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Cross-reactive hypersensitivity to NSAIDs: Experience of a Tunisian allergology center

Réactions d'hypersensibilités croisées aux AINS : expérience d'un centre d'allergologie tunisien

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ABSTRACT

Background. – The accurate diagnosis of cross-reactive reactions (CRR) to nonsteroidal anti-inflammatory drugs (NSAIDs) depends on a careful history and oral drug challenge. In this study, we report the result of a new procedure implemented in Tunisian allergology center to explore CRR to NSAIDs in patients with immediate hypersensitivity (IHS) to NSAIDs.

Methods. – Our structured protocol using oral provocation tests (OPTs) was based on the latest advances in the literature. This protocol was tested in patients with a clinical history of IHS reactions to one or more NSAIDs and referred to the pharmacology department of Sfax (Tunisia) between 2012 and 2018. Patients were classified into 5 subgroups: an ASA subgroup, a multiple NSAIDs subgroup, a single non-selective NSAID subgroup, a paracetamol subgroup, and a celecoxib subgroup.

Results. – A total of 34 patients were enrolled. Personal history of atopy was found in 26 (76.5%). A diagnosis of CRR to NSAIDs was made in 24 patients (70.6%): 6 patients in the ASA subgroup, 12 patients in the multiple NSAIDs subgroup, 4 patients in the single non-selective NSAID subgroup, 1 patient in the paracetamol subgroup and 1 patient in the celecoxib subgroup. Regarding safe alternatives in patients with CRR to NSAIDs ($n = 24$), prevalence of cross-reactivity to paracetamol or celecoxib was found in 20% and 27.3% of patients with confirmed CRR to NSAIDs, respectively.

Conclusion. – Our structured protocol based on standardized oral provocation tests helps physicians to prescribe a suitable drug in patients with a history of IHS reactions to NSAIDs.

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R É S U M É

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Introduction. – Le diagnostic précis des réactions d'hypersensibilités croisées (RHC) aux anti-inflammatoires non stéroïdiens (AINS) est basé sur une histoire clinique minutieuse et des tests de provocation par voie orale. Dans cette étude, nous rapportons les résultats d'une procédure mise en place dans un centre d'allergologie tunisien afin d'explorer les réactions d'hypersensibilités croisées aux AINS chez des patients ayant une histoire d'hypersensibilité immédiate aux AINS.

Méthodes. – Notre protocole structuré a été basé sur les dernières avancées de la littérature. Ce protocole a été évalué chez des patients ayant des antécédents cliniques de réactions d'hypersensibilité immédiate à un ou plusieurs AINS et adressés au service de pharmacologie de Sfax (Tunisie) entre 2012 et 2018. Les patients ont été classés en 5 sous-groupes: sous-groupe AAS, sous-groupe AINS multiples, sous-groupe AINS non sélectif unique, sous-groupe paracétamol et sous-groupe célécoxib.

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Résultats. – Au total, 34 patients ont été inclus. Des antécédents personnels d'atopie ont été retrouvés dans 26 cas (76,5 %). Le diagnostic de RHC aux AINS a été retenu chez 24 patients (70,6 %): 6 patients dans le sous-groupe AAS, 12 patients dans le sous-groupe AINS multiples, 4 patients dans le sous-groupe AINS non sélectif unique, 1 patient dans le sous-groupe paracétamol et 1 patient dans le sous-groupe célécoxib. Concernant l'identification des alternatives thérapeutiques chez les patients ayant un diagnostic certain d'RHC aux AINS ($n = 24$), la prévalence de la réactivité croisée au paracétamol ou au célécoxib a été observée respectivement chez 20 % et 27,3 %.

Conclusion. – Notre protocole structuré basé sur des tests de provocation orale standardisés aide les médecins à prescrire le médicament approprié chez les patients ayant des antécédents d'hypersensibilité immédiate aux AINS.

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1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the drugs most frequently involved in drug hypersensitivity (HS) [1]. NSAID-induced immediate HS (IHS) reactions can be either cross-reactive (i.e. involving reactions to several, chemically non-related NSAIDs) or selective (i.e. induced by a single NSAID or by 2 or more NSAIDs having similar chemical structures) [2,3]. Immediate immunological (allergic) reactions to NSAIDs are characterized by IgE-mediated HS-(acute) [4]. Non-immunologically mediated (cross-reactive) HS to NSAIDs, also known as NSAID intolerance, appear to be caused by changes in arachidonic acid metabolism leading to an imbalance in prostaglandin/leucotriene production caused by inhibition of cyclooxygenase-1 [5]. HS reactive reactions to NSAIDs are characterized by a wide range of symptoms, which may be classed into three major clinical phenotypes:

- NSAID-exacerbated respiratory disease, occurring in patients with underlying chronic upper and lower airway respiratory diseases;
- NSAID-exacerbated cutaneous disease, occurring in patients with a history of chronic urticaria;
- NSAID-induced urticaria/angioedema, occurring in otherwise healthy subjects (without a history of chronic urticaria) [4,6].

The main principles of management for patients with NSAID-induced IHS reactions are accurate diagnosis followed by identification of a safe alternative without unnecessary avoidance of potentially useful NSAIDs [7].

An oral provocation test (OPT) with a culprit drug remains the gold standard for the diagnosis of IHS to NSAIDs [6]. Several studies have investigated the place of OPT in patients with IHS to NSAIDs [2,5,7]; however, there is currently no consensus regarding the management of these patients. Consequently, the goal of the present study is to report the results of a new procedure implemented in a Tunisian allergology center to explore CRR to NASIDs in patients with immediate hypersensitivity (IHS) to NSAIDs.

2. Materials and methods

2.1. Subjects

This retrospective study was conducted in cases of IHS reactions to one or more NSAIDs notified to the pharmacology department in Sfax (Tunisia).

First, the cases were selected from the archive of the pharmacovigilance department of Sfax notified between January 2012 and December 2018. We included all patients with a clinical history of IHS reactions to one or more NSAIDs as documented by a clinical report.

The patients were contacted by telephone and invited to undergo OPT at the allergy unit of the pneumo-allergology department of the Hedi Chaker University Hospital in Sfax (Tunisia) to confirm the diagnosis of CRR to NSAIDs.

Patients with a history of non-immediate reactions (e.g. maculopapular rashes, fixed drug eruptions, bullous drug eruptions, contact dermatitis, etc.) to these drugs were not included.

The study was conducted according to the principles of the Declaration of Helsinki and approved by the relevant Ethics Committees. All participants were informed orally about the study and signed the corresponding informed consent.

2.2. Data collection

The following data were collected from medical records supplemented with direct interviewing:

- demographic characteristics: age, gender;
- a detailed clinical history of NSAID-induced IHS reactions [the index reaction(s)]: number of episodes, clinical symptoms, culprit drug in each episode, time elapsed between drug administration and onset of symptoms, NSAID use and subsequent tolerance;
- nasal polyposis;
- personal history of atopy.

Atopy was defined as a history of allergic conjunctivitis and/or rhinitis and/or asthma, food allergy, and/or atopic dermatitis.

2.3. Oral provocation test (OPT)

All OPTs were performed single-blind according to the EAACI/GA2LEN guidelines [8]. These tests were performed under strict medical surveillance in the hospital ambulatory day center after patients had given their informed consent.

In all patients, antihistamines and other drugs that might affect the result of the provocation test were discontinued at least three days before the oral challenge [8].

On the first day, placebo capsules (lactose) were administered in all cases, and on the next day, increasing doses of NSAIDs were administered orally at 90 min intervals, as summarized in Table 1.

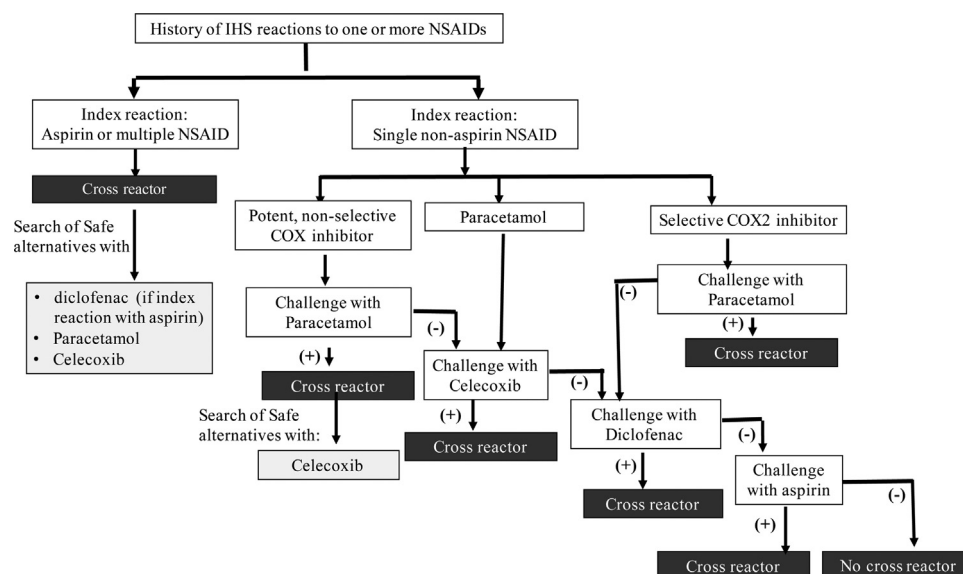
During the challenge procedure, patients were observed carefully, and FEV1 and blood pressure were measured every 30 minutes after each consecutive dose. Patients were also observed 2 hours after administration of the final dose.

The OPTs were considered positive when an objective clinical reaction occurred during or after the test, i.e. urticaria, angioedema, nasal congestion, hypotension, bronchospasm, dyspnea, a 20% fall in FEV1, abdominal cramps, or other rashes. In the case of a positive test, the procedure was stopped, and appropriate medication was administered to treat and relieve the symptoms.

Table 1

Non-steroidal anti-inflammatory drug doses used for oral drug challenge.

Category	Drug	COX1-inhibitor	Dose (total accumulated dose) ^a
Potent, non-selective COX1/COX2 inhibitor	Aspirin	92%	20, 75, 150, 600
	Diclofenac	66%	12.5, 12.5, 25 mg (50 mg)
Weak non-selective COX1/COX2 inhibitor	Paracetamol		50, 100, 350, 500 mg (1000 mg)
Selective COX2 inhibitor	Celecoxib	60%	50, 100, 200

^a All doses 120 min apart. The doses were administered at 90-min intervals.**Fig. 1.** Algorithm for the management of patients with IHS reactions to one or more NSAIDs.

The pattern of management for patients with a history of IHS reactions to one or more NSAIDs is presented in the algorithm shown in Fig. 1. The goal of this approach was to retain the diagnosis of CRR to NSAIDs and to explore safe alternatives. OPT was not performed with the culprit drug and patients were assigned to undergo different types of OPT:

If the index reactions were induced by aspirin (ASA subgroup) or at least two NSAIDs (multiple NSAIDs subgroup) from unrelated chemical groups, the CRR to NSAIDs was diagnosed based on clinical history, and alternative drugs to diclofenac (in the ASA subgroup), paracetamol and celecoxib were tested;

If the index reactions were induced by a single non-aspirin NSAID and tolerance to other NSAIDs was not known, the order of challenge drugs was as follows:

- paracetamol, celecoxib, diclofenac and aspirin where a non-selective COX inhibitor was initially incriminated (single non-selective NSAID subgroup);
- celecoxib, diclofenac and aspirin where paracetamol was initially incriminated (paracetamol subgroup);
- paracetamol, diclofenac and aspirin where a selective COX2 inhibitor was initially incriminated (celecoxib subgroup).

At the end of this exploration, each patient was given a written document containing information on the culprit drug and the safe alternative.

2.4. Statistics

The questionnaire responses and clinical data were entered into the database by the first author. Data analysis was performed with the statistical package SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Demographic and clinical characteristics of study subjects

A total of 87 patients met the inclusion criteria of our study, of whom 34 (40.2%) were successfully contacted by telephone and agreed to undergo an OPT. Their mean age was 44 ± 17.6 years (range: 18 to 69 years), with 38.2% ($n = 13$) being male (Table 2). A personal history of atopy was found in 26 (76.5%). Eighteen had chronic rhinosinusitis and 14 had underlying asthma.

Urticaria/angioedema was the most frequently reported symptom, followed by respiratory symptoms (Table 2).

3.2. OPTs and safe alternatives

The NSAIDs involved are presented in Table III. Six patients reacted to ASA, 12 patients to two different NSAIDs, 10 to a single non-selective COX inhibitor, 4 to paracetamol, and 2 to celecoxib. The mean time between drug administration and index reaction was 122 min (Table 3).

Of the 93 OPT performed, 24 (25.8%) were positive; a detailed description of the results is given in Table 3.

CRR to NSAIDs was diagnosed in 24 of 34 referred patients (70.6%), based on a positive oral challenge in 6 cases (in the non-selective NSAID, paracetamol and celecoxib subgroups), and on clinical history in 18 cases (ASA and multiple NSAIDs subgroups) (Table 3). The symptoms occurring during positive OPTs were localized urticaria in 13 cases, generalized urticaria in 1 case, angioedema in 7 cases, dyspnoea in 2 cases, and repetitive cough with abdominal pain in 1 case.

Regarding safe alternatives in patients with CRR to NSAIDs ($n = 24$), paracetamol was well tolerated in 16 of 20 patients tested, celecoxib in 16 of 22 patients tested, and diclofenac in 2 of 12

Table 2
Demographic and clinical characteristics of study subjects.

	Total (n = 34)	B1 (n = 6)	B2 (n = 12)	B3 (n = 10)	B4 (n = 4)	B5 (n = 2)
Age, years (mean)	44	34.3	48.5	43.6	36.5	67
Male, n	13	4	5	3	1	0
Atopy, n	26	6	11	6	2	1
Rhinitis, n	18	6	6	4	1	1
Asthma, n	14	6	7	1	1	0
Atopic dermatitis, n	4	1	1	1	1	0
Chronic urticaria, n	2	0	2	0	0	0
Food allergy, n	3	0	3	0	0	0
Nasal polyp	7	1	5	1	0	0
Index reaction	47	6	25	10	4	2
Urticaria	30	5	11	8	4	2
Angioedema	26	4	13	6	2	1
Dyspnea	13	2	8	2	1	0
Hypotension	5	1	2	0	1	1
Abdominal cramping	1	1	0	0	0	0
Nausea	1	0	1	0	0	0

B1: ASA subgroup; B2: multiple NSAIDs subgroup; B3: Single non-selective NSAID subgroup; B4: paracetamol subgroup; B5: celecoxib subgroup.

Table 3
NSAID incriminated in index reactions, oral provocation tests and safe alternative.

	Total (n = 34)	B1 (n = 6)	B2 (n = 12)	B3 (n = 10)	B4 (n = 4)	B5 (n = 2)
Time intervals between drug intake and index reaction, min (mean, min)	122	66	146	111.5	116	50
NSAID incriminated in index reactions						
ASA, n	6	6	0	0	0	0
Ketoprofen	3	0	1	2	0	0
Ibuprofen	6	0	5	1	0	0
Naproxen	1	0	1		0	0
Indomethacin	1	0	1		0	0
Mefenamic acid	13	0	8	5	0	0
Piroxicam	5	0	4	1	0	0
Diclofenac	3	0	2	1	0	0
Paracetamol	4	0	0	0	4	0
Celecoxib	4	0	2	0	0	2
OPT: positive test/total number of test	24/93	11/18	5/24	6/34	1/12	1/5
ASA	2/12	NI	NI	1/7	1/4	0/1
Diclofenac	7/19	6/6	NI	0/7	0/4	1/2
Paracetamol	8/30	2/6	3/12	3/10	NI	0/2
Celecoxib	7/32	3/6	2/12	2/10	0/4	NI
Diagnosis of CRR to NSAID	24/34	6/6	12/12	4/10	1/4	1/2
Safe alternative in case of CRR to NSAID						
Paracetamol	16	4	9	1	NI	1
Celecoxib	16	3	10	2	1	NI
Diclofenac	2	0	NI	1	1	0

B1: ASA subgroup; B2: multiple NSAIDs subgroup; B3: Single non-selective NSAID subgroup; B4: paracetamol subgroup; B5: celecoxib subgroup; CRR: cross-reactive reactions; NSAID: Nonsteroidal anti-inflammatory drugs; cross reactive reactions (CRR)

patients tested (Table 3). The prevalence of cross-intolerance to paracetamol and celecoxib was thus 20% and 27.3%, respectively.

4. Discussion

NSAIDs, the most commonly prescribed class of drugs in the world [9], are commonly associated with IHS. Accurate diagnosis of CRR to NSAIDs depends on careful history-taking and oral drug challenge [3,6,10–12]. Based on the latest advances in the literature, we used a structured protocol for patients with a history of IHS reactions to NSAIDs in order to confirm CRR to NSAIDs and identify a safe alternative.

In our sample, the value of OPT was demonstrated since a diagnosis of CRR to NSAIDs was rejected in 29.4% of patients with an unequivocal history of IHS reactions after NSAID intake.

The value of clinical history in establishing a diagnosis of CRR to NSAIDs remains controversial. In our small sample, we used the results of the literature and our knowledge about the patients' clinical history to classify patients with CRR to NSAIDs. This diagnosis was retained in the multiple NSAID subgroup (n = 12) because of

the good concordance between patients experiencing at least two episodes of IHS with two or more non-chemically related NSAIDs and the OPT results [13,14].

We also retained a diagnosis of CRR to NSAIDs in the ASA subgroup (n = 6). The presence of asthma is in fact associated with a higher prevalence of hypersensitivity to aspirin and other NSAIDs [12,15]. Additionally, some studies show that these patients have a greater likelihood of a positive OPT [16,17]. In our sample, we effectively confirmed NSAID cross-reactivity in all asthmatic patients who experienced at least one episode of aspirin-induced IHS since all OPTs with alternative drugs to diclofenac were positive.

However, where the clinical history was doubtful, we performed a provocation test to confirm or rule out the diagnosis. In this case, our approach was based on the COX selectivity of NSAIDs, starting with drugs having greater selectivity for COX-2 than COX-1: celecoxib, then paracetamol, then diclofenac, then aspirin (which is the gold standard) [7,18].

In accordance with the findings of Asero R. et al. [19], a diagnosis of NSAID cross-reactivity was rejected in 10 of 16 patients who developed one episode of IHS to a single NSAID or paracetamol

(62.5%). This finding suggest that OPT is the most reliable method for establishing a diagnosis of NSAID hypersensitivity in such patients [6,8].

Paracetamol, a weak COX inhibitor, and celecoxib, a selective COX-2 inhibitor, are known to be relatively safe therapeutic alternatives for patients with aspirin hypersensitivity [20,21]. However, cross-reactivity among these medications has rarely been explored in the Tunisian population. In the present study, in patients with confirmed CRR to NSAIDs the rate of cross-reactivity to paracetamol or celecoxib was found to be 20% and 27.3%, respectively. In an Asian study, the corresponding rates were 24.8% for paracetamol and 10.3% for celecoxib [22]. Physicians should therefore be aware of possible cross-reactions to these alternative drugs.

This study underlines the importance of a structured approach based on history-taking and standardized oral challenge tests to establish a diagnosis of CRR to NSAIDs in patients presenting acute hypersensitivity reactions to an NSAID. This approach helps physicians to reduce unnecessary avoidance of potentially useful NSAIDs and to prescribe a suitable drug.

Disclosure of interest

The authors declare that they have no competing interest.

References

- [1] Roberts LJ, Marrow JD, Hardman JG, Limbird LE. Analgesic-antipyretic and anti-inflammatory agents and drugs employed in the treatment of Gout in Goodman and Gilman's "The Pharmacological Basis of Therapeutics". *Phar Ther* 2001;687–731.
- [2] Çelik GE, Erkeköl FÖ, Aydın Ö, Demirel YS, Mısırlıgil Z. Are drug provocation tests still necessary to test the safety of COX-2 inhibitors in patients with cross-reactive NSAID hypersensitivity? *Allergol Immunopathol (Madr)* 2013;41(3):181–8.
- [3] Doña I, Blanca-López N, Cornejo-García JA, Torres MJ, Laguna JJ, Fernández J, et al. Characteristics of subjects experiencing hypersensitivity to non-steroidal anti-inflammatory drugs: patterns of response. *Clin Exp Allergy* 2011;41(1):86–95.
- [4] Ponvert C, Scheinmann P. Les réactions allergiques et pseudoallergiques aux antalgiques, antipyrétiques et anti-inflammatoires non stéroïdiens. *Archives de pédiatrie* 2007;14(5):507–12.
- [5] Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy* 2003;58(9):854–63.
- [6] Kowalski ML, Makowska JS, Blanca M, Bavbek S, Bochenek G, Bousquet J, et al. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) – classification, diagnosis and management: review of the EAACI/ENDA(®) and GA2LEN/HANNA*. *Allergy* 2011;66(7):818–29.
- [7] Chaudhry T, Hissaria P, Wiese M, Heddle R, Kette F, Smith WB. Oral drug challenges in non-steroidal anti-inflammatory drug-induced urticaria, angioedema and anaphylaxis. *Intern Med J* 2012;42(6):665–71.
- [8] Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, Swierczyńska M, Picado C, Scadding G, et al. EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy* 2007;62:1111–8.
- [9] Nettis E, Colanardi MC, Ferrannini A, Tursi A. Update on sensitivity to non-steroidal antiinflammatory drugs. current drug targets - immune. *Endoc Metabol Dis* 2001;1(3):233–40.
- [10] Nettis E, Di Paola R, Ferrannini A, Tursi A. Meloxicam in hypersensitivity to NSAIDs. *Allergy* 2001;56(8):803–4.
- [11] Canto MG, Andreu I, Fernandez J, Blanca M. Selective immediate hypersensitivity reactions to NSAIDs. *Curr Opin Allergy Clin Immunol* 2009;9(4):293–7.
- [12] Kowalski ML, Asero R, Bavbek S, Blanca M, Blanca-Lopez N, Bochenek G, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy* 2013;68(10):1219–32.
- [13] Blanca-Lopez N, Torres J, Doña M, Campo I, Rondón P, Seoane Reula C, et al. Value of the clinical history in the diagnosis of urticaria/angioedema induced by NSAIDs with cross-intolerance. *Clin Exp Allergy* 2013;43(1):85–91.
- [14] Nissen CV, Bindslev-Jensen C, Mortz CG. Hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs): classification of a Danish patient cohort according to EAACI/ENDA guidelines. *Clin Transl Allergy* 2015:5.
- [15] Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIAE investigators. european network on aspirin-induced asthma. *Eur Respir J* 2000;16:432–6.
- [16] Dursun AB, Woessner KA, Simon RA, Karasoy D, Stevenson DD. Predicting outcomes of oral aspirin challenges in patients with asthma, nasal polyps, and chronic sinusitis. *Ann Allergy Asthma Immunol* 2008;100(5):420–5.
- [17] Pleskow WW, Stevenson DD, Mathison DA, Simon RA, Schatz M, Zieger RS. Aspirin sensitive rhinosinusitis/asthma: spectrum of adverse reactions to aspirin. *J Allergy Clin Immunol* 1983;71:574–9.
- [18] Tacconelli S, Bruno A, Grande R, Ballerini P, Patrignani P. Nonsteroidal anti-inflammatory drugs and cardiovascular safety - translating pharmacological data into clinical readouts. *Expert Opin Drug Saf* 2017;16(7):791–807.
- [19] Asero R. Oral aspirin challenges in patients with a history of intolerance to single non-steroidal anti-inflammatory drugs. *Clin Exp Allergy* 2005;35(6):713–6.
- [20] Knowles SR, Drucker AM, Weber EA, Shear NH. Management options for patients with aspirin and nonsteroidal antiinflammatory drug sensitivity. *Ann Pharmacother* 2007;41(7):1191–200.
- [21] Kowalski ML, Makowska J. Use of nonsteroidal anti-inflammatory drugs in patients with aspirin hypersensitivity: safety of cyclo-oxygenase-2 inhibitors. *Treat Respir Med* 2006;5(6):399–406.
- [22] Kim YJ, Lim KH, Kim MY, Jo EJ, Lee SY, Lee SE, et al. Cross-reactivity to acetaminophen and celecoxib according to the type of nonsteroidal anti-inflammatory drug hypersensitivity. *Allergy Asthma Immunol Res* 2014;6(2):156–62.