Endoscopic and histological verification of upper GI tract side effects after long-term therapy with alendronate and strontium ranelate

Endoskopowa i histopatologiczna weryfikacja objawów niepożądanych ze strony górnego odcinka przewodu pokarmowego po leczeniu alendronianem oraz ranelinianem strontu

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Key words: upper GI tract side effects, bisphosphonates, strontium ranelate.
Słowa kluczowe: objawy niepożądane, bisfosfoniany, ranelinian strontu.

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Abstract

Aim: The aim of the study was to compare the endoscopic and histological changes in the upper GI tract after Aln and Sr treatment in patients with nausea, dysphagia and abdominal pain, which led to discontinuation of the therapy with alendronate (Aln) and strontium ranelate (Sr).

Material and methods: 31 postmenopausal women treated with 70 mg/daily Aln or Sr 2.0 g/daily for reporting upper GI tract side effects such as abdominal pain and/or discomfort, nausea and vomiting which led to the discontinuation of the therapy within the last 7 days underwent gastroduodenoscopy with standardized biopsy.

Results: In the whole study group, the most common side effects were dyspepsia and epigastric pain. In the stomach, the most frequent histopathological feature in both Aln and Sr groups was inactive chronic inflammation ($p < 0.05$). Visible erythema and/or friability were observed in 38% of patients in the Aln group and in 2 patients of the Sr group (20%) ($p < 0.05$). The frequency of mucosal atrophy was significantly higher in the Sr group ($p < 0.05$).

Conclusions: The incidence of less severe gastric events, such as erythema, mucosal haemorrhages or erosions, was similar in both Aln and Sr groups; however, the occurrence of chronic atrophic gastritis was significantly higher in the Sr group.

Streszczenie

Cel: Celem pracy było porównanie zmian endoskopowych oraz morfologicznych w zakresie górnego odcinka przewodu pokarmowego po leczeniu alendronianem (Aln) i ranelinianem strontu (Rs) u pacjentów, u których wystąpiły objawy niepożądane, takie jak nudności, dysfagia i ból w nadbrzuszu, będące przyczyną przerwania terapii.

Materiał i metody: Trzydziestu jeden pomenopauzalnym kobietom przyjmującym Aln (70 mg/dobę) lub Rs (2 g/dobę), zgłaszającym objawy niepożądane ze strony górnego odcinka przewodu pokarmowego, będące powodem przerwania leczenia w ostatnich 7 dniach, wykonano badanie gastroduodenoskopowe wraz z pobraniem bioptatów błony śluzowej.

Wyniki: W całej grupie badanej najczęściej zgłaszanymi objawami były dyspepsja oraz ból w nadbrzuszu. W odniesieniu do błony śluzowej żołądka w obydwu badanych grupach (Aln i Rs) wyniki badania histopatologicznego najczęściej wykazywały przewlekły stan zapalny o niskim lub umiarkowanym stopniu nasilenia i niewielkiej aktywności ($p < 0,05$). W badaniu endoskopowym wykazano przekrwienie i/lub kruchość śluzówki żołądka u 38% pacjentów leczonych Aln i u dwóch (20%) przyjmujących Rs ($p < 0,05$). Przewlekłe zanikowe zapalenia błony śluzowej żołądka częściej stwierdzano w grupie leczonej Rs ($p < 0,05$).

Wnioski: Częstość występowania niewielkich uszkodzeń śluzówki żołądka, takich jak przekrwienie, drobne ogniska krwotoczne i/lub drobne nadżerki, była podobna w grupach Aln i Rs, natomiast przewlekłe zanikowe zapalenia błony śluzowej częściej stwierdzano w grupie leczonej Rs.

Introduction

A large number of drugs may cause clinical gastrointestinal side effects, which manifest in the majority of cases as diarrhoea, constipation and nausea or vomiting. Although the main drug-induced gastrointestinal macroscopic pathologies such as variable inflammatory processes and ischaemia, ulcerations and strictures are well recognized, the pathology of the injury usually remains unknown [1, 2]. The most common microscopic patterns found are: apoptosis, cytoplasmic vacuolation, and increased intraepithelial lymphocytes and eosinophils [3-6]. However, the main diagnostic problems are that these pathological changes are not drug-specific, and that there is no exact time relationship between a drug and the occurrence of pathology, which in fact means that early drug-induced GI tract injury is generally missed in clinical practice [7]. Instead of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), bisphosphonates are responsible for the commonest gastrointestinal complications accounting for hospital admissions, which usually are oesophageal and gastric ulceration and bleeding.

Bisphosphonates are selective inhibitors of bone resorption and have been shown to be effective in the treatment and prevention of osteoporosis in both women and men. The characteristics of the different bisphosphonates are determined by substitutions on their amino side chains, and among nitrogen-containing bisphosphonates, pamidronate, alendronate and risedronate are approved for use in humans. In several clinical trials, alendronate (Aln), when used in both 10 and 70 mg tablets, was well tolerated with an adverse events ratio of a value similar to those of placebo [8-10]. However, in a large, placebo-controlled double blind, long-term, multicentre study, abdominal pain was significantly more frequent in postmenopausal women treated with 10 mg/day Aln, compared to the placebo group [11]. Moreover, with its widespread use for the treatment and prevention of osteoporosis, reports have emerged that a proportion of patients have experienced adverse gastrointestinal events, such as abdominal pain and nausea [12, 13]. Several reports also showed severe GI tract injures such as severe oesophagitis, oesophageal ulceration, gastric ulceration and bleeding [14, 15]. Pyridinyl bisphosphonate (risedronate) seems to have a somewhat better overall gastrointestinal safety profile, and the differences in their potential to damage the gastrointestinal mucosa may be related to the differences in molecular structure, e.g. side chains which, in part, determine the degree to which they interfere with this mucus barrier [16, 17]. The mechanism by which bisphosphonates develop gastrointestinal injury may be attributed to topical irritation together with compromise of the surface hydrophobic phospholipid barrier of gastric tissue, rather than to any systemic effect [18]. Topical mucosal injury may be potentiated by an acidic environment; however, the precise mechanism has not yet been elucidated [19].

Strontium ranelate (Sr) is a new orally active drug that may dissociate bone formation and bone resorption by allowing continued production of bone while decreasing bone resorption [20]. In the large, placebo-controlled double blind, long-term, multicentre studies, where Sr was administered to postmenopausal osteoporotic women, the number of upper gastrointestinal tract-related adverse events was similar to those of placebo [21, 22]. However, the most common symptoms, such as nausea, diarrhoea, headache, and dermatitis, were more frequent in treated patients during the first 3 months of therapy [21-23].

The primary aim of both bisphosphonate and Sr therapy is a reduction of osteoporotic fracture incidence, which can be achieved only by means of long-term drug administration. In spite of the fact that it is unclear for how long postmenopausal osteoporosis should be treated, and when the treatment should be stopped, it appears that for up to 10 years Aln therapy is effective and safe [24], and similarly in the case of Sr, where the observation period reaches 5 years [21, 22]. However, even during much shorter treatment periods, many patients are not able to maintain adherence to the therapy, either being non-compliant, or non-persistent, or both, which can make the treatment inefficient [25, 26]. Most of the data relating to non-adherence to treatment due to GI tract side effects come from prospective, pre-designed clinical trials which, in fact, have limitations, e.g. they focus only on aspects which have been asked before the start of the study or the hypothesis, they usually do not profoundly analyze the reason for withdrawal by the patient, and finally, they are biased by specific patient selection.

Therefore, we decided to use a retrospective approach to answer the question whether both Aln and Sr related withdrawal in patients with GI tract side effects occurring during therapy was related to the organic pathology. Short-term endoscopy studies are routinely used to assess the effects on the upper gastrointestinal mucosa of drugs with a potential to induce gastrointestinal irritation, and the effects on the gastrointestinal mucosa noted in these studies have correlated well with clinical experience [27]. We

postulate that, at least in the Aln group, the observed symptoms might be induced by mucosal injury which resulted in an inflammatory reaction within the upper gastrointestinal tract mucosa.

Material and methods

Subjects

The study was conducted at the Osteoporosis Outpatient Department and Department of Endoscopy of the Institute of Agricultural Medicine in Lublin. The study was approved by the institution's Research Ethics Board. Each subject provided written, informed consent for participation in the study. Subjects were eligible for the study if they met the following inclusion criteria: prior history of osteoporosis diagnosed by lumbar spine or femoral neck DEXA (dual energy X-ray absorptiometry) measurement and treated with 70 mg/daily Aln or Sr 2.0 g/daily for a period of at least 6 months according to the labelling instructions; upper GI tract side effects such as abdominal pain and/or discomfort, nausea and vomiting which led to the discontinuation of the therapy within the last 7 days. Subjects were excluded from the study if they met any of the following exclusion criteria: prior history of peptic ulcer disease, erosive oesophagitis, or erosive gastritis; prior oesophageal, gastric or duodenal surgery; active treatment with an H_2-receptor antagonist, proton pump inhibitor, sucralfate, misoprostol, cisapride, or metoclopramide; ingestion of aspirin or NSAID within 30 days; known alcohol abuse; surreptitious drug taking; or if they had a significant coexisting illness that contraindicated endoscopic evaluation. Participants also underwent a baseline screening assessment which included a medical history and physical examination.

Procedures

At the screening visit, subjects gave their medical history, underwent a physical examination, and were referred for upper GI tract endoscopy.

Endoscopy

For each subject, the same endoscopist performed the evaluations. Investigators and other personnel participating in the endoscopic evaluations were blinded to the subjects' treatment allocation. The appearance of the mucosa of the oesophagus, stomach, and duodenum was evaluated and scored using oesophago-gastroduodenoscopy scores (EGs) which were mainly based on the Hetzel-Dent grading/scoring system [28] and the Lanza grading system [29] (Table I). Double biopsies for histology were taken from the gastric antrum, body, duodenal bulb and oesophagus (20-30 mm above the "Z" line) and for rapid urease testing (GUT Plus, Gatrex, Warsaw, Poland). Erosions were defined as erythematous superficial mucosal defects that disrupted the epithelium and were not ulcers. Ulcers were defined as breaks in the mucosa ≥ 3 mm in diameter with apparent depth. Ulcer diameter was to be estimated by apposition of endoscopic forceps with defined dimensions [28-30].

Histopathology

The biopsy specimens were fixed in 10% buffered formalin and embedded in paraffin blocks. Next, 3 mm thick sections were cut and routinely stained with haematoxylin and eosin (H & E) and mucicarmine. In each case, the following features were microscopically evaluated using the visual analogue scales (according to the updated Sydney System): inflammation (presence of lymphocytes and plasma cells within the lamina propria) and its activity (presence of neutrophils), glandular atrophy, intestinal metaplasia (complete or incomplete), and presence of *Helicobacter pylori* (HP) in the superficial mucus.

Data analysis

Basic descriptive statistics were calculated, i.e. mean values. To compare results between treatment groups (Aln vs. Sr) Fisher's exact test was used. P-values less than 5% were regarded as statistically significant for each end point. Statistical analysis was performed with the STATISTICA package.

Results

A total of 85 osteoporotic postmenopausal women who had discontinued treatment with Aln or Sr because of upper GI tract side effects were screened. Of these women, 31 fulfilled all inclusion criteria and were referred for upper GI tract endoscopy. Their mean age was 56.2 (range 50-61 years).

Side effects

In the whole study group, the most common side effects were dyspepsia (100% in Aln and Sr groups, respectively) and epigastric pain (87.7% in Aln and 80% in Sr). Both vomiting and nausea were experienced only in the Aln group (14%), whereas diarrhoea and flatulence were noted in the Sr group more frequently when compared to the Aln group (14.3% in Aln and 40% in Sr and 47.6% in Aln and 80% in Sr, respectively) ($p < 0.05$) (Table I).

Histopathological changes

In the oesophagus, no abnormal histological features were observed in the Aln group, whereas in the Sr group, 1 case of chronic inflammation was diagnosed (Table II).

Table I. Most frequent side effects from upper GI tract

Tabela I. *Najczęściej zgłaszane objawy niepożądane ze strony górnego odcinka przewodu pokarmowego*

Symptoms	Treatment	
	Alendronate n = 21 (67.7%)	Strontium ranelate n = 10 (32.3%)
Epigastric pain	18 (87.7%)	8 (80%)
Headache	4 (19.4%)	1 (10%)
Dyspepsia	21 (100%)	10 (100%)
Nausea*	3 (14.3%)	0 (0%)
Vomiting*	3 (14.3%)	0 (0%)
Diarrhoea*	3 (14.3%)	4 (40%)
Flatulence*	10 (47.6%)	8 (80%)

**Statistically significant at p < 0.05 (Fisher's exact test)*

Table II. Histopathological features of oesophagus in osteoporotic postmenopausal women who have discontinued treatment with alendronate or strontium ranelate because of upper GI tract side effects

Tabela II. *Zmiany histopatologiczne w przełyku u pomenopauzalnych kobiet z osteoporozą, które przerwały terapię alendronianem lub ranelinianem strontu z powodu wystąpienia objawów niepożądanych ze strony górnego odcinka przewodu pokarmowego*

Histopathology	Alendronate n = 21 (67.7%)	Strontium ranelate n = 10 (32.3%)
Normal epithelium of the oesophagus*	16 (76%)	6 (60%)
Normal epithelium of the oesophagus (+ hyperplasia)*	2 (9.5%)	3 (30%)
Normal epithelium of the oesophagus (+ parakeratosis)	2 (9.5%)	0 (0%)
Hyperplasia of the stratified squamous epithelium, parakeratosis	1 (4.7%)	0 (0%)
Chronic oesophagitis (+)	0 (0%)	1 (10%)

**Statistically significant at p < 0.05 (Fisher's exact test)*

In the gastric body, the most frequent histopathological feature was inactive chronic inflammation of medium grade severity (85.7% in Aln and 80% in Sr). Similarly, in the antrum, the most frequent histopathological feature in both groups was inactive chronic inflammation of medium grade severity. Active chronic inflammation was diagnosed only in the Aln group (9.5%). The histopathological picture of gastric mucosa chronic inflammation in the Aln group was more diverse than in the Sr group, e.g. intestinal metaplasia (23.7%) and focal foveolar hyperplasia were also seen (9.5%) (Tables III and IV).

With regard to the duodenal bulb, chronic bulbitis was diagnosed in 76.2% of patients in the Aln group, whereas in the Sr group chronic bulbitis was diagnosed in the whole study group (100%) (Table V).

Endoscopic changes and endoscopic grading scales

In general, there were no ulcers or large erosions in both groups of patients treated with Aln or Sr. However, there was a marked difference in type and severity of the endoscopic changes between the Aln and Sr groups.

Table III. Histopathological features of body of stomach in osteoporotic postmenopausal women who have discontinued treatment with alendronate or strontium ranelate because of upper GI tract side effects

Tabela III. *Zmiany histopatologiczne w trzonie żołądka u pomenopauzalnych kobiet z osteoporozą, które przerwały terapię alendronianem lub ranelinianem strontu z powodu wystąpienia objawów niepożądanych ze strony górnego odcinka przewodu pokarmowego*

Histopathology	Alendronate n = 21 (67.7%)	Strontium ranelate n = 10 (32.3%)
Normal gastric mucosa	3 (14%)	4 (20%)
Inactive chronic gastritis (+), HP (–)*	11 (52%)	6 (80%)
Inactive chronic gastritis (+), HP (–), focal haemorrhage of the mucosa	2 (9.5%)	0 (0%)
Active (+) chronic gastritis (+), HP (–)	1 (4.7%)	0 (0%)
Inactive chronic gastritis (++), HP (–)	1 (4.7%)	0 (0%)
Active (+) chronic gastritis (++), HP (–)	2 (9.5%)	0 (0%)
Active (+) chronic gastritis (++), HP (–), focal haemorrhage of the mucosa	1 (4.7%)	0 (0%)

**Statistically significant at p < 0.05 (Fisher's exact test)*

With regard to the stomach, normal mucosa was diagnosed only in 3 patients in the Aln group (14.2%) and in 1 subject in the Sr group (10%). Two points on the EG scale, reflecting visible erythema and/or friability, were observed in 8 (38%) patients in the Aln group and in 2 patients in the Sr group (20%) ($p < 0.05$). The percentage of patients with EGs = 4, which reflected the existence of erosions, was greater in the Sr group, while with EGs = 5 (≤ 3 erosions or an ulcer) it was greater in the Aln group (2 patients, 20% and 2 patients, 9.5%, respectively). Importantly, mucosal atrophy was visible in both study groups; however, the frequency was significantly higher in the Sr group (7 patients, 33.3% vs. 6 patients, 60%, $p < 0.05$). In the duodenum, normal mucosa was diagnosed in 12 patients (57%), 9 in the Aln group and in 4 patients (40%) in the Sr group. Erythema and/or friability (EGs = 2) was noticed in 9 patients (42.8%) in the Aln group and in 6 patients (60%) in the Sr group ($p < 0.05$). Duodenal erosions (EGs = 4) were observed in 1 patient (10%) in the Sr group. No oesophageal lesions were observed in either treatment group.

Oesophageal hiatus hernia was diagnosed in 6 patients (28%) in the Aln group and in 3 patients (30%) in the Sr group.

Four patients (19%) in the Aln group were infected with HP, in whom 1 had (25%) 2 points on the EG scale, reflecting visible erythema and/or friability, while 3 (75%) were diagnosed with chronic atrophic gastritis.

There was no apparent correlation between the occurrence of specific upper gastrointestinal adverse events and endoscopic changes/EG scores in subjects treated with Aln and Sr ($p < 0.05$).

Table IV. Histopathological features of antrum of stomach in osteoporotic postmenopausal women who have discontinued treatment with alendronate or strontium ranelate because of upper GI tract side effects

Tabela IV. *Zmiany histopatologiczne w części przedodźwiernikowej żołądka u pomenopauzalnych kobiet z osteoporozą, które przerwały terapię alendronianem lub ranelinianem strontu z powodu wystąpienia objawów niepożądanych ze strony górnego odcinka przewodu pokarmowego*

Histopathology	Alendronate n = 21 (67.7%)	Strontium ranelate n = 10 (32.3%)
Normal gastric mucosa	0	2 (20%)
Inactive chronic gastritis (+), HP (–)*	12 (57%)	8 (80%)
Inactive chronic gastritis (+), HP (–), focal foveolar hyperplasia	1 (4.7%)	0 (0%)
Active (+) chronic gastritis (+), HP (–)	2 (9.5%)	0 (0%)
Inactive chronic gastritis (+), HP (–), complete intestinal metaplasia (++)	1 (4.7%)	0 (0%)
Inactive chronic gastritis (++), HP (–)	1 (4.7%)	0 (0%)
Inactive chronic gastritis (++), HP (–), incomplete intestinal metaplasia (++)	2 (9.5%)	0 (0%)
Inactive chronic gastritis (++), HP (–), complete intestinal metaplasia (+)	1 (4.7%)	0 (0%)
Inactive chronic gastritis (++), HP (–), focal foveolar hyperplasia	1 (4.7%)	0 (0%)
Inactive chronic gastritis (++), HP (–), complete intestinal metaplasia (+++)	1 (4.7%)	0 (0%)
Inactive chronic gastritis (+++), HP (–)	1 (4.7%)	0 (0%)

**Statistically significant at p < 0.05 (Fisher's exact test)*

Discussion

Long-term treatment with Aln use is considered to be associated with excess risk for upper GI tract complications, especially among the elderly, patients with a history of upper GI tract disease, and patients

Table V. Histopathological features of duodenal bulb in osteoporotic postmenopausal women who have discontinued treatment with alendronate or strontium ranelate because of upper GI tract side effects

Tabela V. *Zmiany histopatologiczne w opuszce dwunastnicy u pomenopauzalnych kobiet z osteoporozą, które przerwały terapię alendronianem lub ranelinianem strontu z powodu wystąpienia objawów niepożądanych ze strony górnego odcinka przewodu pokarmowego*

Histopathology	Alendronate n = 21 (67.7%)	Strontium ranelate n = 10 (32.3%)
Normal duodenal mucosa*	5 (23.8%)	0 (0%)
Chronic bulbitis, HP (–)*	4 (19%)	1 (10%)
Chronic bulbitis (+), HP (–)*	8 (38%)	5 (50%)
Chronic bulbitis (++), HP (–)*	2 (9.5%)	4 (40%)
Active chronic bulbitis, HP (–)	1 (4.7%)	0 (0%)

**Statistically significant at p < 0.05 (Fisher's exact test)*

taking NSAIDs. However, in some studies the effects of age, history of upper GI tract disease, and NSAID use were not visible, suggesting that Aln does not increase the risk of developing oesophageal complications or gastroduodenal ulcerations/bleeding AEs [31]. Several clinical trials have also shown that Aln treatment has a favourable tolerability profile [8, 32, 33]. On the other hand, there are also clinical studies, including both case reports and short-term endoscopic studies, demonstrating that Aln treatment may not be tolerated in a substantial proportion of patients [12, 14, 34-40]. Some clinical observations suggest that about 1 in 3 elderly women taking Aln for osteoporosis report gastrointestinal symptoms, a rate much higher than that found during clinical trials. Moreover, outpatient visits and hospital admissions for acid-related upper gastrointestinal disorder (ARD) among women taking Aln were so frequent that the authors simply suggest including the costs of treating ARD in the cost/benefit analyses of Aln therapy [41]. Postmenopausal women taking Aln were more likely to discontinue treatment because of an oesophageal event, but the possible association has limited importance due to the small number of observed cases [31]. Discontinuation of Aln therapy due to gastroduodenal events is also documented, and the most commonly observed mucosal lesions are gastric erosions [39].

The most important result of our study is that in women who experienced upper GI tract side effects and discontinued the therapy, Aln and Sr at a dose for the treatment and prevention of postmenopausal osteoporosis were not associated with serious complications such as ulcer formation in any region investigated. The absence of an association between Aln and ulcer formation in this study differs from the results of endoscopy studies, in which gastric ulceration occurred consistently in 8-10% of subjects treated [29, 39, 40]. However, drawing conclusions from the direct comparison has its limitations because our population was pre-selected according to the occurrence of GI tract side effects. On the other hand, this also makes our study particularly interesting and original, since in most of the endoscopic studies the duration of treatment evaluated was relatively brief (usually 14 days) [16, 17,

Table VI. Oesophago-gastroduodenoscopy scores for evaluating the condition of mucosa in oesophagus, stomach and duodenum [28, 29] (alendronate n = 21, 67.7%, strontium ranelate n = 10, 32.3%)
Tabela VI. *Endoskopowa ocena zmian śluzówkowych przełyku, żołądka i dwunastnicy [28, 29] (alendronian, n = 21, 67,7%, ranelinian strontu n = 10, 32,3%)*

	Grading	Treatment	
		Al	Sr
Oesophagus			
1	Normal mucosa (no visible abnormalities)	21 (100%)	10 (100%)
2	Erythema, and/or friability visible (no erosions)	0 (0%)	0 (0%)
3	Ulcerations or erosions (< 3 mm) in distal part of oesophagus	0 (0%)	0 (0%)
4	Ulceration or erosions anywhere in the oesophagus	0 (0%)	0 (0%)
5	Stricture	0 (0%)	0 (0%)
Stomach			
1	Normal mucosa (no visible abnormalities)	3 (14.2%)	1 (10%)
2	Erythema, and/or friability visible (no erosions)*	8 (38%)	2 (20%)
3	Mucosal haemorrhages (< 25)	2 (9.5%)	1 (10%)
4	1 to 2 erosions, or > 25 haemorrhages	0 (0%)	2 (20%)
5	≤ 3 erosions or an ulcer	2 (9.5%)	0 (0%)
6	Mucosal atrophy*	7 (33.3%)	6 (60%)
Duodenum			
1	Normal mucosa (no visible abnormalities)	12 (57%)	4 (40%)
2	Erythema, and/or friability visible (no erosions)	9 (42.8%)	6 (60%)
3	Mucosal haemorrhages (< 25)	0 (0%)	0 (0%)
4	1-2 erosions, or > 25 haemorrhages	0 (0%)	1 (10%)
5	≤ 3 erosions or an ulcer	0 (0%)	0 (0%)

**Statistically significant at $p < 0.05$ (Fisher's exact test)*

42], considering that bisphosphonates are usually prescribed continuously for several years. The lack of serious mucosal injures in patients discontinuing therapy with Aln because of GI tract side effects may be explained by the fact that long-term treatment allows mucosal adaptation and alters the severity, pattern and mechanism of injury [42]. This feature was previously demonstrated in studies with, e.g., indomethacin [43].

Surprisingly, gastric erosions occurred in both the Aln and Sr groups (9.5 and 20%, respectively), although they were more severe in the Aln group (gastroduodenal EG scale = 5). The percentage of subjects with non-significant gastric mucosal injury (gastroduodenal EG scale ≤ 4), which consists predominantly of petechial haemorrhages and/or fewer than 3 erosions, was also similar in both treatment groups. This, in fact, means that generally Aln administration was not associated with higher mucosal damage in all the examined locations when compared to Sr. Although the importance of this findings is not clear due to the small number of observations, and, last but not least, because such lesions are common in the general population and do not appear to progress to more serious abnormalities, a true association with both Aln and Sr therapy cannot be ruled out. However, these results also offer no reassurance that significant complications did not occur all, since endoscopy was performed from 1-8 days after the symptoms occurred (mean period = = 3 days, data not shown).

What is of importance here is that during endoscopy in both treatment groups we observed a high rate of chronic gastritis (in concordance with histopathology), which was significantly higher in the Sr group compared to the Aln group (60.0 vs. 33.3%). For half of the cases of chronic gastritis diagnosed in the Aln group, the possible explanation could be HP infection (14.2%); for the remainder, we speculate that chronic gastritis could be the result of both prolonged acute gastritis induced by Aln and/or other factors, and mucosal adaptation to persistent irritation. It is noteworthy that there are no data available concerning whether HP infection will accentuate Aln-induced mucosal damage in humans. The appearance of chronic gastritis among the Sr treated patients needs to be further elucidated, since none of the patients was HP infected or had any other risk factors for chronic gastritis. It is also noteworthy that the results for both human and animal prospective studies showed that Sr does not induce any acute or subchronic toxic effect on the gastric mucosa, the oesophagus or the first part of the duodenum, which means in fact that Sr by the oral route was safe for the gastric mucosa [21-23, 44].

Conclusions

Spontaneously occurring upper GI tract side effects during long-term therapy with both Aln and Sr at standard doses for the treatment of postmenopausal osteoporosis were not associated with the development of oesophageal, gastric or duodenal ulcers in postmenopausal women. These findings contrast with the results of endoscopic studies of Aln in which the gastric ulceration rate ranged from 8 to 10%. The incidence of less severe gastric events, such as erythema, mucosal haemorrhages or erosions, was similar in both Aln and Sr groups; however, the occurrence of chronic atrophic gastritis was significantly higher in the Sr group. Since risk/benefit analyses of Aln therapy are readily available, the results of this study suggest the need for post-marketing surveillance to clarify the nature, frequency and magnitude of gastrointestinal liability associated also with the use of Sr.

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