



Hypersensitivity reactions to proton pump inhibitors

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Purpose of review

Proton pump inhibitors (PPI) are one of most frequently prescribed drugs in the world. The purpose of this review is to describe the hypersensitivity reactions to PPI.

Recent findings

Hypersensitivity reactions to PPI vary from mild symptoms to life-threatening disorders. Cases of urticaria, angioedema, anaphylaxis, cytopenia, vasculitis, acute allergic interstitial nephritis, occupational contact dermatitis, photoallergic dermatitis, maculopapular eruption, erythroderma, Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, Stevens–Johnson syndrome/toxic epidermal necrolysis, and other autoimmune reactions (including cutaneous lupus erythematosus) have been described.

Summary

A high level of clinical suspicion is critical in the diagnosis of PPI-induced hypersensitivity reactions. Physicians should be aware of the possible hypersensitivity reactions due to PPI and routine/empirical prescription for PPI should only be used when clinically indicated.

Keywords

adverse drug reaction, hypersensitivity, proton pump inhibitor

INTRODUCTION

PPI are commonly used for the treatment of acid-related disorders such as gastroesophageal reflux disease, peptic ulcer disease and associated *Helicobacter pylori* infection, as they are potent inhibitors of gastric acid secretion. PPI are generally well tolerated. However, there have been some concerns about potential safety issues related to PPI usage [1^{••}]. When used during *H. pylori* eradication, drug allergy due to concomitant antibiotics (amoxicillin, clarithromycin, metronidazole, tinidazole, tetracyclines) used in triple therapy will also need to be excluded.

Potential safety issues associated with PPI are clopidogrel interaction [unclear but FDA has cautioned against the use of omeprazole (and esomeprazole) by clopidogrel users], *Clostridium difficile*/other enteric infections (probable), pneumonia (probable), hypomagnesemia (rare), idiosyncratic reactions such as acute interstitial nephritis/hepatitis (rare), anaphylaxis (rare), cytochrome P450 interaction (negligible), rebound hypersecretion (negligible), fractures (negligible), and pregnancy risk (likely negligible) [1^{••},2[•]]. PPI also may increase the risk of developing food allergy or IgE-mediated drug allergy in that inhibition or neutralization of gastric acid allow persistence of intact food allergens and protein-bound oral drugs with

enhanced capacity to sensitize and elicit allergic reactions via the oral route [3^{••},4].

This review will mainly focus on allergic and nonallergic hypersensitivity reactions to PPI. The clinical manifestations of PPI-induced hypersensitivity reactions are as follows:

- (1) Urticaria, angioedema, and anaphylaxis,
- (2) Cytopenia,
- (3) Vasculitis,
- (4) Acute allergic interstitial nephritis,
- (5) Contact dermatitis (occupational),
- (6) Photoallergic dermatitis,
- (7) Maculopapular eruption,
- (8) Erythroderma,
- (9) DRESS syndrome,

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KEY POINTS

- Hypersensitivity reactions to PPI may be immediate or nonimmediate.
- Skin prick and intradermal tests may be useful in immediate reactions and diagnosis of potential cross-reactivities.
- A high level of clinical suspicion is essential in the diagnosis of PPI-induced hypersensitivity reactions.
- Physicians should be aware of the possible hypersensitivity reactions due to PPI.
- Routine prescription for PPI should be strongly discouraged.

- (10) Stevens–Johnson syndrome/Toxic epidermal necrolysis, and
- (11) Other autoimmune reactions (including lupus erythematosus).

STRUCTURE OF PROTON PUMP INHIBITORS AND POSSIBLE MECHANISMS FOR HYPERSENSITIVITY

Most of PPI are weak bases composed of two moieties: a substituted pyridine and a benzimidazole. Tenatoprazole that has a longer half-life is an imidazopyridine-derivative. Protonation of the benzimidazole or imidazopyridine activates these pro-drugs, converting them to sulfenic acids/sulfonamides that react covalently with one or more cysteines accessible from the luminal surface of the ATPase (Fig. 1) [5,6].

Although the exact mechanism for PPI-induced hypersensitivity reactions is not revealed yet, three mechanisms such as hapten, prohaptent, and the p–i concept may play roles in the pathogenesis [7^{***}]. We can also assume the underlying mechanisms of the clinical manifestations according to a modified Gell and Coombs classification [8^{***}].

PROTON PUMP INHIBITOR-INDUCED URTICARIA, ANGIOEDEMA, AND ANAPHYLAXIS

Type I hypersensitivity reactions such as urticaria, angioedema, and anaphylaxis to omeprazole, lansoprazole, pantoprazole, and rabeprazole have been reported. Around 22 cases of PPI-induced anaphylaxis have been reported in English literature [6,9,10,11^{***},12,13^{*}].

The onset of symptoms ranged from minutes to hours. The largest case series reported nine patients with omeprazole allergy: urticaria/angioedema

in seven and anaphylaxis in two patients. Eight of the patients (88.9%) showed positive responses to omeprazole with skin prick tests or intradermal tests, which suggested IgE-mediated hypersensitivity. Four patients also showed a positive response to pantoprazole with skin prick test. However, only one patient showed a positive response to pantoprazole during drug provocation testing. Lansoprazole was well tolerated in this study: no one showed positive response with skin prick test or with controlled challenge test. This case series suggested that skin tests and controlled challenge tests should be performed before offering well tolerated alternative drugs [6].

A case of pantoprazole-induced anaphylaxis during general anesthesia has been reported with positive skin tests to pantoprazole demonstrated [12].

A high level of clinical suspicion and temporal relationship is critical in the diagnosis of PPI-induced hypersensitivity reactions. Skin tests (prick/intradermal test) and controlled challenge tests are helpful in the diagnosis of type I hypersensitivity reactions by PPI. Recently it has been proposed that basophil activation test (BAT) could be helpful in the diagnosis of IgE-mediated allergic reactions to PPI as an in-vitro study [6,10].

PROTON PUMP INHIBITOR-INDUCED CYTOPENIA

Cytopenia such as neutropenia and agranulocytosis are rare adverse events associated with PPI treatment. Most of previously published cases of isolated neutropenia have involved omeprazole: a case of omeprazole-induced neutropenia with further recurrence upon pantoprazole treatment has been recently published, which suggested a possible cross-reactivity between omeprazole and pantoprazole. Leukopenia is described as a possible adverse effect in the summary of product characteristics of PPIs [14]. PPI-induced thrombocytopenia, which is rare but could be severe, has also been reported [15,16]. However, one study [16] showed there was no difference in the occurrence of thrombocytopenia between pantoprazole (6.2%) and control group (6.6%). Hemolytic anemia after PPI use also has been reported, in which hemoglobin level was restored after the discontinuation of omeprazole [17].

Although the exact mechanisms are not revealed yet, the possible mechanisms to explain the pathogenesis of PPI-induced cytopenia could be toxic or immune-mediated (type II hypersensitivity reactions) mechanisms [11^{***}].

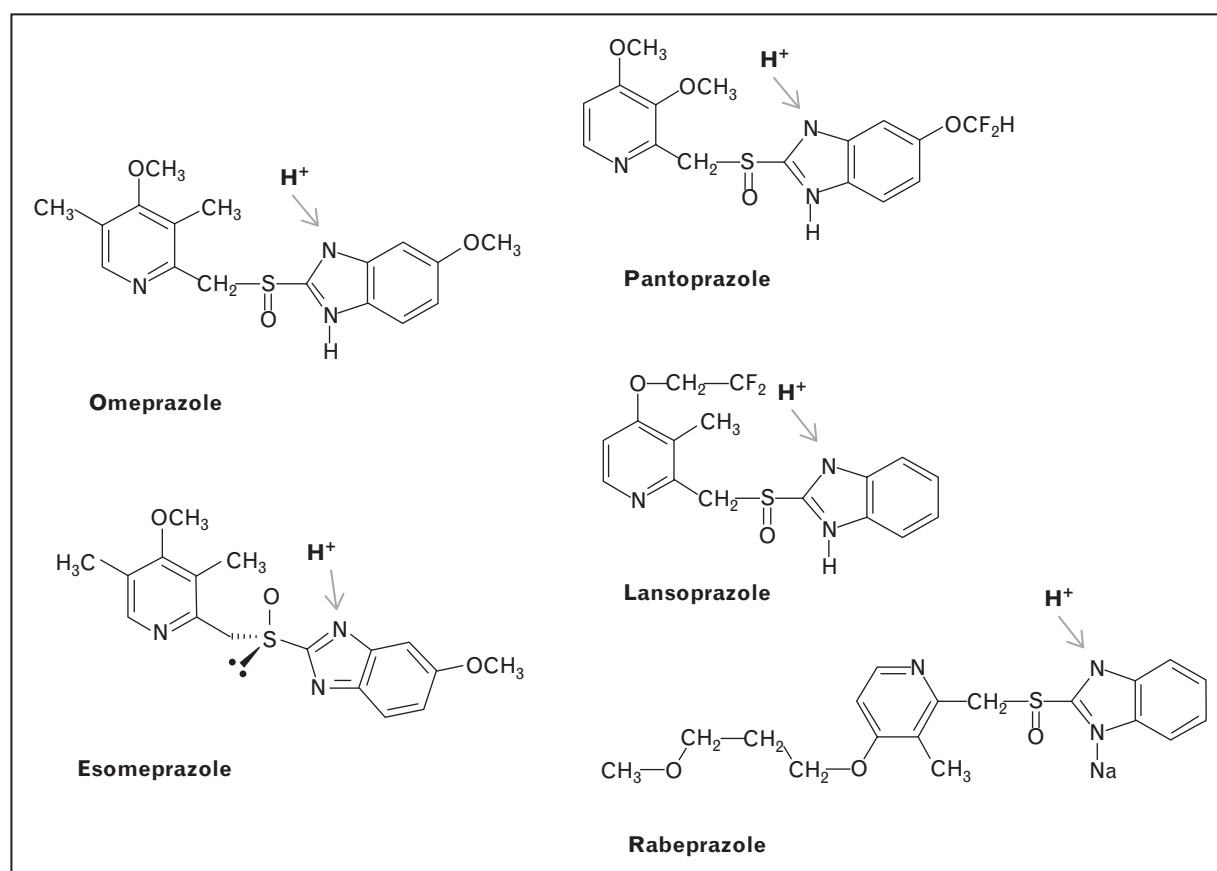


FIGURE 1. The structures of proton pump inhibitors. Protonation of the benzimidazole activates these pro-drugs, converting them to sulfenic acids that react covalently with cysteines accessible from the luminal surface of the ATPase.

PROTON PUMP INHIBITOR-INDUCED VASCULITIS

Cases of PPI-induced vasculitis (not only cutaneous but also systemic vasculitis) have been reported. Jacobs-Kosmin *et al.* [17] reported a case of perinuclear antineutrophil cytoplasmic antibody-associated vasculitis with interstitial nephritis, cutaneous vasculitis in association with pantoprazole. The authors also summarized 12 prior cases of autoimmune manifestations other than interstitial nephritis.

Recently a case of Henoch–Schönlein purpura with rapidly progressive glomerulonephritis secondary to pantoprazole ingestion has been reported. Clinical manifestation included terminal ileitis and rapidly progressing glomerulonephritis, which progressed to renal failure requiring hemodialysis, and intravenous pulse steroids. His renal function recovered after treatment with mycophenolate mofetil [18].

PROTON PUMP INHIBITOR-INDUCED ACUTE ALLERGIC INTERSTITIAL NEPHRITIS

The clinical presentation of acute allergic interstitial nephritis (AIN) can vary; a high level of clinical

suspicion is critical for the diagnosis. However, patients typically present with general symptoms of renal failure such as nausea, vomiting and fatigue. Injury to the medulla can inhibit the ability to concentrate urine, leading to polyuria and polydipsia. Other clinical manifestations of AIN include acute elevation in creatinine levels not because of prerenal or postrenal causes, maculopapular rash, proteinuria, pyuria (in almost all cases), hematuria (in 90% of cases), and eosinophiluria (in 80% of cases). Timely diagnosis is important because early intervention (withdrawal of PPI promptly in the first week) improves the outcome [19^{***}].

In a systematic review, Sierra *et al.* [20] analyzed 64 cases of PPI-associated AIN from 1970 to 2006, 59 of which were proven by biopsy and one by recurrence of AIN upon reinitiating PPI. Renal function recovered within a mean of 35.5 weeks (24–52 weeks) after withdrawal of PPI therapy. Evidence for causality in the cases reviewed was often poor. Reintroduction of the suspected PPI was not done for ethical reasons. All of the PPI were implicated, suggesting a class effect.

PROTON PUMP INHIBITOR-INDUCED CONTACT DERMATITIS

Five cases of occupational airborne contact dermatitis caused by omeprazole, lansoprazole, and pantoprazole in the setting of the pharmaceutical industry have been reported so far (Table 1) [19[■],20–22]. All of the patients were male and the mean age was 42.2 ± 15.8 years. Mean duration of exposure before symptom development was 5.6 ± 1.9 years. The involved areas were mainly eyelids, face, neck, arm, and hands, which suggest the route of sensitization could be airborne contact or inhalation. It is important for pharmaceutical workers to wear protective equipment such as overalls, masks, and gloves. Patch test gave good positive responses to the offending drugs [21–24].

PPI can also cause photoallergic dermatitis. The involved area is usually face and arms. So far, very few cases were reported with omeprazole, rabeprazole, pantoprazole, and esomeprazole [25].

PROTON PUMP INHIBITOR-INDUCED DRESS SYNDROME

Cutaneous reactions to PPI are usually mild and include maculopapular eruptions, pruritus, and urticaria. A case of drug rash with eosinophilia and systemic symptoms (DRESS) from esomeprazole has been reported. Cross-reactivity among almost all other PPI were supported by patch test showing positive responses to esomeprazole, omeprazole, rabeprazole, and lansoprazole but not to rabeprazole. Interestingly the patient experienced a mild erythroderma with facial edema and desquamation 60 h after skin patch test, which lasted for 4 days, requiring treatment with topical steroids and emollients. This case suggests that skin patch tests may induce a flare of DRESS [26[■]].

PROTON PUMP INHIBITOR-INDUCED STEVENS–JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS

Case reports of toxic epidermal necrolysis (TEN) after omeprazole 3 weeks later, [27] and lansoprazole have been reported [28]. Stevens Johnson syndrome following the use of PPI have not been reported in the English literature.

OTHER AUTOIMMUNE MANIFESTATIONS FROM PROTON PUMP INHIBITOR

Cases of PPI-associated lupus erythematosus have been reported. A recent systematic review identified two cases of lansoprazole-associated subacute cutaneous lupus erythematosus and reported that

Table 1. Occupational airborne contact dermatitis caused by proton pump inhibitors

References	Sex	Age	Occupation	Atopy	Duration of exposure before symptom development	Offending drugs	Reactions	SPT	Patch test
[19 [■]]	Male	60	Pharmaceutical company	(–)	8 years	Omeprazole and Fluoxetine	Sporadic episodes of a rash involving face and neck	Omeprazole (+)	Omeprazole (+)
[20]	Male	33	Pharmaceutical company	(+)	6 years	Pantoprazole	Facial and eyelid dermatitis	Fluoxetine (+) NA	Fluoxetine (–) Pantoprazole (+)
[21]	Male	25	Pharmaceutical company	NA	5 years	Omeprazole	Eczematous plaques at eyelids, face, neck, and hands	NA	Omeprazole (+)
	Male	35	Pharmaceutical company	NA	NA	Omeprazole	Itchy dermatitis at eyelids, nose, and perioral area	NA	Omeprazole (+)
[22]	Male	58	Pharmaceutical company	(–)	3.5 years	Lansoprazole	Pruritic papules on the face, neck, and arms		Lansoprazole(+) Omeprazole (+)

NA, not assessed; SPT, skin prick test.

1.7% (two of 117 cases) of drug-induced subacute cutaneous lupus erythematosus was due to PPI [29[■]]. Cases of subacute cutaneous lupus erythematosus with typical histological findings, positive ANA and anti-SSA/Ro autoantibodies but negative anti-dsDNA antibody due to omeprazole, esomeprazole, and pantoprazole have also been reported [2[■],30].

DESENSITIZATION IN PROTON PUMPS INHIBITOR ALLERGY

There is only one case report on desensitization with PPI [31]. They dissolved the granules of omeprazole in bicarbonate and created 10-fold serial dilutions. The starting dose was 0.001 mg (0.5 mL of 0.002 mg/mL solution: 1:10000 of the final required dose). They escalated doses twofold, at 20-min intervals until final dose of 16 mg was reached after 5.6 h. One hour later, the patient could take 20 mg of omeprazole and tolerated 2 weeks of the full therapeutic treatment for *H. pylori* eradication.

CONCLUSION

Hypersensitivity reactions to PPI may be immediate or nonimmediate reactions, and vary from mild symptoms to life-threatening disorders. A high level of clinical suspicion is critical in the diagnosis of PPI-induced hypersensitivity reactions. Physicians should be aware of the possibility of hypersensitivity reactions to PPI, the mechanisms of which remain largely unknown.

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Conflicts of interest

There are no conflicts of interest in relation to this publication.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 440).

1. Parikh N, Howden CW. The safety of drugs used in acid-related disorders and functional gastrointestinal disorders. *Gastroenterol Clin North Am* 2010; 39:529–542.
- This review provides a comprehensive overview of the safety issues of PPI.
2. Chen J, Yuan YC, Leontiadis GI, Howden CW. Recent safety concerns with proton pump inhibitors. *J Clin Gastroenterol* 2012; 46:93–114.
- This review provides a comprehensive overview of the safety issues of PPI, focusing on three specific concerns: the possible interaction between PPIs and clopidogrel, the postulated link between PPI use and fractures, and the possibility that long-term PPI use might lead to hypomagnesemia.

3. Pali-Schöll I, Jensen-Jarolim E. Antacid medication as a risk factor for food allergy. *Allergy* 2011; 66:469–477.
- This review provides a good overview of PPI as a risk factor for food allergy from human and animal studies, in which inhibition or neutralization of gastric acid allows persistence of intact food allergens and protein-bound oral drugs with enhanced capacity to sensitize and elicit allergic reactions via the oral route.
4. Riemer AB, Gruber S, Pali-Schöll I, et al. Suppression of gastric acid increases the risk of developing immunoglobulin E-mediated drug hypersensitivity: human diclofenac sensitization and a murine sensitization model. *Clin Exp Allergy* 2010; 40:486–493.
5. Sachs G, Shin JM, Hunt R. Novel approaches to inhibition of gastric acid secretion. *Curr Gastroenterol Rep* 2010; 12:437–447.
6. Sobrevia Elfau MT, Garcés Sotillos M, Ferrer Claveria L, et al. Study of cross-reactivity between proton pump inhibitors. *J Investig Allergol Clin Immunol* 2010; 20:157–161.
7. Caubet JC, Pichler WJ, Eigenmann PA. Educational case series: mechanisms of drug allergy. *Pediatr Allergy Immunol* 2011; 22:559–567.
- This review provides a very nice overview of the mechanisms of drug allergy with case series.
8. Adam J, Pichler WJ, Yerly D. Delayed drug hypersensitivity: models of T-cell stimulation. *Br J Clin Pharmacol* 2011; 71:701–707.
- This review provides a nice overview of the mechanisms of delayed drug hypersensitivity. It also summarizes the evidence of the p-i concept.
9. Vovolis V, Christogianni K, Koutsostathis N. Immunoglobulin E-mediated anaphylaxis to rabeprazole. *J Investig Allergol Clin Immunol* 2010; 20:360–361.
10. Pérez-Ezquerro PR, Morillas LS, Martínez JJ, et al. Anaphylaxis to omeprazole. Cross-reactivity with the other proton pump inhibitors. *Allergol Immunopathol (Madr)* 2011; 39:54.
11. Lobera T, Navarro B, Del Pozo MD, et al. Nine cases of omeprazole allergy: cross-reactivity between proton pump inhibitors. *J Investig Allergol Clin Immunol* 2009; 19:57–60.
- This review describes in detail cross-reactivity among omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole supported by positive skin prick and intradermal tests. The authors also classified PPI reactors into three groups: selective PPI reactors, cross PPI reactors, cross reactors to only two PPIs (rabeprazole–lansoprazole reactors, and omeprazole–lantoprazole reactors).
12. Lai HC, Hsu SW, Lu CH, et al. Anaphylaxis to pantoprazole during general anesthesia. *J Anesth* 2011; 25:606–608.
13. Gamboa PM, Sanz ML, Urrutia I, et al. CD63 expression by flow cytometry in the in vitro diagnosis of allergy to omeprazole. *Allergy* 2003; 58:538–539.
- First case of omeprazole immediate hypersensitivity with skin test positivity and positive basophil activation test suggesting an IgE-mediated mechanism. Prior to this, in-vitro detection of specific IgE to lansoprazole, omeprazole and pantoprazole had been negative.
14. Gouraud A, Vochelle V, Descotes J, Vial T. Proton pump inhibitor-induced neutropenia: possible cross-reactivity between omeprazole and pantoprazole. *Clin Drug Invest* 2010; 30:559–563.
15. Watson TD, Stark JE, Vesta KS. Pantoprazole-induced thrombocytopenia. *Ann Pharmacother* 2006; 40:758–761.
16. Dotan E, Katz R, Bratcher J, et al. The prevalence of pantoprazole associated thrombocytopenia in a community hospital. *Expert Opin Pharmacother* 2007; 8:2025–2028.
17. Jacobs-Kosmin D, Derk CT, Sandorfi N. Pantoprazole and perinuclear anti-neutrophil cytoplasmic antibody-associated vasculitis. *J Rheumatol* 2006; 33:629–632.
18. Muzaffar M, Taj A, Sethi N, Kaw D. Rapidly progressing glomerulonephritis secondary to henoch–schönlein purpura treated with mycophenolate mofetil: a case report with atypical etiology and presentation. *Am J Ther* 2010; 17:e163–e166.
19. Ricketson J, Kimel G, Spence J, Weir R. Acute allergic interstitial nephritis after use of pantoprazole. *CMAJ* 2009; 180:535–538.
- This case report is accompanied by a well written review of causes of acute drug-induced interstitial nephritis as well as the diagnostic evaluation.
20. Sierra F, Suarez M, Rey M, et al. Systematic review: proton pump inhibitor-associated acute interstitial nephritis. *Aliment Pharmacol Ther* 2007; 26:545–553.
21. Sanz-Gallén P, Nogué S, Herrera-Mozo I, et al. Occupational contact allergy to omeprazole and fluoxetine. *Contact Dermatitis* 2011; 65:118–119.
22. Neumark M, Ingber A, Levin M, Slodownik D. Occupational airborne contact dermatitis caused by pantoprazole. *Contact Dermatitis* 2011; 64:60–61.
23. Conde-Salazar L, Blancas-Espinosa R, Pérez-Hortet C. Occupational airborne contact dermatitis from omeprazole. *Contact Dermatitis* 2007; 56:44–46.
24. Vilaplana J, Romaguera C. Allergic contact dermatitis due to lansoprazole, a proton pump inhibitor. *Contact Dermatitis* 2001; 44:47–48.
25. Shukla A, Mahapatra A, Gogtay N, Khopkar U. Esomeprazole-induced photoallergic dermatitis. *J Postgrad Med* 2010; 56:229–231.

26. Caboni S, Gunera-Saad N, Ktiouet-Abassi S, *et al.* Esomeprazole-induced ■■ DRESS syndrome. Studies of cross-reactivity among proton-pump inhibitor drugs. *Allergy* 2007; 62:1342–1343.

Positive patch tests to esomeprazole, omeprazole, pantoprazole, negative to rabeprazole and lansoprazole, with histological evidence of delayed hypersensitivity over the esomeprazole positive result, and mild erythroderma and facial oedema and desquamation 60 h after patch test.

27. Thakor AS, Burke A, Handfield-Jones S, *et al.* Toxic epidermal necrolysis and neutropaenia: complications of omeprazole. *Australas J Dermatol* 2009; 50:207–210.
28. Heaton NR, Edmonds EV, Francis ND, *et al.* Fatal toxic epidermal necrolysis due to lansoprazole. *Clin Exp Dermatol* 2004; 29:612–613.

29. Lowe G, Henderson CL, Grau RH, *et al.* A systematic review of drug-induced ■ subacute cutaneous lupus erythematosus. *Br J Dermatol* 2011; 164:465–472.

A systematic review of clinical features, histopathological and immunological features of drug-induced versus idiopathic subacute cutaneous lupus erythematosus, with differences from drug induced lupus syndrome.

30. Toms-Whittle LM, John LH, Buckley DA. Drug-induced subacute cutaneous lupus erythematosus associated with omeprazole. *Clin Exp Dermatol* 2011; 36:281–283.
31. Confino-Cohen R, Goldberg A. Anaphylaxis to omeprazole: diagnosis and desensitization protocol. *Ann Allergy Asthma Immunol* 2006; 96:33–36.