Omeprazole and subacute cutaneous lupus erythematosus

Introduction

Omeprazole is a selective and irreversible proton pump inhibitor (PPI). It suppresses gastric acid secretion by specific inhibition of the hydrogen–potassium adenosinetriphosphatase (H⁺, K⁺-ATPase) enzyme system found at the secretory surface of parietal cells. Omeprazole is indicated in benign peptic and duodenal ulcers, reflux esophagitis, severe reflux esophagitis in children above the age of 1 year, treatment of reflux symptoms, acid-related dyspepsia and Zollinger-Ellison syndrome. Beside this, it may be used as prophylaxis in patients, who have to be treated with NSAIDs, but have a medical history of peptic ulcer, erosions or symptoms of dyspepsia. Omeprazole is also used in combination with antibiotics for eradication of Helicobacter pylori in peptic and duodenal ulcers.

Omeprazole is available as capsules (10, 20, and 40 mg), and also as MUPS (Multiple Unit Pellet System) tablets (10, 20, and 40 mg). Omeprazole capsules reached the Dutch market in 1988, omeprazole MUPS in 1998.

The most common adverse reactions described in the SmPC are nausea, vomiting, diarrhoea, constipation, abdominal pain and flatulence and headache. As skin reactions dermatitis, pruritus, skin rash and urticaria, alopecia and photosensitivity are mentioned, but also severe conditions as Erythema Multiforme, Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis; Subacute Cutaneous Lupus Erythematosus (SCLE) is not mentioned [1,2].

Other PPIs available on the Dutch market are pantoprazole (Pantozole®), lansoprazole (Prezal®), rabeprazole (Pariet®) and esomeprazole (Nexium®). SCLE is not mentioned in either of the SmPCs of these drugs [6-9].

Subacute cutaneous lupus erythematosus (SCLE) is a subtype of Cutaneous Lupus Erythematosus that usually manifests as non-scarring annular, polycyclic erythematous scaly plaques or confluent papulosquamous (psoriasiform) lesions on sun-exposed skin with limited systemic involvement [3,4]. Most common areas are upper back, chest, dorsal arms and lateral neck, but also on face and scalp. SCLE is typically associated with positive ANA, SSA/anti-Ro antibodies and anti-La/SSB antibodies findings, but usually negative for antidsDNA antibodies. It correlates with certain HLA types (A1, B8, DR3). Sometimes SLCE is associated with deficiency of complement components such as C2, C4 and C1q [5]. Possible triggers are ultraviolet radiation and cigarette smoking.

Skin biopsy is usually characteristic by a lymphocytic interface dermatitis with vascular degeneration of the epidermal basal layer and necrotic keratinocytes. The diagnosis is based upon clinical and histopathological correlation; direct immunofluorescence and serological tests may be supportive [3].

Reports

Until 15 January 2013, the Netherlands Pharmacovigilance Centre Lareb received 2 reports of SCLE in association with omeprazole.

Lareb report 116381
Patient A is a female aged 71 years or older with SCLE, based upon histopathology diagnosed by a dermatologist, following administration of omeprazole 40 mg daily for reflux oesophagitis with a latency of 7 weeks after start. Concomitant suspected medications were atenolol 25 for hypertension, which
was started 2 years before and simvastatin 20 mg for hypercholesterolaemia, started 7 years before the reaction. The next month omeprazole was switched to ranitidine and one month later also simvastatin was discontinued. Patient recovered within 2 months. Reintroduction of simvastatin did not result in recurrence of complaints, hence omeprazole was assessed as suspected drug for the SCLE. Patient remained without symptoms for the next year. Other chronic concomitant medications were candesartan for hypertension and levothyroxine for hypothyroidism.

Lareb report 137630
Patient B is a female aged 71 years or older, with a medical history of mastectomy and rheumatic polymyalgia ten years ago, for which she had used prednisolone during two years. In the past she suffered from a slight cutaneous reaction after two months use of omeprazole, which recovered after discontinuation. Half a year later she restarted omeprazole 20 mg daily for dyspepsia. After two months she developed increasing skin lesions on arms and chest, diagnosed as SCLE by the reporting rheumatologist. Biopsy showed vacuolar interface dermatitis. Anti SS-B and anti SS-A were both positive, anti-ds DNA and other ENA antibodies were negative. Omeprazole was discontinued and patient was treated with clobetasole cream. Patient was recovering at the time of reporting (2 months after withdrawal). Concomitant medication was not reported.

Other sources of information

Literature
Several case reports describe the association between omeprazole and either induction or exacerbation of SCLE [5,10,11]. Also for other PPIs an association with SLCE is mentioned. The first article, published in 2001, is an association between pantoprazole and discoid lupus [12]. For lansoprazole [13-15] three publications of SCLE are found in the literature. Furthermore, Dam reported a case series of 5 additional patients with SCLE induced or exacerbated by PPIs [3]. Finally a literature review was published upon SCLE and PPI intake, with one additional case on lansoprazole [16]. Mostly women were involved, aged between 51 and 85. In the majority of SCLE patients the latency ranged from three weeks to four months between start of the PPI and onset of symptoms. No improvement could be achieved with substantial immunosuppression, unless the suspected PPI was discontinued. In almost all cases resolution of symptoms took one to two months after discontinuation of the PPI. In two patients the PPI was not discontinued and active disease was present until death due to another cause, two years later. In one patient a positive re-challenge after 5 months was observed [13]. Most of the patients had ANA antibodies and anti-Ro antibodies; none of the reported subjects was positive for anti-histone antibodies, which are linked to drug-induced LE. Histology confirmed the diagnosis of SCLE.

Databases
On January 15, 2013, the database of the Netherlands Pharmacovigilance Centre contained two reports of SCLE in association with omeprazole. No reliable ROR could be calculated because of the low number of cases. SLCE was not reported in association with other proton pump inhibitors (PPIs).

On January 15, 2013, the WHO database of the Uppsala Monitoring Centre contained 24 reports of Cutaneous Lupus Erythematosus (CLE) in association with omeprazole with a ROR of 6.75 (4.49-10.14). This preferred term CLE contains discoid LE, SCLE, acute CLE and chronic CLE as lower level terms. In four of
these omeprazole cases a positive re-challenge was observed. Also for other individual PPIs, including lansoprazole, pantoprazole and esomeprazole, respectively 10, 7 and 7 reports of CLE were observed, all with an individual ROR (95 % CI) >1. The combined ROR for all CLE reports in association with PPIs was also statistically significant (Table 1).

Table 1. Reports of Cutaneous Lupus Erythematosus in association with proton pump inhibitors in the WHO database

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of reports</th>
<th>ROR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>24</td>
<td>6.8 (4.5-10.1)</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>10</td>
<td>10.0 (5.3-18.6)</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>7</td>
<td>7.3 (3.5-15.4)</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>7</td>
<td>2.5 (1.2-5.3)</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>6.0 (4.5-8.0)</td>
</tr>
</tbody>
</table>

On February 13, 2013, the Eudravigilance database of the EMA contained a total of 71 reports of CLE associated with the use of PPIs. The ROR’s for the individual PPIs (except esomeprazole) and the combined ROR for all CLE reports in association with PPIs was statistically significant (Table 3).

Table 3. Reports of Cutaneous Lupus Erythematosus in association with proton pump inhibitors in the Eudravigilance database

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of reports</th>
<th>ROR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>22</td>
<td>7.6 (5.0 – 11.6)</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>30</td>
<td>15.0 (10.4 – 21.6)</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>12</td>
<td>5.2 (2.9 – 9.1)</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>5</td>
<td>1.9 (0.8 – 4.5)</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>71</td>
<td>7.2 (5.6 – 9.2)</td>
</tr>
</tbody>
</table>

Prescription data
The number of patients using proton pump inhibitors in the Netherlands is shown in table 4 [17].

Table 4. Number of patients using proton pump inhibitors in the Netherlands between 2007 and 2011

<table>
<thead>
<tr>
<th>Drug</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>1,039,000</td>
<td>1,220,000</td>
<td>1,376,000</td>
<td>1,596,000</td>
<td>1,700,000</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>510,090</td>
<td>561,880</td>
<td>571,880</td>
<td>622,240</td>
<td>699,060</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>23,971</td>
<td>21,916</td>
<td>19,612</td>
<td>18,653</td>
<td>17,468</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>69,684</td>
<td>71,740</td>
<td>70,307</td>
<td>60,424</td>
<td>56,654</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>284,320</td>
<td>310,670</td>
<td>344,730</td>
<td>340,750</td>
<td>338,020</td>
</tr>
</tbody>
</table>
Mechanism
The pathogenesis of drug induced SLCE remains speculative. Immune response to skin antigens modified by drugs and Fas-dependent apoptosis of epidermal basal keratinocytes are currently proposed as pathomechanisms for inducing and perpetuating skin lesions in SCLE. In SCLE, nuclear antigens such as Ro/SSA, translocate to the keratinocyte surface, where they are targeted by circulating anti-Ro/SSA antibodies and cytotoxic T cells. Finally, low numbers of regulatory T cells have recently been demonstrated in cutaneous LE, suggesting that a defective function of these cells may trigger a crescendo of autoimmunity potentially culminating in the skin illness [18]. No explicit information is available on the specific role of proton pump inhibitors in relation to this process. Beside drugs, this process has also been observed after UV exposure, viral illness and alterations in the cytosolic calcium milieu [14].

Class effects
The Lareb database contains two reports of SCLE for omeprazole. The WHO- and Eudravigilance database contains 48 respectively 71 reports of CLE associated with the use of several PPIs; almost all associations are reported disproportionally. In the literature publications on SLCE in relation to different PPIs can be found. Since all the PPIs have the same mechanism of action it would seem plausible that SCLE is a class effect.

Discussion

Drug induced SCLE versus idiopathic SCLE
There are no diagnostic criteria for drug induced (DI) SCLE. Clinically DI SCLE and idiopathic SCLE cannot be differentiated, but the mean age of patients is greater (59 years) and skin lesions on the lower extremities is suspicious for drug involvement. Histopathologically, perhaps an increased tissue eosinophilia might be present in DI SCLE. Associated drugs are hydrochlorothiazide, antihypertensive agents, statins and terbinafine. It is suggested that there is an association with drugs that cause phototoxicity or with the development of lichenoid eruptions, causing up-regulation of interferon-alpha-production. In DI SCLE there are no drug attributability algorithm. The mean time to onset of cutaneous features is 4-20 weeks from starting the drug and mean time of resolution is within 8 weeks after discontinuation. The Ro antibody remains positive after the clinical features have resolved [3-5,14,15].

Drug induced SCLE in association with proton pump inhibitors
Lareb has received two reports of subacute cutaneous lupus erythematosus in association with omeprazole in two older females. In patient A several concomitant medications were used. Simvastatin was ruled out as causative agent, because of a negative re-challenge. The patient recovered from the SCLE, despite continuation of the other concomitant medications, including atenolol, which, as antihypertensive, might have been a possible confounding drug to cause SCLE. In both reports the latency and resolution were in agreement with time courses in the literature. No results of laboratory tests are available.

SCLE was associated with PPIs in several publications mentioned earlier. It is difficult to differentiate drug induced SCLE from idiopathic SCLE, clinically as well as histologically. In some patients typical skin lesions on lower extremities were present, as is observed in drug induced SCLE. In all publications the temporal association with the start of the drug and the rapid resolution after drug withdrawal
confirmed a relationship with the causative PPI. Discontinuation of these PPIs resulted in a substantial improvement in symptoms, whereas in two cases continuation of the PPI caused a persistent skin rash, with high requirement for immunomodulating topical or systemic treatment.

Conclusion
Lareb has received two reports of subacute cutaneous lupus erythematosus in association with omeprazole. This association was supported by several publications and by the WHO- and Eudravigilance data, also for SCLE in relation to other proton pump inhibitors, hence implying a class effect. For this reason, it is suggested proton pump inhibitors might have a causative role in the occurrence of SCLE.

- New signal of subacute cutaneous lupus erythematosus in association with the use of omeprazole and other proton pump inhibitors.

References
2. Dutch SmPC Losec® MUPS. (version date: 8-10-2012, access date: 15-1-2013) http://db.cbg-meb.nl/IB-teksten/h21684.pdf.
17. College for health insurances. GIP database. (version date: 24-5-2011, access date: 3-11-2011) http://www.gipdatabank.nl/.
This signal has been raised on May 2013. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmwb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).