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HLA-B58 can help the clinical decision on starting allopurinol in patients with chronic renal insufficiency

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Abstract

Background. Although allopurinol is a very effective urate-lowering drug for complicated hyperuricemia, in some patients, it can induce severe cutaneous adverse reactions (SCARs). Recent investigations suggest that HLA-B*5801 is a very strong marker for allopurinol-induced SCARs, especially in the population with a high frequency of HLA-B*5801. Korea is one of the countries with a high frequency of HLA-B*5801 which is the only subtype of HLA-B58 in the Korean population.

Objective. This study was conducted to find out the incidence of allopurinol-induced hypersensitivity on patients with chronic renal insufficiency (CRI) according to HLA-B58 and the clinical implications of HLA-B58 as a risk marker for the development of allopurinol-induced hypersensitivity.

Methods. We retrospectively reviewed the medical records of patients with CRI who took allopurinol and carried out serologic human leukocyte antigen (HLA) typing for kidney transplantation between January 2003 and May 2010.

Results. Among a total of 448 patients with CRI, 16 (3.6%) patients experienced allopurinol hypersensitivity. Nine of these patients (2.0%) were diagnosed with SCARs (two Stevens–Johnson syndrome and seven allopurinol hypersensitivity syndrome) and seven patients (1.6%) had simple maculopapular rashes. The HLA-B58 allele was present in all patients with allopurinol-induced SCARs, while the frequency of HLA-B58 was only 9.5% in allopurinol-tolerant patients ($P < 0.05$). The incidence of allopurinol-induced SCARs in CRI shows a wide disparity according to HLA-B58 [18% in HLA-B58 (+) versus 0% in HLA-B58 (−)]. Among patients without HLA-B58, most (98.2%) of the CRI patients were tolerant to allopurinol and only 1.8% experienced simple rashes after taking allopurinol.

Conclusions. In this study, the incidence of allopurinol-induced SCARs was considerably high in CRI patients with HLA-B58. This finding indicates that the presence of HLA-B58 may increase the risk of allopurinol-induced SCARs. Screening tests for HLA-B58 in CRI patients will be clinically helpful in preventing severe allopurinol hypersensitivity reactions.

Keywords: allopurinol; chronic renal insufficiency; drug hypersensitivity; HLA; Koreans

Introduction

Although the incidence of severe cutaneous adverse reactions (SCARs) is relatively low, these reactions show a high mortality and morbidity. SCARs include Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug hypersensitivity syndrome. The mortality rate has been reported to be 1–5% for SJS, 25–30% for TEN and 10% for drug hypersensitivity syndrome [1].

Allopurinol is an effective xanthine oxidase inhibitor and is the most commonly used urate-lowering agent in clinical practice. The 1989–1993 SCAR study reported that allopurinol infrequently produces SJS and TEN compared to sulfonamides, phenobarbital, oxicam-type nonsteroidal anti-inflammatory drugs, chlormezanone and carbamazepine (CBZ) [2]. However, the 1997–2001 EuroSCAR study showed that allopurinol most commonly produced SCARs because the use of the aforementioned drugs had progressively decreased [3]. Cutaneous adverse reactions attributable to allopurinol occur relatively frequently and occur in 2% of patients who took allopurinol [4]. Allopurinol hypersensitivity syndrome (AHS), a subtype of SCARs, develops in 0.4% of subjects to whom allopurinol has been prescribed [5]. The mortality rate of AHS due to allopurinol is reported to be 25%, which is comparatively higher than other drugs [6]. Considering that the incidence of hyperuricemia is 15–20% in the general population and the incidence of gout is ~1%, the potential number of patients who use allopurinol is estimated to be very large [7].

Previous studies have demonstrated that susceptibility of drug hypersensitivity to allopurinol differs according to the kinds of human leukocyte antigen (HLA), a key molecule of immune responses. HLA-B*5801 is known as a risk marker for the development of allopurinol-induced SJS/TEN or drug hypersensitivity syndrome because of its remarkably high prevalence in patient groups [8–11]. However, the actual incidence of allopurinol hypersensitivity in patients with HLA-B*5801 has not yet been determined, thus, HLA-B*5801 had limited use as a predictor of allopurinol hypersensitivity.

This study was conducted to determine the incidence of allopurinol-induced hypersensitivity in patients with chronic renal insufficiency (CRI) according to HLA-B*5801 and clinical implication of HLA-B*5801 as a risk marker for development of allopurinol-induced hypersensitivity.

Materials and methods

Study subjects

This study included patients with CRI who underwent HLA typing for future kidney transplantation and took allopurinol at Seoul National University Hospital between January 2003 and May 2010. CRI was defined as chronic kidney disease Stages 3–5 or post-kidney transplantation state in this study. The medical records at 6 months and at least two outpatient visits before and after the cessation of allopurinol were thoroughly reviewed by two allergy specialists to determine the incidence of hypersensitivity reactions. We also electronically screened the text 'rash', 'drug eruption', 'erythema', 'itching', 'adverse reaction' and 'pruritus' in English and Korean. Two specialists trained in adverse drug reactions performed the WHO-ART causality assessment and selected events evaluated as 'certain' or 'probable' for allopurinol hypersensitivity reaction. Patients who took allopurinol without any symptoms of hypersensitivity reaction for $\geq$60 days were classified as the allopurinol-tolerant group. Patients who took allopurinol for $<$60 days were excluded from the study although they did not show allopurinol hypersensitivity because of potential risk of delayed hypersensitivity development.

Definition of SCARs

SCARs included SJS/TEN and AHS. SJS was defined as skin detachment of $<$10% of the body surface area, SJS/TEN as skin detachment of 10–30% and TEN as skin detachment of $\geq$30% [12]. AHS was defined when patients met more than two of the following criteria proposed by Wallace *et al.* [6]: (i) worsening of renal function, (ii) acute hepatocellular injury, (iii) a rash including either TEN, SJS, erythema multiforme or diffuse maculopapular or exfoliative dermatitis or more than one of these three criteria plus more than one of the three clinical findings including fever, eosinophilia and leukocytosis.

HLA typing

Serologic HLA typing was performed by using the microlymphocytotoxicity method using a Terasaki Oriental HLA-ABC well tray (One lambda, Canoga Park, CA). For HLA-DR, low-resolution HLA typing was performed using a PCR-SSO kit (Dynal RELI™ SSO HLA Test; Dynal Biotech, Wirral, UK). Since a previous study showed that a 100% coincidence of HLA-B*5801 in serologic-type HLA-B58 in the Korean population, it is thought that HLA-B58 is identical with HLA-B*5801 [13].

Incidence of drug hypersensitivity after the use of benzbromarone

In patients who had taken benzbromarone, another uricosuric agent, hypersensitivity reactions, such as skin rashes, were assessed by the same method as that for allopurinol hypersensitivity.

Statistical analysis

Statistical analyses were performed using SPSS ver. 16.0 (SPSS Inc., Chicago, IL). Values are expressed as mean $\pm$ standard deviation (SD). Comparisons of variables were made with the chi-square, Fischer's exact, Student's *t* and Mann–Whitney tests as appropriate. For comparing allele frequency between the study groups, the data of *HLA-A*, *-Cw*, *-B* and *-DRB1* genes in the Korean population were used [13]. A P-value of $<$0.05 was considered statistically significant.

Results

Characteristics of study patients

Of the 1632 CRI patients who underwent HLA typing, 542 took allopurinol. Of these patients, 16 showed hypersensitivity reactions (Table 1). Allopurinol hypersensitivity reactions occurred in 16 patients, 9 of whom showed SCARs (2 SJS and 7 AHS) and 7 had simple rashes.

Among the other 526 patients who did not show any hypersensitivity reactions during medication, 94 patients who took this drug for $<$60 days were thought to be inappropriate to be defined as a tolerant group and thus excluded from the analysis. A final total of 432 patients were included as the allopurinol-tolerant group in this study (Table 2). The allopurinol hypersensitivity group showed almost an even gender distribution, whereas 73.6% were males in allopurinol-tolerant group.

The medication duration was shorter in the allopurinol hypersensitivity group than in the allopurinol-tolerant group due to the cessation of the drug immediately after the occurrence of drug hypersensitivity reactions.

The daily administered dose of allopurinol was not statistically different between groups. The mean dosage of allopurinol was 101.3 $\pm$ 50.0 mg and 15% of the total patients had been medicated with $>$100 mg of allopurinol. When we analyzed the association between frequency of hypersensitivity reaction and dose of allopurinol, there was no significant statistical significance ($P = 0.1$). We also compared the estimated doses of allopurinol according to each patient's glomerular filtration rate but could not find any correlation between dose and development of hypersensitivity.

The renal function and the combined use of thiazides were not significantly different between the two groups. The frequency of underlying diseases, such as hypertension, diabetes mellitus, nephrotic syndrome or liver disease, was not significantly different between the two groups.

Table 1. HLA types of 16 patients with allopurinol hypersensitivity

Patient's no.	Sex/age	A	Cw	B	DR	Diagnosis
1	M/55	2, 24	3, 7	58, 75	4, 15	SJS
2	M/35	33, 24	3, 7	58, 7	13, 1	SJS
3	F/45	33, 31	3, 1	58, 55	3, 14	AHS
4	F/18	33, 33	3, 3	58, 58	13, 13	AHS
5	M/15	33, 26	NA	58, 44	13, 13	AHS
6	F/56	33, 11	3, 3	58, 62	3, 9	AHS
7	M/44	33, 2	3, 8	58, 48	3, 11	AHS
8	M/58	2, 2	3, 7	58, 7	13, 1	AHS
9	M/48	33, 26	3, 3	58, 62	13, 14	AHS
10	F/44	2, 26	3, 1	27, 60	1, 12	Rash
11	F/48	24, 24	3, 3	35, 51	14, 15	Rash
12	M/42	2, 2	3, 1	13, 46	4, 12	Rash
13	F/37	1, 29	3, 3	7, 35	8, 9	Rash
14	F/38	24, 30	6, 6	13, 52	7, 15	Rash
15	F/17	2, 24	3, 8	48, 62	4, 14	Rash
16	F/62	33, 2	3, 8	35, 61	12, 15	Rash

Table 2. Clinical characteristics according to allopurinol hypersensitivity

	Allopurinol hypersensitivity, $n = 16$ (3.6%)	Allopurinol tolerant, $n = 432$ (96.4%)	P-value
Sex (male %)	7 (43.8%)	318 (73.6%)	0.01
Age (median, year)	41.4 ± 14.4	35.9 ± 18.1	0.2
Duration of allopurinol exposure (day)	59.1 ± 45.5	887.1 ± 821.3	<0.001
Dosage of allopurinol (mg/day)	112.5 ± 38.7	100.0 ± 50.1	0.1
BUN (mg/dL)	65.9 ± 28.4	60.6 ± 51.0	0.3
Creatinine (mg/dL)	4.6 ± 3.1	5.2 ± 3.3	0.4
Estimated Ccr (mL/min)[a]	17.9 ± 9.4	21.7 ± 15.8	0.6
Uric acid	8.8 ± 2.8	8.4 ± 2.2	0.8
Use of thiazide diuretics (%)	0 (0%)	25 (5.8%)	0.4
Underlying diseases (%)			
Hypertension	7 (43.8%)	246 (56.9%)	0.3
Diabetes	2 (12.5%)	72 (16.7%)	0.5
Nephrotic syndrome	0 (0%)	49 (11.6%)	0.2
Liver disease	2 (12.5%)	31 (7.2%)	0.3
Malignancy	0 (0%)	13 (3.0%)	0.6

[a]Estimated Ccr, estimated creatinine clearance rate using the Cockcroft–Gault formula.

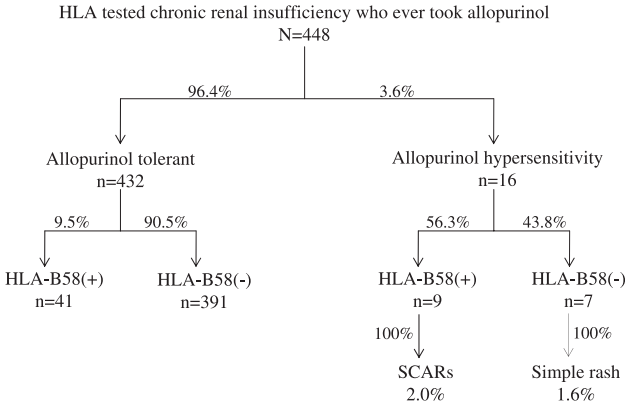

Fig. 1. Flow sheet of total patients. Among a total of 448 patients with CRI, 16 patients experienced allopurinol hypersensitivity. Nine of these patients were diagnosed with SCARs and seven patients had simple maculopapular rashes. The HLA-B58 allele was present in all patients with allopurinol-induced SCARs, while the frequency of HLA-B58 was only 9.5% in allopurinol-tolerant patients.

HLA types and development of allopurinol hypersensitivity

There was no significant difference in the HLA allele frequency between our study subjects and the Korean general population. Allopurinol hypersensitivity developed in 3.6% of the total 448 patients with CRI: 2.0% showed SCARs and 1.6% showed simple rashes (Figure 1). However, the prevalence showed striking difference according to the presence of HLA-B58. SCARs occurred in 18% (9/50) of patients with HLA-B58, while none of (0%) the 398 patients without HLA-B58 developed SCARs.

The positive rate of HLA-B58 was significantly higher in patients with SCARs than in the allopurinol-tolerant group [odds ratio (OR) = 179.24; 95% confidence interval (CI), 10.19–3151.74)] (Table 3). The positive rates to HLA-Cw3, HLA-A33, HLA-DR13 and HLA-DR3 were also significantly higher in patients with SCARs than in the allopurinol-tolerant group (100 versus 46.7%, P = 0.005; 77.8 versus 26.6%, P = 0.002; 55.6 versus 18.1%, P = 0.01 and 33.3 versus 4.4%, P = 0.008, respectively).

Among patients with simple rashes, no one possessed HLA-B58, HLA-DR13 or HLA-DR3, while HLA-Cw3 was still found more frequently (85.7%) when compared with the allopurinol-tolerant group (46.7%) or the general Korean population (45.6%) (P = 0.046 and P = 0.04, respectively). Analyzing the 398 patients negative to HLA-B58, the presence of HLA-Cw3 was related with significantly higher risk of allopurinol-induced simple rashes [4.2 (6/144) versus 0.5% (1/204), P = 0.045; OR = 8.83, 95% CI, 1.0–74.12).

Hypersensitivity reactions to benzbromarone

None of the 113 CRI patients who took benzbromarone showed hypersensitivity reactions. Of these patients, three took benzbromarone after cessation of allopurinol due to the occurrence of allopurinol hypersensitivity including two B58 (+) SCARs patients and one B58 (−) simple rash patient.

Discussion

Because of the serious morbidity and mortality related with SCARs, there has been a sustained effort to find markers that can predict individual susceptibility to these conditions. HLA genes are highly variable from individual to individual and they play an important role in presenting antigens to T cells, and especially, HLA class I is expressed in all nucleated cells and presents antigens to cytotoxic T cells [14]. The relationship between several specific HLA alleles and severe drug hypersensitivity reactions has been extensively studied and HLA has been proposed as a promising tool for assessing individual susceptibility to SCARs. For example, 100% Han Chinese patients with SJS/TEN attributable to CBZ had HLA-B*1502 [15] and 78% of patients with abacavir hypersensitivity presented HLA-B*5701 [16].

However, the relationship between HLA alleles and drug hypersensitivity reactions may differ according to ethnic backgrounds. The strong association between HLA-B*1502 and CBZ-induced SCARs observed in Han Chinese was not replicated in populations with extremely low incidence of HLA-B*1502, such as Caucasians (0–0.1%). The comparatively lower incidence of CBZ-induced TEN/SJS in the Caucasian population seems to be related to its lower frequency of HLA-B*1502 and thereby making it very difficult to deduce the role of HLA-B*1502 as a marker of SCARs [10]. Similarly, the association between HLA-B*5701 and abacavir hypersensitivity was difficult to determine and had no clinical implications in Koreans who had extremely low incidence of HLA-B*5701 (0.41%) in the population [13, 17].

The possible relationship between HLA-B58 and allopurinol-induced drug hypersensitivity was first raised by Chan and Tan [18] in 1989. Since Hung *et al.* reported in

Table 3. Frequencies of the HLA phenotypes in the SCARs group, simple rash group, tolerant group and the Korean general population

HLA alleles	SCARs, $n = 9$ (%)	Simple rash, $n = 7$ (%)	Tolerant group, $n = 432$ (%)	Korean general population, $n = 485$ (%)	SCARs versus simple rash, P-value, OR (95% CI)	SCARs versus tolerant group, P-value, OR (95% CI)	SCARs versus Korean general population, P-value, OR (95% CI)	Simple rash versus tolerant group, P-value, OR (95% CI)	Simple rash versus Korean general population, P-value, OR (95% CI)
B58	9/9 (100.0)	0/7 (0.0)	41/432 (9.5)	59/485 (12.2)	<0.001, 285.00 (11.99–92 503.38)	<0.001, 179.24 (10.19–3151.74)	<0.001, 136.29 (7.79–2380.85)	0.9, 0.63 (0.005–5.32)	0.9, 0.48 (0.03–8.67)
Cw3	8/8 (100.0)[a]	6/7 (85.7)	178/381 (46.7)	221/485 (45.6)	0.5, 3.92 (0.18–612.56)	0.003, 19.38 (1.10–340.58)	0.002, 20.30 (1.16–355.63)	0.05, 4.94 (1.03–47.72)	0.04, 5.17 (1.08–49.92)
A33	7/9 (77.8)	1/7 (14.3)	115/432 (26.6)	140/485 (28.9)	0.04, 13.00 (1.62–184.47)	0.002, 8.25 (2.17–44.63)	0.004, 7.38 (1.94–39.86)	0.7, 0.63 (0.07–3.05)	0.7, 0.57 (0.06–2.73)
DR13	5/9 (55.6)	0/7 (0.0)	78/430 (18.1)	83/485 (17.1)	0.1, 11.00 (0.95–1542.81)	0.01, 5.48 (1.52–20.85)	0.01, 5.89 (1.64–22.34)	0.4, 0.30 (0.02–5.39)	0.6, 0.32 (0.02–5.77)
DR3	3/9 (33.3)	0/7 (0.0)	19/430 (4.4)	28/485 (5.8)	0.2, 8.08 (0.61–1166.49)	0.008, 11.36 (2.55–43.50)	0.02, 8.64 (1.97–32.24)	0.9, 1.41 (0.01–12.29)	0.9, 1.07 (0.008–9.16)

[a]*HLA-Cw* result was available in eight patients.

2005 that HLA-B*5801 was an exceptionally strong marker of allopurinol-induced SCARs, it has been followed by other reports in different ethnic groups. The frequency of the HLA-B*5801 allele varies according to ethnic backgrounds but its racial differences are smaller compared with those in the frequency of HLA-B*1502 or HLA-B*5701 [19]. HLA-B*5801 carrier frequency is reported to be 2–4% in Africans, 1–6% in Caucasians, 3–15% in Asian Indians and 8.8–10.9% in Chinese [19]. Stronger associations between HLA-B*5801 and allopurinol-induced SCARs are noted in races with a higher frequency of HLA-B*5801 [8, 9]. In the Korean population, the frequency of HLA-B*5801 is relatively high (12.2%) [13] and 92.3% of patients with allopurinol-induced SCARs showed positivity to HLA-B*5801 [20]. Despite repeated supporting data emphasizing the importance of HLA-B*5801 as a risk marker of allopurinol-induced SCARs from previous case–control studies, the role of HLA-B*5801 as a screening tool was limited because the exact incidence of allopurinol hypersensitivity was not known in patients with HLA-B*5801. The present study is the first retrospective cohort study and it has enabled us to determine the incidence of allopurinol hypersensitivity among patients with HLA-B58 (clinically identical with B*5801 in Koreans). In the present study, allopurinol-induced SCARs occurred in 2.0% of patients with CRI, which was relatively higher compared with the incidence reported in the current literature (0.4%) [21]. This, however, was expected considering renal insufficiency itself acts as a risk factor. Incidence of SCARs rose to 18% (9/50) in patients with HLA-B58 and it was 45 times higher compared with the general population. In contrast, only 1.8% (7/398) of patients without HLA-B58 produced simple rashes and none of these patients produced SCARs. This result suggests that development of SCARs is dependent on the presence of HLA-B58 and thus identification of HLA-B58 may be useful for predicting development of SCARs before exposure to allopurinol. Although HLA-A33, HLA-C3, HLA-DR3 and HLA-DR13 were also found frequently in patients with allopurinol hypersensitivity, these genes show linkage disequilibrium with HLA-B58 in the Korean general population (Table 4) [13]. The studies focused on the association HLA-B*5801 and allopurinol hypersensitivity and results are summarized in Table 5.

Similar to the relationship between SCARs and HLA-B*5801, ankylosing spondylitis (AS) is closely related with

Table 4. Locus association with HLA-B58 of HLA haplotypes in Koreans[a]

Locus association of HLA haplotypes	Haplotype frequency (%)
B58	6.49
Cw3-B58	6.39
A33-Cw3-B58	5.77
Cw3-B58-DR13	3.30
Cw3-B58-DR3	2.06
A33-B58-DR13	2.98
A33-B58-DR3	1.95
B58-DR13	3.29
B58-DR3	2.16

[a]Adapted from Lee *et al.* [13].

Table 5. Summary of reports revealed the association of HLA-B*5801 and allopurinol-induced SCARs

Ethnicity	Study design	Types of SCARs[a]	Frequency of HLA-B*5801 (%)		P-value	OR (95% CI)	Sensitivity (%)	Specificity (%)	Ref.
			Patients	Controls					
Han Chinese	Case–control	SJS/TEN/HSS	51/51 (100)	20/135 (15.0)[d]	4.7×10^{-24} [d]	580.3 (34.4–9780.9)	100	85.2	[11]
European	Case–control	SJS/TEN	14/27 (55)	28/1822 (1.5)[c]	$<1.0 \times 10^{-6}$ [d]	80 (34–187)	55.6	98.5	[9]
Japanese[e]	Case–control	SJS/TEN	2/10 (20)	6/986 (0.61)[c]	$<1.0 \times 10^{-4}$	40.83 (10.5–158.9)	40	99.4	[21]
Thai	Case–control	SJS/TEN	27/27 (100)	7/54 (13.0)[d]	1.6×10^{-13}	348.3 (19.2–6336.9)	100	87	[8]
Korean	Case–control	SJS/TEN/DIHS	23/25 (92.0)	6/57 (10.5)[d]	2.45×10^{-11} [d]	97.8 (18.3–521.5)	92.0	89.5	[20]
Korean[f]	Retrospective cohort	SJS/TEN/AHS	9/9 (100)	41/432 (9.5)[d]	1.6×10^{-9}	179.24 (10.19–3151.74)	100	90.5	Present study

[a]HSS, hypersensitivity syndrome; DIHS, drug-induced hypersensitivity syndrome.
[b]Data from allopurinol-tolerant patients.
[c]Data from general population of the same ethnicity.
[d]Adjusted P-value after Bonferronni or Hochberg correction.
[e]Calculated based on allele frequency.
[f]Because a 100% coincidence of HLA-B*5801 in serologic-type HLA-B58 in the Korean population, it is thought that HLA-B58 is identical with HLA-B*5801 [13].

HLA-B27. Although 90–95% of patients with AS show positivity to HLA-B27, AS develops in <5% of subjects with HLA-B27. It has been reported that HLA-B27 contributes to the susceptibility of AS at a rate of 20–40% [22]. In clinical practice, HLA-B27 has been widely used for the diagnosis of AS due to its high sensitivity. In the current study, HLA-B58 showed a sensitivity of 100% and a specificity of 90.7% for diagnosing SCARs in patients with CRI and its positive predictive value was 18% and a negative predictive value was 100% in predicting SCARs, which suggests that HLA-B58 may be very useful as a screening test in clinical setting.

Although this study shows the presence of HLA-B58 in all cases of SCARs, the incidence of severe hypersensitivity reactions in Korean subjects treated with allopurinol is still low considering the high frequency of HLA-B*5801 in the general population. This suggests that HLA-B*5801 is not the sole factor determining the development of SCARs.

Clinical application of HLA-B*5801 as a screening test before allopurinol medication draws attention to considering the following aspects. First, since hyperuricemia develops in ~20% of the general population, there are many potential patients who need allopurinol therapy. Second, especially in countries where HLA-B*5801 is highly expressed in the general population such as Korea, China and Thailand, a considerable number of them remain at risk for the potential development of SCARs related with allopurinol.

Hyperuricemia frequently occurs in patients with CRI and many of them require allopurinol therapy. Since chronic renal failure in itself is a risk factor for allopurinol-induced hypersensitivity, drugs should be selected very carefully in patients with impaired renal function. When allopurinol is used in CRI patients who are at high risk of allopurinol-induced hypersensitivity, HLA typing must be performed. Based on the result that 18% of patients with positivity to HLA-B58 produce severe hypersensitivity, we must explain the risk of developing hypersensitivity and administer short-term allopurinol therapy or choose alternative drugs, such as benzbromarone, febuxostat [23] or rasburicase [24]. Even though HLA-B58 is negative, close monitoring of skin rashes is still needed in patients with HLA-Cw3. Long-term allopurinol therapy can be safely administered to patients without HLA-B58 or HLA-Cw3 (Figure 2).

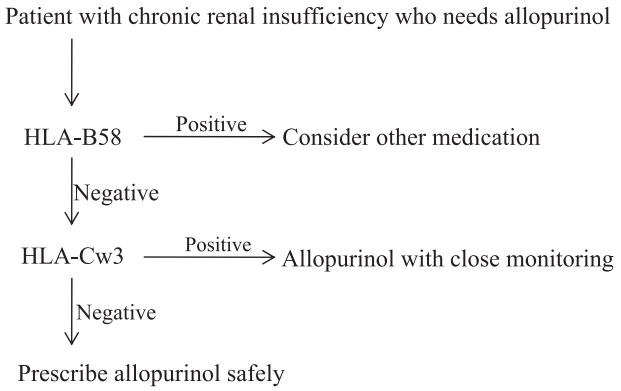

Fig. 2. Recommendation for allopurinol prescription in patients with CRI. When allopurinol is planed to use in CRI patients, HLA typing must be performed. We must explain the risk of developing hypersensitivity and must administer short-term allopurinol therapy or alternative drugs if HLA-B58 is positive. Even though HLA-B58 is negative, close monitoring of skin rashes is needed in patients with HLA-Cw3. Long-term allopurinol therapy can be safely administered to patients without HLA-B58 or HLA-Cw3.

Benzbromarone, an alternative drug, can be used in patients with HLA-B58, who are at high risk of severe adverse reactions. Benzbromarone, which was introduced in the early 1970s, has a urate-lowering effect by inducing renal uric acid leakage. Although in some countries, benzbromarone is not marketed due to its serious liver toxicity [25, 26],

and it is still commercially available in other countries including Korea. Taken together, hypersensitivity reactions did not develop regardless of the presence of HLA-B58 in 113 patients who received benzbromarone. This indicates that benzbromarone can be used as an alternative drug to allopurinol with regular follow-ups of liver function tests.

Long-term allopurinol therapy induces severe hypersensitivity reactions in ~20% of CRI patients with HLA-B58. Therefore, screening tests for HLA-B can help to differentiate patients at high risk of severe adverse reactions related to allopurinol in the population with high frequency of HLA-B*5801.

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Conflict of interest statement. None declared.

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