Optimal maintenance therapy in patients with non-erosive reflux disease reporting mild reflux symptoms – a pilot study

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Abstract

Purpose: This pilot study aimed at finding trend for further investigation of the optimal maintenance therapy with lansoprazole in patients with non-erosive reflux disease (NERD) suffering from mild symptoms.

Material and methods: Sixty consecutive patients with diagnosed NERD reporting mild symptoms were included in the study. After successfully finishing a four-week treatment with lansoprazole (30 mg daily), the patients were randomized into three groups administered: 1 – lansoprazole 30 mg "on--demand", 2 – lansoprazole 15 mg daily, 3 – lansoprazole 30 mg in four-week courses during a relapse. The intensity of symptoms was assessed with the Visual Analogue Scale (VAS) at the baseline, as well after 4 weeks, 3, 6 and 12 months of therapy. The general satisfaction of treatment was evaluated with the Verbal Rating Scale (VRS) at the same time.

Results: At the baseline, the mean intensity of symptoms assessed by VAS was 2.8±1.0 points and fell to 0.4±0.5 points after a 4-week therapy. In Group 1, after 3, 6 and 12 months, it was 0.85±0.6, 1.0±0.8 and 1.0±0.8, in Group 2: 0.65±0.7, 0.65±0.7, 0.5±0.3, and in Group 3: 1.1±0.6, 1.55±0.7, 1.65±0.8 points, respectively. No significant differences were observed between Groups 1 and 2. Intermittent therapy (Group 3) showed a significantly lower efficacy in comparison to other groups ($p<0.05$). "On-demand" therapy was 30% cheaper whereas intermittent therapy was 55% cheaper than the most expensive daily treatment. However, general satisfaction of treatment assessed by VRS was non-significantly different between any of the groups.

Conclusions: In patients with NERD and mild symptoms, both on-demand and daily treatment models of maintenance therapy showed a similar high efficacy, whereas intermittent therapy was significantly less effective. However, general satisfaction of each treatment options was high and non-significantly different between the groups. Due to a pilot character of this study further investigation based on a larger number of patients is necessary to confirm the clinical value of cheaper models of maintenance therapy which could be then recommended as more cost-effective.

Key words: NERD, "on-demand" therapy, intermittent therapy.

Introduction

Complaints typical for gastroesophageal reflux disease (GERD) are experienced daily by 10% of adult population, but as many as 20-40% of adults suffer from such symptoms at least once a month. In the majority of patients (50-70%), no inflammatory lesions are detected in the esophagus and such individuals are diagnosed as suffering from the so-called non-erosive reflux disease (NERD). In view of its persistent and recurrent character, GERD contributes to poorer quality of life in numerous patients. In addition, some individuals with NERD manifest an increased sensitivity to acid, what may lead to a weaker reaction to inhibition of hydrochloric acid secretion as compared to patients with confirmed esophagitis. The objective of an optimum, long-term therapy is the improvement of the quality of life, prevention of complications, as well as prevention of recurrent disease [1-3]. It is estimated that as early as within six months of discontinuing regular administration of proton pump inhibitors (PPI), approximately one half of the patients (40-60%) again develop reflux symptoms. The risk of a recurrent disease is at its maximum in the first year after the diagnosis. The initial phase of the therapy includes the administration

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of PPI once or twice a day continued for approximately 4 to 8 weeks [3,4]. In maintenance therapy, several management models are currently proposed, such as the "step-down" therapy, "on-demand" therapy, intermittent therapy that is employed when the complaints recur, as well as long-term therapy with low PPI doses [4-8]. In view of the high heterogeneity of patients with GERD, their therapeutic requirements may also differ.

To-date, there is no clarity as to which of the above therapeutic protocols is optimal with respect to its efficacy and cost in view of pre-therapeutic complaint intensity in patients with NERD [9].

The objective of this pilot study is determining trend for further investigation of the most optimal method of long-term treatment of reflux disease in patients with NERD who report mild complaints based on three models of pharmacological management using PPI: "on-demand" therapy, maintenance therapy and intermittent therapy. Additionally, the authors evaluate the costs incurred by the employment of particular therapeutic methods.

Material and methods

The study included 65 consecutive patients (36 females and 29 males aged 18 to 71 years, 48.6 in average) with non-erosive reflux disease diagnosed based on characteristic clinical presentation (heartburn, belching, regurgitation) and endoscopic examinations seen at the Outpatient Clinic, Department of Gastroenterology and Hepatology, University Hospital of Cracow, Poland. The inclusion criterion consisted in mild reflux symptoms (baseline intensity of symptoms 4 or less points on VAS) that would not affect daily activities of the patients and persisted for at least three months prior to the visit.

The following patients were excluded from the study: individuals with severe systemic diseases, esophagitis, esophageal ulceration, esophagostenosis, peptic ulcers, past surgery involving the upper gastrointestinal tract or reporting complaints, which in the opinion of the investigators might suggest the irritable bowel syndrome or dyspepsia, medication with any drugs that influence either the lower esophageal sphincter motility or gastric secretion and emptying.

A detailed medical history was taken in all the patients and upper GI tract endoscopy was performed.

The investigation consisted of two stages: stage 1 included a four-week PPI treatment, while stage 2 was an 11-month follow-up. Having completed the preliminary, four-week therapy with PPI (lansoprazole) administered at the dose of 30 mg once a day, the patients in whom the treatment had been successful (success being defined as no complaints whatsoever or not more than one day with mild complaints within 7 days immediately prior to the assessment) were randomized (with sealed envelopes method) to three groups equal in number (n=20, each):

1. Group 1, administered 30 mg lansoprazole as needed ("on-demand" therapy);
2. Group 2, receiving a daily maintenance dose of 15 mg of lansoprazole;
3. Group 3, on a four-week course of lansoprazole at the dose of 30 mg, in case of recurrent symptoms (intermittent therapy).

The patients were asked to report to their physician should their symptoms recur, as well as after 3, 6 and 12 months of therapy. The intensity of symptoms was rated each time using the Visual-Analog Scale (VAS; 0-10 points). Patients marked the intensity of symptoms with a vertical line on a 10-cm segment, with the left end described as "no symptoms at all" and the right end described as "insufferable symptoms". Each evaluation was marked by the patient on a separate evaluation form. For further analysis, data were treated as parametric. The overall satisfaction derived from the therapy was assessed with the 4-point Verbal Rating Scale (VRS; 0 – completely dissatisfied from treatment, 1 – rather dissatisfied, 2 – rather satisfied, 3 – completely satisfied).

The analysis of costs was based on the mean number of tablets taken during the study period. Number of pills taken was reported by each patient in an Individual Patient's Investigation-Book, which was checked during the follow-up visits. The cost of the least expensive pack of medication was taken into consideration.

The sample size was estimated based on the principle of detecting a 30% difference in the intensity of symptoms, overall satisfaction rate or costs of treatment (meaning clinically relevant difference), with 80% probability at $P<0.05$. A commercially available statistical package (STATISTICA; Stat-Soft, Cracow, Poland) was used for calculations of data entered onto a dedicated spreadsheet (Microsoft Excel 2002; Microsoft Corporation, San Jose, CA, USA). Normally distributed continuous data were analyzed using Student's t-test. Categorical data were analyzed using the χ^2-test or Fisher's exact test (F-test) where appropriate. A P value of less than 0.05 was considered statistically significant. Data are presented as mean values ±SD, and percentages (%).

Results

The investigation included 65 patients with non-erosive gastric reflux diagnosed based on typical symptoms (heartburn, belching, regurgitation) and endoscopy. Of these 65 patients, sixty who responded to initial four-week lansoprazole therapy were randomized to three groups equal in number. In the remaining five individuals, the initial lansoprazole therapy failed to alleviate the complaints and they were found not to be eligible for the stage 2 of the study and excluded. *Tab. 1* presents the characteristics of particular patient groups. Prior to therapy, the mean intensity of complaints in all the groups was 2.8±1.0 points on the VAS scale; following the preliminary therapy, the intensity dropped to the mean value of 0.4±0.5 points. The mean intensity of complaints in particular groups in the course of follow-up is presented in *Tab. 2*. No significant differences were noted between Group 1 and 2. In Group 1, the patients took the mean number of 0.3±0.3 PPI capsules per day. On the other hand, intermittent therapy (Group 3) was significantly less effective as compared to "on-demand" therapy (Group 1) after 6 and 12 months of treatment ($p<0.05$), as well as in comparison to daily therapy (Group 2) after 3, 6 and 12 months ($p<0.05$). Throughout the one-year follow-up, 90% of Group 1 patients were satisfied with their therapy; the satisfaction rate in Group 2 reached 95% and in Group 3, it was 85% (*Tab. 3*).

Table 1. **Characteristics of the patients with NERD (n=20 in each group). There were no significant differences between the groups (* F-test and # χ^2-test)**

Variable	Group 1 "On-demand" treatment	Group 2 Daily treatment	Group 3 Intermittent treatment
Mean age (years) *	49±12	48±11	48±13
Males #	10 (50%)	9 (45%)	11 (55%)
Disease duration # <1 year/>1 year (n)	12/8	13/7	11/9
Smoking #	4 (20%)	5 (25%)	3 (15%)
Alcohol intake #	1 (5%)	0	0

Table 2. **Mean intensity of complaints on the VAS scale depending on the type of therapy. Significant differences (F-test, $p<0.05$) were found between group 1 vs 3 after 6 and 12 months of therapy while between group 2 vs 3 after 3, 6 and 12 months of maintenance therapy, respectively**

	Group 1 "On-demand" treatment	Group 2 Daily treatment	Group 3 Intermittent treatment
Baseline	2.75±1.0	2.95±1.0	2.85±0.9
After 1 month	0.4±0.5	0.5±0.4	0.3±0.5
After 3 months	0.85±0.6	0.65±0.7	1.1±0.6
After 6 months	1.0±0.8	0.65±0.7	1.55±0.7
After 12 months	1.1±0.9	0.5±0.3	1.65±0.8

Table 3. **An overall satisfaction from treatment assessed on the VRS (mean ± SD) and the percentage of patients completely satisfied (% CS) with treatment depending on the type of therapy. There were no significant differences between the groups (* F-test and # χ^2-test)**

	Group 1 "On-demand" treatment		Group 2 Daily treatment		Group 3 Intermittent treatment	
	VRS*	% CS#	VRS*	% CS#	VRS*	% CS#
After 3 months	2.85±0.48	90%	3±0	100%	2.85±0.48	90%
After 6 months	2.9±0.3	90%	2.95±0.22	95%	2.8±0.52	85%
After 12 months	2.9±0.3	90%	2.95±0.22	95%	2.75±0.63	85%

The assessment of therapy costs demonstrated the daily regime to be the most expensive, with the mean expenditure of PLN 151.6 per patient. "On-demand" therapy was cheaper by approximately 30%, with the mean cost of PLN 110.2 per person, and the mean cost of intermittent therapy was lower by approximately 55%, amounting to PLN 68.9 per patient.

Discussion

In patients with GERD, both in initial treatment and in maintenance therapy, proton pump inhibitors are the medication of choice [12]. In recent years, several pharmacological treatment protocols for long-term therapy have been developed, including "on-demand" therapy, daily therapy with low PPI doses, and intermittent therapy, consisting in PPI administration over several weeks in case of recurrent symptoms [4,5]. In numerous investigations completed to-date, the effectiveness to the above-mentioned therapeutic protocols has been demonstrated as compared to placebo [6,13-15]. Nevertheless, no study has been yet conducted that would assess treatment efficacy depending on the degree of reflux symptom intensity. Although there is no correlation between symptom intensity and the intensity of inflammatory lesions involving the esophagus, nevertheless, the severity of the complaints may affect the therapeutic requirements of patients with GERD. This has led the present authors to attempt a pilot comparison of the efficacy and costs of employing the above treatment protocols in maintenance therapy in patients with NERD who report mild complaints.

The investigation has confirmed the high effectiveness of both daily therapy with low PPI doses and "on-demand" therapy. In the latter group, the patients took a PPI capsule every third day on the average, what most likely resulted from their taking the medication not only when they actually experienced reflux-associated symptoms, but also as a "preventive" measure. Nevertheless, the patients highly valued this therapeutic method, emphasizing their ability to individually match taking the medication to their personal needs. Thus, "on-demand" therapy was found to be significantly more cost-effective than daily treatment as it was both as high effective and 30% cheaper (significant difference) than daily treatment. On the other hand, intermittent therapy was characterized by a significantly lower efficacy rate (than both daily treatment and "on-demand" therapy) observed as early as within the initial six months of follow-up, yet, nevertheless, it was also well appreciated by the patients in terms of general satisfaction non-significantly different from other analyzed therapeutic models. This therapeutic model was a source of dissatisfaction for those individuals,

who experienced recurrent disease within a very short time. For others, the overall satisfaction rate was not dependant on the maintenance therapy model, as patients suffered from symptoms of mild intensity, not limiting their daily activity, and achieving a longer time between the relapses was a satisfactory outcome for most of them.

The investigation also confirmed the economic benefits resulting from employing "on-demand" therapy and intermittent therapy, similarly as it was demonstrated by other authors [8,9,16,17].

Summing up, the present authors believe that in long-term treatment of patients with NERD characterized by mild complaints, both "on-demand" therapy and intermittent therapy may be beneficial in view of their effectiveness and economic advantages. However, due to a pilot character of this study further investigation based on a larger number of patients is necessary to confirm the clinical value of cheaper models of maintenance therapy which could be then recommended as more cost-effective than much more expensive daily treatment.

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