

ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

Section Editor: Joel E. Richter, MD

Emerging Medical Therapies for the Treatment of GERD

Jan Tack, MD, PhD
 Professor of Medicine
 Translational Research Center for
 Gastrointestinal Disorders
 Head, Department of Pathophysiology
 University of Leuven
 Head of Clinic, Department of Gastroenterology
 University Hospital Gasthuisberg
 Leuven, Belgium

G&H Could you discuss the various drugs currently available for the treatment of gastroesophageal reflux disease and what unmet needs still remain in this area?

JT The cornerstone of medical treatment for gastroesophageal reflux disease (GERD) are the proton pump inhibitors (PPIs). When these drugs first became available, there was great excitement because they offered a level of acid suppression that was unprecedented and showed extremely favorable results for the first time in GERD therapy in terms of healing esophagitis; thus, we thought that we were close to solving the problem of GERD. It took several years of intense and advanced usage of these drugs to become aware of their limitations, of which there are several smaller ones and one large one. One of the smaller limitations is that it takes time for PPIs to start working; they require several days to achieve maximum suppression of acid production, which is a disadvantage if the drugs are needed for intermittent or short-term use only when symptoms occur. (This is not a problem if they are used on a continual basis.) The second limitation is that PPIs have a short half-life, which is the window during which they work; once they are circulating in the blood, they degrade rapidly, which is why some recovery of acid secretion occurs during the course of the day. However, the biggest limitation is that PPIs do not affect

the nonacid component of reflux, so the reflux continues; the reflux is no longer acidic, or is much less acidic, but it still continues to rise up from the stomach into the esophagus. In a large percentage of patients, this is an important cause of their symptoms that persist during PPI therapy.

G&H What new PPI formulations are currently under development to overcome these limitations?

JT Several novel methods have been examined to achieve acid suppression either more rapidly or for a longer period of time. For more rapid suppression, researchers have tried adding an effervescent substance to the classic PPI formulation to produce a rapid alchemization of stomach contents, which, in turn, causes a more rapid action of the PPI with which it is co-administered. This is called an immediate-relief PPI. Mechanistic studies have shown that a faster onset of activity can be achieved; however, I have not seen any large clinical trials demonstrating that these drugs are better in daily practice. My experience with these drugs is very limited, as they are not available in Europe at this time; currently, they are being studied exclusively in the United States, though that might change in the future.

Another approach for modifying the classic PPI formulation for faster action involves blocking the proton pump via a different method. PPIs bind covalently to activated pumps; thus, when they bind the pumps, they are inactivated forever. The drug is in the blood only briefly,

and all of the pumps being produced when the drug is no longer present can still display normal activity. Another way to approach the blocking of pumps is through competitive binding of the potassium-binding site of the proton pump. There have been a number of efforts by different companies to develop a potassium competitive acid pump inhibitor. Several early-phase clinical trials have been conducted, though many of them have been stopped because of issues with liver toxicity, making it difficult to establish an effective and safe formulation. One large trial with potassium competitive acid pump blockers failed to show any benefit over frequently prescribed, gold standard PPIs, so this path has been largely abandoned.

The third option has been looking into the development of long-acting PPIs, trying to find sustained release or a formulation that remains in the blood longer upon ingestion. There has been some success in manufacturing these types of drugs, but, at least in Europe, there have been no full developments until marketing. The realization that nonacid and weakly acidic reflux also contribute to difficult-to-contain symptom patterns has hampered full-out development and enthusiasm to invest in these drugs. In Europe, they have been left on the shelf and my guess is that it is the same in the United States as well.

G&H Could you discuss any recent advances in the use of gamma-aminobutyric acid B agonists for the treatment of GERD?

JT As already discussed, GERD is the return of gastric content in the esophagus, where it causes lesions or symptoms, and PPIs and any acid-directed drugs target the acid component, but not the nonacid component that is also part of the refluxate. The most effective method of targeting the nonacid component would be to shut down the gastroesophageal junction, and there are 2 ways to accomplish this goal. One is surgery, a well-tested and well-established approach, though one that is not suitable for all patients with heartburn or GERD symptoms. The other approach would be to find a drug that would strengthen, and thereby act at, the sphincter. In the past, many efforts have been made to use drugs that increase sphincter pressure, but achieving this goal has not been very successful using the so-called prokinetic drugs. We now know that most reflux events occur when the sphincter transiently loses its tone (ie, the reflex pathway called transient lower esophageal sphincter [LES] relaxation). This is the main cause of reflux events in both healthy people and GERD patients. Several steps in this pathway involve gamma-aminobutyric acid B (GABA_B) agonists; thus, acting through a GABA_B receptor has a very strong inhibitory effect on transient LES relaxations: GABA_B agonists inhibit transient LES relaxation, thus inhibiting

the opening of the sphincter, which underlies most reflux events, whether acidic or nonacidic.

When this concept was discovered in animal research, there was (and currently still is) a GABA_B agonist called baclofen available on the market. Although baclofen is associated with several side effects, making it not very attractive for large-scale use, several proof-of-principle studies have shown that acute and longer-term use allows inhibition of acid and nonacid reflux, which are driven by transient LES relaxation. It also allows longer-term control of reflux symptoms and events (both acidic and nonacidic). Thus, it has a broader spectrum than PPIs in terms of its action. However, it does not have significant potency; it is not a very strong antireflux drug.

Nevertheless, baclofen has been the starting point for exploration of new drug developments, as several companies have been looking at GABA_B agonists with similar or better efficacy and certainly better tolerance. Several trials thus far have been promising. One drug that has been evaluated is R-baclofen from Xenoport, which has shown some efficacy as a single-drug therapy for GERD symptoms. R-baclofen has shown efficacy mainly in patients who have been on a PPI before. More data have been seen with lesogaberan, a new GABA_B agonist developed by AstraZeneca, which showed, in mechanistic studies, the ability to reduce reflux events through a decrease of transient LES relaxations in healthy volunteers and in GERD patients. A proof-of-concept study comparing a single dose of lesogaberan with placebo showed that the drug was able to provide significantly better symptom control in a group of GERD patients who were experiencing ongoing symptoms while on a PPI. Lesogaberan did not appear to have the side effects that are well known for baclofen (nausea and drowsiness, particularly at the beginning of therapy). Thus, this avenue looks promising, and both drugs are being subjected to further studies.

G&H What recent advances have been made in other drugs used to modulate LES pressure and relaxation for GERD treatment?

JT Animal research has shown that there are many other targets, receptors, and neurotransmitters that have the ability to interfere with transient LES relaxations, though many of them are not that attractive for human use. For example, opioid-receptor agonists have the ability to inhibit transient LES relaxation; however, it would not be a good idea to develop a morphine-like substance for a disease such as GERD. There are several other similar receptors that are not very suitable. One receptor that has been looked at, and appears to be very suitable, is the metabotropic glutamate receptor 5. Glutamate is an important signaling molecule in the brain and has

many receptors, either metabotropic or ionotropic. Metabotropic 5 is expressed in pathways that also mediate transient LES relaxations. There have been several proof-of-concept studies examining this drug class (at least 3, to my knowledge, from different companies). A proof-of-efficacy study showed that by taking GERD patients off PPIs one day and offering them a placebo and then the next day a metabotropic glutamate receptor antagonist (MGLuR5) compound from a Swiss company called Addex, the patients experienced much less reflux and symptoms. Data have been presented at meetings showing that this drug is able to decrease transient LES relaxations and is able to improve symptoms in patients with GERD when treated for a longer time. Thus, the proof of concept has been demonstrated that this is an efficacious class of drugs. The first published study did show some side effects of drowsiness, but it appears that a change in formulation has eliminated this side effect for the most part.

Another drug that has been studied from the same class is a Novartis drug, which underwent a short proof-of-principle study in GERD patients, and these data were recently presented at this year's International Motility Meeting in Boston, Massachusetts. These studies showed efficacy of this MGLuR5 antagonist in the same order of magnitude in terms of inhibition of transient LES relaxation and reflux events as seen with a drug such as baclofen. Thus, this drug is another active target for development. The current status of this drug and of the Addex drug (ie, whether they are moving into advanced phase II or III studies) is unclear.

Another class of drugs, a bit surprisingly, involves rimonabant, a cannabinoid type 1 receptor blocker. In healthy volunteers, this drug was able to inhibit transient LES relaxation as well as reflux events. Whether rimonabant could be a target for further drug development is unsure because, when it was used longer term and was on the market for the treatment of obesity in Europe, it was associated with higher incidences of depression. Thus, this drug may not be a viable option unless a peripherally acting agent has a similar efficacy.

Several other drug classes appear to work in animals but did not work that well when studied in humans. One example involves the 5HT₃ antagonists. Another example are the neurokinin type 1 receptor antagonists, which did appear to work in dog models but did not work in healthy volunteer trials in humans.

G&H Are there any other avenues for medical GERD treatment currently under development?

JT There are some data suggesting that GABA_B agonists and MGLuR5 antagonists also have an effect on visceral

sensitivity, though this association has to be further studied and established in humans, as it is mainly derived from animal studies. Sensitivity to the manipulations of the gastrointestinal tract may be beneficial to GERD patients, particularly those experiencing ongoing symptoms during PPI usage, as it has been suggested that they also feel nonacid or weakly acidic reflux because they are more sensitive to nonacid contents coming up in the esophagus. Thus, decreasing esophageal sensitivity may also benefit GERD patients. Several other drugs are being looked at for the ability to decrease the sensitivity of the esophagus. One of these drugs involves blockers of the TRPV1 channel, which is present in many parts of the body on nerve endings and which senses acidity and is sensitive for capsaicin, the pungent component of red pepper. We have TRPV1 receptors in our mouth, as well as in the esophagus, and it is thought that this is one of the ways that we sense upcoming acid and other noxious stimuli such as heat or distention. Blockers of this receptor have the potential to decrease sensitivity to reflux acid, but it is likely that less acidic reflux sensations could also be blocked there. This pathway is currently being looked into. However, one of the problems is that blocking this receptor causes body temperature to rise, which is a disadvantage that needs to be solved.

Other receptors that have been implicated in the sensitivity of the esophagus are tachykinins, which are a group of substances that includes substance P. In theory, blockers of tachykinins could also decrease the sensitivity of the esophagus, but this possibility has only recently been considered and requires further research. This is an important future avenue in terms of drug therapy.

5HT₄ agonists are also being examined for increasing LES pressure to prevent reflux. A number of companies with 5HT₄ agonists are looking to study them in GERD in incomplete PPI responders.

There have also been several proof-of-concept or proof-of-principle studies for motilin receptor agonists and ghrelin receptor agonists. However, for these targets, research is still in the very early stages and I do not know of any active trials being conducted except for a short proof-of-principle study in these 2 classes.

G&H Is the ultimate goal for these drugs for use as first-line therapy and as replacements for existing GERD drugs or for use as add-on therapy?

JT The aim of these drugs is to shut down the LES or gastroesophageal junction to prevent any type of reflux. If this could be effectively achieved, while preserving the normal ability to swallow, and perhaps the normal ability to belch, this would be the ideal drug for GERD. A drug

that would fulfill this goal, in theory, should be a first-line drug. In real life, however, this is unlikely to happen for several reasons. First of all, we are worried about symptoms but also about lesions. PPIs heal lesions very rapidly and very effectively, which is why they will always be a favorite in initial therapy. Second of all, PPIs have been used for so long that they are very well known. Both specialists and primary care physicians know how to use them. PPIs are also available over the counter. It would be difficult to beat PPIs as first-line drugs. These new drugs will be used in individuals who have been on, or are currently on, a PPI, and find that they are providing inadequate relief. Thus, if they become available, these drugs will find their way to the market as add-on therapy. GERD patients will still start with PPIs as first-line therapy; if the PPI helps, they will continue the PPI. If the PPI does not help sufficiently, the patients will switch and add on this second class of drugs currently under development. As for the very rare group of patients who do not tolerate PPIs, this new class of drugs could become a single-therapy option.

G&H Are any of these drugs being developed for use in children?

JT The studies that have been conducted with these new drugs under development have focused on the typical adult reflux patient, and usually the adult reflux patient who was already on a PPI, who was either doing well with the PPI but was willing to stop it for the sake of the study or who was already on a PPI and not helped well enough in terms of heartburn and regurgitation and therefore was willing to step into a study where it was added on in a controlled fashion. A single pediatric study has been conducted with baclofen, which showed that children treated with the drug appeared to have an antireflux effect, tolerated the drug well, and did not experience significant side effects.

G&H Have any of these emerging drugs been examined in nighttime GERD?

JT Several studies focusing on baclofen and the MGLuR5 antagonist showed a very strong effect at night. In some cases, it appeared that these drugs were more effective at night than during the day. It might be attractive to develop these drugs for nocturnal or early supine reflux at night to add to a PPI given in the morning (which works well in the daytime). However, no studies have specifically addressed this idea as of yet.

G&H How safe have these drugs been thus far in studies?

JT At least 1 in 5 patients will experience poor tolerance to baclofen, the parent compound, making it not very attractive as a drug. With lesogaberan, there have been several early reports of tingling feelings in the lower limbs upon the administration of the first dose, but it appears that a new dose formulation has fixed this problem. My understanding of the publications and presentations for this drug is that, currently, the tolerance is good, or appears to be acceptably good, but the number of patients treated is still low. The first study of the MGLuR5 antagonist from Addex involved a small number of patients but showed a somewhat high prevalence of central nervous system side effects in terms of drowsiness or nausea. Again, a change in formulation appears to have taken care of this problem for subsequent studies. However, a press release from the manufacturer noted some liver function abnormalities upon longer use in a fraction of patients, halting the immediate further development of the drug. I am not sure whether this will be a permanent issue for the drug, whether this will be an issue for drugs in this class, or whether this is merely a transient observation that will not be confirmed with other drugs in this class or with the same drug in this class. However, it is still early to discuss safety issues, as these drugs are still in early stages of development and the numbers of patients exposed are very limited. Having exposure to many eligible patients and a good safety record will be a prerequisite for any drug in GERD.

Suggested Reading

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