Anti-relaxation therapy in GORD

J Tack, D Sifrim

Reducing transient LOS relaxations in patients with gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease (GORD), defined as the presence of symptoms or lesions that can be attributed to the reflux of gastric contents into the oesophagus, is one of the most common disorders affecting the gastrointestinal tract. Gastric acid is essential in the development of GORD and the duration of oesophageal acid exposure is a major determinant of the severity of reflux oesophagitis.¹ This is the reason why proton pump inhibitors, with their strong acid suppressing action, have brought relief to the majority of these patients, although most GORD patients do not have increased gastric acid secretion.²

The pathophysiology of GORD is multifactorial, including alterations in the volume, composition, or distribution of gastric contents, anatomical and/or motor dysfunction of the antireflux barrier at the gastro-oesophageal junction, impaired clearance mechanisms, and defective resistance to injury at the mucosal level. Acid suppressive therapy addresses one of the pathophysiological mechanisms—that is, gastric acid volume—without affecting others such as the non-acid component of the gastric contents or the function of the antireflux barrier. In spite of the efficacy of acid suppressive therapy, there have been many attempts to target other aspects of GORD pathophysiology, such as basal lower oesophageal sphincter (LOS) pressure, oesophageal body motility, or gastric emptying. Unfortunately, most of these approaches have been clinically disappointing.

The prerequisite for the development of acid reflux events is the occurrence of functional and/or anatomical failure of the antireflux barrier at the gastro-oesophageal junction. In healthy subjects and in patients with mild to moderate GORD, reflux occurs mainly during transient LOS relaxations (TLOSRS).^{3–7} TLOSRS are LOS relaxations not induced by swallowing, which occur mainly during the first two postprandial hours. In patients with more severe GORD and in those with a hiatal hernia, although TLOSRS account for the majority of reflux episodes, a greater proportion occurs during absent basal LOS pressure and swallow induced LOS relaxations.⁸

Transient LOS relaxations are a neural reflex, triggered mainly by distention of the proximal stomach and organised in the brain stem, with efferent and afferent pathways travelling in the vagus nerve, activating an intramural inhibitory neurone which releases nitric oxide to relax the LOS.⁹ Pharmacological intervention to reduce TLOSRS has been proposed as a non-surgical strategy to improve the antireflux barrier in patients with GORD, and several agents that inhibit the occurrence of TLOSRS were identified, including atropine, cholecystokinin_A receptor antagonists, morphine, and nitric oxide synthase inhibitors.¹⁰ However, an unfavourable pharmacological profile precluded clinical application of these agents. More recently, the gamma aminobutyric acid (GABA) receptor type B agonist baclofen was shown to inhibit TLOSRS, thereby significantly decreasing acid reflux after a meal in healthy controls.¹¹ Inhibitory GABA_B receptors are present at many levels of the vago-vagal pathway that organises TLOSRS.

In this issue of *Gut*, Zhang and colleagues¹² demonstrated that acute administration of baclofen reduced the rate of TLOSRS and reflux events by approximately 40% in a group of patients with reflux oesophagitis (see page 19). Based on these findings, the authors concluded that reduction in the rate of TLOSRS is an appropriate target in GORD. In addition, they suggest that GABA_B agonists may be useful as therapeutic agents for the management of reflux disease. As baclofen is already in use for the long term treatment of spasticity, in higher doses than used in the present study, there is a potential for clinical application in GORD in the not so distant future. However, in spite of the reduction in the number of reflux episodes, baclofen caused no significant decrease in postprandial oesophageal acid exposure in the present study. The lack of a significant effect on acid exposure is at least partly related to patient selection, as many patients had only minimal amounts of acid reflux during the placebo arm of the study. Confirmation of a clinically relevant effect of baclofen in GORD therefore awaits long term studies, with efficacy

assessment on both reflux related symptoms and prolonged pH monitoring, in patients with a high rate of TLOSRS related acid reflux events.

Although initial postprandial motility studies, performed in the right supine position, reported an increased rate of TLOSRS in patients with GORD,^{3–4} recent postprandial studies in the more physiological upright position show a similar rate of TLOSRS in healthy controls and patients with GORD.^{5–7} A more consistent finding among different studies is the higher prevalence of acid reflux during TLOSRS in patients with reflux disease. Because TLOSRS are the major mechanism of reflux, inhibition of TLOSRS has the potential to provide a substantial reduction in acid reflux events in GORD.

Acid suppressive therapy is most successful in patients with mild to moderate reflux disease with predominantly upright reflux, and less successful in patients with more severe reflux oesophagitis and patients with supine reflux.^{13–16} As TLOSRS related acid reflux is predominant in patients with mild to moderate GORD, treatment of these patients by inhibiting TLOSRS may provide an alternative to acid suppression. Furthermore, baclofen or related agents could be used as add-on therapy in GORD patients with incomplete relief by acid suppression and/or in patients with more severe GORD. In about half of patients with persisting reflux symptoms, in spite of standard proton pump inhibitor therapy, refractory acid reflux can be demonstrated which often responds to a further increase in proton pump inhibitor dose.^{15–16} In the remaining patients, symptoms may be related to ongoing non-acid reflux, for which treatment options are limited.^{17–18} As recent data suggest that TLOSRS are the principal mechanism underlying non-acidic reflux episodes as well,⁷ assessment of the therapeutic potential of baclofen or related compounds under these specific circumstances seems warranted.

The relevance of TLOSRS in the pathophysiology of GORD may be more related to what is present at the level of the cardia, at the moment of a TLOSRS, than to their frequency. Postprandial gastric acid secretion and the composition and/or distribution of the fundic contents appear to be critical variables in the development of GORD. Therefore, the most pathophysiologically oriented strategy should aim to minimise the number of “harmful” TLOSRS associated with acid reflux by both reducing the triggering of TLOSRS and modifying the composition and/or distribution of gastric fundic contents.

The paper by Zhang *et al* demonstrates that inhibition of TLOSRS with baclofen reduces the frequency of acid reflux in GORD patients. Both acid suppressive

therapy and reduction of TLOSRS address one important factor of the pathophysiology of GORD. Because the major functional abnormality in reflux disease appears to be the occurrence of acid reflux during TLOSRS, both strategies are not exclusive and may become complementary in the near future.

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Liver disease

Positive suggestions about the anti-HBc positive donor

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What to do with the anti-hepatitis B virus core antigen positive donor liver

The paper by Roque-Afonso *et al* in this issue of *Gut*¹ describes the outcome of recipients following transplantation of livers from organ donors who have detectable antibody to the hepatitis B virus (HBV) core antigen (HBc) but undetectable serum hepatitis B surface antigen (anti-HBc positive, HBsAg negative) (see page 95). Serum anti-HBc positivity simply confirms exposure to HBV. Its presence in the absence of serum HBsAg identifies the patient with resolved infection. Frequently, antibodies to HBsAg (anti-HBs) will be absent, fading in titre for many patients from the time of acute infection. Thus the patient with a past resolved HBV infection will be anti-HBc positive and HBsAg negative, and anti-HBs may or may not be present. Irrespective of the anti-HBs status of the donor, it is known

that the use of anti-HBc positive (HBsAg negative) donor livers will transmit HBV to the recipient and will establish chronic infection and graft damage.^{2–5} This is termed de novo HBV infection. Occasionally, aggressive infection with graft failure and patient death may be observed.⁶ In general, the other organs of the anti-HBc positive donor can be used with little risk of de novo infection to the recipient.² This observation suggests that potentially infectious HBV is present in the liver, but not in other organs, and that reactivation of the virus occurs following transplantation in the context of immunosuppression.

There is considerable geographic variation in the frequency of organ donor anti-HBc positivity. In the UK, reflecting a relatively low lifetime risk of exposure to HBV, donor anti-HBc positivity is

uncommon. However, de novo infection causes significant morbidity for the few unlucky recipients.⁴ In Southern Europe and Japan, the frequency is high, reflecting past exposure to HBV of a large proportion of the potential organ donor pool.^{3,7} Of consecutive organ donors used by the liver transplant surgeons at Hospital Paul Brousse, 22/315 (7%) were anti-HBc positive. Roque-Afonso *et al* from Hospital Paul Brousse present the pretransplant HBV serological status and post-transplant outcome (with or without passive immunoprophylaxis) of the 22 recipients of those anti-HBc positive liver donations. The results are nicely organised and presented in table 1 of their manuscript. Detailed analysis of the data in the table emphasises the important and accepted principles that should be applied to the use of anti-HBc positive livers.

Patient Nos 1–4 are the ideal recipients for these organs. These recipients had HBV associated liver failure as the indication for liver transplantation and required immunoprophylaxis to prevent graft reinfection by HBV. Under this circumstance, it appears that immunoprophylaxis prevented both reinfection and de novo infection by HBV. Thus with no added cost or effort, the anti-HBc positive liver was suitably and safely placed.

Patient Nos 19–22 provide confirmation that the anti-HBc positive liver, when placed into a recipient who lacks pretransplant HBV immunity and who

does not receive post-transplant prophylaxis, will establish de novo infection in the majority of instances.

The outcome of patient Nos 5–9 suggests that passive immunoprophylaxis can prevent de novo infection of most non-immune recipients (only 1/5 treatment failures observed). A similar beneficial impact was observed by Uemoto *et al* who used immunoprophylaxis for three paediatric recipients of living related anti-HBc positive livers.⁵ Recent published work suggests that lamivudine prophylaxis, with or without immunoprophylaxis, may also prevent de novo recipient infection in this at-risk group.^{8,9} Yu *et al* have published a small study using lamivudine (without immunoprophylaxis) to prevent de novo infection of nine recipients of anti-HBc positive livers. However, four recipients were HBV immune pretransplant and three of the remaining patients died soon after transplantation. Thus a sustained effect of lamivudine prophylaxis for non-immune recipients of anti-HBc positive livers was confirmed for only three patients.⁹ Dodson *et al* reported successful results with the combination of lamivudine and immunoglobulin given to 15 recipients, of whom seven were non-immune.⁸ Compared with immunoprophylaxis, lamivudine is inexpensive and easier to administer. Immunoglobulin is plasma derived and therefore its use raises microbiological concerns. Thus patient and doctor acceptance of lamivudine is superior, and compliance with lamivudine prophylaxis is good.

The outcome of patient Nos 10–18 poses more questions than provides answers. These recipients were either anti-HBc or anti-HBs positive pretransplant, most received immunoprophylaxis, and none developed de novo infection. However, the contribution of passive immunoprophylaxis to the favourable outcome of these recipients

cannot be determined. Patient Nos 10–16 may have been protected from de novo infection by their own pre-existing HBV immunity. For these recipients, immunoprophylaxis may represent an unnecessary and costly addition to their care. Indeed, the outcome of patient Nos 17 and 18, who were anti-HBs positive pretransplant, who did not receive prophylaxis, and who did not experience de novo infection, suggests that anti-HBc positive livers may be suitably placed (without the need for prophylaxis) in recipients who have serological evidence of HBV immunity. Other reports support this possibility that recipient anti-HBs and/or anti-HBc positivity may prevent de novo infection from anti-HBc positive livers.⁷

In summary, the data presented by Roque-Afonso *et al* in this issue of *Gut* support the following conclusions and recommendations.

- The use of anti-HBc positive livers without prophylaxis for non-immune recipients can and must be avoided (it follows that the anti-HBc status of the donor and recipient *must* be known).
- If possible, the anti-HBc positive liver should be used for a HBsAg positive recipient (who receives the combination of lamivudine and immunoprophylaxis to prevent graft reinfection and de novo infection). If a liver unit does not have a suitable HBsAg positive recipient for the anti-HBc positive donor, then the donor liver might be offered to a unit that does.
- For the HBsAg negative recipient of the anti-HBc positive liver, it appears that pretransplant immunity to HBV, immunoprophylaxis, or lamivudine (or combinations) significantly reduce the risk of de novo infection. Probably, and despite the fact that conclusive efficacy data are scarce, lamivudine without immunoprophylaxis will be preferred by many transplant units.

Above all, the anti-HBc positive liver can and must be used. In these times of donor organ shortage, a suitable and grateful recipient can always be found.

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