Received: 21 December 2021 | First decision: 6 January 2022 | Accepted: 20 May 2022

DOI: 10.1111/apt.17068

AP&T Alimentary Pharmacology & Therapeutics WILEY

Clinical trial: a controlled trial of baclofen add-on therapy in PPI-refractory gastro-oesophageal reflux symptoms

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Funding information
Ans Pauwels is funded by an FWO Postdoctoral Fellowship (1,278,014 N), Tim Vanuytsel is a senior clinical investigator of the Flanders Research Foundation (FWO). Funding was provided by a Methusalem grant from Leuven University to Jan Tack

Summary

Background: Proton pump inhibitors (PPI) have no effect on non-acid reflux events which can continue to provoke gastro-oesophageal reflux disease (GERD) symptoms. Baclofen, a γ-aminobutyric acid agonist, can decrease non-acid reflux but its symptomatic benefit in refractory GERD symptoms is understudied.

Aims: To assess the efficacy of baclofen 10 mg t.i.d. vs placebo as add-on therapy in PPI-refractory GERD symptoms, in a randomised, double-blind, placebo-controlled study.

Methods: Patients with persisting typical GERD symptoms on b.i.d. PPI therapy were randomised to 4 weeks of baclofen 10 mg or placebo t.i.d. Before and after treatment, patients underwent 24 h impedance-pH monitoring on-PPI. Throughout the study, patients filled out ReQuest diaries. Data were analysed using mixed models.

Results: About 60 patients were included (age 47.5 years [range 19–73], 41f/19 m), 31 patients were randomised to baclofen. One patient withdrew consent and five in the baclofen group stopped treatment due to side effects. There was a trend towards a better response for general wellbeing in the baclofen-treated group compared to placebo ($p = 0.06$). When subdividing patients according to symptom association probability (SAP), only the SAP+ ($n = 25$) group improved significantly with baclofen ($p_{corr} = 0.02$), and worsened with placebo ($p_{corr} = 0.008$). The total number of reflux events decreased over time ($p = 0.01$), mainly due to the baclofen condition ($p_{corr} = 0.1$). The number of reflux events with a high proximal extent dropped significantly after baclofen ($p_{corr} = 0.009$), but not placebo.

Conclusion: Baclofen decreases several reflux parameters in PPI refractory GERD symptoms, but pH-impedance monitoring is necessary before treatment as only SAP+ patients experience clinical benefit after 4 weeks.

The Handling Editor for this article was Dr Colin Howden, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Proton pump inhibitors (PPIs), the first-line treatment for patients with gastro-oesophageal reflux disease (GERD), significantly reduce the proportion of acid reflux, and provide healing of oesophagitis in the majority of patients, but have little to no effect on non-acid reflux.[1,2] Among GERD specific symptoms, heartburn is more commonly linked to acid reflux but regurgitation is reported with similar frequency during acid and non-acid episodes.[1,2]

Combined multichannel intraluminal impedance and pH monitoring (pH-MII) is a technique that allows the detection of both acid and non-acid reflux. It has been demonstrated that in up to half of patients with persisting reflux symptoms in spite of standard PPI therapy, refractory acid reflux can be detected which often responds to a further increase in PPI dose.[3] In the remaining patients, symptoms are possibly related to ongoing non-acid reflux, for which treatment options are limited.[1,2,4]

Reflux events, both acid and non-acid, mainly occur during transient lower oesophageal sphincter relaxations (TLOSRs).[5,6] As TLOSR-related reflux is predominant in patients with mild to moderate GERD, treatment of these patients by reducing TLOSRs may provide an addition to treatment with PPIs by reducing symptoms due to both acid and non-acid reflux. The gamma-aminobutyric acid type B (GABA-B) receptor agonist, baclofen, significantly reduces the occurrence of TLOSRs, thereby significantly decreasing reflux episodes after a meal in both healthy controls and patients with GERD.[7–11] Furthermore, in patients with duodeno-gastro-oesophageal reflux (DGOR) that persisted during PPI treatment, add-on therapy with baclofen improved both the objectively measured DGOR and a composite reflux symptom score.[12,13] GABA-B agonists, therefore, have the potential to provide a next step in the treatment approach of GERD, when reflux symptoms are refractory to PPI use.

However, to date, studies with baclofen as an add-on to PPI therapy have focused on mechanistic aspects such as the number of reflux events and their characteristics.[9,12,14] These studies confirmed that adding baclofen inhibits weakly acidic reflux events that persist during PPI therapy. The symptomatic outcome of add-on baclofen therapy has not received a lot of attention.[9,12,14] For this reason, baclofen is hardly advocated in most of the current treatment algorithms and is at best considered only after pH-MII on PPI therapy established symptomatically relevant ongoing weakly acidic reflux.[15–17] However, pH-MII is not available in every clinical practice, imposes a 24 h invasive measurement and relies on the analysis of the association of symptoms and reflux events, which also has major pitfalls.[18] It remains to be evaluated whether add-on therapy with baclofen could be considered on the basis of persisting typical reflux symptoms on adequately dosed PPI therapy, without additional testing.

The primary objective was to assess improvement of general wellbeing, assessed by a validated reflux symptom questionnaire (ReQuest) of baclofen (Lioresal®) 10 mg three times daily compared to placebo in patients with refractory typical GERD symptoms, selected on a history of insufficient response to adequately dosed PPI therapy. Secondary endpoints were improvement of acid symptoms as assessed by ReQuest, improvement of objective measurements of reflux parameters using 24 h pH-MII, and to assess the predictive value of the reflux assessment by 24 h pH-MII recordings on the primary outcome.

2 | MATERIALS AND METHODS

2.1 | Subjects

Patients aged between 18 and 75 years with an incomplete control of typical GERD symptoms (heartburn and/or regurgitation at least three times per week for 12 weeks) in spite of PPI therapy 12 weeks prior to inclusion, with at least 8 weeks of PPI bid therapy were recruited for participation in this study. Exclusion criteria were endoscopic signs of severe erosive oesophagitis (≥ grade C, Los Angeles classification) during PPI treatment in the 6 months prior to screening, systemic diseases known to affect oesophageal motility, surgery in the thorax or in the upper part of the abdomen, treatment with baclofen prior to the start of the study, and regular use of medications that may affect oesophageal and gastric motility. 85% of patients underwent upper endoscopy in the year prior to inclusion (all but one patient had endoscopic evaluation within 2 years prior to inclusion). Baclofen is not labelled for use in GERD.

The study was approved by the ethics committee of the University Hospital of Leuven (S51996) and was registered at ClinicalTrials.gov (NCT03835442). All patients gave written informed consent before inclusion in the study.

2.2 | Study protocol

This was a randomised, parallel, double-blind, placebo-controlled, outpatient, single-centre study (Figure 1). All patients underwent a 24-hour pH-impedance monitoring on b.i.d. PPI (which did not affect the treatment allocation) as part of the standard clinical work-up for refractory GERD symptoms, and filled out the ReQuest questionnaire at baseline. During a 2-week run-in period, patients were asked to fill out ReQuest daily diaries, after which they were randomly assigned by a computer-generated list to receive either oral baclofen (Lioresal®) or matching placebo t.i.d for a period of 4 weeks. Both patients and investigators were blinded to the treatment allocation. The outcome of the 24 h pH-MII, to which staff entering the patient in the study were blinded, had no impact on the randomisation.

Patients started to take one capsule containing 5 mg baclofen or placebo with meals t.i.d. for 7 days and then one capsule containing 10 mg baclofen or placebo with meals t.i.d. for the remaining 21 days. The medication consisted of identically looking capsules of baclofen or placebo. After 4 weeks patients returned for a second 24 h pH-MII on-PPI and on study medication and

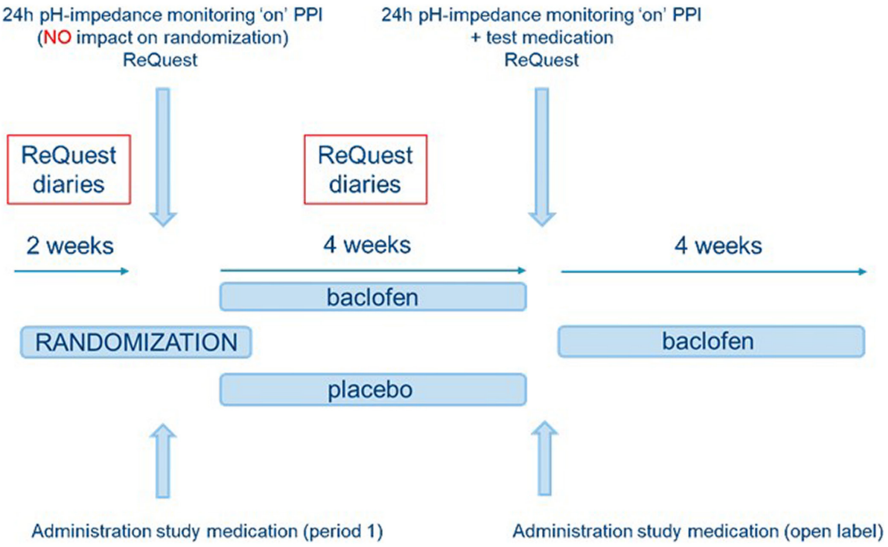

FIGURE 1 Outline of the study protocol (PPI = proton pump inhibitor).

filled out a second ReQuest questionnaire, after which all patients were given the standard dose of baclofen (Lioresal®) 10 mg t.i.d. (open label) for another 4 weeks. The b.i.d. PPI therapy was continued for the entire study duration.

2.3 | Reflux symptom assessment

The Reflux Questionnaire (ReQuest) is a brief, valid, reliable and self-assessed GERD sensitive scale, tracking and quantifying GERD symptoms during treatment.[19] It evaluates general wellbeing, frequency and intensity of acid complaints, upper abdominal complaints, lower abdominal complaints, nausea and sleeping disorders (see File S1). Daily ReQuest diaries were collected from all patients, starting 2 weeks prior to the start of treatment phase one, until the finish of the study. In order to process the data, averages were calculated for every week, except for baseline diaries, which were averaged over the 2 weeks prior to starting the study medication.

2.4 | 24-h ambulatory pH-impedance monitoring

Gastro-oesophageal reflux was assessed using a 24-h oesophageal ambulatory pH-impedance monitoring (pH-MII), the current gold standard in the detection of reflux episodes.[20] The following reflux parameters were investigated for each patient: total number of reflux events, number of acid and non-acidic reflux events, percentage of mixed reflux events (combined gas and liquid reflux), the proximal extent of reflux events defined as the proximal level to which the reflux event caused a drop of impedance, total 24-h oesophageal acid exposure time (AET, %time), symptom association probability (SAP) and symptom index (SI). A positive SAP was defined by a probability of 95% or more that symptoms were associated with reflux, and a positive SI was defined by 50% or more symptoms associated with reflux.[1] Details of the method are provided in the File S1.

2.5 | Statistics

Data were analysed using SAS 9.4 (SAS Institute). All data are shown as mean ± SEM, however, results from pH-impedance measurement are shown as mean ± SD. The results from the intention to treat analysis are shown here, per-protocol analysis is shown in the File S1. The significance level was set at a $p \leq 0.05$. The primary objective was to assess improvement of general well-being, assessed by the ReQuest, by baclofen (Lioresal®) 10 mg three times daily compared to placebo in patients with refractory GERD symptoms on PPI. Secondary endpoints were improvement of acid symptoms as assessed by ReQuest, improvement of objective measurements of reflux parameters, and to assess the predictive value of the reflux assessment by 24 h pH-MII recordings on the primary outcome. The sample size was calculated at 58 subjects, based on a moderate effect size of 0.35, a power of 0.85, and alfa of 0.05.[20] Further information on the analysis of reflux parameters and symptom responses can be found in the File S1.

3 | RESULTS

3.1 | Subjects

Sixty patients were assessed for eligibility and randomised. One patient finally decided not to participate in the study, so 31 patients were allocated to the baclofen arm and 28 to the placebo arm. Five patients dropped out of the study, all in the baclofen arm due to central side effects (drowsiness, dizziness, headache and/or nausea). In total, 26 patients in the baclofen arm and 28 patients in the placebo arm completed the study (Figure 2). No differences in gender, age and BMI were found between both treatment groups (demographics in Table 1).

Based on the pH-MII on PPI prior to inclusion, and using the recent Lyon consensus criteria, 14 patients were classified as having residual symptoms due to true refractory GERD, 18 due to reflux hypersensitivity and 22 due to functional heartburn.[21] The

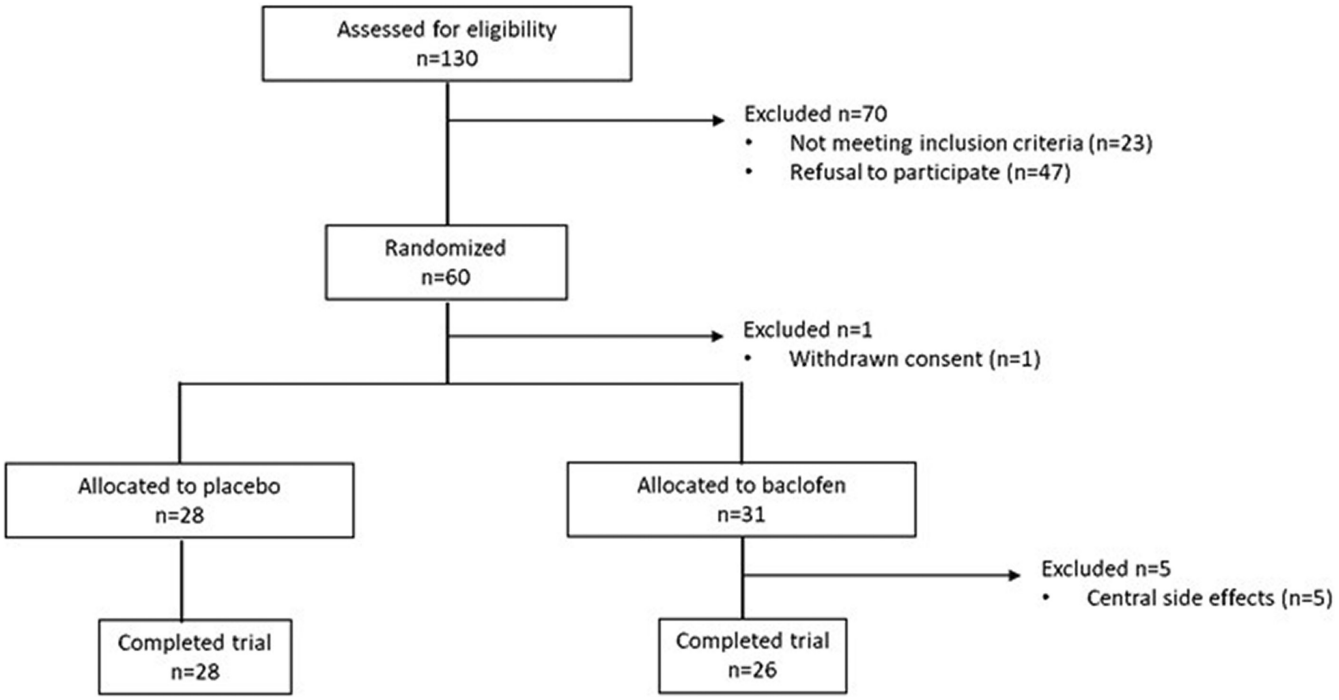

FIGURE 2 Consort trial flow diagram.

TABLE 1 Demographics of the patients included in the analysis

Intention to treat	Baclofen arm (*N* = 31)	Placebo arm (*N* = 28)	*p*-value
Gender (male/female)	10/21	9/19	>0.05
Age, years (median, IQR)	48 (38–58)	44 (39–58)	>0.05
BMI, kg/m^2 (median, IQR)	24.44 (21.45–25.97)	25.69 (22.86–28.13)	>0.05
Per protocol	**Baclofen arm (N = 26)**	**Placebo arm (N = 28)**	***p*-value**
Gender (male/female)	9/17	9/19	>0.05
Age, years (median, IQR)	46.5 (38–58)	44 (39–58)	>0.05
BMI, kg/m^2 (median, IQR)	23.67 (21.36–25.87)	25.69 (22.86–28.13)	>0.05

TABLE 2 Distribution of the GERD classification based on the pH-impedance monitoring on PPI prior to inclusion and using the recent Lyon consensus criteria ($p = 0.95$)[21]

Intention to treat	Baclofen arm (*N* = 31)	Placebo arm (*N* = 28)
True refractory GERD	10	7
Residual reflux hypersensitivity	9	9
Residual functional heartburn	11	10
Per protocol	**Baclofen arm (N = 26)**	**Placebo arm (N = 28)**
True refractory GERD	7	7
Residual reflux hypersensitivity	9	9
Residual functional heartburn	10	12

investigators were kept blinded from these findings during the entire study period. There was no difference in distribution between the baclofen and the placebo group (Table 2).

3.2 | Reflux symptom assessment

As can be seen in Table 3, general well-being improved significantly over the course of the study, with lower scores meaning better general wellbeing ($p = 0.03$). There was a trend towards a better response in the baclofen-treated group compared to the placebo-treated group ($p = 0.06$). In a post hoc within treatment group analysis, general wellbeing only improved in the baclofen group ($p_{corr} = 0.034$), and not in the placebo-group ($p_{corr} = 0.99$). General wellbeing improved significantly in females but not in males, regardless of assigned treatment ($p = 0.029$). Although not significant, this was in part due to a worse general wellbeing at baseline in women compared to men ($p_{corr} = 0.12$).

Acid complaints were significantly better at the end of the study period ($p = 0.02$), however, this was irrespective of the treatment. Also, *upper gastro-intestinal (GI) symptoms* improved over time ($p = 0.001$), again independent of the treatment.

3.2.1 | Subgroup analyses

When patients were divided into SAP positive ($n = 28$) and SAP negative ($n = 29$) subgroups based on baseline pH-MII, we found a significant difference between treatment groups ($p < 0.0001$). The positive SAP group significantly improved in *general wellbeing* when

TABLE 3 Results of reflux symptom assessment using the validated ReQuest score.[19,23] Results are shown as mean ± SEM

	p value	Group	Baseline	Week 4	Within group analysis
Reflux symptom assessment					
General well-being	Main effect of time $p = 0.03$ Treatment-by-time interaction effect: $p = 0.06$ Gender-by-time interaction effect: $p = 0.029$	Baclofen	4.67 ± 0.43	3.62 ± 0.43	$p_{corr} = 0.034$
		Placebo	4.53 ± 0.41	4.14 ± 0.46	$p_{corr} = 0.99$
		Male	3.57 ± 0.39	3.51 ± 0.55	$p_{corr} = 0.91$
		Female	5.13 ± 0.37	4.11 ± 0.38	$p_{corr} = 0.002$
Acid complaints	Main effect of time $p = 0.02$ Treatment main effect: $p = 0.84$ Treatment-by-time interaction effect: $p = 0.27$	Baclofen	11.92 ± 2.17	8.95 ± 2.67	$p_{corr} > 0.05$
		Placebo	15.45 ± 3.42	10.69 ± 2.74	$p_{corr} > 0.05$
Upper GI symptoms	Main effect of time $p = 0.001$ Treatment main effect: $p = 0.57$ Treatment-by-time interaction effect: $p = 0.97$	Baclofen	15.10 ± 2.44	11.22 ± 2.63	$p_{corr} > 0.05$
		Placebo	15.20 ± 3.07	8.75 ± 2.13	$p_{corr} > 0.05$
Total Request	Main effect of time $p = 0.001$	Baclofen	11.17 ± 1.40	7.91 ± 1.77	$p_{corr} > 0.05$
		Placebo	11.14 ± 1.78	8.03 ± 1.53	$p_{corr} > 0.05$
	p value	Group	Baseline	Week 4	Within group analysis
Subgroup analysis					
General well-being	Treatment-by-time-by-SAP interaction effect ($p < 0.0001$)	SAP + Baclofen	5.35 ± 0.60	3.76 ± 0.55	$p_{corr} = 0.02$
		SAP + Placebo	5.01 ± 0.65	5.22 ± 0.64	$p_{corr} = 0.008$
		SAP - Baclofen	3.97 ± 0.56	3.50 ± 0.65	$p_{corr} = 0.43$
		SAP - Placebo	3.95 ± 0.54	2.87 ± 0.55	$p_{corr} = 0.002$
Acid complaints	Treatment-by-time-by-SAP interaction effect ($p = 0.23$)	SAP + Baclofen	12.31 ± 2.46	6.57 ± 2.25	$p_{corr} > 0.05$
		SAP + Placebo	18.56 ± 4.69	16.19 ± 4.17	$p_{corr} > 0.05$
		SAP - Baclofen	13.60 ± 3.80	10.96 ± 4.56	$p_{corr} > 0.05$
		SAP - Placebo	10.97 ± 4.81	3.53 ± 1.40	$p_{corr} > 0.05$
Total reQuest	Treatment-by-time-by-SAP interaction effect ($p = 0.022$)	SAP + Baclofen	13.06 ± 1.69	8.82 ± 2.16	$p_{corr} = 0.13$
		SAP + Placebo	11.99 ± 2.14	10.44 ± 1.91	$p_{corr} > 0.05$
		SAP - Baclofen	9.08 ± 2.17	7.10 ± 2.83	$p_{corr} > 0.05$
		SAP - Placebo	9.91 ± 3.17	4.43 ± 2.05	$p_{corr} = 0.008$

treated with baclofen ($p_{corr} = 0.02$), but worsened when treated with placebo ($p_{corr} = 0.008$). The negative SAP group displayed a large placebo effect ($p_{corr} = 0.002$), but did not respond to baclofen treatment ($p_{corr} = 0.43$). When patients were divided into SI positive ($n = 36$) and SI negative ($n = 21$), we found that patients with a positive SI improved after placebo treatment ($p_{corr} = 0.01$) but not after baclofen treatment ($p_{corr} = 0.16$). No significant differences were found in patients with a negative SI following placebo treatment ($p_{corr} = 0.06$) or baclofen treatment ($p_{corr} = 0.08$).

Acid complaints showed the highest improvement in the SAP positive group receiving baclofen and the SAP negative group receiving placebo, however, this did not reach statistical significance. No differences were found when dividing patients into SI positive and negative.

When looking at the *total ReQuest scores*, a significant interaction effect between time, treatment and SAP was demonstrated ($p = 0.022$). Subgroup analysis revealed a significant decrease in total ReQuest scores in the SAP positive group treated with baclofen, however, significance was lost after correction ($p_{corr} = 0.13$). We did find a significant effect of placebo in the SAP negative group ($p_{corr} = 0.008$).

An overview of symptom scores can be found in Table 3.

3.3 | 24-h ambulatory pH-impedance monitoring

We demonstrated a decrease in the *total number of reflux events* over time ($p = 0.01$). This drop was driven by a significant decrease in the baclofen condition, however, after correction for multiple testing, significance was not retained (68 ± 42 vs 48 ± 24 after 4 weeks, $p_{corr} = 0.08$; placebo: 71 ± 60 vs. 63 ± 53, $p_{corr} = 0.17$). Both baclofen and placebo did not significantly alter the *number of acid reflux episodes*. The *number of non-acid reflux episodes* however tended to decrease after baclofen (46 ± 30 vs 34 ± 21, $p_{corr} = 0.12$), which did not occur after placebo treatment (53 ± 59 vs 49 ± 53, $p_{corr} = 0.74$). After baclofen treatment, the *number of reflux events with a high proximal extent* was significantly lower (22 ± 20 vs 11 ± 10, $p_{corr} = 0.004$), and was unaltered after treatment with placebo (30 ± 41 vs. 24 ± 31, $p = 0.60$). There was no difference in the *total acid exposure time* or *the total bolus exposure time* before and after treatment with baclofen or placebo.

The number of heartburn and regurgitation symptoms indicated on the pH-MII measurement were similar in the baclofen arm and the placebo arm before treatment. After treatment, the number of heartburn and regurgitation events during the pH-MII

monitoring decreased, both in the baclofen and in the placebo condition. However, this did not reach statistical significance.

4 | DISCUSSION

The management of patients with refractory typical reflux symptoms on adequately dosed PPI therapy is challenging. In most cases, there is little or no gain in further increasing acid-suppressive therapy, and anti-reflux surgery is not the appropriate option for the majority of these patients.[15,17] Add-on of agents that modify motility of the stomach, oesophagus and oesophagogastric junction is a potentially attractive option, but there is a lack of options of established efficacy.[15,17]

In patients with refractory GERD symptoms despite PPI, this study showed that baclofen tended to improve *general wellbeing* as measured by the validated ReQuest questionnaire better than placebo. When evaluating subgroups derived from the pH-MII on b.i.d. PPI before inclusion in the study, we found that patients with a positive symptom association by means of a positive SAP, had a significant improvement of general well-being when taking baclofen, while there was no significant placebo effect in this group. In contrast, in patients with a negative SAP (i.e. functional heartburn) general wellbeing improved significantly with placebo, but not with baclofen treatment (Figure 3). Subdividing patients according to SI confirmed the significant placebo effect in patients with a negative SI, but did not show an effect of baclofen in the positive SI group, indicating that SAP but not SI identifies potential responders. General wellbeing improved more in females than in males, but this was probably attributable to a worse general wellbeing at baseline in females compared to males.[22]

Acid-related symptoms tended to improve most in the SAP positive group after baclofen and in the SAP negative group after placebo, again emphasising the susceptibility of patients with functional heartburn to a large placebo effect. Also, *upper GI symptoms* and the *total ReQuest scores* were lowered after treatment with baclofen only in the SAP positive group. Of note, on average symptoms did not improve to a level below the threshold for clinically relevant GERD symptoms of 3.37, as established for the total ReQuest score.[19,23]

The magnitude and importance of the placebo effect in patients with reflux disease have been described before. A meta-analysis by Cremonini et al.[24] found symptomatic improvement in 19% of GERD patients treated with placebo, and this was more common among patients with NERD (18.31% vs 11.87% in erosive oesophagitis). Limsrivilai et al.[25] studied the effect of an 8-week treatment period with imipramine, a tricyclic antidepressant or placebo in patients with reflux hypersensitivity and functional heartburn. Although quality of life improved more in the imipramine group, no difference was found in the percentage of responders (defined as having a >50% improvement of the GERD score) between imipramine and placebo, demonstrating a large placebo effect in reflux hypersensitivity and functional heartburn patients.

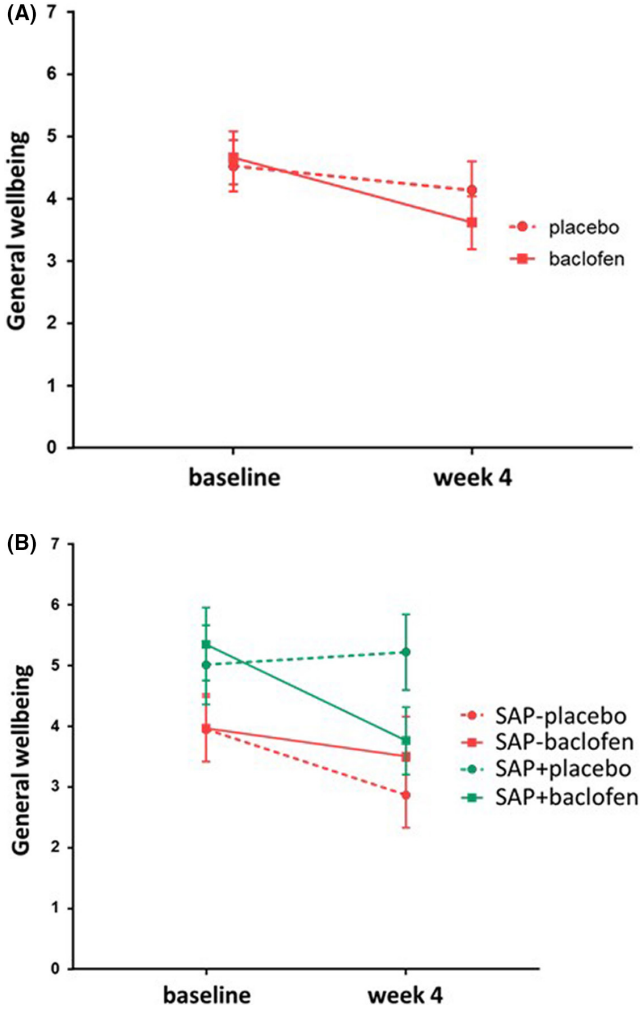

FIGURE 3 (A) General well-being improved significantly in the baclofen (p_{corr} = 0.02) but not in the placebo group. (B) Improvement in general well-being was significant in the SAP positive group that received baclofen (p_{corr} = 0.01) and in the SAP negative group that received placebo (p_{corr} = 0.0003) (SAP = symptom association probability).

As previously mentioned, the majority of studies investigating the effect of baclofen focused on the mechanistic effects of baclofen, and not on change in symptoms over a period of several weeks. Some studies investigated the effect of a single dose of baclofen, and other RCTs looked at symptom registrations during the 24 pH- or pH-MII monitoring, or only used questionnaires at the beginning and end of the treatment period. A study by Cacciglione et al.[13] found that the intensity of symptoms improved with baclofen in a small group of GERD patients (n = 16), but not with placebo, in a 4-week trial with baclofen 10 mg q.i.d. None of the patients in this study however, were refractory GERD patients. In a study by Cossentino et al.,[26] a significant improvement in regurgitation, belching and symptom scores were found after 2 weeks of treatment with baclofen (n = 23). However, all patients in this study were selected based on abnormal acid exposure time on pH-MII at baseline. The authors also described a large placebo effect for heartburn, regurgitation, chest pain and symptom scores (n = 20).

Our study demonstrated that only patients with a positive SAP (and not SI) experience benefit from treatment with baclofen. This implicates that only patients with an established association between reflux and symptoms are good candidates for treatment with baclofen. Rome IV criteria consider reflux hypersensitivity a functional disorder, as there seems to be an increased sensitivity to reflux events within the physiological range. On the other hand, in these patients reflux events are still the trigger.[27] This may explain the beneficial effect of baclofen in the current study and is in line with previous suggestions that these patients, if carefully selected, may benefit from anti-reflux surgery.[28] Patients with a negative SAP, the functional heartburn group, displayed a large placebo effect and in those patients, adding baclofen to a PPI treatment will not have an added value. These data support the hypothesis that symptoms in patients with functional heartburn are not reflux-related, and that this group of patients will not benefit from reflux inhibitors. Patients with functional heartburn might benefit more from therapy with neuromodulators, although more studies are needed to confirm this.[25,29,30]

The *objectively measured reflux parameters* (total number of reflux episodes and the number of reflux episodes with a high proximal extent) decreased after baclofen treatment, but not after placebo treatment (Figure 4). These findings are in line with earlier studies, reporting a decrease in total number of reflux events, the number of acid and non-acid reflux events with baclofen.[9,11–13] We could not demonstrate a difference in the number of acid reflux events, which probably reflects the fact that patients in our study were already on double dose PPIs, with a low residual number of acid reflux events. We demonstrated significantly less reflux episodes with a high proximal extent after baclofen, but not after placebo. Similar findings were obtained in a study by Beaumont et al.[31] Lowering the number of proximal reflux events may be relevant for a decrease in symptoms, which was already alluded to in several studies. Zerbib et al.[32] reported that the proximal extent of reflux was the only factor associated with reflux perception in patients on PPI therapy. Cicala et al.[33] found that in NERD patients, proximal extent is the major determinant of symptom perception. A decrease in the proximal extent of reflux might also suggest a potential therapeutic benefit of baclofen in patients with extra-oesophageal reflux symptoms, but this needs to be further elucidated.

Five out of the 31 patients (16%) allocated to the baclofen treatment arm discontinued the treatment due to central side effects such as drowsiness, dizziness, headache and/or nausea. This number is in line with most previous studies.[13,14,26] We acknowledge that there are several patients that do not tolerate baclofen. However, a subgroup of patients, those with a positive SAP, can benefit from baclofen, and therefore we believe it is worthwhile to try baclofen in this patient group, also in light of the lack of alternative non-surgical treatment options.

This study has some important clinical implications. First of all, empirical add-on therapy with baclofen in GERD patients with persisting typical symptoms in spite of double-dose PPI therapy does not seem justified. The use of baclofen should be limited to patients who display a positive SAP for typical reflux symptoms (heartburn and/or regurgitation) during PPI therapy. Secondly, SAP is a better discriminator to diagnose reflux hypersensitivity compared to SI. Limitations of the study are the focus on typical GERD symptoms only, the setting in specialist care, and the short duration of

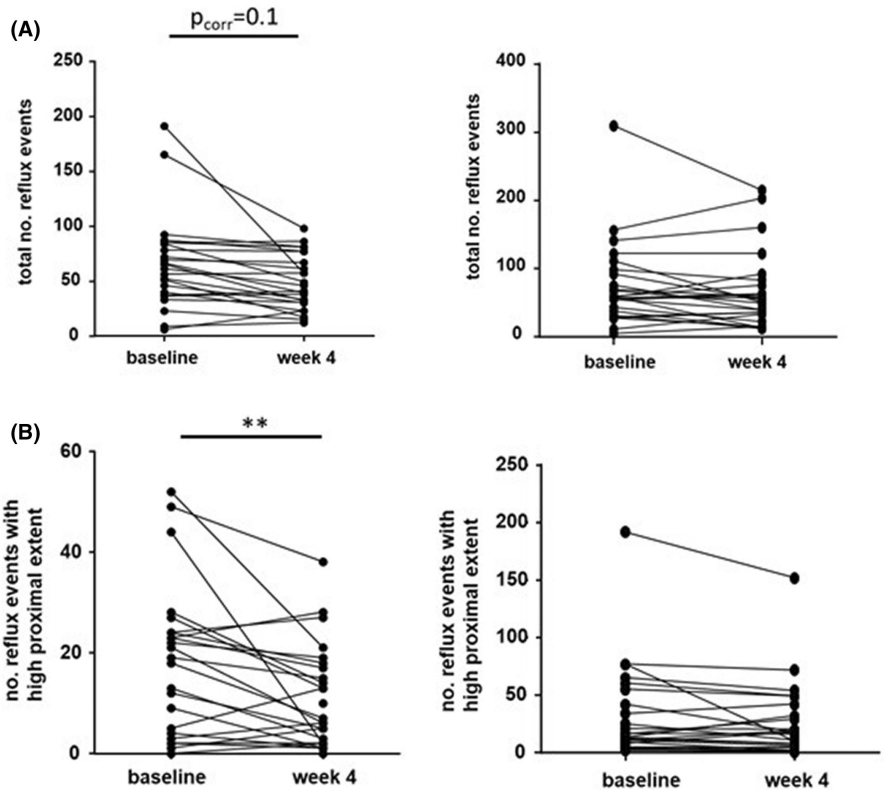

FIGURE 4 (A) The total number of reflux events decreased after baclofen treatment (p_{corr} = 0.1), however, not after placebo treatment. (B) the number of reflux events with a high proximal extent decreased significantly after baclofen (p_{corr} = 0.009) but not after placebo treatment.

treatment. The findings can not necessarily be extrapolated to extra-oesophageal GERD symptoms, to primary care or to treatment periods longer than 4 weeks.

In conclusion, this study demonstrated that baclofen can be used as an add-on therapy in PPI-refractory GERD patients with proven residual reflux hypersensitivity on PPI. However, approximately one in seven patients may not tolerate baclofen. Patients with residual functional heartburn on PPI do not benefit from anti-reflux therapy, which is in line with previous studies.

ACKNOWLEDGEMENT

Declaration of personal interests: None.

AUTHOR CONTRIBUTIONS

Ans Pauwels: Conceptualization (supporting); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); writing – original draft (lead); writing – review and editing (supporting). **Karlien Raymenants:** Data curation (equal); formal analysis (equal); validation (equal); writing – original draft (supporting); writing – review and editing (equal). **Annelies Geeraerts:** Data curation (supporting); validation (supporting); writing – review and editing (supporting). **Veerle Boecxstaens:** Data curation (supporting); formal analysis (supporting); investigation (supporting); methodology (supporting); project administration (supporting); writing – review and editing (supporting). **Imke Masuy:** Conceptualization (supporting); data curation (supporting); formal analysis (equal); investigation (supporting); methodology (supporting); writing – review and editing (supporting). **Charlotte Broers:** Data curation (supporting); formal analysis (supporting); investigation (supporting); methodology (supporting); writing – review and editing (supporting). **Tim Vanuytsel:** Conceptualization (equal); data curation (equal); formal analysis (supporting); investigation (supporting); methodology (equal); supervision (equal); validation (equal); writing – review and editing (lead). **Jan Tack:** Conceptualization (lead); data curation (lead); formal analysis (equal); funding acquisition (lead); investigation (lead); methodology (lead); resources (lead); supervision (lead); validation (lead); writing – original draft (supporting); writing – review and editing (lead).

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REFERENCES

1. Zerbib F, Roman S, Ropert A, des Varannes SB, Pouderoux P, Chaput U, et al. Esophageal pH-impedance monitoring and symptom analysis in GERD: a study in patients off and on therapy. Am J Gastroenterol. 2006;101(9):1956–63.
2. Sifrim D, Mittal R, Fass R, Smout A, Castell D, Tack J, et al. Review article: acidity and volume of the refluxate in the genesis of gastro-oesophageal reflux disease symptoms. Aliment Pharmacol Ther. 2007;25(9):1003–17. https://doi.org/10.1111/j.1365-2036.2007.03281.x
3. Kinoshita Y, Hongo M, Japan TWICE Study Group. Efficacy of twice-daily rabeprazole for reflux esophagitis patients refractory to standard once-daily administration of PPI: the Japan-based TWICE study. Am J Gastroenterol. 2012;107:522–30.
4. Fass R. Proton pump inhibitor failure—what are the therapeutic options? Am J Gastroenterol. 2009;104(S2):S33–8.
5. Dent J, Holloway RH, Toouli J, Dodds WJ. Mechanisms of lower oesophageal sphincter incompetence in patients with symptomatic gastrooesophageal reflux. Gut. 1988;29:1020–8.
6. Schoeman MN, Tippett MD, Akkermans LMA, Dent J, Holloway RH. Mechanisms of gastroesophageal reflux in ambulant healthy human subjects. Gastroenterology. 1995;108(1):83–91.
7. Zhang Q, Lehmann A, Rigda R, Dent J, Holloway RH. Control of transient lower oesophageal sphincter relaxations and reflux by the GABA(B) agonist baclofen in patients with gastro-oesophageal reflux disease. Gut. 2002;50(1):19–24.
8. Wise J, Conklin JL. Gastroesophageal reflux disease and baclofen: is there a light at the end of the tunnel? Curr Gastroenterol Rep. 2004;6:213–9.
9. Vela MF, Tutuian R, Katz PO, Castell DO. Baclofen decreases acid and non-acid post-prandial gastro-oesophageal reflux measured by combined multichannel intraluminal impedance and pH. Aliment Pharmacol Ther. 2003;17:243–51.
10. Gerson LB, Huff JF, Hila A, Hirota WK, Reilley S, Agrawal A, et al. Arbaclofen placarbil decreases postprandial reflux in patients with gastroesophageal reflux disease. Am J Gastroenterol. 2010;105(6):1266–75. https://doi.org/10.1038/ajg.2009.718
11. van Herwaarden MA, Samsom M, Rydholm H, Smout AJPM. The effect of baclofen on gastro-oesophageal reflux, lower oesophageal sphincter function and reflux symptoms in patients with reflux disease. Aliment Pharmacol Ther. 2002;16(9):1655–62.
12. Koek GH, Sifrim D, Lerut T, Janssens J, Tack J. Effect of the GABA(B) agonist baclofen in patients with symptoms and duodeno-gastro-oesophageal reflux refractory to proton pump inhibitors. Gut. 2003;52(10):1397–402.
13. Ciccaglione AF, Marzio L. Effect of acute and chronic administration of the GABA B agonist baclofen on 24 hour pH metry and symptoms in control subjects and in patients with gastro-oesophageal reflux disease. Gut. 2003;52(4):464–70.
14. Beaumont H, Smout A, Aanen M, Rydholm H, Lei A, Lehmann A, et al. The $GABA_B$ receptor agonist AZD9343 inhibits transient lower oesophageal sphincter relaxations and acid reflux in healthy volunteers: a phase I study. Aliment Pharmacol Ther. 2009;30(9):937–46. https://doi.org/10.1111/j.1365-2036.2009.04107.x
15. Sifrim D, Zerbib F. Diagnosis and management of patients with reflux symptoms refractory to proton pump inhibitors. Gut. 2012;61:1340–54.
16. Hershcovici T, Fass R. Gastro-Oesophageal reflux disease. Drugs. 2011;71(18):2381–9.
17. Scarpellini E, Ang D, Pauwels A, De Santis A, Vanuytsel T, Tack J. Management of refractory typical GERD symptoms. Nat Rev Gastroenterol Hepatol. 2016;13(5):281–94.
18. Bredenoord AJ, Smout AJPM. Association between reflux and symptoms during ambulatory reflux monitoring: pros and cons of existing methods. Neurogastroenterol Motil. 2013;25(8):633–7.
19. Mönnikes H, Bardhan KD, Stanghellini V, Berghöfer P, Bethke TD, Armstrong D. Evaluation of GERD symptoms during therapy. Digestion. 2007;75(1):41–7.

20. Vakil NB, Huff FJ, Bian A, Jones DS, Stamler D. Arbaclofen placarbil in GERD: a randomized, double-blind, placebo-controlled study. Am J Gastroenterol. 2011 Aug;106(8):1427–38.
21. Gyawali CP, Kahrilas PJ, Savarino E, Zerbib F, Mion F, Smout AJPM, et al. Modern diagnosis of GERD: the Lyon consensus. Gut. 2018;67(7):1351–62.
22. Eusebi LH, Ratnakumaran R, Yuan Y, Solaymani-Dodaran M, Bazzoli F, Ford AC. Global prevalence of, and risk factors for, gastro-oesophageal reflux symptoms: a meta-analysis. Gut. 2018;67(3):430–40.
23. Bardhan KD, Berghöfer P. Look--but also listen! ReQuest: an essay on a new validated scale to assess the outcome of GERD treatment. Digestion. 2007;75(Suppl 1):87–100.
24. Cremonini F, Ziogas DC, Chang HY, Kokkotou E, Kelley JM, Conboy L, et al. Meta-analysis: the effects of placebo treatment on gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2010;32(1):29–42.
25. Limsrivilai J, Charatcharoenwitthaya P, Pausawasdi N, Leelakusolvong S. Imipramine for treatment of esophageal hypersensitivity and functional heartburn: a randomized placebo-controlled trial. Am J Gastroenterol. 2016;111(2):217–24.
26. Cossentino MJ, Mann K, Armbruster SP, Lake JM, Maydonovitch C, Wong RKH. Randomised clinical trial: the effect of baclofen in patients with gastro-oesophageal reflux—a randomised prospective study. Aliment Pharmacol Ther. 2012;35(9):1036–44.
27. Aziz Q, Fass R, Gyawali CP, Miwa H, Pandolfino JE, Zerbib F. Functional esophageal disorders. Gastroenterology 2016;150(6):1368–79.
28. Broeders JA, Draaisma WA, Bredenoord AJ, de Vries DR, Rijnhart-de Jong HG, Smout AJ, et al. Oesophageal acid hypersensitivity is not a contraindication to Nissen fundoplication. Br J Surg. 2009;96(9):1023–30.
29. Ostovaneh MR, Saeidi B, Hajifathalian K, Farrokhi-Khajeh-Pasha Y, Fotouhi A, Mirbagheri SS, et al. Comparing omeprazole with fluoxetine for treatment of patients with heartburn and normal endoscopy who failed once daily proton pump inhibitors: double-blind placebo-controlled trial. Neurogastroenterol Motil. 2014;26(5):670–8.
30. Viazis N, Keyoglou A, Kanellopoulos AK, Karamanolis G, Vlachogiannakos J, Triantafyllou K, et al. Selective serotonin reuptake inhibitors for the treatment of hypersensitive esophagus: a randomized, double-blind placebo-controlled study. Am J Gastroenterol. 2012;107(11):1662–7.
31. Beaumont H, Boeckxstaens GEE. Does the presence of a hiatal hernia affect the efficacy of the reflux inhibitor baclofen during add-on therapy? Am J Gastroenterol. 2009;104(7):1764–71.
32. Zerbib F, Duriez A, Roman S, Capdepont M, Mion F. Determinants of gastro-oesophageal reflux perception in patients with persistent symptoms despite proton pump inhibitors. Gut. 2008;57(2):156–60.
33. Cicala M, Emerenziani S, Caviglia R, Guarino MPL, Vavassori P, Ribolsi M, et al. Intra-oesophageal distribution and perception of acid reflux in patients with non-erosive gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2003;18(6):605–13.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

How to cite this article: Pauwels A, Raymenants K, Geeraerts A, Boecxstaens V, Masuy I, Broers C, et al. Clinical trial: a controlled trial of baclofen add-on therapy in PPI-refractory gastro-oesophageal reflux symptoms. Aliment Pharmacol Ther. 2022;56:231–239. https://doi.org/10.1111/apt.17068