
Short-term and long-term tolerability of rofecoxib in patients with prior reactions to nonsteroidal anti-inflammatory drugs

Eustachio Nettis, MD; Maria Cristina Colanardi, MD; Antonio Ferrannini, MD; and Alfredo Tursi, MD

Background: Rofecoxib is a selective cyclooxygenase 2 (*COX-2*) inhibitor and is well tolerated as an alternative to nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with a previous adverse reaction to other classes of NSAIDs. Until now, there has not been information in the literature about its long-term tolerability.

Objective: To provide follow-up data on patients with a history of adverse cutaneous reactions to NSAIDs who underwent and tolerated a challenge test with rofecoxib.

Methods: Study patients had historically experienced cutaneous adverse reactions to aspirin and NSAIDs and had undergone single-blind challenges with rofecoxib, 25 mg. A questionnaire was distributed to all participants. In particular, they were asked to clarify any reactive symptoms they had developed after ingestion of the drug. All patients were reexamined 1 to 3 years after testing. At reexamination, they were carefully and personally interviewed using the previously distributed questionnaire.

Results: Of the 182 patients who participated in the study, none reacted to rofecoxib during single-blind challenges. Fifty-one (28%) never received rofecoxib again, whereas 131 (72%) were exposed to rofecoxib, often on multiple occasions. Only 7 (5%) of the 131 patients reported cutaneous reactions to rofecoxib during the 3 years of follow-up.

Conclusions: Rofecoxib appears to be a safe alternative drug among atopic individuals, antibiotic-hypersensitive individuals, and individuals who experienced adverse cutaneous reactions to more than 1 class of NSAIDs, but it is less safe among chronic urticaria patients. Further investigations that include a larger sample are required to confirm our results especially among chronic urticaria patients.

Ann Allergy Asthma Immunol. 2005;94:29–33.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of drugs commonly used to treat a variety of conditions because of their analgesic, anti-inflammatory, and antipyretic properties. The high number of prescriptions of these agents and the spread of self-medication, often leading patients to irrationally and inappropriately use NSAIDs, may account for the incidence of associated hypersensitivity. This may start as anaphylactic shock, bronchospasm, angioedema, urticaria, and various skin eruptions. Patients with hypersensitivity are consistently warned to avoid NSAIDs, and as a result many patients are not receiving adequate anti-inflammatory therapy for a variety of conditions because of the risk of reactions. To find an alternative NSAID for use when necessary, patients could be submitted, in an appropriate medical center, to challenge with an alternative drug whose molecular structure and mechanism of action are different from those of the product associated with the hypersensitive reaction. A number of drugs have been tested and recommended, including paracetamol,¹ nimesulide,² benzydamine,³ floctafenine,⁴ and meloxicam.⁵ However, hypersensitivity to these drugs has

also been reported, with the reactions generally being detected at the challenge.

A new class of NSAIDs, selective cyclooxygenase 2 (*COX-2*) inhibitors, are being tested in NSAID-sensitive patients. As is well known, the mechanism of action of NSAIDs relies on inhibition of the enzyme *COX*. This is present in 2 forms: *COX-1* and *COX-2*. *COX-1* is responsible for the production of “housekeeping” prostaglandins, which are critical for the maintenance of normal renal function, gastric mucosal integrity, vascular homeostasis, and the autocrine response to circulating hormones. The *COX-1* gene is expressed in almost all normal tissues, and it is not up-regulated by inflammatory stimuli. By contrast, *COX-2* is predominantly induced in activated leukocytes and inflammatory sites. Hence, *COX-2* mediates the synthesis of prostaglandins with a critical role in the inflammatory response. The *COX-2* hypothesis proposes that the efficacy of NSAIDs is due to *COX-2* inhibition, whereas *COX-1* inhibition is responsible for their toxicity. The mechanism of the hypersensitivity reaction appears to be related to inhibition of *COX-1*, resulting in a shunt of arachidonic acid to the 5-lipoxygenase pathway. This leads to an increased production of leukotrienes, including leukotriene C₄, leukotriene D₄, and leukotriene E₄, which play a proinflammatory role. On the other hand, *COX* inhibition by NSAIDs causes blockade of generation of bronchodilator and anti-inflammatory prostaglandins of the E series.⁶

Department of Medical Clinic, Immunology and Infectious Diseases, Division of Allergy and Clinical Immunology, University of Bari, Bari, Italy.
Received for publication June 22, 2003.

Accepted for publication in revised form December 9, 2003.

Rofecoxib is a selective *COX-2* inhibitor and has been proposed as an alternative NSAID, which may be tolerated in NSAID-sensitive patients.⁷⁻¹⁰ The clinical tolerance of rofecoxib reported in this study was high, because the percentage of adverse reactions to rofecoxib in patients with NSAID cutaneous reactions ranged from 0% to 0.7%. To date, there have been no studies of the long-term clinical tolerability of rofecoxib. This article provides follow-up data on patients with a history of adverse cutaneous reactions to NSAIDs who underwent and tolerated a challenge test with rofecoxib.

METHODS

This is a retrospective study based on analysis of data from interviews administered to patients who underwent and tolerated a challenge test with rofecoxib performed between April 2000 and May 2002. The patients had been referred to the Allergy Clinic of the University of Bari, Bari, Italy, for well-documented cutaneous adverse reactions to 1 or more NSAIDs diagnosed by an allergologist and/or a dermatologist. Challenges to confirm the patients' cutaneous adverse reactions to drugs were deferred to avoid provoking unnecessary discomfort or risk.

Challenge Tests to Rofecoxib

Between April 2000 and May 2002, peroral challenges were performed with rofecoxib, and it was the first exposure to this drug. No patients presented significant cutaneous or respiratory tract symptoms at the time of testing, and the pulmonary function test showed stable forced expiratory volume in 1 second (FEV₁) of greater than 80% of predicted values in all cases.

Antihistamine use was stopped 2 weeks before challenge (6 weeks for astemizole); use of cromolyn, corticosteroids, leukotriene receptor antagonists, and inhaled sympathicomimetic agents was discontinued 48 hours before the provocation test. The test was performed on 2 different days with placebo (talc) and rofecoxib (Vioxx; Merck Sharp & Dome, Rome, Italy), using inert capsules as a vehicle. On the first day 2 placebo capsules were administered, 1 per hour; 7 days later each patient received divided doses of the total therapeutic dose of 25 mg of rofecoxib: one fourth (6.1 mg) initially and three fourths (18.9 mg) 1 hour later if no reactive symptoms were noted. During execution of the test, arterial pressure and FEV₁ were monitored (30 minutes and every hour after administering each drug or placebo dose or as soon as any symptoms arose). Each patient was kept under medical control in the hospital for at least 6 hours after challenges and was then asked to return after 24 and 48 hours to exclude delayed reactions. Patients with a history of chronic urticaria were challenged during a period of clinical remission of disease. The test result was considered positive if cutaneous and mucosal manifestations (erythema and/or wheals and/or angioedema) appeared or respiratory symptoms or a decrease of at least 20% in the FEV₁ or hypotension developed. Resuscitation equipment was available at all times during the tests.

Questionnaire

At the time of the challenge tests, a questionnaire was distributed to all tested patients. It included questions about the ingestion of rofecoxib. Patients were asked to clarify any reactive symptoms they had developed after ingestion of the drug, their type, intensity, time relation with the drug ingestion, number of rofecoxib doses taken (single or multiple), and any concomitant therapy.

All patients were reexamined 1 to 3 years after testing. At reexamination, they were carefully and personally interviewed using the previously distributed questionnaire designed to evaluate information about rofecoxib intake since the challenge test. Patients' clinical data and questionnaire results were collected in a database that we used for this study. Prior informed written consent was obtained from all patients.

Statistical Analysis

Proportions were compared by χ^2 test. $P < .05$ was considered statistically significant. The relative risk (RR) for independent samples was defined as the odds of the considered risk factor occurring in rofecoxib-sensitive patients relative to the odds of its occurring in patients without reactions to rofecoxib.

RESULTS

A total of 182 patients (132 women and 50 men; mean age, 41.5 years) participated in the study. One hundred twenty patients (66%) had experienced a cutaneous adverse reaction to 1 or more NSAIDs of the same class (among them, 117 reacted to only 1 NSAID, whereas 3 patients reacted to 2 NSAIDs of the same class: 1 to ketoprofen and ibuprofen, 1 to noramidopyrine and propyphenazone, 1 to naproxen and ibuprofen), 41 (22%) reacted adversely to NSAIDs of 2 different classes, and 21 (12%) reacted adversely to NSAIDs of 3 different classes (Table 1). The overall adverse manifestations included urticaria alone in 135 cases (in 5 cases associated with difficulty in breathing), angioedema alone in 87 cases, urticaria plus angioedema in 35, Stevens-Johnson syndrome in 2, and exanthematous eruptions in 9 cases. Twelve patients (7%) were affected by chronic urticaria,

Table 1. Nonsteroidal Anti-inflammatory Drugs Responsible for Adverse Cutaneous Reactions in 182 Patients

Drug class	No. (%)
Acetylsalicylic acid	67 (25)
Pyrazolones	36 (14)
Arylpropionics	54 (20)
Fenetidinics	21 (8)
Arylacetics	22 (8)
Oxicam	5 (2)
Fenamates	8 (3)
Sulphonanilides	52 (19)
Indolics	1 (0.3)
Others	2 (0.7)
Total	268

which was defined as the appearance of hives or wheals on most days for more than 6 weeks. All of the patients reported at least 1 episode of NSAID-related urticaria with or without angioedema.

Of the 182 patients considered, 34 (19%) had a personal history of at least 1 atopic disease: allergic rhinitis or rhinoconjunctivitis in 27 cases (15%), bronchial asthma in 11 cases (6%), and atopic dermatitis in 3 cases (2%). Thirty-one (17%) were also referred to us for adverse reactions to antibiotics: they were caused by β -lactams in 25 patients, sulfamides and trimethoprim in 2, tetracyclines in 2, and macrolides in 2 patients.

At the start of the study, all 182 patients underwent rofecoxib challenges, and there were no reactions to this drug. At the time of reexamination, 51 patients (28%) had not used rofecoxib. In 29 patients (57%) rofecoxib was not needed, whereas 22 patients (43%) had avoided using the drug for fear of possible adverse reactions.

We found that only 7 (5%) of 131 patients who used this drug reported adverse reactions, which had always been diagnosed by a specialist. All 7 patients produced well-documented data from medical reports. Challenges to confirm the patients' adverse reactions to rofecoxib were deferred to avoid provoking unnecessary discomfort or risk. The adverse manifestations included urticaria or angioedema in 6 cases and exanthema in 1. No patients were receiving any concomitant therapy at the time of the adverse reaction. They had taken the drug for the first time between 90 days and 15 months after the test (mean $\pm$ SD, 210 $\pm$ 129.6 days). The remaining 124 patients (95%), who did not experience adverse reactions to rofecoxib, had taken the drug for the first time between 15 days and 33 months after the test (mean $\pm$ SD, 331.6 $\pm$ 252.7 days) and then underwent several treatment cycles with rofecoxib without any adverse reaction.

The percentage of patients who reported a history of reactions to antibiotics before entering the study was higher among patients with adverse reactions to rofecoxib than those who tolerated the drug (3 [43%] of 7 vs 19 [15%] of 124; $P = .32$; RR = 4.14). The percentage of patients who reported a history of cutaneous adverse reactions to more than 1 class of NSAIDs was also higher among patients with adverse reactions to rofecoxib (3 [43%] of 7 vs 43 [35%] of 124; $P = .94$; RR = 1.41). Instead, the percentage of patients who reported a history of atopy was higher among those without adverse reactions to rofecoxib (25 [20%] of 124 vs 1 [14%] of 7; $P = .86$; RR = 0.66). Finally, a nonsignificant association was found between an adverse reaction to rofecoxib and the presence of chronic urticaria (2 [29%] of 7 vs 5 [4%] of 124; $P = .10$; RR = 9.52). The main features of the 7 patients who experienced an adverse reaction to rofecoxib are given in Table 2.

DISCUSSION

Rofecoxib is considered a safe drug in NSAID-sensitive patients. The results of various studies⁷⁻¹⁰ support the hypothesis that *COX-1* inhibition is the main mechanism involved in the pathogenesis of adverse cutaneous reactions, in particular, to NSAIDs. Large, randomized, double-blind, placebo-controlled studies in patients with rheumatoid arthritis, dental pain, or orthopaedic surgery have shown a reduced incidence of gastrointestinal bleeding and a similar efficacy compared with other nonselective NSAIDs.¹¹⁻¹³ In addition, some authors have recently demonstrated improvement of clinical symptoms in patients with chronic sinusitis¹⁴ and chronic urticaria¹⁵ using rofecoxib. In fact, in chronic urticaria, besides histamine, mediators such as prostaglandins and thromboxanes display inflammatory properties. Their production could be decreased using selective *COX-2* inhibitors.

Table 2. Clinical Characteristics of Patients with Adverse Reactions to Rofecoxib

Patient No./ Sex/Age, y	Atopy	Chronic urticaria	NSAID cutaneous adverse reactions*	Antibiotic adverse reactions	Clinical manifestation of adverse reactions to rofecoxib	No. of doses taken	Elapsed time, min	Previous rofecoxib cycles	Medical treatment
1/F/30	No	Yes	Ketoprofen/U	Cefatrizine/U	U	Multiple	30	Yes	Antihistamines and corticosteroids
2/F/27	No	No	Aspirin/A	No	U/A	Multiple	60	No	Antihistamines and corticosteroids
3/F/19	No	Yes	Propyphenazone/A	Cotrimoxazole/A	U	Multiple	10	Yes	No
4/F/22	Atopic dermatitis	No	Propyphenazone/A	No	U	Multiple	15	Yes	No
5/F/37	No	No	Ketorolac/A	No	U/A	Multiple	30	Yes	Corticosteroids
6/F/75	No	No	Nimesulide/U Ketoprofen/U	No	U/A	Multiple	30	Yes	Antihistamines and corticosteroids
7/F/50	No	No	Diclofenac/A Piroxicam/A Aspirin/U	Cotrimoxazole/U	Exanthema	Multiple	3 days	No	Corticosteroids

Abbreviations: A, angioedema; U, urticaria; NSAID, nonsteroidal anti-inflammatory drug.

* Besides rofecoxib.

Until now, only a limited number of rofecoxib-induced hypersensitive reactions have been reported. One case of anaphylactoid reaction 40 minutes after the ingestion of rofecoxib¹⁶ and one case of instant, aquagenic wrinkling of the palmar skin associated with rofecoxib ingestion were described.¹⁷ In addition, there are reported cases of rofecoxib-related fixed eruption,¹⁸ erythema multiforme,¹⁹ aseptic meningitis,²⁰ and urticaria and angioedema.²¹ Our results showed that 5.3% of patients manifested an adverse reaction, mainly urticaria with or without angioedema, following the ingestion of rofecoxib. Cutaneous reactions following the intake of different NSAIDs were referred by these patients. This suggests that the skin is the preferential organ involved in adverse reactions. Although there is no laboratory evidence, we may hypothesize that the mechanism of cutaneous reactions, or at least of urticaria or angioedema, was the same both in cases of COX nonselective NSAIDs and COX-2 selective inhibitors and perhaps other mechanisms could be involved in addition to the COX-related one (eg, the stimulation of mast cells or other inflammatory cells to release leukotrienes and other inflammatory products during the reaction). However, further investigations are required to determine the pathophysiological mechanisms that cause adverse reactions to rofecoxib and, if necessary, to design appropriate diagnostic tests.

Although the number of rofecoxib-sensitive patients in this study is low, some interesting points emerged. Previous observations^{22,23} reported that a history of adverse reactions to antibiotic, atopy, and adverse cutaneous reactions to more than 1 class of NSAIDs are highly associated with adverse reactions to an alternative NSAID, substantially because they can react, likely through a nonimmune mechanism, to several and unrelated substances. The association with atopy could be explained by the fact that both the genes responsible for atopy and the leukotriene C4 synthetase genes are located close together in the same chromosomal region.²⁴ In our study, these strong associations were not found. In addition, it is worth noting that we found no association between adverse reactions to rofecoxib and presence of chronic urticaria. This association between NSAID sensitivity and chronic urticaria is known (the mechanism involved has been attributed to inhibition of the COX-1 enzyme²⁵); in fact, a subpopulation of patients with chronic urticaria experienced flare-ups of hives after taking NSAIDs,²⁶ as well as when chronic urticaria went into remission, and many of these patients become, once again, tolerant of NSAIDs. In our study, at follow-up, 7 of 12 chronic urticaria patients took rofecoxib, and 2 (29%) experienced an adverse reaction. Five chronic urticaria patients had taken the drug more than once, and 4 of them had, during at least one ingestion, concurrent (not treated by any drug) urticaria with no apparent exacerbation. The 2 chronic urticaria patients at follow-up had taken rofecoxib several times, also during active urticaria, without any reactions, whereas at the time of the adverse reaction, no patients had active urticaria. Notwithstanding, considering that the course of chronic urticaria is highly variable and

unpredictable, in these patients it is difficult to ascertain whether rofecoxib-related urticarial reactions were really related to rofecoxib or were a spontaneous urticaria flare-up. By anamnesis and clinical data, we have deduced that the reactions were related to rofecoxib, although, for ethical reasons, no provocative test was performed. An analysis of our data demonstrated that chronic urticaria represents a higher RR than other considered risk factors to have adverse reactions to rofecoxib, although this difference is not statistically significant, perhaps because the number of patients is small (only 7 patients).

Finally, the patients who did not tolerate rofecoxib experienced the reaction following ingestion of multiple doses of the drug (mean, 3.8 capsules) and almost all (5 of 7) after more than 1 treatment cycle (mean, 2.4 treatment cycles). This could suggest that adverse reactions to rofecoxib may be dose dependent, although, on the contrary, it could also suggest that multiple exposures to rofecoxib could activate "immune sensitization" in the patients. The reactions to rofecoxib seem to be IgE mediated, although no tests have yet been made to confirm this hypothesis.

The percentage of adverse reactions to rofecoxib after a negative challenge test result was 5.3% in our study. This percentage is higher than those reported in several studies in which rofecoxib was administered in a single-blind manner to evaluate its tolerability in patients with previous reported adverse reactions to a different class of NSAIDs. Nevertheless, we must stress that the total of 43% of patients who had not used rofecoxib could introduce a bias, leading to overestimation of the actual rate of long-term tolerability. These patients preferred to avoid rofecoxib reexposure, because, notwithstanding the challenge results and our recommendations, they feared the development of adverse reactions like those previously experienced and because their illness did not necessarily require anti-inflammatory treatment.

These findings confirm that the challenge test remains a rapid, safe, and reasonably reliable routine method of predicting drug tolerability in clinical settings. In this study, rofecoxib appears as a safe alternative drug among atopic individuals, antibiotic-hypersensitive individuals, and individuals who experienced adverse cutaneous reactions to more than 1 class of NSAIDs, but it is less safe among chronic urticaria patients. Further investigations that include a larger sample are required to confirm our results, especially among chronic urticaria patients.

ACKNOWLEDGMENTS

We thank Drs. A. Aloia, C. Dapriale, A. Federico, and C. Fitto, University of Bari, for their invaluable collaboration in this study.

REFERENCES

1. Nettis E, Marcandrea M, Ferrannini A, Tursi A. Tolerability of nimesulide and paracetamol in patients with NSAID-induced urticaria/angioedema. *Immunopharmacol Immunotoxicol*. 2001; 23:343-354.

-
2. Andri L, Senna G, Betteli C, et al. Tolerability of nimesulide in aspirin-sensitive patients. *Ann Allergy*. 1994;72:29–32.
 3. Nettis E, Di Paola R, Napoli G, Ferrannini A, Tursi A. Benzydamine: an alternative nonsteroidal anti-inflammatory drug in patients with nimesulide-induced urticaria. *Allergy*. 2002;57:442–445.
 4. Papa G, Romano A, Del Bono A, et al. Floctafenine: a valid alternative in patients with adverse reactions to nonsteroidal anti-inflammatory drugs. *Ann Allergy Asthma Immunol*. 1997;78:74–78.
 5. Nettis E, Di Paola R, Ferrannini A, Tursi A. Meloxicam in hypersensitivity to NSAIDs. *Allergy*. 2001;56:803–804.
 6. Hawkey CJ, Jackson L, Harper SE, Simon TJ, Mortenson E, Lines CR. Review article: the gastrointestinal safety profile of rofecoxib, a highly selective inhibitor of cyclooxygenase-2, in humans. *Aliment Pharmacol Ther*. 2001;15:1–9.
 7. Nettis E, Di Paola R, Ferrannini A, Tursi A. Tolerability of rofecoxib in patients with cutaneous adverse reactions to nonsteroidal anti-inflammatory drugs. *Ann Allergy Asthma Immunol*. 2002;88:331–334.
 8. Pacor ML, Di Lorenzo G, Biasi D, Barbagallo M, Corrocher R. Safety of rofecoxib in subjects with a history of adverse cutaneous reactions to aspirin and non-steroidal anti-inflammatory drugs. *Clin Exp Allergy*. 2002;32:397–400.
 9. Quiralte J, Saenz de San Pedro B, Fernando Florido JJ. Safety of selective cyclooxygenase-2 inhibitor rofecoxib in patients with NSAID-induced cutaneous reactions. *Ann Allergy Asthma Immunol*. 2002;89:63–66.
 10. Berges-Gimeno MP, Camacho-Garrido E, Garcia-Rodriguez RM, Alfaya T, Martin Garcia C, Hinojosa M. Rofecoxib safe in NSAID hypersensitivity. *Allergy*. 2001;56:1017–1018.
 11. Bombardier C, Laine L, Reicin A, et al; VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med*. 2000;343:1520–1528.
 12. Morrison BW, Christensen S, Yuan W, Brown J, Amlani S, Seidenberg B. Analgesic efficacy of the cyclooxygenase-2-specific inhibitor rofecoxib in post-dental surgery pain: a randomised, controlled trial. *Clin Ther*. 1999;21:943–953.
 13. Reicin A, Brown J, Jove M, et al. Efficacy of single dose and multidose rofecoxib in the treatment of post-orthopedic surgery pain. *Am J Orthop*. 2001;30:40–48.
 14. Hoyt Block S. Chronic sinusitis with rofecoxib. *J Allergy Clin Immunol*. 2002;373–374.
 15. Boehncke WH, Ludwig RJ, Zollner TM, Ochsendorf F, Kaufman R, Gibbs BF. The selective cyclooxygenase-2 inhibitor rofecoxib improve the treatment of chronic idiopathic urticaria. *Br J Dermatol*. 2003;148:604–606.
 16. Schellenberg RR, Isserow SH. Anaphylactoid reaction to a cyclooxygenase-2 inhibitor in a patient who had a reaction to a cyclooxygenase-1 inhibitor. *N Engl J Med*. 2001;345:1856.
 17. Carder KR, Weston WL. Rofecoxib-induced instant aquagenic wrinkling of the palms. *Pediatr Dermatol*. 2002;19:353–355.
 18. Charandeep K, Rasimi S, Amrinder JK. Fixed drug eruption of rofecoxib with cross-reactivity to sulfonamides. *Dermatology*. 2001;203:351.
 19. Sarkar R, Kaur C, Kanwar AJ. Erythema multiforme due to rofecoxib. *Dermatology*. 2002;204:304–305.
 20. Bonnel RA, Villalba ML, Karwoski CB, Beitz J. Aseptic meningitis associated with rofecoxib. *Arch Intern Med*. 2002;162:713–715.
 21. Grimm V, Rakoski J, Ring J. Urticaria and angioedema induced by COX-2 inhibitor. *J Allergy Clin Immunol*. 2002;109:370.
 22. Pastorello EA, Zara C, Riario-Sforza GG, Pravettoni V, Incorvaia C. Atopy and intolerance of antimicrobial drugs increase the risk of reactions to acetaminophen and nimesulide in patients allergic to nonsteroidal anti-inflammatory drugs. *Allergy*. 1998;53:880–884.
 23. Asero R. Detection of patients with multiple drug allergy syndrome by elective tolerance tests. *Ann Allergy Asthma Immunol*. 1998;80:185–188.
 24. Sanchez-Borges M, Capriles-Hulett A. Atopy is a risk factor for non-steroidal anti-inflammatory drug sensitivity. *Ann Allergy Asthma Immunol*. 2000;84:101–106.
 25. Namazy JA, Simon RA. Sensitivity to nonsteroidal anti-inflammatory drugs. *Ann Allergy Asthma Immunol*. 2002;89:542–550.
 26. Stevenson DD, Simon RA. Sensitivity to aspirin and nonsteroidal anti-inflammatory drugs. In: Middleton E, Reed CE, Ellis EF, et al, editors. *Allergy: Principles and Practice*. 5th ed. Philadelphia, PA: Mosby-Year Book; 1998:1225–1234.
- Requests for reprints should be addressed to:*
Eustachio Nettis, MD
Cattedra di Allergologia e Immunologia Clinica
Padiglione Chini-Policlinico
Piazza Giulio Cesare
70124 Bari, Italy
E-mail: e.nettis@allergy.uniba.it
-