Year-in-Review

Drug allergy

Department of Internal Medicine, SMG-SNU Boramae Medical Center, Seoul National University College of Medicine

Min-Suk Yang

This article is a selected summary of original articles and reviews published between January 2017 and March 2018 on the subjects of drug allergy. The author selected interesting articles on drug allergy from high impact journals on allergy and clinical immunology: *Journal of Allergy and Clinical Immunology, Allergy, Journal of Allergy and Clinical Immunology - in practice and Allergy, Asthma & Immunology Research.* The articles were presented under several subheadings and sometimes related articles from other journals were also presented when necessary.

I. β-lactam antibiotics

Regarding β-lactam allergy, Infectious Diseases Society of America (IDSA) published guideline for implementation and measurement of antibiotic stewardship intervention in inpatient population in 2016. In the guideline, they recommended penicillin skin testing to the patients with a history of β-lactam allergy as weak recommendation. IDSA commented on the reason for weak recommendation that allergy assessments and penicillin skin testing could enhance use of first-line agents, but the effect of penicillin skin test as a primary antibiotic stewardship program is largely unstudied.[1] Blumental KG, et al. added an evidence.[2] They compared the use of a penicillin or cephalosporin after they started penicillin skin test (ST period) and after they adopted computerized guideline application with decision support (APP period) with baseline period. Although ST period patients did not have increased odds of penicillin or cephalosporin use overall (adjusted odds ratio [aOR] 1.3; 95% CI, 0.8-2.0), they observed significant increased odds of penicillin or cephalosporin use overall in the APP period (aOR, 1.8; 95% CI, 1.1-2.9) and in a per protocol analysis of the skin tested subset (aOR, 5.7; 95% CI, 2.6-12.5). While the skin tested subset in APP period showed an almost 6-fold impact, the computerized guideline significantly increased penicillin or cephalosporin use overall nearly 2-fold.[2]

As inpatient penicillin skin test (with or without oral amoxicillin challenge) is not often readily available and only around 60% of institutions having penicillin skin test available, Sacco KA, et al. performed meta-analysis on the clinical outcomes of penicillin allergy testing.[3] Eighteen studies were included. Inpatient penicillin allergy testing led to a change in antibiotic selection that was greater in the intensive care unit (77.97% [CI 72.0-83.1] vs 54.73% [CI 51.2-58.2], P<.01) and an increased prescription of penicillin (range 9.9%-49%) and cephalosporin (range 10.7%-48%) antibiotics was reported. Vancomycin and fluoroquinolone use was decreased. They concluded that inpatient penicillin allergy testing is safe and effective in ruling out penicillin allergy.[3]

The resenstization rate after repeated doses of intravenous penicillin to patients with a history of penicillin allergy who are found to be skin test negative to penicillin was investigated.[4] Thirty-two patients with previous penicillin-associated reactions ranged from rash to hypotension were included. Thirty-two patients received a total of 111 courses of intravenous penicillins and none developed an immediate hypersensitivity reaction. The most frequently repeated intravenous penicillin overall was piperacillin/tazobactam. They concluded that in patients who report penicillin allergy and have negative penicillin allergy testing, repeated administration of intravenous penicillin antibiotics appears to be safe.[4]

Oral challenge was also investigated. Tucker MH, et al. reported that 328 Marine recruits went directly to amoxicillin challenge without skin testing because of time constraints, and only 5 (1.5 %) had an acute objective challenge reaction.[5] Thus, only 1.2% of all recruits evaluated were documented to have penicillin allergy. There were no cases of anaphylaxis and all 5 were isolated cutaneous reactions except for 1, which included globus. The authors concluded that Amoxicillin challenge without penicillin skin testing in evaluation of penicillin allergy is safe.[5]

For delayed onset penicillin allergy, oral challenge without skin testing was also safe. Patients with non-immediate reaction to penicillins starting longer than 1 hour after last dose administration or starting any time after the first treatment day or patients with vague recollection of their reaction underwent penicillin skin test.[6] Independent of skin test results, patients were challenged with the relevant penicillins. One-tenth of the therapeutic dose followed by the full dose was administered at 1-hour interval and patients continued taking the full dose for 5 days. Among 642 patients, 62.3% had negative, 5.3% positive, and 32.4% equivocal skin tests. A total of 617 (96.1%) patients were challenged. Immediate reaction was observed in 9 patients (1.5%): 1 positive, 7 negative, and 1 equivocal skin test (P= .7). Late reaction to the first-day challenge occurred in 24 patients (4%). An at-home challenge was continued by 491 patients. Complete 5-day and partial challenges were well tolerated by 417 (85%) and 44 patients (8.9%), respectively, disregarding skin test results. Thirty patients (6.1%) developed mild reactions to the home challenge regardless of their skin test results. Thus, a 5-day oral challenge without preceding skin test is safe and sufficient to exclude penicillin allergy.[6] The 5-day challenge was also a safe and effective way to rule out nonimmediate amoxicillin allergy in children.[7]

II. Radiocontrast media (RCM)

Many Korean researchers contributed to the research on RCM hypersensitivity. Park HJ et al. retrospectively evaluated a cohort of patients with moderate-to-severe hypersensitivity reactions (HSR) to low osmolar RCM and underwent contrast-enhanced computed tomography (CT) after the initial HSR from 11 centers.[8] A total of 150 patients with 328 instances of re-exposure were included; the recurrence rate of HSR was 19.5%. The independent risk factors for recurrence of HSR were diabetes, chronic urticaria, drug allergy other than to iodinated RCM and severe initial HSR. The risk of recurrent HSR was 67.1% lower in cases where the implicated ICM was changed to another one (odds ratio: 0.329; P=0.001). However, steroid premedication did not show protective effects against recurrent HSR.[8]

Lee SY, et al. investigated stratified premedication strategy according to the severity of previous reaction for the prevention of RCM hypersensitivity in high risk patients.[9] Among a total of 850 patients who underwent enhanced CT after severity tailored prophylaxis, breakthrough reactions occurred in 17.1%, but most breakthrough reactions (89.0%) were mild and did not require medical treatment. Additional corticosteroid use did not reduce the breakthrough reaction rate in cases with a mild index reaction (16.8% vs 17.2%, P¼.70). However, under premedication with a single dose of corticosteroid revealed significantly higher rates of breakthrough reaction than did double doses of corticosteroid in cases with a severe index reaction (55.6% vs 17.4%, P= .02). Changing the iodinated RCM resulted in an additional reduction of the breakthrough reaction rate overall (14.9% vs 32.1%, P = .001).[9]

Kim SR, et al. estimated the difference in the incidence of immediate adverse reactions to low-osmolar non-ionic iodide RCM.[10] They reviewed 1969 immediate adverse drug reactions from 286,087 RCM-contrasted CT of 142,099 patients and compared the immediate adverse drug reactions of iobitridol, iohexol, iopamidol, and iopromide. Iopromide showed the highest incidence of immediate ADRs (1.03%) and was followed by iopamidol (0.67%), iohexol (0.64%), and iobitridol (0.34%). In cases of anaphylaxis, iopromide also showed the highest incidence (0.041%), followed by iopamidol (0.023%), iohexol (0.018%), and iobitridol (0.012%). Risk of immediate ADR due to multiple CT examinations (1.19%) was significantly higher than the risk due to a single CT examination (0.63%). Risk of anaphylaxis was also higher for multiple CT examinations (0.052%) than for a single CT examination (0.020%).[10]

Cross-reactivity among RCM gains many interests by many researchers. Lerondeau B, et al. analyzed cross-reactivity among RCM in 97 hypersensitivity reactions.[11] They found only 3 patients (6%) with positive prick test results, whereas 33 patients (66%) had positive intradermal test results at 24 hours in the delayed reaction group. Multiple correspondence analyses identified 3 subgroups of RCM in which cross-reactions were frequent: group A (iodixanol, iopamidol, iomeprol, iohexol, ioversol, and ioxitalamate), the members of which share 2 identical N-(2,3-dihydroxypropyl) carbamoyl side chains (except for ioxitalamate); group B (ioxaglate and iobitridol; they could not establish a chemical link between these 2

RCM); and group C with an isolated RCM (amidotrizoate). The results were statistically significant among patients belonging to the ''delayed'' subgroup but less robust for those in the ''immediate reactions'' group. Cross-reactions among RCM do not follow the current chemical classification.[11]

III. Nonsteroidal anti-inflammatory drugs (NSAIDs)

There were also a few publications from Korean researchers in NSAIDs hypersensitivity. Lee HY, et al. suggested four distinct subtypes with different clinical/biochemical findings and asthma exacerbations in a NSAIDs exacerbated respiratory disease (NERD) cohort comprising 302 patients.[12] There were four subtypes of NERDs: subtype 1 (NERD with CRS/atopy and no urticaria), subtype 2 (NERD with CRS and no urticaria/atopy), subtype 3 (NERD without CRS/urticaria), and subtype 4 (NERD with urticaria) and There were four subtypes: subtype 1 (NERD with CRS/atopy and no urticaria), subtype 2 (NERD with CRS and no urticaria/atopy), subtype 3 (NERD without CRS/urticaria), and subtype 4 (NERD with urticaria). A higher frequency of asthma exacerbations was noted in subtype 1 compared to subtype 3. Metabolomic analysis showed that the four subtypes of NERD had a higher serum leukotriene E4 (LTE4) level than those with aspirin-tolerant asthma. The patients with subtypes 1 and 3 had a higher urine LTE4 level than those with subtype 2.[12]

The same group reported the results on the metabolomic approach from NERD patients. Ban GY, et al. performed an untargeted profile of serum from asthmatics in the first cohort comprising 45 NERD, 44 patients with aspirin-tolerant asthma (ATA), and 28 normal controls was developed using the ultra-high-performance liquid chromatography/QToF MS system.[13] Metabolites that discriminate AERD from ATA were quantified in both serum and urine, which were collected before (baseline) and after the lysine-aspirin bronchoprovocation test (Lys-ASA BPT). A clear discrimination of metabolomes was found between patients with NERD and ATA. Serum levels of LTE4 and LTE4/PGF2a ratio before and after the LysASA BPT were significantly higher in patients with NERD than in patients with ATA ($P < 0.05$ for each), and urine baseline levels of these two metabolites were significantly higher in patients with NERD. The result was replicated from the second cohort comprising 50 patients with NERD and 50 patients with ATA. This result suggests that serum metabolite level of LTE4 and LTE4/PGF2a ratio was identified as potential in vitro diagnostic biomarkers for NERD, which were closely associated with major pathogenetic mechanisms underlying NERD.[13]

The European Academy of Allergy and Clinical Immunology Drug Allergy Interest Group reported the outcome of aspirin (ASA) desensitization or challenge to the patients with ASA hypersensitivity and coronary artery disease.[14] Of the 310 subjects, 138 had an acute coronary syndrome (ACS), 101 of whom underwent desensitizations, whereas 172 suffered from a chronic ischemic heart disease (CIHD), 126 of whom underwent challenges. Overall, 163 subjects underwent challenges and 147 subjects underwent

desensitizations; 86 of the latter had index reactions to ASA doses of 300 mg or less. Ten subjects reacted to challenges, seven at doses up to 500 mg, three at a cumulative dose of 110 mg. The desensitization failure rate was 1.4%. They recommended that in patients with stable CIHD and histories of nonsevere hypersensitivity reactions to ASA/NSAIDs, an ASA challenge is advisable. Patients with an ACS and histories of hypersensitivity reactions to ASA, especially following doses lower than 100 mg, should directly undergo desensitization.[14]

In the U.S., Waldram J, et al. evaluated the safety and outcomes of outpatient ASA desensitization.[15] All of the 167 reactors, including 23 who were classified as severe reactors, were successfully desensitized in the outpatient setting. The average desensitization duration among reactors was 1.67 days, and the average duration for gastrointestinal reactors was 2.29 days. The Sino-Nasal Outcome Test score might be able to predict more severe reactions and merits further study. Omalizumab did not block breakthrough reactions during ASA desensitization.[15]

IV. Antineoplastic agents

Sohn KH, et al. reported the incidence and risk of oxaliplatin-induced hypersensitivity in patients with asymptomatic prior exposure.[16] They prospectively observed 793 patients and 148 (18.7%) experienced an HSR. The HSR incidence was 15.2% among oxaliplatin-naive patients but increased to 31.9% among those with a history of asymptomatic exposure and 75.0% among those with a history of oxaliplatin HSRs during the previous exposure, despite prophylaxis. Prior exposure to oxaliplatin (odds ratio [OR], 3.78; 95% confidence interval [CI], 2.46-5.79) and a longer oxaliplatin-free interval (36 months; OR, 4.85; 95% CI, 1.60-14.37) were independent risk factors for HSRs.[16]

Galvão VR, et al. evaluated the impact of BRCA mutation on carboplatin allergic patients who were undergoing desensitization.[17] BRCA positive patients had more initial immediate HSR than BRCA negative patients ($p=0.03$). Reactions during RDD occurred in 51% of patients with the BRCA1/2 mutation versus 27% of patients without the mutation ($p<0.01$). The severity of rapid drug desensitization reactions had a similar distribution between groups ($p=0.72$).[17]

Wong JT and Long A analyzed data from 25 rituximab hypersensitivity patients.[18] The 25 patients underwent 170 continuous intravenous desensitizations based on 3 related protocols, with most based on the intermediate protocol. All but 2 desensitizations were completed successfully. Overall 24% of the desensitizations were complicated by hypersensitivity reactions. Two patients with serum sickness and a patient with mast cell disorder were also successfully managed. Skin test status was not helpful for risk stratification for hypersensitivity reactions.[18]

V. Fluoroquinolone

Demer S, et al. studied 54 patients with 57 hypersensitivity reactions due to different quinolones and 10 non-atopic quinolone tolerable control subjects.[19] A detailed clinical history, skin test (ST), and single-blind placebo-controlled drug provocation test (SBPCDPT), as well as basophil activation test (BAT) and lymphocyte transformation test (LTT) were performed with the culprit and alternative quinolones including ciprofloxacin (CFX), moxifloxacin (MFX), levofloxacin (LFX), ofloxacin (OFX), and GFX. The majority (75.9%) of the patients reported immediate type reactions to various quinolones. A quarter of the patients (24.1%) reacted to SBPCDPTs, although their STs were negative; while false ST positivity was 3.5% and ST/SBPCDPTs concordance was only 1.8%. Both BAT and LTT were not found useful in quinolone hypersensitivity. Cross-reactivity was primarily observed between LFX and OFX (50.0%), whereas it was the least between MFX and the others, and in GFX hypersensitive patients the degree of cross-reactivity to the other quinolones was 16.7%. These results suggest that STs, BAT, and LTT are not supportive in the diagnosis of a hypersensitivity reaction to quinolone as well as in the prediction of cross-reactivity.[19]

The lack of reliable diagnostic tests for fluoroquinolone hypersensitivity was repeatedly reported from other studies.[20,21]

VI. Proton pump inhibitors (PPIs)

Mota I, et al. reported case series of 5 PPI induced anaphylaxis patients.[22] All patients showed positive response to the culprit drug, either in SPT or in IDT with nonirritating concentrations. Regarding cross-reactivity, according to the skin tests results, esomeprazole might be a safe alternative for some patients, but others reacted to all PPIs.

Laguna JJ, et al enrolled more patients (n = 42) with omeprazole induced immediate hypersensitivities and they found that sensitivity and specificity of skin test were 66.7% and 100%, respectively.[23] BAT using CD63 with a stimulation index of more than 2 as positive revealed a sensitivity of 73.8%, a specificity of 100%. They could correctly diagnose 85.7% of patients with immediate allergy to omeprazole by combining ST and BAT.

PPI could induce delayed type hypersensitivity. Lim CY, et al. retrospectively ananlyzed 69 patients with PPI-related delayed hypersensitivity reaction.[24] There were 69 cases of PPI-related DHR, including SJS/TEN (n=27) and DRESS (n=10). The LAT by measuring granulysin showed a sensitivity of 59.3% and specificity of 96.4%. Esomeprazole was the most commonly involved in PPI-related DHR (51%). Thirteen patients allergic to one kind of PPI could tolerate other structurally different PPI without cross-hypersensitivity reactions, whereas three patients developed cross-hypersensitivity reactions to alternative structurally similar PPI.

VII. Delayed hypersensitivity

Gibson A, et al. investigated the origin of drug and drug metabolite-specific T cells from drug naïve and sulfamethoxazole (SMX) hypersensitive donors.[25] They stimulated both naïve and memory T cells from naïve and sulfamethoxazole with SMX and its downstream metabolite nitroso sulfamethoxazole (SMX-NO). SMX and SMX-NO activated both naïve and memory T cells. They conclude that not only the priming of naive T cells but also the activation of preexisting memory T cells by SMX-derived antigens may play a role in the onset of SMX hypersensitivity.

Sullivan A, et al studied the nature of the drug-specific T-cell response induced in the blood and skin of hypersensitive patients and healthy volunteers using piperacillin as a model of β-lactam hypersensitivity. PBMC and T-cell clones (n=570, 84% CD4+) from blood of piperacillin-hypersensitive patients proliferated and secreted TH1/TH2 cytokines alongside IL-22 after drug stimulation. Drug-specific clones from inflamed skin (n=96, 83% CD4+) secreted a similar profile of cytokines but displayed greater cytolytic activity, secreting perforin, granzyme B, and Fas ligand when activated. Blood- and skin-derived clones expressed high levels of skin-homing chemokine receptors and migrated in the presence of the ligands CCL17 and CCL27. Piperacillin-primed naive T cells from healthy volunteers also secreted IFN-g, IL-13, IL-22, and cytolytic molecules. The authors concluded that circulating and skin-resident, antigen-specific, IL-22-secreting T cells are detectable in patients with β-lactam hypersensitivity.

The HLA B*58:01 allele has been worldwide reported as a pharmacogenetic susceptibility to allopurinol-induced severe cutaneous adverse reactions (SCARs). To prevent these life-threatening conditions, the American College of Rheumatology recommended that the HLA-B*58:01 be screened prior to the initiation of allopurinol therapy. As current screening tests for HLAB5801 was expensive and time consuming, Nguyen DV, et al. developed a rapid, robust, inexpensive screening method using SYBR® Green real time PCR to detect the HLA-B*58:01 allele. This new method was as correct as other tests, while the cost was much lower.[26]

Lee HK et al. reported that patients with SJS/TEN who took NSAIDs showed a significantly higher rate (28.57%) of high chronic ocular complications than those who did not take NSAIDs (5.36%) (OR: 7.067; P<.001).[27] However, in an editorial, Roujeau J. et al raised strong doubts on the causative role of “cold medicine” because nonspecific symptoms, which developed prodromal phase of SJS/TEN were often treated with “cold medicines”.[28]

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