

asthma and control groups. Furthermore, no significant associations were found between the 4 SNPs and asthma-related clinical parameters, including atopy, serum total IgE, the level of PC₂₀ methacholine, and forced expiratory volume in 1 second. No significant association was seen in the genotype frequencies between severe and nonsevere asthma groups, where the American Thoracic Society definition of severe asthma was applied.⁸ Serum MBL level was significantly higher in the asthma group than in the control group (Fig 1; 686.73 ± 339.16 vs 376.63 ± 169.1 $\mu\text{g/L}$; $P < .001$). Patients with asthma carrying the GG genotype at $-554 \text{ G} > \text{C}$ or the GG genotype at $226 \text{ G} > \text{A}$ of *MBL2* showed significantly higher serum MBL levels compared with those with other genotypes (GG vs GC/CC, 854.33 ± 365.88 $\mu\text{g/L}$ vs 606.23 ± 287.51 $\mu\text{g/L}$, $P = .010$; GG vs GA/AA, 750.16 ± 376.00 $\mu\text{g/L}$ vs 575.73 ± 229.94 $\mu\text{g/L}$, $P = .046$; respectively). Moreover, the patients with asthma having haplotype 1 [GAGG] of the *MBL2* gene showed a significantly higher serum MBL level compared with those with other haplotypes (870.51 ± 370.45 $\mu\text{g/L}$ vs 606.23 ± 287.51 $\mu\text{g/L}$, $P = .004$). However, the serum MBL level was not significantly different between the severe and non-severe asthma groups.

Mannose-binding lectin, a key molecule in innate immunity, acts as an acute phase protein, but it also involves in chronic airway inflammation.^{9,10} Previous studies suggested that a lower serum MBL level may represent an immune deficiency state by predisposing a patient to severe infections, including upper respiratory infections,² whereas study in pediatric patients with asthma demonstrated that an increased serum MBL level is correlated with blood eosinophil count.¹⁰ In the present study, nevertheless, no significant associations were found among the 4 SNPs of *MBL2* and the phenotypes of adult asthma in a Korean cohort; the serum MBL level was significantly higher in the adult asthma group. Although the mechanism of increased MBL production in patients with asthma is unclear, chronic airway inflammation in patients with asthma may stimulate MBL production by hepatocytes, which induces complement activation and potentiates Th2-derived airway inflammation. These findings may differ according to *MBL2* genotype.

In conclusion, adult patients with asthma have higher serum MBL levels. Two genetic polymorphisms at *MBL* $-554 \text{ G} > \text{C}$ and $226 \text{ G} > \text{A}$, could affect serum MBL levels.

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Rapid desensitization to doxycycline

A 48-year-old woman had a well-documented history of an anaphylactic reaction to doxycycline prescribed for the treatment of a febrile illness associated with headache, myalgia, facial pain, and cervical lymphadenopathy. She presented to the Emergency Department 15 minutes after taking her first dose, with generalized urticaria, facial angioedema, throat constriction, hoarseness, shortness of breath, and expiratory wheeze. The reaction was promptly reversed with intramuscular administration of epinephrine and inhalation of high-flow oxygen and nebulized salbutamol. She was able to tolerate doxycycline previously. Her prolonged febrile illness was eventually diagnosed as Q fever, and 4 months after her anaphylaxis and failure to respond to an empirical trial of other antimicrobial agents a request for desensitization was made by the treating physician. However, no such protocol was available in the literature.

There is no standardized skin testing protocol or specific immunoglobulin E assay for doxycycline. An oral challenge was deemed an excessive risk. Although serum tryptase levels were not measured, her presentation to the Emergency Department with objective signs of anaphylaxis and no other agents likely to have caused the reaction was compelling enough evidence that the patient had anaphylaxis to doxycycline. An oral desensitization

regimen was not feasible, because the oral formulations of doxycycline were not sufficiently soluble to prepare very low concentrations of the drug. Therefore, a protocol was formulated using an intravenous preparation (Table 1) with the administration of slow intravenous pushes, and the patient was desensitized in the intensive care unit, which allowed for continuous monitoring and supervision. For simplicity in our unit, we preferred to use 4 different escalating concentrations of the intravenous preparation to administer as bolus injections, but other methods such as the 12-step, 3-bag desensitization protocol from the Brigham and Women's Hospital Rapid Drug Desensitization Program also could have been a feasible option.¹

The intravenous component of the rapid desensitization protocol was successful and occurred without an adverse event, and a cumulative dose of 98.888 mg was attained. This dose approximated half of the daily dose prescribed for the patient. The remainder of the daily dose was administered in oral form to ensure that the patient was able to tolerate the formulation that she was prescribed for the treatment of her infection. The patient was subsequently able to tolerate several weeks of doxycycline 100 mg twice per day orally.

Anaphylaxis to tetracyclines is rare, and there is only previous report of an adverse reaction to doxycycline, which involved the intravenous administration of the drug.² The mechanism of anaphylaxis to tetracyclines is unclear, and in only 3 case reports

Table 1
Rapid desensitization schedule for doxycycline phase 1: intravenous phase^a

Time (min)	Concentration (mg/mL)	Volume administered (mL)	Dose (mg)	Cumulative dose (mg)
0	0.01	0.1	0.001	0.001
15	0.01	0.2	0.002	0.003
30	0.01	0.5	0.005	0.008
45	0.1	0.1	0.01	0.018
60	0.1	0.2	0.02	0.038
75	0.1	0.5	0.05	0.088
90	1	0.1	0.1	0.188
105	1	0.2	0.2	0.388
120	1	0.5	0.5	0.888
135	10	0.1	1	1.888
150	10	0.2	2	3.888
165	10	0.5	5	8.888
180	10	1	10	18.888
195	10	2.5	25	43.888
210	10	5.5	55	98.888
Phase 2.				
oral phase				
240			100	198.88

^aEach dose is administered as an individual intravenous push.

have further investigations been performed showing the drug itself to be the allergen.^{3–5} In both of these cases, tetracycline hydrochloride was the culprit. The tetracyclines, which also include doxycycline and minocycline, share a common core structure but have different side chains,⁶ and therefore anti-immunoglobulin E-mediated reactions may be class or drug specific. Desensitization was preserved across the different routes of administration in our case. The excipients and other ingredients in intravenous doxycycline are mannitol and ascorbic acid, whereas those in the tablet preparation are ethylcellulose, hypromellose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl

sulfate, talc, titanium dioxide, and Yellow 6 Lake, suggesting that doxycycline rather than one of the other ingredients is the allergen.

This is the first published report of anaphylaxis to oral doxycycline and successful desensitization to this drug and, moreover, to a tetracycline. It would be now be important to determine a protocol for skin testing to doxycycline using this index patient and a sizeable number of control subjects.

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Hypersensitivity to nabumetone: cross reactivity with naproxen

Nabumetone is a nonsteroidal anti-inflammatory drug (NSAID) and the only 1-naphthaleneacetic acid derivative that is rapidly metabolized in the liver to a major active metabolite, 6-methoxy-2-naphthyl-acetic acid, which is structurally similar to naproxen (Fig 1).

Given that the active metabolite of nabumetone inhibits the cyclooxygenase (COX) enzyme and preferentially blocks COX-2 activity, it is usually (but not always) a safe alternative in patients with hypersensitivity reactions to NSAIDs.¹

We report 3 patients who developed urticaria/angioedema after taking nabumetone. Two showed good tolerance to naproxen, whereas 1 patient experienced urticaria/angioedema during naproxen single-blind oral challenge test (OCT). None had a history of spontaneous urticaria.

Patient 1

A 46-year-old woman, with no known allergies, had been treated with nabumetone (previously tolerated) for arthrosis pain. Ninety minutes after intake, she complained of pruritus, angioedema in her lips, and pruritic wheals on the abdomen, breasts, and legs. Nabumetone was stopped, and the symptoms resolved in less than 24 hours with oral antihistamines.

Patient 2

A 35-year-old woman complained of pruritus, erythema (face, neck, and chest) and angioedema of the lips 6 hours after taking

nabumetone (1 g) for the first time. She was treated with corticosteroids and antihistamines, and the reaction disappeared with no residual lesions in 48 hours. She had previously tolerated ibuprofen and naproxen.

Patient 3

A 25-year-old woman presented generalized urticaria 6 hours after treatment with nabumetone (1 g) and tetrazepam. Symptoms subsided within 20 minutes after 10 mg intramuscular chlorpheniramine. She tolerated tetrazepam after this reaction. The only NSAID she remembered having taken previously was paracetamol.

After written informed consent, OCTs with nabumetone (250, 500, and 1000 mg) at 1-hour intervals were performed.²

The OCT was positive in all 3 patients with the same dose of nabumetone, the last one (1,000 mg, cumulative dose of 1,750 mg) with an onset period of 60 to 90 minutes. The 3 patients experienced urticaria and angioedema of the lips.

All of them responded well to intramuscular methylprednisolone and chlorpheniramine, and treatment with epinephrine was not necessary.

To investigate cross-reactivity with other NSAIDs, we tested with aspirin (1,000 mg) according the protocol of the European Academy of Allergy and Clinical Immunology.³ All of the results were negative.

Considering the similar structure of both drugs (nabumetone and naproxen), we also performed an OCT with naproxen (125, 250, and 500 mg).