of sirolimus therapy in combination with cyclosporine against chronic rejection in a pediatric liver transplant patient（第 112 回米国臨床薬理学会年会（ASCPT）、2011.3.2-5、Hyatt Regency Dallas、Dallas、USA）（一般ポスター）

(11) Satohiro Masuda: Tubular drug transporters in progressive renal failure. (*"Impact of Disease States on Drug Disposition Involving Transporters"* 4th APISSX meeting, April 22-25 College of Medicine, National Cheng Kung University (NCKU), Tainan, Taiwan)（招聘講演）

・国内学会

(1) 増田智先「薬剤性腎障害の発現機構解明とバイオマーカーの探索」（第１７回 HAB 研究機構学術年会；シンポジウム；５月２１、２２日、昭和大学上条行動、東京都）（招聘講演）

(2) 中村高規、米澤　淳、橋本真弥、増田智先、桂　敏也、乾　賢一「シスプラチンの腎毒性発現における H^+/有機カチオンアンチポータ MATE1 の役割」（日本薬剤学会第２５年会；５月１２～１４日、あわぎんホール徳島県郷土文化会館、徳島市、徳島県）

(3) 増田智先、中川俊作、西原久美子、乾　賢一「mTOR 阻害薬の腎への作用」（ワークショップ 1「腎細胞癌の分子標的薬：内科的マネジメント」）（第 53 回日本腎臓学会学術総会；6 月 16～18 日、神戸国際会議場ほか、神戸市）

(4) 中川俊作、増田智先、西原久美子、乾　賢一「慢性腎不全時における Kidney injury molecule-1 の発現に関する検討」（第 53 回日本腎臓学会学術総会；6 月 16～18 日、神戸国際会議場ほか、神戸市）

(5) 西原久美子、増田智先、米澤 淳、小澤愛子、乾　賢一「近位尿細管遺伝子発現解析によるシスプラチン腎症のマーカー探索」（第 53 回日本腎臓学会学術総会；6 月 16～18 日、神戸国際会議場ほか、神戸市）

(6) 山本　崇、増田智先、安田幸代、吉田優子、寺中裕美、西岡由貴、矢野育子、桂 敏也、乾 賢一「タクロリムス血中濃度管理に及ぼす測定法の影響とトラフモニタリングの有用性」（第 27 回日本 TDM 学会・学術大会；6 月 26、27 日、札幌サンプラザ、札幌市）

(7) 安田幸代、増田智先、杉本充弘、山本　崇、西岡由貴、小川絵里、米川幸秀、岡本晋弥、海道利実、矢野育子、桂　敏也、上本伸二、乾　賢一「脳死小腸移植症例の周術期におけるタクロリムス血中濃

度管理」(第27回日本TDM学会・学術大会；6月26、27日、札幌サンプラザ、札幌市)

(8) 西岡由貴、増田智先、安田幸代、山本崇、丸山志穂子、仲瀬裕志、千葉　勉、矢野育子、桂　敏也、乾　賢一「潰瘍性大腸炎患者におけるタクロリムス血中濃度推移と臨床経過の比較解析」(医療薬学フォーラム2010；7月10，11日、広島国際会議場、広島市)

(9) 米澤　淳、中村 高規、増田 智先、桂 敏也、乾　賢一「有機カチオン排出トランスポーターMate1 KOマウスと薬物性腎障害」(FRONT-J第2回学術集会；8月21日、グランドプリンスホテル新高輪、東京)

(10) 増田智先：シンポジウム2「個別化医療の実践に向けて」「免疫抑制剤の投与設計」(第17回薬と医療シンポジウム「個別化医療の基礎と臨床」；8月21日、常翔学園OITホール)

(11) 本山慎也、増田智先、佐藤朋子、桂 敏也「ヒト腎H^+/有機カチオンアンチポータ hMATE1 及び hMATE2-K とグアニジン化合物との相互作用」(第60回日本薬学会近畿支部総会・大会；10月30日、摂南大学)

(12) 増田智先、乾　賢一「タクロリムスの血中濃度測定の精度管理と評価2010」(第46回日本移植学会総会；みやこメッセ、10月21日)

(13) Hiroki Yoshimatsu, Atsushi Yonezawa, Yoshiaki Yao, Satohiro Masuda, Toshiya Katsura and Ken-ichi Inui: Involvement of novel human riboflavin transporters hRFTs in riboflavin uptake by intestinal T84 cells.(日本薬物動態学会第25年会、10月7-9日、大宮ソニックシティ、さいたま市、埼玉県)

(14) Moto Kajiwara, Tomohiro Terada, Shingo Watanabe, Satohiro Masuda, Toshiya Katsura and Ken-ichi Inui: Multidrug and toxin extrusion 1 mediated tubular secretion of varenicline.(日本薬物動態学会第25年会、10月7-9日、大宮ソニックシティ、さいたま市、埼玉県)

(15) Tomoko Sato, Satohiro Masuda, Toshiya Katsura and Ken-ichi Inui: OCT2/MATE2-K double transfectant, as an in vitro model of renal handling of cationic drugs in human kidney.(日本薬物動態学会第25年会、10月7-9日、大宮ソニックシティ、さいたま市、埼玉県)

(16) Shin-ya Motoyama, Satohiro Masuda, Tomoko Sato, Toshiya Katsura and Ken-ichi Inui: Interaction between guanidino compounds and human multidrug and toxin extrusion (hMATE)1 AND hMATE2-K.(日本薬物動態学会第25年会、10月7-9

日、大宮ソニックシティ、さいたま市、埼玉県）

(17) 杉本充弘、矢野育子、増田智先、福土将秀、吉田優子、安田幸代、江川裕人、上本伸二、桂　敏也、乾　賢一「成人生体肝移植患者におけるタクロリムストラフモニタリングの有用性」（第 13 回宝ヶ池セミナー；11 月 13 日、国立京都国際会館）

(18) 水野知行、増田智先、石橋直哉、福土将秀、矢野育子、桂 敏也「質量分析法を用いた経口チロシンキナーゼ阻害薬 6 種の一斉定量法の確立」（第 20 回日本医療薬学会年会；11 月 13, 14 日、幕張メッセほか、千葉市、千葉県）

(19) 増田智先「近位尿細管トランスクリプトームに基づく薬剤性尿中バイオマーカーの探索」（第 31 回臨床薬理学会年会、シンポジウム 8「トキシコゲノミクスプロジェクトの基礎と臨床」、12 月 1-3 日、京都）

(20) 遠山佳奈、米澤　淳、津田真弘、増田智先、矢野育子、大澤理代 [1]、細川雅也、藤本新平、稲垣暢也、桂　敏也、乾　賢一「H^+/有機カチオンアンチポータ MATE の遺伝子多型によるメトホルミンの体内動態変化」（第 31 回臨床薬理学会年会、12 月 1-3 日、京都）

(21) 上杉美和、増田智先、米澤　淳、杉本充弘、深津祥央、矢野育子、桂 敏也、秦 浩一郎、小倉靖弘、海道利美、上本伸二「生体肝移植後のタクロリムス関連腎障害の発症における CYP3A5 遺伝子多型の影響」（第 31 回臨床薬理学会年会、12 月 1-3 日、京都）

(22) 柴田茉衣、矢野育子、安田幸代、増田智先、桂　敏也「LC/MS/MS による TDM 対象薬物一斉分析法のバリデーション試験」（第 31 回臨床薬理学会年会、12 月 1-3 日、京都）

(23) 河合知喜、増田智先、米澤　淳、杉本充弘、深津祥央、矢野育子、桂 敏也、秦 浩一郎、小倉靖弘、海道利美、上本伸二「生体肝移植患者の術後経過に及ぼす遺伝的背景の影響」（第 31 回臨床薬理学会年会、12 月 1-3 日、京都）

(24) 増田智先「慢性拒絶の診断後にシロリムスが奏功した小児肝移植症例について」（第 12 回肝移植術後管理検討会；1 月 29 日、メルパルク京都、京都市）

(25) 増田智先「薬剤性腎障害の非侵襲性バイオマーカーの探索」平成 22 年度厚生労働科学研究費補助金 創薬基盤推進研究事業（創薬バイオマーカー探索研究事業）の「トキシコゲノミクスデーターベースを活用した毒性メカニズムに基づく医薬品安全性評価に関する研究」

発表会（2月28日、日本薬学会長井記念ホール、東京都渋谷区）

(26) Atsushi Yonezawa, Satohiro Masuda, Toshiya Katsura, Ken-ichi Inui: S7創薬と薬物治療における薬物トランスポータ研究の最前線"Renal handling of platinum agents via organic cation transporters"（日本薬学会第131年会、静岡、東日本大震災のため年会は中止となったが研究発表は成立）

(27) 小澤愛子、増田智先、中川俊作、桂　敏也「代償性腎不全モデルラットにおけるシスプラチン腎症マーカーの探索」（日本薬学会第131年会、静岡、東日本大震災のため年会は中止となったが研究発表は成立）

(28) 木村匡宏、増田智先、福土将秀、矢野育子、桂　敏也「カルシニューリン阻害薬の効果発現における白血球P-糖蛋白質の役割」（日本薬学会第131年会、静岡、東日本大震災のため年会は中止となったが研究発表は成立）

(29) 石橋直哉、尾上雅英、増田智先、池見泰明、寺田智祐、乾　賢一、桂　敏也「電子カルテを用いたUGT1A1遺伝子多型解析業務システムの構築」（日本薬学会第131年会、静岡、東日本大震災のため年会は中止となったが研究発表は成立）

H．知的財産権の出願・登録状況
（予定を含む。）

本研究で見いだしたバイオマーカー候補分子について、「薬剤性腎障害の尿中バイオマーカー」として京都大学知財部の協力を得ながら特許出願の予定である。

厚生労働科学研究費補助金（創薬基盤推進研究事業（創薬バイオマーカー探索研究））
分担研究報告書

腎組織標本の損傷スコア解析とヒト腎生検組織標本の収集

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研究要旨

腎生検による病理学的診断は、腎臓病患者に対する治療方針の選択に有用性が高い。一方、血清クレアチニン値が高い患者においては、検査そのものの危険性とのバランスから適応外となる。従って、薬剤性 AKI を呈したと考えられる患者由来の生検採取は困難であるが、免疫学的原疾患の腎臓病患者由来の生検組織を用いることによって、非特異的かつ原疾患由来の情報をあらかじめ整理することによって、トランスクリプトームで得られる情報の絞込に極めて重要かつ貴重な情報を提供しうると考えられる。本研究では、IgA 腎症などの確定診断のために腎生検採取の適応となった患者に協力を得て、トランスクリプトームに使用すると同時に、病理学的診断とスコア化を行い、データ解析の一助とすることを目的とした。これまで 41 例の協力を得ることができ、20 例程については尿中バイオマーカーの定量データも得た。

A. 研究目的

薬剤性腎障害には、患者個々の腎機能に応じた個別化投与設計による回避と並び早期の腎代替療法導入による増悪阻止という双方の適切な対応が求められる。Acute Kidney Injury (AKI)は、直近 48 時間以内における血清クレアチニンや尿量の変化を指標に分類されるが、AKI 発症から血清クレアチニン値上昇に要する時間には個体差が大きく、より迅速かつ的確に AKI を診断するためのバイオマーカーの特定と臨床応用が必要である。

本研究では、ヒト尿検体を中心としたプロテオミクス解析による薬剤性腎障害の非侵襲性マーカーを探索し、その臨床的重要性を明らかにすることを到達目標とする。薬剤による腎障害には糸球体障害と尿細管間質障害があり、さらに後者にはアレルギー性障害、尿細管細胞への直接の障害、尿管腔からの再吸収あるいは直接の障害、尿中での析出などが成因と考えられる。実際臨床でこれらを確定することは頻度的

にも、技術的にも困難である。分担研究者はヒト腎生検の病理組織標本を収集し、それを評価する定量的スコア化システムの構築および臨床的所見（糸球体濾過量、蛋白尿定量およびその分析、尿細管障害指標マーカーなど）を検討することによって、マーカー候補分子の妥当性および臨床的意義、とくに薬剤性腎症に特徴的な所見を評価する方法を検討する。

B. 研究方法

（1）腎生検の採取

臨床的に的確な適応と判断し腎生検を行った腎疾患患者より、あらかじめインフォームドコンセントに基づいて承諾の得られた患者の組織標本について、糸球体面積、尿細管の病理所見（拡張、細胞変性、細胞脱落、萎縮、円柱、尿細管炎）、間質の病理所見（間質浮腫、細胞浸潤、線維化）を半定量化しスコア化した。これと尿中マーカーであるオステオポンティン、L 型脂肪酸蛋白（L-FABP）、β2 ミクログロブリン、シスタチン C の相関を調べた。いずれも尿中クレアチニンで補正した。現在まで５３例の腎生検標本について検討性している。対象は IgA 腎症１５例（紫斑病性腎炎１例を含む、様々な尿細管間質病変を含む）、膜性腎症５例（尿細管間質病変は軽度）、微小変化群４例（尿細管間質病変は病理的にはなし、ただし腎機能障害のあるものを含む）、ループス腎炎４例、ANCA 関連腎症２例、サルコイドーシス１例（高度の尿細管間質障害を伴う）などであり、病理的な尿細管、間質の所見の評価ならびに蛋白尿が尿細管に及ぼす影響、血管炎からくる障害などがみられこれらの評価も行っている。

（2）倫理面への配慮

本研究は、ヘルシンキ宣言（1975 年、東京総会で修正）を尊重し計画されたものであり、対象患者個人の人権擁護を最優先する。すなわち、自由意志による同意が得られた場合にのみ実施対象とすること、同意した場合でも随時撤回できそれによる不利益を受けないこと、血液や組織由来の核酸が他の目的で使用されないこと、実施対象者の個人識別情報は連結不可能匿名化方式で厳重に管理保護されていること、遺伝子解析結果を含むすべての検査結果については守秘義務を守ること、研究成果の発表に際しては個人が特定できない方法でのみ行うこと、を遵守している。なお、ヒト腎生検を用いた網羅的遺伝子解析及びヒト尿検体を用いた解析については「薬剤性腎障害の非侵襲マーカーの探索に関する研究」（G-306、平成 21 年 4 月 7 日付承認）、一方、腎生検採取を伴わない患者由来の尿検体を用いた解析については「尿中バイオマーカー候補分子のプロファイルと薬剤性腎障害との相関解析」

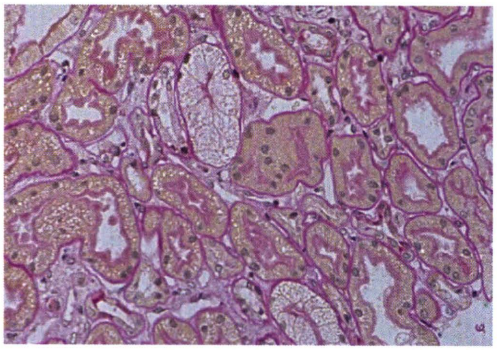
（E-640、平成 21 年 6 月 17 日付承認）という題目で、京都大学大学院医学研究科・医学部医の倫理委員会による審査・承認を受けている。本計画は平成 17 年 6 月 29 日に改正された「ヒトゲノム・遺伝子解析研究に関する倫理指針」（文部科学省、厚生労働省、経済産業省）、「臨床研究に関する倫理指針」（平成 20 年 7 月 30 日全部改正; 平成 21 年 4 月 1 日施行；厚生労働省）を遵守するものである。（上記 2 つの研究課題は、これまでの研究計画書「腎疾患患者における薬物輸送体の発現量並びに遺伝子多型に関する臨床研究」（G-159、代表者 京都大学医学部附属病院教授・薬剤部長 乾　賢一、研究代表者 増田智先及び研究分担者 深津敦司は分担研究者として参画）に対し、本申請計画に特化した内容で改めて倫理委員会の審査・承認を受けた）。

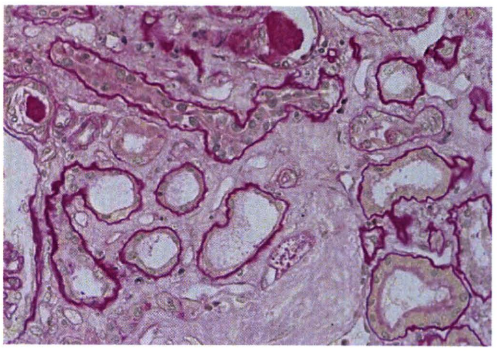
C. 研究結果

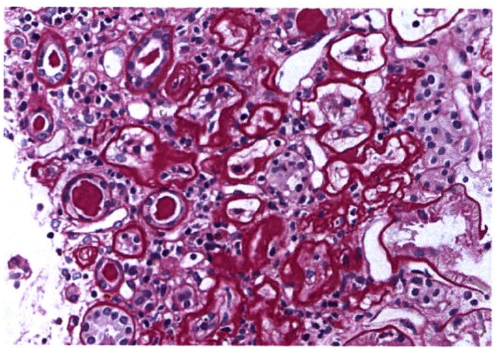
現時点で収集した５３例の腎生検組織の原疾患としては、IgA 腎症（１５例）、膜性腎症（７例）、微小変化群（４例）、ループす腎炎（４例）、アミロイドーシス（３例）などである。

腎生検入院中にイヌリンクリアランスで GFR を測定し、尿タンパク量、尿中ＮＡＧなどを計測した。

病理組織標本の評価としては、以下のようなパラメーターを半定量した。



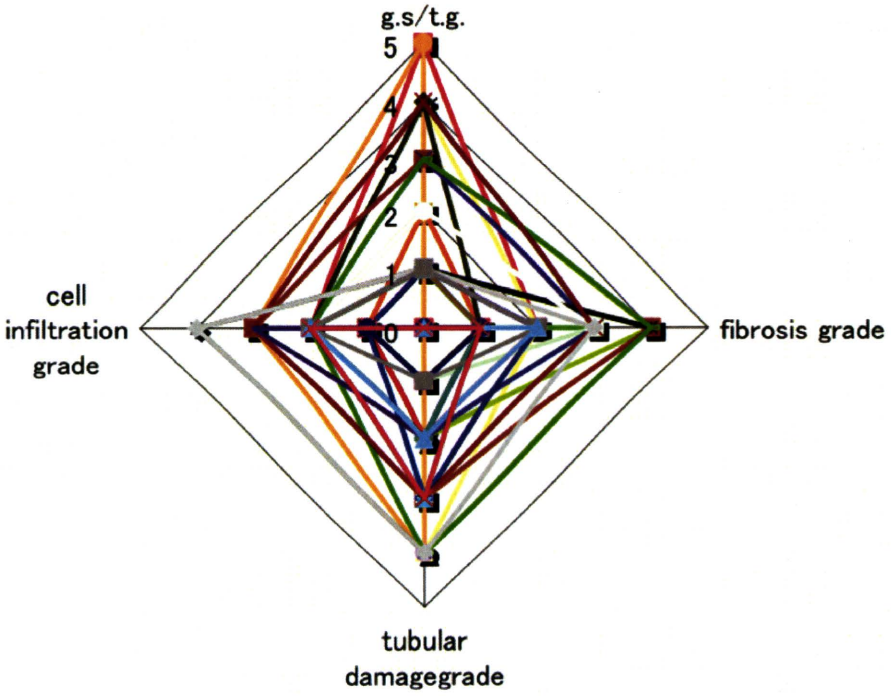




１）糸球体硬化率（硬化糸球体／糸球体数）：糸球体硬化が尿細管間質に影響を与える（尿細管萎縮、線維化）ためその程度の指標とした。

２）尿細管細胞障害　グレード　0−4
細胞障害（膨化、刷子縁剥離、細胞剝離）　全尿細管間質面積における障害部位の割合を評価：　急性期に細胞障害の程度を評価

０：細胞障害　５％未満



１：　　5-１０％
２：　　１０-３０％
３：　　３０-５０％
４：　　５０％以上

３）細胞浸潤　細胞浸潤のみられる部位の全尿細管間質に対する面積の割合
グレード　0-4　アレルギー性間質障害の診断と間質に及ぶ尿細管障害の程度を評価
グレーディング　２）と同様

４）間質線維化
慢性期の腎病変の指標
グレーディング　２）と同様

図１は代表例で上から細胞障害　グレード１、２、４となっている。

各症例における４つのパラメーターの相関を図２に示した。
尿細管障害と細胞浸潤が高度で糸球体硬化が少ない症例ほど尿細管間質の障害が主体と考えられる。

D. 考察
現在以下の相関について検討を行っている。

１）組織障害の特性（尿細管細胞障害、細胞浸潤、線維化）と現在測定中の

尿中排泄マーカーとの相関

2）各種疾患と尿中マーカーとの相関。とくに尿細管障害が生じる疾患（尿細管間質性腎炎、サルコイドーシスなど）

3） 微小変化群については組織的には変化に乏しくても腎機能障害を認める例があり、尿中マーカーと腎機能との相関

4）蛋白尿、尿細管障害と尿中マーカーとの相関：尿中マーカーの起源を推測する

E. 結論

以上のように、組織学的評価基準によるグレーディングには限界があり、遺伝子発現サブセット、尿中マーカーのサブセットなどより定量性の高いマーカーが必要であることが示された。

G. 研究発表

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H. 知的財産権の出願・登録状況
（予定を含む。）

本研究で見いだしたバイオマーカー候補分子について、京都大学知財部の協力を得ながら順次特許出願をする予定である。

III. 研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Yamamoto et al.	Tacrolimus Therapy as an Alternative to Thiopurines for Maintaining Remission in Patients With Refractory Ulcerative Colitis	J Clin Gastroenterol	印刷中		2011
Sugiyama H et al.	Committee for Standardization of Renal Pathological Diagnosis and Working Group for Renal Biopsy Database; Japanese Society of Nephrology, Tokyo, Japan: Japan Renal Biopsy Registry: the first nationwide, web-based, and prospective registry system of renal biopsies in Japan	Clin Exp Nephrol	印刷中		2011
Mima A et al.	Activation of Src Mediates PDGF-Induced Smad1 Phosphorylation and Contributes to the Progression of Glomerulosclerosis in Glomerulonephritis	PLoS ONE	6: 3	e17929	2011
Ho et al.	Maternal riboflavin deficiency, resulting in transient neonatal-onset glutaric aciduria Type 2, is caused by a microdeletion in the riboflavin transporter gene GPR172B	Hum Mutat	32: 1	E1976-1984	2010
増田智先	高齢者における薬物投与の注意	Geriatric Medicine	48: 8	1057-1061	2010
増田智先	高度医療における医薬品情報提供と薬剤師の役割 移植医療における情報提供 肝臓移植	薬事	52: 13	2019-2024	2010
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Toyama et al.	Heterozygous variants of multidrug and toxin extrusions (MATE1 and MATE2-K) have little influence on the disposition of metformin in diabetic patients	Pharmacogenet Genomics	20: 2	135-138	2010
Ichikawa et al.	Time-saving multiplex detection of single nucleotide polymorphisms by	J Biochem	148: 5	557-563	2010
Tanaka et al.	Loss of the BMP antagonist USAG-1 ameliorates disease in a mouse model of the progressive hereditary kidney disease Alport syndrome	J Clin Invest	120: 3	768-777	2010
深津敦司	透析療法の選択についてひとこと-腹膜透析か血液透析か	臨牀透析	26: 5	509-510	2010
Mima et al.	Successful treatment of membranoproliferative glomerulonephritis associated with hepatitis B and C virus simultaneous infection patient.	Clin Nephrol	73: 2	167-169	2010

Ⅳ．研究成果の刊行物・別刷

Tacrolimus Therapy as an Alternative to Thiopurines for Maintaining Remission in Patients With Refractory Ulcerative Colitis

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Background: Although the efficacy of tacrolimus for inducing remission of refractory ulcerative colitis (UC) is established, its efficacy for maintaining remission of UC has not been evaluated.

Aim: The aim of this study was to evaluate the efficacy of tacrolimus compared with thiopurines for maintaining remission in patients with refractory UC.

Methods: Twenty-four UC patients treated with tacrolimus and 34 treated with thiopurines to maintain remission were enrolled as the tacrolimus group and the thiopurine group, respectively. In the tacrolimus group, 82.8% of the patients were treated with tacrolimus for induction of the remission, whereas 70% of the patients in the thiopurine group were induced remission with either corticosteroid or cytapheresis. Proportions of patients who kept steroid-free remission between the tacrolimus and the thiopurine groups were compared. Maintenance of remission using tacrolimus or thiopurines was defined as no need for other therapies other than aminosalicylates without relapse for at least 3 months. Secondarily, to determine whether the response to thiopurines affects the long-term efficacy of tacrolimus maintenance therapy, the overall cumulative relapse-free survival based on the Kaplan-Meier method was estimated in thiopurine-naive or thiopurine-intolerant patients and thiopurine-refractory ones in the tacrolimus group.

Results: Remission was successfully maintained in 17 patients (70.8%) of the tacrolimus group, and 28 patients (82.4%) of the thiopurine group. The overall cumulative relapse-free survival of thiopurine-naive or thiopurine-intolerant patients in the tacrolimus group was similar to that in the thiopurine group, and significantly higher than that of thiopurine-refractory patients in the tacrolimus group.

Conclusion: Maintenance therapy with tacrolimus for patients with UC could be considered an alternative to thiopurine therapy.

Key Words: ulcerative colitis, tacrolimus, thiopurines, remission maintenance therapy

(*J Clin Gastroenterol* 2011;00:000–000)

Ulcerative colitis (UC) is an idiopathic, chronic, and inflammatory disorder characterized by diarrhea, rectal bleeding, abdominal pain, fever, anemia, and body weight loss.[1] Corticosteroid (CS) therapy is used for patients with UC who do not respond to aminosalicylates or those with a severe attack.[1,2] Although most patients with UC initially respond to CS, approximately 20% of patients with UC become steroid-dependent within 1 year after initiating CS therapy.[3] CS is not used as maintenance therapy for patients with UC because of undesirable side-effects such as opportunistic infections, diabetes mellitus, osteoporosis, etc.[4] Therefore, steroid-free remission is an important issue for patients with UC.

Tacrolimus is effective for patients with UC refractory to or dependent on CS, and is usually used as a rescue and bridging therapy before initiating azathioprine (AZA) or 6-mercaptopurine (6-MP) therapy.[5–11] Several studies have reported the long-term outcomes after tacrolimus therapy for the induction of remission[6–9]; in all of these case series, however, patients received maintenance therapy with other agents, including thiopurines, and infliximab after the induction of clinical remission. To our knowledge, except for a couple of case reports,[6,12] there are no reports on the effect of tacrolimus as maintenance therapy for patients with refractory UC. Here, we evaluated the efficacy of tacrolimus therapy for maintaining remission in patients with refractory UC in comparison with thiopurines, currently the most widely used treatment to maintain steroid-free remission in patients with refractory UC.[1,2]

PATIENTS AND METHODS

Patients

Between April 2001 and October 2009, 42 patients with UC who were resistant to or could not be treated with conventional therapy were treated with tacrolimus, and 29 (69.0%) achieved clinical remission. Of those, 23 patients received tacrolimus subsequently for the maintenance of remission. In addition, 1 patient in whom tacrolimus therapy failed for inducing remission was maintained remission with tacrolimus after the induction of remission

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Supported by a Grant-in-Aid for Scientific Research (C) from the Ministry of Culture and Science of Japan (grant 18590677); the Kato Memorial Trust for Nambyo Research; the Japan Foundation for Applied Enzymology; the Shimizu Foundation for the Promotion of Immunology Research (to Hiroshi Nakase); by Grants-in-Aid for Scientific Research (16017240, 16017249, 17013051, 17659212, and 18012029) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan; Grants-in-Aid for Scientific Research (15209024 and 18209027) from JSPS; and a Grant-in-Aid for Research on Measures for Intractable Disease, and Research on Advanced Medical Technology (nano005) from the Ministry of Health, Labor, and Welfare, Japan (to Tsutomu Chiba). No conflicts of interest exist.
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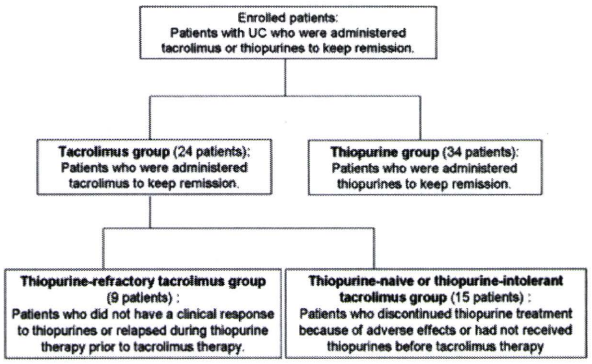

FIGURE 1. A flow chart of patients in different groups and subgroups. UC indicates ulcerative colitis.

by inflixmab. These 24 patients with UC who were treated with tacrolimus to maintain remission after achieving remission were enrolled in this retrospective, observational, single-center study (tacrolimus group). To compare the effect of tacrolimus for maintaining remission of UC, 34 patients who were administered thiopurines to maintain remission during the same period were enrolled as the thiopurine group.

In addition, tacrolimus group was divided into 2 subgroups according to the response to thiopurines; that is, thiopurine-refractory tacrolimus group (9 patients did not have a clinical response to thiopurines or relapsed during thiopurine therapy before tacrolimus administration) and thiopurine-naive or thiopurine-intolerant tacrolimus group (3 patients discontinued thiopurine treatment because of adverse effects and 12 patients had not received thiopurines before tacrolimus therapy). Flow chart of the patients in different groups and subgroups is shown in Figure 1.

This study was reviewed and approved by the Institutional Review Board of Kyoto University. Patients were informed about the potential risks and benefits of tacrolimus therapy and provided written consent to its use. In all cases, the diagnosis was established according to standardized criteria by prior clinical assessment, radiology, endoscopy, and histology.

Definition of Response

Disease activity was measured using a modified Truelove Witts severity index (MTWSI)[13]; details are shown in Table 1. Clinical remission was retrospectively defined as an estimated MTWSI score of 4 or less. Relapse was defined as an increase in the MTWSI score to 5 or higher with additional therapies required. To remove the influence of other drugs as much as possible when comparing the efficacy of tacrolimus and thiopurines for steroid-free remission, maintenance of remission was defined as no need for concomitant treatment other than aminosalicylates and topical steroid therapy in addition to tacrolimus or thiopurines without relapse for at least 3 months.

Patients were classified as steroid-resistant or steroid-dependent in accordance with the earlier published definition of Ogata et al.[5]

Treatment

Tacrolimus was administered in its oral formulation. Dosage was adjusted to produce trough tacrolimus whole-blood levels of 10 to 15 ng/mL to induce remission. After inducing clinical remission, tacrolimus whole-blood trough concentrations were maintained at a lower level, between 5 and 10 ng/mL.[9] The initial dose of tacrolimus was 0.1 mg/kg body weight per day. The mean doses of tacrolimus for inducing and maintaining remission were 7.7 mg/d (range: 2.0 to 12.0 mg/d) and 5.7 mg/d (range: 2.0 to 10.0 mg/d), respectively.

For thiopurine maintenance therapy, the dose of AZA or 6-MP was adapted to achieve white blood cell counts between 3000 and 5000/μL, or 6-thioguanine nucleotide concentrations between 250 and 500 pmol/8×10^8 red blood cells. Twenty-four and 10 patients were treated with AZA and 6-MP, respectively. The mean initial doses of AZA and 6-MP were 30.5 mg/d (range: 25 to 100 mg/d) and 13.3 mg/d (range: 5 to 30 mg/d), respectively. The mean doses of AZA and 6-MP for the remission phase were 53.0 mg/d (range: 25 to 100 mg/d) and 25.0 mg/d (range: 5 to 40 mg/d), respectively.

Assessment and Statistics

The primary endpoint of this study was the proportion of patients in whom remission was successfully maintained. Secondary endpoints included relapse-free survival and treatment safety.

Proportions between groups were compared by Fisher exact test and continuous variables were compared by Mann-Whitney *U* test. Relapse-free survival was assessed using the Kaplan-Meier method. Relapse-free survival of patients who could not maintain remission without concomitant therapies other than aminosalicylates and topical steroid therapy were set as 0 month. A *P* value of less than 0.05 was considered to be statistically significant.

TABLE 1. Modified Truelove Witts Severity Index[13]

Score	0	1	2	3	4	5
Bowel movement	0-2	3-4	5-6	7-9	≥10	
Nocturnal diarrhea	No	Yes				
Visible blood in stool (%)	0	< 50	≥50	100		
Abdominal tenderness	None	Mild	Moderate	Severe		
Abdominal pain/cramping	None	Mild	Moderate	Severe		
Need for antidiarrheals	No	Yes				
General status	Perfect	Very good	Good	Average	Poor	Terrible
Fecal incontinence	No	Yes				

Remission category: 4 or less.

RESULTS

Patient Characteristics

Baseline characteristics of the patients in each group and subgroup of the tacrolimus group are shown in Tables 2 and 3, respectively. Except for treatment duration, these baseline characteristics of the tacrolimus group were similar to those of thiopurine group (Table 2).

All patients in the tacrolimus group were treated with aminosalicylates. Four patients (16.7%) were steroid resistant, 17 patients (70.8%) were steroid dependent, and the remaining 3 patients (12.5%) had not been treated with CS. Two patients had received infliximab for the induction of remission. No other patients had been treated with biologics before tacrolimus maintenance therapy.

Therapies for the induction of remission that preceded remission maintenance therapy are summarized in Table 4. In tacrolimus group, 3 patients received 2 courses of tacrolimus maintenance therapy and 1 patient received 3 treatment courses, and in thiopurine group, 6 patients received 2 courses of thiopurine maintenance therapy. Therefore, a total 29 and 40 remission induction therapies were performed before remission maintenance therapy in tacrolimus and thiopurine group, respectively.

Maintenance of Remission

In tacrolimus group, remission ratio at 3 and 6 months was 70.8% (17 of 24 patients) and 54.2% (13 of 24 patients), respectively. In thiopurine group, remission ratio at 3 and 6 months was 82.4% (28 of 34 patients) and 73.5% (25 of 34 patients), respectively. Proportions of patients who were stayed in remission at 3 and 6 months were not statistically different between the 2 groups ($P = 0.3494$ and 0.1647, respectively; Fisher exact test). The mean durations of steroid-free remission in the tacrolimus and the thiopurine groups were 9.2 months (range: 0 to 50.7 mo) and 14.0 months (range: 0 to 51.6 mo), respectively. There was no statistical difference between the 2 groups again ($P = 0.1114$; Mann-Whitney U test).

Although there was no significant difference between the 2 groups, the duration of remission in the tacrolimus group tended to be shorter than that in thiopurine group. Therefore, to determine whether the response to thiopurine therapy affects the long-term efficacy of tacrolimus maintenance therapy, the overall cumulative relapse-free survival based on the Kaplan-Meier method was estimated in the thiopurine-naive or thiopurine-intolerant tacrolimus group and the thiopurine-refractory tacrolimus group. Relapse-free survival in patients in the thiopurine-naive or thiopurine-intolerant tacrolimus group was comparable with that in the thiopurine group ($P = 0.5594$; log-rank test) and was significantly higher than that in the thiopurine-refractory tacrolimus group ($P = 0.0104$; log-rank test; Fig. 2).

Adverse Effects

The frequency of adverse events during tacrolimus therapy is shown in Table 5. Tacrolimus withdrawal was

TABLE 2. Patients' Baseline Characteristics in the Tacrolimus and the Thiopurine Groups

	Tacrolimus Group	Thiopurine Group	P
Age at diagnosis [median (range)] (y)	23.4 (11.9-74.7)	29.3 (15.3-60.8)	0.4334
Age at start of the therapy [median (range)] (y)	27.5 (15.9-78.1)	36.2 (16.8-65.0)	0.3619
Disease duration prior the therapy [median (range)] (y)	3.6 (0.4-22.8)	3.6 (0.8-31.6)	0.7116
Follow-up duration [median (range)] (mo)	23.0 (5.1-87.1)	34.4 (3.4-86.0)	0.4207
Treatment duration [median (range)] (mo)	13.2 (1.8-53.7)	25.7 (3.4-61.5)	0.0187
Sex			0.2913
Men (%)	12 (50)	22 (64.7)	
Women (%)	12 (50)	12 (35.3)	
Disease extent			1.0000
Extensive (%)	17 (70.8)	24 (70.6)	
Left-sided (%)	7 (29.2)	10 (29.4)	
Response to corticosteroids			0.3428
Steroid resistance (%)	4 (16.7)	5 (14.7)	
Steroid dependence (%)	17 (70.8)	28 (82.4)	
Steroid naive (%)	3 (12.5)	1 (2.9)	

Numbers of patients are shown unless specified.

TABLE 3. Baseline Characteristics of Patients in Each Tacrolimus Subgroup

	Thiopurine-refractory Group	Thiopurine-naive Intolerant Group	P
Age at diagnosis [median (range)] (y)	21.7 (15.3-56.0)	23.8 (11.9-74.7)	0.4207
Age at start of the therapy [median (range)] (y)	30.4 (16.5-67.7)	27.2 (15.9-78.1)	0.7565
Disease duration prior the therapy [median (range)] (y)	4.8 (1-22.8)	3.4 (0.4-4.8)	0.0131
Follow-up duration [median (range)] (y)	12.67 (5.1-61.2)	44.6 (6.5-87.1)	0.1440
Treatment duration [median (range)] (mo)	12.67 (5.1-44.4)	15.6 (1.8-53. 7)	0.5711
Sex			0.4003
Men (%)	3 (33.3)	9 (60.0)	
Women (%)	6 (66.7)	6 (40.0)	
Disease extent			1.0000
Extensive (%)	6 (66.7)	11 (73.3)	
Left-sided (%)	3 (33.3)	4 (26.7)	
Response to corticosteroids			0.8241
Steroid resistance (%)	1 (11.1)	3 (20.0)	
Steroid dependence (%)	7 (77.8)	10 (66.7)	
Steroid naive (%)	1 (11.1)	2 (13.3)	

Numbers of patients are shown unless specified.

TABLE 4. Therapies for the Induction of Remission Before Maintenance Therapies

	Tacrolimus Group	Thiopurine Group
Prednisolone (%)	1 (3.4)	20 (50.0)
Tacrolimus (%)	24 (82.8)	11 (27.5)
Infliximab (%)	2 (6.9)	1 (2.5)
Cytoapheresis (%)	2 (6.9)	8 (20.0)

Numbers of patients are shown.

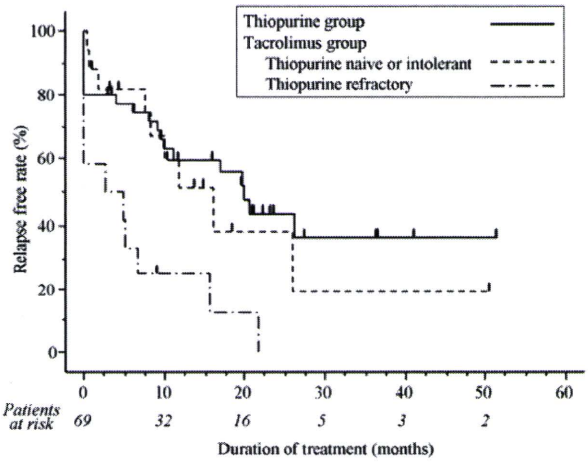

FIGURE 2. Relapse-free time intervals of thiopurine-refractory patients and thiopurine-naive or thiopurine-intolerant patients in the tacrolimus group and in the thiopurine group. The overall cumulative relapse-free survival of thiopurine-refractory patients in the tacrolimus group was significantly lower than that in the other 2 groups [log-rank test; $P=0.0104$ (vs thiopurine-naive or intolerant patients) and $P=0.0008$ (vs thiopurine group)]. There was no statistical difference between the thiopurine-naive or thiopurine-intolerant tacrolimus and thiopurine groups ($P=0.5594$).

necessary in 4 patients (16.7%). One patient (4.2%) contracted bacterial pneumonia. He had received a combination of tacrolimus and AZA, and recovered with antibiotic administration and discontinuation of the tacrolimus and AZA. A temporary rise in serum creatinine levels above 1.3 mg/dL occurred in 4 patients (16.7%). In 3 cases, tacrolimus withdrawal was necessary and serum creatinine levels normalized after discontinuation. In the other case, renal function normalized with dose reduction of tacrolimus.

The thiopurines were discontinued because of side effects in 5 (14.7%) of 34 patients undergoing thiopurine maintenance therapy. Of those, 1 patient (2.9%) contracted bacterial pneumonia as described above, 1 patient (2.9%) developed leukopenia, 1 patient (2.9%) developed pancreatitis, and 2 patients (5.9%) experienced nausea. Herpes progenitalis (2.9%, n = 1) and mild leukopenias (5.9%, n = 2) were also observed.

All of the patients in both groups recovered with conventional therapy. There was no mortality in either of the groups.

TABLE 5. Adverse Events That Developed During Tacrolimus Treatment

Adverse Events	Cases (%)
Tremor	5 (20.8)
Renal function impairment (rise in creatinine above 1.3 mg/dL)*	4 (16.7)
Hot flashes	3 (12.5)
Bacterial pneumonia	1 (4.2)
Hyperkalemia	1 (4.2)
Epigastralgia	1 (4.2)
Headache	1 (4.2)

*In 1 case, tacrolimus withdrawal was not necessary.

DISCUSSION

The findings of this study showed that the effects of tacrolimus as maintenance therapy in thiopurine-naive or thiopurine-intolerant patients with UC are comparable with those of thiopurines. To our knowledge, this is the first study to show that tacrolimus therapy is valuable for maintaining remission in patients with refractory UC in comparison with thiopurine therapy.

First, we investigated the efficacy of thiopurines for maintaining remission in patients with refractory UC enrolled in this study. Our study showed that the proportions of UC patients maintaining steroid-free remission with thiopurines at 1 and 3 years were 59.2% and 36.5%, respectively (Fig. 2). In a prospective, observational cohort study by Chebli et al,[14] the proportion of patients with steroid-dependent UC who received AZA for 3 years and remained in steroid-free remission was 45% and 57.5% on an intention-to-treat basis and per protocol basis, respectively. Fraser et al[15] reviewed the clinical notes of 622 patients with inflammatory bowel disease (272 Crohn's disease, 346 UC, and 4 indeterminate colitis) who were treated with AZA to maintain remission and showed that the relapse-free rate based on a Cox regression analysis was 63% at 60 months. Although the relapse-free rate in the later study seems to be higher than that in thiopurine therapy in an earlier study and in this study, patients who received AZA for less than 3 months were excluded in the study by Fraser et al, whereas all patients who were administered thiopurines were enrolled in other studies. Thus, in our study, the clinical outcome of patients treated with thiopurines was similar to that in earlier reports.[14,15]

Then, we investigated the efficacy of tacrolimus as maintenance therapy for patients with refractory UC in comparison with thiopurines. Our study showed that the proportions of patients intolerant or naive to thiopurines who could maintain steroid-free remission with tacrolimus at 1 and 3 years were 51.1% and 19.2%, respectively (Fig. 2), which was similar to that in patients with thiopurines. In contrast, the proportions of patients who were refractory to thiopurines at 1 and 3 years were 25.0% and 0%, respectively (Fig. 2). Relapse-free survival in this group was significantly lower than that in thiopurine group. These data suggested that administration of tacrolimus with trough levels of 5 to 10 ng/mL as maintenance therapy could be an alternative therapy for UC patients intolerant to thiopurines, but might be less effective in thiopurine-refractory patients with UC.

Some reports recommend tacrolimus trough levels of 5 to 10 ng/mL for long-term administration to avoid rejection in patients with liver, renal, and small bowel transplantation.[16,17] Our earlier report also showed that the same trough level range might be optimal for maintaining remission in patients with refractory UC based on its effect and safety.[9] According to these earlier reports, in this study, we treated UC patients by adjusting the tacrolimus trough levels to 5 to 10 ng/mL. Our data suggested, however, that patients with UC who are refractory to thiopurines should be controlled with higher trough levels of tacrolimus, a combination of thiopurines and tacrolimus, or infliximab.

One limitation of this study concerns the difference of the induction therapy between the tacrolimus and the thiopurine groups. In fact, 82.8% of the patients in the tacrolimus group were treated with tacrolimus, whereas 70% of the patients in the thiopurine group received either CS or cytapheresis (Table 4). Therefore, we could not

exclude the possibility that patients in the thiopurine group had less severe disease than those in the tacrolimus group. To solve this issue, additional studies might be required with enrolling patients who received the same induction therapies.

Finally, we evaluated the adverse effects related to long-term administration of tacrolimus therapy. In this study, tremor was the most frequent side-effect and severe adverse events rarely occurred during tacrolimus maintenance therapy. The frequency of drug withdrawal because of side effects was similar between the tacrolimus and thiopurine groups, indicating that long-term tacrolimus administration with trough levels of 5 to 10 ng/mL could be tolerable in patients with refractory UC.

In conclusion, our study showed that tacrolimus therapy is a viable alternative for maintaining steroid-free remission in UC patients intolerant to thiopurines, although its efficacy and the therapeutic strategy for thiopurine-refractory UC remains to be established.

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ORIGINAL ARTICLE

Japan Renal Biopsy Registry: the first nationwide, web-based, and prospective registry system of renal biopsies in Japan

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Abstract
Background The Committee for the Standardization of Renal Pathological Diagnosis and the Working Group for Renal Biopsy Database of the Japanese Society of Nephrology started the first nationwide, web-based, and prospective registry system, the Japan Renal Biopsy Registry (J-RBR), to record the pathological, clinical, and laboratory data of renal biopsies in 2007.
Methods The patient data including age, gender, laboratory data, and clinical and pathological diagnoses were recorded on the web page of the J-RBR, which utilizes the system of the Internet Data and Information Center for Medical Research in the University Hospital Medical Information Network. We analyzed the clinical and pathological diagnoses registered on the J-RBR in 2007 and 2008.
Results Data were collected from 818 patients from 18 centers in 2007 and 1582 patients from 23 centers in 2008, including the affiliated hospitals. Renal biopsies were obtained from 726 native kidneys (88.8%) and 92 renal grafts (11.2%) in 2007, and 1400 native kidneys (88.5%) and 182 renal grafts (11.5%) in 2008. The most common clinical diagnosis was chronic nephritic syndrome (47.4%), followed by nephrotic syndrome (16.8%) and renal

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transplantation (11.2%) in 2007. A similar frequency of the clinical diagnoses was recognized in 2008. Of the native kidneys, the most frequent pathological diagnosis as classified by pathogenesis was immunoglobulin (Ig) A nephropathy (IgAN) both in 2007 (32.9%) and 2008 (30.2%). Among the primary glomerular diseases (except IgAN), membranous nephropathy (MN) was the most common disease both in 2007 (31.4%) and 2008 (25.7%). *Conclusions* In a cross-sectional study, the J-RBR has shown IgAN to be the most common disease in renal biopsies in 2007 and 2008, consistent with previous Japanese studies. MN predominated in the primary glomerular diseases (except for IgAN). The frequency of the disease and the clinical and demographic correlations should be investigated in further analyses by the J-RBR.

Keywords Glomerulonephritis · Tubulointerstitial disorder · Renal vascular disease · Renal grafts · National registry

Introduction

There has been no national registry of renal biopsies in Japan. The Committee for the Standardization of Renal Pathological Diagnosis and the Working Group for Renal Biopsy Database in the Japanese Society of Nephrology established the first nationwide, web-based, and prospective registry system, the Japan Renal Biopsy Registry (J-RBR), to record pathological, clinical, and laboratory data regarding all renal biopsies performed in 2007.

To date, the epidemiological and clinical data of renal diseases are available from nationwide registries of renal biopsies from the United Kingdom [1], Italy [2], Denmark [3], Spain [4], the Czech Republic [5], and Australia [6]. The role of a renal biopsy registry has been recently encouraged [7]. In Japan, several surveys were temporarily conducted for patients with restricted renal diseases, including primary glomerulonephritis [8], idiopathic membranous nephropathy (MN) [9], and immunoglobulin (Ig) A nephropathy (IgAN) [10]. However, there has been no web-based, nationwide, or prospective registry system of overall renal biopsies in Japan. The aim of the current study was to provide data to investigate the epidemiology and frequency of renal diseases with a histological diagnosis for patients registered in 2007 and 2008 on the J-RBR.

Subjects and methods

Registry system and patients

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