ADVANCES IN UPPER GI DISORDERS

Current Developments in the Management of Upper GI Disorders

Section Editor: Colin W. Howden, MD

Novel Pharmacologic Approaches to Eosinophilic Esophagitis

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G&H Could you provide a brief overview of the currently available and approved pharmacologic treatments for eosinophilic esophagitis?

ES Current treatments for eosinophilic esophagitis (EoE) include diet, which is a common and approved therapy for EoE, and proton pump inhibitors (PPIs), which are used off-label because they were never approved for this indication, and they lack well-conducted randomized controlled trials to prove their efficacy. On the other hand, there are data as well as a recently published meta-analysis showing that PPIs, when administered twice per day, are effective in approximately 60% of cases in terms of clinical remission and in approximately 50% of cases in terms of histologic remission (ie, the main and more important therapeutic target in EoE management). Other than diet and PPIs, topical corticosteroid budesonide—the oral suspension (Eohilia, Takeda) in the United States and the orodispersible tablet (Jorveza, Dr. Falk Pharma UK) in Europe and Canada—may be used. The topical corticosteroid formulations differ in terms of degree of efficacy, both for clinical and histologic remission. Of course, a comparison between these two drugs is impossible owing to the differences in phase 3 study designs and outcomes. However, Jorveza seems to be more effective. Jorveza reached a very high rate of clinical and endoscopic remission, approximately 85% to 90%, and this is what is seen in clinical practice and real-world studies. Finally, in 2022, the first biologic drug, dupilumab (Dupixent, Sanofi and Regeneron Pharmaceuticals), was approved for EoE treatment. This monoclonal antibody acts against the typical EoE-related inflammatory response by downregulating the activity of interleukin (IL)-4 and IL-13, both of them playing a crucial role in every T helper type 2 (Th-2)–mediated disease. Indeed, dupilumab has been approved for multiple Th-2 indications, such as prurigo nodularis, nasal polyposis, asthma, atopic dermatitis, and chronic obstructive pulmonary disease, and when its development and positioning are completed, it will have more than 10 different indications. In parallel to diet and pharmacologic treatment, dilatation may be performed to manage fibrostenotic complications of the disease (strictures and narrowing esophagus).

Other drugs (eg, sialic acid-binding Ig-like lectin 8, benralizumab, and mepolizumab) have been tested in the last few years, but their development was stopped because they failed to prove clinical efficacy. Indeed, these drugs were very effective in decreasing the targeted cells (eg, mast cells and eosinophils), but they did not achieve clinical response, which is the reduction of dysphagia.

G&H What is the evidence supporting the recently approved and emerging swallowed topical corticosteroid preparations?

ES There is enough evidence, including well-designed phase 3 randomized controlled trials, to prove the efficacy of swallowed topical corticosteroids in clinical practice. Of note, usually low doses of corticosteroids are used, and because they act topically, not systemically, the probability of having side effects is quite rare, so patients can be treated safely and efficaciously in the short and mid-term (up to 3 years for orodispersible budesonide). What is lacking is data on their long-term safety. For US-based providers, I want to emphasize the recently US Food and Drug Administration (FDA)–approved budesonide oral suspension Eohilia, which has been shown to be both effective and safe for treating EoE patients. For physicians, it is nice to have different options for patients.

G&H Could bioadhesive agents improve pharmacologic therapy for EoE?

ES A recently published clinical trial by Lucendo and col-

leagues evaluated a different way of delivering the active principle of mometasone furoate into the esophagus. Use of a mucoadhesive device loaded with the drug was found to be superior to placebo in terms of endoscopic and histologic remission, without observing a clear difference in terms of clinical remission. Moreover, the drug was safe and well tolerated. This novel mode of delivery may represent the next step of delivering new drugs to the esophageal mucosa. Indeed, the future use of mucoadhesive devices may prolong the adhesiveness of any drug to the mucosal surface, making the compound much more effective after its administration. This is probably one of the key reasons why many drugs failed in achieving clinical and histologic response.

G&H What are the mechanisms of action of biologic agents that are being tested in EoE?

ES The 3 main cytokines involved in the pathogenesis of EoE are IL-4, IL-5, and IL-13. The biologic agents that have been tested so far, with only one approved (eg, dupilumab) act against 1 or 2 of these 3 cytokines. Benralizumab and mepolizumab, two anti–IL-5 drugs, failed to achieve the clinical endpoint, although they obtained histologic remission. On the other hand, the drug tested against IL-13, cendakimab, in a very recent phase 3 study was found to be effective in achieving the two co-primary clinical and histologic endpoints. However, surprisingly and unclearly its development has been discontinued by the manufacturer Bristol Myers Squibb.

Currently, there are other drugs with different mechanisms of action being tested in randomized placebo-controlled studies. One of the more promising acts against the thymic stromal lymphopoietin (TSLP). An ongoing phase 3 randomized controlled trial is evaluating tezepelumab (Tezspire, AstraZeneca) in EoE (CROSSING, NCT05583227). This anti-TSLP treatment is already approved for use in patients with severe asthma in both the United States and Europe. My colleagues and I at the Azienda Ospedale Università Padova were part of this phase 3 trial. We enrolled many patients with EoE, and the impression was quite good. AstraZeneca has reported that the primary aim was achieved in other Th-2 conditions treated with tezepelumab, and other companies are developing drugs with similar mechanisms of action.

G&H Which therapeutic targets are showing the most promise in EoE?

ES As mentioned, it has been shown that biologics acting only against IL-5 are not effective. On the other hand, recent phase 2 and phase 3 studies have proven that targeting IL-4 and IL-13, or only IL-13, is effective. However, when one compares the efficacy of dupilumab, which acts against IL-4 and IL-13, with that of cendakimab, which acts only against IL-13, it is clear that acting on both cytokines seems to provide greater results.

G&H What other therapeutic pathways are being explored?

ES In addition to TSLP, there are other cytokines involved in EoE pathogenesis that are targets of novel treatments. For instance, barzolvolimab (CDX-0159), a humanized antibody that inhibits KIT activation, is being evaluated in a phase 2 study. Furthermore, CALY-002, a monoclonal antibody that neutralizes with equally high potency free and IL-15α–complexed IL-15, has been shown to reverse esophageal inflammation—eosinophilia and morphologic tissue damage. Etrasimod, a sphingosine-1-phosphate receptor modulator that works by trapping immune cells in lymph nodes, was studied as a treatment for EoE in a double-blind, placebo-controlled, randomized, phase 2 trial (VOYAGE), where the drug led to sustained histologic and endoscopic improvements in EoE over 52 weeks, and symptom improvement. However, it is quite early to say whether one of these drugs will enter into the market as effective treatment for EoE.

G&H What are the advantages and disadvantages of these novel pharmacologic approaches for EoE compared with other commonly used drugs (eg, PPIs)?

ES PPIs are able to induce clinical and histologic remission in approximately half of the EoE population, but their mechanism of action has not been fully elucidated. They seem to reduce the inflammatory burden owing to their anti-inflammatory effect by blocking the inflammatory signal eotaxin-3, which is responsible for calling eosinophils to the esophagus, thereby reducing their recruitment and easing symptoms. Moreover, by suppressing stomach acid, PPIs can help heal the esophageal lining, making it less permeable to allergens and other irritants that trigger the immune response. On the other hand, biologics target directly the cytokines involved in the inflammatory cascade of EoE, thus acting directly on the disease pathogenesis, which is usually the best way of treating any known disease. This goes in parallel with the fact that the safety of biologics seems very good, with very rare side effects recorded so far. As far as I know, more than 1 million people worldwide have been treated with dupilumab, and the number of adverse effects reported is very low. This is a key point in favor of the use of dupilumab and hopefully other biologics. As for the topical corticosteroids, again, they are very good drugs in terms

of inflammatory burden reduction, but similarly to PPIs they are symptomatic drugs. They do not work mechanistically, in contrast with biologics, and this may represent a limitation of such compounds. By the way, it is important to note that head-to-head trials between the different available drugs for treating EoE are lacking, and all these drugs—the biologics and topical corticosteroids—have been used for a few years (less than 5), so all the data are in the short term. It is not known whether in 10 or more years something will change.

G&H Is there a role for potassium-competitive acid blockers in EoE?

ES As mentioned, the ability of PPIs to be effective does not depend only on acid suppression and reduction of esophageal mucosa permeability. PPIs present an anti-inflammatory effect, which is likely shared by potassium-competitive acid blockers (P-CABs). Indeed, there is some evidence, mainly investigations from Japan, showing that P-CABs could be as effective as PPIs in treating EoE. The evidence of effectiveness for P-CABs is very limited, to be honest. There are only a few cohort studies with small sample size; however, the P-CABs seem to work in a similar way to PPIs, with studies reporting rates of clinical effectiveness up to 60% to 70% and histologic remission of approximately 50%.

G&H Where should the recently FDA-approved therapies fit into the EoE treatment algorithm?

ES There are no head-to-head studies on these treatments stating that one drug is working better than another one. Therefore, when positioning a drug, the prescriber has to pay attention to several factors, including efficacy, safety, patients' demographics and comorbidities, and costs. This is quite challenging in clinical practice. Nevertheless, current guidelines, such as those from the American College of Gastroenterology and from the Italian Society of Gastroenterology, suggest that the first step should be to treat the patient with a topical treatment—or a conventional treatment, as it is now called by the FDA and European Medicines Agency. This means treating the patient with a PPI or oral suspension/orodispersible tablet budesonide. If this treatment fails, then the second step is to use a biologic (ie, dupilumab). Of course, for a patient presenting with more than one Th-2 disease (eg, if a patient with EoE also has nasal polyposis, asthma, rhinitis, or atopic dermatitis), there is no reason not to use one drug for treating all the conditions, instead of using multiple drugs for each atopic condition. I strongly believe that dupilumab should be used as first-line treatment in the presence of multiple Th-2–mediated diseases requiring medical therapies.

G&H What knowledge gaps would you like to see addressed in future studies?

ES One of the big unmet needs in clinical practice for the management of EoE is the lack of a noninvasive biomarker of the disease. Without a fecal, blood, or saliva biomarker, the patient must undergo endoscopy for a diagnosis and for every follow-up—to see if the therapy is going well or to evaluate for loss of response. This is cumbersome for the patient and for the health care system because of the expense to perform upper endoscopy and sedation, and so on. Another unmet need is the lack of evidence regarding the frequency and duration of long-term follow-up with endoscopy of patients with EoE on maintenance treatment. In terms of pathogenesis, a better understanding of the cells involved in the Th-2 response of EoE is needed. Eosinophils are important and clear biomarkers of the inflammatory burden in the esophagus, but they are probably not the only actors involved in the pathogenesis of the disease. How the cells interact in order to induce the symptomatology that cannot be cured by current therapies needs to be investigated. The rising prevalence of EoE in the United States and worldwide is another topic for future studies to explore.

Disclosures

Professor Savarino has served as a speaker for AbbVie, Aboca, Abivax, Agave, AGPharma, Alfasigma, Apoteca, Biosline, CaDiGroup, Celltrion, Dr. Falk, EG Stada Group, Eli Lilly, Fenix Pharma, Galapagos, Giuliani, Johnson & Johnson, JB Pharmaceuticals, Innovamedica/Adacyte, Lionhealth, Malesci, Mayoly Biohealth, Montefarco, Novartis, Omega Pharma, Pfizer, Rafa, Reckitt Benckiser, Recordati, Sandoz, Sanofi/Regeneron, SILA, Takeda, Tillotts, and Unifarco; has served as a consultant for AbbVie, Alfasigma, Apogee, AstraZeneca, Biogen, Bristol Myers Squibb, Celltrion, Dr. Falk, Eli Lilly, Fenix Pharma, Ferring, Giuliani, Grunenthal, Johnson & Johnson, JB Pharmaceuticals, Merck & Co, Nestlè, Pfizer, PRO.MED.CS Praha a.s., Reckitt Benckiser, Recordati, Sanofi/Regeneron, SILA, Takeda, and Unifarco; and has received research support from Bonollo, Difass, Pfizer, Reckitt Benckiser, Sanofi/Regeneron, SILA, Unifarco, and Zeta Farmaceutici.

Suggested Reading

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