

Data on Symptom Association Analysis in Patients Undergoing Endoscopic Therapy Is Useful to Better Define a Successful Therapeutic Approach

Salvatore Tolone, MD¹, Manuele Furnari, MD², Nicola de Bortoli, MD³ and Edoardo Savarino, MD, PhD⁴

doi:10.1038/ajg.2015.323

To The Editor: We read the article by Witteman *et al.* (1) on the efficacy of EsophyX-2 Transoral Incisionless Fundoplication (TIF) in patients with gastroesophageal reflux disease (GERD). The authors randomized 60 proton pump inhibitor (PPI)-responder patients to TIF ($n=40$) vs. continuative PPI-therapy ($n=20$). Subjects underwent symptomatic clinical assessment, endoscopy, manometry, and impedance-pH monitoring off-PPI. The latter test was carried out in order to objectively prove the presence of pathological acid exposure time (AET) at baseline. Then, the same tests were repeated at 6 and 12 months after surgical and medical therapies. At 6 months follow-up, TIF significantly improved quality of life and reflux symptoms than the PPI group, whereas AET, total number of reflux events (NREs), and esophagitis relief were similar in both the groups.

This study provides interesting data on the potential use of endotherapy for symptomatic relief in GERD, even if only in the short term, but given the mild effect of this technique on AET and NREs, we believe that the interpretation of their findings would have improved if the results of symptom association analysis (SAA) before and after TIF were also reported. In fact, even if the presence of a pathological reflux was an inclusion criteria, it is unclear which and how many symptoms were associated to reflux. Actually,

impedance-pH monitoring allows to measure all kind of reflux events, thus increasing the diagnostic yield of traditional reflux monitoring (pH-metry) by using the reflux-SAA (2–4). Indeed, several recent studies have shown that GERD patients, in particular those with non-erosive reflux disease, have frequently a normal AET (2–6), but a positive SAA. Moreover, recent data suggests a role of impedance-detected SAA in predicting the outcome in GERD patients treated with medical or surgical therapy (6). Thus, providing this information may be useful to understand whether a particular group of patients should be treated with alternative surgical or endoscopic therapies, and if the benefit of this technique can be associated to a reduction of reflux-symptom association rather than to a change in AET or number of reflux episodes.

So, data concerning the SAA should be investigated and reported also pre- and post-operatively in all studies evaluating the efficacy of any anti-reflux procedure in GERD patients. This would clarify the role of SAA in determining the indication of surgical or endoscopic therapies and would help to understand its role as a parameter to define an anti-reflux successful approach.

CONFLICT OF INTEREST

Guarantor of the article: Salvatore Tolone, MD.

Specific author contributions: All authors contributed to the design of the study, writing of the manuscript, and approving the final version.

Financial support: None.

Potential competing interests: None.

REFERENCES

1. Witteman BP, Conchillo JM, Rinsma NF *et al.* Randomized controlled trial of transoral incisionless fundoplication vs. proton pump inhibitors for treatment of gastroesophageal reflux disease. *Am J Gastroenterol* 2015;110:531–42.
2. Savarino E, Zentilin P, Tutuian R *et al.* The role of non-acid reflux in NERD: lessons learned from impedance-pH monitoring in 150 patients off therapy. *Am J Gastroenterol* 2008;103:2685–93.
3. Savarino E, Zentilin P, Frazzoni M *et al.* Characteristics of gastro-esophageal reflux episodes in Barrett's esophagus, erosive esophagitis and healthy volunteers. *Neurogastroenterol Motil* 2010;22:1061–e280.

4. Ribolsi M, Savarino E, De Bortoli N *et al.* Reflux pattern and role of impedance-pH variables in predicting PPI response in patients with suspected GERD-related chronic cough. *Aliment Pharmacol Ther* 2014;40:966–73.
5. Savarino E, Zentilin P, Tutuian R *et al.* Impedance-pH reflux patterns can differentiate non-erosive reflux disease from functional heartburn patients. *J Gastroenterol* 2012;47:159–68.
6. Patel A, Sayuk GS, Gyawali CP. Parameters on esophageal pH-impedance monitoring that predict outcomes of patients with gastroesophageal reflux disease. *Clin Gastroenterol Hepatol* 2015;13:884–91.

¹Department of Surgery, Division of Surgery, Second University of Naples, Naples, Italy;

²Department of Internal Medicine, Gastroenterology Unit, University of Genoa, Genoa, Italy;

³Department of Internal Medicine, Gastroenterology Unit, University of Pisa, Pisa, Italy; ⁴Department of Surgery, Oncology and Gastroenterology, Gastroenterology Unit, University of Padua, Padua, Italy. Correspondence: Salvatore Tolone, MD, Department of Surgery, Division of Surgery, Second University of Naples, Naples 80131, Italy. E-mail: salvatore.tolone@unina2.it

Randomized Controlled Trial of Transoral Incisionless Fundoplication Vs. Proton Pump Inhibitors for Treatment of Gastroesophageal Reflux Disease

Reginald C.W. Bell, MD, FACS¹

doi:10.1038/ajg.2015.324

To the Editor: I read with great interest the paper by Witteman *et al.* (1), titled “Randomized Controlled Trial of Transoral Incisionless Fundoplication Vs. Proton Pump Inhibitors for Treatment of Gastroesophageal Reflux Disease”, published in the April 2015 issue of the *American Journal of Gastroenterology*. In the paper, the authors report results from what appears to be a

single-center, unblinded, European randomized trial evaluating the performance of endoscopic fundoplication compared with proton pump inhibitors (PPIs). At 6-month follow-up, transoral incisionless fundoplication (TIF) improved gastroesophageal reflux disease (GERD) symptoms significantly better than PPIs ($P<0.001$), with similar improvement in distal esophageal acid exposure (EAE). However, at 12-month follow-up, and despite improved symptoms and quality of life in the TIF group, no improvement in EAE compared with baseline was found ($P=0.171$), and 61% of TIF patients resumed PPI therapy. The authors concluded that endoscopic fundoplication provided a short-term improvement; however, no long-term reflux control was achieved, and therefore the study was terminated.

As a surgeon who has participated in three separate clinical trials, including the most-recent double-blind, randomized sham-controlled trial, and performed over 200 TIF procedures, I would appreciate the opportunity to offer commentary both on the study design and the reported results.

The study by Wittman *et al.* (1) was designed back in 2008 to evaluate the first iteration of the TIF procedure (ELF—gastrogastric fundoplication (clinicaltrials.gov, record first received 09 March 2009, last updated 17 April 2009; accessed 27 April 2015). The study enrolled patients from 2008 to 2011. It is worth pointing out that the TIF procedure has evolved over time. It is well documented that improvements in the TIF technique were made, culminating in the July 2011 publication (2). In that report, the authors reported the addition of the rotational component to the TIF procedure, designed to improve objective outcomes, in particular pH normalization. From the current report, it is unclear whether patients were treated with the ELF procedure or with the advanced TIF technique (esophagogastric fundoplication).

The most glaring difference between the current study and other recent reports on the TIF procedure is the discordance between GERD-HRQL quality of life scores off PPIs and resumption of PPI

use between 6 and 12 months. After TIF, GERD-HRQL scores improved from 27.1 (8.4) to 11.1 (9.7) at 6 months off PPI therapy and remained stable at 12 months at 10.3 (7.8) off PPI therapy (1). The number of reflux episodes was reduced at 6 months and steady between 6 and 12 months. Mean time percentage pH<4 did not change significantly. However, daily PPI use increased from 15% at 6 months to 44% at 12 months. Many other studies have shown that resumption of PPI use after an antireflux procedure is often due to other factors, including the wide availability of the medication and a tendency to resume use without clearly documenting its efficacy. For this reason, PPI resumption is the weakest indicator of success or failure of an antireflux procedure. The authors do not address this discrepancy and the likelihood that PPI use was perhaps not necessary in the majority of patients who resumed it.

Most importantly, in the study by Wittman *et al.* (1), based on 34 patients with preoperative Hill grade assessments (Baseline characteristics, Table 1), 41% of the patients in the study had grade 3 or 4 valves, configurations that suggest a larger hernia than may have been underestimated on initial endoscopy. These are patients who would not currently be offered the TIF procedure based on past TIF studies and have generally been excluded from more-recent double-blinded and open label randomized reports in the United States (3,4). The fact that 20% of patients in the study by Wittman *et al.* (1) at 6 months had a 3cm hiatal hernia clearly raises the possibility that hernia size was not accurately assessed during preoperative endoscopies. Poor patient selection likely contributed to outcomes that are not as good as the outcomes seen in more-recent randomized United States studies (3,4), which are, surprisingly, not referenced in the current Wittman article. In fact, none of the TIF papers published after 2012 are referenced in the current report.

The study introduction indicates that the TIF procedure was intended as an alternative for patients well controlled on PPIs. However, the stated end point of “treatment

success was defined by a significantly ($P<0.05$) higher number of patients with $\geq 50\%$ improvement in scores in the TIF group vs. PPI group at 6 months,” (1) indicates that patients were not well controlled on PPI use at entry. In truth, most patients seeking an antireflux procedure are not happy with their current regimen; many will be happy if their symptoms are controlled after an antireflux procedure even if they still take some antacid medication.

In addition, the number of fasteners used to repair the gastroesophageal valve has been documented to significantly impact outcomes following the TIF procedure (3). The number of fasteners used in the most-recent randomized reports has been consistently, on average, >20 with a minimum of 12 fasteners. We were intrigued with the fact that, in Wittman’s report, some procedures were completed with only 7 fasteners. The number of fasteners used to create fundoplication, in addition to poor selection criteria, may be a primary contributing factor affecting outcomes in this report.

Finally, reported pH normalization in the PPI group (63%) in the current study is higher than the most cited article reporting pH outcomes following PPI treatment (~50% while being on PPI therapy) (5). Nevertheless, the primary goal of GERD treatment is relief of symptoms and preventing complications. It appears that, in this study, TIF improved GERD symptoms without complications and introduction of *de novo* post-fundoplication side effects, commonly associated with fundoplication. The accumulated studies on TIF indicate that it is successful, with a serious procedure-related complication rate of <0.6%. This exemplary safety profile, combined with a significant body of clinical evidence, including three recently published randomized reports, led to surgeon and gastroenterologist specialty support (SAGES, AGA, ASGE, and ACG) and a co-sponsored CPT code application. Early this year, the Center for Medicare and Medicaid Services (CMS) granted TIF a category 1 CPT code—indicating the willingness of Medicare to cover the cost of the procedure beginning

in 2016. This is a safe procedure that has demonstrated benefit to chronic well-selected GERD patients in several well-designed US trials, including the most recent blinded sham-controlled trial.

CONFLICT OF INTEREST

Guarantor of the article: Reginald C.W. Bell, MD, FACS.

Specific author contributions: Reginald C.W. Bell, MD, FACS is the sole author.

Financial support: None.

Potential competing interests: Research grants from and serves on the Scientific Advisory Board of EndoGastric Solutions, Inc. (Redmond, WA). I have carried out consulting for EndoGastric Solutions, the manufacturer of the device used in the above-referenced studies. I make no apology for this relationship—it is only through working with device manufacturers that the technique can be perfected and the devices improved. I assure that any compensation received for consulting does not even begin to offset the costs of being away from my patient practice.

REFERENCES

1. Wittemen BP, Conchillo JM, Rinsma NF *et al.* Randomized controlled trial of transoral incisionless fundoplication vs. proton pump inhibitors for treatment of gastroesophageal reflux disease. *Am J Gastroenterol* 2015;110:532–42.
2. Bell RC, Cadiere GB. Transoral rotational esophagogastric fundoplication: technical, anatomical, and safety considerations. *Surg Endosc* 2011;25:2388–99.
3. Hunter JG, Kahrilas PJ, Bell RC *et al.* Efficacy of transoral fundoplication vs omeprazole for treatment of regurgitation in a randomized controlled trial. *Gastroenterology* 2015;148:324–33.
4. Trad KS, Simoni G, Barnes WE *et al.* Efficacy of transoral fundoplication for treatment of chronic gastroesophageal reflux disease incompletely controlled with high-dose proton-pump inhibitors therapy: a randomized, multicenter, open label, crossover study. *BMC Gastroenterol* 2014;6:174.
5. Milkes D, Gerson LB, Triadafilopoulos G. Complete elimination of reflux symptoms does not guarantee normalization of intraesophageal and intragastric pH in patients with gastroesophageal reflux disease (GERD). *Am J Gastroenterol* 2004;99:991–6.

¹SurgOne Foregut Institute, Englewood, Colorado, USA. Correspondence: Reginald C.W. Bell, MD, FACS, SurgOne Foregut Institute, 401 W Hampden Place Suite 230, Englewood, Colorado 80110, USA. E-mail: rbell@surgone.com

Transient and Persistent Antibodies Against TNF-Inhibitors in IBD

Casper Steenholdt, MD, PhD¹

doi:10.1038/ajg.2015.325

To the Editor: In a case series, Paul *et al.* (1) reported that neither antibodies (Abs) against adalimumab (ADL) persisting at repeat assessments over time in 4 patients, nor transiently detected anti-ADL Abs in 5 patients, had impact on clinical outcomes of ADL therapy. These findings contrast with observations regarding anti-infliximab (IFX) Abs (2–4), as well as findings presented in our recent study on anti-ADL Abs (5), that transient anti-drug Abs roughly detected in one-fourth of IBD patients treated with tumor necrosis factor (TNF) inhibitors do not appear to influence clinical outcomes as opposed to persistent anti-drug Abs which associate with diminished drug detection and treatment failure.

Transient anti-drug Abs can present as functional, drug neutralizing anti-drug Abs, or as biologically inactive anti-drug Abs circulating as immune complexes bound to the anti-TNF agent *in vivo* (3,5,6). The etiology of transiency remains to be elucidated. Transiency has been suggested to result from drug-induced immunological high-zone tolerance (2,3). This hypothesis has indirectly been supported by observations that anti-IFX Abs detected at time of IFX treatment failure were undetectable at reassessment after 12 weeks of intensified IFX regimen, both when assessed by a functional cell-based reporter gene assay and by a drug-tolerant homogeneous mobility shift-binding assay (6). Support has also come from a case series reporting that addition of conventional immunosuppressive agents at IFX treatment failure in the presence of neutralizing anti-IFX Abs was followed by eliminated anti-IFX Ab detection, restored detection of IFX, and regained clinical response over time (7). However, the hypothesis of a capacity to induce immunological tolerance to TNF-inhibitors once anti-drug Abs have developed

cannot currently be proved as this would require direct testing of Ab production by anti-TNF-challenged immune cells from patients with assumed tolerance.

Indeed, alternative explanations for anti-drug Ab transiency exist. For example, drug/anti-drug Ab-immune complexes may have been completely cleared from the circulation at time of trough re-sampling thus being undetectable but with anti-drug Abs produced continuously at subsequent anti-TNF drug administrations (2,5). This, along with a false-negative anti-drug Ab test result at time of reassessment owing to e.g., interference with drug present in the sample, will give rise to misinterpretations, as anti-drug Abs would still be produced and thus still be present in the circulation and potentially lead to efficacy and safety problems if anti-TNF therapy is continued (5). Finally, an initial false-positive anti-drug Ab testing will also be misinterpreted as transiency at subsequent negative anti-drug Ab testings (5). These methodological biases may well have influenced observations by Paul *et al.* (1) owing to the use of a drug sensitive anti-drug Ab ELISA known to yield false-positive and false-negative anti-drug Ab test results (8).

In conclusion, potential transiency complicates interpretation of the clinical relevance of anti-drug Ab test results. This can be accommodated by use of validated assays and repeated assessments during the course of treatment to monitor the temporal evolution of anti-drug Abs. Irrespectively, patients presenting with anti-TNF treatment failure in the presence of detectable anti-drug Abs and low drug levels should switch to another TNF-inhibitor to secure optimal treatment outcomes (9).

CONFLICT OF INTEREST

Guarantor of the article: Casper Steenholdt, MD, PhD.

Financial support: None.

Potential competing interests: In past 2 years, I have served as a speaker for Abbvie, Pfizer, and MSD; and as an advisory board member for Pfizer and Takeda Pharmaceuticals.

REFERENCES

1. Paul S, Dronne W, Roblin X. Kinetics of antibodies against adalimumab are not associated with poor outcomes in IBD. *Am J Gastroenterol* 2015;110:777–8.