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簡　介

一、宗　旨

本討論會擬經由制度法規、臨床實務、實證醫學、案例剖析等面向之探討，強化病人安全，提升醫療品質，紓解醫療爭議，建置優質安全之醫療環境。

二、目　的

藉由藥害救濟審議案例及臨床實務之探討，使醫療人員瞭解降尿酸藥之風險與效益，促使審慎用藥以提升用藥合理性及安全性，並透過皮膚不良反應常見臨床表現型態之介紹，增進醫療人員早期診斷與及時處置之專業技能，加強藥害預防的策略，避免嚴重藥害發生。

三、緣　起

合理用藥情況下，仍可能發生無法預期之藥物不良反應，導致病患嚴重殘疾甚至死亡事件時有所聞，為保護受害者權益，並維護醫療機構及產業的健全發展，台灣有藥害救濟制度予以保障。施行藥害救濟制度近16年來，降尿酸藥在給付案件之可疑藥品排行榜上常名列前茅，使該藥品之風險廣受關注；惟仍有部分與降尿酸藥有關之藥害案件未能獲得救濟，尤其是無症狀高尿酸血症之治療，常以「適應症外用藥」為之，其處方合理性及適當性成為是否適用藥害救濟之關鍵。本次討論會藉由藥害救濟審議案例分析，探討降尿酸藥之使用與風險、藥害救濟審議原則及臨床實務，以作為醫療人員處方時審慎評估風險及效益之參考。

另外，由於降尿酸藥物所引起的不良反應多為皮膚及皮下組織疾患，皮膚症狀之表現雖多變，但仍屬於較易被早期觀察及發現的藥害癥兆，第一線醫療人員對藥物過敏之皮膚表癥若有所警覺，有助於早期診斷、及時處置，可避免更嚴重藥害發生。

四、討論方式

本次主題之藥害救濟審議案例由財團法人藥害救濟基金會提供，以案例分享與臨床實務為中心，邀請專家學者發表評論，提供相關建言供醫界、主管機關參考，以強化醫療安全、提升醫療品質。

致歡迎詞

蘇清泉　中華民國醫師公會全國聯合會理事長

各位長官、醫界前輩，以及目前正在全國各地即時連線會場的醫界同仁、貴賓們，大家好：

本人謹代表中華民國醫師公會全國聯合會感謝諸位蒞臨，強化醫療安全，提升醫療品質為醫界長遠之目標，中華民國醫師公會全國聯合會、臺灣醫學會、台大醫院、財團法人醫院評鑑暨醫療品質策進會共同合辦「醫療安全暨品質研討系列」。希望經由臨床實務、實證醫學、倫理、法律等面向之探討，強化病人安全，提升醫療品質，紓解醫療爭議，建置優質安全之醫療環境。

今天的研討主題為「從藥害救濟審議案例探討降尿酸藥之使用」，藉由藥害救濟審議案例及臨床實務之探討，使醫療人員瞭解降尿酸藥之風險與效益，促使審慎用藥以提升用藥合理性及安全性，並透過皮膚不良反應常見臨床表現型態之介紹，增進醫療人員早期診斷與及時處置之專業技能，加強藥害預防的策略，避免嚴重藥害發生。。

研討會分為三場，第一場「從藥害救濟審議案例探討降尿酸藥之使用」，由台北榮民總醫院內科部黃以信醫師主講；第二場「處方降尿酸藥於治療高尿酸血症之合理性探討」，由國泰綜合醫院內科部林世昌部長主講；第三場「降尿酸藥引起嚴重皮膚不良反應之診斷及預防」，由長庚醫院皮膚科暨藥物過敏中心鐘文宏主任主講。與會人員如有任何疑問及建言，歡迎在綜合討論時間踴躍提出。而今日研討會內容將刊載於台灣醫界雜誌，也會置放在醫師公會全聯會網站，歡迎醫界同仁多加利用這些管道以獲取相關資料，繼續進修、自我終身學習。

本次研討會邀請專家學者共同討論，提供相關建言供醫界參考，如獲共識，將建請相關單位共同推動。清泉先預祝今日會議圓滿順利，並祝福大家身體健康萬事如意。

從藥害救濟審議案例探討降尿酸藥之使用

節目表

時　　間：104年12月12日（星期六）13：30~15：30
主 持 人：【台北市】黃富源教授、蘇清泉理事長
【台中市】周德陽院長、羅倫樾理事長
【彰化縣】黃明和總裁、巫喜得理事長
【台南市】郭宗正院長、黃仁享理事長
【高雄市】鍾飲文院長、蘇榮茂理事長
【屏東縣】蔡宗昌院長、鄭英傑理事長

時　間	議　程　表
13:00~13:30	報　到
13:30~13:45	致歡迎詞：蘇清泉理事長（中華民國醫師公會全國聯合會） 貴賓致詞： 主 持 人 台北現場：黃富源教授(馬偕紀念醫院) 蘇清泉理事長(中華民國醫師公會全國聯合會) 台 中 市：周德陽院長(中國醫藥大學附設醫院) 羅倫樾理事長(臺中市醫師公會) 彰 化 縣：黃明和總裁(彰濱秀傳紀念醫院) 巫喜得理事長（彰化縣醫師公會） 台 南 市：郭宗正院長(郭綜合醫院) 黃仁享理事長(台南市醫師公會) 高 雄 市：鍾飲文院長(高雄醫學大學附設醫院) 蘇榮茂理事長(高雄市醫師公會) 屏 東 縣：蔡宗昌院長(安泰醫院) 鄭英傑理事長(屏東縣醫師公會)
13:45~14:10	第一場：從藥害救濟審議案例探討降尿酸藥之使用 主講者：黃以信醫師(衛生福利部藥害救濟審議委員/台北榮民總醫院內科部主治醫師)
14:10~14:35	第二場：處方降尿酸藥於治療高尿酸血症之合理性探討 主講者：林世昌醫師(國泰綜合醫院內科部部長)
14:35~15:00	第三場：降尿酸藥引起嚴重皮膚不良反應之診斷及預防 主講者：鐘文宏醫師(衛生福利部藥害救濟審議委員/長庚醫院皮膚科暨藥物過敏中心主任)
15:00~15:30	綜合討論（主持人及所有主講人）

醫療安全暨品質研討系列【82】

主持人簡介

黃富源教授

一、現職：

馬偕紀念醫院小兒科資深主治醫師

二、學歷：

1961-1968　臺灣大學醫學院醫科畢業

三、經歷：

1996.5~2007.6　馬偕紀念醫院副院長
2004.5~2005.1　行政院政務顧問
2003.1~2003.11　中華民國感染症醫學會理事長
2002.7~2003.12　行政院衛生署顧問
2002.5~2005.4　臺灣兒科醫學會理事長
2000.5~2002.6　行政院衛生署副署長(借調)
1998.2~迄今　臺大醫學院、臺北醫學院兼任教授
1997.10　教育部部定教授
1996.3~2000.12　中華民國早產兒基金會董事長
1992.7~1996.6　馬偕紀念醫院醫學研究科主任
1975.7~1986.6　馬偕紀念醫院小兒科主任
1969.7~1972.6　臺大醫院小兒科住院醫師

三、專長：

感染症、新生兒科、小兒腎臟、一般兒科

蘇清泉醫師立委

一、現職：

中華民國醫師公會全國聯合會理事長
第八屆立法委員
立法院厚生會副會長
安泰醫療社團法人安泰醫院榮譽院長
中華民國區域醫院協會榮譽理事長
台灣私立醫療院所協會榮譽理事長
私立美和科技大學助理教授

二、學歷：

中山醫學大學醫學博士
中山醫學大學醫學碩士
中山醫學大學醫學系

三、經歷：

中國國民黨立法院黨團副書記長
中華民國醫師公會全國聯合會常務理事
台灣醫院協會副理事長
衛生福利部醫院暨教學醫院評鑑委員
財團法人台灣更生保護會屏東分會委員
屏東縣警察之友會東港辦事處主任
基督復臨安息日會醫療財團法人董事
中華民國心臟血管外科專科指導醫師
台北馬偕紀念醫院胸腔心臟血管、外科總醫師、主治醫師

四、專科醫師：

中華民國外科專科醫師
台灣胸腔心臟外科專科醫師
中華民國急救加護醫學專科醫師
中華民國重症醫學專科醫師
台灣血管外科專科醫師
台灣外傷醫學會專科醫師
心臟血管外科專科指導醫師
重症醫學專科指導醫師
胸腔重症專科指導醫師

第一場

從藥害救濟審議案例探討降尿酸藥之使用

第一場
從藥害救濟審議案例探討降尿酸藥之使用

黃以信醫師

一、現職

台北榮民總醫院內科部胃腸科主治醫師兼病房主任

國立陽明大學醫學院部定教授

二、學歷

台北醫學院醫學系

三、經歷

台北榮民總醫院內科部住院醫師

台北榮民總醫院內科部總醫師

台北榮民總醫院內科部胃腸科主治醫師

國立陽明大學醫學院部定講師

國立陽明大學醫學院副教授

從藥害救濟審議案例探討降尿酸藥之使用

黃以信 Yi-Shin Huang, MD, FACG
台北榮民總醫院胃腸肝膽科醫師
國立陽明大學醫學院教授
衛福部藥害救濟審議委員會委員
衛福部藥物安全評估委員會委員
衛福部醫療器材審議委員會委員
衛福部藥品諮詢委員會委員/專家

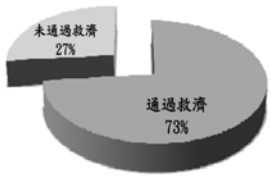
藥害救濟給付前10名藥品

88年-104年7月(1～224次審議)

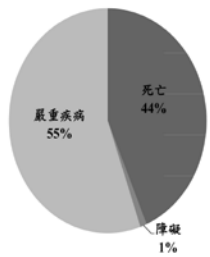
藥物名稱	案例數
Allopurinol	214
Phenytoin	135
Carbamazepine	116
Rifampin/Isoniazid/Pyrazinamide (單方或複方)	85
Diclofenac	60
Lamotrigine	38
Co-trimoxazole	37
Mefenamic acid	37
Ibuprofen	36
Cefazolin	31

Allopurinol之藥害救濟分析

- 88年至104年7月，總申請案件2446件: allopurinol佔11.9%
- allopurinol之申請案中:73%通過救濟，27 %未通過救濟

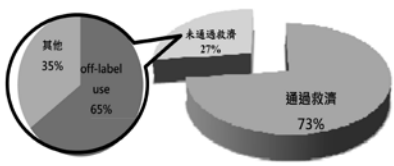


Allopurinol通過救濟之案件分析



Allopurinol未通過救濟之案件分析

- 68件未通過救濟之案例中，其中44件(65%)原因為off-label use
- 另分析因off-label use而未通過救濟之申請案，當中12件申請救濟類別為死亡



本圖表計算區間為88~104年7月，惟100年5月後已將過應症外用藥有條件納入藥害救濟範圍

Case-allopurinol induced Stevens-Johnson syndrome (SJS)

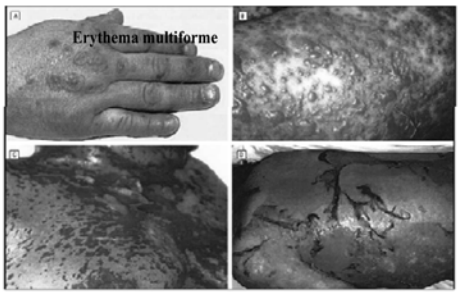
【背景】

- 77 歲男性，無已知藥物過敏史，有高血壓、陳舊性腦中風、腎功能不全等病史
- 至醫院接受成人健檢，檢驗值：Cr：2.55 mg/dL、eGFR：26.2 mL/min/1.73m^2、UA：9.7 mg/dL，診斷為高尿酸血症、慢性腎衰竭等，處方allopurinol 100 mg qd (慢箋90日)

【不良反應】

- 約2.5個月後皮膚突發大量紅斑丘疹且有口腔潰瘍，就醫後經診斷為史蒂文生氏-強生症候群，最後因多重器官衰竭死亡

Stevens-Johnson Syndrome (SJS): < 10% BSA
Toxic Epidermal Necrolysis (TEN): >30% BSA
SJS－TEN overlap: 10-30% BSA



Case-allopurinol induced Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

【背景】

- 21 歲女性，無已知藥物過敏史
- 101/7體檢發現有慢性腎臟病、高血壓等病症
- 101/12至醫院腎臟科就醫，檢驗值：UA：8.5 mg/dL、Cr：3.5 mg/dL，為減緩慢性腎病進展相關之併發症，故處方allopurinol 100 mg qd

【不良反應】

- 101/1因發燒、喉嚨痛、全身紅疹等病癥急診就醫，檢驗值：WBC：8410 /μL、Eos：6.2 %、BUN/Cr：126.7/10 mg/dL、GOT/GPT：269/565 U/L，經會診皮膚科，診斷為藥物疹合併嗜伊紅性白血球症及全身症狀，住院治療後病情穩定出院

【案例解析】

- 目前我國核准allopurinol之適應症為「痛風症、痛風性關節炎、尿酸結石、癌症或經化學治療產生之高尿酸血症」
- 上述案例用於治療「高尿酸血症」或「減緩慢性腎病進展相關之併發症」，且相關病歷資料亦查無有罹患痛風、痛風性關節炎等臨床症狀或過往疾病史之紀錄或描述，故皆屬適應症外之使用
- 上述案例因不符合前行政院衛生署（現為衛生福利部）於100年9月28日署授食字第1001403071號令：核釋「符合當時醫學原理及用藥適當性」之審議原則，故屬藥害救濟法第13條第8款：「未依藥物許可證所載之適應症或效能而為藥物之使用，不得申請藥害救濟」規定之情形，不符合救濟條件

適應症外使用藥品之審議原則

（100.09.28行政院衛生署令）

藥害救濟法第十三條第八款所稱「符合當時醫學原理及用藥適當性者不在此限」，其審議原則如下：

（一）十大醫藥先進國家已經核准之適應症，而我國尚未核准
（二）已收載於國內外專科醫學會或政府出版之臨床診治指引
（三）屬於傳統治療方法，且已廣為臨床醫學教學書籍收載列為治療可選用藥物(drugs of choice)，並符合目前醫學常規

必要時可由本署藥害救濟審議委員會請相關專科醫學會提供專業治療指引

衛福部藥品適應症外使用原則規定

1. 基於治療疾病的需要(正當理由)；
2. 符合醫學原理及臨床藥理(合理使用)；
3. 應據實告知病人
4. 不得違法藥品使用當時，已知的、具公信力的醫學文獻
5. 盡量以單方為主，如同時使用多種藥品，應特別注意其綜合使用的療效、藥品交互作用或不良反應等問題

Case-allopurinol induced SJS

【背景】

- 83歲女性，無已知藥物過敏史
- 因痛風性關節炎，UA：12.1 mg/dL，被處方allopurinol 100 mg qd使用

【不良反應】

- 約一個月後，出現發燒、口腔潰瘍、全身紅疹搔癢情形，且進展至skin detachment，上肢有水疱(bullae)形成，HLA-B*5801檢驗為陽性，經診斷為史蒂文生氏-強生症候群，住院治療後erosion wound與 skin detachment逐漸癒合，但個案既有許多underlying diseases，最後仍因肺炎併呼吸衰竭、菌血症等疾病死亡

【案例解析】

- 本例因痛風性關節炎使用allopurinol治療，引起史蒂文生氏-強生症候群而住院，因本身亦有許多underlying diseases，故考量個案具體情狀暨死亡與使用藥品產生不良反應之關聯程度酌予救濟
- 帶有HLA-B*5801基因的病人服用allopurinol發生SJS/TEN之嚴重藥物不良反應風險較未帶有HLA-B*5801基因的病人高，而臺灣族群帶有此基因的盛行率比歐洲族群及日本族群高。故於使用藥物前宜考慮篩檢HLA-B*5801基因，但長期使用後沒有不良反應的病人不建議基因篩檢
- 基因篩檢並不能取代適當的臨床安全監視及病患處置。未帶有HLA-B*5801基因的病患，無論人種，仍可能發生SJS/TEN的副作用

Case-allopurinol induced SJS

【背景】

- 71歲女性，，無已知藥物過敏史，有痛風病史
- 103/3就醫主訴右足背腫痛 3-4 天，皮膚局部紅腫等症狀，UA：10.4 mg/dL，診斷包含痛風性關節病變，一週後回診時予allopurinol 100 mg qd使用

【不良反應】

- 103/4/24至眼科診所就醫，主訴雙眼結膜紅，有分泌物，予眼藥水治療
- 103/4/25因臉頰、頸、胸等部位出現風疹塊(wheal)至皮膚科就醫，診斷為急性蕁麻疹、血管神經性水腫，給予抗組織胺與類固醇藥物治療

【不良反應】

- 103/4/25亦至耳鼻喉科就醫，主訴喉嚨痛，吞嚥困難，診斷為急性鼻竇炎，給予ibuprofen等藥治療
- 103/4/26，因口腔潰瘍、吞嚥困難至醫院急診，理學檢查有多處口潰瘍，頸部皮膚發紅，診斷為食道、口腔潰瘍，r/o 念珠菌感染，處方mefenamic acid 、dexchlorpheniramine、fluconazole等藥
- 103/4/28，因間歇發燒，喉嚨痛，全身皮膚紅疹搔癢多日、口腔潰瘍至醫學中心急診，診斷為史蒂文生氏-強生症候群，停用allopurinol，經住院治療後病情穩定出院

【案例解析】

- 本例因痛風使用allopurinol治療，引起史蒂文生氏-強生症候群而住院，符合適應症，故有獲得藥害救濟之嚴重疾病給付
- SJS/TEN的早期症狀與URI十分類似，常見有喉痛、發燒、結膜紅、皮膚紅疹等S/S，故診斷上容易忽略是藥物所致的不良反應。若能透過詳細詢問用藥史與留意紅疹、黏膜潰瘍等相關症狀，便能在第一時間給予正確的治療藥物與停藥，降低不良反應所造成的傷害

無症狀高尿酸血症
asymptomatic hyperuricemia, AH

- 大多數AH病人不會發展成痛風
- 雖然有文獻研究顯示AH是心血管疾病、高血壓、慢性腎臟病、代謝症候群的相關因子，但到目前為止，因果關係並未被證明，也沒有證據顯示以藥品治療降低尿酸可以預防心血管、代謝性及腎臟疾病或減少死亡率
- AH之病人大部分是不需治療的。在考量allopurinol不良反應之機率與嚴重度，權衡利弊得失，一般而言，以allopurinol來治療AH在目前無法被認為是適當的

Harrison's Internal Medicine 19th ed. 2015 a432e-4: Asymptomatic Hyperuricemia

- Hyperuricemia is present in ~21% of the population.
- The vast majority of hyperuricemic persons are at no clinical risk.
- In the past, the association of hyperuricemia with cardiovascular disease and renal failure led to the use of urate-lowering agents for patients with asymptomatic hyperuricemia.
- This practice is no longer recommended except for individuals receiving cytolytic therapy for neoplastic disease, who are treated with urate-lowering agents in an effort to prevent uric acid nephropathy.
- Most hyperuricemic persons never develop gout, and prophylactic treatment is not indicated.

Harrison's Internal Medicine 19th ed. 2015 a432e-4: Asymptomatic Hyperuricemia

- Neither structural kidney damage nor tophi are identifiable before the first attack.
- Reduced renal function cannot be attributed to asymptomatic hyperuricemia, and treatment of asymptomatic hyperuricemia does not alter the progression of renal dysfunction in patients with renal disease. An increased risk of stone formation in those with asymptomatic hyperuricemia has not been established.
- Thus, because treatment with specific antihyperuricemic agents entails inconvenience, cost, and potential toxicity, routine treatment of asymptomatic hyperuricemia cannot be justified.

Harrison's Internal Medicine 19th ed. 2015 a432e-4: Asymptomatic Hyperuricemia

- Routine screening for asymptomatic hyperuricemia is not recommended.
- If hyperuricemia is diagnosed, however, the cause should be determined.
- Causal factors should be corrected if the condition is secondary, and associated problems such as hypertension, hypercholesterolemia, diabetes mellitus, and obesity should be treated.

Systemic review of allopurinol on renal function in patients with asymptomatic hyperuricemia

Author	Country	Renal function	Case/Control	Duration of Tx (Months)	marker	outcome	Quality
Siu 2006	HK	CKD	26/28	12	Cr	↓	poor
Kanbay 2007	Turkey	Normal	48/21	3	eGFR	↑	poor
Kanbay 2011	Turkey	Normal	32/40	4	eGFR	↑	poor
Goicoechea 2010	Spain	CKD	57/56	24	eGFR	↑	poor
Goicoechea 2015	Spain	CKD	57/56	24 + 36M?	eGFR	↑	poor
Sezer 2014	Turkey	CKD	47/49	12	GFR	↑	poor

Treatment of Asymptomatic Hyperuricemia for the Prevention of Gouty Arthritis, Renal Disease, and CV Events: A Systematic Literature Review

- Very limited data are available on the treatment of HU in asymptomatic patients.
- Only 3 studies; meta-analysis could not be done.
- There is currently insufficient empiric evidence to suggest that lowering serum uric acid level in asymptomatic patients with HU can prevent gouty arthritis, renal disease, or cardiovascular events.
- Underlined by Division of Rheumatology, Toronto, Canada, USA, Australia, Netherland, etc.

J Rheumatol Suppl 2014;92:70–4

Systemic review of allopurinol on CV risk and mortality in pts with asymptomatic hyperuricemia

Author	Country	Underly-ing dis.	Case/Control	Duration of tx (Mo)	CV risk	Mortality	Quality
Luk 2009	USA	Multiple	2483/7441	variable		↓	poor
Wu 2010	USA	AHF	115/1037	36	↑	↑	fair
Malek 2012	Czech	AHF	266/989	60	↑	↑	poor
Sezer 2014	Turkey	CKD	47/49	12	↓		
Goicoechea 2015	Spain	CKD	57/56	24 +36M?	↓		poor
deAbajo 2015	Spain	Multiple	66/354	variable	↓		poor
Dubreuil 2015	USA	Multiple	5927/5927	60		↓	poor
Kim 2015	USA	Multiple	24108/24108	variable	No difference		poor
Givertz 2015	USA	AHF	126/127	24	No difference	No difference	fair

有事實足以認定藥害之產生應由受害人、醫師或其他之人負其責任（13條第一款）

- ✓受害人未經醫師處方擅自至藥局購買使用 allopurinol
- ✓SJS發生之後，不遵醫囑自行出院，拒絕治療導致死亡
- ✓醫師未注意個案已有allopurinol 過敏史再度投予
- ✓已明顯出現過敏症狀，未能適時停藥
- ✓腎功能不良情況下劑量明顯偏高

Wrap up - 1

- Allopurinol多年來一直是國內藥害救濟之首要藥物，它可能會引起高死亡率之SJS、TEN以及DRESS等嚴重皮膚不良反應
- 我國食藥署核准之allopurinol仿單適應症為:痛風症、痛風性關節炎、尿酸結石、癌症或經化學治療產生之高尿酸血症。國內外衛生主管機關核准之allopurinol仿單適應症均不包括無症狀高尿酸血症，故請只處方allopurinol於核准之適應症
- 現階段國際文獻有關allopurinol可預防腎臟病、心血管疾病與死亡率之證據仍不足

Wrap up - 2

- 國內外相關之學會與經典教科書亦不建議使用allopurinol於無症狀之高尿酸血症
- 處方本藥前，宜作HLA-B*5801之基因檢測，陽性者不宜服用
- 腎功能不良者，宜減少開始劑量
- 服用本藥後，若有喉痛、結膜炎、發燒、皮疹等S/S，宜懷疑為本藥之藥物不良反應，並考慮停藥

第二場

處方降尿酸藥於治療高尿酸血症之合理性探討

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處方降尿酸藥於治療高尿酸血症之合理性探討

國泰綜合醫院
林世昌醫師

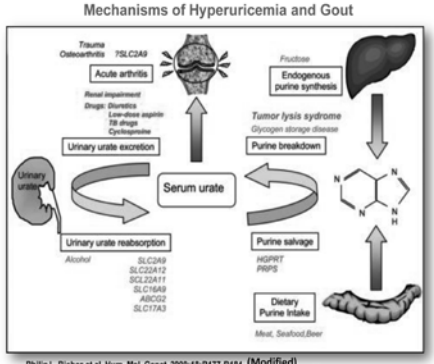
1

Topics

- Introduction to hyperuricemia and gout
- Medication for hyperuricemia and gouty arthritis
- Guidelines for management of hyperuricemia and gout

2

Mechanisms of Hyperuricemia and Gout

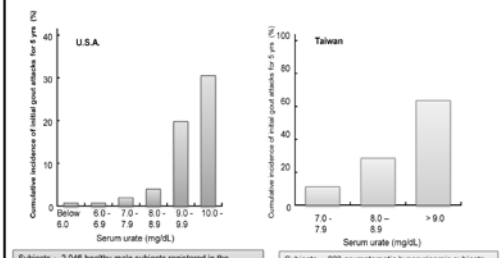


Philip L. Riches et al. Hum. Mol. Genet. 2009;18:R177-R184 (Modified)

Human Molecular Genetics

3

Hyperuricemia and The risk of Gouty Arthritis



Subjects : 2,046 healthy male subjects registered in the 'Normative Aging Study'
Method : A prospective cohort study to observe the relationship between serum urate levels at the start of the study and the cumulative initial gouty attack frequency.
Results : Cumulative incidence of initial gouty attacks increased with increase in serum urate levels.

Campion EW, et al. Am J Med 82: 421-426, 1987

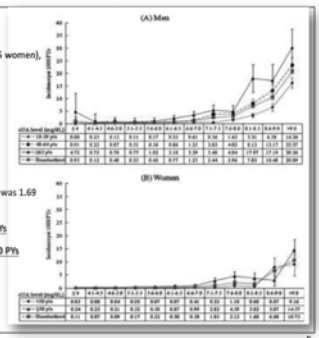
Subjects : 223 asymptomatic hyperuricemic subjects
Method : Five-year cumulative incidence of onset of gout was investigated.
Results : The incidence increased with increase in serum urate levels.

Lin KC, et al. J Rheumatol 27: 1501-1505, 2000

4

Relationship Between Incidence of Gout and Serum Uric Acid Levels by Sex and by Age in Taiwan

- Subjects: 1,606 (1,341 men and 265 women), aged ≥18 years
- Follow up for 7.31 years
- The standardized overall incidence was 1.69 per 1,000 PYs
- Incidence in men: 3.09 per 1,000 PYs
- Incidence in women: 0.53 per 1,000 PYs

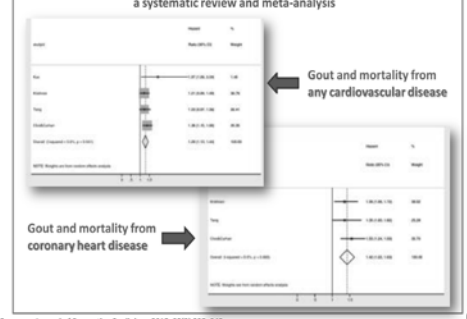


Clin Rheumatol (2012) 31:239–245

5

Association of Hyperuricemia with cardiovascular disease

Increased cardiovascular mortality associated with **gout:**
a systematic review and meta-analysis

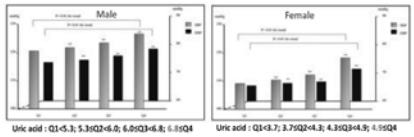


European Journal of Preventive Cardiology 2015, 22(3) 335–343

6

Association Between Hyperuricemia and Hypertension/Arterial Diseases

- Association Between Serum Uric Acid Levels/Hyperuricemia and Hypertension Among 85,286 Japanese Workers. (J Clin Hypertens (Greenwich). 2015)



Uric acid : Q1<5.3; 5.3≤Q2<6.0; 6.0≤Q3<6.8; 6.8≤Q4 Uric acid : Q1<3.7; 3.7≤Q2<4.3; 4.3≤Q3<4.9; 4.9≤Q4

- Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism
  - Hyperuricemic rats developed elevated blood pressure after 3 weeks, which was prevented by allopurinol or benzbromarone (Hypertension. 2001;38:1101-1106.)
- Levels of uric acid may predict the future development of pulmonary hypertension in systemic lupus erythematosus: a seven-year follow-up study. Lupus. 2015
- Hyperuricemia was associated with greater risk of arterial stiffness
  - Serum uric acid concentration and asymptomatic hyperuricemia with subclinical organ damage in general population. (Li Y et al. Angiology. 2014 Aug;65(7):634-40)
  - Correlation of asymptomatic hyperuricaemia and serum uric acid levels with arterial stiffness in women with systemic lupus erythematosus without clinically evident atherosclerotic cardiovascular disease. (Sabio JM et al Lupus. 2010 Apr;19(5):591-8)

7

Association of Hyperuricemia with Renal Functions

Renal function in gout patients in Taiwan

Renal functions between pure gout patients and controls

Variable	Pure-gout patients (n = 80)	Controls (n = 72)	p
Age, years	57.63 ± 13.10	55.32 ± 8.60	NS
Serum urate, mg/dl	10.15 ± 1.99	5.08 ± 1.14	0.0001
Serum creatinine, mg/dl	1.56 ± 0.64	0.90 ± 0.16	0.0001
Creatinine clearance, ml/min	59.91 ± 30.90	97.10 ± 27.19	0.0001

Renal functions in pure gout patients between no tophi patients and tophi patients

Variable	Pure-gout patients (n = 80)		p
	without tophi (n = 59)	with tophi (n = 21)	
Age, years	58.51 ± 13.19	55.24 ± 12.87	NS
Duration of gout, years	5.29 ± 5.98	11.29 ± 9.62	0.013
Serum urate, mg/dl	9.83 ± 1.71	11.01 ± 2.44	0.034
Serum creatinine, mg/dl	1.44 ± 0.48	1.89 ± 0.90	0.040
Creatinine clearance, ml/min	64.40 ± 29.53	47.27 ± 31.90	0.030

Renal functions between pure gout patients and gout with hypertension patients

Variable	Pure-gout patients (n = 80)	Patients with gout and HTN (n = 72)	p
Age, years	57.63 ± 13.10	64.63 ± 7.16	0.0001
Serum urate, mg/dl	10.15 ± 1.99	10.34 ± 2.12	NS
Serum creatinine, mg/dl	1.56 ± 0.64	2.10 ± 0.97	0.0001
Creatinine clearance, ml/min	59.91 ± 30.90	45.06 ± 24.69	0.0029

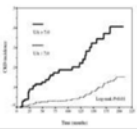
Pure gout was defined as gout or tophaceous gout without any history of hypertension, diabetes mellitus, arteriosclerosis, pre-existing renal disorders, occupational exposure, or episode of acute renal failure

Tarng DC, Am J Nephrol 1995; 15:31-37

8

Asymptomatic Hyperuricemia and CKD

- Allopurinol treatment improves renal function in patients with type 2 diabetes and asymptomatic hyperuricemia: 3-year randomized parallel-controlled study. (Liu P et al. Clin Endocrinol (Oxf). 2014)
  - Long-term effective control of serum uric acid can decrease urinary albumin excretion rate and serum creatinine, increase GFR and may exert kidney protection effects in patients with type 2 diabetes and asymptomatic hyperuricemia.
- Efficacy of febuxostat for slowing the GFR decline in patients with CKD and asymptomatic hyperuricemia: A 6-Month, Double-Blind, Randomized, Placebo-Controlled Trial. (Sircar D et al. Am J Kidney Dis. 2015)
  - Febuxostat slowed the decline in eGFR in CKD stages 3 and 4 compared to placebo
- Association between asymptomatic hyperuricemia and new-onset chronic kidney disease in Japanese male workers: a long-term retrospective cohort study. (BMC Nephrol. 2011;12:31)



9

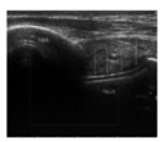
Asymptomatic Hyperuricemia and Arterial Diseases

- Treatment of asymptomatic hyperuricemia and prevention of vascular disease: a decision analytic approach. (Akkineni R et al. J Rheumatol. 2014 Apr;41(4):739-48).
  - Treating asymptomatic hyperuricemia with allopurinol is most effective in preventing vascular events at a serum urate above 7.0 mg/dl in men and 5.0 mg/dl in women.
- The effects of allopurinol on the carotid intima-media thickness in patients with type 2 diabetes and asymptomatic hyperuricemia: a three-year randomized parallel-controlled study. (Intern Med. 2015;54(17):2129-37)
  - The long-term effective control of serum uric acid by allopurinol may improve insulin resistance, decrease the serum levels of hs-CRP, reduce the carotid intima-media thickness, and may delay the development of atherosclerosis in patients with T2DM and asymptomatic hyperuricemia.
- Allopurinol reduces cardiovascular risks and improves renal function in pre-dialysis chronic kidney disease patients with hyperuricemia (Sezer S et al. Saudi J Kidney Dis Transpl. 2014;25(2):316-20)
- Correlation of asymptomatic hyperuricaemia and serum uric acid levels with arterial stiffness in women with systemic lupus erythematosus without clinically evident atherosclerotic cardiovascular disease. (Lupus. 2010 Apr;19(5):591-8)
- Asymptomatic hyperuricemia and serum uric acid concentration correlate with subclinical atherosclerosis in psoriatic arthritis patients without clinically evident cardiovascular disease. (Gonzalez-Gay MA et al. Semin Arthritis Rheum. 2009 Dec;39(3):157-62.

10

Imaging in Gout

- Conventional radiography
- Ultrasonography
  - Several ultrasound studies disclosed monosodium urate deposits in a large proportion of asymptomatic hyperuricemic patients
- Computed tomography
- Dual energy computed tomography
- Magnetic resonance imaging (MRI)
- Nuclear medicine

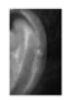


Ther Adv Musculoskel Dis 2014, Vol. 6(4) 131–143

11

Tophi can be the first manifestation of gout

- Tophi generally developed after an average of 11.6 years of gouty arthritis before uric acid lowering therapy became available
- Tophi were reported to occur in 12% of gout patients after 5 years, and 55% after 20 years of untreated disease
- Tophi can develop without the concomitant arthritis
  - The term 'gout nodulosis' to describe the subcutaneous deposits of monosodium urate in the absence of initial manifestation of gouty arthritis



- Silent deposition of monosodium urate crystals as a result of hyperuricemia may occur and lead to early destructive skeletal changes
  - Asymptomatic MSU crystals deposits can now be identified and precede the onset of gout flares

BMC Res Notes 2013 Nov 21;6:480
Eur Rev Med Pharmacol Sci. 2014;18(9):1295-306

12

Management of Hyperuricemia

- Lifestyle change and diet control
- Urate-lowering therapy (ULT)
- Medication change: some drugs may increase the serum uric acid level
- Management of co-morbidities

13

Drugs in Urate-Lowering Therapy (ULT)

Xanthine oxidase inhibitor

- Allopurinol
- Febuxostat

- First-line therapy in USA
- Preferred in patients with renal function impairment, renal stone, tophi, or tumor lysis syndrome
- Should not be used with azathioprine

Uricosuric agents

- Probenecid
- Benzbromarone
- Sulfinpyrazone

- Second-line therapy for patients with allopurinol intolerance in USA
- May be used in combination with allopurinol/febuxostat
- May precipitate renal stone

Recombinant uricase

- Rasburicase: short-term use to prevent tumor lysis syndrome
- Pegloticase: PEGylated uricase, "debulking" of tophi

immunogenic

14

Hypouricemic Therapy

(Harrison's Principles of Internal Medicine)

- The decision to initiate hypouricemic therapy usually is made taking into consideration
  - The number of acute attacks (urate lowering may be cost-effective after two attacks)
  - Serum uric acid levels [progression is more rapid in patients with serum uric acid >535 μmol/L (>9.0 mg/dL)]
  - The patient's willingness to commit to lifelong therapy
  - The presence of uric acid stones
- Urate-lowering therapy should be initiated in any patient who already has tophi or chronic gouty arthritis
- Xanthine oxidase inhibitor allopurinol is most commonly used
  - Best drug to lower serum urate in overproducers, urate stone formers, and patients with renal disease

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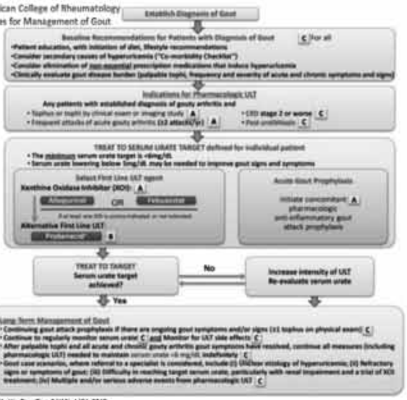
2013 台灣痛風指引
無症狀高尿酸血症的治療

- 降尿酸藥物的投予與否則未有全球一致的定論
- 需要由醫師及患者依據病患個人發展為痛風的風險因子及相關疾病(如進行性慢性腎功能不全)情形，共同達成臨床決定，除非合併有HGPRT 酵素(Hypoxanthine-Guanine Phosphoribosyl Transferase)缺乏等經確定的基因異常、或血液疾病或癌症將接受化學治療、或器官移植患者使用環孢靈造成尿酸值升高，否則通常不一定必須用藥物降低血尿酸。
- 但仍應充份告知患者血尿酸值越高，未來產生痛風性關節炎的危險性越高，及即使血尿酸值持續偏高也不意謂著一定會產生痛風的正反雙面事實，因此無併發症風險的單純無症狀高尿酸血症並非長期使用降尿酸藥物治療的適應症。
- 但對無症狀的高尿酸血症患者，建議每6個月追蹤檢驗一次血尿酸值。

16

2012 American College of Rheumatology Guidelines for Management of Gout



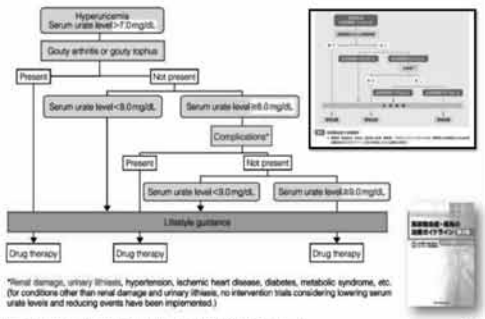
Khanna D. et al.: Arthritis Care Res. 64(10): 1431, 2012

17

European League Against Rheumatism (EULAR) 2011 Gout Guideline

18

Hyperuricemia Treatment Guidelines in Japan



*Renal damage, urinary lithiasis, hypertension, ischemic heart disease, diabetes, metabolic syndrome, etc. (for conditions other than renal damage and urinary lithiasis, no intervention trials considering lowering serum urate levels and reducing events have been implemented.)

Journal of the Japan Medical Association (Vol. 140, No. 2, 2011, pages 259–273), English version.

19

Uricosuric Agents

Sulfinpyrazone

Probenecid

Benzbromarone

Allopurinol

Febuxostat (Feburic)

Feburic® 80 mg, film - coated tablets

Conclusions

- Studies showed hyperuricemia and gout are associated with hypertension, cardiovascular disease, renal damage and metabolic syndrome
- More study data indicate that hyperuricemia is an independent risk factor for hypertension, cardiovascular disease, and renal damage
- Data from some clinical trials showed that urate-lowering therapy improves renal function in asymptomatic hyperuricemia patients
- Treatment guidelines for gout in USA and Europe: no need to treat asymptomatic hyperuricemia, but considering more aggressive treatment in gout patients with co-morbidities
- Treatment guideline for gout and hyperuricemia in Taiwan: do not favor treating asymptomatic hyperuricemia, but considering in asymptomatic hyperuricemia persons with co-morbidities
- Treatment guideline for gout and hyperuricemia in Japan: treat asymptomatic hyperuricemia patients with more than 9 mg/dL of serum uric acid level

第三場

降尿酸藥引起嚴重皮膚不良反應之診斷及預防

第三場
降尿酸藥引起嚴重皮膚不良反應之診斷及預防

鐘文宏醫師

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長庚醫院皮膚科醫師研究員

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長庚大學醫學系、長庚醫院學術組專任副教授

Insights into allopurinol-induced severe cutaneous adverse reactions (SCARs): risk factors, prognosis and preventive polices

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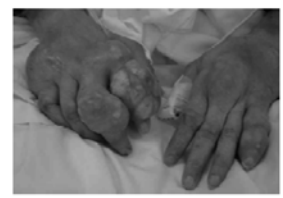
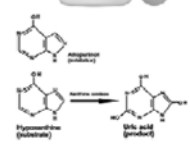
Department of Dermatology
Drug Hypersensitivity Clinical and Research Center,
Chang Gung Memorial Hospital,
Chang Gung University, Taiwan

Allopurinol

A xanthine oxidase inhibitor, has been used for decades as the first-line treatment for hyperuricaemia and gout.





Allopurinol hypersensitivity

- Allopurinol hypersensitivity:

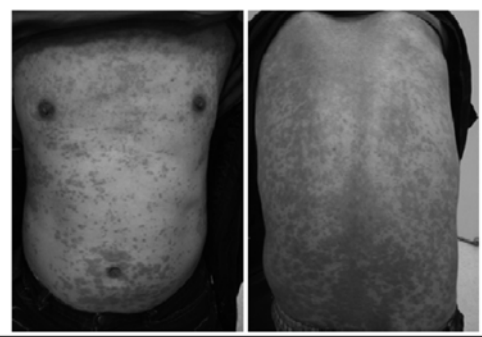
  Mild skin rash: 2 % of users

  Severe cutaneous adverse reactions(SCARs): 0.4 % of users, including hypersensitivity syndrome(DIHS or DRESS), SJS and TEN.

(The Annals of Pharmacotherapy, 1993)

Maculopapular exanthema(MPE)

Milder drug hypersensitivity reaction

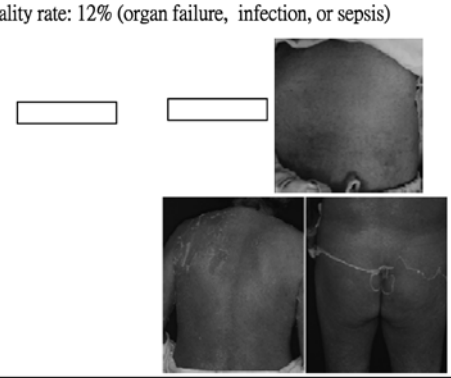


Drug induced hypersensitivity syndrome (DIHS) =Drug rush with eosinophilia and systemic symptom (DRESS)

- - acute occurrence of an **exanthema** with **fever** (above 38°C)
  - **lymphnode** enlargement
  - involvement of at least one **internal organ**
  - **blood changes** (e.g. eosinophilia, atypical lymphocytes, lymphocytopenia or lymphocytosis, thrombopenia)

Drug-induced hypersensitivity syndrome

mortality rate: 12% (organ failure, infection, or sepsis)



Allopurinol-induced SCARs: hypersensitivity syndrome or Drug rash with eosinophilia and systemic symptoms (DRESS)

62/F: CV OPD, Alloprurinol for hyperuricemia

CV OPD: DC Alloprurinol

↑LFT & ↑Cre

CGMH ER

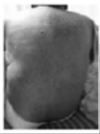
Admission

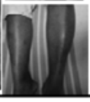
2011-10/26 — 11/20 — 11/23 — 11/29 — 11/30

Skin rash

intermittent fever
mild epigastric pain
severe oral ulcer

Alloprurinol



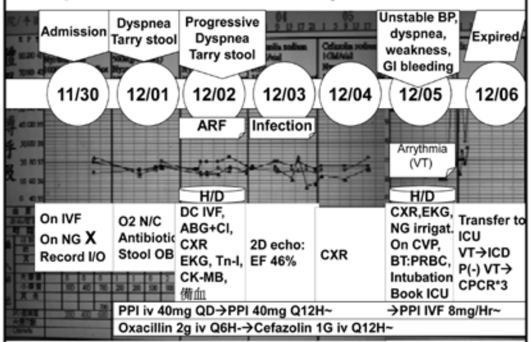


Allopurinol-DRESS: multi-organ involvement

檢驗項目	單位	1001015	1001129	1001130	1001202	1001203	1001205	1001205	1001205	1001206
WBC	1000/uL	10.2	18.1		19.2		15.0	16.7	22.7	20.3
RBC	million/uL	[illegible]	4.77		[illegible]		[illegible]		[illegible]	3.77
Hemoglobin	g/dL	11.3	12.7		10.9	11.0	9.7	7.2	8.8	8.0
Hematocrit	%	35.7	37.0		31.4	32.6	28.8	21.4	26.9	25.1
MCV	fL	92.0	84.7		86.0		87.3		89.1	90.6
MCH	pg/Cell	29.1	29.1		29.9		29.4		29.1	28.9
MCHC	gHb/dL	31.7	34.3		34.7		33.7		32.7	31.9
RDW	%	14.9	14.7		15.2		15.9		15.1	14.9
Platelets	1000/uL	182	180		256		232		198	191
Nucleated RBC	/100 WBC							2.0	3.0	4.3
Atypical Lymphocyte	%		1.0		1.0		5.0	1.0	2.0	9.0
Myelocyte	%				[illegible]		[illegible]	[illegible]	[illegible]	[illegible]
Meta-Myelocyte	%				1.0		1.0		2.0	2.5
Segment	%		47.0		46.0		40.0	74.0	62.5	41.0
Band	%				4.0		5.0	1.0	4.0	26.0
Lymphocyte	%		2.0		2.0		12.0	5.0	13.0	9.0
Monocyte	%		2.0		2.0		7.0	6.0	9.5	8.5
Eosinophil	%		47.0		42.0		27.0	12.0	3.0	3.0
Basophil	%		0.0		0.0		0.0	0.0	0.5	0.5

檢驗項目	單位	1001015	1001123	1001129	1001130	1001202	1001203	1001205	1001205	1001205	1001206
生化類(B)											
BUN (B)	mg/dL		40.7		123.0	127.1	102.3	128.7		122.1	122.1
Creatinine(B)	mg/dL		2.17	3.17		3.09	2.83	2.83		2.72	2.77
Total Bilirubin	mg/dL			0.9		0.4					0.4
AST/GOT	U/L		202		139	84				36	91
ALT/GPT	U/L			199		123				16	25

Allopurinol-DRESS: mortality: 10~20%



Stevens-Johnson syndrome

Toxic Epidermal Necrolysis

Blister/ skin detachment ≥ 30%

Allopurinol-induced SJS progressing to TEN

39/M: chronic kidney disease and gout

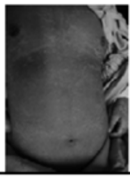
Admission

2012-1/20 — 2/07 — 2/12

Skin rash

severe oral ulcer, generalized blistering lesions with erythema

Alloprurinol



Progressed to TEN

2012-2-27: ARF, Sepsis, DIC

Complication of SJS/TEN

High morbidity and mortality : SJS(5~15%), TEN(30-40%)

Lung: sloughing of the respiratory tract mucosa, bronchial obstruction adult respiratory distress syndrome

Gastrointestinal: esophageal and gastrointestinal bleeding, colonic perforation

Heart: myocarditis and myocardial infarction

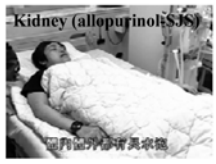
Liver: Hepatitis

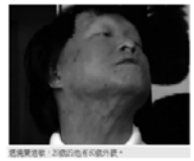
Kidney: acute renal failure

Eye: entropion and ectropion, corneal opacities or scarring, blindness.

Secondary infection, pneumonia, sepsis

Permanent complication of SJS





（2005. 8. 2）

2007/12/15 16:09

Allopurinol is the most common cause for SCARs in Taiwan

Taiwan Drug relief foundation (1999~2014/10)

藥害救濟給付案之可疑藥品前十名

(1999～2014.10)

1

1	Allopurinol	196
2	Phenytoin	131
3	Carbamazepine	113
4	Rifampin/Isoniazid/Pyrazinamide	73/70/68
5	Diclofenac	54
6	Co-trimoxazole	37
7	Mefenamic acid	34
8	Lamotrigine	32
9	Ibuprofen	32
10	Cefazolin	29

/www.tdrf.org.tw/

Death related to allopurinol-SJS/TEN in Taiwan

- More than 62 death in Taiwan caused by allopurinol in past 11 years

藥物救濟申請案件(data from Taiwan Drug Relief Foundation): 1999~2010
Allopurinol –induced SJS/TEN: total 145 SJS/TEN cases

救濟90件 (reimbursement)	女(F)	男(M)	小計	不救濟52件 (no reimbursement)	女	男	小計
死亡(death)	21	22	**43**	**死亡(death)**	8	11	**19**
障礙 (disable)	2	—	2	障礙	3	—	3
嚴重疾病 (severe)	20	25	45	嚴重疾病	18	12	30
合計	43	47	90	合計	29	23	52

不救濟理由52件: 涉及人為責任(18件)、本法施行前(1件)、未使用合法藥物(1件)、未達嚴重程度(2件)、未依核准適應症(2件)、常見且可預期(9件)。

Taiwan Drug Relief Foundation

Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel

Nona Halevy, MD,[a] Pierre-Dominique Ghislain, MD,[b] Maja Mockenhaupt, MD, PhD,[c] Jean-Paul Fagot, PharmD,[d] Jan Nico Bouwes Bavinck, MD, PhD,[e] Alexis Sidoroff, MD,[f] Issip Natsh, MD,[g] Arsène Dunant, MS,[h,i] Cecile Viboud, PhD,[h] and Jean-Claude Roujeau, MD,[h] for the EuroSCAR Study Group
BeerSheva, Israel; Créteil, Paris, and Villejuif, France; Freiburg, Germany; Leiden, The Netherlands; Innsbruck, Austria; and Bergamo, Italy

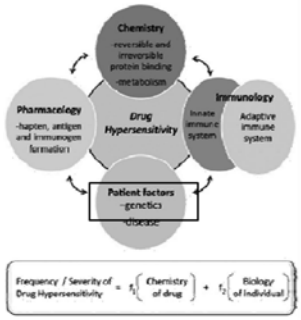
EurpSCAR/RegiSCAR

(J Am Acad Dermatol 2008;58:25-32.)

Table I. Estimates of odds ratio for the 7 high-risk drugs most often associated with Stevens-Johnson syndrome or toxic epidermal necrolysis in the EuroSCAR study

Drug*	Patients (%) n = 379	Control subjects (%) n = 1505	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Allopurinol†	66 (17.4)	28 (1.9)	11 (7.0-18)	18 (11-32)
Carbamazepine	31 (8.2)	4 (0.3)	33 (12-95)	72 (23-225)
Cotrimoxazole	24 (6.3)	1 (0.1)	102 (14-754)	ND
Nevirapine	21 (5.5)	0	∞ (22-∞)	ND
Phenobarbital‡	20 (5.3)	5 (0.3)	17 (6.2-45)	16 (5.0-50)
Phenytoin	19 (5.0)	3 (0.2)	26 (7.8-90)	17 (4.1-68)
Lamotrigine	14 (3.7)	0	∞ (14-∞)	ND

Pathogenesis of drug hypersensitivity



Werner J. Pichler,et al. J Allergy Clin Immunol 2011;127:S74-81

HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol

Shuen-Iu Hung[a,b], Wen-Hung Chung[a,b,c,d], Lieh-Bang Liou[e], Chen-Chung Chu[f], Marko Lin[f], Helen Ping Huang[g], Yen-Ling Lin[a], Joung-Liang Lan[h], Li-Cheng Yang[i], Hong-Shang Hong[j], Ming-Jing Chen[e], Ping-Chin Lai[k], Mai-Szu Wu[k], Chia-Yu Chu[l], Kuo-Hsien Wang[i], Chien-Hsun Chen[m], Cathy S. J. Fann[n], Jer-Yuarn Wu[n,o], and Yuan-Tsong Chen[n,p,q]

4134–4139 | PNAS | March 15, 2005 | vol. 102 | no. 11

Table 3. Frequencies of individual or combined loci of HLA-B*5801 extended haplotype in patients with allopurinol-induced SCAR, allopurinol tolerant control, and general population control

Genotype	Allopurinol-SCAR (n = 51)	Tolerant control (n = 135)	Odds ratio	Pc value[a]	General population control (n = 93)	Odds ratio	Pc value[a]
B*5801	51 (100)	20 (15)	580.3	4.7×10^{-28}	19 (20)	220.5	8.1×10^{-16}
Cw*0302	48 (94)	19 (14)	97.7	1.4×10^{-19}	19 (20)	62.3	2.5×10^{-10}
A*3303	34 (67)	24 (18)	9.8	2.2×10^{-4}	20 (22)	7.3	4.7×10^{-2}
DRB1*0301	33 (65)	17 (13)	12.7	2.8×10^{-5}	14 (15)	10.3	8.5×10^{-4}
B*5801, Cw*0302	48 (94)	19 (14)	97.7	1.4×10^{-19}	19 (20)	62.3	2.6×10^{-10}
B*5801, Cw*0302, A*3303	34 (67)	17 (13)	13.9	5.4×10^{-7}	16 (17)	9.6	1.7×10^{-2}
B*5801, Cw*0302, DRB1*0301	30 (59)	11 (8)	16.1	7.4×10^{-7}	10 (11)	11.9	7.8×10^{-4}
B*5801, Cw*0302, A*3303, DRB1*0301	21 (41)	9 (7)	9.8	0.039	9 (10)	6.5	>0.05

Numbers in parenthese indicate percentage.
[a]The Pc values were adjusted by using Bonferroni's correction for multiple comparisons to account for the observed alleles.

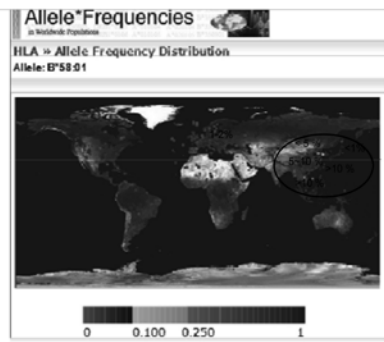
Validate the association between HLA-B*5801 and Allopurinol-SCAR(SJS/TEN, DRESS) in different populations

Table 1. HLA-B*5801 in Allopurinol-induced Severe Cutaneous Adverse reactions (SCAR).

Study number	1	2 (European study)		3	4
Study population	Han Chinese[a]	Caucasian[b]	Non-European ancestry (two Asians)	Japanese[c]	Thai[d]
Case	51/51 (100%)	15/27 (55%)	4/4 (100%)	7/13 (54%)	27/27 (100%)
Control	20/135 (15%)	28/1822 (1.5%)		6/493 (1.2%)	7/54 (13%)
Odds ratio	580.3	80		94.7	348.3
(95% C.I.)	(34.4 - 9780.9)	(34 - 187)		(24.4-367.3)	(19.2 – 6336.9)
P value	4.7×10^{-28} *	$<10^{-6}$ *		1.71×10^{-9}	1.61×10^{-19}
Reference	Hung, et al. PNAS, 2005.	Lonjou, et al. Pharmacogenetics and Genomics, 2008.		Kaniwa, et al. Pharmacogenomics , 2008. Dainichi, et al. Dermatology, 2007.	Wichitra, et al., Pharmacogenetics and Genomics, 2009.

[a]Case: Allopurinol-SCAR; Control: Tolerant control.
[b]Case: Allopurinol-SJS/TEN; Control: A mixed European population.
[c]Case: Allopurinol-SJS/TEN; Control: Japanese population.
[d]Case: Allopurinol-SJS/TEN; Control: Tolerant control.
* Adjusted using Bonferroni's correction for multiple comparisons to account for observed alleles.

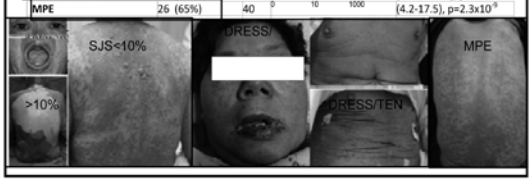
Higher Allele frequency of HLA-B*58:01 in Asians

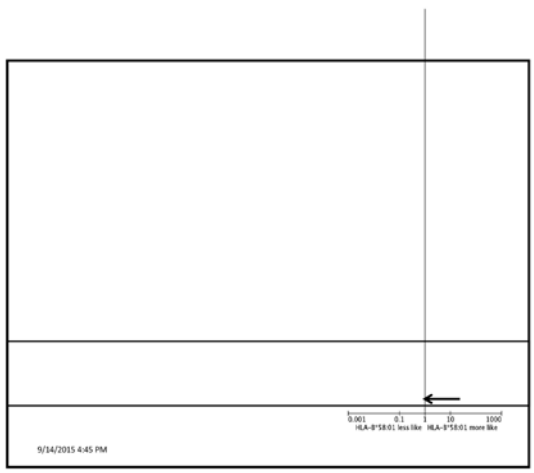


http://www.allelefrequencies.net/

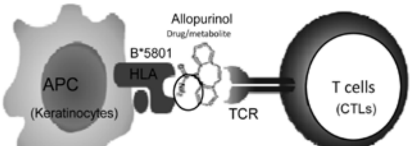
Phenotype & Genotype : HLA-B*5801 in allopurinol-cADR Follow-up study in Taiwan (n=123 vs 285 tolerant control)

Phenotypes (% BSA detachment)	No. with HLA-B*58:01 (%)	Total No.	Odds Ratio	(95% CI), p-value
cADRs	123(83%)	149	21.7	(12.9-36.5), $p=2.2 \times 10^{-60}$
SCARs	96 (91%)	106	44.0	(21.5-90.3), $p=2.6 \times 10^{-61}$
SJS/TEN ≥10%	14 (100%)	14	132.	(7.8-2249.6), $p=1.6 \times 10^{-10}$
SJS <10%	28 (88%)	32	32.1	(10.8-95.6), $p=3.1 \times 10^{-15}$
DRESS	52 (91%)	57	47.7	(18.2-125.4), $p=1.0 \times 10^{-26}$
DRESS-SJS/TEN	3 (100%)	3	31.9	(1.62-626.6), p=0.01
MPE	26 (65%)	40	8.5	(4.2-17.5), $p=2.3 \times 10^{-9}$





Hypothesis model for drug hypersensitivity



1) Genetic polymorphisms of HLA genes, 2) TCR rearrangements, 3) drug/peptides

➔Form the immune synapse

➔Elicit the drug-specific T cells activation and proliferation

➔Activate mediators of innate reactions (e.g., cytokines, chemokines, cytotoxic proteins, immune alarmins)

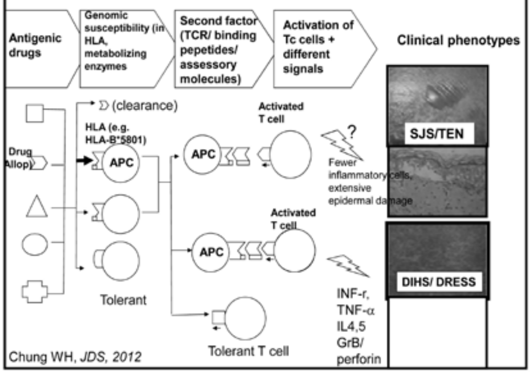
➔ Inflammation, cell death, dysfunction of organs

Association of serious drug hypersensitivity and HLA alleles

Phillips EJ, Chung WH et al. J Allergy Clin Immunol. 2011(modified)

Drug	HLA association	Hypersensitivity reactions	Reference
Carbamazepine	**B*1502**	**SJS/TEN**	Chung WH, Nature 2004
Allopurinol	**B*5801**	**SJS/TEN**/HSS	Hung SI, PNAS 2005
Abacavir	B*5701	MPE/HSS	Mallal S, NEJM, 2008
Flucloxacillin	B*5701	Hepatotoxicity	Daly AK, , Nat Genet. 2009
Lumiracoxib	DRB1*1501, DQB1*0602, DRB5*0101, DQA1*0102	Hepatotoxicity	Singer JB, Nat Genet. 2010
Dapsone	B*13:01	Hypersensitivty syndrome(MPE/HSS)	Zhang FR, N Engl J Med. 2013
Nevirapine	DRB1*0101	MPE/HSS	Martin AM, AIDS 2005
Methazolamide	HLA-B*5901	SJS/TEN	Kim SH, Pharmacogenomics. 2010

Molecular mechanism of drug hypersensitivity



Chung WH, *JDS, 2012*

Renal function and initial dose of allopurinol ?

Starting dose is a risk factor for allopurinol hypersensitivity syndrome: a proposed safe starting dose of allopurinol

Stamp LK et al. Arthritis Rheum. 2012

Conclusion. **Our findings indicate that starting allopurinol at a dose of 1.5 mg per unit of estimated GFR may be associated with a reduced risk of AHS. In patients who tolerate allopurinol, the dose can be gradually increased to achieve the target serum urate level.**

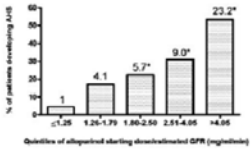


Table 4. Proposed starting dosage of allopurinol based on 1.5 mg per estimated GFR*

Estimated GFR, ml/minute/1.73 m²	Allopurinol starting dosage
<5	50 mg/week
5–15	50 mg twice weekly
16–30	50 mg every 2 days
31–45	50 mg/day
46–60	50 mg and 100 mg on alternate days
61–90	100 mg/day
91–130	150 mg/day
>130	200 mg/day

* Consideration should be given to starting allopurinol at even lower doses in patients at high risk of developing allopurinol hypersensitivity syndrome, such as those with HLA–B*5801. Estimated GFR = estimated glomerular filtration rate.

Clinical and epidemiological research

EXTENDED REPORT

Insights into the poor prognosis of allopurinol-induced severe cutaneous adverse reactions: the impact of renal insufficiency, high plasma levels of oxypurinol and granulysin

Wen-Hung Chung, Wan-Chun Chang, Sophie L Stocker, Chiun-Gung Juo, Garry G Graham, Ming-Han H Lee, Kenneth M Williams, Ya-Chung Tian, Kuo-Chang Juan, Yeong-Jian Jan Wu, Chih-Hsun Yang, Chee-Jen Chang, Yu-Jr Lin, Richard O Day, Shuen-Iu Hung

Ann Rheum Dis. 2014 Aug 12

Table 1 Demographic characteristics of allopurinol-tolerant controls and patients with allopurinol-induced severe cutaneous adverse reactions (SCAR)

	SJS/TEN (n=26)	DRESS (n=22)	SCAR (n=48)	Tolerant control (n=138)	SCAR vs tolerant control, Univariate analysis: p Value	OR (95% CI)
Allopurinol exposure						
All subjects						
Initial dosage, mean (SD); range (mg/day)	144 (87.0); 50–300	133 (61.3); 50–300	138 (75.5); 50–300	117 (43.7); 50–300	0.078	
Maintenance dosage, mean (SD); range (mg/day)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
Duration, mean; range (day or month)	30 days; 1–86 days	33 days; 10–58 days	31 days; 1–86 days	25 months; 6–152 months	<0.001	
Baseline eGFR, mean (SD); range (mL/min/1.73 m²)	40.1 (32.5); 4–114	26.9 (23.0); 5–86	34.0 (29.0); 4–114	67.5 (32.4); 5–151	<0.001	
Initial dosage/eGFR, mean (SD); range (mg/mL/min)	6.6 (6.8); 0.4–25	10.0 (8.3); 1.2–28.6	8.2 (7.6); 0.4–28.6	2.7 (3.3); 0.8–20.0	<0.001	
Diuretics usage, n (%)	5 (19.2%)	10 (45.5%)	15 (31.3%)	30 (21.7%)	0.240	
Subjects with renal impairment* eGFR<30						
Number, n (%)	15 (58%)	14 (64%)	29 (60%)	22 (15.9%)	<0.001	8.0 (3.9 to 16.0)
Initial dosage, mean (SD); range (mg/day)	135 (87.3); 50–300	125 (51.0); 50–200	130 (69.7); 50–300	141 (50.3); 100–200	0.528	
Maintenance dosage, mean (SD); range (mg/day)	142 (81.3); 50–300	120.6 (46.9); 100–200	135 (64.0); 50–300	148 (50.0); 100–300	0.460	
Duration, mean; range (day or month)	30 days; 1–55 days	33 days; 10–58 days	32 days; 1–58 days	29 months; 6–76 months	<0.001	
Baseline eGFR, mean (SD); range (mL/min/1.73 m²)	17.5 (8.5); 4–29	13.1 (7.5); 5–27	15.4 (8.2); 4–29	19.1 (8.7); 5–29	0.127	
Initial dosage/eGFR, mean (SD); range (mg/mL/min)	9.8 (7.6); 3.3–25	12.8 (8.3); 3.8–28.6	11.3 (8.0); 3.3–28.6	8.9 (4.6); 4.5–20	0.178	
Diuretics usage, n (%)	4 (26.7%)	10 (71.4%)	14 (48.3%)	13 (59.1%)	0.573	

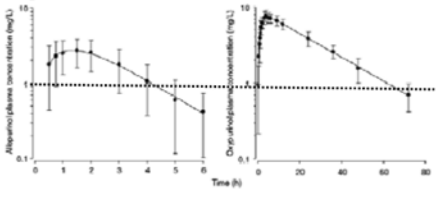
*Renal impairment refers to patients with eGFR <30 mL/min/1.73 m² calculated using the Modification of Diet in Renal Disease (MDRD) study equation.

DRESS, drug rash with eosinophilia and systemic symptoms; eGFR, estimated glomerular filtration rate; HLA, human leucocyte antigen; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrosis.

Normal metabolism of allopurinol:

Allopurinol=> oxypurinol => clearance through kidney

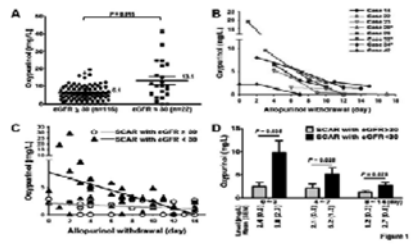
Plasma oxypurinol: < 1 mg/L after 3 days of allopurinol withdrawal



The time course of the plasma concentrations of allopurinol and oxypurinol following oral dosage of 300mg of allopurinol

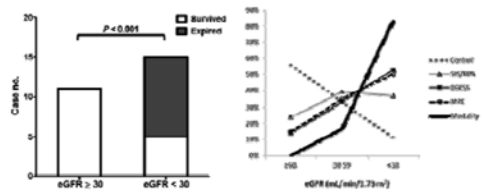
Day RO, et al. clin Pharmakinet2007

Correlation between the levels of plasma oxypurinol and renal function



Chung WH et al., Ann Rheum Dis. 2014

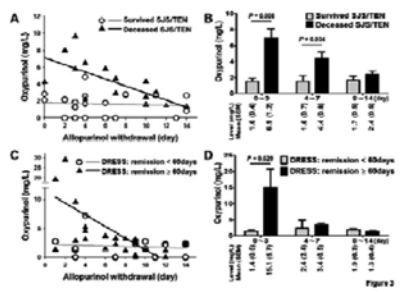
Increased mortality of allopurinol-induced SJS/TEN with renal function impairment



2012/6/25

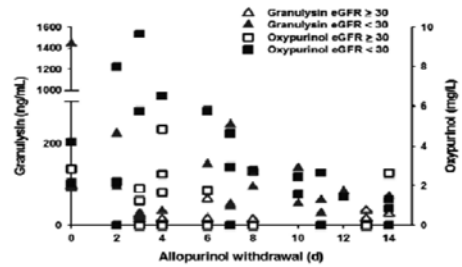
Chung WH et al., Ann Rheum Dis. 2014

Correlation between the levels of plasma oxypurinol and prognosis of allopurinol-SCARs



Chung WH et al., Ann Rheum Dis. 2014

Correlation between plasma granulysin and oxypurinol in allopurinol-SJS/TEN patients (n=20) after allopurinol withdrawal



2012/6/25

Chung WH et al., Ann Rheum Dis. 2014

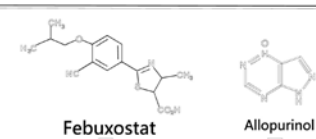
Strategy to reduce allopurinol hypersensitivity

1. Check the gene (HLA-B*5801)?

⇨ Not 100% protective:
~90% in Chinese,
54% in European,
55% in Japanese allopurinol-SCAR patients

2. Avoid to use in poor renal function?
3. Change to alternative new XOI (e.g. febuxostat)?

New xanthine oxidase inhibitor: Febuxostat



	Febuxostat	Allopurinol
Selectivity	**Selective** inhibitor of xanthine oxidase	Non-selective inhibitor of xanthine oxidase
Chemical structure	**Non-purine based**	Purine analogue
Range of inhibition	Inhibits **both** oxidized and reduced forms of xanthine oxidase	Inhibits only reduced forms of xanthine oxidase
Excretion	Excreted into **urine** and **faeces**	Mainly excreted into **urine**
Renal insufficiency	Relatively safe for mild or moderate cases	High risk, dose adjustment is necessary

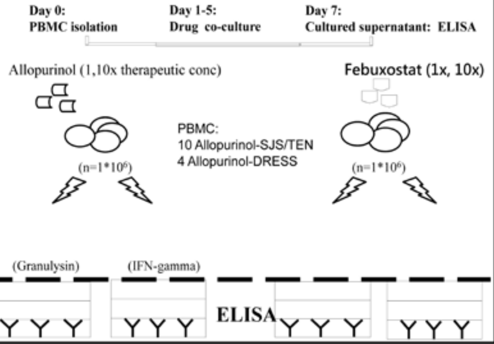
Safety of Febuxostat

- No confirmed report of febuxostat induced SJS/TEN in literatures

One case report of febuxostat hypersensitivity who had previous history of allopurinol hypersensitivity and CRI (Abeles AM, J Rheumatol. 2012)

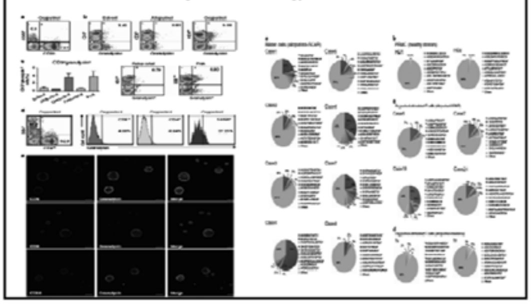
- 12 of 13 patients with previously severe allopurinol reactions were well tolerant with febuxostat; one developed cutaneous leukocytoclastic vasculitis (likely but not definitively FEB-related) (Chohan S. J Rheumatol. 2011)

In vitro cross-reactivity study of febuxostat with T cells of allopurinol-induced SCARs



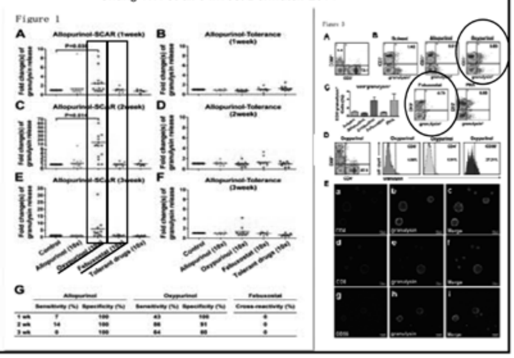
Oxypurinol-Specific T Cells Possess Preferential TCR Clonotypes and Express Granulysin in Allopurinol-Induced Severe Cutaneous Adverse Reactions

J Investigative Dermatology. 2015 June 4.



No cross reaction of allopurinol-SJS T cells with febuxostat

Chung WH et al. J Invest Dermatol. 2014



Pharmacoeconomic study

Risk of allopurinol induced adverse drug reactions: a nationwide cost-effectiveness analysis of 933,397 new users during 2002 to 2011 in Taiwan

Chien-Yi Yang[1], Chi-Hua Chen[1], Shin-Tarng Deng[1], Chi-Shan Huang[2] Yu-Jr Lin[3] Yi-Ju Chen[4,5],Chun-Ying Wu[4,5,6] Shuen-Iu Hung[7] , Wen-Hung Chung[8,9]

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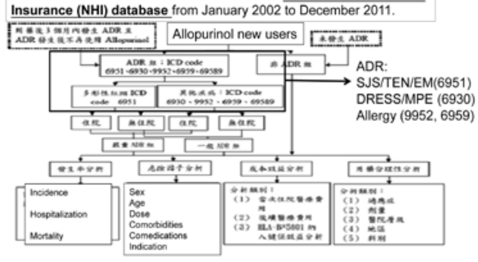
[9] College of Medicine, Chang Gung University, Taoyuan, Taiwan.

Retrospective analysis of risk of allopurinol-induced adverse drug reactions from 2002 to 2011 bon data from the **Taiwan National Health Insurance (NHI) database** from January 2002 to December 2011.



Taiwan started the NHI program in March 1995, offering a universal and unified health insurance to all citizens. NHI consists of detailed health care data from more than 21 million enrollees, representing more than 99% of the entire population of Taiwan. NHI database provide comprehensive materials for evidence-based medical research.

(unpublished)

Table 1. The number of new allopurinol users, incidence of allopurinol–induced ADR and associated mortality, hospitalization, and renal insufficiency by year.

Year	Number of prescriptions	Total allopurinol users	New allopurinol users	Number of patients with ADR (‰) [1]	Number of ADR-related deaths (‰) [1]	Number of patients with severe ADR-related hospitalization (‰) [1]	Renal insufficiency patients during 2 months after ADR (%) [2]
2005	1,337,822	244,309	84,025	312 (3.71)	30 (0.36)	137 (1.63)	12 (3.85)
2006	1,298,684	231,855	79,180	318 (4.02)	29 (0.37)	151 (1.91)	11 (3.46)
2007	1,312,678	227,842	71,717	302 (4.21)	22 (0.31)	138 (1.92)	3 (0.99)
2008	1,374,479	227,658	69,932	356 (5.09)	33 (0.47)	143 (2.04)	14 (3.93)
2009	1,422,262	228,270	64,478	341 (5.29)	27 (0.42)	154 (2.39)	10 (2.93)
2010	1,468,407	227,853	67,056	329 (4.91)	29 (0.43)	141 (2.10)	6 (1.82)
2011	1,507,448	225,932	59,475	364 (6.12)	23 (0.39)	140 (2.35)	8 (2.20)
Total	13,605,917	2,405,644	933,223	3,290 (3.53)	277 (0.30)	1,390 (1.49)	97 (2.95)

[1] The ‰ is the number of patients per thousand new users.
[2] The % is the number of patients per hundred ADR patients.
Abbreviation: ADR, adverse drug reaction.

Table 2. Multivariate logistic regression analysis of risk factors associated with allopurinol–induced ADR and mortality.

Variables	ADR			Mortality		
	OR	(95% CI)	p - value	OR	(95% CI)	p - value
Gender						
Male	1.00			1.00		
Female	1.44	(1.34, 1.55)	<0.001*	1.59	(1.25, 2.03)	<0.001*
Age (years)						
0~39	1.00			1.00		
40~59	0.99	(0.88, 1.10)	0.810	0.90	(0.42, 1.92)	0.780
60~79	1.43	(1.28, 1.61)	<0.001*	4.97	(2.56, 9.66)	<0.001*
80 +	2.36	(2.06, 2.71)	<0.001*	12.53	(6.36, 24.71)	<0.001*
Chronic kidney diseases						
No	1.00			1.00		
Yes	1.27	(1.15, 1.39)	<0.001*	1.74	(1.33, 2.26)	<0.001*
Diabetes mellitus						
No	1.00			1.00		
Yes	0.98	(0.90, 1.07)	0.630	1.25	(0.97, 1.61)	0.080
Cancer						
No	1.00			1.00		
Yes	1.02	(0.89, 1.16)	0.810	1.09	(0.75, 1.58)	0.670
Prescribed with antibiotic						
No	1.00			1.00		

Conclusion

- Allopurinol is a high risk to induce life-threatening SJS/TEN or DRESS
- Poor renal function decrease allopurinol metabolism (oxypurinol clearance) and increase mortality in patients with allopurinol induced SCARs
- HLA-B*5801 is strongly associated with allopurinol-SCARs; however, as a predictive marker, it is not 100%
- New generation xanthine oxidase inhibitors- febuxostate is structurally different from allopurinol and has low potential to cause cross-hypersensitivty for allopurinol-SCARs patients.

Acknowledgements

China

States

P