, posing a significant restriction in their immediate widespread adoption when compared with the cheaper topical corticosteroids delivered via drops or spray. However, long-term data interrogating their long-term impact on revision surgery and medication usage are required before conclusions can be drawn on their cost-effectiveness.

Novel Surgical Procedures

When Harold Hopkins pioneered the development of rod–lens endoscopes in 1959, he brought about a paradigm shift in sinus surgery, opening a window to an unparalleled view of sinonasal anatomy. The ESS has largely taken over from open or microscope-aided techniques, accounting for over 90% of procedures.[31] Refinements of the rod–lens endoscope system have included angled lenses, permitting access to the frontal recess, skull base, and lateral views of the maxillary sinus, and the development of high-definition video capture, which free the surgeon from the endoscope eyepiece and allow high-quality recording of procedures.

The next step in sinus surgical technology appears to be techniques that layer the endoscopic image with additional information, which can aid the surgeon in orientation and navigation. One such technique that is already well established in practice is the use of "image guidance," whereby a surgeon can dynamically compare the position of either an infrared or electromagnetic pointer with a preoperative computed tomography (CT) scan. In principle, this allows the surgeon to identify proximity to critical structures that neighbor the paranasal sinuses and reduce iatrogenic injury to them. The American Academy of Otolaryngology-Head and Neck Surgery has endorsed the use of this technology as an aid for particular circumstances, such as revision surgery, extensive polypoidal disease, and for access to the frontal, posterior ethmoid, and sphenoid sinuses.[32] However, this position statement emphasizes that its use is at the discretion of the operating surgeon. This reflects the fact that while image guidance systems are gaining in popularity,[33] there is no definitive evidence to suggest that it improves outcomes or reduces the incidence of serious complications after ESS.[34] Additionally, its use is not associated with a reduction in liability from medicolegal consequences.[35] Despite this, as more health care

providers invest in hardware to support image guidance, its use is likely to increase over time and further data are likely to become available about its utility in improving outcomes after ESS. Further developments in image guidance may include the use of augmented reality to actively overlay information about proximity of critical structures onto the endoscopic image, or to issue warnings when the "antitargets" (such as the optic nerve) are at risk from imminent injury. This has been pioneered in neurosurgery,[36,37] but remains an experimental technique due to problems with cumbersome hardware, setup, and perceived inaccuracy of proximity warnings. This type of technology is critically dependent upon the quality of preoperative images, and in the future, there may be parallel developments in both high-resolution CT scans and software, which makes augmented reality as routine as the use of the endoscope in sinus surgery.

One of the original criticisms of the rod–lens endoscope was the two-dimensional (2D) image obtained compared with the binocular, three-dimensional (3D) view of the microscope. Developments in microchip technology have allowed dual optical channels to be placed in endoscopes, relaying an output in 3D, which may be viewed either through a special 3D headset or through two separate conventional 2D images. Small case series have piloted the use of 3D endoscopic views in sinus and pituitary surgery;[38,39] it appears to be a safe and feasible technology, but whether it offers genuine advantage over 2D views remains to be seen. The 3D views in head and neck surgery are already obtainable via robotic systems. The sheer bulk of currently available robot-operating arms limit their use transnasally, and their heritage as primarily abdominal/pelvic tools means there is a limited range of instruments for bony dissection. Cadaveric studies have demonstrated the feasibility of a transantral approach to the skull base via bilateral Caldwell–Luc incisions,[40] with advantages of binocular vision, stable camera views, and two-handed operating but a clear disadvantage of incision site morbidity compared with endoscopic transnasal approaches. Undoubtedly, the passage of time will see refinements in the size of the robotic camera and operating arms, and may unlock a new world of rhinologists operating remotely upon a patient's sinuses.

Although the basic principles of ESS are now well established, there continues to be debate regarding how extensive sinus surgery should be. There are significant geographical variations in the rates of surgical intervention, and the degree of variability in rates of sinus surgery is far greater than for comparable procedures, such as hip replacement or cholecystectomy.[41] Rates of frontal sinus surgery and the extent of ESS are also highly variable. One paper that examined trends in the United States between 2000 and 2009 found a substantial increase in the extent of sinus surgery performed for patients, with a 150% increase in the rate of frontal sinus procedures and a 200% increase in the number of patients in whom all four paranasal sinuses were operated upon.[42] A firm conclusion cannot be drawn about the roots of this trend, but two significant correlations were found. Firstly, the use of image guidance was associated with more extensive surgery. Secondly, surgeons with the highest annual case volumes tended to perform the most extensive surgery. Unfortunately, this study did not have access to data about the severity of disease or operative outcomes, but these findings suggest that specialist rhinologists with a high-volume ESS caseload and access to image guidance are more likely to perform more extensive surgery, although of course further data are required to validate this hypothesis.

One well-designed cohort study examined the outcomes of "full house" ESS *vs* minimally invasive sinus surgery, and found that although there was a trend toward greater postoperative improvement with more extensive surgery, this trend did not reach statistical significance.[43] A difficulty in examining outcome data in studies, such as this is the lack of randomization, with the individual surgeon deciding what extent of surgery is appropriate for each patient. The role of extended procedures, such as the Draf III frontal sinus drainage remains a controversial topic in meetings, and there is a paucity of strong evidence upon which to base decisions about extent of surgery at present. Retrospective analysis of patient outcomes suggests that patient factors, such as severe polypoidal disease, coexisting asthma, and narrow frontal ostia are more likely to be associated with failure of traditional frontal sinusotomy.[44] Based on this finding, there is the suggestion that some of these patients would be appropriate candidates to be offered Draf III at their initial surgery. Refinements of the Draf III technique have been proposed that may reduce postoperative stenosis, such as the use of allied mucosal flap grafting[45,46] or shorten operating times, such as the "outside-in" technique.[47,48] Thus, one prediction for the future direction of sinus surgery is that complex patients at high risk of disease recurrence may be offered more extensive initial surgery, performed by specialist rhinologists with high case volumes and access to image guidance. However, with evidence limited to nonrandomized, observational studies, it is likely that debates about the extent of sinus surgery are likely to entertain conference delegates for many years to come.

CONCLUSION

Chronic rhinosinusitis remains a common disease with significant associated morbidity. Exciting new avenues

for treatment are being developed, addressing both medical and surgical approaches to management, with developments expected in biomedical, pharmacological, and surgical technologies that promise improved care for the patient with sinus disease.

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